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FACILITATORS

Cover Image: Top: "Yo Soy-ee Blaxican", Vincent Valdez.
Bottom: "Ah Yes, That Notorious Place Everyone Speaks Of", Vincent Valdez.

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Richard J. Barohn, MD

Welcome to Vol 2 / Issue 3 of the RRNMF Neuromuscular Journal. This issue once again contains a plethora of new neuromuscular information. In addition, we once again are publishing some wonderful pieces from the arts and sciences that are not neuromuscular at all, but very much worth reading. The first section begins with "What's on Your Mind?," and I have asked Dr. Joshua Freeman to again allow us to publish one of his insightful articles he posts on his blog sites (he has two of them) about the dangers surrounding medically related direct-to-consumer advertising on TV. I have an article I first wrote for one of my Executive Vice Chancellor messages at the University of Missouri in honor of Black History Month; I highlighted the amazing career of Dr. Patricia Bath, a pioneer in Ophthalmology. Dr. Raghav Govindarajan has another great article about a journey he and a patient took together through their physician-patient relationship he titled "The Last Ride". In an attempt to expose my neuromuscular colleagues to some old-fashioned psychoanalytic thinking, I have asked my good friend and psychoanalyst Walter Ricci MD to allow us to publish two of his short pieces on the role of "shame" in our lives. This year is also the 25th anniversary of the Kansas City Psychoanalytic Institute, which Dr. Ricci founded with several colleagues. We are publishing a short piece Dr. Ricci wrote for that organization's newsletter. Yes, my neuromuscular friends, despite rumors of its demise, psychoanalysis is alive and thriving in the United States.

Back to neuromuscular disease and New Stuff! Dr. Mehta and the University of Missouri group discuss their experience using botulinum toxin for cramps in patients with neuropathy. Dr. Pocock and the group from Seattle have an intriguing article on the possible relationship between amyotrophic lateral sclerosis and multiple sclerosis. Dr. Menon, Dr. Brill and colleagues from the University of Toronto and CSL Behring report a sub-analysis from the pivotal polyneuropathy and treatment with Hizentra (PATH) study by investigating the distal compound muscle action potential and temporal dispersion as variables and secondary outcome measures. Dr. Rashid and colleagues from KabaFusion report their large home infusion experience of over 11,000 infusions and how infusion rate influences side effects of intravenous immunoglobulin (IVIG) infusions.

In the Clinic Stuff category, Dr. Menon and Brill (and Dr. Alnajjar) from the University of Toronto have another article in this issue describing a patient with a distal acquired demyelinating symmetric (DADS) neuropathy phenotype who ended up being diagnosed with primary amyloidosis and they ask the question: are the two related? Drs. Bhagavan, Beladakere Ramaswamy and Govindarajan from the University of Missouri report elevated liver transaminase enzyme elevation in a patient with Guillain Barre Syndrome (GBS). The neurology group in Philadelphia led by Dr. Prabhu has an interesting case first authored by student Ryan Fogg of a myasthenia gravis (MG) patient with a thymoma and the complication of pericarditis. Drs Rim and Li from the Cleveland Clinic describe the association of GNE myopathy and thrombocytopenia, which interestingly has previously been reported, and they review the literature. Dr. Alcantara and her team in Toronto, led by Dr. Hans Katzberg, describe a complicated case presenting with dyspnea and sleep apnea who was ultimately diagnosed with MG and MuSK antibodies and who responded to Rituximab.

In the Proposed Stuff category, we are publishing two grants: one that was not funded and one that was funded. The Kansas/Missouri group is publishing an unsuccessful PCORI grant we submitted several years ago. This was a proposal to do a comparative effectiveness study in CIDP of intravenous immunoglobulin (IVIg) versus subcutaneous immunoglobulin (SCIg). We are attaching the critiques from the reviewers, the ultimate (and painful) peer review. The purpose of publishing unfunded grant attempts and critiques is several-fold. If others are considering studying this clinical question, they do not have to start from ground zero and can see where others have tread and failed. If that happens, hopefully another group will take what we proposed and the critiques and come up with a better and findable approach. Another is of course that a great deal of time, effort, and teamwork goes into preparing these complicated multi-center trials. It seems reasonable to expect that at the least the team can potentially publish their work, along with the criticisms. Why no one has thought of publishing failed and accepted grants with critiques before is beyond me, but I am unaware of any other journal that does this.

In addition, we are publishing the successfully funded FDA Orphan Products Division RO1, Phase II study of Arimoclomol in IBM. This was funded in 2015. Dr Mazen Dimachkie was, and is, the principal investigator. In Volume 2, Issue 2 of the RRNMF Neuromuscular Journal, he and his team published the story of the evolution of the arimoclomol in IBM project. In this issue we publish the actual grant that was funded with the critiques from the study section. Again, the ultimate peer review. The project that the grant finished is now winding down and results will be published soon.

Finally, in the section we are calling "Art and other stuff" we have two poems and a screenplay. On the arts end of the spectrum, I invited my good colleagues Drs. Vernon (Bud) and Elizabeth (Betsy) Rowe to publish some of their poetry in this journal. Both Dr. Rowes are impressive neuroscientists, and they also are equally impressive and well published poets. Also in the arts category, I have asked my friend Walter (also a "Bud") Anderson to allow us to publish a new screenplay he has written, "27 Crossroads." Bud and I were in the Medical Corp of the U.S. Air Force

together, stationed at RAF Alconbury in the United Kingdom in the early 1980s. We were roommates, living in "The Longhouse" in a village called Over, on the Ouse River near Cambridge. Those were wonderful times and Bud and I have stayed fast friends over the decades. He went on to have a very successful career as a sound engineer on the sets of movies and television productions and lives in Manhattan Beach, California with his family. He is an excellent writer as well and has a couple of plays written. I thought this would be a good place for one of them to be published so my other medical friends can learn more about the talents of my good friend on the West Coast. This play takes place in England and you will be surprised who the characters turn out to be, and the bluesman they may have been influenced by.

The wonderful art on the cover is a diptych by San Antonio artist Vincent Valdez from the Barohn art collection. The blue painting is called "Yo Soy-ee Blaxican" and the red painting is called "Ah Yes, That Notorious Place Everyone Speaks Of".

I am looking forward to the next issue of the RRNMF Neuromuscular Journal as in that issue we will publish the abstracts from the upcoming Muscle Study Group meeting on Oct 1 through 3. This year again the annual MSG meeting will be virtual due to the covid pandemic. We are also hoping that many of the presenters of abstracts will have submitted full length articles for that issue as well. This will be a new feature for the journal- to publish full length articles that will be presented at the meeting in addition to all of the abstracts. We will also, for the first time, provide our industry partners who support the MSG meeting a space for information about their company or their products. We plan to publish that issue in mid-September. To register for the MSG meeting go to https://musclestudygroup.org/events/2021-muscle-study-group-annual-scientific-meeting/

Rick

DTC Advertising on TV Illustrates the Corruption and Inequity of the US Medical Care System

Joshua Freeman, MD

Originally published in the *Medicine and Social Justice* blog, https://medicinesocialjustice.blogspot.com/2021/03/dtc-advertising-on-tv-illustrates.html

I don't watch a lot of live daytime TV. (In fact, I don't watch a lot of live TV at any time.) I do see it several times a week for the 45 minutes I spend on the elliptical at the gym, which requires that the two TVs be tuned to sports. In practice, that means ESPN and ESPN2 and I try to position myself between them so I can look at whichever has the least boring talk. Daytime is not a time for actual sports; it is all sports talk. And mostly I listen to music in my headphones.

But I did seem to notice a really lot of the commercials were medically-related and aimed at my demographic (ie., "old"). Since I was recently in the hospital for several days and had the TV on different stations, I can attest that this pattern is not limited to sports shows; it is absolutely as ubiquitous on CNN, MSNBC, etc. (can't personally attest to FoxNews, but I bet it is also true there). Sure, there are a few non-medically related commercials aimed at my demographic (e.g., reverse mortgages) and once in a while even something of more general generational interest – I particularly liked a half-hour infomercial for the NuWave Bravo air fryer/convection oven. But the medically related dominate.

Such commercials include those related to insurance (Medicare supplements and in particular Medicare Advantage – which seems a bit odd, since open enrollment doesn't start until October), those advertising medical treatments for disease of the age-challenged, and lots of commercials for incredibly expensive recombinant DNA (anything ending in "-ab") and other biologics for relatively uncommon diseases. This last group is in the traditional (if your idea of "tradition" is 40 years) mode of direct-to-consumer (DTC) advertising first legalized under the Reagan administration: "ask your doctor if this is right for you". The implication is that it probably is, although the litany of unpleasant side effects that always starts with bloating, and moves to serious infections, and ends in death, should give us pause. It is certainly right for the drug manufacturer, who – shock! – makes HUGE HUGE HUGE amounts of money on these things. Some of these drugs cost $100,000 a year. There are neurologic drugs that cost $30,000 a MONTH. Or more. Thus it is worth advertising to lots of people in the hope that even a small percentage will "bite".

NOTE: Most doctors hate this DTC advertising. Yes, it is in part because of how irritating and time consuming it is for patients to come in and keep asking about whether they should be on these drugs. But more important, it is because they are trying to take care of you, to best manage your condition using drugs (when drugs are appropriate) that are the most effective, have the fewest and least dangerous side-effects, and are affordable for you. Why on earth anyone would ever think that a multi-drillion-dollar multi-national drug company would have your health interests at heart more than your doctor? If you think that, 1) you're wrong, 2) you've been watching too much TV.

In addition to the insurance and drug commercials, there are multitudes of miscellaneous others, especially for devices. You can get an app for your phone that will check your EKG. You can get endless numbers of devices that will monitor your blood sugar, many of which apparently come with the added benefit of turning you into a totally fit mountain biker! Indeed, if you have always wanted to play the flute, direct a play, or kayak whitewater, these devices are for you! Also, the you-know-what. And let's not forget the "mobility devices" like scooters, available at "no cost to you" (although such ads seem a little less common since some of the big operators have been imprisoned). These commercials provide a regular source of income for actors in their 50s playing people in their 70s. Even the ones in scooters look not very old, not very sick, and not very obese. Of course, sometimes they feature a real person in their 70s, if they're famous. Joe Namath, is, I think, 77.

There seem to be endless ways for the companies to make money off of your Medicare benefit. Medicare Advantage is one issue that deserves a little more discussion, since they often seem to (and may) offer you actual advantage. Medicare Advantage (Medicare Part "C") takes the money that traditional Medicare would pay, usually has you put in more, and basically puts you in an HMO. You get the benefits of an HMO – stuff not covered by traditional Medicare like maybe eye, ear, dental, or other stuff. Also, the disadvantages, like limited choice of doctors, hospitals, etc., especially if you're not in your usual geographic area. People with traditional Medicare do not get bills from doctors who are out of network (unless, and this is rare, they have opted out of Medicare altogether), but Medicare Advantage patients do. So, if you never leave your home area, and are

happy with the hospitals and doctors in the network, it may be a good choice for you, just as an HMO may be for anyone ***(disclaimer: probably, however, if you are to choose one, it shouldn't be the one advertising on TV!)***

That's about you, though. Societally, it is much worse. Medicare Advantage plans, compared to traditional Medicare, have way higher overhead costs (about 12-18% vs about 2%). They also get paid extra by the federal government. Why? Well, you'd have to ask Reagan and his GOP successors; essentially it is part of an effort to privatize as much as possible. And, like most efforts to privatize, actually costs more. And we all, as taxpayers, pay for it.

This is not a benign process, for Medicare, for drugs, for devices. They are selling us very expensive stuff and making a huge profit, while millions of Americans have no health insurance and millions more are grossly underinsured. Discussions about national health insurance proposals often focus on cost, but the stuff being sold in these commercials is part of the structure that causes amazingly inflated costs, making our health system the most expensive (2-3x as much per capita as other industrialized countries) while maintaining among the worst health outcomes of that group of nations. And the burden is not spread equally; those most in need, those who are the poorest, disproportionately minority group members, are the hardest hit. It is inequitable, discriminatory, and immoral.

The bottom line is that all of these commercials propagate a system that is not only vastly inequitable, but is medically inappropriate. A system in which the goal is not to maximize the health of the population, in any fashion but certainly not an equitable one, but rather to maximize the profit for the companies that are advertising, to take money from the rest of the economy and accrue it to themselves. This, of course, is the nature of modern capitalism, but that doesn't make it good. You have to decide if your health, and the health of your friends, family, community and nation are a core public benefit or a product to be sold, ***caveat emptor.***

The bottom line for the individual is the same as it is for all commercials. They are NOT about YOU. They are about MAKING MONEY for the company sponsoring the commercial. That is all. You are nothing but the vehicle, or perhaps more technically, "sucker", who will channel that money their way. If you read the fine print it is scary, and that is only the stuff that they are legally required to tell you. Anything that they are not legally required to tell you will not be there. Do not trust them at all. Do not watch them. They are dangerous.

Although I am going to look at see how *Consumer Reports* rates the NuWave Bravo...

Remembering Dr. Patricia Bath for Women's History Month: Ophthalmologist, inventor and humanitarian with many firsts

Richard J. Barohn, MD

I recently became aware of a physician, educator and inventor, Dr. Patricia Bath (1942-2019). For those of you who do not know her remarkable story, I felt compelled to share it with you during Women's History Month.

Patricia Bath was born in Harlem and was recognized early as being gifted. Her father was the **first** Black motorman for the New York City subway system. He served in the U.S. Merchant Marines, traveled the world and was an occasional newspaper columnist. Her mother was a homemaker and a domestic worker who used her earnings to make sure her children had an excellent education. Both parents encouraged Patricia to excel in school, and with their support she attended Charles Evans Hughes High School in New York.

As a student, Patricia was selected for a National Science Foundation summer research program in biology at Yeshiva University. When classes were over, she worked in a cancer lab. Patricia became part of the science team, analyzing experimental data, and developed a math equation to predict cancer cell growth. Her mentor, Dr. Robert Barnard, listed her as a co-author on a research report. This led to her receiving Mademoiselle magazine's Merit Award in 1960 at age 17 (1).

She was off to a fast start. After attending Hunter College in New York City, she went to medical school at Howard University, where for the first time she was exposed to Black professors who became her mentors. At Howard, she received several National Institutes of Health student fellowships and spent a summer in Yugoslavia on a children's health project. She became motivated to help disadvantaged people and served as a medical coordinator for the Poor People's Campaign that marched in Washington, D.C., for economic rights in 1968.

After medical school, she interned at Harlem Hospital followed by an ophthalmology residency at Columbia University. As an ophthalmology trainee in New York City, she learned that African Americans had a high frequency of blindness due to glaucoma, cataracts and other disorders. She performed community-based research by establishing an eye clinic system that increased the amount of eye care to those who could not afford to see medical professionals (2). When Dr. Bath graduated from the ophthalmology residency program in 1973, she was the **first** African American to complete a residency in ophthalmology in the United States.

Her career took her to California as an assistant professor of surgery at both Charles R. Drew University and at the University of California, Los Angeles, where she became the **first** female faculty member in the Department of Ophthalmology and the **first** African American woman to serve on staff as a surgeon at UCLA Medical Center. In 1976, she co-founded the American Institute for the Prevention of Blindness (AIPB), which proclaimed that "eyesight was a basic right." In 1977 and 1978, she served on the White House Counsel for National and International Blindness Prevention Program. Then in 1983, she had another **first** when she created the ophthalmology residency training program at UCLA-Drew, becoming the **first** woman to lead a post-graduate training program in ophthalmology.

That is a lot of **firsts**, but Dr. Bath was not done. Laser surgery for cataracts was in its early stages and she wanted to learn more. In 1981, she went to the Rothschild Eye Institute of Paris and then to the University of Berlin where she became a laser researcher. She did experiments with excimer laser photoablation on human eyes in eye tissue banks. She invented the term "Laserphaco" for the process, which is short for laser PHotoAblative Cataract surgery. As a result of her research and investigations, she developed a less painful and more precise device called the Laserphaco Probe to ablate and remove cataracts (3). In 1988, she was awarded a patent for this instrument, becoming the **first** African American female doctor to receive a patent for a medical invention. The Laserphaco produces a powerful concentrated beam that quickly and painlessly dissolves a cataract with a laser, irrigates and cleans the eye, and permits the easy insertion of a new lens. The device is now used throughout the world. The Laserphaco is responsible

for improving and restoring sight to thousands of people. Dr. Bath continued to improve on her device and had additional patents awarded in 1998, 1999, 2000 and 2003.

In 1993, she retired from UCLA and became the **first** woman elected to the honorary staff of UCLA Medical Center. She returned to Howard University, where she was named a "Howard University Pioneer in Academic Medicine" in 1993. Hunter College had previously placed her in its Hall of Fame in 1988. A children's book on her life and work was published in 2017 (5). Through the AIPB, she traveled the world performing surgeries, teaching and lecturing at universities. In Africa, the AIPB provided computers and other resources for visually impaired students. In recognition of her philanthropy, President Obama placed her on his commission for digital accessibility for blind children. In 2019, Dr. Bath testified about gender disparities in the STEM field and lack of female inventors in a hearing called "Trailblazers and Lost Einsteins: Women Inventors and the Future of American Innovation" (6).

In 2017, Medscape named her one of 12 "Women Physicians who Changed the Course of American Medicine" (7). In the same year, another **first** as Time magazine highlighted her in their "Firsts: Women who are Changing the World" for being the **first** to invent and demonstrate Laserphaco cataract surgery (8).

Dr. Bath died in 2019 at age 76. Recently, I came across a story of how her children were lobbying to have her inducted into the National Inventors Hall of Fame, the most prestigious society for inventors in the United States (9). The sad reality is that she was nominated 11 times before she died! One can only wonder why she was never elected into this society while she was alive. Apparently, the society does not give the award to inventors posthumously. Her children are trying to get this changed, and this video provides a look into those efforts. I suspect it will be another **first** for this remarkable woman.

References

1. Teenage Scientist is Named one of the Ten Young Women of the Year. Atlanta Daily World. December 31, 1960

2. Bath, Patricia. Rational for a program in community Opthalmology. Natl Med Assoc 71 1978;71:145-148

3. Bath PE. Laserphaco: an introduction and review. Ophthalmic Laser Therapy 1988;3:75-82

4. US patent 4744360. "Apparatus for a lasting and removing cataract lenses" Issued May 17, 1988

5. Mosca, Julia Finley (2017). The Doctor with an Eye for Eyes: the Story of Dr Patricia Bath (Amazing Scientist). The Innovation Press. ISBN 9781943147311

6. Trailblazers and Lost Einsteins: Women Inventors and the Future of American Innovation. United States Senate Committee on the Judiciary. Www.judiciary.senate.gov. Retrieved May 9, 2020

7. https://www.medscape.com/features/slideshow/women-physicians#page=13

8. Time Magazine: Firsts: Women who are Changing the World: The INVENTOR: Patricia Bath: First Person to Invent and demonstrate Laserphaco cataract surgery, 2017 Time Magazine

9. https://abc7.com/dr-patricia-bath-doctor-eyes-surgery/10321774/

The Last Ride

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As medical trainees we were always in awe of those physicians who seemed to know it all. They were like walking encyclopedias filled with exotic medical knowledge and everybody sought their advice on diagnosis and treatment. They served as role models and we wanted to be like them when we grew up and became "doctors". Physicians are fiercely competitive and these doctors occupied the rarefied stratosphere among them.

For as far as I can remember I always wanted be a surgeon. But soon after entering medical school I realized I liked the intricacies of brain and nervous system. The pathways, decussations, tracts, columns, horns and most of all localization won me over. As a child I spent many hours reading about the adventures of Sherlock Holmes and with neurology I could finally be like my childhood hero and put different clues together (localization) and identify the villain (disease) and save the day. Perhaps I felt that one day I could be like one of those physicians with exotic knowledge of the brain and nervous system who live in the rarified stratosphere.

I met Paul, a 60-year-old gentleman at the hospital for the first time. As fate would have it, the patient who was previously scheduled for EMG-electromyography (electrical testing of nerve and muscles) cancelled his appointment and Paul was scheduled in his place. He was having numerous falls and the ordering physician wanted to know if his "nerves" were causing the falls.

Paul called himself a farmer and flying enthusiast and took frequent trips in his two seater plane, a 1980 Piper Tomahawk, across his farms and the lake. He told me it made him happy and he felt part of something larger. But in the last couple of years he had difficulty getting in and out of the plane. He also had difficulty holding onto the controls and at his family's insistence he had stopped the plane rides. His condition deteriorated further and he had difficulty walking and had to use a walker. He had frequent falls. He saw a physician who recommended back surgery. After back surgery his condition worsened instead of getting better. His weakness worsened and he hardly left the house. He also had developed difficulty swallowing and could no longer enjoy his favorite steak. He saw another physician who recommended stretching his food pipe which he underwent with no benefit. By the time he saw me, he was evaluated by almost 10 different physicians.

His 'case' challenged and fascinated me and I wanted to slay the villain afflicting Paul just as my hero Holmes had slayed his arch nemesis Professor Moriarty. Further, the fact that he had been evaluated by 10 physicians with no answer made it even more intriguing. Could solving this case send me to the rarified stratosphere where my role models were and I so yearned for?

I carefully examined Paul and collected clues just as my hero. I completed the EMG but to my dismay the answer I had for Paul was not something I want any of my patients to have. Paul's weakness was due to Amyotrophic Lateral Sclerosis-ALS (also known as Lou Gehrig disease). ALS is a progressive neurological condition that causes weakness and wasting of muscles affecting all limbs, speech/swallowing and ultimately breathing, with no known cure.

As I saw Paul back in the clinic every few months he got weaker and the disease had slowly eaten away his muscles leaving only skin and bones. He spent most of his time in the electric wheelchair whose joystick he still could operate. He was losing weight and could barely swallow but still refused the feeding tube.

During the last clinic visit he confided to me that he was afraid and didn't want to die. For a moment I panicked and didn't know what to say. What would my hero Holmes do in this situation? What if the villain is invincible and can't be slayed? Will Sherlock Holmes still be the same if he could no longer solve the case and banish the villain? Will people still come to him with their problems?

Sensing my panic Paul joked that he would want to go back flying. I remembered Paul's love of his plane and the flight itself. Much to the dismay of his family I recommended he go back to flying as I had nothing else to offer him.

The last time I saw Paul, he was admitted to the hospital with pneumonia. He had decided to pursue hospice care at home. We spent a long time talking about his family and grandchildren. Paul then told me he was no longer afraid of dying. He had taken the flight over the farm and lake I recommended and he was very happy and satisfied with all that he had accomplished. As I left the room I had a strange sense of calmness and even joy of having solved the "case". A few days later I received a call from his family about his death.

Diagnosis and treatment are an important part of neurology. While treatment traditionally involves

medications, surgery or combination of the two, there are diseases for which there are no treatments or the treatments are inadequate. Yet I realized as a physician the treatment I offer goes way beyond simple medications and procedures. My recommendation for Paul to fly was probably the best treatment I could offer him. I did not learn Paul's treatment in medical school/residency/fellowship and definitely not in the countless exams and board certifications I took. But instead it was through listening to him and providing that human touch which we all so desperately seek and yearn.

I did not cure Paul's disease but I did cure Paul's illness.

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Some Notes on the Subject of Shame and Recovery

Walter F. Ricci, M.D.

All of us as part of humanity, live connected to some standard of perfection. Whether we are aware of this or not, there is a system and powerful structurein our minds that is quickly activated if there is a gap or deviation in our preestablished standards and values. The distance between that level and theone of our actual performance, appraised either subjectively or objectively, will be experienced by us as a state of pride or shame. Thus, any experiencethat engages the evaluation of the self, according to the valence that we attribute to that moment, will be subjectively felt as deadening or enlivening. Like an inexorable law, whatever does not increase our pride will increase our shame, whether this is perceived or not. Like a light touch or an intense blow, it is omnipresent with the same inescapability as the law of gravity. The degree of the perceived lack of achievement interacting with our resiliency and coping mechanisms, will determine the final configuration that the activation of shame will produce. The activation of shame will usually be experienced as deadening, while the perception of pride is felt as enlivening. To be ashamed is to be disconnected; we are shorn off from ourselves or the parts of ourselves that make us acceptable and lovable. Furthermore, the feeling of shame may disconnect us from others in our lives and in our community with whom we are deeply engrossed. Connectedness is vital for the integrity of our psychic cohesion, for our state of wellbeing, and for our very survival. When we disconnect even parts of ourselves, we are sequestered from the sources of vitality necessary to maintain the existence of those parts, and keep us fully alive. Like a fox or a wolf caught in a trap, who will amputate its own leg to be free of the trap, that same sacrifice of part of ourselves to ensure the chancesof survival of the rest of our feeling and experiencing selves will occur. That aspect of our self that is segregated or eliminated is the part that is found as unacceptable or too painful for exposure to the prying eyes of the other, or even worse, the implacable eye of our unconscious. The sentinel of our values dozes off lightly but awakens quickly to the slightest deviation of our values, and lets us know with a roar that it has awakened. Part of our self is sensed as damaged or defective, and the rest is the pained and relentless witness of that defect just revealed. The witnessed sentinel of the observing self, based on previous experiences and history, will oscillate between nurturing and compassion, and ruthless judgement.

Steps in Restoring Our Cohesiveness

To reconnect with others as well as with ourselves, we must first be able to recognize that the bond between the missing connection and the experience of our wellbeing has been broken. This means that we have to activate a basic resiliency in order to take the first step toward recovery, and this first most important step is the most challenging: that being our awareness of what has occurred. Awareness can be brutal. It means trading the serenity of our anesthetized ignorance for the pain of our shameful condition. The difficulty is in questioning and confronting the role we play in our perpetual victimization. By this confrontation, we exchange the oxygen-deprived, highly isolated stance of always being the judge of the others' lack of worth for the tragedy of our own debacle. Whatever our defensive maneuver, whether it is engaged automatically or not, we must reign in our defenses. By so doing, we shall bring the light of insight to our eyes along with undesirable sounds to our ears, and feelings of torment to our souls. This is a Herculean task, and one that many are not ready to confront. This confrontation will mean a radical change in the manner in which we see ourselves, like exchanging the role of the master for the one of the slave, or the perfection of pride for the ignominy of humiliation. This must be balanced with the awareness that the energy required and the price to be paid in keeping our self deception alive, is in fact energy ill spent, and leading us to the destruction of our lives and the lives of others.

Shame and State of the Self and Its Implications for Technique

Walter F. Ricci, M.D.
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"Who is there?" asks God.
"It is I"
"Go away", God says....
Later...
"Who is there?" asks God.
"It is thou."
"Enter," replies God.

From "Everyday Zen"

ABSTRACT

The author reflects on the vicissitudes of the state of the self as it unfolds during the analytical encounter. He delineates the presence and the ubiquity of shame during the interaction between patient and analyst. An important mention is given to the concept of the subject and object polarity. As such, special emphasis is given to the rapid variation of the state of the self. This requires dedicated attention to the state of the self and its awareness, regarding how invalidating shame is to both members of the dyad during their exchanges. The outcome of this attention will be the resulting lack of emotional attunement or validation during the exchange.

Introduction: Self Disclosure & Shame

There was a time when self-disclosure was a debated and divisive subject in psychoanalytic circles. There still is a structuring that, although invisible, is an oppressive culture that creates an inhibiting self-interrogation, that goes like this, "How will I be seen in the eyes and the mind of others, if I operate differently than the traditional standard dictates?" Streaks of coercive tones camouflaged with terms like "slippery slope," "boundary violations" and "acting out" create an intrinsic context of an authoritarian state within the subjectivity of our minds. This state inhibits us from the more natural context of enlightenment and inquiry, required for optimal responsiveness. The imposition of an external meaning imbedded in the technique, but without a system of review or recourse, paradoxically fosters a situation in which what it is supposed to prevent still happens. Conversely, what may need to happen, is stymied.

Some of the tenets established by tradition, although may be based on desires to create an environment of safety and inquiry, when used unreflectively, fall in the category of emotive language. Emotivism is defined by Horner and Westacott (1) as "the view the ethical utterances are merely expressions of feeling of the speaker and not statements which can be either true or false." They continue, "Words have the power to suggest much more than the strict dictionary definition. Associations stick to them obstinately, like fluff to Velcro, evoking feelings and images of the listener or writer. These associations can be charged with positive or negative feelings." They concluded with a warning, "It is vital that we keep our critical faculties awake, that we do not assume something has been proved simply because our feeling has been aroused."

Interactional Dynamics

Frank Broucek and I extensively reviewed the role of shame in the development of Sigmund Freud's technique (2). We also described the important influence of shame dynamics in helping to hold together the psychoanalytic movement. As we learned to recognize the intricacies of the intersubjective field and hermeneutics, it became clear that a dogmatic formulation of a teachable technique is tantamount to an unshakeable and pathological belief. Intersubjectivity is unique in that it can be understood only by acknowledging the interplay of historicity and biases (prejudices and the theories that we follow). Donnel Stern (3), citing Gadamer states, "Understanding requires us to extricate ourselves from preconceptions, from prejudice or prejudgments." Then he further states, "Insight always involves an escape from something that has deceived us and kept us captive." Thus, for Gadamer, understanding is a matter of choosing selectively one interpretation from the multiple possibilities that exist.

These are the pillars on which we base our understanding of the interaction. The limits of self-disclosure or self-absence would emerge from what is required at the moment. The attuned analyst is aware that he has wishes of wanting to know the analyzand. He also frequently feels the tension between wanting to be known by the "other" and the opposite wish to remain anonymous to him. Broucek (1991) in his book Shame and the Self (2) said, "Shame frequently has to do with experiencing oneself being treated as an object when one is attempting to relate to the other in a intersubjective mode". To be treated differently than one would have hoped for in the intersubjective exchange is at the root of triggering shame responses in the analytical space.

Karen Hanson, in her chapter "Reason for Shame," (4) refering to J. P. Sartre's works (1956) in Being and Nothingness, mentions the issue of, "consciousness at the keyhole." She comments on Sartre clearly establishing a reciprocal relationship between self and another in the

analysis of shame. In the "Existence of Others", Sartre says, "moved by jealousy, curiosity, or vice," I am listening at a door, looking through a keyhole. Alone in the hallway, I grasp the spectacle on the other side of the door as "to be seen," the conversation as, "to be heard," and I am absorbed in the acts of listening and looking. I am, as Sartre puts it, "a pure consciousness of things." "But all of a sudden, I hear footsteps in the hall. Someone is looking at me," and seeing me stooped in the hall, seeing me bent over at the door, seeing me looking through the keyhole. I am now conscious of myself; I discover myself, I exist for myself in shame. I see myself because somebody sees me. Shame "reveals to me the Other's look, and myself at the end of that look." Shame "is the recognition of the fact that I am indeed that object which the other is looking at and judging." This sudden exposure in a context different than we would like to be seen in is an important component of the shame experience.

In this passage, Sartre masterly described a metaphor of the relationship between the analyst and the patient, of being either an object or a subject. This relationship has prominent phenomenological underlying implications for the principles of anonymity, neutrality and abstinence in classical technique. The shame of the analyst, acknowledged or not, is not that he is looking or spying on the patient, but rather that he is not allowing the same prerogative to the patient.

Sartre presents the dilemma that exists at the core of self-disclosure. The analyst's posture of seeing and hearing without being heard or seen, to be absent and to be present at the same time. The principle of anonymity insures and supports the position that the analyst will not be seen or heard. Broucek (1991) says "the therapist is hiding and attempting to render himself as a person invulnerable (2). He is refusing to be an object and insisting on being a subject only." In the classical technique, the objectification of the patient was essential and the invisibility and protection of the analyst was assured. Using Sartre's example as a result of enforcement of the principle of anonymity that the analyst utilizes as a technical device, the analyst avoids being caught by the patient while peeking through the keyhole.

The traditional posture of the patient allowing himself to be known by someone who is unknown to him is not only unsafe but also somewhat sinister. Of course, along with the unobjectionable positive transference, there were unavoidable revelations caused simply by the fact that affects are usually synchronized (contagion) and experienced whether they are verbalized or not. A firm adherence to the principle of anonymity has the effect of communicating to the patient (whether intended or not) a message that says, "Let me get to know you, it's safe and healing; however it is not safe or appropriate for you to want to know me." In a previous paper, Broucek and I wrote of the following dream told by a very perceptive patient. Occasionally, she had asked me if I was in a depressed or sad mood. After my not addressing her inquiry, she had the following dream:

"I am at a nudist beach, very sunny and full of nature loving people. I am feeling well. I see walking around a man, dressed in a three piece suit with a necktie, very uncomfortable and perspiring."

It is clear that for some psychoanalysts and patients, it is safe and required by the situation to have a position of relative anonymity that eventually will evolve into what is optimal for that situation. Conversely, there are others who feel more effective maintaining a position of relative responsiveness and self-disclosure. Any approach has to be original and take into account the inter-subjective affective configuration of that moment. The personal styles of the patient and of the analyst always need to be the focus of inquiry and reflections in that dyad.

I found here the ideas of Sylvan Tomkins (5) very useful, in this respect as a guide to orient oneself about the compatibility of the style. Tomkins defines ideology "as any highly organized articulate set of ideas of anything." The main position he describes are the humanistic, the normative and the middle of the road positions (which is a combination of the other positions." The humanist attempts to maximize positive affects for the individual and his interpersonal relationships. In the normative position, norm compliance is the primary value and the positive affect is a consequence of norm compliance. The humanistic position stresses fairness and tolerance of diversity with global respect for the "other." The main concern is the avoidance of guilt. As such effect attention should be paid to the subjective state of the "other."

In the normative individual the stressed values are competence and self-assertion, thus, the primary concern is the avoidance of shame and the maintenance of the inviolability of the self. As such effect, pride, strength and orthodoxy are the main subscribed values. The integrity of the ideology to develop in analysis is one of complementarity and balance. To implement this attitude one needs to be aware of the possibility of an automatic posture that is assumed during the analytic situation.

This broadening approach provides us with the opportunity to do psychoanalysis tailored to the special idiosyncrasies of the analytical encounter. Each dyad sets the temperature of the interactions according to the meeting of their individualities, which can be explored only within that context. This approach does not dictate self-disclosure or self-concealment without first evaluating the meaning that the expression or withholding of that sharing has for the dyad.

Orange and Stolorow (6) mentioned in one of their papers about self-disclosure, that technique for them is "for things with no mind." The analyst's attitude, which is based on the premise of promoting growth, is one of being an experiential model of vulnerability, intimacy, and affect modulation. To be known and understood by someone who respects and is respected by us is the underpinning of the affective communication between patient and analyst. The construction of modern psychoanalysis is based on the understanding and application of one of the earliest tenets of analytical theory, which is often mentioned but seldom, adhered to: "Always follow the affect."

Current research on procedural and emotional memory confirms an intuition long suspected by many clinicians: that not all the unconscious can be made conscious. Certainly the symbolic achievement of reflective thought is one of the goals of psychoanalysis, but not all emotional experiences can be articulated. Nonetheless these unconscious memories have to be modulated and integrated, if not in words, then in experiences. Donna Orange (7) states, "attending to emotional memory has other implications for psychoanalytic understanding - informally we might say that our attention needs to shift at least in part from the words to the tune." Many theorists acknowledge that many nonverbal elements enter the treatment process and require analysis. Often, however, this is expressed as concession, betraying again the psychoanalytic bias in favor of verbalization. On the contrary, I believe that, while words can be rich resources for the expression and emphatic understanding of emotional experience, and can help patients' respect and appreciate their emotional lives, affective memory can be only partly articulated. I also think that the psychoanalytic emphasis on verbalization reflects a Cartesian mind-body dualism. It perpetrates the devotion to the conceptualizations found in the "Myth of the Isolated Mind" (Stolorow & Atwood) (8) and in Ryle's "Ghost in the Machine" (9), from which there is much to be rejected. This renunciation will lead us to avoid characterizing nonverbal expressions of history and development in pejorative terms like "enactments" or "acting out." Then we can begin to value and explore the nonverbal expressions and responses of both patient and analyst.

Shame and the State of Self in the Intersubjective Field

Lichtenberg (10) defined the self as "an independent center for initiating, organizing and integrating motivation." The sense of self arises from experiencing. It has an active (agent) and passive (receptor) mode. Robert Emde (11) wrote about a prerepresentational "Affective core of the self." This conception for the self and the affective core lead us to the understanding of primacy of affect as the main motivational factor in the organization of experience. The changing emphasis from drive to affects directs us to a shift from an intrapsychic stance to the intersubjective.

From birth our affective experience is regulated within an intersubjective system of reciprocal mutual influence (Beebe and Lachman) (12). In 1987 Stolorow, Brandchaft and Atwood wrote: "Affects can be seen as organizers of self experience throughout development if met with the requisite affirming, accepting, synthesizing and containing responses from caregivers. An absence of a steady, attuned responsiveness to the child's affect leads to significant derailments of optimal affective integration and to a propensity to disassociate or disavow affective reactions." In the process of affects integration when this derailment occurs the intersubjective triggers of the shame affects can be found.

Broucek (1981) has offered an account of the intersubjective origins of shame that emphasizes the caregiver's failure to respond supportively to the child's needs (14). The child thus acquires the painful sense of being viewed as an object rather than a subject. As I mentioned above, Emde (1983) describes a pre-representational affective core of the self. This core is made mostly of traces of affective memories, which organize and give meaning to our experiences. Thus, the pre-representational self will include misattuned moments that will become the experience's organizer. (11)

Daniel Stern, in his developmental studies, coined the concept of RIGS (Representations of Interactions Generalized) (15). Stern distinguishes between specific and prototypic memories: "Since the representation is an abstracted accumulation, undergoing constant updating of historical events, it will be a very conservative force upon interpreting any currently lived-event (the interpersonal reality). In other words, past experiences will have an enormous weight in the construction of present subjective experience. People will repeat the same behaviors, selective inattentions, interpretations, etc". Therefore, the analyst should provide the exploration of these past experiences and should encourage a new chance for the development of the aspects of the patient's self that were not supported in their development.

Thus, the sector of the self will come to be a co-creation of the intersubjective space with each participant contributing his or her own experience. This may be synchronized and could match with the experience of the other or not. It is crucial to clarify and be aware of the different possibilities and potential combinations of the various states of self and the "other."

Modern studies of attachment systems have shown the communication of the state of mind between mother

and child. The therapist alignment of self of states allows him to have an experience as close as possible to that of the patient. The attuned reciprocity of the therapist allows him to receive signals, which he will respond with his own correspondent state. Daniel Siegel in his book The Developing Mind says, "The sensitivity to signals and attunement between child and parent, or between patient and therapist, involves the intermittent alignment of states of mind (16). As two individuals' states are brought into alignment, a form what we can call "mental state resonance" can occur, in which each person's state both influences and is influenced by that of the other. There are moments in which people also need to be alone and not in alignment process. Intimate relationships involve this circular dance of attuned communication; in which there are alternating moments of engaged alignment and distanced autonomy. At the root of such attunement is the capacity to read the signals (often nonverbal) that indicate the need for engagement or disengagement."

In order to create a system of understanding the different states of the self, I propose to explore the different possibilities and potential combination of different states of the self and the "other." The patient operationally will assimilate his experience with the analyst according to the template, which organizes his relation with the other. The task of the analyst is to recognize in the fast pace of the clinical exchange the different experiential alternatives that are possible. This is always an approximate inference since he should assess the continuous shifting of intersubjectivity within himself and thus his influence on the "other" that changes from moment to moment.

Broucek in his paper "Shame and Early Development" (1991) defines Objective Self Awareness (OSA) as " an awareness of one's self as an object for others and through the mirroring of the observing other taking oneself as an object of reflection (objectifying self)." (17) He continues, " with the appearance of the OSA is the end of the Primary Communion". Later he says "the self becomes split into the immediate 'I' and the mediated objectified 'me' and the self-experience of the other, which also becomes split into other who relates herself to myself in an attuned way as to maintain my subjective sense of self, and the other who objectifies me and thus becomes a potential source of shame."

In another section, Broucek says, "the earliest developmental trigger for shame is a sense of inefficacy (a perceived failure to initiate, maintain or extend a desired emotional engagement with a caretaker)." Building on the ideas of Broucek, I came to realize that the lack of fundamental clarity about the variety and multifaceted nature of the self allowed the potential to impose guidelines in technique that obliviously did violence to the process that it was supposed to facilitate and energize. The restarting of the stunted growth of the self thus was transformed into a painful retraumatizing experience.

A very important contribution to the clarification of the informational-experiential process is the concept of emotional schemas. This concept contributes to the comprehension of the formation and workings of the inter-subjective world. These schemas develop in a nonverbal, sub-symbolic and symbolic images. They are the prototypical representation of the relationship of the self and others. They are constructed through repetitions of scenes with mutually shared affective states. These affective states are series of sensory-visceral and motoric elements which may occur in a sub-symbolic form with or without consciousness. These states are activated repeatedly, regularly and consistently in response to particular persons or situations. These prototypical episodes are structured in memories that build these emotional schemas. These schemas in turn are modified by new events and determine how a new experience is going to be given a meaning.

A useful guide to follow the fluid action in the clinical encounter is the one that I developed to conceptualize the different states of being with the self and the other. Each state of the self of the patient or the therapist is activated with a corresponding affective state specific to that self state.

Thus the affective activation connects with a characteristic constellation of different aspects of the self associated with separate emotional state. Thus each self perception of what is activated (role) is connected with a specific emotional arousal.

- I-I: "I" as being experienced subjectively as an agent, agency being defined as the sense of having volition and control over self generated actions as differentiated from the actions of others.
- I-Me: I as an object of the others' subjectivity.
- I-Thou: (M. Buber) subject – subject in a reciprocal relation imbedded in an intersubjective field. The subjective world of both participants is considered meaningful. Both participants are acknowledged as subjects of experience. (18)
- I(me)–You : self-object function in which the analyst is mostly recognized as someone with a subjectivity of his own, but at the moment it is suspended or receding to the background in order to serve the needs of the patient's subjectivity. In the situation in which we accept the I(me) role in the exercise of our freedom of choice it would enhance our self-esteem and pride. When the

situation is one in which we are forced to the I(me) role without choice or alternative, it will decrease our self-esteem and induce shame or humiliation.

- I(it)-you: (Buber) self state of the analyst functioning as a self object exclusively with his/her subjectivity denied or ignored. Shame experience, diminution of sense of self is connected with this objectification.
- I-You: object- to -object, mostly focused on the formal and public exchange with subjectivity mostly in the background.
- I-You(it): the subject-to-object relation established by the analyst and herbiases (personality and theory). It is objectifying (shaming) and dehumanizing of the patient because the analyst does not engage the patient with her full personhood, i.e., optimal responsiveness in that particular moment based on the patient's needs.
- I-He or She: thus when one feels that they have been addressed as a third person.

To summarize, the main possibilities are:

- I-I
- I-Me
- I-Thou I-You
- I(me)-you
- I(it)-you (the "it" refers to the transformation to a genderless indefinite nonhuman state.
- I-you(it)
- I-He or She

Reviewing the different relational options, it appears that conflicted interactions are an intrinsic part of the nature of every analysis. When there is a misattuned connection of a different state of self that should have been recognized, the process will derail until an awareness of the different selves with which we are trying to establish a dialog is clarified. Specific experiences are reworked and promoted in the analysis to allow the aspects of the self that were not supported to have "a second chance" (Orange 1995) (7). Only enough immersion of the self in the I-Thou could afford increased moments of I (Me) or I (It) without signs of fragmentation or retraumatization. One of the purposes of training analysis could be to allow in the trainee enough I-Thou development that could allow him to endure, as an analyst extended periods in which He-She would be treated as an I-Me, I-It by a regressed or demanding patient.

In the following example, I will illustrate the situation of an analyst being subjected to extended periods in which he experiences himself to be treated as an "it". Susan is a 29-year-old woman who entered analysis because of depression and a generalized constriction of her affect. Initially her analysis proceeded in an orderly fashion and she was actively engaged, giving accounts of her life history and events in an energized fashion. As the months passed, frequent silences began to appear. Concomitantly, she became irritable and hostile. One of the recurrent themes was the feeling she had of being "just a patient". This theme became very repetitive during her second year of treatment. Continuous interpretive effort by me, relating the present situation to a reenactment of the lack of sensitivity by her alcoholic mother during her childhood,seemed to increase her sense of being mistreated and ignored. As my efforts to understand the situation failed, my mounting sense of frustration reached the point of my "secretly wanting her to get lost." In one of those sessions, after an agitated rejection of my attempts to communicatethat I really cared about her, I, at wit's end, told her "in moments like this, I don't know what else to do. It reminds me of when I was in school and I was to solve algebra problems in front ofthe whole class. I felt clumsy and stupid without having a clue of what to do." To my surprise, her demeanor and behavior changed completely and with a very gentle voice, she said, "I know. I also had a terrible problem with algebra." This sudden self-disclosure shifted, in the patient's experience, the I-You (it) to an I-Thou which created an immediate empathic response. As I continued with measured responses of a more casual tone, and specifically attuned deshaming self-revelations, the patient for the first time felt understood and began actively to recount memories of harsh treatment at the hands of her stupefied alcoholic mother. I, in my frustration, revealed my subjectivity and history, which gave to the patient the experience of being engaged in a level of humanity that she had painfully missed in her upbringing. Her protected and vulnerable self responded in an enlivened fashion when, instead of being treated as a you (it), shewas treated as I-Thou and felt rehumanized with a hope of continuous development now possible. When developing intimacy between two persons there is a process of mutual self- disclosure. If one person expresses feelings and desires about another, and the other person failsto respond at the same level, the first person is going to experience shame. At another level, thesecond person is also feels shame for failing to meet the first person on the same level of intimacy and self-disclosure.

This calculated, but eventually more spontaneous, revelation, which I call "specifically attuned deshaming revelation," when properly used, allows a development of a twinship experience which decreases or soothes the level of intensity of shame. In the case of humiliation,this is even

more necessary. In this context, humiliation can be seen as the tarnished and obliterated self, with the rest of the mind left as a pained, suffering witness.

In the case of Susan, the analyst's sharing of his inner experience had almost a magical transforming effect. Suddenly, she was catapulted from being a target, a thing, and a recipient of vacuous intentions and theories, to someone who was on an equal footing among the living.

With this disclosure I announced that I was willing to remove my mask, and that she was more important than my theory and posture. I gave the full message that to reveal oneself was safe, and more importantly, that she was worthy, since I cared enough to show my undisguised self. The previous clinical stance had conveyed to her the message that "it is necessary and safe for you to reveal your subjectivity, but it is not safe or prudent for me to do the same."

The Irish philosopher Bishop Berkely said, "Esse est percipi" (to be is to be perceived) (Broucek, 1991) (17). I changed this to "To be is to be responded to." Thus, the response that she needed and was unable to articulate was finally given to her. The theory outside that vital encounter had been like a straightjacket for the analyst, dictating the behavior while oblivious toboth humans' needs. However, in the course of an analysis, the analyst needs to be careful while offering himself as a developmental and emotional model for the patient. For example, sometimes the patient has to be guided and scaffolded to the next level with the secure and unintrusive presence of an analyst who facilitates but is also willing to intervene when the obstacle to the patient's development seems to be unassailable. In other words, it is an operative experiential moment when the patient is supported effectively to take the next step, which he hadnot attempted before because of the lack of the attuned validated response of the caretaker.

The appraisal of the state of the self of the patient and analyst is always approximate, because the experiences of their own the historicity and biases are differently organized. The situation at times is as swift and elusive as mercury. For example, as soon as we may try to give words to the experience I-Thou, it is changed to the I-You(it), and thus the transformation is from the subjective experience to one of an objective scientific event. Only by our recognizing when this disruption occurred will we be allow to cure it and to restore the intersubjective dialogue in which the growth and validation of our experience resides. The recognition of the state of the self and also, these new developments in the way of conceptualizing, help us to further clarify the essence of psychotherapy and psychoanalysis. Along these lines, the nature of the therapy will evolve to encompass the recognition and respect of the otherness of the other, with the required wisdom and resiliency to tolerate the difference or separateness. Then there will be no urgency to impose meaning and behavior on the other. This will be the base from where we facilitate and explore enriching and problematic experiences in our lives. The tasks ofhelping to come to terms with the patient's own perspective will be greatly facilitated with this approach. Applying this approach, our respect for another human being will be expressed by ourefforts, especially when we are in a position of influence or power over the other. We should do our utmost so that the other person does not experience that power or influence (M. Hoffman,commentary) (19).

In summary, as Broucek and I stated in a previous paper, "Self Disclosure or Self Presence", "the analyst's disciplined and reflective self-disclosure is one more tool in the analytical procedure as we try to reach further and deeper into the core of the human experience" (20). The great challenge and required "heroism" of this approach is that this launches the analyst from a position of a detached and dispassionate voyeur and scientific observer, to one of a reflective human being fully embedded in the co-creation of the interaction and its understanding.

The article submitted contains all contents of Dr. Walter Ricci's presentation at the 22nd Annual IAPSP International Conference in Toronto, Canada in October 1999.

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References

1. Thinking through Philosophy: An Introduction by Chris Horner and Emrys Westacott. Cambridge University Press. Pages 122-123 (Oct 2, 2000)

2. Broucek, Francis (1991) Shame and Objective Self Awareness. In Shame and the Self. The Guilford Press, Chapter 4, Chapter 7.

3. http://web.ed.ntnu.edu.tw/~t04008/frontpage/online../hermeneutics/h-educationch4.pdf

4. Hanson, Karen (1997) Reasons for Shame. The Widening Scope of Shame. The Analytic Press, Inc. Chapter 6, Page 171

5. Sylvan Tomkins, Exploring Affects: Selective Writings. The Structure of Ideology. Cambridge University Press, 1995. Pages 111-115

6. Orange, D. and Stolorow Robert Self Disclosure From the Perspective of Intersubjective Theory (unpublished) for the Psychoanalytic Inquiry. Page 1

7. Orange D. (1995) Emotional Memory. Emotion Understanding The Guilford Press, Chapter 8, Page 121

8 . Robert D. Stolorow, Ph.D. and George E. Atwood, Ph.D. (1996). Psychoanalytic Review, 83:181-194. The Intersubjective Perspective

9. Gilbert Ryle's Concept of Mind, written in 1949 (derogatory description for René Descartes' mind-body dualism. The phrase was introduced in Ryle's book.

10. Lichtenberg, J. 1989 Introduction Psychoanalysis and Motivation The Analytic Press Chapter 1, Page 1

11. Emde, R. (1983) Prerepresentational Self and Its Affective Core. Psychoanalytic Studies of the Child, 38 – 165-192.

12. Beebe and Lachman, (1998), Mother Infant and Mutual Influence and Precursors of Psychic Structure in Arnold Goldberg (Ed.) Frontiers of Self Psychology, Pages 3-25. Hillsdale, N.J. The Analytic Press.

13. Stolorow, R., Brandchaft, B., & Atwood, G. (1987). Psychoanalytic treatment: An intersubjective approach. Hillsdale, NJ: The Analytic Press.

14. Broucek 1991. Shame and the Self: Shame and objective self-awareness. Guilford Press. Pages 46-49.

15. Stern, D. (1985) The Interpersonal World of the Infant, New York Basic Books.

16. Daniel J. Siegel (1999) The Developing Mind, Guilford Press, Chapter 3, Page 70.

17. Broucek, 1991. Shame and it's relation to early narcissistic developments. International Journal of Psychoanalysis, 63:369-378. 1991

18. Martin Buber 1970. I-Thou. New York Charles Scribner. Page 69

19. Irwin Z. Hoffman, Ph.D. Therapeutic Passion in the Countertransference. Psychoanalytic Dialogues, 19:617–637, 2009. Copyright © Taylor & Francis Group, LLC. ISSN: 1048-1885 print / 1940-9222 online. DOI: 10.1080/10481880903340141

20. Ricci, W. and Broucek, F. (1998) "Self Disclosure or Self Presence" Bulletin of The Menninger Clinic, Volume 62, No. 4, Fall 1998.

On the 25th Anniversary of the Kansas City Psychoanalytic Institute

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My own history and the history of the Greater Kansas City Psychoanalytic Institute (GKCPI) are inextricably tied, in a history of some fifty years.

"Ex nihilo nihil". Nothing comes from nothing. Following Parmenides' wisdom, I searched within myself the origin of my desires to be a psychoanalyst.

My first contact with the name 'Freud' occurred in my father's medical office. I should admit that my curiosity was awakened not only by the name, but by the content, as it was 'Freud on Sexuality'. Following that, I was rewarded by a lecture by Heinrich Racker.

First GKCPI class back in 1996

Dr. Walter Ricci, Dr. Pam Seator, Dr. Carol Smith, Dr. Mary Lorton, Mr. John Parker, and Dr. Salomon Alfie.

This caused immediate enlightenment of my mind and heart. Studying A. Garma and E. Pichon Riviere, I became fascinated by the subject matter, and in spite of my naïve ignorance, realized that there was something missing in my curriculum at my medical school, something that I had never experienced, something I can only say opened my eyes to the fact that the mystery of the mind and emotions was a subject to be endlessly explored.

I began my personal journey in Buenos Aires, Argentina. I graduated as a psychiatrist in 1962. My goal to relocate to the United States was accomplished in 1965. I applied to the Topeka Institute for Psychoanalysis (TIP), but first, due to my training in another country, had to repeat my psychiatry residency. While so doing, I became acquainted with a psychoanalytic study group comprised of five psychoanalysts working in Kansas City. These five distinguished psychoanalysts included Dr. Harold Meyers, Dr. Gerald Ehrenreich, Dr. Sigmund Gundle, Dr. Ivy Bennett, and Dr. Irv Kartus. All of them were faculty educators at Western Missouri Mental Health Center (WMMHC).

I went on to train at TIP. Dr. Harold Meyers was my training psychoanalyst. It was my good fortune to have trained with this wonderful man. Harold, (as he wished to be called) was very humanistic, open, flexible, and capable of engaging during our sessions. He had a respectful warm disposition while he led us in our exploratory search and analysis. During one of my sessions, I had just been called by Jefferson City and offered the position of superintendent of WMMHC. This was a full training facility with over 1500 employees and 8000 to 10000 admissions per year. I conveyed my terror to Harold. He listened and then simply said, "You can do this. This could be a major step toward having our own psychoanalytic institute in Kansas City." Though scared, I felt supported, and with the sense of a mission in mind, I accepted this position and stayed on as superintendent for eight years.

The task of creating a group at our institute, with diversity and an open orientation, was not easy. Using all that TIP had given me, and the desire to have an institute dedicated to the teachings of Freud, combined with the passion of pioneers such as Dr. Frank Broucek (and his understanding of shame), along with Dr. Hans Uffelmann (a renowned philosopher with disciplined reasoning), and Dr. Salomon Alfie (who I had hired to be the director of the department of child psychiatry, and of the child psychiatric residency), I brought together these exceptional individuals with my own contributions from Dr. Heinz Kohut and Dr. Joe Lichtenberg -- and our GKCPI was born.

Our mission of forming this institute with a mission of teaching and learning in an atmosphere of respect, curiosity, compassion, and acceptance of diversity was no longer just a dream, but a reality.

The first class in 1996 including Dr. Mary Lorton, Dr. Pam Seator, Dr. Carol Smith, Dr. Badresh Parikh, and Mr. John Parker was launched, but it was a precarious time. We convened in a conference room in my former office on Shawnee Mission Parkway. We had no administrative staff, no funding, and no assets, just our intense commitment and desire to succeed. Many times, we were doubtful of our ability to bring this to fruition, but we prevailed. The Menninger Clinic had moved out of Kansas, and those professionals remaining in Topeka came to join with us, and they contributed to our development. Thus, over time, the trip from Kansas City to Topeka became reversed.

Figure 1. The first GKCPI class in 1996. Dr. Walter Ricci, Dr. Pam Seator, Dr. Carol Smith, Dr. Mary Lorton, Mr. John Parker, and Dr. Salomon Alfie.

Many professionals from Topeka came to us, and we always received them with welcoming arms.

I was the first director of the institute for two years, but because of some differences in philosophical orientation (with the committee for new institutes of the APsaA), I resigned as director and Dr. Michael Harty, an excellent contributor, assumed this position.

It is with such pride, that I look back on this seed of desire that has become a fully accredited institute. I want to thank all of you who are here, and all who came before and are no longer with us for this tremendous accomplishment.

Efficacy of Botulinum Toxin for Treating Cramps in Peripheral Neuropathy

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ABSTRACT

Introduction: Muscle cramps are a common occurrence in patients with peripheral neuropathy and are known to cause significant distress and decrease the quality of life. Although several drug formulations have been used in the management of cramps, there is significant variability in terms of efficacy and tolerability in patients with peripheral neuropathy. This study aims to assess the efficacy of botulinum toxin A in the management of lower limb cramps in patients with peripheral neuropathy.

Methods: This retrospective chart review included a total of ten patients with peripheral neuropathy with cramps. Relevant data such as age, gender, race, pain score and cause of peripheral neuropathy were documented. Statistical analyses to compare the variables were done using the Wilcoxon Test. The pain score before the administration, at 3-month, 6-month and 9-month follow up were compared.

Results: All patients enrolled in the study showed improvement of pain assessed by visual pain analog scale. An improvement of 1.60 (95%CI, $p<0.05$), 2.70 (95%CI, $p<0.05$) and 3.50 (95%CI, $p=0.05$) was noted between test scores from before administration of botulinum toxin to 3-month, 6-month and 9-month follow up respectively.

Conclusion: Local BTX-A infiltration is likely an efficacious and safe procedure for improving pain associated with cramps in patients with peripheral neuropathy.

Keywords: *cramps, peripheral neuropathy, botulinum toxin, lower limb, efficacy*

Introduction

Muscle cramps are paroxysmal, painful and involuntary contraction of a muscle group or a single muscle.[1] They may occur spontaneously or be triggered by the contraction of muscle. It can manifest as a part of physiological conditions such as pregnancy, muscle fatigue and aging or be a symptom of pathological conditions affecting the neurological, metabolic or endocrinological disorders.[2] They occur frequently in general adult population and may range from mild and infrequent to severe.[3,4] The severity and frequency of cramps has been reported to affect the quality of life of several patients due to the acute pain and soreness which may last for several days and has been known to affect sleep as well.[5,6] To manage the distressing and disabling effects of cramps, several agents such as quinine, anti-epileptic drugs and magnesium have been used but have been reported to provide insufficient relief and in some cases are poorly tolerated.[7-10]

Theorized to occur as a result of abnormal hyperexcitation of terminal branches of motor axons and the hyper excitability of motor neurons at the spinal level, the exact mechanism of cramp origin and initiation remains a mystery.[11-13] Lambert *et al*. in 1969 reported the inability of muscle cramps to be evoked in curarized muscles.[14] This finding led to the realization that a long-standing block at the neuromuscular junction may prove to be useful in managing cramps. Botulinum toxin A (BTX-A) is known to reduce hyperactivity of a muscle by blockade of acetylcholine release at neuromuscular junction thereby leading to muscle relaxation[14,15] This property of botulinum toxin has been used successfully to manage cramps in patients with diabetic neuropathy and patients with benign fasciculation syndrome.[16,17]

Our study aims to assess the efficacy of botulinum toxin A (BTX A) in a well-defined cohort of patients with peripheral neuropathy who suffered from cramps due to various etiologies.

Methods

This study is a retrospective chart review of patients attending a University based hospital approved by the Institutional review board (IRB). The study population included patients with peripheral neuropathy aged more than 18 years who were undergoing care at the University hospital for peripheral neuropathy.

These patients had undergone BTX A administration for managing cramps by the same physician. Only patients with lower limb cramps and at least a 12-month follow up during the study period were included in the study. All patients in this study had tried and failed two oral medications for cramps (either reached maximum dose with no benefit or had side effects resulting in discontinuation or dose limitation). The standardized injection sites for botulinum toxin included bilateral gastrocnemius and intrinsic muscles of the foot. 100 units for each limb bilaterally was administered for each patient with 75 units injected to gastrocnemius and 25 units into intrinsic muscles of the foot. A total of 10 patients fulfilled the criteria and were made a part of the study.

Information including age, gender, race, cause of peripheral neuropathy and visual analog pain score were collected for these 10 patients. The 10-point visual analog pain score was used to record the pain level at baseline before the administration of botulinum toxin and was followed up at 3-month, 6-month and 9-month intervals from the first injection by the physician.

The analysis of the data included summarizing patient demographics and pain scores in form of descriptive statistical variables including mean, standard deviation, ranges and percentages. Comparison of the pain scale at different intervals was done by using Wilcoxon signed rank test and a correlation between them was done. All statistical analyses were done using SPSS v22 software (IBM, Armonk, NY).

Results

The subjects of our study had a mean age of 64.3 ± 6.9 years. The study population belonged to Caucasian ethnicity and with 80% men. The cause of peripheral neuropathy in the majority of these patients (60%) was diabetic neuropathy followed by bortezomib induced peripheral neuropathy (20%). Monoclonal gammopathy of undetermined significance (MGUS) and Tri sulfate disaccharide IdoA2S-GlcNS6S (TS-HDS) neuropathy each constituted 10 % of the total study population (Table 1). For all patients, botulinum toxin was well tolerated and no side effects were reported.

The data analyzed reported a significant change in pain scores from before administration and at 3-month and 6-month intervals. The average pain score of patients reported before the administration of botulinum toxin and at 3-month, 6-month and 9-month intervals were 8.50±0.97, 6.90±0.73, 5.70±1.15 and 5.00±0.66 respectively. Figure 1 demonstrates the change in average pain scores at different time intervals. The improvement of pain score from before and at 3-month, 6-month and 9-month follow up was 1.6 (95%CI, $p<0.05$), 2.7 (95%CI, $p<0.05$) and 3.50 (95%CI, $p = 0.05$) with ranges of 4, 6 and 6, respectively.

Table 1. Patient demographics.

Characteristics of the patient	Detail of the patient
Age (years)	64.3 ± 6.9
Gender (female/male)	2/8
Ethnicity (Caucasians)	10
Cause of peripheral neuropathy	
Diabetes mellitus	6
Bortezomib induced peripheral neuropathy	2
MGUS	1
TS-HDS	1

Discussion

This study shows that patients with peripheral neuropathy of varying causes having cramps showed an improvement of pain due to cramps at 3-month, 6-month and 9-month intervals when compared to that before administration of botulinum toxin. Majority of the patients in our study (6 patients out of 10) suffered from diabetic neuropathy which is a common cause of neuropathy and of cramps.[18] Other causes of peripheral neuropathy in our study included MGUS (1 patient), TS-HDS (1 patient) and chemotherapy induced peripheral neuropathy (2 patients). The agent used in both these patients was Bortezomib, a potent proteasome inhibitor which has been used as a cornerstone for the treatment of newly diagnosed or relapsing multiple myeloma.[19] Our study showed improvement in their pain score with no issues with tolerability. This can be owed to the less adverse effect profile with botulinum toxin and its administration after several weeks in comparison to the regular use of other medications which often have a higher chance of developing adverse effects and issue with tolerability.

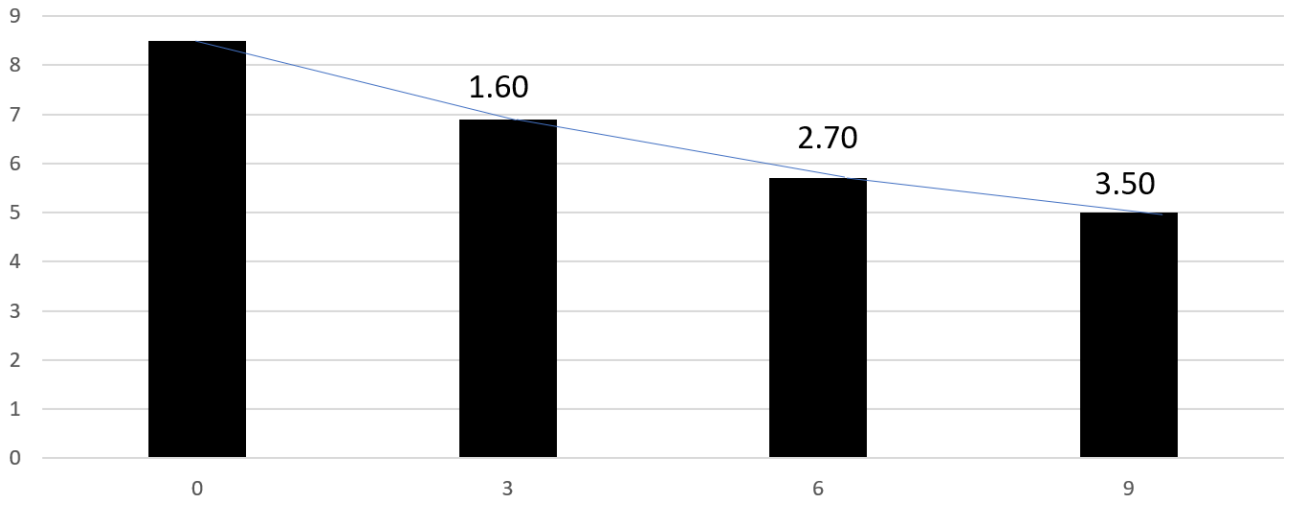

Figure 1. Chart depicting change in average pain score over different intervals during a 9-month period. The digits on the top of the graphs show the improvement in pain score from before the administration of botulinum toxin to that particular interval of time. The x axis depicts the months and the y axis depicts the pain score.

Our study reported significant improvement in pain scores from before to the 3-month and 6-month intervals. The improvement noted was 1.60 at the 3-month interval and 2.70 at the 6-month interval. This significant improvement in pain score is comparable to the results of the study conducted in 1997 by Bertolasi et al where they used botulinum toxin to manage cramps in 5 patients with benign cramps — fasciculation syndrome.[16] The study used clinical and neurophysiological variables collected before and after the administration of botulinum toxin to assess its effects. A significant lowering of clinical cramp severity scores and a significant increase in cramp threshold frequencies was noted. However, the muscle strength remained unchanged in these patients.[18] This pilot study showed that intra muscular injection of botulinum toxin is a safe, effective and long-lasting treatment of muscle cramps and fasciculations.

A recent study by Restivo et al also depicted the efficacy of botulinum toxin in management of cramps due to diabetic neuropathy.[17] The placebo controlled, double blind, perspective study assigned fifty diabetic patients randomly to each of the arms with variables including change in pain intensity, cramp frequency and cramp threshold frequency noted for all patients at different intervals of time. Significant improvements in all outcome measures were reported by patients who were administered botulinum toxin. Twenty of these twenty-five patients responded positively reporting improvements as early as 1 week after the administration and effects lasting up to 14 weeks. The remaining five patients were non responders.[17] Our study, while being retrospective in nature, included patients with peripheral neuropathy due to different causes and showed the efficacy of botulinum toxin in managing cramps due to peripheral neuropathy irrespective of its cause. Table 2 summarizes the studies where botulinum toxin was used to manage cramps and are contrasted with our study.

Costa et al in 2005 reported a case of 56-year-old man with S1 radiculopathy who presented with painful right calf hypertrophy, fasciculations and cramps which were aggravated by long standing and walking.[20] Administration of botulinum toxin led to marked subjective improvement in pain, cramp, fasciculation and calf hypertrophy within 15

Table 2. A comparison of studies conducted to assess the efficacy of botulinum toxin for managing cramps

Study reference number	Type of study	Number of subjects	Cause of cramps	Variables used to assess efficacy	Result
16	Prospective	5	Benign cramp fasciculation syndrome	Cramp severity score, Cramp threshold frequency	Significant decrease in cramp severity score and increase in cramp threshold frequency
17	Placebo controlled, double blind prospective	25 in placebo group and 25 in botulinum toxin group	Diabetic neuropathy	Patient diary, cramp severity score, cramp threshold frequency	Decreased pain intensity and cramp severity score, increase in cramp threshold frequency in 20 patients
20	Case report	1	S1 radiculopathy	Subjective clinical benefit, calf diameter, side effects if any, muscular electrical activity.	Marked subjective improvement, decreased spontaneous muscular activity, no change in calf diameter
21	Randomized clinical trial	45 (21 from the conservative treatment with gabapentin and 24 from botulinum toxin group)	Lumbar spinal stenosis	Pain numeric rating scale, Oswestry disability index, subjective grading of cramps, Insomnia severity index	Leg pain, cramp severity, cramp frequency and insomnia improved.
Our study	Retrospective chart review	10	Diabetic neuropathy, chemotherapy induced neuropathy, MGUS and TS-HDS	Visual analog pain scale	Decrease in average pain scale score in all patients

days of administration. This time frame of feeling relieved by the action of botulinum toxin is comparable to studies mentioned above showing the average time of action to be similar.

A randomized clinical trial conducted Korean researchers involving fifty patients with lumbar spinal stenosis (LSS) suffering from nocturnal cramps aimed to assess the clinical effectiveness of botulinum toxin.[21] The patients were randomly assigned to the treatment arms – conservative management with gabapentin and botulinum toxin alone. Patients administered with botulinum toxin reported decreased leg pain intensity, cramp frequency and cramp severity. Insomnia in these patients improved as well. The study showed the superiority of botulinum toxin in managing nocturnal cramps.

Our study, however, has notable limitations including a small sample size and the changes in electrophysiological parameters to back the subjective assessment of improvement in cramp pain. Larger studies including randomized clinical trials should be conducted to have a definitive conclusion about the efficacy and tolerability of using botulinum toxin in the management of cramps due to peripheral neuropathies from different etiologies.

Conclusion

Local BTX-A infiltration is likely an efficacious and safe procedure for improving pain associated with cramps in patients with peripheral neuropathy.

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References

1. Layzer RB. Muscle pain, cramps, and fatigue. In: Engel AG, Franzini-Armstrong C, eds. Myology. New York: McGraw-Hill 1994:3462-3497

2. Layzer RB. The origin of muscle fasciculations and cramps. Muscle Nerve 1994; 17:1243-1249

3. Abdulla AJ, Jones PW, Pearce VR. Leg cramps in the elderly: prevalence, drug and disease associations. Int J Clin Pract 1999;53: 494–6.

4. Naylor JR, Young JB. A general population survey of rest cramps. Age Ageing 1994; 23:418–20.

5. Hawke F, Chuter V, Burns J. Impact of nocturnal calf cramping on quality of sleep and health-related quality of life. Qual Life Res. 2013 Aug;22(6):1281-6. doi: 10.1007/s11136-012-0274-8. Epub 2012 Sep 26.

6. Blyton F, Chuter V, Burns J. Unknotting night-time muscle cramp: a survey of patient experience, help-seeking behaviour and perceived treatment effectiveness. J Foot Ankle Res 2012; 5:7.

7. Sidorov J. Quinine sulfate for leg cramps: does it work? J Am Geriatr Soc 1993; 41:498–500.

8. Garrison SR, Allan GM, Sekhon RK, et al. Magnesium for skeletal muscle cramps. Cochrane Database Syst Rev 2012;(9):CD009402.

9. Bialer M. Why are antiepileptic drugs used for nonepileptic condi- tions? Epilepsia 2012;53(suppl 7):26–33.

10. Cornelius VR, Sauzet O, Williams JE, et al. Adverse event reporting in randomised controlled trials of neuropathic pain: considerations for future practice. Pain 2013; 154:213–220.

11. Baldissera F, Cavallari P, Dworzak F. Motor neuron 'bistability'. A pathogenetic mechanism for cramps and myokymia. *Brain* 1994;117(Pt 5):929–39. [PUBMED:7953602]

12. Norris FH, Gasteiger EL, Chatfield PO. An electromyographic study of induced and spontaneous muscle cramps. *Electroencephalography and Clinical Neurophysiology* 1957;9(1):139–47. [PUBMED:13404940]

13. Ross BH, Thomas CK. Human motor unit activity during induced muscle cramp. *Brain* 1995;118 (Pt 4):983–93. [PUBMED:7655893]

14. Simpson LL. The origin, structure and pharmacological activity of botulinum toxin. Pharmacol Rev 1981; 33:155-188

15. Pavone F, Luvisetto S. Botulinum neurotoxin for pain management: insights from animal models. Toxins (Basel) 2010; 2:2890–2913.

16. Bertolasi L, Priori A, Tomelleri G, et al. Botulinum toxin treatment of muscle cramps: a clinical and neurophysiological study. Ann Neurol 1997; 41:181–186

17. Restivo DA, Casabona A, Frittitta L et al. Efficacy of Botulinum Toxin A for Treating Cramps in Diabetic Neuropathy. Ann Neurol. 2018 Nov;84(5):674-682. doi: 10.1002/ana.25340. Epub 2018 Oct 16.

18. Katzberg H, Kokokyi S, Halpern E, et al. Prevalence of muscle cramps in patients with diabetes. Diabetes Care 2014;37: e17–e18.

19. Vangsted A, Klausen TW, Vogel U. Genetic variations in multiple myeloma II: association with effect of treatment. *Eur J Haematol*. 2012;88(2):93–117.

20. Costa J, Graca P, Evangelista T, de Carvalho M. Pain and calf hypertrophy associated with spontaneous repetitive discharges treated with botulinum toxin. Clin Neurophysiol. 2005 Dec;116(12):2847-52. Epub 2005 Oct 25.

21. Park SJ, Yoon KB, Yoon DM, Kim SH. Botulinum toxin treatment for nocturnal calf cramps in patients with lumbar spinal stenosis: a randomized clinical trial. Arch Phys Med Rehabil. 2017 May;98(5):957-963. doi: 10.1016/j.apmr.2017.01.017. Epub 2017 Feb 14.

Amyotrophic Lateral Sclerosis and Multiple Sclerosis: More Evidence Suggesting a Link

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ABSTRACT

Objectives: Previous reports of the concurrence of multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) in the same patients suggest shared pathogenesis, with the *C9orf72* mutation as a possible shared genetic link.

Methods: Symptoms, neuroimaging, and laboratory data were summarized for patients with ALS and MS within our ALS registry. Using age adjusted MS prevalence rates, we calculated the expected co-occurrence using the binomial test.

Results: Clinical and demographic features of the five patients (four female, one male) with ALS and MS are described. Because ALS more frequently occurs in men, observing 4/5 female patients with concurrent ALS/MS showed a borderline expectation difference (P=0.073). The observed co-occurrence of ALS and MS was 5X times higher than the expected frequency of 0.98 (P <0.004). Four patients were found negative for *C9orf72*.

Discussion: Our results suggest a non-random association between MS and ALS, although shared genetic etiology was not found.

Keywords: *amyotrophic lateral sclerosis, central nervous system, gene, autoimmune disease, case report*

Introduction

Multiple sclerosis (MS) is a demyelinating central nervous system disease with an overall US reported prevalence of 309/100,000.[1] Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with a prevalence of 5.2/100,000.[2] If the MS/ALS association was random, their observed concurrence should be extremely rare (1.6 per 10 million).[3] However, the growing number of case reports suggests possible shared pathogenesis for these diseases. One-hundred sixty-eight cases of concomitant MS and ALS have been reported in the literature; however, only 25 patients have been described in clinical detail (summarized in Table 1).[3]

Genetic susceptibility for MS has been demonstrated.[4] The *C9orf72* mutation has been reported in patients with concurrent ALS and MS suggesting a possible shared genetic link; however, recent studies have not supported this.[1,4] Increased risk of developing ALS in patients with prior autoimmune disease has also been observed.[5] While immune dysregulation is known to be part of MS pathogenesis, ALS pathogenesis remains poorly characterized, but neuroinflammation and immune dysregulation may be disease mediators.[3] For this reason, various anti-inflammatory and immune-modulating therapies are currently being studied in ALS.

In this study, we describe five patients with concurrent MS and ALS and hypothesize this concurrence rate is greater than what would be expected by chance.

Methods

Data Collection

Two of our physicians at the Swedish Neuroscience Institute (KP and ME) had encountered six ALS patients with co-occurring MS diagnoses. Their medical charts were examined to confirm MS diagnoses using the MacDonald criteria. One patient was excluded due to inconclusive neuroimaging. To confirm our manual search, the Epic™ SlicerDicer program was used to collect aggregate counts of ICD-10 codes for MS within our ALS registry over the same timeframe. This computerized search yielded the same patients as our manual search. Finding identical results with two different strategies gave us confidence that we had not overlooked patients with MS/ALS dual diagnoses, nor had we extracted patients for whom strict MS and ALS criteria would not hold up to scrutiny.

We reviewed charts and characterized the demographic, clinical, and neurogenetic features of our patients with MS and ALS. The Swedish Institutional Review Board determined that this case report series as submitted does not meet the definition of human subjects' research and does not require IRB review as defined in the federal regulations. The fifth case report was not included prior to IRB consideration.

Data Analysis

Our calculations were based on the total number of ALS patients in our ALS clinic registry (N=213) from August 2016-July 2019 and the expected prevalence of MS within a similar age (55-64 years old) and region (Western US) matched cohort bases from data reported in 2019.[1] Averaging the high and low estimates for the 55-64 year old cohort in the Western US yielded an MS prevalence estimate of 461/100,000. That prevalence estimate was

Table 1. Demographic and clinical features of previously described patients with co-occurring MS/ALS diagnoses.

		Multiple Sclerosis			Amyotrophic Lateral Sclerosis	
Gender	**Cases**	**Mean Age of Onset (years)**	**Subtype**	**Mean Time Lapse Between Diagnoses (years)**	**Mean Age of Onset (years)**	**Site of Onset**
F	18	40.4	RRMS (7) PPMS (4) SPMS (4) Unk (3)	7.9	51.0	Bulbar (5) Limb (11) Unk (2)
M	7	34.0	RRMS (2) PPMS (2) SPMS (2) Unk (1)	4.3	51.1	Bulbar (4) Limb (3)

then used to calculate the probability of the observed result (5/213 with both conditions) using the binomial test. GraphPad QuickCalc was used to create these binomial calculations (https://www.graphpad.com/quickcalcs/binomial1/). $P<0.05$ was our significance criterion.

Case Reports

Patient 1 was a 68-year-old woman who developed right leg weakness. She was diagnosed with relapsing remitting MS (RRMS) and treated with glatiramer acetate. MRI brain revealed periventricular demyelination (Figure 1). Cerebrospinal fluid revealed oligoclonal bands. At age 70 she developed left leg weakness. Electromyography (EMG) demonstrated widespread active and chronic denervation. She was diagnosed with ALS and treated with riluzole. *C9orf72* testing was not completed. She died two years after ALS onset.

Patient 2 was a 72-year-old woman with longstanding RRMS, initially presenting with left-sided numbness and 10 months of bulbar weakness; treated with interferon beta-1a. Neuroimaging revealed stable demyelination (Figure 1). EMG demonstrated diffuse active and chronic denervation. She was diagnosed with ALS and treated with riluzole. *C9orf72* testing was negative. She expired within 6 months of diagnosis.

Patient 3 is a 54-year-old woman with longstanding MS, initially presenting with left-sided numbness, 2.5 years of bulbar weakness and treated with natalizumab and ocrelizumab. MRI brain revealed stable demyelinating changes (Figure 1). EMG confirmed ALS. *C9orf72* testing was negative. The patient is currently in hospice.

Patient 4 is a 49 year-old woman with a 9-month history of left leg and arm weakness. MRI demonstrated active demyelinating disease (Figure 1). Cerebrospinal fluid revealed no oligoclonal bands. EMG revealed widespread active and chronic denervation. She was diagnosed with MS and ALS simultaneously and treated with ocrelizumab and

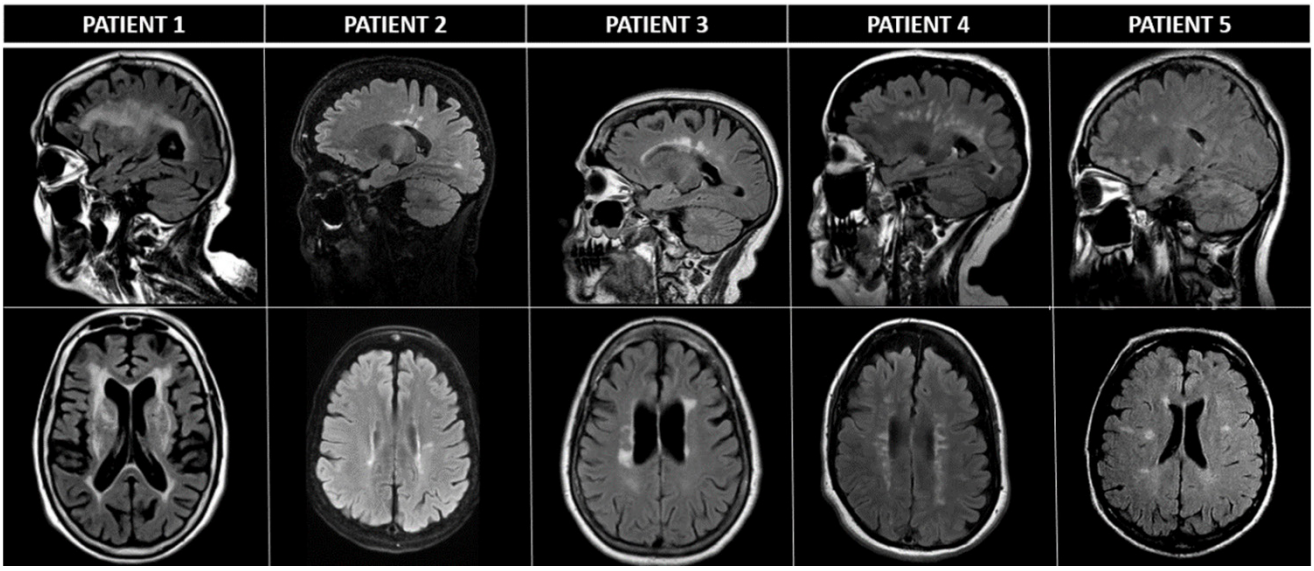

Figure 1. **MRI brain imaging demonstrating demyelinating white matter lesions for Patients 1 through 5.** Sagittal FLAIR sequences are displayed above their corresponding axial FLAIR images.

riluzole. She is currently wheelchair-bound and ventilator-dependent 1.5 years after ALS diagnosis.

Patient 5 is a 64-year-old man with a one-year history of dyspnea, weight loss, and left hand weakness. MRI demonstrated chronic demyelinating changes in the brain and cervical spine (Figure 1). EMG revealed widespread active and chronic denervation. He was diagnosed with ALS. *C9orf72* testing was negative. MS treatment was deferred to focus on supportive ALS care. Six months after ALS diagnosis, he is currently wheelchair-bound and ventilator-dependent.

Results

In our cohort we found that the observed prevalence of concurrent MS and ALS was five times greater than the expected frequency of 0.98 ($P < 0.004$). Given that the ratio of ALS cases in males to females is 1.6:1 (61% male predominance), the female predominance observed in our study at a ratio of 4:1 showed a borderline difference from expectation (P=0.073, binomial test).[2] Our patients' demographic, clinical, and neurogenetic features are summarized in Table 2.

Discussion

The concurrence of MS and ALS has now been reported in detail in 30 patients. The majority of our patients demonstrated sequential disease occurrence, with MS preceding ALS by an average of 6.6 years, similar to previous literature reports.[3] This finding is likely explained by the earlier age of onset and longer life expectancy observed in MS populations relative to ALS. In the now total 30 reported cases, there are none in which ALS onset precedes MS. We describe two patients in which MS and ALS were diagnosed simultaneously; however, neuroimaging revealed chronic demyelinating disease suggesting that subclinical MS predated ALS.

Most of our patients exhibited more aggressive subtypes of MS and ALS. The majority of our cohort developed progressive MS disease (SPMS or PPMS). Sixty percent of our patients developed either bulbar or respiratory-onset ALS, subtypes with worse outcomes.[6] The bulbar predominance in our report is consistent with Guennoc's findings, wherein 50% of patients developed non-limb disease onset.[3] The predominance of non-limb onset ALS in our cohort is striking, as limb-onset disease has been reported to represent up to 74% of cases.[10]

We did not find increased abnormal expansion of the *C9orf72* gene, consistent with previous literature. [4] The female predominance we observed in our study is consistent with the 72% female predominance observed in the 25 MS/ALS co-occurrence cases reported to date, a gender pattern similar to that observed in MS.[9,10] In contrast a recent Centers for Disease Control and Prevention survey of ALS prevalence in the US found 61% to be male.[2]

There are possible explanations for the observation of increased MS/ALS co-occurrence in our cohort. Improved MS therapies have resulted in longer life expectancies, allowing for this population to develop other diseases, including ALS. Additionally, we note that our average age at clinically evident MS/ALS co-occurrence was 61.0 years.

Table 2. **Demographic, clinical, and neurogenetic features of our patients with co-occurring MS/ALS diagnoses.** M = Male. F = Female. Unk = unknown. RRMS = Relapsing Remitting Multiple Sclerosis. SPMS = Secondary Progressive Multiple Sclerosis. PPMS = Primary Progressive Multiple Sclerosis. Neg = Negative. *Patients 3-5 are still living 60, 12, and 18 months later at the time of this report, respectively.

Multiple Sclerosis					Amyotrophic Lateral Sclerosis			
Patient	**Gender**	**Age at Diagnosis (years)**	**Subtype**	**Time Lapse Between Diagnoses (years)**	**Age at Onset**	**Site of Onset**	**Time from ALS symptom onset to death (months)**	**C9orf72 Status**
1	F	68	RRMS	2	70	Limb	24	Unk
2	F	49	RRMS	23	72	Bulbar	16	Neg
3	F	44	SPMS	8	51	Bulbar	≥60*	Neg
4	F	49	PPMS	0	49	Limb	≥12*	Neg
5	M	64	SPMS	0	63	Respiratory	≥18*	Neg
Mean		**54.8**		**6.6**	**61.0**			
SD		**9.4**		**8.7**	**9.5**			

If our patient sampling was truncated at 50 years old, we would have detected only 1/5 MS/ALS co-occurrences.

In summary, our observed prevalence of concurrent MS/ALS was five times higher than expected suggesting that a preceding autoimmune disease may increase ALS risk.[5] Of all autoimmune diseases reported associated with increased ALS risk, MS relative risk was one of the greatest (MS relative risk = 4.25).[5] It may be that the neurologic autoimmune process confers a greater effect compared to other systemic autoimmune diseases. The reasons for our observed MS/ALS concurrence deserves further investigation and may yield helpful clues into ALS pathogenesis.

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References

1. Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, et al. The prevalence of MS in the United States. A population-based estimate using health claims data. Neurology, 2019;92:e1029-e1040.

2. Mehta PM, Kaye W, Raymond J, Punjani R, et al. Prevalence of Amyotrophic Lateral Sclerosis – United States, 2015. Center for Disease Control and Prevention Morbidity and Mortality Weekly Report, 2018;67(46):1285-1289.

3. Guennoc A, Maud P, Le Page E, Le Port D, et al. Co-occurrence of MS and ALS: a clue in favor of common pathophysiological findings? Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2018; 19: 500-505.

4. Goris A, van Setten J, Diekstra F, Ripke S, et al. No evidence for shared genetic basis of common variants in multiple sclerosis and amyotrophic lateral sclerosis. Human Molecular Genetics, 2014; 23 (7):19161922.

5. Turner MR, Goldacre R, Talbot K, Goldacre MJ. Autoimmune disease preceding amyotrophic lateral sclerosis – An epidemiologic study. Neurology, 2013;81:1222-1225.

6. Chio, Adriano, et al. "Prognostic factors in ALS: a critical review." Amyotrophic lateral sclerosis 10.5-6 (2009): 310-323.

7. Orton SM, Ramagopalan SV, Brocklebank D, Herrera BM, Dyment DA, Yee IM, Sadovnick AD, Ebers GC. Effect of immigration on multiple sclerosis sex ratio in Canada: the Canadian Collaborative Study. J Neurol Neurosurg Psychiatry. 2010 Jan;81(1):31-6.

8. Wallin MT, Culpepper WJ, Coffman P, Pulaski S, Maloni H, Mahan CM, Haselkorn JK, Kurtzke JF; Veterans Affairs Multiple Sclerosis Centres of Excellence Epidemiology Group.The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. Brain. 2012 Jun;135(Pt 6):1778-85.

9. Compston A, Coles A. Multiple sclerosis. Lancet. 2002 Apr 6;359(9313):1221-31.

10. Walhout, Renée, et al. "Patterns of symptom development in patients with motor neuron disease." Amyotrophic lateral sclerosis and frontotemporal degeneration 19.1-2 (2018): 21-28.

Duration and temporal dispersion measurements in CIDP subjects from the Polyneuropathy and Treatment with Hizentra (PATH) study

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ABSTRACT

Introduction: Distal compound muscle action potential (dCMAP) duration and temporal dispersion (TD) are electrophysiological hallmarks of demyelination and important for the diagnosis of CIDP. While the impact of CIDP treatment on other nerve conduction parameters has been examined, the effects on dCMAP and TD remain unexplored. The aim of the study was to examine the impact of withdrawal of immunoglobulin treatment on dCMAP duration and TD, and also the influence of the measurement technique on dCMAP duration and TD.

Methods: Nerve conduction studies were analyzed from the PATH (Polyneuropathy and Treatment with Hizentra) study which randomized patients with CIDP to two doses of IgPro 20 and placebo. Distal CMAP duration and TD were obtained by two methods of measurements (D1 and D2, TD1 and TD2) from the median and peroneal nerves.

Results: The dCMAP and TD were obtained from 480 tracings. While the two methods of measurement showed differences in D1 and D2 with D2 longer than D1 in all the three groups, there was no difference between the TD1 and TD2. There was no difference at baseline in dCMAP duration or TD among the three groups. At the end of treatment, patients in the placebo arm had no worsening of dCMAP and TD compared to baseline or the treated groups.

Conclusion: dCMAP duration and TD did not show a difference between treated and placebo groups, and may be less sensitive measures than other nerve conduction parameters when evaluating changes in treatment. The method of dCMAP duration measurement does not affect TD as long as a consistent method is followed.

Keywords: *cmap duration, temporal dispersion, chronic inflammatory demyelinating polyneuropathy*

Introduction

Nerve conduction studies form a corner stone in the diagnosis of CIDP but their role as a biomarker of treatment response has been questionable [1]. Studies have shown conflicting results in this regard but recent evidence shows nerve conduction changes can reflect the response to treatment and clinical outcome and could even be a potential marker of prognosis [2–5]. Patients with CIDP who were newly treated with IVIG had an improvement in conduction block and CMAP amplitudes and the improvement in the latter had a clear correlation with clinical outcomes [6]. In addition, deterioration of distal motor latency, conduction velocity and conduction block (CB) has been demonstrated with withdrawal of treatment leading to worsening of these conduction parameters along large nerve fibres [2]. Among the various electrophysiological features of demyelination, prolonged distal compound muscle action potential (dCMAP) duration and abnormal temporal dispersion (TD) are two hallmark features of non-uniform demyelination and are included in the EFNS/PNS guidelines for evidence of CIDP [1]. However, unlike other nerve conduction parameters in CIDP, changes in these parameters in response to treatment have not been explored. Measurement of dCAMP duration, and from it TD, are not as straightforward as are other NCS measures, and different methods have been used over the years to calculate CMAP duration. The measurement of TD is less ambiguous but dependent on CMAP duration and is the percentage increase between proximal and distal CMAP duration, with more than 30% considered abnormal [1]. The current study examines the impact of withdrawal of immunoglobulin treatment on dCMAP duration and TD, and also the influence of different methods of measurement of dCMAP duration and thus, temporal dispersion.

Methods

The nerve conduction data analyzed in this study are obtained from the PATH study, the protocol of which has been described in detail previously [2,7]. As a brief overview, subjects with CIDP who were IVIG-dependent were randomized to receive 0.2 g/kg (low dose) and 0.4 g/kg (high dose) body weight weekly doses of SCIG (IgPro20 [Hizentra®]; CSL Behring, King of Prussia, PA, USA) or placebo (albumin). 57 subjects were assigned to 0.2 g/kg bodyweight IgPro20, 58 subjects to 0.4 g/kg body weight IgPro20 and 57 subjects were assigned to placebo. The nerve conduction studies (NCS) were performed at the start and end of the subcutaneous treatment interval at the Week 25 visit. A core lab monitored all procedures and approved all tracings for compliance with protocol. This included first

testing healthy volunteers to use as controls and ensuring all waveforms were reviewed by the core lab to validate the data against the controls. Two motor nerves: median in the upper limb and peroneal in the lower limb were measured according to standards of the AANEM/CSCN. The stimulation sites were at the elbow and wrist for the median nerve and lateral popliteal fossa, below the fibular head and ankle for the peroneal nerves. All studies were done with surface stimulating and recording electrodes, under careful temperature controls so that the upper limb temperature was maintained at ≥ 32°C and the lower limb at ≥ 31°C. We randomly selected the tracings of 20 subjects from each group for the current study. The parameters assessed in the current study included distal CMAP (dCMAP) duration and temporal dispersion (TD) which we measured as per the AANEM guidelines as well as the European Federation of Neurological Societies/Peripheral Nerve Societies (EFNS/PNS) 2010 electrodiagnostic criteria for CIDP. Accordingly, we measured dCMAP duration (D1) by measuring the duration from the onset of first negative peak to first baseline crossing and used these measurements to obtain TD1 [8]. We also calculated dCMAP and TD as per the definitions of EFNS/PNS 2010 electrodiagnostic criteria for CIDP whereby we measured dCMAP duration (D2) from onset of first negative peak to return to baseline of last negative peak and from it, TD (TD2). TD was measured as percentage duration increase of the proximal from the distal negative peak of CMAP, with more than or equal to 30% being abnormal (Figure 1) [1]. Each tracing from median and peroneal nerves from the wrist and elbow, ankle and fibular head, respectively, was analyzed from the tracings obtained at the beginning and at the end of treatment and dCMAP duration (D1 and D2) and TD (TD1 and TD) were calculated. We excluded those tracings if the CMAP amplitude was less than 20% of normal or inelicitable (12 in high dose, 36 in low dose and 8 in placebo). Subsequent analysis was done independently for both measurements by comparing the dCMAP duration (D1 and D2) and TD (TD1 and TD2) for peroneal and median nerves at the start and at the end of the treatment for the three treatment groups.

Analysis was done using SPSS version 20, IBM® Armonk, New York. The dCMAP duration and TD for the three groups are expressed as means with standard deviation. Box whisker plots are used to represent the TD (TD1 and TD2) and dCMAP duration (D1 and D2) at baseline and last visit for high dose, low dose and placebo groups. The tests of normality confirmed the non-normal distribution of data and non-parametric tests were used to compare the TD and dCMAP durations at baseline and final visit (Wilcoxon signed rank test) and also to compare between the two measurements methods, for the three treatment groups (D1 vs D2; TD1 vs TD2; Mann Whitney U test), and between treatments at baseline (Kruskal-Wallis test).

Results of these exploratory analyses were not adjusted for multiplicity and were considered statistically significant if $p < 0.05$.

Results

A total of 480 tracings from median and peroneal nerves were reviewed from the high dose SCIG, low dose SCIG and placebo groups and 424 tracings were included for analysis. The mean dCMAP duration in milliseconds and the mean TD in percentage prolongation by both methods at baseline and at end of treatment are shown in table 1, figures 1 and 2. At baseline, there was no difference in the dCMAP duration or temporal dispersion among the three groups with either measurement method (Table 2). A significant difference was found between baseline dCMAP durations calculated by the two measurement methods (D1 vs D2) with mean dCMAP duration longer for D2 than D1. However, there was no difference in the TD at baseline with either method (Table 3). The results were the same for comparisons at the end of the treatment intervals as well (Table 4).

Lastly, comparison was made between the corresponding parameters at baseline and end of treatment to determine if withdrawal of treatment produced any change. There was no significant difference in any of the parameters, using either method of measurement, for dCMAP or TD at baseline or at end of the treatment (Table 5). A separate analysis combining the two treatment arms as compared with the placebo group also did not reveal any significant difference (Table 6). We performed the analysis separately for median and peroneal nerve parameters for

Table 1: Baseline and final dCMAP duration (D1 and D2) and TD (TD1 and TD2) for high dose, low dose and placebo groups

Measurement	N	Mean ± standard deviation
High dose baseline D1†	35	6.4 ± 1.5
High dose final D1	35	6.4 ± 2.2
High dose baseline D2	35	10.4 ± 3.8
High dose final D2	35	11.4 ± 4.1
High dose baseline TD1‡	33	18.9 ± 21.3
High dose final TD1	33	19.5 ± 21.8
High dose baseline TD2	34	22.2 ± 32.6
High dose final TD2	34	18.7 ± 25.4
Low dose baseline D1†	32	6.9 ± 2.5
Low dose final D1	32	6.5 ± 3.1
Low dose baseline D2	31	11.8 ± 5.1
Low dose final D2	31	11.7 ± 5.6
Low dose baseline TD1‡	24	19.0 ± 21.9
Low dose final TD1	24	18.1 ± 24.5
Low dose baseline TD2	24	29.1 ± 54.9
Low dose final TD2	24	22.6 ± 46.2
Placebo baseline D1†	36	6.7 ± 2.1
Placebo final D1	36	6.8 ± 2.2
Placebo baseline D2	36	12.6 ± 4.7
Placebo final D2	36	13.7 ± 9.7
Placebo baseline TD1‡	35	14.7 ± 15.4
Placebo final TD1	35	17.9 ± 19.2
Placebo baseline TD2	34	17.4 ± 19.8
Placebo final TD2	34	22.2 ± 32.8

† in milliseconds, ‡ percentage prolongation

Table 2: Comparison of the baseline variables

Measurement (n)	Mean ± standard deviation	P*
High dose baseline D1† (35)	6.4 ± 1.5	0.687
Low dose baseline D1 (32)	6.9 ± 2.6	
Placebo baseline D1 (36)	6.8 ± 2.2	
High dose baseline TD1‡ (33)	19.6 ± 21.9	0.763
Low dose baseline TD1 (24)	19.0 ± 21.9	
Placebo baseline TD1 (35)	14.8 ± 15.5	
High dose baseline D2† (35)	10.4 ± 3.8	0.684
Low dose baseline D2 (31)	11.9 ± 5.1	
Placebo baseline D2 (36)	12.7 ± 4.7	
High dose baseline TD 2‡ (34)	22.4 ± 32.7	0.833
Low dose baseline TD2 (24)	29.2 ± 54.9	
Placebo baseline TD2 (34)	17.5 ± 19.8	

*Kruskal Wallis test, † in milliseconds, ‡ percentage prolongation

Table 3: Comparison of the dCMAP duration and TD calculated at baseline

Measurement by two methods	Mean ± standard deviation	P*
High dose baseline D1† (35)	6.4 ± 1.5	<0.0001
High dose baseline D2 (35)	10.4 ± 3.8	
High dose baseline TD1‡ (33)	18.9 ± 21.3	0.712
High dose baseline TD2 (34)	22.4 ± 32.7	
Low dose baseline D1† (32)	6.9 ± 2.6	<0.0001
Low dose baseline D2 (31)	11.9 ± 5.1	
Low dose baseline TD1‡ (24)	19.0 ± 21.9	0.895
Low dose baseline TD2 (24)	22.7 ± 46.3	
Placebo baseline D1† (36)	6.7 ± 2.1	<0.0001
Placebo baseline D2 (36)	12.7 ± 4.7	
Placebo baseline TD1‡ (35)	14.8 ± 15.5	0.772
Placebo baseline TD2 (34)	17.5 ± 19.8	

*Mann Whitney U test, † in milliseconds, ‡ percentage prolongation

Table 4: Comparison of the variables at end of treatment

Measurement (n)	Mean ± standard deviation	P*
High dose final D1† (35)	6.4 ± 2.1	0.773
Low dose final D1 (32)	6.6 ± 3.1	
Placebo final D1 (36)	6.7 ± 2.1	
High dose final TD1‡ (33)	18.9 ± 21.3	0.893
Low dose final TD1 (24)	18.2 ± 24.6	
Placebo final TD1 (35)	17.9 ± 19.2	
High dose final D2† (35)	11.4 ± 4.1	0.664
Low dose final D2 (31)	11.7 ± 5.6	
Placebo final D2 (36)	13.7 ± 9.8	
High dose final TD2‡ (34)	18.7 ± 25.5	0.876
Low dose final TD2 (24)	22.7 ± 46.3	
Placebo final TD2 (34)	22.2 ± 32.9	

*Kruskal Wallis test

Table 5: Comparison between the baseline and final dCMAP duration and TD before and after the high dose, low dose and placebo groups

Comparison of means	Mean difference‡ ± standard deviation	95% confidence interval of difference		P*
		Lower limit	Upper limit	
High dose baseline D1 vs High dose final D1	0.02 ± 1.6	-.55	.58	0.586
High dose baseline D2 vs High dose final D2	-0.96 ± 3.3	-2.1	.17	0.051
High dose baseline TD1 vs High dose final TD1	-0.6 ± 22.6	-8.6	7.4	0.787
High dose baseline TD2 vs High dose final TD2	3.4 ± 30.1	-7.1	13.9	0.318
Low dose baseline D1 vs Low dose final D1	0.35 ± 2.8	-.65	1.34	0.713
Low dose baseline D2 vs Low dose final D2	0.17 ± 5.5	-1.8	2.2	0.263
Low dose baseline TD1 vs Low dose final TD1	0.85 ± 12.9	-4.6	6.3	0.823
Low dose baseline TD2 vs Low dose final TD2	6.5 ± 60.8	-19.2	32.2	0.263
Placebo baseline D1 vs Placebo final D1	-0.12 ± 0.81	-0.39	0.16	0.451
Placebo baseline D2 vs Placebo final D2	-1.1 ± 10.8	-4.8	2.5	0.819
Placebo baseline TD1 vs Placebo final TD1	-3.2 ± 18.9	-9.7	3.3	0.330
Placebo baseline TD2 vs Placebo final TD2	-4.7 ± 33.9	-16.5	7.1	0.971

*Wilcoxon singed rank test

Table 6: Comparison of variables between the treatment (low dose and high dose SCIG combined) with placebo arm

Measurement (n)	Mean ± standard deviation	P*
Treated baseline D1 (67)	6.6 ± 2.1	0.885
Placebo baseline D1 (36)	6.7 ± 2.1	
Treated baseline D2 (66)	11.1 ± 4.5	0.175
Placebo baseline D2 (36)	12.6 ± 4.8	
Treated baseline TD1 (52)	19.8 ± 22.2	0.463
Placebo baseline TD1 (35)	14.7 ± 15.4	
Treated baseline TD2 (58)	24.5 ± 41.1	0.836
Placebo baseline TD2 (34)	18.2 ± 9.9	
Treated final D1 (67)	6.5 ± 2.6	0.562
Placebo final D1 (36)	6.7 ± 2.3	
Treated final D2 (66)	11.6 ± 4.8	0.462
Placebo final D2 (36)	13.6 ± 9.7	
Treated final TD1 (57)	19.5 ± 22.7	0.753
Placebo final TD1 (35)	19.7 ± 19.6	
Treated final TD2 (58)	22.5 ± 37.5	0.681
Placebo final TD2 (34)	22.3 ± 32.4	

*Mann Whitney U test

the three groups, with the same results.

Discussion

The current study did not find any difference in dCMAP duration or TD, between the baseline and at the end of the treatment, in patients with CIDP withdrawn from immunoglobulin treatment. There was no worsening in these parameters in patients treated with placebo compared to those remaining on treatment with subcutaneous immunoglobulin. We employed two methods of measurement for dCMAP duration and TD, and while these methods demonstrated a significant difference in dCMAP durations, there was no difference in the calculated TDs with either method. dCMAP duration and TD did not change on withdrawal of immunoglobulin treatment despite the method in which these parameters were measured. The measurements showed high variability, and since only small changes are expected in this short duration study, it may be that the measures lack sufficient precision to show change.

Prolonged distal CMAP duration and temporal dispersion are markers of demyelination and are used in the electrophysiological diagnosis of CIDP [1]. Although conventionally most authorities prefer measuring CMAP duration from the initial negative deflection to first return to baseline, in CIDP it is recommended that the CMAP duration be measured from the onset of the first negative deflection to return to baseline of the last negative deflection to baseline [1,9–12]. Some authorities have also

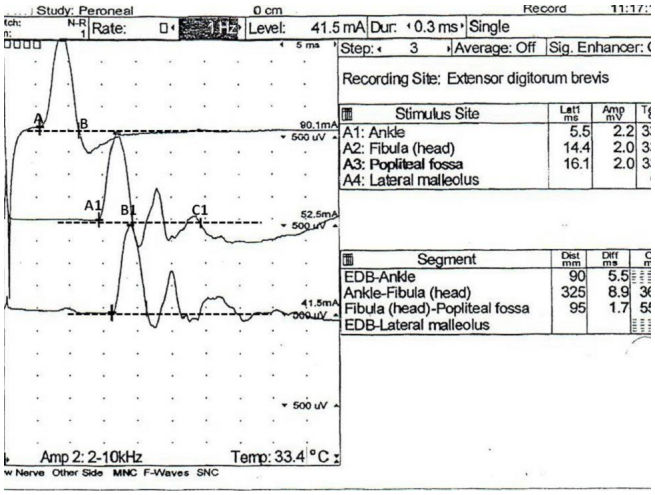

Figure 1: Caption: Representative nerve conduction study from peroneal nerve showing the measurement of duration 1 (D1) and duration 2 (D2) and corresponding temporal dispersions (TD1 and TD2)

Legend: In A1 tracing the distal CMAP (dCMAP) duration D1 was measured as interval between A and B in milliseconds. Here, since point B is the return to baseline of the only negative peak, D1 will be equal to D2. In tracing A2, proximal D1 will be equal to interval between A1 and B1 and proximal D2 will be equal to interval between A1 and C1, the latter being the return to baseline of the last negative peak. Temporal dispersion is then calculated as the percentage prolongation of proximal D1 to distal D1 and proximal D2 to distal D2, which respectively gives TD1 and TD2.

compared the negative peak duration with total duration of CMAP and found slight advantages favoring each method, but measuring the negative peak duration is less technically demanding [13,14]. Practically, the return to baseline of the last negative peak, especially in a multiphasic CMAP (Figure 1, tracing A3), is not easy to identify and even minor differences in cursor placement alter the results of the duration value and therefore the TD2, as this relies on comparison of the distal to proximal CMAP duration. It has been speculated that measurement of CMAP duration by either method is acceptable with the use of additional qualifiers such as multiple turns or a multiphasic CMAP to provide further clarity [15]. Our findings demonstrate that while there are obvious differences in the dCMAP duration measurements obtained with the two methods, the calculated TD does not vary as long as the method is consistent for measuring distal and proximal CMAP durations.

The positive impact of immunoglobulins in treatment of CIDP is well recognized. However, the mechanism by which immunoglobulins bring about rapid improvement is unclear and is unlikely to be due to remyelination or axonal regeneration. Nerve excitability studies showed rapid changes post-IVIG preceding clinical and routine nerve conduction changes in CIDP and might be due to restoration of persistent inward sodium currents and membrane properties [16–18]. Several nerve conduction parameters of demyelination, including distal motor latency, conduction velocity, CMAP amplitude and conduction block (CB), showed changes with immunoglobulins or withdrawal of this therapy [2,3,19,5]. Definite correlations with clinical improvement have been shown in some studies and not others, although the largest study to date did show such correlations [2,3,5,20–22]. Additional evidence of the treatment responsiveness of NCS is given by the fact that patients who were initially responsive to IVIG had worsening in distal motor latency and conduction velocity when switched to placebo, but at the same time, patients who continued to receive immunoglobulins remained stable [2]. Despite being important markers of demyelination, dCMAP duration and TD have not received wide attention in the setting of CIDP, perhaps due to a lack of a physiological correlates, unlike CMAP amplitudes and CB. But these parameters do have electrophysiological importance, and abnormal TD precludes a diagnosis of CB [11]. Besides, TD has been found to improve significantly in multifocal motor neuropathy with conduction block with treatment and is perhaps a more sensitive marker of improvement than other NCS parameters in this disorder [23]. Thus intuitively, both CMAP duration and its derivative TD would be expected to change with treatment in CIDP. However, our study did not show any difference at the end of 24 weeks for the placebo arm when treatment was withdrawn. This may be because the duration of treatment withdrawal was too short at 6 months, although other NCS parameters such as conduction velocity did change [2]. Another reason might be that these various measures that are thought to show 'demyelination' have different underlying pathophysiological mechanisms. CMAP duration and temporal dispersion are thought to be classical features of acquired demyelination manifesting due to diffuse differential slowing of conduction along nerve fibers and the resulting asynchrony of the CMAP. On the other hand, CB is focal and experimental studies show that CB can start within an hour of an inciting event, well before any structural changes of demyelination set in [24]. This may be due to paranodal disruption of ion channels which is more amenable to rapid reversal with immunoglobulins, while in contrast, features such as temporal dispersion and prolonged duration may be due to structural demyelination and thus take longer to recover or manifest [18]. In addition, the associated secondary axonal changes also would invariably color the nerve conduction findings and is recognized as one of the reasons for poor response to IVIG. In a case of CIDP, the actual electrophysiological picture would thus be the net effect of all these differing pathophysiological mechanisms, each of which may respond differently to treatment or withdrawal of treatment. The duration of the disease and follow-up may also have an impact on the nerve conduction findings which can evolve more rapidly in the short term, when disease duration is shorter, and more slowly with longer disease duration. The precision of the different electrophysiological measures will also influence the observed changes.

Our study has a few limitations. Having focused purely on the electrophysiological parameters, this study lacks information on the clinical characteristics and treatment responsiveness. Data on the full cohort in each treatment arm was not obtained so that the results may have differed with a larger sample size. Even though the study analyzed a large number of nerve tracings in patients with CIDP, the actual number of nerve conduction studies with abnormal dCMAP duration and TD was relatively low which also would impact the generalizability, although all patients in this study fulfilled EFNS/PNS criteria for CIDP. This suggests a low sensitivity of duration and TD in CIDP.

Conclusion

The current study found that dCMAP duration and TD did not differ between the treated and placebo arms in patients with CIDP. These results suggest that duration and TD are less sensitive to withdrawal of treatment than other NCS parameters such as motor latencies and conduction

velocities that changed as immunoglobulin therapy was removed. While the exact method of measuring dCMAP duration has been a topic of debate, the method does not have a bearing on TD as long as consistency in method is followed and this is relevant for routine practice. Further studies are needed to look at the correlation between dCMAP and TD with other electrophysiological parameters and patient outcomes.

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References

[1] Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - First Revision. Journal of the Peripheral Nervous System 2010;15:1–9. https://doi.org/10.1111/j.1529-8027.2010.00245.x.

[2] Bril V, Hartung H-P, Lawo J-P, Durn BL, Mielke O. Electrophysiological testing in chronic inflammatory demyelinating polyneuropathy patients treated with subcutaneous immunoglobulin: The Polyneuropathy And Treatment with Hizentra (PATH) study. Clinical Neurophysiology 2020. https://doi.org/10.1016/j.clinph.2020.09.001.

[3] Bril V, Katzberg H, Donofrio P, Banach M, Dalakas MC, Deng C, et al. Electrophysiology in chronic inflammatory demyelinating polyneuropathy with IGIV. Muscle Nerve 2009;39:448–55. https://doi.org/10.1002/mus.21236.

[4] Chin RL, Deng C, Bril V, Hartung H-P, Merkies ISJ, Donofrio PD, et al. Follow-up nerve conduction studies in CIDP after treatment with IGIV-C: Comparison of patients with and without subsequent relapse. Muscle Nerve 2015;52:498–502. https://doi.org/10.1002/mus.24624.

[5] Ellrichmann G, Gold R, Ayzenberg I, Yoon M-S, Schneider-Gold C. Two years' long-term follow up in chronic inflammatory demyelinating polyradiculoneuropathy: efficacy of intravenous immunoglobulin treatment. Ther Adv Neurol Disord 2017;10:91–101. https://doi.org/10.1177/1756285616679369.

[6] Bril V, Banach M, Dalakas MC, Deng C, Donofrio P, Hanna K, et al. Electrophysiologic correlations with clinical outcomes in CIDP. Muscle & Nerve 2010;42:492–7. https://doi.org/10.1002/mus.21733.

[7] van Schaik IN, Bril V, van Geloven N, Hartung H-P, Lewis RA, Sobue G, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Neurology 2018;17:35–46. https://doi.org/10.1016/S1474-4422(17)30378-2.

[8] guidelineConsensusCriteria.pdf n.d.

[9] Preston DC, Shapiro BE. 3 - Basic Nerve Conduction Studies. In: Preston DC, Shapiro BE, editors. Electromyography and Neuromuscular Disorders (Third Edition), London: W.B. Saunders; 2013, p. 19–35. https://doi.org/10.1016/B978-1-4557-2672-1.00003-9.

[10] Thaisetthawatkul P, Logigian EL, Herrmann DN. Dispersion of the distal compound muscle action potential as a diagnostic criterion for chronic inflammatory demyelinating polyneuropathy. Neurology 2002;59:1526–32. https://doi.org/10.1212/01.WNL.0000034172.47882.20.

[11] guidelineConsensusCriteria.pdf n.d.

[12] Ferrante MA, Bs TS, Tsao BE. Principles of Nerve Conduction Studies and Needle EMG n.d.:35.

[13] Oh SJ, Kim DE, Kuruoglu HR. What is the best diagnostic index of conduction block and temporal dispersion? Muscle & Nerve 1994;17:489–93. https://doi.org/10.1002/mus.880170504.

[14] Lagarde J, Viala K, Fournier E. Is total duration of distal compound muscle action potential better than negative peak duration in the diagnosis of chronic inflammatory demyelinating polyneuropathy? Muscle Nerve 2014;49:895–9. https://doi.org/10.1002/mus.24080.

[15] Sander HW, Oh SJ. Temporal Dispersion Terminology: Multiphasic and Multiturn CMAPs. Journal of Clinical Neuromuscular Disease 2006;7:173–4. https://doi.org/10.1097/01.cnd.0000203642.77005.27.

[16] Boërio D, Créange A, Hogrel J-Y, Guéguen A, Bertrand D, Lefaucheur J-P. Nerve excitability changes after intravenous immunoglobulin infusions in multifocal motor neuropathy and chronic inflammatory demyelinating neuropathy. J Neurol Sci 2010;292:63–71. https://doi.org/10.1016/j.jns.2010.02.002.

[17] Lin CS-Y, Krishnan AV, Park SB, Kiernan MC. Modulatory effects on axonal function after intravenous immunoglobulin therapy in chronic inflammatory demyelinating polyneuropathy. Arch Neurol 2011;68:862–9. https://doi.org/10.1001/archneurol.2011.137.

[18] Berger M, McCallus DE, Lin CS-Y. Rapid and reversible responses to IVIG in autoimmune neuromuscular

diseases suggest mechanisms of action involving competition with functionally important autoantibodies. Journal of the Peripheral Nervous System 2013;18:275–96. https://doi.org/10.1111/jns5.12048.

[19] Iijima M, Yamamoto M, Hirayama M, Tanaka F, Katsuno M, Mori K, et al. Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP. Neurology 2005;64:1471–5. https://doi.org/10.1212/01.WNL.0000158680.89323.F8.

[20] Khoo A, Frasca J, Schultz D. Measuring disease activity and predicting response to intravenous immunoglobulin in chronic inflammatory demyelinating polyneuropathy. Biomark Res 2019;7. https://doi.org/10.1186/s40364-019-0154-2.

[21] Harbo T, Andersen H, Jakobsen J. Acute motor response following a single IVIG treatment course in chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2009;39:439–47. https://doi.org/10.1002/mus.21305.

[22] Khomand P, Katzberg H, Ngo M, Bril V. Electrophysiological Responsiveness to Long-Term Therapy in Chronic Inflammatory Demyelinating Polyneuropathy: Case Report. CRN 2020;12:40–4. https://doi.org/10.1159/000505234.

[23] Ghosh A, Virgincar A, Kennett R, Busby M, Donaghy M. The effect of treatment upon temporal dispersion in IvIg responsive multifocal motor neuropathy. J Neurol Neurosurg Psychiatry 2005;76:1269–72. https://doi.org/10.1136/jnnp.2004.050252.

[24] Lafontaine S, Rasminsky M, Saida T, Sumner AJ. Conduction block in rat myelinated fibres following acute exposure to antigalactocerebroside serum. J Physiol 1982;323:287–306.

Rapid Rate Intravenous Immunoglobulin Administration: Safety Outcomes in 11,334 Infusions

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ABSTRACT

A national home infusion services provider (KabaFusion, LLC) has traditionally administered intravenous immunoglobulin (IVIG) at conservative maximum infusion rates to minimize adverse drug reactions (ADRs). The objective of this retrospective, observational study was to identify the impact of increased on-label infusion rates of a specific, high-purity product (Octagam) on patient safety. The study included all patients who received IVIG over a 10-year period. The study population was composed of both adult and pediatric patients with neuroimmune, neuromuscular disorders and primary immune deficiency diseases warranting IVIG treatment. Patients were divided into two randomized groups to provide an even distribution for analysis: those who received IVIG infusions at a rate of <110 mL/hr (Group 1) and those who received IVIG at ≥110 mL/hr (Group 2). There were 489 patients identified for inclusion in Group 1 (n=245) and Group 2 (n=244). Demographics (gender and age) and exposure (number of infusions) were similar between both groups.

The study data included 11,334 total IVIG infusions with a total of 282 ADRs (2.5%). The total number of ADRs (1.3% vs. 3.7% in Group 1, $p<0.0001$) and the number of patients with ADRs (10.7% vs. 31.0% in Group 1, $p<0.0001$) in the high infusion rate group (Group 2) were significantly lower. Based on these results, high infusion rates of specific high-purity IVIG products were associated with a significantly lower amount (both statistically and clinically) of non-serious and serious ADRs in both the adult and pediatric populations. These results can be of great utility in clinical application, if applied within the manufacturer's recommended guidelines, to ease the burden of time required for patients undergoing IVIG infusions.

Keywords: *patient safety, all neuromuscular disease, harm/risk analysis, IVIG, Octagam*

Introduction

High-dose IVIG therapy is accepted as an effective and well-tolerated treatment of neuroimmune and neuromuscular disorders as well as primary immune deficiency diseases (PIDD). It has been estimated that neurologic indications account for up to 43% of IVIG used in clinical practice.[1] Clinical trials have shown that IVIG can be infused at high rates without compromising safety, which is especially beneficial in patients with neuroimmunologic disorders who often receive high-dose IVIG in clinical practice.[2,3] Currently, high-dose IVIG therapy for neuroimmune disorders is defined as >1.0 g/kg per month, compared with low-dose IVIG therapy used for patients with PIDD (0.1-0.4 g/kg per month).[4,5] Though the use of IVIG can yield positive clinical outcomes, its administration can lead to different types of ADRs, most of which are mild, transient, and non-serious.[4-7] Prior studies have evaluated the administration of high-dose IVIG within different patient groups with neuroimmune and immunological diseases.[4-7] However, safety remains a concern with the use of IVIG administered at rapid rates.

KabaFusion, a national, patient-centered home infusion pharmacy within the United States (U.S.), has traditionally administered IVIG at conservative maximum rates to minimize ADRs. However, the total time and cost required to infuse IVIG therapy at lower rates may be burdensome for patients and healthcare providers, particularly for patients with neuroimmune disorders receiving high-dose IVIG regularly. If infusion rates can be safely increased, this could represent both a time- and cost-saving measure that would benefit patients and providers.[4,7] An internal audit prior to this study revealed the mean infusion rate for patients receiving IVIG at KabaFusion was 124 mL/hr. However, following the assessment of recommended standard rates for a high-purity IVIG product (Octagam), with infusion rates up to 504 mL/hr in a 70-kg patient,[8,9] as well as an assessment of industry standards, KabaFusion determined that an evaluation of infusion rates, and corresponding safety outcomes, could potentially add value to the current literature and provide clinical information for healthcare providers. The objective of this study was to identify the impact on patient safety of increasing on-label infusion rates[8,9] of a specific, high-purity IVIG product (Octagam).

Methods

Study Design and Patient Selection

A retrospective, observational study was conducted using adult and pediatric patient medical data collected

from KabaFusion from March 1, 2008 to May 31, 2018. Patients were included if they received IVIG infusions of Octagam 5% or Octagam 10%, at differing rates, abiding by the manufacturer's recommendations for maximum infusion rates of 294 mL/hr and 504 mL/hr (in a 70-kg patient), respectively.[8,9] Patients were excluded if they did not receive one full IVIG infusion of Octagam. Patients who met the criteria for inclusion were further divided into two groups with different IVIG infusion rates: Group 1 (<110 mL/hr) and Group 2 (≥110 mL/hr). Baseline characteristics (age, gender, diagnoses, and comorbidities) were collected, and retrospective patient data were evaluated.

Safety Outcomes

ADRs were collected from the KabaFusion electronic medical record (EMR) for all eligible patients and were further categorized into non-serious and serious categories. Serious adverse drug reactions (SADRs) were defined as any event in which a patient required urgent care, an emergency room (ER) visit, or hospital admission. The primary endpoint of the study was the comparison of ADRs in patients receiving IVIG at lower maximum infusion rates (Group 1: <110 mL/hr) with ADRs in those receiving IVIG at higher maximum infusion rates (Group 2: ≥110 mL/hr). The ADRs were those experienced by patients and subsequently evaluated and documented by registered nurses (RNs) and/or medical providers (MDs). Each ADR type experienced by a patient was considered one event. The data were then evaluated to determine the safety of increasing infusion rates with a specific high-purity IVIG product.

Statistical Analysis

Unadjusted descriptive statistics, including mean, standard deviation (SD) for continuous variables, and percentages for categorical variables were conducted to summarize the baseline characteristics between the two study groups. Statistical differences between the two study groups were tested using Student's t-test for continuous variables and using chi-square and Fisher's exact tests for categorical variables. Analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). An unpaired, two-sided *P* value <0.05 was considered statistically significant.

Data Availability

Anonymized data not published within this article will be made available to any qualified investigator following a request to the corresponding author.

Results

Study Population

There were 489 patients identified for inclusion: Group 1 with infusion rates of <110 mL/hr (n=245) and Group 2 with infusion rates of ≥110 mL/hr (n=244). Patients were matched in terms of prior history of allergies, then similarly distributed within both groups in terms of gender (male [45%], female [55%]), age [mean=59 years], and number of infusions (Table 1). Per baseline diagnoses, chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) was found to be >30% in both groups. Evaluating the baseline comorbidities, Group 2 had higher rates of concomitant comorbidities than Group 1, such as obesity (body mass index [BMI] >35 kg/m^2) (14.3% vs. 11.0%, p=0.0182), hypertension (11.9% vs. 7.3%, p=0.0329), history of arrythmia (6.1% vs. 2.9%, p<0.001), and coronary artery disease (2.0% vs. 0.8%, p=0.0127), respectively (Table 1).

Safety Outcomes

Patients eligible for inclusion received 11,334 total IVIG infusions (Group 1: 5,736; Group 2: 5,598). The

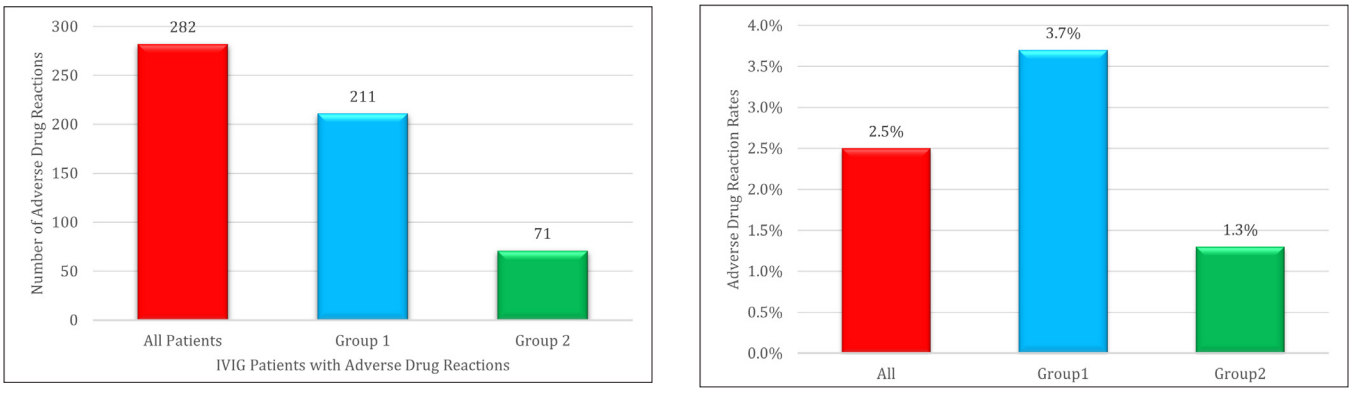

Figure 1. Adverse drug reactions: Number and rates per infusion (%). **P value <0.05 is considered statistically significant*

Table 1. Baseline patient characteristics

Characteristic	All Patients	Group 1 (<110 mL/hr)	Group 2 (≥110 mL/hr)	*P Value*
	n=489	**n=245**	**n=244**	
Male, n (%)	221 (45%)	111 (45%)	110 (45%)	0.8281
Female, n (%)	268 (55%)	134 (55%)	134 (55%)	
Age, Years, Mean (Range)	59 (10-95)	61 (10-91)	58 (14-95)	0.7102
Number of Infusions	11,334	5,736	5,598	
Infusion Rate - mL/hr, Mean (Range)	127 (20-480)	92 (20-108)	163 (110-480)	
Diagnosis, n (%)				
CIDP	165 (33.7%)	88 (35.9%)	77 (31.6%)	0.0526
Myasthenia Gravis	88 (18.0%)	36 (14.7%)	52 (21.3%)	<**0.0001**
PIDD	40 (8.1%)	19 (7.8%)	21 (8.6%)	0.8129
Pemphigus/Pemphigoid	26 (5.3%)	12 (4.9%)	14 (5.7%)	0.4291
GBS	24 (4.9%)	13 (5.3%)	11 (4.5%)	0.8201
Dermatopolymyositis/Polymyositis	24 (4.9%)	15 (6.1%)	9 (3.7%)	**0.0281**
Other Polyneuropathy/Neuropathies	21 (4.3%)	16 (6.5%)	5 (2.0%)	<**0.001**
Multiple Sclerosis	14 (2.9%)	5 (2.0%)	9 (3.7%)	0.7235
Stiff-Person Syndrome	10 (2.0%)	5 (2.0%)	5 (2.0%)	0.8216
Other	77 (15.7%)	36 (14.7%)	41 (16.8%)	0.2011
Comorbidities, n (%)				
Diabetes Mellitus	71 (14.5%)	35 (14.3%)	36 (14.8%)	0.7211
Obesity (BMI >35 kg/m^2)	62 (12.7%)	27 (11.0%)	35 (14.3%)	**0.0182**
Hypertension	47 (9.6%)	18 (7.3%)	29 (11.9%)	**0.0329**
Coagulation Disorder	40 (8.2%)	18 (7.3%)	22 (9.0%)	0.5298
Migraine	36 (7.4%)	19 (7.8%)	17 (7.0%)	0.8821
Arrythmia	22 (4.5%)	7 (2.9%)	15 (6.1%)	<**0.001**
Renal Disease	19 (3.9%)	8 (3.3%)	11 (4.5%)	0.6121
COPD	17 (3.5%)	12 (4.9%)	5 (2.0%)	0.0619
Immobility	9 (1.8%)	2 (0.8%)	7 (2.9%)	**0.0139**
CHF	7 (1.4%)	3 (1.2%)	4 (1.6%)	0.8214
CAD	7 (1.4%)	2 (0.8%)	5 (2.0%)	**0.0127**
CVA	3 (0.6%)	2 (0.8%)	1 (0.4%)	0.5201

CIPD=chronic inflammatory demyelinating polyradiculoneuropathy; PIDD=primary immune deficiency disorder; GBS=Guillain-Barré syndrome; Dx=diagnosis; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CHF=congestive heart failure; CAD=coronary artery disease; CVA= cerebrovascular accident. A *P* value of <0.05 was found to be statistically significant.

mean infusion rate was 92 mL/hr (range: 20-108 mL/hr) for Group 1 and 163 mL/hr (range: 110-480 mL/hr) for Group 2 (Table 1). The total number of ADRs for all 11,334 infusions was 282 (2.5%) (Figure 1A). The total number of ADRs (71 vs. 211 in Group 1, p<0.0001) and the number of patients with ADRs (10.7% vs. 31.0% in Group 1, p<0.0001) were lower in the high infusion rate group, Group 2 (Figure 1B & Figure 2). The most common, non-serious ADRs included nausea, vomiting, increased blood pressure, blisters, pruritus, and tachycardia. Of the non-serious ADRs, nausea, rash, increased blood pressure, and fatigue were shown to be significantly less in the high infusion rate group, Group 2 (Table 2, p<0.05). The most common SADRs were headache, nausea/vomiting, chills, gastrointestinal (GI) events, flu-like symptoms, and shortness of breath. Of the SADRs, headache, fever/chills, and urticaria were shown to be significantly less in the high infusion rate group, Group 2 (Table 2, p<0.05). There were no deaths reported due to SADRs.

Table 2. Adverse drug reactions

Characteristic	All Patients	Group 1 (<110 mL/hr)	Group 2 (≥110 mL/hr)	*P Value*
	n=489	n=245	n=244	
Total Number of Infusions with ADR, n (%)	276 (2.4%)	205 (3.6%)	71 (1.3%)	<**0.0001**
Total ADR Number	282	211	71	<**0.0001**
ADR Rate	2.5%	3.7%	1.3%	<**0.0001**
Number of Patients with ADR	102 (20.9%)	76 (31.0%)	26 (10.7%)	<**0.0001**
Headaches	57 (11.7%)	40 (16.3%)	17 (7%)	**0.0013**
Nausea	27 (5.5%)	20 (8.2%)	7 (2.9%)	**0.0104**
Rash	34 (7%)	26 (10.6%)	8 (3.3%)	**0.0014**
Increased Blood Pressure	17 (3.5%)	14 (5.7%)	3 (1.2%)	**0.0113**
Vomiting	7 (1.4%)	5 (2%)	2 (0.8%)	0.4497
GI ADR/Diarrhea	3 (0.6%)	3 (1.2%)	0 (0%)	0.2485
Pain (any, body, muscle, generalized)	16 (3.3%)	12 (4.9%)	4 (1.6%)	0.0721
SOB/Wheezing	3 (0.6%)	2 (0.8%)	1 (0.4%)	1
Urinary Tract Infection	0 (0%)	0 (0%)	0 (0%)	-
Pruritis	7 (1.4%)	4 (1.6%)	3 (1.2%)	1
Flu-like Symptoms	5 (1%)	4 (1.6%)	1 (0.4%)	0.7243
Fever/Chills	17 (3.5%)	13 (5.3%)	4 (1.6%)	**0.0452**
Tachycardia/Palpitation	5 (1%)	2 (0.8%)	3 (1.2%)	0.6856
Dizziness/Vertigo	3 (0.6%)	3 (1.2%)	0 (0%)	0.2485
Neuropathy	4 (0.8%)	4 (1.6%)	0 (0%)	0.1235
Fatigue/Tiredness	19 (3.9%)	15 (6.1%)	4 (1.6%)	**0.017**
Poor Appetite	2 (0.4%)	2 (0.8%)	0 (0%)	0.499
Chest Pain/Tightness	14 (2.9%)	10 (4.1%)	4 (1.6%)	0.1733
Urticaria	34 (7%)	26 (10.6%)	8 (3.3%)	**0.0021**
Blurry Vision/Photosensitivity	3 (0.6%)	3 (1.2%)	0 (0%)	0.2485
Swelling/Edema	3 (0.6%)	2 (0.8%)	1 (0.4%)	1
Aseptic Meningitis	2 (0.4%)	1 (0.4%)	1 (0.4%)	1

ADR=adverse drug reaction; GI=gastrointestinal; SOB=shortness of breath. A *P* value of <0.05 was found to be statistically significant.

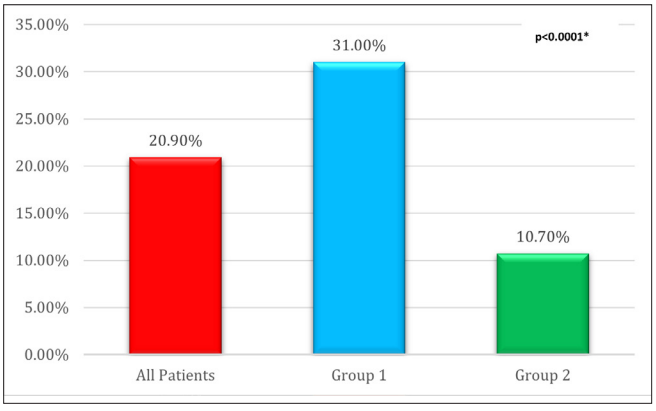

Figure 2. Percentage of Patients with Adverse Drug Reactions Compared with All Patients Who Received IV Immunoglobulin Infusions. *P value <0.05 is considered statistically significant

Discussion

This study was conducted to add evidence and valuable safety information to support informed decision-making by healthcare providers, especially those treating neuroimmune patients receiving high-dose IVIG. This study is extremely unique for multiple reasons. This study is conducted on a significantly large population of 489 patients, treated with multiple high-dose IVIG infusions and representing over 11,334 infusions conducted over a 10-year period. Additionally, the study focuses on both adult and pediatric populations from 10 to 95 years of age, therefore representing an unprecedented, wide age range. It also includes a large spectrum of neurological and immunological disorders. By way of comparison, the pivotal,

multicenter trial for Octagam in immune thrombocytopenic purpura (ITP) had 116 patients and only accounted for the adult population.[9]

In this study, >70% of the patients presented with neuroimmune/neuromuscular disorders, and widespread use of IVIG in this patient population has prompted awareness of ADRs (both non-serious and serious).[4-7] Because the effectiveness and safety of IVIG therapy are of primary concern, healthcare providers (including those from KabaFusion) have developed specific premedication regimens, including analgesics, antihistamines, and anti-inflammatory agents, to help prevent the occurrence of potential ADRs.[5-7] As a result, all of the patients in the current study received premedication prior to their IVIG infusion; by contrast, in the pivotal trial for Octagam, premedication was offered to patients but was only administered in one patient.[9]

Patients in Group 1 and Group 2 were found to have some differences in the types of ADRs reported. This could possibly be associated with specific patient characteristics and comorbidities. The study results have been stratified on the basis of multiple factors, including allergy history, age, and gender, to allow for a robust analysis. Nevertheless, patient outcomes were analyzed based on each patient's individual profile. It is also important to note that patients with neurological disorders tend to be associated with multiple comorbidities and with more complicated patient profiles (Table 1).

KabaFusion used data gathered over a period of 10 years and evaluated the impact of increased on-label infusion rates on patient safety. In a prior study, conducted by Rigas et al., the overall ADR rate per infusion was 4.7%.[4] In the current study, the overall ADR rate was 2.5%, with a higher ADR rate for slower IVIG infusions (3.7% vs. 1.3%, $p<0.0001$). Furthermore, the percentage of patients with ADRs who were receiving slower IVIG infusions was higher than in those receiving high-rate IVIG administration (31% vs. 10.7%, $p<0.0001$). Based on these results, infusion rates of specific high-purity IVIG products were associated with a significantly lower amount (both statistically and clinically) of non-serious and serious ADRs in both the adult and pediatric populations. These results can be of great utility in clinical application if applied within the manufacturer's recommended guidelines, to ease the burden of time required for patients undergoing IVIG infusions.

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Author Contributions

All authors: conception, organization, execution of the research described in the manuscript, statistical analysis, result interpretation, in addition to review and critique of the manuscript.

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Conflict of Interest

Dr. Rashid, Dr. Rigas, Dr. Piracha, and Dr. Alqadri report no disclosures.

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References

1. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol*. 2017;139:S1-S46.

2. Kriván G, Königs C, Bernatowska E, et al. An open, prospective trial investigating the pharmacokinetics and safety, and the tolerability of escalating infusion rates of a 10% human normal immunoglobulin for intravenous infusion (IVIg), BT090, in patients with primary immunodeficiency disease. Vox Sang. 2015;3:248–256

3. Sleasman JW, Duff CM, Dunaway T, et al. Tolerability of a new 10% liquid immunoglobulin for intravenous use, Privigen, at different infusion rates. *J Clin Immunol*. 2010;30:442–448.

4. Rigas M, Tandan R, Sterling RJ. Safety of liquid intravenous immunoglobulin for neuroimmunologic disorders in the home setting: a retrospective analysis of 1085 infusions. *J Clin Neuromusc Dis*. 2008;10:52-55.

5. Souayah N, Pahwa A, Burawski L, et al. A retrospective analysis of the safety profile of intravenous immunoglobulin in 1176 patients receiving home infusion therapy. *J Clin Neuromusc Dis*. 2018;19:181-195.

6. Souayah N, Pahwa A, Burawski L, et al. The safety profile of home infusion of intravenous immunoglobulin in patients with neuroimmunologic disorders. *J Clin Neuromusc Dis*. 2011;12:S1-S10.

7. Sparado G, Vultaggio A, Bosia A, et al. Rapid infusions of human immunoglobulin 50 g/l are safe and well tolerated in immunodeficiencies and immune thrombocytopenia. *Intl Immunopharm*. 2017;44:38-42.

8. Octagam 5%. Human Normal Immunoglobulin. Solution for Infusion. Prescribing Information, Octapharma.

9. Octagam 10%. Human Normal Immunoglobulin. Solution for Infusion. Prescribing Information, Octapharma.

Long Standing DADS Variant of CIDP Preceding AL amyloidosis: A sentinel event or serendipitous association?

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Keywords: *chronic inflammatory demyelinating polyneuropathy, distal acquired demyelinating symmetric neuropathy, monoclonal gammopathy of unknown significance, amyloidosis, free light chain assay*

Introduction

Diagnosis, treatment and long-term term monitoring of patients with chronic inflammatory neuropathies can be difficult with many pitfalls. This is particularly true when patients on immunomodulatory therapy (IMT) worsen as the worsening could be due to a relapse, emergence of an associated or unrelated disorder or due to an error in the primary diagnosis. Primary amyloidosis (AL) is often called the 'great imitator' due to its indolent and multisystemic presentation and is often the least considered amongst the heterogeneous spectrum of paraproteinemic neuropathies.[1] When a paraproteinemia is encountered during evaluation of neuropathy, failing to think beyond MGUS can delay the diagnosis of AL until so advanced that treatment is ineffective.[2] Here we present a case of a patient with idiopathic distal acquired demyelinating symmetric neuropathy (DADS-I) who succumbed to AL after two decades. We explore the association of AL neuropathy with DADS, both paraprotein-related neuropathies.

Case Report

A 35-year-old dentist presented with a two-year history of insidious numbness and paresthesia over the toes, feet and fingertips. These symptoms progressed to include unsteadiness of gait, loss of distal dexterity and hand tremors preventing him from performing his job. He did not have pain, autonomic symptoms or any constitutional complaints. His family history was notable for an unusual sensorimotor polyneuropathy in his father who also had IgG paraproteinemia and an elevated CSF protein. The neurological examination showed mild distal weakness with MRC grade 4+/5 power in ankle dorsiflexion and 4/5 of intrinsic hand and foot muscles. He had diffuse areflexia, impaired large and small fiber sensation distally and a positive Romberg test. He also had postural tremor of both hands persisting on intentional movements. The nerve conduction studies during the first visit revealed a demyelinating severe sensorimotor polyneuropathy. (Table 1)

Prior investigations showed a CSF protein of 128gm/L and normal laboratory tests including CBC, ESR, renal function, vitamin B12, glycosylated hemoglobin, 2-hour glucose tolerance test, serum protein electrophoresis, serum immunoelectrophoresis, levels of IgG, IgA and IgM, and anti MAG level. A sural nerve biopsy reviewed with a neuropathologist showed an inflammatory neuropathy with marked loss of myelinated nerve fibers, hypermyelinated fibres, scattered CD45+ lymphocytes and occasional CD68+ macrophages consistent with CIDP. Congo red staining did not reveal any amyloid deposition.

A diagnosis of CIDP was made and he was started on prednisone and propranolol for tremor. He stopped progressing, his balance normalized and his dexterity improved although not back to normal and he had to change his career. Whenever steroid tapering was attempted, he had worsening of symptoms and function. Low dose prednisone was continued and IVIG added. He remained on this maintenance therapy and was doing well clinically and electrically. The nerve conduction studies done in eleven years from the baseline were somewhat improved compared to baseline. (Table 1) Any attempts at increasing IVIG intervals or reducing dosage was met with worsening symptoms. Trials of cyclophosphamide, azathioprine and rituximab as steroid-sparing agents failed. After 18 years, the patient deteriorated despite maintenance steroid and IVIG and was re-investigated. (Table 2) Laboratory testing showed a monoclonal peak of IgG lambda with M protein level of 10gm/L with a second value about 8 months later of 11gm/L. Within six months, he developed progressive pedal edema and was diagnosed with nephrotic syndrome. Renal biopsy showed mild to moderate mesangial expansion by pale staining material which was also found in vessel walls and which stained positive with Congo red stain, and immunofluorescent microscopy showed IgG lambda deposits. With a positive family history of neuropathy, genetic studies were performed for an autosomal dominant hereditary amyloidosis and no pathogenic variants were found in (transthyretin) TTR, fibrinogen alpha chain (FGA), lysozyme (LYZ) and ApoA1 genes. He was treated with cyclophosphamide and bortezomib and later lenalidomide

Table 1. Motor nerve conduction studies during the course of illness

	Latency			Velocity (m/s)			Amplitude (mv)		
Time in years	0	11	18	0	11	18	0	11	18
Median nerve APB Wrist	6.7	5.9	5.4				9.6	12.3	8.2
Elbow	15.8	15.7	16.2	27	27	24	5.6	7.3	4.3
Axilla	18.8	19.2	19.4	33	36	30	4.9	7.2	4.1
Peroneal nerve EDB Ankle	10.0	8.8	10.3				1.5	1.8	0.2
Fibular head	28.2	25.3	25.3	17	18	20	0.2	1.2	0.1
Popliteal fossa	32.3	30.2	29.7	20	20	20	0.3	1.1	0.1
Peroneal nerve TA Fibular head	*	5.4	6.0				*	12.0	5.2
Popliteal fossa	*	8.8	9.5				*	11.6	4.9

APB- abductor pollicis brevis, EDB- extensor digitorum brevis, TA- tibialis anterior, * not done

without response. He underwent autologous bone marrow transplantation in, but his condition was complicated by cardiomyopathy and bilateral pulmonary emboli. At the last clinic visit, he had mild distal motor weakness, sluggish to absent reflexes and significant loss of sensation affecting ambulation and was wheelchair-bound. He had subsequent worsening with sepsis, progressive cardiac and renal dysfunction and succumbed to his illness within 2 years of the neurological deterioration. Figure 1 outlines his disease course and treatment.

Discussion

The current report highlights a case of DADS-I variant of CIDP initially responsive to IMT for almost two decades. Late in the course, paraproteinemia was detected and was confirmed to be due to AL. This case raises several complex questions about the long-term monitoring of inflammatory and paraproteinemia associated neuropathies.

The cornerstone in the evaluation of neuropathy is the appropriate classification of the syndrome based on clinical phenotype, nerve conduction studies and laboratory investigation. Since the initial description by Katz et al in early 2000 of the distinct distal sensory predominant neuropathy associated with M protein, the spectrum of paraproteinemic neuropathy has expanded.[3,4] . SPEP and SIEP are usually ordered and if a paraproteinemia is detected, both physician and patient are often reassured that the diagnosis is MGUS and paraproteinemic neuropathy. However, another plasma cell dyscrasia which is often missed is AL. Amyloidosis refers to a group of conditions in which misfolded insoluble protein fibrils with unique beta pleated structure and staining properties accumulate in the extracellular tissue, and can either be localized or systemic, acquired or inherited.[5] AL or primary systemic amyloidosis arises due to the deposition of monoclonal immunoglobulin light chain which in turn is produced by a clonal plasma cell expansion. In fact AL is a plasma cell dyscrasia along the same lines as multiple myeloma (MM), and the pathogenic mechanism which leads the clonal expansion down the path to MM or to systemic amyloidosis remains unknown.[6,7] Peripheral neuropathy is seen in 17 to 35% of AL patients and is not a common presenting symptom, but when it is, the diagnosis of AL is significantly delayed.[8–10] While the commonest neuropathic presentation is sensory predominant neuropathy with autonomic symptoms resembling hereditary transthyretin amyloidosis, presentations including cranial neuropathies, lumbosacral plexopathies, mononeuropathies and CIDP have been described.[11–16]

However, it does not appear that our patient had AL presenting as a DADS variant of CIDP at onset. The patient had a phenotype most suggestive of DADS and never had any autonomic symptoms. In addition, the absence of amyloid deposits but rather features consistent with CIDP in the nerve biopsy, a positive response both clinically and electrically with IMT and a duration of illness spread over two decades do not appear to be consistent with a CIDP-like presentation of AL. The diagnosis of AL in this case was made after reinvestigation prompted by clinical deterioration after many years of stability on IMT.

When evaluating and monitoring patients with paraproteinemia, besides progression to MM it has to be borne in mind that all forms of MGUS can potentially progress to AL. [17] In a series from the Mayo Clinic, 9% of

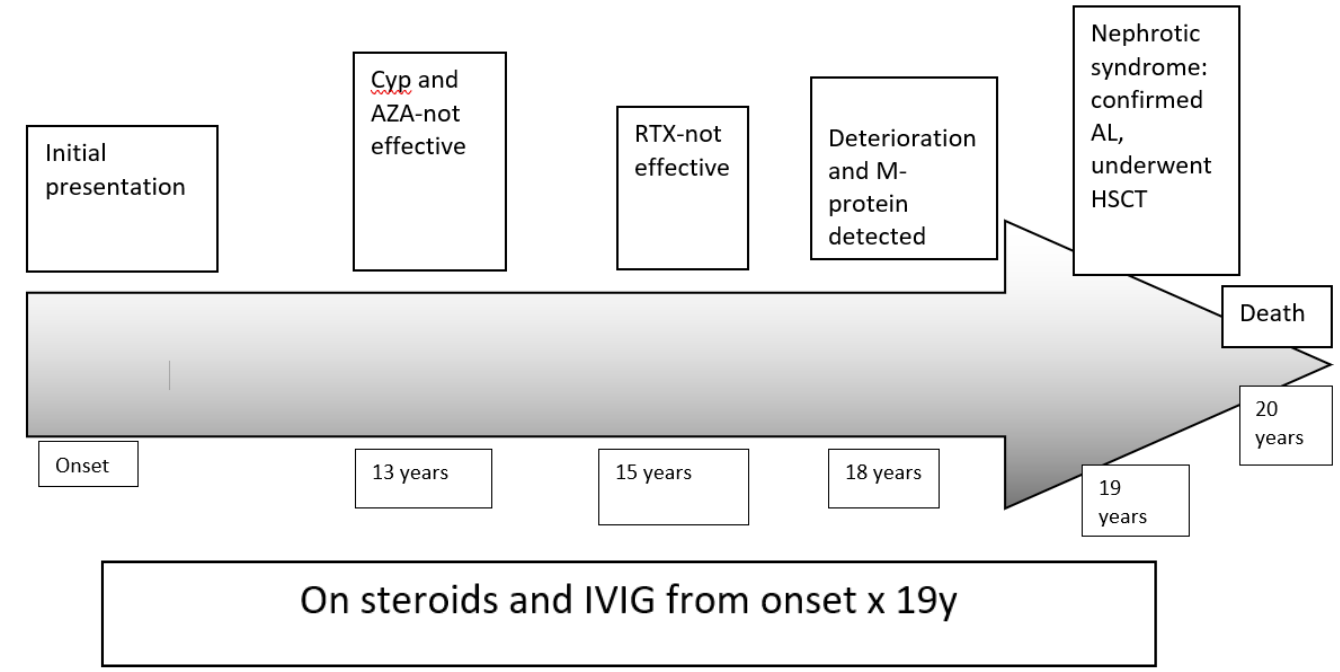

Figure 1. Timeline of disease course

all patients with a monoclonal gammopathy were ultimately proven to have light chain amyloidosis.[18] Features that demand special attention include predominantly axonal polyneuropathy, bilateral CTS, debilitating symptoms and rapid neuropathy progression. Many AL characteristic systemic symptoms and signs, such as periorbital purpura, macroglossia and shoulder pad signs, are seen only in a minority of AL patients.[1,5,19] Evaluation should include free light chain (FLC) assay and kappa:lambda ratio in addition to the SIEP and SPEP. Negative SPEP, SIEP and FLC in serum and urine effectively rule out AL.[5] Direct organ biopsy is rarely needed, and less invasive investigations such as abdominal fat aspiration, lip or rectal biopsy and immunohistochemistry or mass spectroscopy are useful to identify amyloid protein. Recommendations for monitoring of patients with MGUS is risk stratified based on quantity and type of M protein and FLC ratio. High risk patients need extensive evaluation including bone marrow biopsy not only to look for evidence of malignancy but also for AL.[20]

Unfortunately, our patient developed systemic manifestations of AL within a short interval from the detection of paraproteinemia, and had a rapid downhill course despite chemotherapy and bone marrow transplant. This rapid decline makes one suspect that the patient had a paraproteinemia for some time, but there was nothing to prompt re-investigation until the patient had worsening of neuropathy. Although the patient had the DADS phenotype, he had been evaluated for M protein previously with negative results. Whether initial titres were too low for detection by the then standard assays, or whether patients with DADS-I require frequent monitoring for development of paraproteinemia are questions that remain unanswered at present. Although there is no conclusive proof, the final worsening of neuropathy in this case is likely related to development AL. Interestingly, a recent large population based study showed that MGUS conferred a 2.9 fold increased risk of progression to AL when associated with peripheral neuropathy.[21] The majority of cases with MGUS-related neuropathy progressing to AL do so within the first year which is consistent with the course in our patient.

The family history of an unusual neuropathy related to paraproteinemia and its significance also remains unexplained. We found one report of a similar father-son presentation, so a rare genetic mechanism might be responsible.[22]

The diagnosis of MGUS opens a window of opportunity to the diagnosis of AL since virtually all cases of AL are preceded by MGUS. This is particularly true in the setting of a neuropathic presentation since there is increased risk of progression of MGUS to AL with such an association. Since

an M protein is associated with 50-70% of DADS cases, it may be worthwhile to monitor all DADS patients for AL frequently, even if the initial testing is negative. The need for FLC and kappa:lambda ratio along with the assessments SPEP and SIEP in serum and urine in screening and monitoring MGUS patients has to be stressed. Finally, when a patient with CIDP who is doing well on IMT fails, the novel development of MGUS or AL should be considered.

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References

1. Vaxman I, Gertz M. When to Suspect a Diagnosis of Amyloidosis. AHA 2020;143:304–11. https://doi.org/10.1159/000506617.

2. Karam C, Moshe-Lilie O, Chahin N, Ragole T, Medvedova E, Silbermann R. Diagnosis of paraproteinemic neuropathy: Room for improvement. J Neurol Sci 2020;415:116902. https://doi.org/10.1016/j.jns.2020.116902.

3. Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ. Distal acquired demyelinating symmetric neuropathy. Neurology 2000;54:615–20. https://doi.org/10.1212/wnl.54.3.615.

4. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J Peripher Nerv Syst 2010;15:185–95. https://doi.org/10.1111/j.1529-8027.2010.00278.x.

5. Gertz MA. Immunoglobulin light chain amyloidosis: 2020 update on diagnosis, prognosis, and treatment. Am J Hematol 2020;95:848–60. https://doi.org/10.1002/ajh.25819.

6. Zingone A, Kuehl WM. Pathogenesis of Monoclonal Gammopathy of Undetermined Significance (MGUS) and Progression to Multiple Myeloma. Semin Hematol 2011;48:4–12. https://doi.org/10.1053/j.seminhematol.2010.11.003.

7. Merlini G, Palladini G. Differential diagnosis of monoclonal gammopathy of undetermined significance. Hematology 2012;2012:595–603. https://doi.org/10.1182/asheducation.V2012.1.595.3798563.

8. Duston MA, Skinner M, Anderson J, Cohen AS. Peripheral neuropathy as an early marker of AL amyloidosis. Arch Intern Med 1989;149:358–60.

9. Kaku M, Berk JL. Neuropathy Associated with Systemic Amyloidosis. Semin Neurol 2019;39:578–88. https://doi.org/10.1055/s-0039-1688994.

10. Rajkumar SV, Gertz MA, Kyle RA. Prognosis of patients with primary systemic amyloidosis who present with dominant neuropathy. Am J Med 1998;104:232–7. https://doi.org/10.1016/s0002-9343(98)00037-0.

11. Matsuda M, Gono T, Morita H, Katoh N, Kodaira M, Ikeda S. Peripheral nerve involvement in primary systemic AL amyloidosis: a clinical and electrophysiological study. Eur J Neurol 2011;18:604–10. https://doi.org/10.1111/j.1468-1331.2010.03215.x.

12. Traynor AE, Gertz MA, Kyle RA. Cranial neuropathy associated with primary amyloidosis. Ann Neurol 1991;29:451–4. https://doi.org/10.1002/ana.410290421.

13. Adams D, Lozeron P, Theaudin M, Denier C, Fagniez O, Rerat K, et al. Varied patterns of inaugural light-chain (AL) amyloid polyneuropathy: a monocentric study of 24 patients. Amyloid 2011;18:98–100. https://doi.org/10.3109/13506129.2011.574354036.

14. Cheng RR, Eskandari R, Welsh CT, Varma AK. A case of isolated amyloid light-chain amyloidosis of the radial nerve. J Neurosurg 2016;125:598–602. https://doi.org/10.3171/2015.10.JNS151095.

15. Mathis S, Magy L, Diallo L, Boukhris S, Vallat J-M. Amyloid neuropathy mimicking chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2012;45:26–31. https://doi.org/10.1002/mus.22229.

16. Li J, Li Y, Chen H, Xing S, Feng H, Liu D, et al. Autonomic Neuropathy and Albuminocytologic Dissociation in Cerebrospinal Fluid As the Presenting Features of Primary Amyloidosis: A Case Report. Front Neurol 2017;8. https://doi.org/10.3389/fneur.2017.00368.

17. Chaudhry HM, Mauermann ML, Rajkumar SV. Monoclonal Gammopathy Associated Peripheral Neuropathy: Diagnosis and Management. Mayo Clin Proc 2017;92:838–50. https://doi.org/10.1016/j.mayocp.2017.02.003.

18. Gertz MA. Immunoglobulin light chain amyloidosis diagnosis and treatment algorithm 2018. Blood Cancer Journal 2018;8:1–8. https://doi.org/10.1038/s41408-018-0080-9.

19. Dispenzieri A, Kyle R, Merlini G, Miguel JS, Ludwig H, Hajek R, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 2009;23:215–24. https://doi.org/10.1038/leu.2008.307.

20. Kyle RA, Durie BGM, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010;24:1121–7. https://doi.org/10.1038/leu.2010.60.

21. Rögnvaldsson S, Turesson I, Björkholm M, Landgren O, Kristinsson SY. Peripheral Neuropathy in MGUS and Progression to Amyloid Light-Chain Amyloidosis: A Population-Based Study Including 15,351 MGUS Cases. Blood 2019;134:5444–5444. https://doi.org/10.1182/blood-2019-131514.

22. Enqvist S, Mellqvist U-H, Mölne J, Sletten K, Murphy C, Solomon A, et al. A father and his son with systemic AL amyloidosis. Haematologica 2009;94:437–9. https://doi.org/10.3324/haematol.13640.

Significance of Transaminitis in Guillian Barre Syndrome

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Keywords: *Guillian Barre syndrome, liver function disturbances, transaminitis*

ABSTRACT

Guillian Barre Syndrome (GBS) is an immune-mediated disorder with a wide variety of predisposing factors and varied clinical manifestations. In this case, we report a 19-year-old male presenting with GBS of AIDP type associated with transiently elevated liver enzymes (AST/ALT) about 4-5 times above baseline that lasted for 1-2 weeks and start declining towards baseline after 2 weeks. We conclude that the majority of the time no cause can be attributable to such liver function disturbances (LFD). Therefore, treatment for GBS might be continued despite having LFD as this phenomenon is transient and does not interfere with treatment of GBS.

Introduction

Guillain-Barre syndrome (GBS) is an acute inflammatory immune-mediated polyradiculoneuropathy presenting typically with tingling, progressive weakness, pain and sometimes respiratory difficulties. According to recent epidemiology, the incidence of GBS ranges between 0.81 and 1.89 (median 1.11) cases per 100,000 person-years [1]. The clinical course, severity, and outcomes of GBS are highly variable.

Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) are liver enzymes where increased levels usually indicate hepatocyte injury. Both the parameters are increased in a wide range of conditions that affect the liver including infections, malignancy, trauma and excess alcohol consumption. In this report, we discuss a unique case of GBS having elevated AST and ALT following admission to the hospital, its possible causes and influence on treatment of GBS.

Case

A 19-year-old gentleman was admitted to the hospital for bilateral lower limb weakness followed by left upper limb weakness. Electrophysiological studies showed early GBS of AIDP type. The patient was started on five doses of plasma exchange over 10 days. He denied any nausea, vomiting, coffee-ground emesis, jaundice, clay-colored stools, melena or hematochezia. He has no history of heavy alcohol abuse, IV drug intake, recent immunization or travel outside the country. He denied any family history of liver disease. On day 0 of admission his AST/ALT was 49/53 which was slightly above the upper limit (Normal 0-40/10-50) with an increasing trend until day 5 (154/240), which was about 4-5 times the upper limit and then started showing a decline (Figure 1A, 1B). His total bilirubin, PTT/PT/INR, total protein, albumin, ALP, fibrinogen, ceruloplasmin levels were in the normal range throughout. His viral panel (HAV IgM, HBcAb IgM, HBsAg, HCV A, CMV, EBV, autoimmune hepatitis workup), fluorescent anti-nuclear antibody (FANA), alpha 1 anti-trypsin, anti-smooth muscle Ab, and anti-mitochondrial Ab were negative. His abdominal ultrasound was unremarkable for any liver pathology. His liver function test was down trending and was completely normal when evaluated in his next clinic follow up after two months.

Discussion

As the pathophysiology of GBS would have started before hospital admission, this liver function disturbance can still be a part of GBS. There are a wide range of causes that can precede GBS and cause LFD like cytomegalovirus (CMV), Epstein–Barr virus (EBV), hepatitis (A, B, and E), and several other bacterial and viral infections. Vaccines

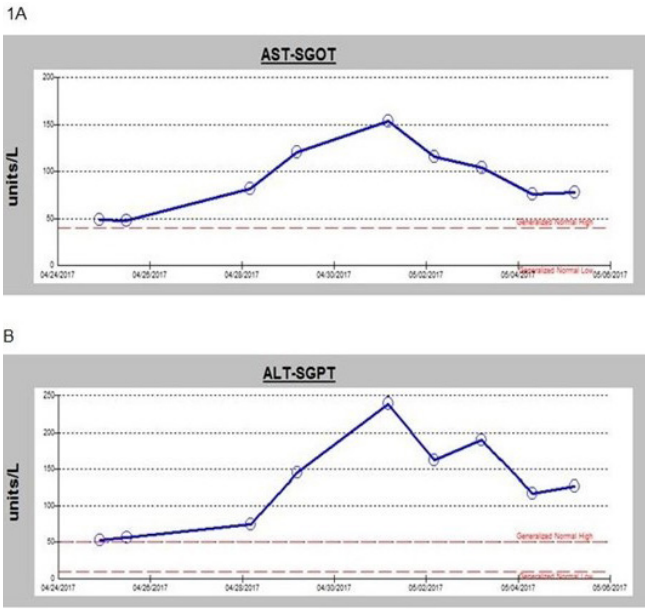

Figure 1. Trend of AST/ALT over the course of admission to discharge.

such as hepatitis A and B, yellow fever, influenza A, H1N1, and MMR have also been considered as a possible trigger of GBS [1] and LFD [2,3].

So far, there have been no extensive studies of LFD in GBS. The most likely explanation is immune-mediated liver dysfunction along with the peripheral nervous system dysfunction that occurs in GBS [4,5,6]. This could explain his slightly elevated ALT/AST at the time of admission and that the course of elevation of the enzymes is likely to be independent of the course of GBS. Another possible explanation for the presence of LFD would be that of infectious agents like hepatitis A and B. These infections occur more often than is reported because of high false-negative serologic tests. Though the level of transaminases was >2.5 times in this case, the LFD was of short duration; the peak was within one week after hospitalization and hence less likely to be hepatitis considering the duration [7]. Certain bacterial endotoxins can cause LFD with a common cause being Campylobacter jejuni. [6,8]. Although numerous factors might cause LFD in GBS, most of the time extensive investigations may not yield any reasonable cause. Oomes *et. al* [6] performed a prospective longitudinal study of measuring liver function in 100 patients. They found an increase in patients with LFD in the IVIG treatment group while no LFD was seen in the plasma exchange treatment group. After about one month, the significant difference in LFD had disappeared and by six months the percentage of patients with LFD was significantly lower in both IVIG and plasma exchange groups. It was determined that transient liver dysfunction was through an unknown mechanism. However, removal of plasma in plasma exchange may reduce the transient elevation of liver enzymes that might have been seen if the patients had not undergone this therapy and therefore LFD in IVIG as compared to plasma exchange could be artifactual. [9]

The course of the LFD seems to be benign and asymptomatic, increasing rapidly for about a week and declining thereafter. Most of the time this does not warrant stopping IVIG or plasma exchange. Other causes affecting LFD in GBS as mentioned above should be kept in mind and evaluated if there is symptomatic elevation of AST/ALT or if there is persistent elevation for >2 weeks.

Conclusion

GBS is a heterogeneous condition with numerous clinical associations and various inciting factors. LFD is one such association in which liver enzymes AST/ALT are transiently elevated that parallel the course of GBS without any cause attributed in the majority of cases. Therefore, treatment for GBS might be continued and the cause for these disturbances evaluated when it is persistently high or symptomatic.

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References

1. Sejvar JJ, Baughman AL, Wise M, et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011; 36:123–133.

2. Jasti AK, Selmi C, Sarmiento-Monroy JC, Vega DA, Anaya JM, Gershwin ME. Guillain-Barré syndrome: causes, immunopathogenic mechanisms and treatment. Expert Rev Clin Immunol. 2016 Nov;12(11):1175-1189. doi: 10.1080/1744666X.2016.1193006. Epub 2016 Jun 21. PMID: 27292311.

3. D'alò GL, Zorzoli E, Capanna A, Gervasi G, Terracciano E, Zaratti L, Franco E. Frequently asked questions on seven rare adverse events following immunization. J Prev Med Hyg. 2017 Mar;58(1):E13-E26. PMID: 28515627; PMCID: PMC5432774.

4. Ropper AH, Wijdicks EFM, Truax BT. Guillain-Barre syndrome. In Contemporary neurology series. Vol. 34. Philadelphia: FA Davis, 1991.

5. Van Doom PA, Brand A, Vermeulen M. Clinical significance of antibodies against peripheral nerve tissue in inflammatory polyneuropathy. Neurology 1987; 37:1798 -1802.

6. Oomes PG, van der Meché FG, Kleyweg RP. Liver function disturbances in Guillain-Barré syndrome: a prospective longitudinal study in 100 patients. Dutch Guillain-Barré Study Group. Neurology. 1996 Jan;46(1):96-100. doi: 10.1212/wnl.46.1.96. PMID: 8559429.

7. Gutteridge CN, Veys P, Newland AC. Safety of intravenous immunoglobulin for treatment of autoimmune thrombocytopenia. Acta Haematol 1988; 79:88-90.

8. Hanson M, Polesky HF. Factors affecting alanine aminotransferase in blood donors. In Proceedings international hepatitis workshop. Edinburgh: Nuclear Enterprises, 1982:93-97.

9. Lisak R. Liver Function in GBS Neurology Dec 1996, 47 (6) 1606; DOI: 10.1212/WNL.47.6.1606

Myasthenia Gravis and Pericarditis in a Patient with Thymoma

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Keywords: *myasthenia gravis, pericarditis, myocarditis, cardiac involvement*

Introduction

Cardiac involvement in myasthenia gravis (MG) is rare but has been described in the literature.[1] Manifestations of cardiac involvement in MG are varied but include (and are not limited to) pericarditis[2], giant cell myocarditis[3], Takotsubo cardiomyopathy[4], and a variety of arrhythmias[5]. The exact pathogenesis of cardiac involvement in MG is unclear and is likely dependent on the specific cardiac manifestation. However, there has been an association with the production of antibodies against striated muscle in these patients, especially in those with thymoma[6]. In fact, anti-striational antibodies have been described in 97% of patients with thymoma with cardiac involvement.[7] Specific antibodies that have been implicated in the literature include anti-Titin, anti-Ryanodine, anti-Mitochondrial 7, anti-Smooth muscle alpha, anti-Citrate acid extract.[8] The prognosis of cardiac involvement in MG is varied and it is unclear whether the presence of specific antibodies is predictive of disease course. Myocarditis associated with MG can be rapidly fatal.[9] In this report, we describe a case of pericarditis in a patient with MG and thymoma with no prior cardiac history.

Case Report

Patient Presentation

A 27-year-old African American male presented to our Emergency Department with dyspnea, fatigable weakness, and an inability to hold his head up. He had been diagnosed at an outside hospital with MG two weeks prior after an episode of respiratory failure requiring intubation. There, he was found to have a large anterior mediastinal mass on imaging concerning for thymoma, and he was anti acetylcholine receptor antibody positive. He was treated with intravenous immunoglobulin as per protocol and discharged home on pyridostigmine. Aside from his new diagnosis of MG, his past medical history was unremarkable. He was given a course of doxycycline for suspected Lyme disease 2 months prior, which on rare occasions is known to unmask symptoms of MG. He was not taking any medications at the time aside from the pyridostigmine after being diagnosed with MG. There was no family history of malignancy or autoimmune disease.

At time of presentation to our hospital, about two weeks after initial diagnosis, he was noted to have respiratory distress and generalized weakness with fatigue. He was afebrile, his heart rate was in the mid-90's, his blood pressure was 132/74, and his respiratory rate was 34. Pulse oximetry revealed an O_2 saturation of 86%. On physical exam, he displayed decreased air movement without wheezes or rales. His cardiac exam was unremarkable aside from tachycardia. His neurologic exam showed marked facial weakness, ptosis worse on the left side, 2/5 strength in his proximal upper extremities, 3/5 strength in his proximal lower extremities, and no distal weakness. Deep tendon reflexes and sensation were intact. Due to his hypoxia and respiratory distress, an arterial blood gas (ABG) was performed which showed respiratory acidosis. A presumptive diagnosis of acute hypoxic respiratory failure due to myasthenic crisis was made, and the patient was intubated and sent to the Intensive Care Unit. His serum was *positive* for anti-acetylcholine receptor antibodies (binding +, blocking +, modulating -) and *positive* for anti-striational antibodies.

Hospital Course

The patient was started on an increased dose of pyridostigmine. Initially, his ptosis and weakness were slow to resolve. On the third day of his hospitalization, he developed a fever of 38 and tachycardia to the 110's. An echocardiogram was obtained out of concern for infective endocarditis and was negative for vegetations but did show an ejection fraction of 40-45% with global diffuse hypokinesis. Due to concern for myocarditis associated with thymoma, a cardiac MRI was ordered. A creatine kinase (CK) was ordered to rule out concurrent polymyositis and was 63 IU/L (Normal reference range 29-168 IU/L). The cardiac MRI showed constrictive pericarditis with pericardial effusion and mild subepicardial enhancement of the lateral wall (Figure 1).

The patient was started on metoprolol and lisinopril. On hospital day 5, the patient was started on plasma exchange for a total of 5 sessions. The delay in starting his plasma exchange was likely related to a combination of factors –

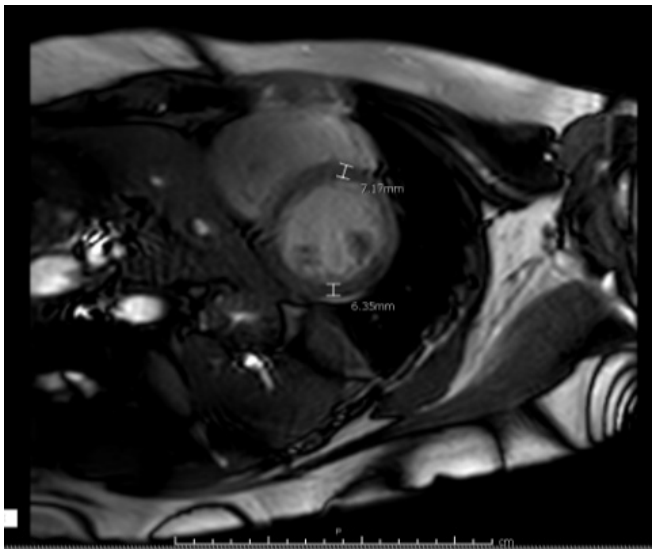

Figure 1. Cardiac MRI showing constrictive pericarditis with pericardial effusion.

his recent treatment with IVIG (Plasma exchange would remove the infused immunoglobulins) as well as his fever on day 3 with suspected infection related exacerbation. We did not start him on IVIG initially because we believed that though it helped him transiently, he would likely not benefit with a repeat dose in 2 weeks.

He began to experience improvement midway through his plasma exchanges and was extubated; however, he was re-intubated on hospital day 6 due to increasing respiratory fatigue. Upon completion of plasma exchange, the patient had improved significantly and was extubated successfully on hospital day 10. A repeat echocardiogram showed improved ejection fraction of >55%. He was eventually discharged on a steroid taper, lisinopril, and metoprolol. Close outpatient follow-up has been kept with the patient. He has experienced some weight gain while on 15 mg of prednisone and such dose was reduced in subsequent visits. He is taking prednisone 10 g daily as well as Mestinon 60 mg every 8 hours. His steroids are being slowly tapered to a stop. He is adhering to a strict exercise routine and his overall health is under control.

Follow-Up

At the time of his diagnosis of MG, the patient received a CT thorax with contrast, which showed a 41 x 32 x 45 mm anterior mediastinal mass with no thoracic adenopathy or pericardial involvement. The patient was referred to cardiothoracic surgery for video-assisted thoracoscopic thymectomy, which proceeded about 3 months after initial diagnosis without complication (Figure 2).

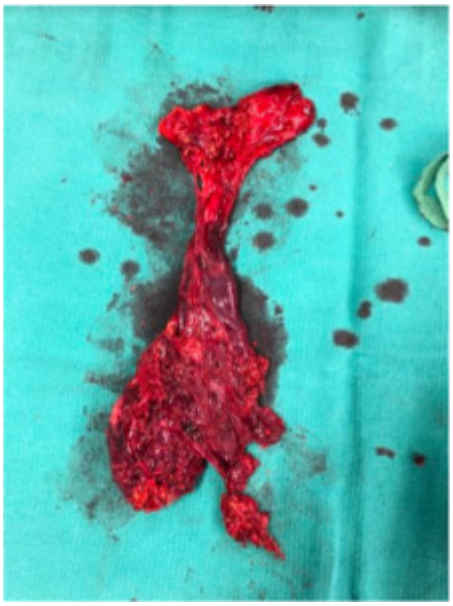

Figure 2. Image of patient's thymoma post-surgical resection.

Surgical pathology confirmed thymoma. He received postoperative proton therapy for eradication of additional thymoma tissue. The patient continues to follow-up with neurology and cardiology as well as CT surgery. He complains of continued hoarseness, however his weakness and ptosis have resolved. He has had no further episodes of myasthenic crisis for 15 months following thymectomy. The patient has stayed on metoprolol and lisinopril, Repeat echocardiogram four months after hospitalization did not show any lasting abnormalities.

Discussion

Pericarditis in association with MG is extremely rare but has been previously reported.[2] More commonly, MG is associated with myocarditis, with or without concurrent myositis, especially in patients taking immune checkpoint inhibitors.[10-12] Myocarditis in MG has been associated with the production of antibodies against striated muscle (anti-striational), however there is not an association in the literature with pericarditis in MG and anti-striational antibodies. Anti-striational antibodies are positive in many patients with thymoma,[13] which is likely the reason for the positive test in our patient.

Several mechanisms of pericarditis in MG have been described in the literature. These include constrictive pericarditis with invasion of thymoma into the pericardium,[14] as well as post-radiation pericarditis.[15] We propose antibodies from the patient's thymoma created immune complexes, which deposited in the pericardium, leading

to inflammation and a concomitant decreased ejection fraction. We also hypothesize that this immune-complex mediated mechanism is why this patient responded well to plasma exchange, and why the patient's cardiac function returned to normal after treatment. Though rare, cardiac involvement should always be on the radar of the physician treating a patient with MG, and unrecognized pericarditis in particular can progress to constriction and tamponade, further complicating tenuous respiratory and cardiac status of patients with myasthenic crisis.

Other cardiac manifestations of myasthenia gravis include a wide spectrum that ranges from asymptomatic patients to severe cases of arrhythmias and cardiac arrest.[16] Some patients, especially those with MG associated with thymoma are known to have a propensity for heart related disease. The electrocardiographic manifestation of cardiac involvement of myasthenia gravis are nonspecific.[17] A rare manifestation of myasthenia gravis mostly seen on thymoma-associated MG is myasthenia-related myocarditis which can be lymphocytic and involve giant cells. Few cases have been reported describing this condition and the pathogenesis is unknown. Stress-induced cardiomyopathy is also being described and is mostly related with myasthenia gravis exacerbation.[18]

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References

1. Guglin, Maya, et al. "Cardiac Disease in Myasthenia Gravis: A Literature Review." *Journal of Clinical Neuromuscular Disease*, vol. 4, no. 4, 2003, pp. 199–203., doi:10.1097/00131402-200306000-00006

2. Vats, Hemender S., et al. "Pericarditis in Myasthenia Gravis." *Cardiology in Review*, vol. 12, no. 3, 2004, pp. 134–137., doi:10.1097/01.crd.0000117762.62596.8d.

3. Priemer, David S, et al. "Giant Cell Polymyositis and Myocarditis in a Patient With Thymoma and Myasthenia Gravis: A Postviral Autoimmune Process?" *Journal of Neuropathology & Experimental Neurology*, vol. 77, no. 8, 2018, pp. 661–664., doi:10.1093/jnen/nly041.

4. Finsterer J, Stollberger C. "Stress from Myasthenic Crisis Triggers Takotsubo (broken heart) Syndrome." *Int J Cardiol* 2016; 203: 616-617.

5. Hofstad H, Ohm OJ, Mork SJ, et al. "Heart disease in myasthenia gravis." *Acta Neurol Scand*. 1984; 70:176-184.

6. Romi F, Skeie G, Gilhus N, Aarli J. "Striational Antibodies in Myasthenia Gravis: reactivity and possible clinical significance." *Arch Neurol* 2005;62(3): 442-446.

7. Shivamurthy, Poojita, and Matthew W. Parker. "Cardiac Manifestations of Myasthenia Gravis: A Systematic Review." *IJC Metabolic & Endocrine*, vol. 5, 2014, pp. 3–6., doi:10.1016/j.ijcme.2014.08.003.

8. Suzuki, Shigeaki, et al. "Three Types of Striational Antibodies in Myasthenia Gravis." *Autoimmune Diseases*, vol. 2011, 2011, pp. 1–7., doi:10.4061/2011/740583.

9. Glennon, P. E., et al. "Fatal Giant Cell Myocarditis after Resection of Thymoma." *Heart*, vol. 75, no. 5, 1996, pp. 531–532., doi:10.1136/hrt.75.5.531.

10. Suzuki, Shigeaki, et al. "Nivolumab-Related Myasthenia Gravis with Myositis and Myocarditis in Japan." *Neurology*, vol. 89, no. 11, 2017, pp. 1127–1134., doi:10.1212/wnl.0000000000004359.

11. Rota, Eugenia, et al. "Concomitant Myasthenia Gravis, Myositis, Myocarditis and Polyneuropathy, Induced by Immune-Checkpoint Inhibitors: A Life–Threatening Continuum of Neuromuscular and Cardiac Toxicity." *ENeurologicalSci*, vol. 14, 2019, pp. 4–5., doi:10.1016/j.ensci.2018.11.023.

12. So, Hayato, et al. "PD-1 Inhibitor-Associated Severe Myasthenia Gravis with Necrotizing Myopathy and Myocarditis." *Journal of the Neurological Sciences*, vol. 399, 2019, pp. 97–100., doi:10.1016/j.jns.2019.02.023.

13. Yamamoto, Ana Maria, et al. "Anti-Titin Antibodies in Myasthenia Gravis." *Archives of Neurology*, vol. 58, no. 6, 2001, p. 885., doi:10.1001/archneur.58.6.885.

14. Wanner, William R., et al. "Postoperative Pericarditis Following Thymectomy for Myasthenia Gravis." *Chest*, vol. 83, no. 4, 1983, pp. 647–649., doi:10.1378/chest.83.4.647.

15. Hikosaka, Yu, et al. "Post-Irradiation Constrictive Pericarditis Following Thymoma Treatment: a Report of Two Cases." *General Thoracic and Cardiovascular Surgery*, vol. 63, no. 7, 2013, pp. 413–415., doi:10.1007/s11748-013-0302-9.

16. Călin C, Savu O, Dumitru D, Ghiorghiu I, Călin A, Capraru C, Popescu BA, Croitoru M, Vîlciu C, Ginghină C. Cardiac involvement in myasthenia gravis--is there a

specific pattern? Rom J Intern Med. 2009;47(2):179-89. PMID: 20067169.

17. Mygland A, Gilhus NE, Hofstad H, Aarli JA, Thunold S. Hjerteaffeksjon ved myasthenia gravis [Heart disease in myasthenia gravis]. Tidsskr Nor Laegeforen. 1990 Apr 10;110(10):1209-11. Norwegian. PMID: 2333646.

18. Kaustubh Limaye, Shrikanth Vallurupalli, Ricky W. Lee, Myasthenia of the Heart, The American Journal of Medicine, Volume 129, Issue 6, 2016, Pages e19-e21, ISSN 0002-9343.

GNE myopathy with thrombocytopenia: a case report and review of the literature

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Keywords: *muscle disease, GNE, GNE myopathy, genetic testing, thrombocytopenia, leukopenia*

Case description

A 34-year-old man presented with bilateral leg weakness that had been slowly progressive for 3 years. At the initial visit, he reported bilateral foot drop, left being worse than right. He denied weakness in the upper extremities or sensory symptoms. Past medical history was unremarkable, and there was no family history of neuromuscular disorders. Neurologic exam revealed normal mentation, language and cranial nerve examination. Muscle strength exam revealed the following (Medical Research Council scale): shoulder abductors 4, elbow flexors 5, elbow extensors 5, finger abductors 3, deep finger flexors 4, hip flexors 3, knee extensors 4, knee flexors 3, dorsiflexors 2, and plantar flexors 2. Diffuse hyporeflexia was present. The remaining neurological examination was unremarkable.

Blood tests for electrolytes, thyroid, renal and liver function, and immunological evaluation were normal. Serum creatine kinase was elevated at 498 U/L (normal range: 51 to 298 U/L). Electrodiagnostic testing revealed the presence of short-duration and small-amplitude motor unit potentials and fibrillations/positive sharp wave discharges in the distal and proximal muscles of the left upper and lower extremities. Pulmonary function test and echocardiogram revealed normal findings. Genetic panel analysis of 98 myopathy-causative genes identified the following findings in the glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (*GNE*) gene (NM.001128227): a nonsense c.1937C>G (p.Ser646Ter) and a missense c.304 A>T (p.Arg102Trp) mutation. The c.1937C>G mutation resulting in the creation of a stop codon was previously reported as being pathogenic for GNE myopathy.[1] Homozygous c.304 A>T mutation was previously detected in a 44-year-old female with GNE myopathy.[1] Parental analysis of our patient revealed that he was a compound heterozygote for these mutations, confirming the diagnosis of GNE myopathy.

During myopathy evaluation, patient was noted to have reduced platelet count of 91, 000 cells/μl (normal range: 150,000 to 400,000 cells/μl), leukocyte count of 2,700 cells/μl (normal range: 3,700 to 11,000 cells/μl) and neutrophil count of 1,200 cells/μl (normal range: 1,450 to 7,500 cells/μl). Peripheral blood smear showed normal blood cell morphology. A bone marrow aspiration showed no evidence of increased blasts or significant morphologic dysplasia. Ultrasound of abdomen revealed the presence of mild splenomegaly. A hematological evaluation did not reveal an etiology for his abnormal blood count. No prior excessive bleeding tendency or frequent infection was encountered.

Discussion

As a rare form of hereditary inclusion body myopathy, GNE myopathy is a slowly progressive adult-onset myopathy that preferentially affects the tibialis anterior muscle. Muscle histopathology typically reveals fiber atrophy with rimmed vacuoles in the absence of inflammation. In the literature, several reports described occurrence of thrombocytopenia in patients with *GNE* mutations.[2-8] In these patients, thrombocytopenia can be mild without clinically evident platelet dysfunction, similar to our patient.[2] However, thrombocytopenia can also be severe, occurring in early infancy, resulting easy bruising, epistaxis, menorrhagia, hemorrhage or hematoma.[4,7] Cases of requiring red blood cell and platelet transfusions were previously described.[7] On peripheral blood smear analysis, platelets tend to be abnormally large in GNE myopathy patients.[4,6-8]

Thrombocytopenia and myopathy due to *GNE* mutations may occur on the same individual or separately. Revel-Vilk et al. described 9 individuals with thrombocytopenia due to *GNE* mutations. In their report, 8 patients had no evidence of myopathy and the remaining patient had muscle weakness but muscle biopsy did not reveal typical findings of GNE myopathy.[7] A national database of GNE myopathy reported that 3 of 121(2.5%) Japanese patients with GNE myopathy reported thrombocytopenia.[3] Table 1 lists all reported patients with *GNE* mutations and thrombocytopenia. Among the 10 patients in Table 1, 5 were given diagnoses of idiopathic or immune-mediated thrombocytopenia, and 2 patients were found to have splenomegaly. In all patients, thrombocytopenia occurred earlier than myopathy or was found during the workup for myopathy.

Thrombocytopenia in *GNE* myopathy is likely secondary to shortened platelet lifetime rather than ineffective thrombopoiesis. The *GNE* enzyme is responsible

for intracellular sialic acid synthesis. Sialic acid residues are important for platelet longevity, and proper aggregation and adhesion. Without proper sialylation of the cell wall, platelets cannot aggregate properly and are cleared more rapidly from the peripheral circulation.[7]

In our patient, mild leukopenia and neutropenia were observed, together with thrombocytopenia. Such a presentation has not been described previously in individuals with *GNE* mutations. We are unsure whether the occurrence of leukopenia and neutropenia is secondary to splenomegaly in our patient. As the *GNE* enzyme is expressed within all cells of the hematopoietic lineage, it is possible that the mutation may also result in leukopenia and neutropenia.

In patients who are highly suspected of having an inherited myopathy, a finding of unexplained thrombocytopenia, including a prior history of idiopathic thrombocytopenia, should bring GNE myopathy to the forefront of differential diagnosis.

Abbreviation

GNE : UDP-N-acetyl)-2-epimerase/
N-acetylmannosamine kinase

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References

1. Saechao C, Valles-Ayoub Y, Esfandiarifard S, et al. Novel GNE mutations in hereditary inclusion body myopathy patients of non-Middle Eastern descent. *Genet Test Mol Biomarkers*. 2010;14(2):157-162.

2. Zhen C, Guo F, Fang X, Liu Y, Wang X. A family with distal myopathy with rimmed vacuoles associated with thrombocytopenia. *Neurol Sci*. 2014;35(9):1479-1481.

3. Mori-Yoshimura M, Hayashi YK, Yonemoto N, et al. Nationwide patient registry for GNE myopathy in Japan. *Orphanet J Rare Dis*. 2014;9:150.

4. Izumi R, Niihori T, Suzuki N, et al. GNE myopathy associated with congenital thrombocytopenia: a report of two siblings. *Neuromuscul Disord*. 2014;24(12):1068-1072.

5. Behnam M, Jin-Hong S, Kim D-S, Basiri K, Nilipour Y, Sedghi M. A novel missense mutation in the GNE gene in an Iranian patient with hereditary inclusion body myopathy. *J Res Med Sci*. 2014;19(8):792-794.

6. Paul P, Liewluck T. Distal myopathy and thrombocytopenia due to a novel GNE mutation. *J Neurol Sci*. 2020;415:116954.

7. Revel-Vilk S, Shai E, Turro E, et al. GNE variants causing autosomal recessive macrothrombocytopenia without associated muscle wasting. *Blood*. 2018;132(17):1851-1854.

8. Futterer J, Dalby A, Lowe GC, et al. Mutation in GNE is associated with severe congenital thrombocytopenia. *Blood*. 2018;132(17):1855-1858.

Table 1. Cases of GNE myopathy with thrombocytopenia

Source	No. of patients	Mutation	Onset age of myopathy	Onset age of thrombocytopenia	Hematology workup
Zhen (2014)	2	p.Tyr217His and p.Asp546Glnfs*2 for both	Indiv 1: 25 years Indiv 2: 24 years	Indiv 1: 29 years Indiv 2: 26 years	Platelet count of 36,000 cells/µl for indiv 1, and 45,000 cells/µl for indiv 2. Megakaryocytes in the bone marrow increased for both subjects.
Mori-Yushimura (2014)	3	Indiv 1: p.Arg420X and p.Val572Leu Indiv 2: p.383insT and p.Val572Leu Indiv 3: p.Arg8X and P.Val572Leu	NA	NA	Platelet count of 9,500 cells/µl for indiv 1, 10,300 cells/µl for indiv 2 and 7,100 cells /µl for invid 3. All three were diagnosed as with idiopathic thrombocytopenia.
Izumi (2014)	2	p.Val603Leu and p.Gly739Ser for both	Indiv 1: adolescence Indiv 2: 18 years	Indiv 1: neonate Indiv 2: 2 years	Platelet count of 1,700-16,200 cells/µl for indiv 1, and 1,100-9,000 cells/µl for indiv 2. Bone marrow megakaryocytes increased for indiv 1 and normal for indiv 2. Splenomegaly for indiv 2.
Behnam (2014)	1	p.Cys612Gly	28 years	unclear	History of immune hrombocytopenic purpura
Paul (2020)	1	p.Leu634Phe and p.Arg42Gln	Twenties years	4 years	Platelet count of 71,000 cells/µl, and bone marrow showed increased megakaryocytes and abnormal platelet morphology. Diagnosed with idiopathic thrombocytopenia.
Our patient	1	p.Ser646X and p.Arg102Trp	31 years	Detected during myopathy evaluation	Platelet count of 91, 000 cells/µl, leukocyte count of 2,700 cells/µl and neutrophil count of 1200 cells/µl. Bone marrow exam normal. Splenomegaly present.

Abbreviations: GNE, UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase; indiv, individual

MuSK+ Myasthenia Gravis Presenting with Severe Sleep Apnea, Respiratory Dysfunction and Response to Rituximab

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Keywords: *Myasthenia gravis, MuSK myasthenia, respiratory, neuromuscular junction, apnea, hypoventilation*

Introduction

MuSK+ MG is a rare subtype of MG that affects predominantly female individuals and manifests with striking features of cranial, bulbar and respiratory muscle weakness during the disease course (1). Isolated or predominantly respiratory failure is rare at presentation, however progression to severe bulbar weakness and respiratory crisis are distinctive features of MuSK+ MG, which poses significant diagnostic challenges, considering the low prevalence of the disease (2-4). Furthermore, patients frequently have poor response to standard immunotherapies and higher rate of life-threatening crisis, adding significant challenges for disease management. We report a case of reversible respiratory muscle dysfunction at disease onset, leading to dyspnea, sleep apnea and hypoventilation in a patient with MuSK+ MG. While it is acknowledged that the current case is a rare presentation of a rare disease, it raises a number of treatment considerations and as such we wish to highlight these features through this report.

Case Report

Clinical presentation and initial investigations

A 53-year-old woman presented to the emergency department with dyspnea and orthopnea that progressed over 5 months. Past medical history was relevant for type 2 diabetes (HbA1C of 6.4%, without any micro or macrovascular complications), hypertension and depression. She had recently been diagnosed with severe obstructive sleep apnea (OSA). The sleep study done at another facility showed a total apnea-hypopnea index (AHI) of 53.4/hour in NREM and 63.1/hour in REM sleep, along with sustained oxygen desaturation suggestive of hypoventilation (minimum saturation of 55.1% and 94.8% time spent below 90% saturation). On initial neurologic examination, cranial nerves were normal. There was no facial, or bulbar weakness, ptosis or restricted ocular movements and palate elevation was symmetric. Muscle power was mildly reduced in neck extension/flexion, arm abductors and hip flexors (4+/5 MRC - Medical Research Council muscle scale). She had an unremarkable cardio-respiratory examination and was of normal body mass index (BMI).

Nocturnal non-invasive ventilation with bi-level positive airway pressure ST (Resmed Stellar™ 150) plus supplemental oxygen was started following her admission to hospital. She required an inspiratory positive airway pressure (IPAP) of 21cmH2O, an expiratory positive airway pressure (EPAP) of 9cmH2O and a backup rate of 16 breaths per minute to abolish the obstructive events and improve gas exchange.

Chest CT was normal, with no mediastinal or pulmonary masses, infiltrative or infectious processes. Diaphragm M mode/two-dimensional B mode ultrasound imaging during quiet inspiration showed normal baseline thickness and a normal thickening fraction of 35% with inspiration. A transthoracic echocardiogram was normal. Forced vital capacity (FVC) was 1.18 liters seated and 0.69 liters supine (supine: seated FVC difference of 41.5%). Venous blood gas measurements showed pH of 7.38, pCO2 of 60mm Hg, pO2 of 52mmHg, HCO3 of 36 mmol/L. Phrenic nerve conduction studies were normal. Repetitive nerve stimulation of the facial and accessory nerves showed no significant decrement in amplitude (4% in the frontalis, 2% in trapezius). Electromyography of the upper limb

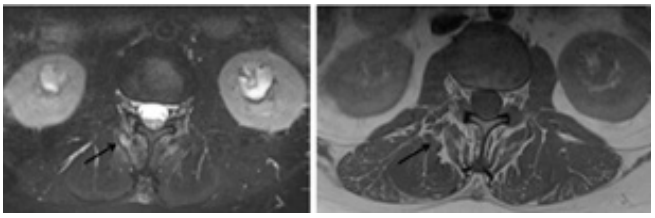

Figure 1. Axial T2 images with fat suppression of the lumbar paraspinal muscles showing atrophy of the intrinsic paraspinal musculature and fatty replacement at L3 spinal level (arrows).

muscles was normal, but there were myopathic motor unit action potentials and early recruitment in the hip flexors and paraspinal muscles, with fibrillation potentials and complex repetitive discharges. MRI spine showed atrophy and edema of the intrinsic paraspinal musculature, fatty replacement, with normal sign and muscle volumes in bilateral hip and thigh muscles (Figure 1). CK was 39 U/L (normal <149). A dried blood spot test for acid maltase deficiency was normal.

A latissimus dorsi biopsy was done in the seated position as she could not tolerate prone position due to respiratory distress. A Next Generation Sequencing gene panel including 90 genes encompassing limb-girdle muscular dystrophies, rigid spine, nemaline, myofibrillar and centronuclear myopathies, inclusion myopathies, metabolic myopathies and congenital myasthenic syndromes was also done and did not find any pathogenic gene mutations or variants of unknown significance. Single-fiber EMG of the frontalis muscle was abnormal, showing 56% abnormal pairs, 44% blocking and mean elevated jitter at 270.1µs. Acetylcholine receptor (AchR), low-density lipoprotein receptor-related protein 4 (LRP4), and Anti-MUSK antibodies were requested.

Clinical Progression and Treatment

Symptoms progressed over the next month with increased dyspnea and orthopnea, new-onset diplopia, mild dysphagia and dysarthria, mild left-sided fatigable ptosis, mild bilateral facial weakness and restricted extra-ocular movements with diplopia on extreme gaze. The patient developed a constant head drop (neck extension 3/5 MRC), and strength was reduced in the hip and shoulder girdle muscles. Myasthenia Gravis Foundation of America (MGFA)(5) class was IVb, as defined as severe weakness predominantly affecting oropharyngeal and respiratory muscles. Myasthenia Gravis Impairment Index (MGII)(6) was 46 out of 84 possible points (higher scores meaning more severe disease) and she was again admitted to the hospital to facilitate treatment and for monitoring.

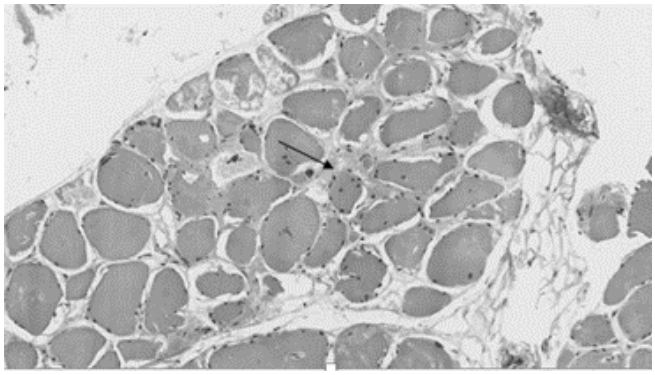

Figure 1. Morphological findings in latissimus dorsi muscle biopsy showing moderate variability in fiber size, scattered atrophic fibers and focal endomysial fibrosis (arrow).

A formal clinical swallowing assessment was not suggestive of pharyngeal propulsion impairment and there were no signs of laryngeal penetration. Muscle biopsy showed focal endomysial fibrosis, fatty infiltration, normal glycogen content and no inflammatory changes (Figure 2). Gomori trichrome did not show any ragged red fibres, nemaline bodies or rimmed vacuoles. NADH showed normal checkerboard pattern without cores. PAS showed normal glycogen content and ORO showed normal lipid content. Congo red did not demonstrate any amyloid deposit. Immunostain for TDP-43 was negative.

Acetylcholine receptor (AchR) and low-density lipoprotein receptor-related protein 4 (LRP4) were negative. Anti-MUSK antibodies were positive, with high titers at 52 nmol/L (normal <13nmol/L), confirming the diagnosis of MUSK+ MG.

During this hospitalization she received a 5-day course of intravenous immunoglobulin (IVIG, 2g/Kg), and started a course of oral prednisone at a dose of 50mg/day (0.6mg/Kg/day). This therapy was chosen due to the recent progression of weakness, head drop, respiratory and bulbar symptoms given the likely favorable/fast response in severe sudden clinical deterioration. Plasmapheresis was considered, but given the restricted availability, this treatment was deferred and would be considered in case of further deterioration. Over the following two weeks, she had a significant improvement in diplopia/ptosis, however, no effect on respiratory and bulbar dysfunction, which prohibited safe discharge from hospital.

She was subsequently started on Rituximab infusions (710mg intravenous once a week, corresponding to approximately 375 mg/m2) and after the second infusion she had a significant improvement of her overall strength, shortness of breath and orthopnea; complete resolution of diplopia, ptosis, dysarthria and dysphagia. Given the clinical improvement and to minimize time in hospital, the remaining 2 weekly infusions were performed in an infusion centre, as the first wave of the COVID-19 pandemic accelerated in the Province of Ontario, including outbreaks in the hospital where she was admitted.

One month after the last rituximab infusion, she had a significant improvement of her neck weakness, without any need to support her head (MRC 4) and could ambulate for several blocks with no shortness of breath. There was minimal proximal weakness in her lower limbs (4+) and no fatigability. MGII score was 3 out of possible 64 points on the score questionnaire. MGFA class was now IIIb. Prednisone was progressively tapered to 10mg over the following 2 months to optimize type 2 diabetes mellitus control. Her IPAP settings were adjusted to 14cm H_2O,

EPAP to 8cmH2O, improved since the initial adjustment, with complete resolution of her sleep apnea symptoms. Arterial blood gas measurements normalized: pH of 7.42, pCO2 of 31mm Hg, pO2 of 104 mm Hg, HCO3 of 20 mmol/L. Additionally, at the 3-month mark, there was a significant improvement in FVC (3.3 litres), respiratory pressures were also normal (MIP 60cmH2O, MEP 95cm H2O, SNIP max 91cmH2O). She could lie flat for longer periods and no longer experienced orthopnea.

Discussion

We report a 53-year-old woman presenting with dyspnea and sleep apnea for 6 months and mild proximal weakness on examination who demonstrated myopathic changes on paraclinical tests and was ultimately diagnosed with MuSK +myasthenia gravis. She exhibited partial response to IVIG and steroids and subsequent near complete response to Rituximab. Although there have been previous reports of MuSK + MG producing respiratory dysfunction, myopathic changes and response to Rituximab, our case is unique due to the early presentation with isolated sleep apnea and hypoventilation, followed by mild limb and bulbar weakness, severe neck weakness, the comprehensive clinical neuromuscular characterization, association with markedly high MuSK antibody titres and treatment decisions posed by the rapidly progressing COVID-19 pandemic.

Isolated respiratory dysfunction at presentation has been reported in a minority (2% of patients) in two large cohorts and in smaller case series of patients which included MuSK+ MG. (2-4). In spite of the rarity of a respiratory presentation, respiratory crisis (MGFA class V) can occur at some point in the disease course in 32 to 52% of MuSK+ MG cases reported in the literature (1, 7). Our patient developed mild limb and bulbar weakness and neck weakness only after presenting with respiratory dysfunction for 6 months, imposing significant challenges for clinical diagnosis and treatment.

In the only previously reported case of MuSK+ MG presenting with severe OSA (AHI of 31/hour), the patient had concurrent bulbar dysfunction as part of their presentation, something not observed in our case initially. An increased prevalence of sleep disordered breathing/ OSA has been reported in some studies including patients who are AChR antibody positive as well as in children with MG (8, 9); however, not all studies have found this association (10). In a recent single-center study, the risk of OSA in MG patients was associated with the same risk factors as the overall population, including male sex and obesity (11). Risk factors leading to sleep apnea in MuSK+ MG are lacking in the literature, and notably our patient was neither male nor obese. She also did not have prominent bulbar symptoms until later in the disease course, which has also been implicated as a cause of airway obstruction during sleep leading to apnea. As such, it is difficult to conclusively determine the mechanism leading to OSA in our patient, however, the marked improvement in OSA after immunotherapy implicates MG as the major reason for this finding.

Our patient did appear to show signs of diaphragmatic dysfunction which was worse in REM sleep and associated with supine changes in FVC of 41.5%, exceeding the 25% limit, which is usually associated with diaphragmatic weakness (12). In our patient, normal diaphragmatic ultrasound and evidence of myopathic changes in the paraspinal and proximal muscles tested indicates that the diaphragm was neither the sole driver of respiratory dysfunction nor severely damaged or atrophied (13). We could not directly assess whether myopathic changes in respiratory muscles could have contributed to her respiratory weakness, as we did not perform electromyography of the diaphragm or intercostal muscles. Hemidiaphragm atrophy has been reported in one patient with MuSK+ MG who presented with isolated dyspnea and had decreased diaphragmatic thickness and excursion with inspiration (12). This is in contrast to our patient with normal thickness and thickening fraction, and is not surprising given the reversible nature of the respiratory deficits.

Chronic myopathic changes including muscle atrophy and fatty replacement on MRI imaging in limb, facial and ocular muscles have been previously reported in patients with MuSK + MG (14, 15). Experimental studies suggest that MuSK plays a significant role in the development and maintenance of the neuromuscular junction, with anterograde and retrograde signaling roles, resulting in AChR clustering in the post-synaptic folds, a process essential for neuromuscular transmission (16). Histologic analysis in MuSK+ MG involved muscles shows increase in cytochrome c oxidase (COX)-negative fibres, mitochondrial aggregates and myofibrillar disarray, implicating mitochondrial dysfunction as a contributor to pathophysiology (14, 17, 18). Our patient had edema and fatty replacement of the intrinsic paraspinal muscles, along with chronic myopathic changes, which indicate that part of her weakness might be due to an underlying myopathic process. An extended genetic panel for myopathy was negative, and as such, the possibility of a concomitant hereditary myopathy is highly unlikely. After confirming the diagnosis of MuSK + MG, additional staining and electron microscopy were deferred.

We believe that the clinical presentation in our patient could be related to markedly elevated serum concentrations

of MuSK Immunoglobulin G4 (IgG4) antibodies, as those levels correlate with clinical changes (1, 19). High levels of MuSK antibodies have been associated with severe presentations, such as respiratory failure, as was the case in our patient. To our knowledge this is the highest reported antibody titer (52 nmol/L) as compared to other cases in the literature (4, 20). Also, improvement in response to Rituximab infusions seems to correlate with MuSK antibody titers as was the case in our patient (20). In recent years, there is growing evidence that Rituximab treatment in refractory MG, particularly MuSK+ MG leads to significant and sustained improvement and should be considered an early therapeutic option in severe cases (3, 21, 22).

Although steroids can induce early clinical remission in some MuSK+ patients, progressive deterioration often occurs in spite of prolonged, high dose steroids and can result in a fixed steroid-induced myopathy (1, 23, 24). Our patient experienced improvement in bulbar and respiratory function only after the first Rituximab infusion, in contrast to IVIG and steroid treatment, which only resulted in improvement of the ocular symptoms. Although some patients can have a delayed response to steroid or IVIG treatment, this is uncommon, and in our case, it was felt that the additional time spent in the hospital waiting for a response would confer additional risk of COVID-19 infection. Although the MGFA COVID-19 management recommendations (25) state that other immunomodulatory treatments should be considered prior to Rituximab, we propose this clinical scenario as one example where this treatment should be considered early, and ideally while self-isolating.

In summary, we highlight through this case that respiratory muscle dysfunction leading to dyspnea and hypoventilation can be an isolated presentation of MuSK + MG. Our case further provides evidence that myopathic changes can occur in MuSK + MG and contribute to respiratory symptoms through reversible dysfunction of diaphragm and accessory breathing muscles. Additionally, in patients being considered for neuromuscular causes of respiratory dysfunction including sleep apnea, single fiber EMG and reflexive MG antibody panels, including MuSK testing is necessary to completely exclude patients with MuSK+ MG who can present in this manner. Finally, we recommend that early treatment with Rituximab should be considered in bulbar and respiratory presentations of MUSK+ MG, as this can cause rapid improvement and avoid complications and ineffectiveness of more traditional immunotherapy.

References

1. Evoli A, Alboini PE, Damato V, Iorio R, Provenzano C, Bartoccioni E, et al. Myasthenia gravis with antibodies to MuSK: an update. Ann N Y Acad Sci. 2018;1412(1):82-9.
2. Evoli A, Tonali PA, Padua L, Monaco ML, Scuderi F, Batocchi AP, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain. 2003;126(Pt 10):2304-11.
3. Guptill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. Muscle Nerve. 2011;44(1):36-40.
4. Sanders DB, El-Salem K, Massey JM, McConville J, Vincent A. Clinical aspects of MuSK antibody positive seronegative MG. Neurology. 2003;60(12):1978-80.
5. Jaretzki A, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg. 2000;70(1):327-34.
6. Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM. Development and validation of the Myasthenia Gravis Impairment Index. Neurology. 2016;87(9):879-86.
7. Padua L, Tonali P, Aprile I, Caliandro P, Bartoccioni E, Evoli A. Seronegative myasthenia gravis: comparison of neurophysiological picture in MuSK+ and MuSK- patients. Eur J Neurol. 2006;13(3):273-6.
8. Prudlo J, Koenig J, Ermert S, Juhász J. Sleep disordered breathing in medically stable patients with myasthenia gravis. Eur J Neurol. 2007;14(3):321-6.
9. Katzberg HD, Vajsar J, Vezina K, Qashqari H, Selvadurai S, Chrestian N, et al. Respiratory Dysfunction and Sleep-Disordered Breathing in Children With Myasthenia Gravis. J Child Neurol. 2020;35(9):600-6.
10. Fernandes Oliveira E, Nacif SR, Alves Pereira N, Fonseca NT, Urbano JJ, Perez EA, et al. Sleep disorders in patients with myasthenia gravis: a systematic review. J Phys Ther Sci. 2015;27(6):2013-8.
11. Heo SJ, Jun JS, Park D, Lee HW, Kim JS, Park JS. Characteristics of obstructive sleep apnea in myasthenia gravis patients: a single center study. Neurol Sci. 2019;40(4):719-24.
12. Fromageot C, Lofaso F, Annane D, Falaize L, Lejaille M, Clair B, et al. Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil. 2001;82(1):123-8.
13. Sarwal A, Walker FO, Cartwright MS. Neuromuscular ultrasound for evaluation of the diaphragm.

Muscle Nerve. 2013;47(3):319-29.

14. Nikolić AV, Bačić GG, Daković M, Lavrnić S, Rakočević Stojanović VM, Basta IZ, et al. Myopathy, muscle atrophy and tongue lipid composition in MuSK myasthenia gravis. Acta Neurol Belg. 2015;115(3):361-5.

15. Zouvelou V, Rentzos M, Toulas P, Evdokimidis I. MRI evidence of early muscle atrophy in MuSK positive myasthenia gravis. J Neuroimaging. 2011;21(3):303-5.

16. Niks EH, Kuks JB, Wokke JH, Veldman H, Bakker E, Verschuuren JJ, et al. Pre- and postsynaptic neuromuscular junction abnormalities in musk myasthenia. Muscle Nerve. 2010;42(2):283-8.

17. Martignago S, Fanin M, Albertini E, Pegoraro E, Angelini C. Muscle histopathology in myasthenia gravis with antibodies against MuSK and AChR. Neuropathol Appl Neurobiol. 2009;35(1):103-10.

18. Cenacchi G, Papa V, Valentina P, Fanin M, Marina F, Pegoraro E, et al. Comparison of muscle ultrastructure in myasthenia gravis with anti-MuSK and anti-AChR antibodies. J Neurol. 2011;258(5):746-52.

19. Niks EH, van Leeuwen Y, Leite MI, Dekker FW, Wintzen AR, Wirtz PW, et al. Clinical fluctuations in MuSK myasthenia gravis are related to antigen-specific IgG4 instead of IgG1. J Neuroimmunol. 2008;195(1-2):151-6.

20. Marino M, Basile U, Spagni G, Napodano C, Iorio R, Gulli F, et al. Long-Lasting Rituximab-Induced Reduction of Specific-But Not Total-IgG4 in MuSK-Positive Myasthenia Gravis. Front Immunol. 2020;11:613.

21. Iorio R, Damato V, Alboini PE, Evoli A. Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. J Neurol. 2015;262(5):1115-9.

22. Tandan R, Hehir MK, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: A systematic review. Muscle Nerve. 2017;56(2):185-96.

23. Evoli A, Bianchi MR, Riso R, Minicuci GM, Batocchi AP, Servidei S, et al. Response to therapy in myasthenia gravis with anti-MuSK antibodies. Ann N Y Acad Sci. 2008;1132:76-83.

24. Evoli A, Padua L. Diagnosis and therapy of myasthenia gravis with antibodies to muscle-specific kinase. Autoimmun Rev. 2013;12(9):931-5.

25. Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, Howard JF, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci. 2020;412:116803.

Comparative Effectiveness of Intravenous Immunoglobulin (IVIg) and Subcutaneous Immunoglobulin (SCIg) versus Historical Controls in Management of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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Grant was: Not Funded

This was a grant we submitted to PCORI as a comparative effectiveness study comparing IVIg and SCIg for CIDP. It was reviewed but not funded. We believe there was and is merit in such a study and therefore are publishing our grant and the critiques for others to read. We may try to pursue this avenue again in the future, but if others are willing to try to get such a study funded they are welcome to see our work as it might be helpful. The proposed study would randomize 50 CIDP patients, in an open label prospective design, to IVIg or SCIg. The IVIg arm would receive a loading dose of 2g/kg followed by 1 gm/kg every three weeks for 24 weeks. The SCIg arm would receive 0.4 gm/kg weekly divided over three days per week for 24 weeks. The SCIg group would get no prior IV loading dose. So, we were asking both: are the treatments comparable, and do SC patients need a loading dose? The endpoint measure was the INCAT scale and we used the definition of improvement used in the pivotal ICE trial (1). In that trial the placebo group had a 22.4% response rate. We considered this a historical placebo control group. Therefore, the primary analysis was to determine the proportion of favorable outcomes that is bigger than or equal to 22.4%. We prespecified that a clinically relevant effects size would be 25% absolute difference in favorable outcome proportions. To achieve 80% power, we needed 25 subjects in each group. The study planned to leverage the Greater Plains Collaborative (GPC) PCORnet which at the time included Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic , Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio and University of Texas Southwestern Medical Center.

We are attaching the Research Plan and the PCORI Summary Statement/Critiques. The reviewers appreciated the question we were trying to address although they were not very impressed that we were willing to tackle the comparison of IVIg to SCIg. We clearly did not explain the issue well as one reviewer said we did not describe or give data on the number of patients that seek IV versus subcutaneous treatment. We did not explain well that currently all patients begin with IV and then some choose to be converted and that this trial was a head to head comparison of IVIg versus SCIg as initial treatments. One reviewer was critical that we did not have insurance companies as stakeholders. They were critical that our dissemination plan did not include venues outside of the neurology world. We had neurologists at all GPC sites do letters of support but one reviewer sited as a major weakness that they were identical template letters and did not include what they would have considered statements of interest or demonstrate a need to answer the clinical question. One reviewer stated that while we adhered to PCORI Methodology Standards, they were skeptical about our use of what we called "historical controls" from the ICE study. They were critical for not justifying the effect size of 25% we said we could demonstrate with 50 subjects and this is probably a reasonable criticism. As usual, they were skeptical due to all my administrative responsibilities whether I would have time to devote to this study! A frequent criticism when I submit grants, but on the other hand they always say my background is ideal to do studies like these.

As you can see, PCORI reviewers are tough. And the critiques are different from NIH critiques. There is always a lot of emphasis on whether we have patient engagement, have adequate stakeholders, and conform to PCORI methodology. We do not know if we will try again to do a CER like this. If any of you want to take it on, we hope our proposal and the critiques will be helpful.

Reference

1. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate- chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial. Lancet Neurol 2008; 7: 136-144.

RESEARCH STRATEGY

A. Specific Aims

Chronic Inflammatory Demyelinating Neuropathy (CIDP) is an acquired autoimmune neurological condition that affects about 4.7 per 100,000 people. Intravenous immunoglobulin (IVIg) has been approved for treatment of CIDP based on prior trials showing its efficacy[15] and recently the PATH study compared relapse rates in patients given subcutaneous immunoglobulin (SCIg) versus placebo in patients who responded to IVIg previously and has shown SCIg to be more efficacious than placebo[18]. A meta-analysis of studies looking at SCIg vs IVIg in CIDP and Multifocal Motor Neuropathy (MMN) patients showed no difference in the motor strength outcomes in the two groups and efficacy of SCIg is similar to IVIg for CIDP and MMN and has significant safety profile of SCIg, similar to IVIg for CIDP and MMN[21]. In both these studies, patients were already in IVIg before converting to SCIg. However, there is no literature comparing the effectiveness of IVIg with SCIg in CIDP[18]. This study will help address the decision to use either SCIg or IVIg for CIDP. In other words, we will conduct two one-sample tests comparing SCIg vs historical control rate, and separately, IVIg vs historical control rate. This will allow us to assess how each treatment performs relative to control with a sample size of 25 patients in each of the two arms. Otherwise a two-arm (SCIg vs IVIg) comparison would require twice as many patients which would not be feasible for this rare disease.

Aim 1: Determine if IVIg or SCIg in CIDP management is more effective than historical control data
Aim 2. Determine which of the two treatments (IVIg or SCIg) has less side effects

B. Background

CIDP is an acquired neurological, demyelinating neuropathy with an assumed autoimmune mediated pathogenesis. The clinical course can be relapsing/remitting or chronic and progressive,[1, 2] the former being much more common in young adults. The prevalence of CIDP is estimated to be about 4.7 per 100,000 adults[3] and about 0.5 per 100,000 children.[2, 4] In addition to the significant medical burden, it has a significant economic impact, with disease-related expenses and high costs related to the immune therapies used to treat this condition. [5] The first line treatments presently being used include corticosteroids, intravenous immunoglobulins and plasmapheresis.[6] Other immunosuppressive therapies including azathioprine, cyclophosphamide, cyclosporin, etanercept, mycophenolate, rituximab and tacrolimus are considered in patients who do not improve with corticosteroids or have frequent relapses with attempts at weaning the corticosteroids.[7] Although case studies and small series report apparent benefit from each there is no consensus about whether they work and which is the best.[8] Approximately two-thirds of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) need long-term intravenous immunoglobulin.[7, 9] Subcutaneous immunoglobulin (SCIg) recently has been shown to be an option for patients already responding to IVIg.[10] The greatest evidence is in CIDP, otherwise when the decision to use immunoglobulin is considered SCIg is as effective as IVIg for CIDP. There is no data on this. SCIg does not require IV access and patients can self-administer the medication. Then overtime patients can continue to perform their activities of daily living during the treatments. This would lower the burden of the disease and the treatment. Both IVIg and SCIg avoid the complications of prednisone treatment

For this study, we are collaborating with the GBS|CIDP Foundation. The GBS|CIDP Foundation has agreed to allow access and data linkages to their CIDP patient registry, which is managed by the National Organization for Rare Diseases (NORD). By partnering with the GBS|CIDP Foundation and NORD, we will be able to recruit patients from the registry while also providing data and study results to both organizations through the KUMC REDCap database. We are also collaborating with NuFactor, a specialty infusion company. NuFactor has agreed to provide the infusion services to IVIg patients for this study as in-kind support. RMS Medical Products has agreed to collaborate on this study as well. RMS Medical Products is a leading developer and manufacturer of medical devices and supplies. They have agreed to provide

infusion equipment for SCIg patients in in-kind support. Making these important community contributions will bring future rapport between partners and patients with both nonprofit and industry partners. As a result of this relationship, both the GBS| CIDP International Foundation and external industry collaborators are eager to work with other projects stemming from PCORnet especially for immune -related neuropathy research as well as any other disease states that require infusion care.

GPC and PCORnet were new networks in 2013. We now: (1) contribute regularly to large pragmatic observational studies and respond quickly to national queries, (2) are testing PCORnet's capacity to characterize molecular testing and therapeutics, (3) have seen IRB reciprocity in the GPC blossom into SmartIRB nationally, (4) integrate patients and other stakeholders in our networks as collaborators, and (5) account for a third of enrolling ADAPTABLE sites and second by volume.

The University of Kansas Medical Center is the lead site for the Greater Plains Collaborative (GPC), a PCORNet network of 12 leading medical centers in 9 surrounding states. We plan to use each member of the GPC (Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic Research Institute, Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center) as a site for this study.

The GPC network is committed to a shared vision of improving healthcare delivery through ongoing learning, adoption of evidence - based practices, and active research dissemination. The GPC builds on strong research programs at our sites, existing community engagement and informatics infrastructures and data warehouses developed through the NIH Clinical and Translational Science Award (CTSA) initiative at most of our sites, extensive expertise with commercial EHR systems and terminology standardization, and strong working relationships between investigators and healthcare system information technology departments. Our network brings together a diverse population of over 19 million patients across 1,300 miles covering 9 states with a combined area of 679,159 square miles.

GPC has streamlined data governance and technical processes to be highly responsive to PCORnet queries and share opportunities across our communities. Our bi-weekly Data Request Oversight Committee meetings provide a forum for peer discussion amongst data honest brokers, patients, and regulators; making streamlined data access an expectation that benefits PCORnet and our research communities. GPC sites have outstanding response times for menu driven and SAS queries (~5 and 10 days respectively).

The GPC builds on strong research programs at our sites, existing community engagement and informatics infrastructures and data warehouses developed through the NIH Clinical and Translational Science Award (CTSA) initiative at most of our sites, extensive expertise with commercial EHR systems and terminology standardization, and strong working relationships between investigators and healthcare system information technology departments.

Greater Plains Collaborative CDRN Collaboration

Collaboration is critical to address many research questions in clinical and translational sciences. There has been extensive interest from CDRNs, PPRNs, community partners, academia in general, and private industry to collaborate with the Greater Plains Collaborative CDRN.

Collaboration Overview

Collaboration Activities include, but are not limited to, the following:

- Development and validation of computable phenotypes (algorithms to identify patients)
- Prep to Research activities such as obtaining counts for feasibility or sample size estimates
- Research on de-identified and limited electronic health record data
- Identification of patients across the Greater Plains Collaborative CDRN
- Contact of potential study subjects through phone, email, and other modalities

- Survey Research
- Observational research
- Pragmatic clinical research
- Hypothesis Generation
- Stakeholder Engagement (Patients/Families, Clinicians, Clinics, etc)
- Health Information Technology support for patient-facing studies
    - Electronic survey
    - Electronic payment
    - Electronic decision support for trial delivery

GPC pursued several collaborations with the Multiple Sclerosis and DuchenneConnect Patient Powered Networks building upon established relationships between GPC clinicians and patient advocates.

C. Significance

IVIg is an approved treatment for several immunodeficiency syndromes[11-14] and more recently has been approved for the management of two other autoimmune neuromuscular disorders, chronic inflammatory demyelinating polyneuropathy (CIDP)[15] and multifocal motor neuropathy.[16] Intravenous immunoglobulin (IVIg), a pooled gammaglobulin product from several thousand blood donors, has a complex immunomodulatory mechanism of action. It is thought to involve pathogenic autoantibody production modulation and binding inhibition, pro-inflammatory cytokinesuppression, Fc receptor blockade, macrophage colony stimulating factor and monocyte chemotactant protein-1 increase, alteration in T cell function, decrease in circulating CD54 lymphocytes, and inhibition of cell transmigration into the muscle.[17] More recently, investigators from the Rockefeller found that Fc core polysaccharide 2,6-sialylation mediates the anti-inflammatory properties of IVIg.[18]

IVIg is administered as an induction dose of 2 gm/kg over 2 to 5 days, followed by monthly maintenance doses of 0.4-2.0 gm/kg given every 2 to 4 weeks. While it is generally infused no faster than 150 to 200 cc/h, a recent report described infusion rates of up to 800 cc/h in 50 patients, which was reasonably well tolerated.[9] Lee and colleagues treated two CIDP patients with subcutaneous infusion of immunoglobulins (SCIg) after IVIg therapy was shown to be effective.[10] Application of SCIg was well tolerated and led to stabilization of the disease course.[10]

IgPro20 (Hizentra®) is a ready-to-use formulation of human Immunoglobulin with ≥98% purity for subcutaneous (SC) administration. It is approved in the United States of America (US), in the EU, in Switzerland, and in Canada under the brand name Hizentra® for SC application in primary immune deficiency (PID) syndromes, recently FDA approved in US for CIDP and is manufactured at CSL Behring's (CSLB's) facility in Berne, Switzerland. It is a 20% liquid formulation (200 mg/mL) of human normal immunoglobulin for subcutaneous use, administered SC weekly or biweekly (ie-using 2x the weekly dose). Bioavailability and pharmacokinetics of SCIg and intravenous Immunoglobulin (IVIg) differ in patients with primary immunodeficiencies. Based on area under the curve (AUC) of serum Immunoglobulin versus time and trough level ratios (TLRs) on SCIg/IVIg, the mean dose adjustments required for non-inferior AUCs with multiple different SCIg preparations were 142% (± 11, with no real difference between different preparations.[19] However, there were wide variations between adjustments required by different subjects. Combined data from multiple studies allow estimation of the ratio of Immunoglobulin levels with different dose adjustments, and of the steady state serum levels with different SCIg doses. When switching a patient from IVIg to SCIg, individualizing the dosage based on measured serum Immunoglobulin levels and the clinical response is preferable to using mean pharmacokinetic parameters.[19]

Preparation and Planning for Authentic Patient and Stakeholder Engagement: Patients and physicians have shaped the research question from inception, and they strongly endorse the study's approach and intended outcomes. For the proposed intervention, patient partners (those with a lived experience) informed the project from original concept to

implementation plan to help the project be as successful as possible. Additionally, clinicians who provide care also contributed to the design and implementation plan.

The decisional dilemma of choosing between intravenous and subcutaneous delivery presents a challenge for both physician and patient. For the physician, no clear evidence guides a recommendation of one administration route versus the other. Interviews with clinicians, however, revealed biases and assumptions about patient preference for one administration modality vs. the other. These assumptions informed the questions and discussion guide developed to conduct two patient focus groups – one with patients who self-administer Immunoglobulin and one with patients who receive Immunoglobulin therapy at an infusion center or via infusion with support from home health. Each focus group was conducted to encourage a profile of facilitators, barriers and factors operant in the process of selecting the "right" administration option.

We learned that for patients, a wide array of personal, social and cost-related factors are involved with each administration option. A focus group with patients currently receiving Immunoglobulin therapy through home health or by traveling to an infusion center revealed a rich set of personal and social issues that characterize their choice of care. Some focus group participants shared that receiving intravenous medication motivated them to maintain their daily routines of bathing, dressing and leaving their homes for care. Without the need to travel to an infusion center, focus group participants said they feared they would become house-bound or socially isolated. They noted that there is a social solidarity formed with other patients who receive IV care at their local infusion center, and this sustains their positive outlook. For at least one participant however, this value was diminished because all the patients at their site were receiving cancer treatment, so being able to relate in terms of the specific disease attributes of CIDP were absent. For some patients receiving IV care at home, their sense of self-empowerment as well as the care they receive from their families, neighbors and faith community provides them with a sense of support they found reassuring and meaningful. Being home allowed their friends, family and community volunteers to stop by and visit while infusion was occurring, prepare meals in their presence and offer social and emotional support during the process. Some of these participants reported that their community support was crucial by providing them with a planned calendar and system of offering support to enable them to remain in their homes, alone, but getting the care they need. By contrast, patients who self-administer subcutaneous Immunoglobulin report very high self-efficacy and independence that they assume they would lose if they depended on IV administration. The travel costs, time requirements, the dependency-on-others and the rigor of the IV administration process are onerous and perceived to interfere with quality of life. What patients who use subcutaneous Immunoglobulin report is that they feel free to manage their health entirely on their own; in fact they all highlight that they maintain a totally "normal" daily schedule, and that "people have no clue" that they have a medical condition requiring self-care. A few focus group participants likened their choice to someone who has diabetes or other disease requiring self-monitoring and being about to do so with "no one knowing". Not surprisingly, all focus group participants were able to rationalize and support their choice while respecting that others with CIPD made their own personal selection based on their own, personal priorities. What all patients appreciated was that their physician could not use evidence-based research to quantify or adequately describe the advantages and disadvantages of each method (which they would prefer), leaving them instead to consider a variety of non-medical factors.

<u>Engagement Plan:</u> The engagement plan includes the following features to reflect engagement in planning the study, conducting the study and disseminating the study. Each feature also ensures that the four pillars of engagement principles are adhered to: reciprocity, co-learning, partnership and transparency/honesty/trust.

Engagement Feature 1: Patient-Centered Input for Design and Refinement of Research Question
As described above, focus groups of patients who receive Immunoglobulin via the two administration modalities of interest, informed: 1)the factors they most felt were relevant in the selection process and 2) patient reported outcomes of greatest interest. They also emphasized features of their care that were underappreciated by their clinician caregivers (i.e., social connectedness) that should be captured during the study.

Engagement Feature 2: Patient Advisory Council
To ensure that CIDP patients' and caregivers' voices continue to infuse the project, a Patient Advisory Council (PAC) composed of a equal number of subcutaneous and infusion delivered patients and/or their caregivers will collaborate with the research team throughout the conduct of the study and with disseminating findings to diverse audiences. The PAC will meet virtually using Zoom or GotoMeeting so that they may choose to visually be seen by the group (or remain connect via voice only) on a monthly basis. Dr. Kimminau will facilitate the PAC establishing norms and interaction expectations with each other as well as with researchers, statisticians, informaticians and study personnel. Dr. Kimminau will facilitate PAC discussions and she will elicit the PAC's preferred channel(s) for information, desired contact frequency with individuals on the research team and she will serve as a conduit to the project PI (at the direction of the PAC). The PAC may review items such as the informed consent document, project summaries, preliminary reports, statistical/graphical outputs etc. throughout the course of the study. The PAC will be involved extensively in discussion of recruitment and retention of participants in the study as well as guiding how to frame the results of the study to provide the greatest benefit to stakeholders. Our intent is to fully engage the PAC throughout the course of the trial and in every aspect of the study. We recognize that ongoing feedback is essential, and we will ask PAC members for feedback after each conference call and meeting using a group-developed and approved evaluation tool to make adjustments and remain responsive to their ideas of how to improve and perform better as a team.

Engagement Feature 3: Patient Voice Sessions with Investigators and Clinicians
We plan to use what was learned during the formative, development of the research question with patients to expand the opportunity for clinician learning. Asking patients to lead discussions and to share their journey and decision-making process will be illuminating for clinicians and their care teams. Patients using each administration modality have much to offer clinicians in terms of insights to their decision-making process and to the daily challenges they face. This engagement feature will showcase patients as the experts in the lived experience of CIPD in a way not often revealed in non-patient-centered, "traditional" research clinical trials. The addition of this engagement feature is unique and likely to be impactful well beyond the boundaries of this particular trial to the clinicians who offer medical care for this condition.

Engagement Feature 4: Transparency and Processes for Continuous Quality Improvement
When continuous quality improvement (CQI) is included by design, rapid cycles of modification or adjustment result in timely and transparent change. To maintain fidelity to reciprocity, co-learning, partnership and transparency/honesty/trust, the PAC and research team have and will continue to co-develop a set of shared objectives and activities related to the conduct of the study and the dissemination of results. The experience of working together to build and revise this plan using CQI principles will strengthen trust, encourage openness demonstrate the value placed on the partnership with stakeholders

D. Study Design or Approach
This study will be a randomized, open labelled prospective comparative effectiveness trial of IVIg vs SCIg. Fifty patients with either newly diagnosed CIDP (fulfilling the EFNS criteria) or patients who have persistent symptoms needing alternative therapy and/or other immunosuppressive therapies will be invited to enroll in this study. Patients will be randomly allocated to either the IVIg or SCIg arm with a 1:1 randomization. Patients in the IVIg arm will receive 2g/kg bolus treatment with infusions divided over 3 days, followed by 1g/kg every 3 weeks maintenance dose for total of 24 weeks. Patients in the SCIg arm will receive 0.4g/kg weekly infusions divided over 3 days per week for 24 weeks. The dose adjustments will be made based on patient tolerance. While patients receiving IVIg will be given a loading dose of 2g/kg, patients receiving SCIg will start at 0.4g/kg and will remain on that does for the rest of the study.

- ***Data Linkages:***

Our proposal will link GBS|CIDP Foundation Registry with KUMC's study specific REDCap database for consistent data quality, data linkage and recruitment methods to provide a platform for comparing the effectiveness of Intravenous Immunoglobulin (IVIg) vs. Subcutaneous Immunoglobulin (SCIg) in management of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). This proposal will develop an approach with Datavant or a similar linkage solution and its use of data linking to connect Registry with REDCap database.

This study will pursue a data linkage strategy utilizing Datavant or similar technology and hope to enroll subjects in the GBS|CIDP Foundation Registry and integrate Registry with REDCap database for data collection in a streamline fashion. We will also use PCORnet Common Data Model (CDM) at sites to identify and recruit patient and gather patient data using CDM.

The proposal will serve as prototype for linkage technology's ability to target data exchange and trials for specific clinical populations and also leverage pragmatic data collection as a byproduct of healthcare delivery in contract to staffing retention efforts and data abstraction for traditional registries.

The approach will allow us to integrate and analyze data from a variety of sources (e.g. EMR (CDM), Registry, REDCap) to develop a more complete model of health for people with CIDP and understand quality of life (e.g., diagnoses, conditions health outcomes) and environmental (e.g. service utilization, access to services) factors that influence health.

Our goal will be to work collaboratively with program officers and Registry staff/contractors to implement streamlined linkage methods that integrate GBS|CIDP Registry and REDCap database for increasing data richness for CIDP research community.

We will evaluate the applicability of Datavant or similar deidentified linkage software. However, primarily our focus is on utilizing Datavant (https://datavant.com/), which is recently selected by PCORnet for consistent data linkage across its national network. The proposal is to integrate Registry with REDCap database utilizing Datavant to support study population. We are estimating the costs to configure the GBS|CIDP Registry System with Datavant at $40,000.

Datavant is used for data de-identification, patient token creation and token transformation to enable de-identified linking of disparate data sets. Datavant's DeID application transforms input data into de-identified and tokenized output data.

DeID application creates irreversible, site-specific tokens by involving Hashing and Encryption. Hashing makes tokens irreversible, securing from employee or business associate regulatory violations. Encryption makes tokens site-specific, protecting each site from a partner's security breach (Figure 1).

The Link application enables secure transfer of tokens within Datavant ecosystem (Figure 1).

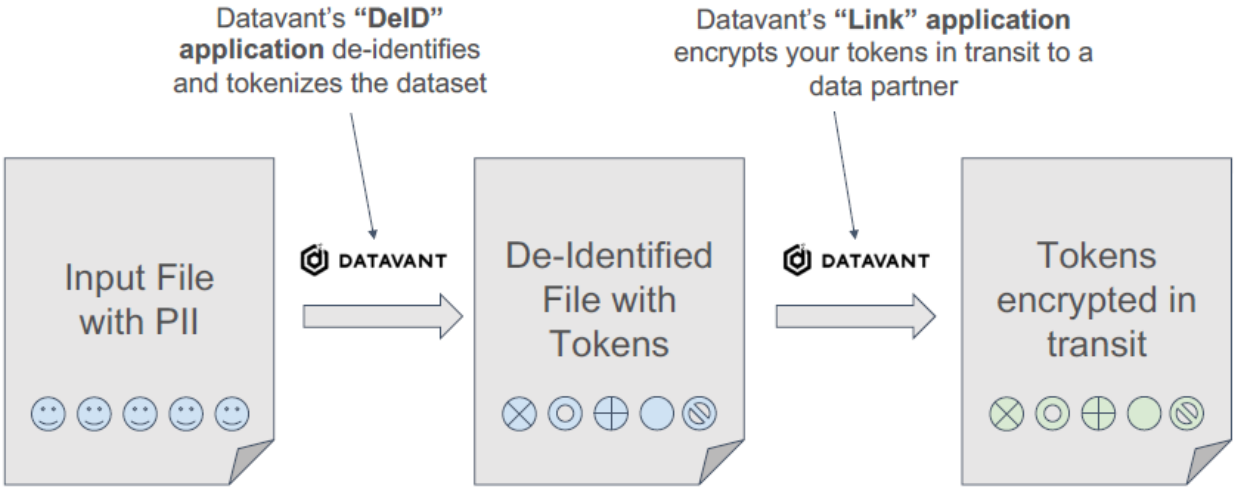

Figure 1. Datavant Applications: DeID and Link

If Datavant or a similar linkage solution is not applicable for this study, our strategy will be to follow ADAPTABLE's use of a trial invitation identifier to link the de-identified pat_id identifiers used in the PCORnet CDM to the invited patient's specific enrollment in CIDP Registry. In this scenario, the study team will generate random identifiers (trial_invite_code) centrally for each recruiting site who will track their relationship to the random identifiers used to uniquely identify patients in their site PCORnet CDM (e.g. pat_id). Sites then distribute these trial_invite_codes to the subject when they are approached for participating in CIDP Registry and the study. Upon enrollment, the subject will enter their trial_invite_code into the Registry directly. Upon enrollment, Registry will send back to the sites the trial_invite_codes of the patients who have enrolled and consented to share their Registry data. These codes and the definitions for this specific study are logged in the PCORNET_TRIAL table (Figure 2) with column definitions described in the CDM specifications (https://pcornet.org/pcornet-common-data-model/).

- ***Existing Resources:***

At the University of Kansas Medical Center (KUMC), we currently use the Streamlined, Multisite, Accelerated Resources for Trials Institutional Review Board (SMART IRB) for our multi-center studies. For sites that currently do not use this method, we establish a reliance agreement, so that their site will allow KUMC to be the IRB of Record. Within the Greater Plains Collaborative, our sites have established a 'central' contracting form. The PCORnet 2.0 infrastructure will be used to streamline administrative aspects of the trial, including centralization of institutional review board (IRB) functions and contracts, electronic consent and use of EHR data standardized into the CDM format.

- ***Comparators:***

This is the first head to head study of IVIg vs SCIg. A previous CIDP study compared relapse rates in patients given SCIg versus placebo and showed SCIg to be more efficacious than placebo.[18] One Italian study compared the SCIg costs with IVIg therapy in CIDP and found that SCIg may be cost saving in Italian CIDP patients.[19] A meta-analysis of studies looking at SCIg vs IVIg in CIDP patients found no difference in the motor strength outcomes in the two groups, and that efficacy and safety profile of SCIg was similar to IVIg for CIDP.[20] However, there is very limited literature comparing the effectiveness of IVIg with SCIg in CIDP. This study will help address the decision to use either SCIg or IVIg for CIDP.

- ***Outcomes:***

Subjects will be asked about the functionality of their upper and lower extremities using the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, which will serve as the primary outcome. They will also undergo strength testing using the Medical Research Council (MRC) sum score, perform grip strength testing, and will be asked about their ability to perform everyday tasks using the Inflammatory Rasch-built Overall Disability Scale (I-RODS). Short forms for the PROMIS instruments for physical function (20 items) and upper extremity (7 items) measure signs and symptoms using general questions without a temporal reference. Short forms for the Patient Reported Outcomes Measurement Information System (PROMIS) instruments for fatigue (8 items) and dyspnea severity (10 items) measure signs and symptoms over the past 7 days. A 5-point scale is used for each instrument (though responses may vary within or among instruments), and a total score is generated for each instrument. Patient input during the project development phase revealed a substantial interest in patient-reported outcomes in self-efficacy. Both focus groups identified their high level of satisfaction with their selected administration mode because it supported their values in disease self-care management. As a result, the research team is including a secondary outcome of self-efficacy to be responsive to patient priority. We will use the validated PROMIS® self-efficacy instrument to collect baseline and post-study individual-level metrics to assess change.

Subjects will be interviewed at each visit about possible side effects of medications and CIDP-related symptoms. Patient safety will also be assessed by physical examinations and vital signs at clinic visits. At each visit, patients will be questioned about the development of any new symptoms including deep vein thrombosis assessments. If an unscheduled visit is deemed necessary, the patient will be asked to return for a clinic visit within 48 hours where the site investigator will evaluate the subjects and determine if intervention is necessary. At all scheduled/unscheduled clinic visits, the site investigator will complete a Treatment Failure Questionnaire if the patients meet any of the criteria for treatment failure.

- ***Study Design:***

This study will be a randomized, open labelled prospective comparative effectiveness trial of IVIg vs SCIg. Fifty patients with either newly diagnosed CIDP (fulfilling the EFNS criteria) or patients who have persistent symptoms needing alternative therapy and/or other immunosuppressive therapies will be invited to enroll in this study. Patients will be randomly allocated to either the IVIg or SCIg arm with a 1:1 randomization. Patients in the IVIg arm will receive 2g/kg bolus treatment with infusions divided over 3 days, followed by 1g/kg every 3 weeks maintenance dose for total of 24 weeks. Patients in the SCIg arm will receive 0.4g/kg weekly infusions divided over 3 days per week for 24 weeks. The dose adjustments will be made based on patient tolerance. While patients receiving IVIg will be given a loading dose of 2g/kg, patients receiving SCIg will start at 0.4g/kg and will remain on that does for the rest of the study.

- ***Analytic Plan:***

The primary analysis will be a one group Chi-square test that proportion of favorable outcomes is bigger than or equal to 22.4%. This 22.4% was based on the placebo response in ICE15 trial. This test is done for both the IVIg group and the SCIg group. There are no pre-specified subgroup analyses.

As shown in the sample size and power section it is required to have 50 patients with endpoint data. If a patient withdraws from the study they will be replaced with a new patient to be randomized. Also specified are some secondary analyses. The IVIg and SCIg groups will be compared using a Ch-square test for investigating therapy differences. Additionally, all secondary measures will be investigated using multivariate analysis of variance. If omnibus test across the two groups us significant ($p<.05$) then the secondary analyses will be performed using two-sample t-tests for the measures Medical Research Council (MRC) sum score, perform grip strength testing, and Inflammatory Rasch-built Overall Disability Scale (I-RODS).

- ***Study Population and Setting:***

Fifty patients newly diagnosed CIDP will be invited to participate in this study. Patient selection will be based on a diagnosis of CIDP and the following significant inclusion/exclusion criteria:

Inclusion Criteria:
(1) CIDP diagnosed according to the EFNS/PNS criteria 2010;
(2) Patient's signs and symptoms should not be better explained by another disease process;
(3) If taking prednisone or steroid equivalent, there must be no dose change for 2 weeks from baseline;
(4) Patients can be on the following medications as long as there has been no change in dose 60 days prior to the baseline visit: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, or other immunosuppressive drugs;
(5) INCAT score ≥ 2

Exclusion Criteria:
(1) Prior treatment of IVIg or SCIg for any reason;
(2) Presence of any other causes of polyneuropathy or multifocal motor neuropathy;
(3) Other neurologic or orthopedic condition causing weakness;
(4) Treatment with PLEX within the last 30 days from baseline or rituximab within the past 12 months;
(5) Participation in another trial within the last 3 months;
(6) Latent tuberculosis or active infection;
(7) Previous or present use of IVIg or SCIg;
(8) Previous or present Infection with hepatitis C and hepatitis B;
(9) Evidence of renal insufficiency or liver disease;
(10) Skin disease that would interfere with assessment of injection site reaction;
(11) History of thrombotic episodes within the last year prior to enrollment;
(12) History of IgA deficiency or evidence of IgA deficiency

Recruitment Plan for Prospective Studies

1. Estimated number of potentially eligible study participants (describe how you determined this number [e.g., EHR, claims data, clinic logs, administrative data, other])	125
2. Total number of study participants you expect to screen	65
3. Total number of study participants you expect to be eligible of those screened	55
4. Target sample size (use same number stated in milestones)	50
5. If applicable, total number of practices or centers that will enroll participants	12
6. Projected month first participant enrolled (month after project initiation)	June 2020
7. Projected month last participant enrolled (month after project initiation)	January 2022
8. Projected rate of enrollment (anticipated number enrolled per month of enrollment period)	2-3
9. Estimated percentage of participant dropout	10%

- ***Sample Size and Power:***

The primary endpoint is favorable outcome at 6 months post randomization, where favorable outcome is defined according to the dichotomy of the INCAT as described above. A clinically relevant effect size of 25% absolute difference

in favorable outcome proportions is prespecified. In order to achieve 80% power with a two-sided type I error probability of 0.025, 25 subjects are required for both the SCIg and IVIg groups for a total of 50 subjects.

In an effort to sustain PCORnet collaboration and engagement, we have decided to invite sites that are members of the Greater Plains Collaborative to participate in this study. The University of Kansas Medical Center is the lead site for the Greater Plains Collaborative with the other sites being Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic Research Institute, Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center.

These sites share a vision of improving healthcare delivery through active research dissemination. Each site has a strong research program, informatics infrastructures, and strong working relationships between investigators and healthcare system information technology departments.

Research Team and Environment

Richard Barohn, MD is a renowned clinical leader in neuromuscular disease. He is the PI on our CTSA and is Director of Frontiers, the University of Kansas Clinical and Translational Science Institute. In his CTSA role, he was a co-leader in a NIH supplement which recommended GCP training for all personnel involved in clinical trials and this has since become NIH policy. He is involved in many federally- and foundation-funded clinical research studies for rare neuromuscular diseases, such as amyotrophic lateral sclerosis, myasthenia gravis, inflammatory myopathies, and muscular dystrophies. He was the co-PI on the NeuroNEXT trial of rituximab for myasthenia gravis. He has had leadership positions in two NIH Rare Disease Consortiums: CINCH and CReATe. He was the PI on three completed multicenter R01 grants: 1) mexiletine in non-dystrophic myotonia; 2) methotrexate in MG; 3) rasagiline in ALS. He is the PI or co-leader on two other multicenter R01 grants through the FDA OPD which we coordinate at KUMC (memantine for ALS and arimoclomol for IBM). He is the rare disease leader on our Greater Plains Consortium PCORNet CDRN, in which the rare disease we study is ALS. As stated above, he was PI on a recently completed PCORI comparative effectiveness study for drugs in painful neuropathy. He was made Vice Chancellor for Research of KU Medical Center and President of the Research Institute in 2014 and in those capacities as well as the Director of Frontiers, he has the authority to provide the resources and space at our institution needed to accomplish the aims we propose in this application.

Mamatha Pasnoor, MD is an Associate Professor in the Department of Neurology at the University of Kansas Medical Center (KUMC). She and Dr. Barohn will equally share leadership roles and will be able to act on each other's behalf for all study decisions. She co-Directs the peripheral neuropathy clinic at KUMC and works closely with the national Foundation for Peripheral Neuropathy. She is a leader in the diabetic neuropathy field and has been actively involved in collaborative studies in diabetic neuropathy She is a coinvestigator for the University of UTAH and University of Kansas NIH funded diabetic neuropathy exercise intervention study (ADAPT study). Along as serving as co-Investigator in our ongoing multi-center ADAPT study, she is site PI on our current Topiramate study through NeuroNEXT. With Dr Barohn, she was the co-leader of the recently completed FDA-OPD RO1 funded methotrexate trial in Myasthenia gravis which was published in Journal of Neurology as the primary author. This was a 20-site study in which she played a similar role as she played in PCORI study by facilitating coordination among on the sites, so that study completion was accomplished on time.

Byron Gajewski, PhD, Professor in the Department of Biostatistics is a nationally recognized leader in the Bayesian adaptive design. He received his training in the Bayesian adaptive design from Scott M Berry PhD, who is an Adjunct Professor in the Department of Biostatistics at KUMC. Dr. Gajewski developed the statistical plan used in the PCORI-funded PAIN-CONTRoLS study.

Lemuel Russell (Russ) Waitman, PhD is the Director of Medical Informatics at the KUMC. Dr. Waitman is a national informatics leader and the director in the CTSA Informatics core at KUMC. He was responsible with the development of REDCapTM database that data from PAIN-CONTRoLS is entered. His department was responsible for the training of personnel at the sites. Medical Informatics would generate the reports presented at the DSMB meetings. They took part of the monthly study calls, DSMB and if needed the patient advisory groups.

Andrew Heim, BSc, Project Manager has been involved in neuromuscular research for over three years. He has served as project manager for approximately one year. During this time, he has project managed two other studies and helped submit many grant applications to various funding agencies.

Kim Kimminau PhD. Dr. Kimminau is Associate Director of Frontiers, the K CTSA supported institute. She is a leader in community-based research and a facilitator of patient focus groups to obtain patient perspective and advice on

research. She facilitated the patient focus groups for the original PAIN-CONTRoLS and she will continue to do so. In the first year, she will establish a patient/community committee to work with and advice the steering committee in the trial. One member of the patient/community committee will serve on the overall steering committee.

The Neuromuscular Research team at the University of Kansas Medical Center is housed at the Fairway North Building which is in close proximity to the Clinical Research Center and neuromuscular clinic. The team is composed of 7 physicians that specialize in neuromuscular practice, 4 project managers, 7 research coordinators, 2 administrative assistants, 2 clinical evaluators, and 1 budget analyst. Each staff member has a dedicated space, a computer that is linked to a secure network server, phone and access to a copier that can fax and scan. With Dr. Barohn serving as PI, the other 6 neuromuscular physicians will serve as sub-I's for this study. KUMC will also dedicate one project manager and one research coordinator to this project.

Neuromuscular clinic is held primarily on Tuesday's and Thursday's, but patient's with CIDP may be seen any weekday. Annually, approximately 10 new CIDP patients are seen at KUMC. The clinics are staffed with research assistants/coordinators that approach every patient regarding available research opportunities. The research assistants/coordinators screen all of the charts before the clinic visits to determine if the patients are eligible for any of the ongoing clinical trials. This will be the practice for this study.

Two companies, NuFactor and RMS Medical Products have agreed to donate services via in-kind support. NuFactor will donate infusion services to patients randomized to the IVIg arm. RMS Medical Products has agreed to donate supplies to patients randomized to the SCIg arm. The total amount of services being provided total $1,150,625.

Since 1995, NuFactor has been providing the specialty products and care that infusion patients deserve, to help solve the acute problems of availability, affordability and safety in chronic care. NuFactor provides nationwide patient customized home infusion services.

RMS Medical Products is a fully integrated medical device company (eg. Research & Commercialization) that focuses on home and specialty infusion solutions, emphasizing responsive problem-solving for our customers, and careful consideration for the patient experience. We are dedicated to providing safe, effective, and cost-conscious drug delivery solutions to global healthcare markets.

The GBS/CIDP Foundation International is working for a future when no one with Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and related syndromes such as multifocal motor neuropathy (MMN) suffers alone and that everyone has access to the right diagnosis and the right treatment, right away.

Since the Orphan Drug Act, NORD has served as the hub of the rare disease community, leading efforts to connect patients and patient organizations with other stakeholders and driving progress for all. Since 1989, NORD has administered a Research Program through which we provide grants that have resulted in numerous published advances and at least two FDA-approved therapies. NORD is also working with rare disease organizations to launch disease-specific registries to support research.

The University of Kansas Medical Center is the lead site for the Greater Plains Collaborative (GPC), a PCORNet network of 12 leading medical centers in 9 surrounding states. We plan to use each member of the GPC (Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic Research Institute, Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center) as a site for this study.

DISSEMINATION AND IMPLEMENTATION POTENTIAL

Describe the potential for disseminating and implementing the results of this research in other settings.

A. Describe how you will make study results available to study participants after you complete your analyses.

1. The study will be registered with ClinicalTrials.gov after notice of award and prior to enrolling participants. Registration data elements submitted to ClinicalTrials.gov will include descriptive information, recruitment information, location and contract information, and administrative data. Results information will be submitted to ClinicalTrials.gov no later than 12 months after the primary completion date. Results information data elements to be submitted to ClinicalTrials.gov include participate flow, demographic and baseline characteristics, outcomes and statistical analysis, adverse events, the protocol and statistical analysis plan, and administrative information.

2. The informed consent documents for the clinical trial will include a specific statement relation to posting of the clinical trial information at ClinicalTrials.gov.

3. The University of Kansas Medical Center Research Institute, Inc. (KUMCRI) has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements. The office of Clinical Research Administration (CRA) manages and executes the regulatory elements for clinical trials at KUMCRI. After notice of award, a CRA compliance office will be notified and will confirm the submission meets all requirements for registration in ClinicalTrials.gov, and that proper data elements are include dint he initial registration. After initial registration, the compliance officer will monitor and confirm study updates are posted in ClinicalTrials.gov with the required timeline.

4. In addition to posting on clinicaltrials.gov, results will be presented to participants and their family members via a webinar which will be posted online.

5. We will announce the study in the GBS|CIDP Foundation newsletters and we will use our broad patient and community engagement network to organize a webinar to present the results to the broader community of people with CIDP and their family members.

6. We will use our associations with patient advocacy groups, to ensure the results are widely distributed to physicians who treat patients with CIDP.

7. In addition, we will ensure our clinical trial methodology outcomes are also widely distributed.

8. We will use the PCORnet and Greater Plains Consortium to disseminate this data and will present at national and international meetings. Data on clinical trial results as well as process improvement will be prepared for publication in scientific communications.

B. Describe possible barriers to disseminating and implementing the results of this research in other settings.

1. Not all patients may have access to clinicaltrials.gov.

2. After receiving their diagnosis, patients sometimes choose to not be followed in a GBS|CIDP Foundation Center of Excellence.

3. Not all patients have access to CIDP clinicians. Therefore, these clinicians may not understand the latest CIDP research.

PROTECTION OF HUMAN SUBJECTS

Describe the protection of human subjects involved in your research.

The University of Kansas Medical Center will serve as the single Internal Review Board (IRB) of record for this study for all sites. Each site must obtain approval from their IRB as well as from the IRB of record (KUMC) before enrollment at their site can begin. This process will be followed carefully by the Research Institute Regulatory Affairs office at KUMC to ensure that all sites comply.
Each consent form must contain the information found on the National Institutes of Health (NIH) website (www.grants.nih.gov/grants/funding/phs398/phs398.doc). The components of the consent form must contain the following information (copied from the above website):

I. Risks to Human Subjects
a. ***Human Subjects Involvement, Characteristics, and Design***

Chronic Inflammatory Demyelinating Polyneuropathy is a characterized by the occurrence of symmetrical weakness in both proximal and distal muscles that progressively increases for more than two months. The condition is associated with impaired sensation, absent or diminished tendon reflexes, an elevated cerebrospinal fluid protein level, demyelinating nerve-conduction studies, and signs of demyelination in nerve-biopsy specimens. The course can be relapsing or chronic and progressive, the former being much more common in young adults. CIDP has an estimated prevalence of 0.5 per 100,000 children and 1 to 2 per 100,000 adults.

We will include all CIDP patients more than 18 years of age who meet the EFNS/PNS diagnosis criteria, have an INCAT score ≥2, have been stable on concomitant medications according to protocol, and have symptoms that are not explained better by another disease process. We are using these criteria so that all patients enrolled and randomized to therapy will be able to obtain standard of care approval. Recruitment will be done through site specific clinics, using and Electronic Health Records to identify potential subjects and facilitate electronic screening, contact, and enrollment with the site clinical teams, and through the data linkage with the GBS|CIDP Foundation patient registry.
Randomization will be a 1:1 ratio using the REDCap database system managed by the KUMC Research Informatics team.
The dose and frequency of immunoglobulin therapy will be administered per standard of care treatment.
Collaborating sites will be responsible for recruiting and enrolling patients for this study. Data from all sites will be obtained by study staff and will be managed and protected using the REDCap database system.

b. ***Sources of Materials***
The research material that is being collected in this study mostly coincides with other CIDP research studies and standard of care procedures. We will utilize as many SOC procedures as possible during the course of this study. If a site doesn't normally collect the INCAT, I-RODS, or MRC score during clinic, then this element will be collected by research staff. Some samples of SOC items include forced vital capacity, physical exam, vital signs and safety labs. Items including consenting, obtaining medical history, demographics, adverse events, and concomitant medications will be collected by research staff during their visits.

Data will be collected by local study staff only. No private health information will be collected by the study. Patients will be deidentified and assigned a study number. Patient information will be stored at local site research facilities where it is only accessible to study staff. Electronic data will be collected, managed, and protected via the REDCap EDC system. Study staff at local sites will have access to their patient data only. The project manager and statistician will have access

to all study data for monitoring, compliance, and statistical analysis purposes. By collected mostly standard of care data and aligning research visits with clinic visits, it is our hope that this will prevent missing data from occurring.

c. ***Potential Risks***
Most patients tolerate IVIg therapy well. Mild and moderate side effects of intravenous IG (IVIg) are headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension. Headaches and their more severe form, migraines, tend to be one of the more common side effects.

For SCIg patients, the most common side effects include headaches and local irritation (redness, swelling, itching, blanching) at the needle site. Some reactions, especially for patients new to SCIg therapy, are expected, and most decrease with time once the body becomes accustomed to the therapy.

Serious side effects are rare, and most can be reduced by screening the patient for factors predisposing them to complications. Serious side effects can include acute renal failure, thrombosis, Stevens-Johnson syndrome, serum sickness, aseptic meningitis and anaphylaxis. The most severe form of IG-related headache comes from aseptic meningitis, and in fact, patients with a history of migraines appear to be more susceptible to aseptic meningitis.

There may be unforeseen financial risks due to cost of immunoglobulin therapy. These medications will be billed to the participants insurance, but the infusion costs will be donated in-kind. Participants can withdraw from the study at any time if the financial risks become intolerable. We have budgeted $600 for the duration of the study to offset insurance copays. We do not anticipate any psychological, legal, or social risks.

Since we are studying the only two FDA-approved medications for ALS, the only options for alternate treatment are investigational medications or no treatment at all.

II. Adequacy of Protection Against Risks

a. ***Recruitment and Informed Consent***
Patients will be recruited through each local site's clinic and through the GBS|CIDP Foundation registry. Patients that meet the entry criteria will be approached about participating in this study. We will also deploy computable phenotypes against data repositories and electronic health records to identify potential subjects.

Informed consent will be sought and done by local study staff that are delegated to do so. Consenting will take place in a private room. Subjects will be given sufficient time to make a decision and ask any questions regarding the study to the study staff. All study procedures, a background of CIDP, why the study is being done, any financial/legal details, voluntary participation, and protection of private health information will be explained to the subject. HIPAA laws will be included in the main consent form. Documentation of consent will be done per each local site standard operating procedures.

We will not enroll children in this study and therefore will not need an assent form.

b. ***Protections Against Risk***
Both medications being studied have a potential to cause physical risks, but these risks are minimal. For this study we propose real-time safety monitoring which will be AE reporting monthly. Safety will be monitored by our investigators and coordinators, by KUMC compliance office, and by our DSMB.
We do not plan to enroll any patients that fall in the 'vulnerable populations' category.

All adverse effects will be graded, reported, and handled by the local site PI. Local site PI's will be responsible for using best clinical judgement when addressing adverse effects and patient safety. Data and safety results will be will be monitored by both principal investigators, the medical monitor, and the data and safety monitoring board. The DSMB will meet quarterly to discuss. During the study the ongoing monitoring of data quality and subject safety will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. An independent DSMB will be established and is responsible for periodic review of the data related to Adverse Events throughout the trial. The DSMB will consider study data including information on all Serious Adverse Events, other Adverse Events, laboratory test results, recruitment and retention, data completeness and data quality. The DSMB will act independently to review ongoing data.

III. Potential Benefits of the Proposed Research to Human Subjects and Others

Patients will receive minimal benefit from participating in this study. By being placed on an FDA approved medication, the research conduct will parallel standard of care treatment. It is our hope that subject payment will benefit patients to help offset some costs that might be associated with medication co-pay. By participating in this research project, participants will help future CIDP patients make an informed decision on medication use and administration.
While there is minimal benefit to this research project, there is also minimal risk. The potential side effects of both drugs are known and the drugs have been proven to be safe. Bleeding/bruising may occur during blood draws, but this procedure is typically done as part of standard of care as well. We hope to assist in any financial risk by providing patient stipends.

IV. Importance of the Knowledge to be Gained

When patients are diagnosed with CIDP, they face the tough decision of what medications they should take. Immunoglobulin therapy has proven to be effective therapy for most patients diagnosed with CIDP. When the patient and clinician agree to use immunoglobulin therapy, the patient is faced with the choice of receiving the medication either intravenously or subcutaneously. There are several factors patients must consider when making this decision, such as cost and convenience. What has yet to be studied, however, is the effectiveness of the two administrations for patients that are newly diagnosed. By doing this study, we hope to gain knowledge on the effect of both administrations after a 6 month time period and disseminate the information to clinicians and patients alike.

Estimated Final Racial/Ethnic and Gender Enrollment Table

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	1	0	1
Asian	1	1	2
Black/African American	4	4	8
Hawaiian/Pacific Islander	0	1	1
White	18	17	35
Multirace	1	2	3
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	3	5	8
Non-Hispanic	20	22	42

CONSORTIUM CONTRACTUAL ARRANGEMENTS

For detailed instructions, refer to the Application Guidelines for this PFA. Do not exceed 10 pages.

Describe the proposed research projects that subcontracted organizations will perform. Explain the strengths that these partners bring to the overall project to ensure successful submission of contract deliverables in accordance with the milestone schedule.

REFERENCES CITED

For detailed instructions, refer to the Application Guidelines for this PFA. Do not exceed 10 pages.

Follow scholarly citation practice and list the source material cited in your Research Plan. PCORI suggests using American Medical Association citation style, but other citation styles are acceptable.

1. Koller H, Schroeter M, Kieseier BC, Hartung HP. Chronic inflammatory demyelinating polyneuropathy--update on pathogenesis, diagnostic criteria and therapy. Curr Opin Neurol 2005;18:273-278.
2. Koller H, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. N Engl J Med 2005;352:1343-1356.
3. Joint Task Force of the E, the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. J Peripher Nerv Syst 2005;10:220-228.
4. Connolly AM. Chronic inflammatory demyelinating polyneuropathy in childhood. Pediatr Neurol 2001;24:177-182.
5. Owens GM. The economic burden and managed care implications of chronic inflammatory demyelinating polyneuropathy. Am J Manag Care 2018;24:S380-S384.
6. Mehndiratta MM, Hughes RA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2002:CD002062.
7. van Schaik IN, Winer JB, de Haan R, Vermeulen M. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. Lancet Neurol 2002;1:491-498.
8. Mehndiratta MM, Hughes RA, Agarwal P. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2004:CD003906.
9. Mendell JR, Barohn RJ, Freimer ML, et al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 2001;56:445-449.
10. Lee DH, Linker RA, Paulus W, Schneider-Gold C, Chan A, Gold R. Subcutaneous immunoglobulin infusion: a new therapeutic option in chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2008;37:406-409.
11. Paquin-Proulx D, Santos BA, Carvalho KI, et al. IVIg immune reconstitution treatment alleviates the state of persistent immune activation and suppressed CD4 T cell counts in CVID. PLoS One 2013;8:e75199.
12. Paquin-Proulx D, Santos BA, Carvalho KI, et al. Dysregulated CD1 profile in myeloid dendritic cells in CVID is normalized by IVIg treatment. Blood 2013;121:4963-4964.
13. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet 1981;1:1228-1231.
14. Debre M, Bonnet MC, Fridman WH, et al. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. Lancet 1993;342:945-949.
15. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 2008;7:136-144.
16. Dimachkie MM, Barohn RJ. Chronic inflammatory demyelinating polyneuropathy. Curr Treat Options Neurol 2013;15:350-366.
17. Berger M, Rojavin M, Kiessling P, Zenker O. Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. Clin Immunol 2011;139:133-141.
18. Berger M, Harbo T, Cornblath DR, Mielke O. IgPro20, the Polyneuropathy and Treatment with Hizentra((R)) study (PATH), and the treatment of chronic inflammatory demyelinating polyradiculoneuropathy with subcutaneous IgG. Immunotherapy 2018;10:919-933.

19. Perraudin C, Bourdin A, Spertini F, Berger J, Bugnon O. Switching Patients to Home-Based Subcutaneous Immunoglobulin: an Economic Evaluation of an Interprofessional Drug Therapy Management Program. J Clin Immunol 2016;36:502-510.
20. Racosta JM, Sposato LA, Kimpinski K. Subcutaneous versus intravenous immunoglobulin for chronic autoimmune neuropathies: A meta-analysis. Muscle Nerve 2017;55:802-809

APPENDIX

INCAT Disability Scale Score

ARM SCALE

Does the patient have any symptoms in their hands or arms, e.g., tingling, numbness, pain or weakness?

☐ Yes ☐ No (If no, please go to 'legs section')

Is the patient affected in their ability to: (mark one option: ☒)

	Not affected	Affected but not prevented	Prevented
doing all zips and buttons?	☐	☐	☐
washing or brushing hair?	☐	☐	☐
using a knife and fork together?	☐	☐	☐
handling small coins?	☐	☐	☐

ARM GRADE

Work out the score from the answers to the questions using the scoring criteria.

0 = No upper limb problems
1 = Minor symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zippers *and* buttons, washing or brushing hair, using knife and fork together, handling small coins
2 = Disability, in one or both arms, affecting but not preventing any of functions listed above
3 = Disability, in 1 arm or both arms, preventing 1 or 2 of functions listed above
4 = Disability, in 1 arm or both arms, preventing 3 or all of functions listed above, but some purposeful movements still possible
5 = Inability to use either arm for any purposeful movement

Score = ☐

LEG SCALE

(mark one option on each line: ☑)

	Yes	No	Not applicable
Is the walking of the patient affected?	☐	☐	☐
How do they mobilise outdoors?			
without aid (independently)	☐	☐	☐
with one stick or crutch or holding someone's arm	☐	☐	☐
with two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
with a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk a few steps with the help of one person?	☐	☐	☐

LEG GRADE

Work out the score from the answers to the questions using the scoring criteria

0 = Walking not affected
1 = Walking affected, but walks independently outdoors
2 = Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors
3 = Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors
4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps
5 = Restricted to wheelchair, unable to stand and walk a few steps with help

Score = ☐

Final INCAT Disability Scale Score = ☐
Arm grade + Leg grade

Estimated time: 5-8 minutes

MEDICAL RESEARCH COUNCIL (MRC) SUM SCORE

MRC grading

	Left side of the body	**Right side of the body**
Movement[a]		
Shoulder abduction		
Elbow flexion		
Wrist extension		
First dorsal enterosseos		
Hip flexion		
Knee extension		
Ankle dorsiflexion		
Extensor halluces longus		

Total for each body side		
Total		
MRC grades:	**Description:**	
0	no movement, no contraction	
1	visible contraction without movement	
2	movement, but only with gravity eliminated	
3	movement against gravity	
4	movement against resistance, but weaker than normal	
5	normal strength	

The MRC sum score ranges form 0 (paralysis) to 80 (normal strength).

Inflammatory Rasch-built Overall Disability Scale (I-RODS)

Are you able to	Mark the best option with "x"		
Task	Not possible to perform [0]	Possible, but with some difficulty [1]	Possible, without any difficulty [2]
1. read a newspaper/book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash upper body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. make a sandwich?	☐	☐	☐
7. dress upper body?	☐	☐	☐
8. wash lower body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐
11. go to the general practitioner?	☐	☐	☐
12. take a shower?	☐	☐	☐
13. do the dishes?	☐	☐	☐

14.	do the shopping?	☐	☐	☐
15.	catch an object (e.g., ball)?	☐	☐	☐
16.	bend and pick up an object?	☐	☐	☐
17.	walk one flight of stairs?	☐	☐	☐
18.	travel by public transportation?	☐	☐	☐
19.	walk and avoid obstacles?	☐	☐	☐
20.	walk outdoor < 1 km?	☐	☐	☐
21.	carry and put down a heavy object?	☐	☐	☐
22.	dance?	☐	☐	☐
23.	stand for hours?	☐	☐	☐
24.	run?	☐	☐	☐

General Self-Efficacy

Please respond to each item by marking one box per row.

For the next set of questions, please read each sentence and rate your level of confidence in managing various situations, problems, and events.

	Rate your level of confidence.	I am not at all confident	I am a little confident	I am somewhat confident	I am quite confident	I am very confident
GSE11_C	I can manage to solve difficult problems if I try hard enough.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE12_C	If someone opposes me, I can find the means and ways to get what I want.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE13_C	It is easy for me to stick to my aims and accomplish my goals	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE14_C	I am confident that I could deal efficiently with unexpected events.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE15_C	Thanks to my talents and skills, I know how to handle unexpected situations.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE16_C	I can solve most problems if I try hard enough.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE17_C	I stay calm when facing difficulties because I can handle them.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE18_C	When I have a problem, I can find several ways to solve it	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE19_C	If I am in trouble, I can think of a solution.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE20_C	I can handle whatever comes my way.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE
SUMMARY STATEMENT
(Privileged Communication)

Principal Investigator:	Richard Barohn
Organization:	University of Kansas Medical Center Research Institute, Inc.
Project Title:	Comparative effectiveness of IVIg and SCIg vs Historical Control Data in management of CIDP
PCORI Funding Announcement:	Partnerships to Conduct Research within PCORnet (PaCR)
Review Cycle:	Off-Cycle 19C1
Request ID:	17149

NOTE: PCORI's Merit Review process includes written online critique and in-person discussion phases. All applications go through the online written critique phase, but only a subset continue to the in-person discussion phase. If an application does not progress to in-person discussion, the Summary Statement includes only the written online critiques. If an application progresses to in-person discussion, the summary statement includes in-person panel discussion notes; final average overall score; written online critiques; and, in some cases, application quartile, to help applicants understand how they did relative to other discussed applications.

Criterion 1: Potential for the study to fill critical gaps in evidence

Reviewer 1:

Strengths:
• The application by Barohn et al addresses a rare but potentially severely disabling acquired autoimmune neurological condition called Chronic Inflammatory Demyelinating Neuropathy (CIDP) that affects about 4.7 per 100,000 people. The authors describe the clinical burden of CIDP well and describe the limitations of the current management options too. Intravenous immunoglobulin (IVIG) is an approved treatment of CIDP and a recent small trial suggests the effectiveness of subcutaneously administered Ig (SCIG) in CIDP patients compared to those treated with placebo (MAJOR).
• The researchers identify a gap in the field where there is a lack of data comparing effectiveness of IVIG with SCIG in CIDP (MAJOR).
• This study proposes to determine if IVIG or SCIG is more effective in CIDP management compared to historical control group data from prior CIDP trials. The study will also compare the safety profile of the two treatments. The primary endpoint is improvement in Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. This will be the first study that will compare IVIG vs SCIG (MINOR).

Weaknesses:

• Weaknesses noted under scientific merit cast doubt on the likelihood that this study would address the evidence gap identified (MAJOR).

Reviewer 2:

Strengths:

- The study would allow a better understanding of the effectiveness of intravenous administration of immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) in the Chronic Inflammatory Demyelinating Neuropathy (CIDP) population.
- The researchers clearly identify the information gap between the efficacy of delivery methods of IVIg vs SCIg.
- The proposal explains the clinical burden on patients with CIDP and how this work might shift the time and financial burden of this chronic disease.

Weaknesses:

- MINOR WEAKNESS: The evidence gap should be further explained since the safety and efficacy of immunoglobulin therapy for CIDP has already been demonstrated.
- MINOR WEAKNESS: This research would be adding evidence to the decision-making process for patients and clinicians as to delivery methods but the focus group information provided already defines that process for most patients (convenience, cost, socialization, etc).

Reviewer 3:

Strengths:

- The clinical burden of Chronic Inflammatory Demyelinating Neuropathy (CIDP) is well explained. (moderate)
- Both intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg) have been found to be effective treatments in meta-analysis, but there is no literature comparing the effectiveness of IVIg with SCIg in CIDP. (moderate)

Weaknesses:

- This study proposes to conduct two one-sample tests, each separately comparing SCIg or IVIg to historical control. Such an experimental design is unlikely to address the evidence gap in the comparative effectiveness of IVIg vs SCIg. (major)

Reviewer 4:

Strengths:

- major strength – there are no other studies that have compared these two therapies in this patient population
- major strength – the two therapies being studied are the only options for these patients (besides no treatment)
- minor strength - the proposed randomized control trial (RCT) can empirically conclude which treatment is better for these patients

Weaknesses:

- none noted

Reviewer 5:

Strengths:

- Chronic Inflammatory Demyelinating Neuropathy (CIDP) is a rare condition that affects 4.7 per 100,000 people; there are clear diagnostic criteria, mature patient advocacy groups, active programs of research and patient registries.
- Immunoglobulin therapy has proven to be effective therapy for most patients diagnosed with CIDP but there is no evidence on the comparative effectiveness of intravenous versus subcutaneous administration.
- A randomized design and evaluation of the effectiveness of each route of administration, subcutaneous immunoglobulin therapy (SCIg) versus IV immunoglobulin therapy (IVIg), could inform patient and physician decision-making.
- The study is targeting newly diagnosed patients.

Weaknesses:

- There is no description or preliminary data to understand the relative number of patients that seek IV versus subcutaneous treatment. (Major weakness)
- There is no discussion of physician attitudes or reasons for prescribing IV versus subcutaneous treatment. (Major weakness)
- No conceptual model of choices for treatment is presented. Important criteria (cost, convenience, and efficacy) are mentioned, with the latter (efficacy) being the focus of this proposal. However, the cost and convenience factors of the two therapies are not well-described and there are no plans to collect patient perceptions and satisfaction of the different Ig approaches. (Moderate weakness)
- There is no discussion about potential bias in the selection or eligibility of patients for different treatments. (The application does mention variability in insurance coverage for Immunoglobulin therapy and mentions that travel and costs are barriers for IVIg and possibly study participation, but there is not mention of how this would impact the study sample and generalizability of results.) (Moderate weakness)

Criterion 2: Potential for the study findings to be adopted into clinical practice and improve delivery of care

Reviewer 1:

Strengths:
• The application describes well the local and national stakeholders, including patients, caregivers, clinicians, and pharmaceutical companies about demand for this study comparing IVIG vs SCIG for CIDP and describes their input for the need for such studies as well (MAJOR).
• The application describes well the plans to disseminate study findings beyond publication in peer-reviewed journals and at national conferences (MAJOR).

Weaknesses:
• While the application describes the current decision-making process for CIDP management and how various stakeholders participate in that, the most significant factor in clinical practice for access to drugs is the insurance companies, and they will be important stakeholders in this drug choice decision-making. This barrier to adoption should

be acknowledged and addressed (MAJOR).

- The small sample size of the study and the comparison to the historical controls seems like a challenging enough problem that even with positive results, some doubts about the study's ability to inform decision-making could be raised (MAJOR).

Reviewer 2:

Strengths:

- The dissemination plan includes coordinating efforts through the GBS/CIDP Foundation to reach patients and their families, as well as clinicians. There is discussion of the clinician and patient decisional dilemma when prescribing treatment methods because there is no evidence-based research to support IVIg over SCIg or vice versa.
- Clinicians will be the primary end-user of this research study's results and there is an outreach plan noted on how to get this information to them for dissemination to their individual patients.
- The patient focus groups held led to better understanding of the patient administration preferences and showed strengths for both IVIg and SCIg; this study may give greater insight to those personal preference reasons.

Weaknesses:

- MINOR WEAKNESS: The proposal does not address any opportunities for publishing the results to the professional community for wider dissemination of results outside the CIDP network and Greater Plains Collaborative (GPC) members.

Reviewer 3:

Strengths:

- Evaluating the comparative effectiveness of IVIg vs SCIg can support decision-making by physicians and patients in choosing the appropriate treatment. Interviews with clinicians and patient focus groups have shown the need of such a study. (moderate)
- This study establishes a partnership among academic (Kansas University Medical Center), non-profit (GBS|CIDP Foundation) and industry (NuFactor and RMS Medical Products) partners. The streamlined governance and technical processes can help others reproduce the research findings. (moderate)
- Besides journals and conferences, study results will be disseminated through GBS|CIDP Foundation newsletters as well as PCORnet and Greater Plains Consortium (GPC). Possible barriers to dissemination and implementation have been well discussed. (moderate)

Weaknesses:

- None noted

Reviewer 4:

Strengths:

- major strength – because both therapies are standard of care, it will be seamless for patients and clinicians to

modify treatment based on results
- minor strength - investigators indicate that both patients and clinicians are interested in knowing which treatment is better; as such, these groups will be targeted for dissemination of results

Weaknesses:

- minor weakness – items 6 and 7 in the dissemination plan are vague and do not describe how they will "ensure" distribution of results; clinicaltrials.gov is a federal regulation for all clinical trials and is not a novel way of disseminating results (described in items 1, 2, and 3 of dissemination plan); likewise, item 8 in the dissemination plan is also not novel (academic presentation/publication); only item 5 (CIPD newsletters and participant webinar) provides sufficient detail and is customized for this study
- minor weakness – proposal does not address solutions to the potential barriers they identify in dissemination
- minor weakness – this is a very rare disease so the impact of study results is limited in scope

Reviewer 5:

Strengths:

- The clinical problem is clearly stated and well justified. (Moderate strength)
- The patient-motivation for this question is well described. (Major strength)
- Comparative efficacy and side effect profiles for the two administration strategies for Ig is unknown and justify a comparative effectiveness study. (Moderate strength)
- Applicants are aware that cost and convenience (and perhaps other factors) currently drive the decisions between IVIg versus SCIg. (Moderate strength)

Weaknesses:

- No indication on Letters of Support (LOS) from physicians or patients that they are aware of or motivated by the question. The LOS are all template/identical letters that indicate agreement to participate, but do not include statements of interest or need to answer this clinical question. (Major weakness)
- No evidence or description that physicians are looking for the answer to this CER question, or what their information needs are. (However, the patient-motivation for this question is well described as noted above). (Minor weakness)
- The proposal does not clearly identify who will make the decision (i.e., the decision-maker) or use (i.e., the end-user) the study findings (not the intervention) that this study produces, such as local and national stakeholders. (Minor weakness)
- The proposal does not describe a plan for how to disseminate study findings beyond publication in peer-reviewed journals and at national conferences. (Minor weakness)

Criterion 3: Scientific merit (research design, analysis, data linkages, and outcomes)

Reviewer 1:

Strengths:
• The applicants describe a clear conceptual framework for the study and describe the background literature that informs the design, key variables, and relationship between interventions and outcomes being tested (MAJOR).
• The randomized study design is appropriate for this proposal (MAJOR).

• Primary outcome of the study includes functionality of the subjects upper and lower extremities using the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, and strength testing using the Medical Research Council (MRC) sum score, grip strength testing, and the Inflammatory Rasch-built Overall Disability Scale (I-RODS) will be used for secondary outcomes. These outcome measures in addition to the other outcomes are well justified, validated and appropriate for the population (MAJOR).
• For this study, data linkages will be performed with a patient registry of the GBS|CIDP Foundation, which is managed by the National Organization for Rare Diseases (NORD). This study will pursue a data linkage strategy utilizing Datavant or similar technology to enroll subjects in the GBS/CIDP Foundation Registry and integrate registry with REDCap database for data collection. The proposal describes that they will use the PCORnet Common Data Model (CDM) at sites to identify and recruit patients and gather patient data using the CDM. The application describes that data linkages will be done using Datavant (which is selected by PCORnet for consistent data linkage across its network) (MAJOR).
• Linkages between the required data sources to facilitate the conduct of the proposed study and the proposed data linkage work will contribute to PCORnet methodologies (MAJOR).
• The study design section of the proposed project describes the opportunity to utilize and enhance aspects of the PCORnet 2.0 infrastructure and it appears to adhere to PCORnet 2.0 governance. The application describes well the use of PCORnet infrastructure resources including the Coordinating Center, having streamlined IRBs, contracting, engagement and consenting processes and standardized data resources training (MAJOR).
• The project timeline could be realistic assuming the partner sites are able to recruit the subjects in time. Milestones are described well in the proposal. The study will need multiple sites to recruit from, hence the strategy for recruiting participants appears feasible (MINOR).

Weaknesses:
• While the Research Plan describes methods that demonstrate adherence to the PCORI Methodology Standards, the comparison of the study subjects to the historical controls (from prior studies) seems somewhat less feasible and/or valid, and raises doubts about study results informing decision-making. The study proposes 50 patients with newly diagnosed CIDP to be randomized to either IVIG or SCIG. From clinical experience, heterogeneity seen in the CIDP population may limit finding the comparable historical controls (from the prior CIDP trials) and hence risk compromising the study results or completion. Applicants should provide some additional data supporting the feasibility of subject enrollment with control arms selection to make the proposal more convincing (MAJOR).
• Study design/sample size: Although the applicants justify the sample size and effect size, these aspects might need additional review by a statistician (MINOR).
• The applicants propose in the study design/analytical plan that if a patient withdraws from the study they will be replaced with a new patient to be randomized. This plan may impact the study completion time (MINOR).

Reviewer 2:

Strengths:

- The researchers will use the PCORnet Common Data Model in their queries and database linkage. This is one of the few points where PCORnet resources are incorporated into the proposal.
- The proposal notes that the Smart IRB model will be used for this research. While this is an NIH developed process, it is endorsed by PCORnet to maximize resources and consistency of IRB processes across institutions.

Weaknesses:

- MODERATE WEAKNESS: The total patient enrollment number is 50, 25 for each method of delivery. This small sample size can be quickly influenced by patients dropping out of the study before its completion.
- MODERATE WEAKNESS: The use of PCORnet resources in this proposal appear to be limited and mentioned just briefly. Further explanation of how the coordinating center resources would be used would correct this weakness.
- MODERATE WEAKNESS: The data linkage of REDCap and the Registry with electronic health records (EHRs) and

other patient records is not adequately explained in the proposal.

Reviewer 3:

Strengths:

- The recruitment plan is reasonable. A dropout rate of 10% is assumed. (minor)
- The conceptual frame work is clear. The selection of interventions and outcomes are supported by background literature. (moderate)
- PCORnet 2.0 infrastructure and governance such as streamlined IRBs will be utilized. (moderate)
- The two comparators (IVIg and SCIg) are currently used in clinical practice. The primary outcome based on the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score is reasonable. (moderate)

Weaknesses:

- The study population is unclear. In "Study Design" (Page 8, Research Plan), it is stated that either newly diagnosed CIDP patients or patients who have persistent symptoms will be enrolled. In "Study Population and Setting" (Page 9, Research Plan), however, only newly diagnosed CIDP patients will be enrolled. (major)
- The knowledge gap lies in the comparison between IVIg and SCIg. The proposed separate comparisons with historical control are unlikely to address the knowledge gap. (moderate)
- The dosage for SCIg of 0.4 g/kg in the clinical trial is not justified. This single dosage is concerning because on page 3 (of the Research Plan) it states that "when switching a patient from IVIg to SCIg, individualizing the dosage based on measured serum immunoglobin levels and clinical response is preferable." (major)
- The plan for data linkage lacks detail. It is also unclear what data elements will be contributed from the CIDP registry and what from the KUMC database. Hence the benefit or necessity of data linkage is unexplained. (moderate)
- Justification for the effect size of 25% absolute difference is not provided. Sample size justification is for a separate comparison with historical controls, not for the comparison between IVIg and SCIg. Furthermore, it is unclear what the historical control is or how it is selected. No description or citation was provided. In sample size justification, the baseline rate in the historical control is not presented. (moderate)

Reviewer 4:

Strengths:

- major strength – study compares two standard treatments for CIDP in randomized fashion with CER tenets
- minor strength – study leverages PCORnet and CIDP to identify a very rare patient cohort that could not otherwise be studied at a single institution

Weaknesses:

- major weakness – there is no detailed plan for study visits and assessments; this is an RCT of two therapeutic interventions which leverages standard of care, but it is impossible to determine if study procedures overlap with standard clinical visits, labs, examinations, etc. because the investigators have not included a study grid, patient timeline, or any details about what data is being collected in conjunction with the study
- major weakness – the specific aims section describes a control group integral to the study design; said control group is not mentioned in proposal again, therefore there is no information on how that cohort will be identified/defined/etc.

- major weakness – investigators acknowledge that they have not begun to think about how to perform the data linkage necessary to connect the CIDP registry with their study database; the proposal includes a best guess for the possible cost of using Datavant, but investigators explain that linkage may be pursued with a different product
- moderate weakness – the proposal indicates that only about half of the full pool of CIDP patients in PCORnet and CIDP registry combined will qualify for their study and they expect that all but 5 of them will consent; this rate of consent is highly ambitious and, given the small numbers in this patient cohort of newly diagnosed or refractory CIDP, it is concerning that the study will not meet its enrollment goal for statistical significance
- minor weakness – inclusion/exclusion criteria do not include considerations for patients under 18 or pregnant women but human subjects protections section indicate that those populations will be excluded
- minor weakness – it is unclear how PCORnet will be leveraged for data other than to identify patients

Reviewer 5:

Strengths:

- Randomization is a positive feature of this proposed study and can mitigate the effects of bias and confounding factors. (Major strength)
- Focus on newly diagnosed patients can reduce potential of patients experiencing both treatments or other treatments. (Major strength)
- Each of the comparators (IVIg and SCIg arms) are clearly justified and well defined. (Moderate strength)
- CIDP diagnosis is classified with published EFNS/PNS criteria (2010). (Major strength)
- This study will pursue a data linkage strategy (Datavant or similar) to integrate data from the GBS|CIDP Foundation Registry with data from PCORnet sites using a REDCap database. (Major strength)
- The proposal mentions the use of PCORnet and PCRF infrastructure resources (e.g., Coordinating Center, streamlined IRBs, etc.) (Major strength)
- The proposal does specify that the PCORnet Common Data Model (CDM) will be used across all sites to identify and recruit patient and gather patient data using the CDM. (Major strength)
- The Greater Plains Collaborative (GPC) is a member of PCORnet and has engaged in many data queries. (Major strength)

Weaknesses:

- The duration of treatment (6 months) is noted but the study plan does not clearly state when and how many measurements will occur. The proposed methods for ascertainment of outcomes and schedule of visits is not mentioned. (Major weakness)
- Aim 1 is to compare each treatment arm (IV versus subcutaneous Ig) to "historical control data" yet this is not defined anywhere in the proposal. It is not clear whether important assessment scales are collected historically. It is likely that the historical data is baseline visit data, but that it not clearly stated. (Major weakness)
- The data collection (use) and data analysis for Aim 1 (determine if IVIg or SCIg is more effective than historical control data) is not clearly defined. For example, what the definition of 'more effective' is and why the comparator is historical data rather than baseline data. Also, how far back it will be reasonable to look for historical data is not clear. (Major weakness)
- Similarly, the data collection or analysis for Aim 2 (determine which of the two treatments has less side effects) are not specifically addressed. (Major weakness)
- Aim 2 (the collection and analysis of side effects for each administration (IVIg versus SCIg)) could be better ascertained with an observational study on a larger sample. (Major weakness)
- The application does not include any description of the GBS/CIDP patient registry, including number of registrants, type of data, or connection of GBS/CIDP registry to PCORnet/GPC study sites. (Major weakness)

- A sample size of 50 is referenced, but no discussion of how these patients will be identified (specifically) and approximately how many patients will be identified at each site. (Major weakness)
- No preliminary data to support the estimates for sample size. (Major weakness)
- Since IVIg and SCIg are standard of care, and previous treatment is an exclusion criterion, the study team will have to recruit incident cases. There is no detailed information provided on the number of prevalent or incident cases at each site. The timeline indicates 2-3 patients will be enrolled per month for the duration of this study, but there is no way to know if this is realistic number. (Major weakness)
- Inclusion criteria are subjective ("patient's signs and symptoms should not be better explained by another disease process") and complicated ("If taking prednisone or steroid equivalent, there must be no dose change for 2 weeks from baseline"; ... other medications should have..."no change in dose 60 days prior to the baseline visit.") The application does not describe how these subjective and complex criteria will be operationalized for screening. (Moderate weakness)
- Application should include a specification for which inclusion data elements are expected to be in the electronic medical record (EMR) and how they are coded. (Major weakness)
- Patients are randomized, but there is a risk that patients can differentially participate in one arm versus another (based on costs or other barriers). There is no plan to assess or address the risk of this. (Minor weakness)
- There is no discussion of the validity of the scales or appropriateness of the selected outcomes for the study. (Major weakness)
- The application does not provide justification or supporting references that the outcome measures are validated and appropriate for the population. In particular, there have been concerns about the INCAT scale (e.g., methodological quality of validation studies; failure to properly capture activity limitations due to proximal arm weakness or fatigue; heavy individual item weighting; and poor sensitivity for detection of clinically important change). (Major weakness)
- The application does not describe how adverse events (AEs) will be collected and coded. Nor does it describe how the number and type of AEs will be compared between treatment arms for Aim 2. (Moderate weakness)
- Sample sizes and power estimates are not well justified and the anticipated effect size is not adequately described or justified. (Major weakness)
- It is difficult to evaluate the feasibility of this study as there is no preliminary data or justification for recruitment goals. Also, there is little description of strategies for recruiting participants. Participant attrition rates are not provided. (Moderate weakness)
- The application does not sufficiently describe data linkages using the PCORnet 2.0 Common Data Linkage Method between the required data sources (i.e., EHR/EMR data, newly collected research data, and external patient registry data) to facilitate the conduct of the proposed study. Specifically, the application does not address which data elements will be used from each source. (Minor weakness)
- There are inconsistencies in the proposal and support letters from the National Organization for Rare Disorders (NORD) and patient advocacy groups on how patients will be recruited for this study, i.e., whether they are recruited from sites or from the patient registry. (Major weakness)
- The application does not state which sites will utilize SMART IRB. (Moderate weakness)

Criterion 4: Investigator(s) and environment

Reviewer 1:

Strengths:
• Dr. Richard Barohn, a professor of Neurology at the University of Kansas, is the contact PI and serves as the Vice Chancellor of Research at KUMC and the University of Kansas Clinical and Translational Science Institute, and hence is capable to manage the overall administrative and fiscal management of the project. In this role, he is well positioned to coordinate activities related to the study and ensure all participating sites leverage all available resources for implementation of the study. He has served as PI and co-PI on several multi-center NIH and PCORI grants. Dr. Mamatha Pasnoor will co-lead the development and implementation of this study (with Dr. Barohn) and seems well qualified to do so. Dr. Waitman, as the Director of the Center for Medical Informatics and Enterprise Analytics University of Kansas

Medical Center, has expertise in biomedical informatics, electronic health records, clinical research informatics, and developing reusable research data infrastructure for driving pragmatics comparative effectiveness research and is well suited to advancing Dr. Barohn's proposal (MAJOR).
• The Department of Neurology at KUMC, with 7 neuromuscular specialists who focus on neuromuscular clinic and CIDP patients seems well equipped to conduct this study. Annually, approximately 10 new CIDP patients are diagnosed at KUMC. The clinics are staffed with research assistants/coordinators that approach every patient regarding available research opportunities (MAJOR).
• Other Centers participating in the study will include the University of Nebraska Medical Center Neuromuscular Clinic/Nebraska Medicine Neuromuscular clinic, Medical College of Wisconsin, University of Missouri, University of Texas Health Science Center at San Antonio and University of Utah (MAJOR).
• There are no concerns with the PIs, collaborators, and other researchers to conduct the proposed activities. There appears to be sufficient clinical and statistical expertise for the proposal. The investigators and co-investigators have demonstrated experience conducting projects of a similar size, scope, and complexity. The investigators have complementary and integrated expertise (MAJOR).
• The leadership, governance, and organizational structures appear appropriate for the project. In this Dual-PI study, the Leadership Plan adequately describes and justifies the PI roles and areas of responsibility (MAJOR).
• The application describes adequate availability of and access to facilities and resources (including patient populations, samples, and collaborative arrangements) to carry out the proposed research. Overall, the institutional support is appropriate for the proposed research (MAJOR).

Weaknesses:
• With so many administrative responsibilities, it is unclear how much effort Dr. Barohn may be able to put in the study execution. The project coordinator likely needs more effort than as proposed (MINOR).

Reviewer 2:

Strengths:

- The research team's credentials include experience with CIDP as well as large scale research projects.
- The investigator has ample experience with successful funding and completion of research grants/awards.
- The research team's home institutions have indicated their support of this work.

Weaknesses:

- MINOR WEAKNESS: GPC and the CIDP registry numbers of people living with this disease is not specified and understanding access to this population would be beneficial. For example, knowing whether the participating research sites are at clinics with specific expertise in the disease that draw patients with CIDP.
- MINOR WEAKNESS: The recruitment plan estimates identifying 125 potential participants but does not explain how the estimated patients are identified (EHRs, clinic notes, claims data).

Reviewer 3:

Strengths:

- The PI is and other team members are very experienced researchers with complementary expertise. The research team includes an experienced biostatistician to support analysis and study design. (moderate)
- The leadership plan is well developed with clearly defined roles and responsibilities for the dual-PIs. (minor)
- The level of effort for each team member is appropriate to accomplish the proposed work. (moderate)
- Institutional support and facility are appropriate. (moderate)

Weaknesses:

- None noted

Reviewer 4:

Strengths:

- major strength – study investigators are at the lead site for the Greater Plains Collaborative (GPC)
- major strength – study investigators have appropriate clinical expertise

Weaknesses:

- moderate weakness – while investigators do have brief letters of support from each collaborating institution/organization mentioned in the study plan, the section on contractual arrangements is entirely blank; this prompts concern that participation and/or budgetary considerations are not finalized and/or could fall through with critical collaborators after award
- moderate weakness - the explanation given about why Barohn and Pasnoor need to share PI oversight is lacking (other than because one PI may not be available for all necessary meetings/interactions); more thought needs to go into how to appropriately develop this partnership and/or if dual-PI is truly needed for this study
- minor weakness – number of sites in recruitment plan is different than the number of sites identified in the performance sites section, likewise budget justification and actual budget are disparate when it comes to number of sites and when/how they will be reimbursed for potential participation (perhaps this is because investigators did not procure letters of support from all institutional members of GPC)
- minor weakness – in performance sites section, the body of content for Medical College of Wisconsin actually describes Utah
- minor weakness – because IRB approval has not been awarded, reliance agreements have not been started, and Data Safety Monitoring Board (DSMB) and Patient Advisory Council (PAC) have not been assembled, it is unlikely that much (if any) enrollment will happen in the first year of award
- minor weakness - combined effort of support staff (key personnel other than PI/dual-PI) totals 1.5 full-time positions; given the large scope of the proposed study, investigators should consider having at least one full-time position for project continuity (such as the current project manager who is only listed with 40% effort) in order to push the study forward and facilitate greater likelihood of success

Reviewer 5:

Strengths:

- The investigative team have strong research background in neurology and CIDP in particular. Dr. Mamatha Pasnoor has recent experience as PI of 20-site trial. (Major strength)
- The Leadership Plan provides adequate description and justification of PI roles and responsibilities. (Moderate strength)
- A statistician and informaticist (L.R. Waitman) are included on the study team and are well suited to advise the statistical and informatics issues – particularly collection of data across PCORnet/GPC sites. (Major strength)
- Dr. Kimminau is a leader in community-based research and a facilitator of patient focus groups to obtain patient perspective and advice on research. She will support the Patient Advisory Council (PAC) and patient-lead development of study dissemination. (Major strength)
- Support of NuFactor and RMS Medical Products enhances the feasibility of the study, and addresses the stated

aims of the PFA. (Moderate strength)

Weaknesses:

- Although the PIs have experience supporting multi-site studies, the application does not address any procedures or approaches or logistics of coordinating 12 sites. (Moderate weakness)
- The application states that patients will be recruited from 12 clinical sites in the GPC, but neither the application nor the letters of support provide an estimate of the number of potentially eligible patients at each site. (Major weakness)

Criterion 5: Patient-centeredness

Reviewer 1:

Strengths:
• The study as proposed focuses on improving patient-centered outcomes for CIDP and employs a patient-centered research design. The application describes well the outcomes important to patients (effectiveness, safety, convenience of administration), and these outcomes are included in the study plan (MAJOR).
• The application describes the significance of closing the evidence gap to patients and other stakeholders (MINOR).
• The interventions (IVIG and SCIG) are available to patients now, and seem to be the best options for comparison since patients and their healthcare providers would choose them for managing CIDP (MINOR).

Weaknesses:
• The historical control arm aspect of the study as described in Criterion 3 makes the study somewhat less robust (MAJOR).

Reviewer 2:

Strengths:

- The research team clearly took the time to listen to people with CIDP and incorporate their questions of efficiency of resources into this proposal.
- The research question of IVIg vs SCIg delivery methods efficacy is identified as a key concern to both patients and clinicians.

Weaknesses:

- MINOR WEAKNESS: The patient focus groups showed each method of administration has its benefits, dependent on personal preference. These patient-reported outcomes (PROs) are not captured in the study design.
- MAJOR WEAKNESS: The mention of financial resources to support patients in this project are contradictory. The proposal states there will be financial support for the patients to assist with the burden of participation in the trial but also lists the burden of the financial costs are a potential risk to patients and a reason they might withdraw early (page 15, Research Plan). Then the proposal goes on to say that subject pay and stipends (page 16, Research Plan) will offset costs. The budget does not reflect these payments and this area is murky, at best, and is confusing.
- MAJOR WEAKNESS: PROs are captured through the self-efficacy PROMIS survey as a secondary outcome. Looking for meaningful outcomes in this study should include PROs in a more prominent manner.

Reviewer 3:

Strengths:

- The primary outcome, INCAT Disability Score, is important to patients. Other patient-reported outcomes (PROs) such as self-efficacy will be measured using the PROMIS instruments. (moderate)
- Closing the evidence gap regarding the comparative effectiveness of IVIg vs SCIg has the potential to support decision-making by patients and physicians and improve the quality of care. (moderate)
- The two comparators, IVIg and SCIg, are available to patients now and evaluating their relative benefit and harm is critically needed to address the decisional dilemma. (moderate)

Weaknesses:

- None noted

Reviewer 4:

Strengths:

- major strength – the study team clearly took time and effort to engage meaningfully with patients and caregivers prior to this application to seek their input and opinions on the grant (focus groups)
- major strength – a secondary aim of the study was added (with associated tool) based entirely on feedback from patients about what was important to them (self-efficacy)

Weaknesses:

- minor weakness – given that patients expressed great satisfaction and advocated strongly for their preferences with both therapies, there will clearly be a group of patients who will become markedly dissatisfied if one of the two study treatments stops being offered as a therapy to this patient group (i.e., if IVIG is found to have equal therapeutic benefit but is more expensive to administer, insurance may no longer cover that therapy and therefore those patients who appreciated the social benefits of going to infusion clinic will lose satisfaction)

Reviewer 5:

Strengths:

- Two prior focus groups with patients were conducted to understand the experiences and reasons for choosing different treatments. (Major Strength)
- Patient Advisory Committee (PAC) can provide a mechanism to engage patients and integrate their perspectives in the study conduct and dissemination of results. (Major strength)
- Patients are modestly compensated for phone calls; travel to meetings is compensated but no honorarium. (Minor strength)
- NORD and GBS/CIPD advocacy organizations are participating as study as advisors. (Major strength)

Weaknesses:

- It would be helpful to know when and where the patient focus groups were conducted, and how many patients participated and how they were selected. (Minor weakness)
- There is no LOS from affected patients. (Minor weakness)
- The LOS from the NORD and GBS/CIPD advocacy organizations do not convey genuine interest in the question or participating in the study as advisors. (Minor weakness)
- There is no estimate of the burden of these assessments on patients. For example, there is no description of how long the assessments will take, whether they'll be administered electronically or by an interviewer, or whether there are special administration issues or concerns for certain groups (e.g., low SES, low literacy). There is also no discussion of patients' thoughts on the relevance and understandability of the assessment items. (Moderate weakness)

Criterion 6: Patient and stakeholder engagement

Reviewer 1:

Strengths:
• The application provides a well-justified description of the research team incorporating stakeholder involvement that includes patients, caregivers, clinicians, policymakers and other healthcare system stakeholders. This strengthens the study for successful conduct and completion (MAJOR).
• The study has received support from the PCORnet 2.0 Steering Committee (MAJOR).
• The application shows evidence of active engagement among scientists, patients, and other stakeholders throughout the research process such as during formulating questions, identifying outcomes, monitoring the study, disseminating plan and result implementation. The active engagement and support of the stakeholders make the study highly relevant. The frequency and level of patient and stakeholder involvement appears sufficient to support the study goals except as described in the weakness section (MAJOR).
• The application demonstrates the potential for future partnerships/collaboration with the co-funder (MINOR).
• The proposed Engagement Plan appears appropriate and tailored to the study, except as described in weaknesses (MINOR).
• The roles and the decision-making authority of all study partners are clearly described. The organizational structure and resources are appropriate to engage patients and stakeholders throughout the project (MAJOR).

Weaknesses:
• One of the key stakeholders in this research question are the insurance companies/payers. Their primary interest is in cost savings and hence the application should address their concerns more clearly (MAJOR).

Reviewer 2:

Strengths:

- The proposal clearly outlines multiple ways the team intends to engage patients, using advisory panels, focus groups and Patient Voice Sessions with clinicians.
- The use of Patient Voice Sessions with investigators and clinicians is a novel way to infuse the patient experience into the understanding of the research results. It would be helpful to know how often these sessions might be convened during this project.

Weaknesses:

- MAJOR WEAKNESS: There is not a clear understanding of how the research team will use the resources available through PCORnet 2.0 and the coordinating center. The sole mention of PCORnet 2.0 infrastructure (page 7, Research Plan) consists of one sentence and does not elaborate on how those resources might be used or

strengthened through this project.

- MAJOR WEAKNESS: This may be merely a clerical error but the external vendors supporting this project are providing in-kind services. RMS Medical Products is listed as a partner and as providing infusion equipment to the SCIg arm of the study. SCIg is delivered subcutaneously and not intravenously. What RMS is providing for this research needs to be explained further.

Reviewer 3:

Strengths:

- Input from patient focus groups (about patient-reported outcomes of interest and factors relevant in the decision process) have been incorporated into the study design. (moderate)

Weaknesses:

- The engagement plan lacks detail. It is unclear how many patients will be involved in the Patient Advisory Council (PAC). For the patient voice sessions with investigators and clinicians, it is unclear how often the sessions will be held or how they will be organized. (moderate)
- The roles and decision-making authority of study partners are not explained. (moderate)
- There is no formal engagement plan with stakeholders other than patients (clinicians, insurance, policy makers, etc). (moderate)
- With the under-developed engagement plan, the potential for this study to foster future collaboration is limited. (moderate)

Reviewer 4:

Strengths:

- major strength – partnerships with the GBS/CIDP Foundation and National Organization for Rare Disorders (NORD) demonstrate excellent insight into working with appropriate stakeholders to increase study success
- major strength – in-kind support from industry sponsors (NuFactor and RMS Medical) is appropriately responsive to this funding mechanism and supplies necessary study resources
- major strength – engagement plan is detailed and describes equal/reciprocal partnerships with patients well
- minor strength – study team indicates that industry sponsors may be interested in pursuing partnerships for other diseases requiring infusion therapies

Weaknesses:

- minor weakness – given that the electronic linkage between the study team and CIDP registry has not been explored/designed yet, it is unclear if this partnership will lead to sustained collaboration
- minor weakness - it is unclear how, other than financially, the stakeholder partners (industry sponsors) will participate in the overall execution of the study (and/or contribute intellectually)

Reviewer 5:

Strengths:

- Patient Advisory Committee (PAC) provides a good mechanism for patient involvement. (Moderate strength)
- The compensation for patients to generate video "stories" of their experience can be informative for clinical decisions. (Minor strength)
- Dr. Kimminau has excellent experience soliciting patient input in research. (Major strength)
- The roles and the decision-making authority of all study partners is sufficiently described. (Moderate strength)
- The project does have the potential for future research collaboration with the co-funders. (Moderate strength)

Weaknesses:

- It is not clear what services or data the NORD and GSB/CIDP Foundation will provide. They have a large amount budgeted for "operations" with no clearly defined tasks. (Major weakness)
- Although it is clear that patients (or at least data from focus groups of patients) motivated this proposal, the application does not show evidence of active engagement among scientists, patients, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating, implementing). A missed opportunity is the engagement of patients in the development of assessments and data collection. (Moderate weakness)
- There is no inclusion of patients on the study team. Although a PAC is mentioned, no one is named for that role. (Minor weakness)
- Dr. Kimminau is listed as stakeholder/partner in part of the application, but it appears from her affiliation that she is not truly a patient stakeholder herself. (Moderate weakness)

Does the application have acceptable risks and/or adequate protections for human subjects?

Reviewer 1: Yes
No concerns.

Reviewer 2: No
The statement "Participants can withdraw from the study at any time if the financial risks become intolerable" is difficult to understand in the context of being a PCOR study and one which will have a small population to recruit from. Listing financial hardship as a protection item without also having clearly defined plans to assist with this hardship is not acceptable from the patient reviewer perspective.

Note: Page 15 has the following statement which leaves much confusion and might be a cut and paste error from a different application - "Since we are studying the only two FDA-approved medications for ALS, the only options for alternate treatment are investigational medications or no treatment at all."

Reviewer 3: Yes

Reviewer 4:
The proposal indicates a budget of $600 to contribute to co-pays to assist those who incur a financial burden (unsure if this is per patient or total for study); equity of patient enrollment is a consideration given that not all patients may be able to pay out-of-pocket costs to participate if their insurance fails to pay because they are participating in research.

Reviewer 5: Yes
This is a randomized comparative effectiveness study of 2 FDA approved standard of care administration approaches to Ig therapy. The investigators state that the study is low risk. They include a DSMB but propose that the DSMB meet 3 times per year. This seems excessive and this reviewer wonders if perhaps this language was borrowed from a previous application. In any case, the criteria and selection process for DSMB members is not clear, nor is their charge or scope of work. There is no discussion of how adverse events and other data will be collected and reported to the DSMB.

Overall Comments:

Reviewer 1:

The application by Barohn et al addresses a rare but potentially severely disabling acquired autoimmune neurological condition, CIDP and proposes to conduct a randomized controlled study with a sample size of 50 newly diagnosed CIDP patients to determine if IVIG or SCIG is more effective in CIDP management compared to historical control. The study will also compare the safety profile of the two treatments. While the study has several strengths that include: a good research idea, well-chosen primary and secondary outcomes, good data linkage strategies and using PCORnet CDM at sites to identify and recruit patients, a very strong investigator team and environment, strong stakeholders engagement and their interest in this study, several concerns as summarized below should be addressed by the applicants to make this an even stronger application.

The comparison of the two Ig groups (IVIG or SCIG) to the historical control group data from prior CIDP trial seems somewhat concerning as heterogeneity in the CIDP populations and finding the right control from the prior CIDP trials could be challenging and may compromise the study results or completion. Another important aspect of this study that deserves some discussion by the applicants is the impact on the health care costs with the two forms of IVIG since cost savings are important for payers as well as the patients. In summary, there is moderate likelihood of the project to have a significant impact on practice and/or healthcare delivery in the field of CIDP.

Reviewer 2:

This application looks to compare the effectiveness of delivery methods of immunoglobulin treatments for people affected by Chronic Inflammatory Demyelinating Neuropathy (CIDP). CIDP is a rare disease with a small population in the US, making research on the disease a challenge. The proposal will use historical data gathered from a variety of sources as the control and then compare patient response to either intravenous administration of immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) to the control. They are not proposing to do a head-to-head comparison of IVIg vs SCIg, but the study looks to develop a better understanding of treatment effectiveness of one method over the other. The researchers have identified two aims for this study, the first being to see if either IVIg or SCIg is superior to the historical control data and the second to determine which treatment has less side effects.

The burden of care for people with CIDP receiving IVIg includes travel, infusion clinic costs, and additional time for treatment. Using SCIg would free the person from having to do their treatment in an infusion clinic setting, and presumes it would lessen then burden on the patient. Of note, in focus groups some patients identified being in a clinic setting with other people receiving infusions has benefits to socialization and a positive side toward motivating people to go outside their personal boundaries.

The study calls for a total of 50 people, split between the IVIg and SCIg treatments. The patients will be treatment naïve and identified through patient registries as well as PCORnet and CRNs. The patient population with CIDP is relatively small, and finding 50 treatment naïve patients within the Great Plains Collaborative (GPC) in the proposed time frame may present a problem.

The study includes sites from the GPC, a PCORnet clinical data research network (CDRN) comprised of 12 medical centers in 9 different states. The researchers have gained experience with large data research, capture of electronic health records, and patient-centered research through their connection with GPC.

There are two commercial partners for this research, demonstrating the interest and ability to bring in outside revenue for sustainability. The partners support infusion equipment and injection supplies. There is a question as to what in-kind services these partners will provide and needs to be further explained in the proposal or given more detail in the budget.

The common practice of taking prior proposals and adapting them to a current PFA to maximize resources for an institution is acceptable and understandable, but leaving key details from other applications that do not apply to the current PFA is sloppy. In particular, the mention of the lack of ALS drugs (page 15, Research Plan) is a glaring example. The confusion in other sections of this proposal may also be an result of this process and care should be taken in future applications to ensure only relevant material is included.

This proposal has several unanswered points, including how it might benefit the work of PCORnet and strengthen PCORnet processes. The capacity for data linkage with REDCap to other CRNs through the use of the PCORnet Common Data Model should be elaborated on further to demonstrate this project would test PCORnet's readiness to support research.

Reviewer 3:

This study proposes a randomized trial to assess the comparative effectiveness of IVIg vs SCIg in CIDP patients. Addressing this evidence gap has the potential to support decision-making by clinicians and patients and improve quality of care. The PI and other team members are highly qualified and experienced with adequate institutional support. There are several major concerns about this project. It proposes to conduct two one-sample tests, each separately comparing SCIg or IVIg to historical control. This setup is not very helpful in clarifying the comparative effectiveness of IVIg vs SCIg. The description of the study population is inconsistent within the proposal. It is concerning that a single dosage will be used for SCIg, although individualized dosage has been recommended in clinical practice. The purpose or the process of data linkage between the CIDP registry and KUMC database is not well explained. No description or citation was provided for the historical control. In the sample size justification, the assumption of "25% absolute difference" is not justified. The baseline rate in the historical control is not presented. The engagement plan lacks detail, especially for engagement with non-patient stakeholders. Overall, this study has many serious weaknesses and is unlikely to have significant impact on clinical practice/health delivery.

Reviewer 4:

This randomized control trial of IVIG versus SCIG for treatment of new or refractory CIDP certainly addresses a gap in the current literature. Study investigators are embedded in the hub of PCORnet's Greater Plains Collaborative (GPC) and have established connections with stakeholders highly engaged with these patients (NORD and GBS/CIDP Foundation). Responsive to this PFA, the study team has partnered with industry to acquire necessary supplies for this study. Patient-centeredness is high; there was thoughtful engagement with patients prior to developing the application, a secondary aim was added as a result of patient interest, and the investigators provide great detail into how they will partner with patients for successful engagement.

This application loses its merit primarily due to the lack of detail regarding the design of the study. Beyond a single paragraph describing medication and dose, there is no detail about study visits, timelines, labs, etc. and other pertinent study data; there is also no definition or description of how the study team plans to compile the control cohort and

data. Another critical consideration is the lack of support from all GPC sites, as well as a lack of legal contracts with any collaborators outside the Kansas team. This leads to concerns about how ready the study team truly is to execute the project if funded and/or if the study team indeed has everything secured to be successful. The application also falls short in responsiveness to the PFA related to the use of PCORnet resources and infrastructure, given that they have done no planning for data linkages between the GBS/CIDP Foundation Registry and PCORnet, and have included no detail in their proposal about how they will capitalize on the use of PCORnet data other than to identify patients for possible participation.

Reviewer 5:

The proposed study will compare the impact of intravenous (IV) versus subcutaneous (SC) administration of Immunoglobulin therapy for Chronic Inflammatory Demyelinating Neuropathy (CIDP), a rare condition. Immunoglobulin therapy has been shown to be effective in treating CIDP but the comparative efficacy of IV and SC administration is unknown. Because there are costs and burdens associated with IV treatment, the effectiveness results can inform treatment decisions for patients. The investigators are expert neurologists and experienced researchers in CIDP and have a long track record of engagement in PCORnet and leadership in the PCORnet Greater Plains Consortium.

Despite the importance of the clinical question and experience of the investigators and their research team, this application does not provide clear description or justification of the study size, data collection, and data analysis approaches. The proposed study includes a randomized design for 50 patients, 25 for IVIg and 25 for SCIg. Each arm will be compared with historical data (not defined in the proposal). Sample size considerations are used to justify this approach over direct comparison of the 2 arms. However, the sample size and clinical effect size criteria are not discussed. Further, the data sources and specific variables of interest are not clearly defined and it is not clear how this study will leverage PCORnet data resources. Two patient advocacy groups are included on the project as advisors to support the use of a registry for recruiting patients and providing data to the study, but there is not a description of the registry participants or data elements. There are several examples of conflicting information in the application, particularly around how study subjects will be identified and recruited, and how the safety aspects of this study will be managed. The feasibility of the study and relevance of the results to inform real-world treatment decisions in CIDP cannot be assessed because the application provides no preliminary data on the number of patients at each site, their features, and current treatment patterns.

Phase II Study of Arimoclomol in IBM FDA-OOPD (Orphan Products Division) R01

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In the prior issue of the RRNMF journal, we published the history of research and development of arimoclomol in IBM in the last 15 years (1). In this report, we provide the protocol that was ultimately approved for funding by the FDA OOPD and the associated reviewer comments. We had submitted the protocol to the same funding agency twice prior to being funded as of June 01, 2015. There were several constructive reviewer comments that we addressed along the way. Support and advice from the arimoclomol investigative team that met yearly at the annual Muscle Study Group (MSG) meetings helped us tremendously in responding to reviewer's comments and amplified the energy driving this process. This grant was an official MSG project. It was approved by the MSG executive committee. The plan was for it to be managed by the MSG coordinating center (Drs. McDermott, Tawil, and Martens). After this was funded, Orphazyme became more involved as a partner and took over the data management. Dr. McDermott remained on-board as a leader of the statistics team. There were 12 MSG sites in the study: University of Kansas Medical Center; HonorHealth; The University of California, Irvine Medical Center; University College London; Houston Neurocare Pa; The Johns Hopkins University School of Medicine; Brigham and Women's Hospital; University of Rochester Medical Center; The Ohio State University Wexner Medical Center; University of Colorado Denver; University of Virginia Health Sciences Center; University of Utah Health.

As you can imagine, it was really discouraging to be turned down the 1st time and then a 2nd time. However, with drug development and funding, persistence is very important to move clinical research and discovery forward. Having the right team of investigators and support of the MSG Data Coordinating Center were critically important to our success. We hope you enjoy and get inspired by reading about our arduous journey to what ultimately became the Phase 2/3 Study of Arimoclomol in IBM.

Reference

1. Dimachkie, M., Machado, P., Sundgreen, C., Blaettler, T., Statland, J., Heim, A., Herbelin, L., Greensmith, L., Hanna, M., & Barohn, R. J. (2021). The Early History of Arimoclomol for Inclusion Body Myositis. RRNMF Neuromuscular Journal, 2(2). https://doi.org/10.17161/rrnmf.v2i2.15404

Phase II Study of Arimoclomol in IBM
FDA-IND # 76,773
Version date: 10/13/2014

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Abstract

Sporadic inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy presenting after age 50 years. It presents with chronic insidious proximal leg and distal arm asymmetric muscle weakness. Muscle histopathology reveals endomysial inflammatory exudates surrounding and invading non-necrotic muscle fibers often times accompanied by rimmed vacuoles and inclusions. Unlike polymyositis and dermatomyositis, patients with IBM do not improve with therapy; at present there is no effective treatment for IBM. The histopathological features and lack of response to immunotherapies has led many experts in the field to believe that IBM is primarily a degenerative disorder of muscle with secondary inflammation.

We completed a randomized controlled pilot study in 24 IBM subjects, 18 of whom received arimoclomol 100 mg PO TID for four months and 8 were on placebo. Arimoclomol increases heat shock proteins and may prevent protein misfolding. We found arimoclomol to be safe. The IBM functional rating scale (IBMFRS) decline at 1 year was less in the arimoclomol group compared to placebo with the p value approaching significance at 8 months.

We are therefore proposing a twenty months randomized, placebo-controlled Phase II study of arimoclomol in 150 IBM subjects. The primary aim is to assess the efficacy and safety of arimoclomol (200 mg TID). The primary efficacy endpoint is the IBMFRS. Secondary efficacy outcomes will include different measures of strength and function: manual muscle testing (MMT), maximum voluntary isometric contraction (MVICT) of quadriceps, grip and pinch test, modified timed up and go (mTUG), 6 minute walk test with 2 minute distance captured; a general physical function measure: Health Assessment Questionnaire (HAQ- DI); a Health-Related Quality of Life (HRQoL) measure using SF36. Safety laboratory and adverse events will be collected. Our long-term goal is to find an effective treatment for people with IBM.

1. Summary of Specific Aims

The primary objective of the proposed Phase II study is to assess the efficacy of arimoclomol (200 mg TID) as compared with placebo over twenty months of treatment in 150 patients with Inclusion Body Myositis (IBM); 75 randomized to arimoclomol and 75 to placebo.

Specific Aim # 1
To determine if arimoclomol 200 mg TID can slow down the rate of IBM disease progression over 20 months of treatment. The primary outcome measures will be the comparison of the rate of decline in the Inclusion Body Myositis Functional Rating Scale (IBMFRS) [1,2] between control and experimental subjects. Conservatively, we have an 80% power to detect a 40% or greater difference between the 2 groups at 12 months. Although the above sample size justification applies to the 12-month change in IBMFRS score; it will also apply to the 20-month change in IBMFRS score if, as expected, the magnitude of the treatment effect relative to the magnitude of the standard deviation of the change in IBMFRS does not diminish over time.

Specific Aim # 2

The second aim is to determine if secondary endpoint measures are affected by arimoclomol. This includes muscle strength testing (manual muscle testing and maximal voluntary isometric contraction), grip and pinch, 6 minute walk test (with distance at 2 minutes captured), number of falls, modified timed up and go (mTUG), quality of life and self-reported disability. We will also compare the change in these parameters between placebo and arimoclomol at twenty months.

Specific Aim # 3

The third aim is to collect safety and tolerability information on arimoclomol (200 mg TID) for up to twenty months in IBM. We currently have safety data on arimoclomol 100 mg TID for 4 months in IBM subjects. Whereas 200 mg dose was safe in ALS over 1 year (personal communication by Dr. Michael Benatar), we intend to determine if these findings can be extended to a different clinical patient population in IBM for twelve and twenty months.

2. Background and Significance

Clinical Features: IBM is the most common progressive and debilitating muscle disease beginning in persons over age 50 years, with an annual incidence estimated at 1-2:100,000.[3-9] Because biopsies of IBM muscle contain lymphocytic inflammatory cells, IBM was originally grouped with the inflammatory idiopathic myopathies: polymyositis and dermatomyositis. However, pathologic studies during the past 25 years have clearly defined it as a unique pathogenic entity.[10-11] IBM is a progressive, debilitating disease causing both proximal and distal muscle weakness, characteristically most prominent in the quadriceps and finger flexors.[12-15] Over time it can lead to severe disability, including falls due to quadriceps muscle weakness and foot drop, dysphagia, and eventually respiratory muscle weakness.[11, 16-18] IBM seldom affects patients under 40 and is much more common over the age of 50. Men are affected more frequently than women.[19] The natural history of IBM has been followed prospectively in three studies.[20-24] Rose et al. followed 11 subjects for six months, and found an overall four percent decrease of strength from baseline. [21] Data collection from 136 IBM patients from the Paris and Oxford groups was completed either during a clinic visit (52%), or by extraction from previous medical records (48%). After a median duration of 14 years from onset, 75% of patients had significant walking difficulties and 37% used a wheelchair.[24] Patients were treated with immunosuppression agents (prednisone, intravenous immunoglobulins, methotrexate or azathioprine) for a median duration of 41 months were more severely disabled on last assessment. We performed a retrospective chart review of 51 IBM cases from the University of Kansas.[11,25] After a 7.5-year mean disease duration, 56% of our cases required an assistive device, with 20% requiring a wheelchair or motorized scooter (Table 1).[11]

Table 1: Retrospective chart review of IBM from 2000 to 2010 at KUMC

Male:female ratio	1.7:1
Ethnicity (n=51)	49 Caucasian; 2 Hispanics
Mean age at onset (yrs)	61 (45-80)
Symptom onset before age 50 yrs:	12%
Mean time to diagnosis (yrs)	5.1 (1-15)
Mean follow up period (yrs)	2.5 (0.5-8)
CK (IU/L)	609 (59-3000)
Nerve conductions with axon loss neuropathy	32%
Electromyography	60% irritative myopathy 12% non-irritative myopathy 28% mixed neuropathic/ myopathic pattern
Asymmetry	90%
Non-dominant side weaker	85%
Typical phenotype: Weak Finger Flexor (FF) and quadriceps (quads)	39/51 (76%): 13 - Classic phenotype (FF and quads weakest)

	11 - Classic FF, no preferential quads weakness 6 - Classic quads, no preferential FF weakness 9 - FF and quads weak but not weakest
Atypical phenotype	12/51 (24%): 5/12: classic FF with leg weakness sparing quads 4/12: limb-girdle weakness 3/12: other atypical phenotypes (FF arm only, hip flexion/ankle dorsiflexion, facioscapulohumeral)
Muscle pathology	43: inflammation and rimmed vacuoles 8: phenotypic IBM with inflammation but no vacuoles
Mobility Outcome	75%: recurrent falls 56%: assistive device use at mean 7.5 years 20%: wheelchair or scooter
Bulbar dysfunction	51%: dysphagia 55%: facial weakness

There is also myonuclear degeneration early on in IBM because the majority of rimmed vacuoles are lined with nuclear membrane proteins. IBM myonuclei are often abnormally filled with neurofilaments and this may be the earliest detectable pathologic change in IBM.[3]

In IBM, myofibers contain nonnuclear sarcoplasmic Tar DNA binding protein 43 (TDP-43) accumulations together with a reduction of the normal nuclear TDP-43 content. This suggests that TDP-43 has redistributed from nuclei to sarcoplasm in a large percentage of IBM myofibers.[26] The extranuclear accumulation of TDP-43 may be toxic to cells perhaps through altered binding to and splicing of mRNA. Immunohistochemically, TDP-43 and p62 were the most sensitive markers, accumulating in all definite IBM and in 31% and 37%, respectively, of possible IBM cases.[27] Therefore, IBM muscle accumulates multiple toxic protein aggregates suggesting a disorder of protein homeostasis.

The degenerative theory of IBM hypothesizes that IBM is a degenerative muscle disease occurring in an aged cellular environment, associated with cellular accumulation and aggregation of several proteins, involving abnormal signal transduction and transcription, protein misfolding, inhibition of the cellular protein degradation pathway, and mitochondrial dysfunction.[28] The lymphocytic infiltrate is considered likely to be secondary to muscle fiber degeneration.

A model of pathogenesis in IBM has been proposed (see Figure 1).[29] In this model the aging muscle intracellular environment, combined with environmental factors like oxidative stress, viruses, or other toxins, and in combination with mutations in predisposing genes leads to up-regulation of Aβ precursor protein. This leads to abnormal accumulation of Aβ 40 and 42 fragments. The Aβ 42 fragment in particular has a hydrophilic face and tends to aggregate into cytotoxic oligomers. Increased transcription of Aβ precursor protein leads to up-regulation of other proteins which co-aggregate with Aβ fragments. The effects of these toxic oligomers cause oxidative stress in the cell, phosphorylation of tau protein, an increase in misfolded proteins, and inhibition of the proteosome protein degradation pathway. This creates a positive feedback cascade. The cell increases its levels

of heat shock proteins to help counteract this increase in misfolded proteins, in particular HSP70, but cannot keep up with increasing levels of toxic protein products. This upregulation of Aβ precursor protein can also lead to mitochondrial defects, further exacerbating the cycle. In support of this theory, cultured muscle fibers with overexpressing Aβ precursor proteins display similar pathology to that seen in human IBM muscle biopsies. Accumulation of these misfolded proteins eventually leads to the characteristic Aβ amyloid inclusions and paired helical fibers containing phosphorylated tau seen in IBM muscle biopsy specimens. [28,30-32]

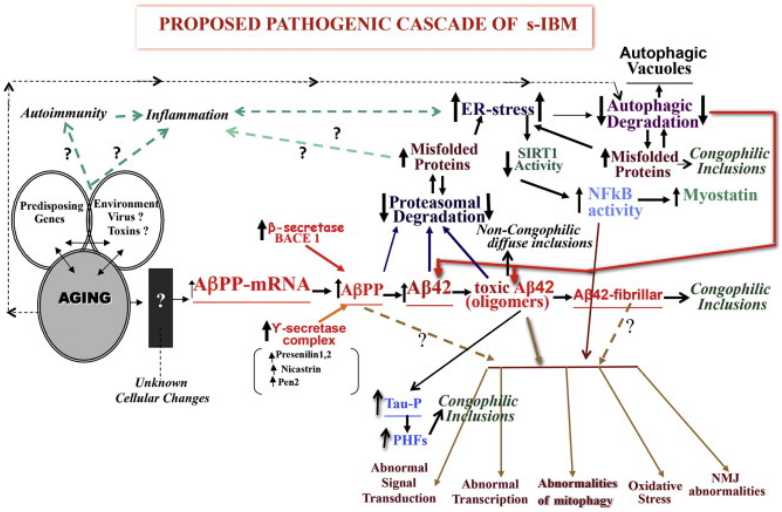

Figure 1. Proposed pathogenic cascade of sIBM [29]

Six of 7 IBM patients showed increased PIB levels in at least 1 gastrocnemius muscle, and the median PIB of the gastrocnemius muscles was significantly higher in IBM patients than in non-IBM subjects. [33] In two patients, muscle biopsies available from the gastrocnemius muscle with increased PIB uptake showed several fibers with dense amyloid-β and PIB positive inclusions on immunostaining. However, another IBM patient with normal deltoid muscle PIB uptake was amyloid-β positive without any detectable PIB positive inclusions.

Protein Misfolding: Many systemic and neurodegenerative disorders, termed 'protein-misfolding disorders' are characterized by the accumulation of intracellular or extracellular protein aggregates [32]. The initiating event in the disease process may be a crucial conformational change that occurs in the disease protein, possibly mediated by physical trauma, oxidative damage, or an infectious agent that leads to protein aggregates. These aggregates, or more likely their intermediate oligomeric precursor forms, can act to catalyze the process of additional aggregation, accelerating the "sequestration" of the normal protein and potentially trapping other important proteins that are prone to aggregation. In most instances these aggregated protein products are found to be cytotoxic, although the exact mechanism of toxicity is unclear.

A highly conserved class of proteins called molecular chaperones has evolved to prevent inappropriate interactions within and between non-native polypeptides, to enhance the efficiency of *de novo* protein folding, and to promote the refolding repair of proteins that have become misfolded as a result of cellular stress [34-36] (see Figure 2). In addition to this protein repair activity, chaperones can mediate targeting to the proteasome system or to lysosomes, resulting in selective degradation of the misfolded protein when the chaperones cannot repair the misfolded proteins. These activities of the molecular chaperones may be sufficient to prevent the normal accumulation of misfolded proteins. Under conditions of cellular stress, chaperone activity is increased, adjusting to the consequent increase in damaged proteins. However, under certain pathological conditions (perhaps due to prolonged exposure during chronic disease), the capacity of this protein quality

control machinery can be exceeded, and misfolded proteins accumulate to dangerous levels.

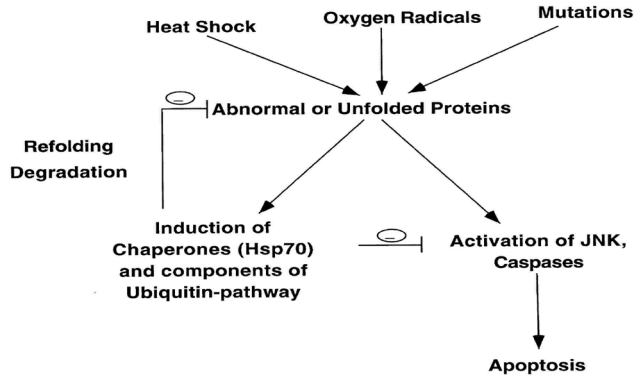

Figure 2. Schematic of the mechanism of action of HSP70 [34]

Arimoclomol: Arimoclomol (/+/-(2R),(Z)-N-[2-hydroxy-3-(piperidin-1-yl)propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (1:1)) (BRX-345) is an analog of bimoclomol, a hydroxylamine derivative that acts as a co-inducer of "heat shock" or "molecular chaperone" gene expression. This compound has been developed by a small biotechnology company, CytRx and currently owned by Orphazyme. Although the precise molecular mechanism of action of arimoclomol is not known, the compound has been shown to co-induce molecular chaperone genes, meaning that it further elevates the chaperone protein levels already induced by physical or metabolic stresses in cell lines and in isolated cells/tissues (see Figure 3). It apparently accomplishes this by stabilizing the active phosphorylated trimer of the transcription factor, Heat Shock Factor-1 (HSF-1). Recent evidence suggests protein misfolding and aggregation play a key role in pathogenesis in IBM. Indeed HSP70 levels have been shown to be increased in IBM muscle biopsies. Arimoclomol may slow down the process of protein misfolding and aggregation in IBM by helping the muscle fiber to up-regulate inducible heat shock proteins. It may also slow progression of muscle degeneration in this progressively debilitating disease.

Trials assessing immunotherapeutic agents have not demonstrated significant efficacy against IBM. If arimoclomol were found to be beneficial for the treatment of IBM, this would represent the only effective treatment for this otherwise progressive disease. Preliminary studies in healthy volunteers have shown arimoclomol to be relatively safe and well-tolerated. We also present in the next section preclinical and clinical research study data. Linda Greensmith is a neuroscientist at the University College of London (Institute of Neurology) who studies the effects of arimoclomol in cell cultures and in an animal model of IBM. We also present data from our pilot safety study of arimoclomol in humans with IBM. We also describe our research in MR imaging of IBM muscle.

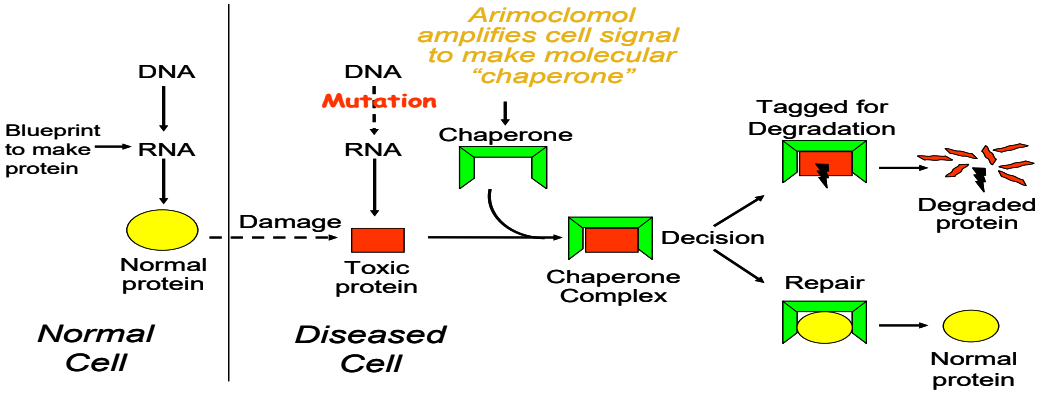

Figure 3. Arimoclomol amplifies cell signal to make molecular chaperones.

3. Preliminary Studies, with Figures

HSP70 is increased 4.5 times above normal in muscle biopsies of patients with IBM and has been shown by immunocytochemistry to co-localize with Aβ amyloid deposits. [30-31] In the SOD1 mouse model of amyotrophic lateral sclerosis, arimoclomol significantly increased levels of HSP70 and HSP90 in the spinal cords of mice and increased survival [37] (see Figure 4). In a manner similar to ALS, HSP70 levels are already upregulated in IBM; however, they may be sequestered in Aβ amyloid aggregates and thus rendered less effective. Increasing the availability of heat shock proteins in IBM may therefore be of therapeutic importance.

Arimoclomol has also been shown to interact with acidic lipids, including cardiolipin, a lipid component specific to the mitochondria. This lipid interaction may play a role in the protection of the mitochondria and prevention of apoptosis. In IBM cell culture models, mitochondria are thought to be affected by Aβ precursor protein and Aβ fragment over-expression. [30] Mitochondrial abnormalities are found in IBM muscle biopsies at a higher frequency than in the normal population. [38-39] Arimoclomol may help stabilize mitochondria in this environment.

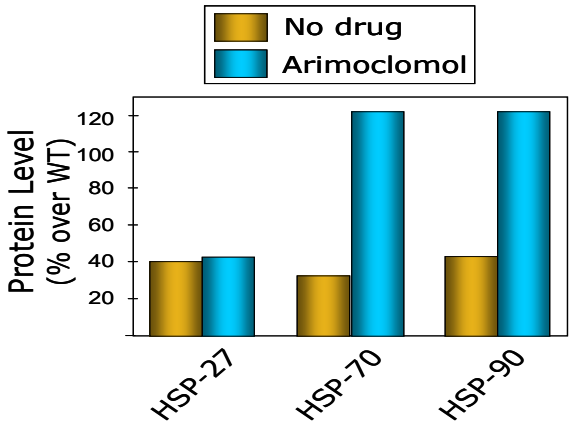

Figure 4. Arimoclomol-induced increase in HSP70 and HSP90 in SOD1 mice [37]

In vitro cell model of IBM:

We have recently developed and characterized an in vitro model in which primary rat muscle cells in vitro were transfected with β-APP in order to model the protein mishandling features of the disease. Over-expression of human β-APP in primary rat muscle cells recapitulated several of the key pathological characteristics of IBM, including the formation of intracellular inclusion bodies which were immunoreactive for β-APP and ubiquitin as well as AB-42, TDP-43, p-Tau, caspase-3 Hsp70 and p62. In addition, β-APP transfection resulted in activation of the NFkB cascade, as demonstrated by nuclear translocation of the p65 subunit, as well as ER stress.

Using this model, we examined the effects of treatment with arimoclomol on these IBM-like pathological characteristics by assessing the following outcome measures: i) cell survival; ii) formation of inclusion bodies; iii) HSP expression; iv) TDP-43 translocation from the nucleus to the cytoplasm; v) NFkB activation; iv) ER Stress.

Following treatment with arimoclomol, there was a significant increase cell survival, an increase in Hsp70 expression and a significant reduction in the formation of ubiquitinated inclusions in β-APP transfected myotubes. In addition, in untreated β-APP transfected cultures, cytoplasmic mis-localisation of TDP-53 was observed in 52.2% of myotubes by 4 DIV, and this was dramatically

reduced to only 2.4% of myotubes in arimoclomol-treated cultures (P<0.0001). Furthermore, the proportion of β-APP transfected myotubes in which the NFkB cascade was activated was also reduced by treatment with arimoclomol, so that the proportion of myotubes demonstrating p65 nuclear staining was reduced from 43% in untreated cultures to 23% in arimoclomol-treated cultures (p<0.05). Finally, examination of ER calcium handling and markers of ER stress revealed that β-APP transfection resulted in a significant reduction in ER [Ca^{2+}] (an indicator of ER stress), compared to empty vector treated controls (190nM compared to 280nM; p<0.05), a deficit that was completely prevented by arimoclomol (ER [Ca^{2+}] 290nM). This dramatic and beneficial effect of arimoclomol on ER stress was reflected in a reduction in the expression of th e ER stress markers CHOP and BiP in arimoclomol-treated β-APP transfected myotubes, compared to untreated cultures. [40-42]

Together these results indicate that arimoclomol ameliorates several key pathological features of IBM-like pathology, at least in an in vitro model of the disease (see Figure 5).

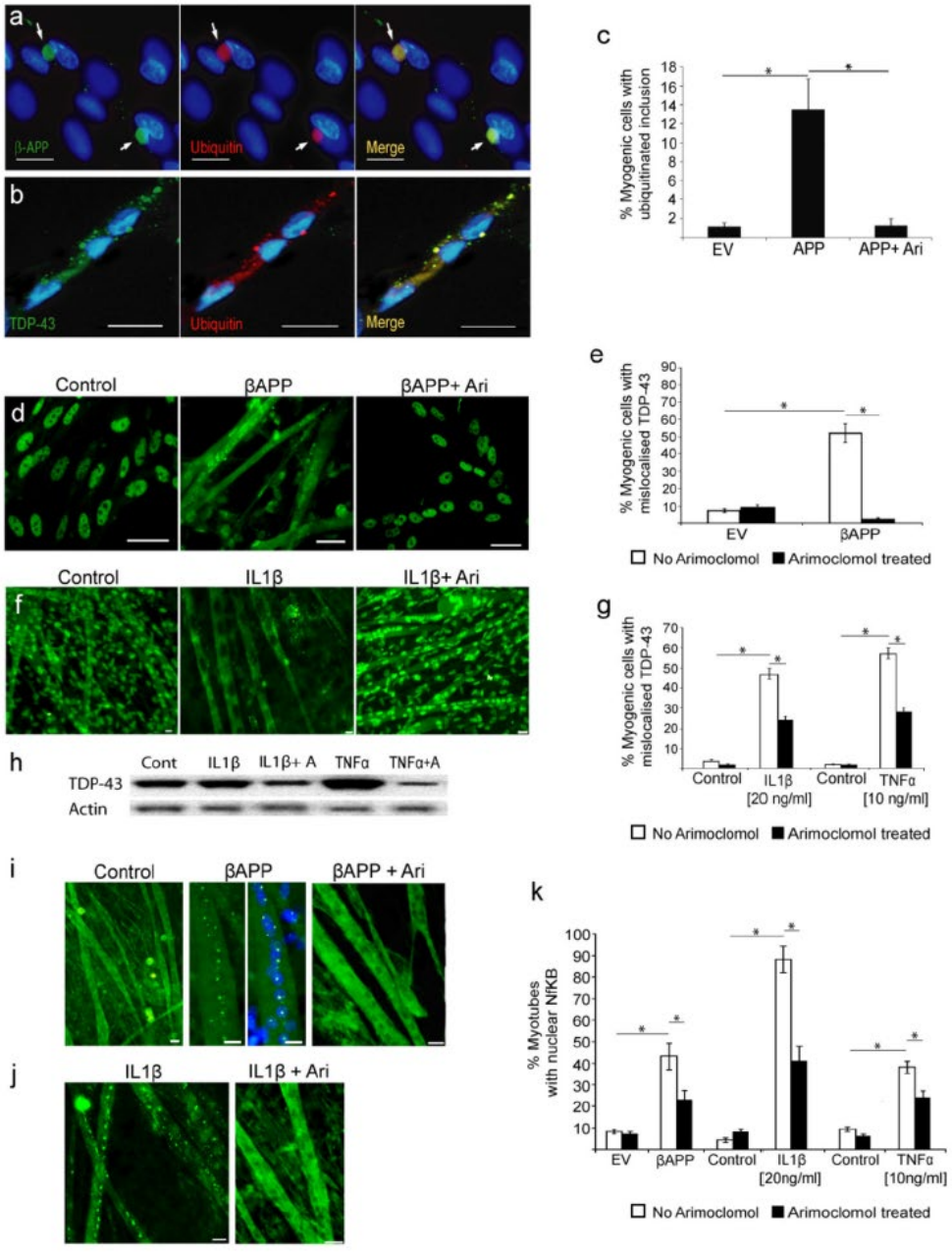

Figure 5. *Over-expression of β-APP and exposure to inflammatory mediators induces IBMlike pathology in cultured myocytes which is ameliorated by treatment with Arimoclomol.* Formation of cytoplasmic inclusion bodies in myocytes immunoreactive for (a) β-APP and ubiquitin and (b) TDP-43. The bar chart (c) shows the percentage of myocytes containing ubiquitinated inclusion bodies. (d) Expression of TDP-43 (green) following β-APP transfection and Arimoclomol treatment and (e) quantification of the number of cells with cytoplasmic mislocalisation of TDP-43. (f) TDP-43 expression (green) following exposure to inflammatory mediators and Arimoclomol treatment and (g) quantification of TDP-43 mislocalisation in inflammatory mediator exposed cultures. (h) Western blot analysis of TDP-43 expression in myocyte cultures exposed to inflammatory mediators in the presence and absence of Arimoclomol. (i) Images show the expression of NFkB subunit p65 (green) in β-APP transfected cultures (DAPI labelled nuclei in blue) and (j) cultures exposed to inflammatory mediators, in the presence and absence of Arimoclomol. (k) The bar chart shows the percentage of cells with nuclear NFkB subunit p65 under all culture conditions investigated. Error bars= S.E.M; Scale bars: a, b =10μm, d, i and j =20μm

In vivo model of IBM

We have recently completed an efficacy trial of Arimoclomol in a mouse model which recapitulates several key features of IBM.[43] Patients with an A232E mutation in valosin-containing protein (VCP), a protein involved in numerous cellular functions including protein degradation, present with a condition called Inclusion body myopathy with Pagets' disease and Frontotemporal Dementia (IBMPFD). Transgenic mice over-expressing the same human mutation in VCP display a muscle pathology that closely resembles that of IBM, including muscle weakness and histopathological signs of IBM such as rimmed vacuoles and TDP-43 and ubiquitin-positive pathology. We treated mutant VCP (mVCP) mice treated with Arimoclomol (120mg/kg per day, orally, in drinking water) from the start of symptom onset at 4 months until 14 months of age, a late stage of disease. Transgenic mice over-expressing wild-type human VCP (wt-VCP) were used as controls, and 10 male mice per group were studied. Muscle strength was assessed longitudinally by performing grip-strength measurements fortnightly from the start of treatment (see Fig.6a). In addition, muscle force was also established using isometric muscle force measurements performed on terminally anaesthetized mice at 14 months of age (Fig. 6b,c). In control wt-VCP mice, there was no significant reduction in grip strength relative to body weight between 4 (6.44g +/- 0.49 SEM) and 14 months of age (5.91g +/- 0.62 SEM). In contrast, in mVCP mice, there was a 44.1% reduction in grip strength during the same period (from 7.19g +/- 0.39g SEM to 4.02g +/- 0.3g SEM). However, in mVCP mice treated with Arimoclomol, there was no significant reduction in grip strength over time; with only a mild reduction from 6.24g +/- 0.42g SEM to 5.18g +/- 0.34g SEM by 14 months. These longitudinal readouts of muscle strength were reflected in the maximal tetanic force measurements obtained from extensor digitorum longus (EDL) muscles of mice examined at 14 months of age. In mVCP mice, EDL muscles generated significantly less force (16.59g +/- 1.86g SEM) than EDL muscles in wt-VCP controls (24.18g +/- 1.94g SEM). However, in Arimoclomol treated mVCP mice, there was no significant difference in the force output of EDL muscles (22.47g+/- 1.84g SEM) compared to controls. These results show that treatment with Arimoclomol prevents the loss in muscle force that occurs as disease progresses in mVCP mice.

Histological assessment of the hindlimb muscles of mVCP mice showed remarkable pathological changes which correspond with characteristic IBM features seen in patient muscle biopsies (Fig 6d,e). Tibialis anterior (TA) muscles of mVCP mice showed clear signs of degenerating and atrophied fibres of irregular sizes, infiltration of inflammatory cells, presence of vacuoles and proteinaceous aggregates. Furthermore, an increase in the number of centralized nuclei was observed which is regarded as a feature of regenerating muscle fibres. Examination of muscle from Arimoclomol treated mVCP mice however showed a greatly reduced level of degenerating and atrophied fibres (Fig. 6f). Quantification of the number fibres containing centralized nuclei showed that Arimoclomol treated mVCP mice had significantly more fibres with centralised nuclei (35.28% +/- 4.51% SEM) compared to untreated mVCP

mice (18.67% +/- 3.43% SEM) or wt-VCP mice (3.09% +/- 3.39% SEM), suggesting a greater extent of regeneration in the muscle of Arimoclomol treated mice.

Since Arimoclomol is known to be a co-inducer of the HSR, we also examined whether the beneficial effects of Arimoclomol on the muscle pathology in mVCP mice was reflected in a change in expression of Hsp70. As can be seen in Fig. 6h, Western blot analysis of muscle from mVCP mice treated with Arimoclomol showed a two-fold increase in the expression of HSP70 compared to that of untreated mVCP mice.

The results of this *in vivo* efficacy study in a mouse that models key aspects of IBM confirm that treatment with Arimoclomol prevents the decline in muscle strength and improves the histopathological characteristics of IBM, most likely as a result of an upregulation in Hsps.

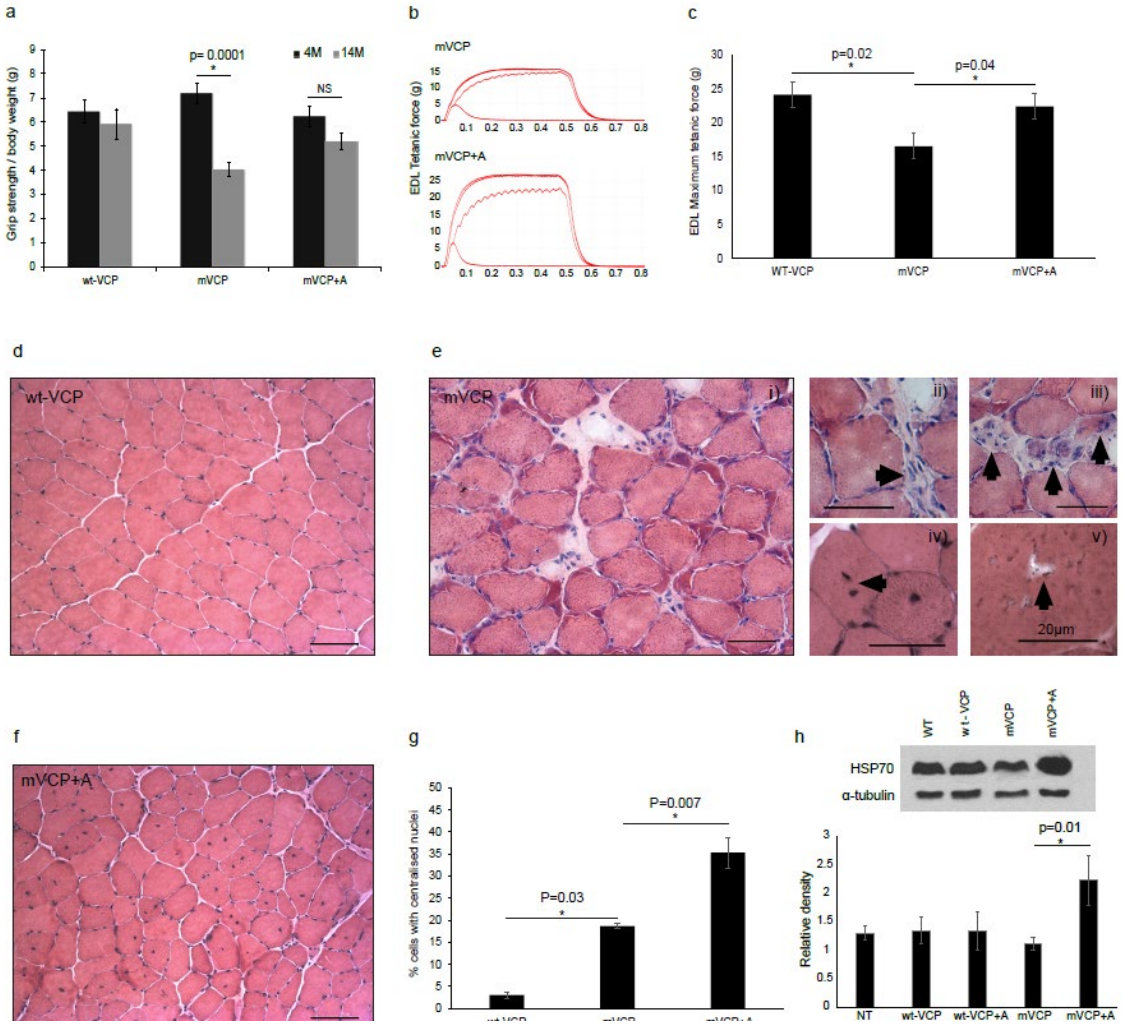

Figure 6. *Treatment with Arimoclomol prevents the loss in muscle force and appearance of IBM-like pathology in mutant VCP mice.* a) Longitudinal analysis of grip strength shows that there is a significant decline in grip strength in mVCP mice between 4 and 14 months of age which is prevented in mice treated with Arimoclomol. b) Typical traces of maximum tetanic force of EDL muscles in anaesthetized mVCP and Arimoclomol treated mVCP mice are shown. C) The bar chart shows that treatment with Arimoclomol prevents the loss in EDL force that occurs in mVCP mice by 14 months of age. Histopathological (H&E) analysis of TA muscles reveals the presence of key IBM-like pathological characteristics in mVCP mice. Compared to wt-VCP mice (d) TA muscles from mVCP mice (ei-v) show atrophied and degenerating fibres, inflammatory cell infiltration, centralized nuclei and the presence of rimmed vacuoles. In contrast, TA muscles from mVCP mice treated with

Arimoclomol shows few if any of these pathological changes (f). Quantification of the number of fibres with centralized nuclei (g) shows that there is a significant increase in the number of fibres with centralized nuclei in Arimoclomol-treated mVCP TA muscles which is indicative of active regeneration. H) Western blot analysis shows that here is a significant increase in the expression of Hsp70 in TA muscles of mVCP mice treated with Arimoclomol, compared to either untreated mVCP or wt-VCP mice. [43]

Non-clinical Safety Studies:

The acute effects of arimoclomol at doses of 100-400 mg/kg have been determined in mice, rats, guinea pigs, and dogs. Long-term toxicity studies have been performed to evaluate the safety of arimoclomol at doses up to 1500 mg/kg/day in rats and up to 210 mg/kg/day in beagle dogs. In preclinical safety studies, the no-observed-adverse-effect level (NOAEL) was 375 mg/kg in rats (28-day toxicity study), 200 mg/kg/day in rats (180-day toxicity study), 70 mg/kg in dogs (28-day toxicity study), and 50 mg/kg in dogs (90-day toxicity study). Short- and long-term animal studies suggest that no observed adverse effects of arimoclomol are observed below doses of 50 mg/kg/day, or at least 8-10 times higher than that proposed for humans in this study. Twelve-month toxicity studies in rodents were completed, and this data has been filed with the FDA by CytRx (the previous owner of the drug). The drug is now owned by Orphazyme. Arimoclomol has been shown to produce damage to chromosomes in hamster cells. Chromosomal damage is known in humans to be the cause of some genetic diseases such as cancer. However, the relationship between effects observed in cells and those in humans is not completely understood.

In a toxicity study performed in rats, sudden and unexplained deaths occurred in animals receiving arimoclomol alone, riluzole alone, and arimoclomol in combination with riluzole. The currently available data indicate that arimoclomol alone is lethal in rats at 1800 mg/kg, but not 900 mg/kg, and that lethality is notably increased when arimoclomol is administered in combination with riluzole. All of the animals which survived the 800 mg/kg dosing were found to have had cataract formation.

Human Safety Profile*:*

Arimoclomol has been tested in two double-blind, placebo-controlled human safety studies in normal subjects. It has been found safe and well-tolerated when administered to 12 healthy male volunteers in single ascending oral dosages up to 800 mg. There were no serious adverse events or deaths reported during the study. Two subjects reported mild sleepiness (approx. 2-2.5 hours duration) after administration of the 400 mg dose. The duration of these events was 2.25 and 5.50 hours, and they were stated by the investigators as “possibly related” to the study treatment. However, after unblinding, it was noted that one of these patients was treated with placebo at that dose level. Following these events both patients continued the study and took the capsules of higher dose levels without any adverse event. No changes in any safety parameters (such as laboratory parameters, vital signs, or electrocardiogram (EKGs) were reported during the study. The pharmacokinetics of arimoclomol after single-ascending oral doses was also assessed. Arimoclomol was absorbed rapidly with Tmax values ranging between 0.5 and 1.1 hours. Mean $t_{½}$ values ranged between 2.5 and 6.2 hours. There was a good dose-proportional increase in AUC and Cmax values.

Arimoclomol was also found safe and well-tolerated when multiple oral doses of 50 mg t.i.d. and 100 mg t.i.d. were administered to a total of 18 healthy young male subjects divided into two groups. Subjects of group A received 50 mg arimoclomol as a single dose on the morning of day one; then 50 mg arimoclomol t.i.d. on days two through nine; and a single 50 mg dose on the morning of day 10. Subjects of group B were treated with 100 mg arimoclomol in a similar regimen. Randomization was stratified by dose and was in the ratio of three placebos to six active treatments. There were no

serious adverse events or deaths reported during the study. Arimoclomol was generally well-tolerated by the study subjects. Fourteen subjects reported 31 adverse events. Seven events were reported by the subjects receiving placebo; 11 adverse events were reported by subjects receiving the 150 mg per day BRX-345 (arimoclomol) treatment; and 20 adverse events were reported on the 300 mg per day BRX-345 treatment. The intensity of these events was rated as mild to moderate. There was no evidence of clinically significant drug effects on vital signs or EKG assessments. There were no statistically significant changes in laboratory parameters. One subject had elevated eosinophils at screening and on day 11 in the 150 mg per day arimoclomol group, and another subject assigned to placebo had elevated eosinophils at day five. Overall, serum creatinine elevation was not found to be statistically significant. However, modest increases were observed in a number of volunteers. The increases were within the clinically accepted normal range and resolved after completion of the dosing regimen. Sleepiness is also a possible drug-related side effect. Maximal tolerated doses were not reached in these studies.

To assess its safety, tolerability, and pharmacokinetics in ALS, eighty-four participants received arimoclomol at one of three oral doses (25, 50, or 100 mg three times daily) or placebo. Participants who completed 12 weeks of treatment could enroll in a 6-month open-label study. Arimoclomol at doses up to 300 mg/day was well tolerated and safe. Serum pharmacokinetic profiles support dosing of three times per day. Arimoclomol at dosages up to 300 mg/day is well tolerated and safe in amyotrophic lateral sclerosis.[44]

A FDA OPD funded clinical trial using Arimoclomol at a dosage of 200mg three times per day is currently recruiting patients (http://clinicaltrials.gov/ct2/show/study/NCT00706147). The purpose of this study will be to demonstrate the safety, tolerability, and efficacy of arimoclomol in subjects with SOD1 positive familial Amyotrophic Lateral Sclerosis (ALS). The primary study objective is to demonstrate the efficacy of Arimoclomol, at a dosage of 200 mg three times per day, as compared with placebo, over 12 months of treatment in people with rapidly progressive familial ALS who harbor a mutation in the superoxide dismutase-1 (SOD1) gene. The primary hypothesis is that Arimoclomol will reduce by at least 30% the rate of progression of disease as measured by changes in the revised ALS functional rating scale (ALSFRS-R). In this study of arimoclomol by Dr. Benatar, PI at the University of Miami, the drug is well tolerated at the 200 mg TID dose (personal communication).

24 patient safety study in arimoclomol in IBM:

The University College of London (UCL) and University of Kansas Medical Center (KUMC) groups have been leaders in collaborating across the Atlantic in investigating the role of arimoclomol in IBM. Over the last decade, the UCL group, led by Michael Hanna, and the KUMC group, led by Richard Barohn, has had a keen interest in the study of the biologic effects of arimoclomol in IBM in vitro and in-vivo. To that extent Linda Greensmith's extensive preclinical laboratory research in IBM is described above in this section. Despite absence of adequate funding, both groups have been tremendously interested in arimoclomol, an interest which converged ultimately to the design, initiation and completion of the 24-patient pilot study by pooling internal resources.

The IBMFRS is a quickly administered (10-minute) ordinal rating scale (ratings 0-40) used to determine patients' assessment of their capability and independence in 10 functional activities. The scale was developed by the MSG investigators and was utilized in the beta-interferon-IBM trials [21-22]. All 10 activities are relevant in IBM. The advantages of the IBMFRS are that the categories are relevant to IBM, it is a sensitive and reliable tool for assessing activities of daily living function in patients with IBM, and it is quickly administered. In the beta-interferon trial, the IBMFRS correlated well with MVICT, MMT, SF-36, and the ALS-FRS [45].

The Inclusion Body Myositis Functional Rating Scale (IBMFRS) was derived from the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) which is another patient-derived subjective scale currently accepted as the primary endpoint measure for nearly all ALS clinical trials for the last 15 years. The IBMFRS has been validated in its use with IBM patients as it correlated well with objective strength measures (Maximum Voluntary Isometric Contraction and Manual Muscle Testing) and quality of life as assessed by the SF-36 [1]. Last year, we presented analysis of prospective IBMFRS data collected over several years in 127 IBM cases from the UK and USA [46].

1. SWALLOWING 4 Normal 3 Early eating problems – occasional choking 2 Dietary consistency changes 1 Frequent choking 0 Needs tube feeding **2. HANDWRITING (*with dominant hand prior to IBM onset)*** 4 Normal 3 Slow or sloppy; all words are legible 2 Not all words are legible 1 Able to grip pen but unable to write 0 Unable to grip pen **3. CUTTING FOOD AND HANDLING UTENSILS** 4 Normal 3. Somewhat slow and clumsy, but no help needed 2 Can cut most foods, although clumsy & slow; some help needed 1 Food must be cut by someone but can still feed slowly 0 Needs to be fed	**4. FINE MOTOR TASKS *(opening doors, using keys, picking up small objects)*** 4 Independent 3 Slow or clumsy in completing task 2 Independent but requires modified techniques or assistive devices 1 Frequently requires assistance from caregiver 0 Unable **5. DRESSING** 4 Normal 3 Independent but with increased effort or decreased efficiency 2 Independent but requires assistive devices or modified techniques (Velcro snaps, shirts without buttons, etc.) 1 Requires assistance from caregiver for some clothing items 0 Total dependence **6. HYGIENE *(Bathing and toileting)*** 4 Normal 3 Independent but with increased effort or decreased activity 2 Independent but requires use of assistive devices (shower chair, raised toilet seat, etc.) 1 Requires occasional assistance from caregiver 0 Completely dependent	**7. TURNING IN BED & ADJUSTING COVERS** 4 Normal 3 Somewhat slow & clumsy but no help needed 2 Can turn alone or adjust sheets but with great difficulty 1 Can initiate but not turn or adjust sheets alone **8. SIT TO STAND** 4 Independent (without use of arms) 3 Performs with substitute motions (leaning forward, rocking) but without use of arms) 2 Requires use of arms 1 Requires assistance from device/person 0 Unable to stand **9. WALKING** 4 Normal 3 Slow or mild unsteadiness 2 Intermittent use of assistive device (AFO, cane, walker) 1 Dependent on assistive device 0 Wheelchair dependent **10. CLIMBING STAIRS** 4 normal 3 Slow with hesitation or increased effort; uses handrail intermittently 2 Dependent on handrail 1 Dependent on handrail and additional support (cane or person) 0 Cannot climb stairs

The IBMFRS scale demonstrated good fit and reliability of items and is therefore ready for use as a Patient-Reported Outcomes Measures (PROM)..Furthermore, over the last 4-5 years, research has focused on subjects' functional ability or at least their perceived functional ability over strength with PROM.

Based on Rasch analysis, the IBMFRS is of good fit and reliability of items and is therefore ready for use as a PROM. Participants were of higher ability than the difficulty level of the scale. Based on this and the above supporting facts, we firmly believe that the IBMFRS is valid and will reliably capture IBM PROM.

Our pilot study consisted of a randomized placebo-controlled safety study of arimoclomol 100 mg PO TID administered for 4 months (the maximum time allowed by the FDA-IND office at the time), with an 8 month follow up period.[43] Twenty-four IBM subjects received arimoclomol or placebo with a 2/1 ratio. We obtained monthly safety data, strength and functional measures at the 2 participating sites: the UCL-Institute of Neurology-Neuromuscular Centre and the KUMC-Neurology Department-Neuromuscular Section. We enrolled 17 men and 7 women with a mean age of 69 years (53-81) and a diagnosis of definite (10) or probable (14) IBM. There were 8 treatment-possibly-related adverse events in the placebo group and 14 in the arimoclomol group, the most common adverse event being gastrointestinal (see below under *Expected Adverse Events* section). There was one Serious Adverse Event but none of the adverse events led to drug discontinuation. We detected a trend of slower decline in the manual muscle testing (MMT) sum score in the arimoclomol group (figure 7), but no differences were seen on the maximal isometric voluntary contraction or dual-energy X-ray absorptiometry. Though baseline IBMFRS values were lower by 0.9 points at randomization in the placebo group, the p value for that difference at baseline was not significant (0.375) and the yearly IBMFRS decline in the placebo group was 3.5 points (SD=3.3) and 2.1 (SD=2.7) in the treatment group (p=0.538). We identified at 8 months a trend for slower decline in the mean IBMFRS as compared to placebo (figure 8) (p=0.055) and in the average MMT score (p=0.147). [47] Our preliminary data indicates that arimoclomol is safe and well-tolerated in IBM. The IBMFRS is a useful primary outcome measure for future IBM research studies. Given the observed IBMFRS and MMT trends, we feel that further investigation of arimoclomol in a larger IBM patient population is warranted. While we used a dose of 100 mg TID in our pilot study, we are going to use the 200 mg TID dose in the proposed phase II safety and efficacy study. Our reasoning is that the higher dose is being used in the SOD1 positive familial ALS study and is well tolerated. We may be seeing an effect on the IBMFRS and the dose was 100 TID. Therefore, it seems reasonable to use the higher dose for our next IBM study.

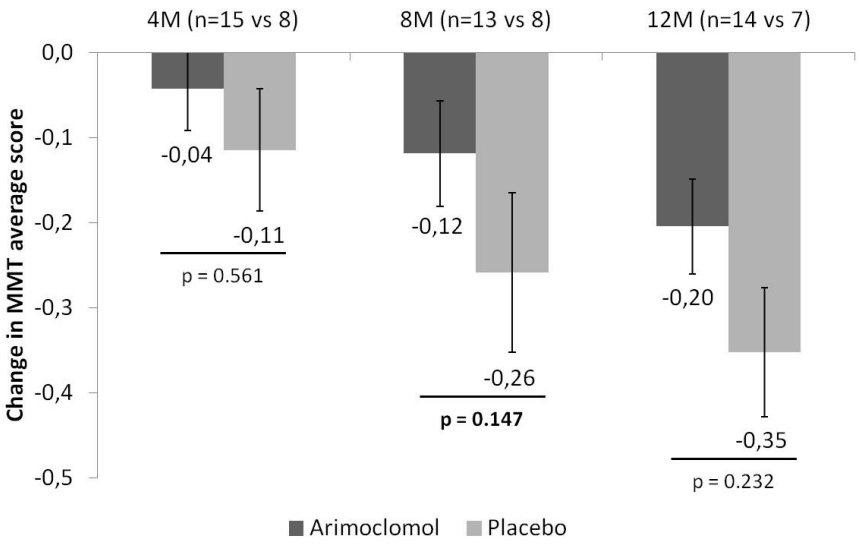

Figure 7. Bar charts showing change from baseline to endpoint (mean ± SEM) in mean MMT score

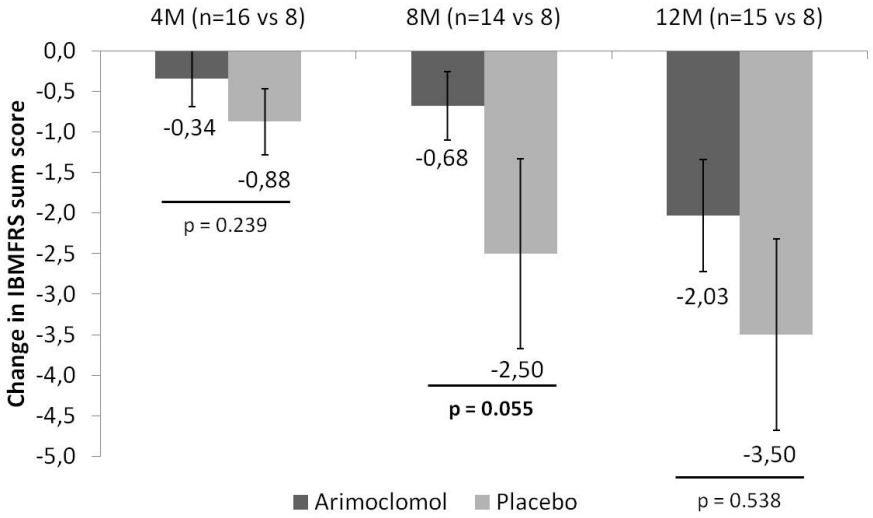

Figure 8. Bar charts showing change from baseline to endpoint (mean ± SEM) in IBMFRS score

Investigators Experience:
Dr. Mazen Dimachkie is Professor of Neurology at the KUMC and Director of the Neuromuscular Section in the Neurology Department at the University of Kansas Medical Center (KUMC). As Director of Neuromuscular Research, he has overseen the conduct of 60 clinical studies. He has had long-standing experience working with IBM patients and being engaged with the local myositis support group for IBM and IIM. He is a member of the International Myositis Assessment & Clinical Studies Group Scientific Committee (IMACS). In that capacity, he is the PI on IMACS Project 2, identifying myositis phenotypes that predict treatment response in the IIM. Dr. Dimachkie has participated in all aspects relating to the conduct of arimoclomol in IBM pilot study. He is the lead author on several publications in IBM [10-13,19,25] and actively participated in other recent IBM studies, both pharma-sponsored and investigator initiated. He is involved in a variety of federally-funded neuromuscular research projects as well Pharma-sponsored studies, nationally and internationally.

Professor Hanna is Director of the UCL institute of Neurology, Director of the MRC Centre for translational research in MRC Centre for Neuromuscular Diseases, chairman of the British Myology Society and co-chair of the North American Muscle Study Group. Professor Hanna has participated in all aspects relating to the conduct of arimoclomol in IBM pilot study, has co-lead two recent international workshops in IBM [48-49] and has brought together one of the world's largest consortia of internationally recognized IBM experts (spanning Europe, USA, Canada and Australia) providing a previously unparalleled IBM DNA bank for genetic studies. In addition Professor Hanna has led the establishment of the UK-wide prospective cohort of IBM patients linked 8 UK centres - "IBM-net". Professor Hanna and the MRC Centre for translational research have existing partnerships with the major patient organizations linked to IBM namely the myositis support group where Professor Hanna is an advisor helped plan annual patient meetings and the Muscular Dystrophy Campaign that also support IBM patient groups. Professor Hanna is actively engaged with the cross party parliamentary group for neuromuscular diseases including IBM and has given evidence in parliament about the impact of neuromuscular diseases including IBM and has worked with this group and the commissioners to develop standards of care for patients- this work is ongoing. Professor Hanna has

been an author of over 175 peer reviewed full publications and has received over 10 million pounds in peer reviewed external grant funding over the last 6 years.

Dr. Pedro Machado works at the MRC Centre for Neuromuscular Diseases, London, UK, and has extensive experience in diagnosing and managing patients with muscle diseases, including IBM. Together with Professor Michael Hanna, Dr Machado has participated in all aspects relating to the conduct of arimoclomol in IBM pilot study and is on the Steering Committee of the International IBM Consortium Genetic Study. Dr Machado is actively engaged in all major IBM research projects conducted at the MRC Centre for Neuromuscular Diseases, namely the UK-wide prospective cohort of IBM patients, MRI studies in IBM and an ongoing exercise trial in IBM. Dr Machado has also had training in clinical epidemiology and statistics and has published several articles related to outcome assessment in musculoskeletal diseases. He is a member of the Muscle Study Group.

Dr. Richard Barohn has had considerable experience working with patients with IBM. Dr. Barohn helped establish the diagnostic criteria for IBM. [7] He is the co-chair of the Muscle Study Group, a multi-center cooperative of neuromuscular specialists committed to pooling their resources to study neuromuscular disorders. He has been an investigator on many treatment trials in IBM. [5-7,22-23,50-51]

Natural History Study in IBM: The natural history of IBM was investigated prospectively by following 11 subjects for six months. [21] Prospective measurements of muscle strength, muscle mass, and lean body mass were performed. Overall a four percent decrease in strength was seen over the six-month period compared to baseline. One-third of the patients stabilized or improved in muscle strength. In our pilot study and using the IBMFRS as the endpoint measure, all but one placebo recipient experienced a decline at 12 month when compared to screen visit. The single exception was a subject in whom the IBMFRS remained stable at 12 month. In the largest study to date reviewing progression of 136 sporadic IBM patients from two European centers, all cases progressed despite therapy.[24]

Beta-Interferon 1A in IBM: This was a double-blind, placebo-controlled trial of Beta-Interferon 1A (30 micrograms) in IBM performed by the MSG. [22] Although this was a phase 1 trial, efficacy was evaluated by looking at changes in strength, functional scores, and SF36. Six muscle groups were tested with maximal voluntary isometric contraction testing (MVICT) on each side (biceps, triceps, quadriceps, hamstrings, ankle flexors, and hand grip), and a composite MVICT score was derived by averaging the standardized (normalized) scores. Strength was also measured by manual muscle testing (MMT) in 34 muscle groups. All testing procedures were done at baseline and repeated on weeks four, 12, and 24. No significant differences between treatment groups were noted in any of these scores.

High-dose Beta-Interferon 1A in IBM: This was a double-blind, placebo-controlled trial of Beta-Interferon 1A (60 micrograms) in IBM performed by the MSG, utilizing similar outcome measures as in our earlier study. [23] No significant differences between treatment groups were noted in any of these scores.

Muscle Study Group: The principal investigator and the co-investigators are members of the Muscle Study Group and have extensive experience in treatment trials in a variety of neuromuscular diseases including IBM, myasthenia gravis, amyotrophic lateral sclerosis, muscular dystrophies, inflammatory myopathies, and peripheral neuropathies. In addition to the two key sites, we recruited 10 sites from the Muscle Study Group to conduct this study. All centers to be chosen have experience in recruiting and enrolling patients into clinical trials. In addition, all of the centers are accustomed to working together as a group in clinical trials.

4. Methods, Expected Results, Data Analysis, Interpretations, and Significance

Study Design

This is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of arimoclomol in subjects with IBM. One hundred and fifty subjects will be randomized to one of two groups: placebo (75 patients) or arimoclomol (75 patients) 200 mg TID. Participants will receive study medication for twenty months. Subjects will be seen at screening, day 0 (Baseline) and months 1, 4, 8, 12, 16 and 20. They will be contacted by phone at months 2, 3, 6, 10, 14, and 18. There will be a follow-up phone call 30 days post treatment.

Study Eligibility

Inclusion Criteria

Study subjects must meet all of the following criteria:

1. Meet any of the European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria 2011 categories for IBM. [52] (see appendix A)
2. Able to ambulate with or without assistive device
3. Age at onset > 45years
4. Women of childbearing age must have a negative pregnancy test prior to dosing with study medication.
5. Able to give informed consent.

Exclusion Criteria

1. The presence of any of the following excludes subject participation in the study: chronic infection; cancer other than basal cell cancer less than five years prior; or other chronic serious medical illnesses.
2. Presence of any of the following on routine blood screening: WBC<3000; Platelets < 100,000; hematocrit < 30%; BUN > 30 mg %; creatinine > 1.5 mg%; symptomatic liver disease with serum albumin < 3 G/DL.
3. History of non-compliance with other therapies.
4. Coexistence of other neuromuscular disease.
5. Drug or alcohol abuse within past three months.
6. Participation in a recent drug study in the last 30 days prior to screen visit.
7. Women who are lactating or unwilling to use adequate method of birth control who are not surgically sterile. Adequate birth control includes use of intrauterine device, abstinence, or oral contraceptives or a double barrier method, e.g. condom plus diaphragm.

Study Procedures

Screening and Informed Consent: During the participant's first study visit, written informed consent will be obtained by the study investigator or his/her designee. Before any study-specific procedures or assessments are done, each participant will be given a consent form that explains the aims, methods, anticipated benefits, and potential hazards of the study. Each participant will be given adequate time to first read the consent form and then to discuss any questions with the investigator. After the participant willingly agrees to take part in the study, the investigator will then review the inclusion/exclusion criteria. A medical history, physical examination will also be completed. Subjects will be given a falls diary to record the number of falls they experience. Vital signs, weight, and

concomitant medications will be recorded. Safety laboratory tests will be performed including complete blood count (CBC) with differential and Chem 12.

Randomization: The site investigator will review all inclusion and exclusion criteria and safety laboratory tests prior to randomization. If the subject passes all screening procedures and is confirmed as eligible, the baseline visit can be scheduled. Randomization for each site will be performed at baseline visit using the RedCap system at the University of Rochester Data Management Center.

Baseline: Baseline evaluations will include vital signs, weight check and urine pregnancy test, concomitant medication review, adverse events, completion of the IBMFRS, MMT, MVICT of quadriceps and grip, mTUG, Grip and Pinch, and 6 minute walk test with 2 minute distance. We will obtain the Health Assessment Questionnaire (HAQ-DI) and SF-36. A new falls diary will be given to subjects. Subjects will receive their study medication after all baseline procedures are performed. The subject will be observed for 1 hour after the initial dosing of the medication. The study medication will be dispensed for the initial one-month period, and the patient will be given instructions regarding dosing schedule and study requirements. If the patients are seen within 2-4 weeks from screening, lab tests will not need to be repeated.

Follow-up Visits: All follow-up visits will be performed at month 1, month 4, month 8, month 12, month 16 and month 20. Phone calls will be made at month 2, month 3, month 6, month 10, month 14, month 18, and 28 days after the month 20 visit. Every month is made up of 28 days. There is a 3 day window from the visit date. At month 1, participants will be assessed with a physical examination, IBMFRS, CBC and Chem 12. At month 4, month 8, month 12, month 16 and month 20, participants will be assessed with a physical exam, IBMFRS, MMT, MVICT of quadriceps and grip, mTUG, Grip and Pinch, and 6 minute walk test with 2 minute distance, CBC and Chem 12, SF-36 and HAQ-DI. A new falls diary will be given out. Concomitant medications, and adverse events, will be assessed at each study time point. Unscheduled visits to evaluate potential adverse events can occur at any time. Phone visits: Subjects will be contacted by phone at months 2, 3, 6, 10, 14, and 18 to capture IBMFRS, adverse events and concomitant medications. There will be a follow-up phone call 30 days post treatment.

Figure 8: Study Visit Schedule

Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Month	-1 (Sc)	0 (Base)	1	2	3	4	6	8	10	12	14	16	18	20	Phone call
Consent/Eligibility	X														
Medical History	X														
Physical Exam	X		X			X		X		X		X		X	
Safety Labs*	X		X			X		X		X		X		X	
Urine Preg**		X													
Dispensing of Medication		X	X			X		X		X		X			
Return of Medication			X			X		X		X		X		X	
Muscle Testing (MMT, MVICT)		X				X		X		X		X		X	
6 min walk test		X				X		X		X		X		X	
SF-36		X				X		X		X		X		X	
HAQ-DI		X				X		X		X		X		X	
Falls diary		X	X			X		X		X		X		X	
Grip and pinch		X				X		X		X		X		X	
IBMFRS		X	X	X	X	X	X	X	X	X	X	X	X	X	
mTUG		X				X		X		X		X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X

* = **Full Safety Labs:** CBC and Chem 12, Serum pregnancy
**= Urine pregnancy prior to dispensing study medication
MMT, Manual Muscle Testing; MVICT, Maximum Voluntary Isometric Contraction Testing, SF-36, Short Form Health Survey 36; HAQ-DI, Health Assessment Questionnaire Disability Index; IBMFRS, Inclusion Body Myositis Functional Rating Scale; mTUG, modified Timed Up and Go Test;.

IBM Functional Rating Scale: The IBMFRS is a quickly administered (10-minute) ordinal rating scale used to determine patients' assessment of their capability and independence. It includes 10 measures (swallowing, handwriting, cutting food and handling utensils, fine motor tasks, dressing, hygiene, turning in bed and adjusting covers, changing position from sitting to standing, walking, and climbing stairs), graded on a Likert scale from 0 (being unable to perform) to 4 (normal). The sum of the 10 items gives a value between 0 and 40, with a higher score representing less functional limitation.

Muscle Strength Testing: We will measure MVICT using the Quantitative Muscle Assessment (QMA) system designed by Computer Source, Atlanta, GA. The system uses an adjustible cuff to attach the patient's arm or leg to an inelastic strap that is connected to force transducer with a load of 0.5 to 1,000 Newtons. Two muscle groups are tested bilaterally (i.e., quadriceps, and hand grip). Each muscle is tested twice while the patient is encouraged by the CE to exert maximal effort. The

maximum force generated by the patient from the two trials is recorded for each muscle group. MVICT has been shown to be reliable and valid in several neuromuscular disorders. We have used MVICT in natural history and treatment trials of various myopathies, including FSHD [53-57], DMD [58-63], and IBM. [21-23] Our CEs have demonstrated excellent intra-rater and inter-rater reliability in regards to MVICT with intraclass correlation coefficients ranging from 0.86-0.99. [64-65] We will measure MMT of 26 muscle groups. [22-23]

Health Assessment Questionnaire (HAQ- DI): This is a self-report functional status (disability) measure based on the five patient-centered dimensions (death, disability, discomfort, drug toxicity and dollar costs). [66-67]

Modified Timed Up and Go (mTUG)*:* We will measure the patient's ability to get up from a chair allowing subjects to use their arms (since most with sIBM cannot perform the task without pushing off), walk 3 meters, turn around and walk back to the chair and sit down. The use of nearby walls, or assistance from a caregiver was not allowed. This test will be performed twice and the fastest time was used in the data analysis. [68-70]

6 minute walk test with 2 minute distance captured: We will assess the distance IBM patients can walk in 6 minutes. [68,71-72] Subjects were instructed to walk down one side of the track and back along the opposite side as quickly and safely as possible for 6 minutes. Subjects were allowed to take break as needed during the walking period, but timing continued during breaks. Time to complete each 50-meter lap and distance walked in meters is recorded after 2 minutes and 6 minutes.

Grip and Pinch: We will measure grip and pinch strength using the Jamar dynamometer and Jamar pinch device.

Falls diary: Each subject will record the number of falls within each four months.

5. **Study medication: Arimoclomol**

Dose and formulation

Arimoclomol will be administered at 200 mg orally TID in this study using the following up titration plan. As Arimoclomol 100 mg orally TID was well tolerated dose in our pilot study, we will initiate subjects on that dose or matching placebo. If this dose level is well tolerated for one week, Arimoclomol dose will be increased to 200 mg orally TID and maintained at that dose for the remainder of the study. Since the main adverse event recorded in our data is related to mild to moderate gastrointestinal tolerability, a drug-related severe gastrointestinal adverse event will lead to drug dose reduction down to the lower initial dose level; if the severe drug-related adverse event persists for more than one week after dose reduction, we might be consider discontinuation of the treatment for this subject. Then, the patient will be followed up as planned per protocol for adverse events recording.

Drug Supply

We have a letter of support from Orphazyme to supply drug and placebo to support this study.

Drug dispensing, labeling and storage

Medication will be shipped to each site. The medications will be stored at room temperature and protected from light.

Compliance and return of study drug

Subjects will receive study medication at clinic visits baseline, month 1, 4, 8,12 and 16. Subjects will use a medication log and will be instructed to return all unused study medication at each clinic visit. Compliance will be assessed by review of the medication log at each visit and by documentation of unused study medication.

Concomitant medications

Concomitant medication use, including over-the-counter supplements, will be documented throughout the study. The entry will include the dose, regimen, route, indication, and dates of use. Antioxidants and vitamins will be allowed.

6. Adverse events and serious adverse events

Adverse Events: An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, laboratory or physiologic observations occurring in study participants. The safety of arimoclomol will be evaluated using vital signs and weight, clinical laboratory determinations, physical examination, reporting of AEs, deaths and other serious adverse events (SAEs), and treatment discontinuations due to AEs. Information on adverse effects and on intercurrent events will be determined at each visit by direct questioning of the subjects, clinical examination, and laboratory tests. Tolerability will be determined by the ability to complete the study on the assigned experimental medication. AEs will be assessed using the MedDRA system of coding. The site PI or Co-I will monitor AEs monthly, grade them, and indicate if the AE is related to the study medication (probable, possible, unrelated). Patients will be instructed to call the PI's office (or on-call resident if at night or on the weekend) to report events that occur between study visits.

Expected Adverse Events:

Arimoclomol. Based on the two studies in healthy volunteers, no significant adverse events can be predicted. In the 10-day, multiple-dose study, there was slight serum creatinine elevation noted in some volunteers, although serum creatinine never exceeded the normal range. Other dose-related events noted in experimental animals were slight increases in cholesterol and bilirubin. In either obese or diabetic rats, arimoclomol treatment resulted in a slight reduction in serum glucose and improvement of any abnormalities on glucose tolerance tests. No significant changes in serum glucose are expected in non-diabetic human subjects. Safety laboratory tests will be performed at each visit and monitored for significant changes.

In the twenty-four patient pilot study we conducted, there were no significant differences between treatment groups regarding the rate, type and severity of adverse events (AEs) (Table 2). There were 8 treatment-possibly-related AEs in the placebo group and 14 with Arimoclomol, the most common being gastrointestinal. The 14 AEs in the Arimoclomol group were constipation (*n*=3), hyponatremia (*n*=2), loose stools (*n*=2) and 1 of each of the following: bowel movement problems, gas pains, nausea, cramps, dizziness/tinnitus, hypertension and rheumatoid arthritis flare. In the Arimoclomol group, one serious AE was reported: a study subject requiring overnight hospitalization after the first trial muscle biopsy as a result of persistent high blood pressure. This

patient had known poorly controlled hypertension and the muscle biopsy was identified as a stressful event that raised the patient´s blood pressure. Blood pressure normalized after adjustment of the patient´s antihypertensive medication and kept within normal range throughout the remainder of the trial. Hypertensive episodes were also observed in two placebo patients, under similar circumstances, although these cases did not require hospitalization. Two cases of hyponatremia and one case of high thyroxine levels were observed in the Arimoclomol group, however these changes were transient, asymptomatic and did not require treatment. The episode of hematuria in the Arimoclomol group was also limited and did not require treatment. All infections resolved with standard treatments, with or without antibiotics, and did not require hospitalization. Ocular toxicity and arrhythmia were not observed in any study subjects.

Table 2 Summary of all adverse events over the course of 1 year.*

MedDRA System Organ Class	Arimoclomol (16 patients)	Placebo (8 patients)
Blood and lymphatic system disorders	-	-
Cardiac disorders	Palpitations (*n*=1)	
Congenital, familial and genetic disorders	-	-
Ear and labyrinth disorders	Dizziness/tinnitus (*n*=2)	
Endocrine disorders	-	-
Eye disorders	Conjunctivitis (*n*=1), eye pain (*n*=1)	Dry eyes (*n*=1)
Gastrointestinal disorders	Constipation (*n*=4), throat irritation (*n*=4), loose stools (*n*=2), nausea (*n*=2), dry mouth (*n*=2), bowel movement problems (*n*=1), epigastralgia (*n*=1), gas pain (*n*=1), pyrosis (*n*=1), vomiting (*n*=1), geographic tongue (*n*=1)	Constipation (*n*=4), loose stools (*n*=4), painful parotids (*n*=2)
General disorders and administration site conditions	Weight loss (*n*=1), dizziness (*n*=1), loss of consciousness (*n*=1)	Fatigue (*n*=1)
Hepatobiliary disorders	-	-
Immune system disorders	-	-
Infections and infestations	Sinus infection (*n*=2), upper respiratory tract infection (*n*=7), lower respiratory tract infection (*n*=2), erysipelas (*n*=1), tooth infection (*n*=1)	Tooth infection (*n*=4), upper respiratory tract infection (*n*=3), cellulitis (*n*=1), leg ulcer infection (*n*=1)
Injury, poisoning and procedural complications	Fall/contusion (*n*=23), post-biopsy pain (*n*=3), post-biopsy fatigue (*n*=1)	Fall/contusion (*n*=9), post-biopsy pain (*n*=1), pruritus in biopsy scar (*n*=1), finger cut (*n*=1)
Investigations	Hyponatremia (*n*=2), high thyroxine levels (*n*=1)	Spinal stenosis (*n*=1), herniated disk (*n*=1)
Metabolism and nutrition disorders	-	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain (*n*=10), cramps (*n*=1), rheumatoid arthritis flare (*n*=1), heat and soreness of proximal lower limbs (*n*=1)	Musculoskeletal pain (*n*=2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-
Nervous system disorders	Headache (*n*=7), worsening of restless leg syndrome (*n*=1),	Headache (*n*=3), paresthesia (*n*=1), stroke (*n*=1)

	paresthesia (*n*=1)	
Pregnancy, puerperium and perinatal conditions	-	-
Psychiatric disorders	-	-
Renal and urinary disorders	Hematuria (*n*=1)	-
Reproductive system and breast disorders	-	Decreased libido (*n*=1)
Respiratory, thoracic and mediastinal disorders	Cough (*n*=2)	Cough (*n*=1)
Skin and subcutaneous tissue disorders	Rash (*n*=2), rosacea (*n*=1), insect bite with erythema (*n*=1), cold sores (*n*=1)	Rash (*n*=1)
Social circumstances		
Surgical and medical procedures	Tooth extraction (*n*=1), sinus surgery (*n*=1), solar lentigines removal (*n*=1)	Tooth extraction (*n*=1)
Vascular disorders	Hypertension (*n*=3), edema (*n*=2)	Hypertension (*n*=3), edema (*n*=3)
Average number of adverse events (AEs) per patient	**AEs = 6.8/patient**	**AEs = 6.5/patient**

Recording adverse events

Definition - adverse events are clinical abnormalities (illness, signs, or symptoms) that begin or worsen during the course of the study whether or not the abnormality is believed by the investigator to be related to the study medication, and for the purposes of this study, are not thought to be directly related to the expected course of IBM itself.

Recording - the investigator will monitor each patient closely and record all adverse events on the adverse event page of the case report form.

Severity - adverse events should be graded for severity:

Mild: causing no limitation of usual activities
Moderate: causing some limitation of usual activities
Severe: causing inability to carry out usual activities

The investigator will indicate his/her opinion as to the relationship of the event to the study drug. If the investigator believes that the adverse event is not related to the study medication, he should indicate what he believes to be the probable cause of the adverse event.

Causality will be defined by the following:

Not Related:
Exposure to drug has not occurred
OR
The administration of study medication and the occurrence of the AE are not reasonably related in time
OR
The AE is considered likely to be related to an etiology other than the use of study medication

Possibly Related:

The administration of study medication and the occurrence of the AE are reasonably related in time AND
The AE could be explained equally well by factors or causes other than exposure to study medication

Probably Related:
The administration of study medication and the occurrence of the AE are reasonably related in time AND
The AE is more likely explained by exposure to study medication than by other factors or causes.

All AEs are considered unexpected except if listed in the investigator brochure. Otherwise they are considered related

Serious adverse events

Definition: Serious adverse events are life threatening, fatal, result in hospitalization or prolonged hospitalization, permanent disability, congenital anomaly, cancer, or overdose, or are any event that the investigator believes is very unusual or potentially serious.

Report: Any serious adverse event will be reported immediately (within 24 hours). All serious adverse events will be recorded on the standard adverse events page of the case report form, and a serious adverse event form will be completed. The coordinating center will be notified within 24 hours.

Follow-up of Adverse Events: The site investigator is responsible for appropriate medical management and laboratory tests for adverse events until the event is resolved. The management and resolution of each adverse event should be recorded on the adverse event page of the case report form.

Serious adverse events and adverse events will be entered into the computerized research informatics system at the University of Rochester. The study coordinator and investigator from each site are responsible for accuracy and completeness of all events. Mazen Dimachkie, MD, and Michael Hanna, MD will be notified by email of all serious adverse events.

Serious adverse events will be reported to the Human Subjects Committees at the University of Kansas Medical Center. All sites will receive notification as well. The FDA Orphan Products Division will be notified as needed.

7. Statistical Considerations

The MSG Biostatistics Center will randomize patients to the treatment assignments. The randomization will be stratified by center and will include blocking to facilitate approximate balance in the number of subjects assigned to each treatment group within each center. The programmer will provide (by mail) the appropriate treatment assignments to each site.

In accordance with the intention-to-treat principle, all randomized participants will be included in the statistical analysis according to the treatment group to which they were originally assigned. All randomized subjects will be considered able to be evaluated for the primary and secondary outcome measures. Every effort will be made to retain subjects in this trial, to promote adherence to the study protocol, and to collect all data at every visit. If a subject cannot tolerate or refuses to continue taking study medication, we will continue to follow and evaluate that subject if he/she is willing. If a subject withdraws from the trial, attempts will be made to bring the subject in for a final evaluation.

Compliance with trial procedures, subject disposition, and reasons for subject withdrawal will be carefully tracked throughout the study.

Subject identity will be protected by unique study identification variable. This code will be used for all data faxed from the other sites. The information will be kept in a key-locked office.

Study sample size calculation:

The primary outcome variable is the change from baseline to Month 20 in the IBMFRS. In the arimoclomol pilot study, the standard deviation of the 12-month change in IBMFRS was 2.9. The mean change in the placebo group was -3.5 and the mean change in the arimoclomol group was -2.1. A sample size of 68 subjects per group (136 total) will provide 80% power to detect a treatment group difference in mean response of 1.4 points, using a two-sample t-test and a 5% significance level (two-tailed). To account for an anticipated 10% drop-out rate, the sample size will be inflated to 75 subjects per group (150 total).

Analysis of Efficacy Outcomes

The primary statistical analysis will involve the use of a repeated measures analysis of covariance model for the IBMFRS (i.e., the so-called “mixed model repeated measures”, or MMRM, analysis strategy) [73], with terms for treatment group (arimoclomol, placebo), center, baseline IBMFRS score, month (treated as a categorical variable), and interaction terms for baseline IBMFRS and time and treatment group and time. The covariance matrix for the within-subject observations will be modeled using an unstructured pattern. Ninety-five percent confidence intervals for treatment effects (differences in adjusted group means) at each visit will be computed using this model, with the Month 20 time point being of primary interest. A test for significance of the treatment effect at Month 20 will likewise be performed with this model using a significance level of 5% (two-tailed). Similar analyses will be performed for the secondary outcome variables for efficacy including strength outcomes (MVICT and MMT scores, grip strength, pinch strength), HAQ-DI , modified timed up and go, and distance walked in 6 minutes.

The underlying assumptions of the repeated measures analysis of covariance models will be thoroughly checked (normality, linearity, etc.) and remedial measures (e.g., transformations) will be taken if serious violations of these assumptions are detected. These are not anticipated to be violated for the IBMFRS in this study.

The primary analyses will be performed according to the intention-to-treat principle and will include all available data from all randomized subjects. The repeated measures analysis of covariance model to be used for the primary analyses uses maximum likelihood to estimate the parameters of interest (treatment effects) using available data from all subjects. This direct likelihood method accommodates missing data in a valid manner under the missing at random assumption [73]. Other strategies for dealing with missing data such as pattern-mixture models [74] will be attempted as well; these models will be used to perform sensitivity analyses since they rely on assumptions about the missing data mechanism that are difficult to verify. It is hoped that the overall conclusions regarding the effect of arimoclomol will not depend greatly on the analysis strategy used, particularly if subject withdrawal is minimized.

Analysis of Safety Outcomes

Adverse events (AEs) will be summarized by treatment group, maximum severity, and perceived relationship to study medication. For each adverse event (MedDRA preferred term), the treatment groups will be compared regarding the occurrence of at least one event using Fisher's exact test. The comparisons will be repeated excluding all mild symptoms. Similar analyses will be performed after grouping adverse events by MedDRA system organ class. Individual adverse events will be listed, with particular attention paid to serious adverse events, including death.

Analyses of tolerability outcomes (e.g., ability to complete the trial on the assigned dosage of study medication; ability to complete the trial) will be performed using Fisher's exact tests.

Continuous measures of safety (vital signs, laboratory test results) will be performed using models similar to those used for the primary outcome variable for efficacy (MMRM).

Compliance data will be summarized by treatment group, overall and by visit.

8. ***Data management and case report forms***

Data will be collected on paper case report forms (CRFs). The compiled information from these forms will be remotely entered by study site personnel into a Redcap database at the University of Rochester. A web-based database system designed specifically for this clinical trial will be used. A data manager will be responsible for the database. All corrections to the CRFs will be initialed and dated by the study coordinator, clinical evaluator, or investigator. Subject folders will contain copies of CRFs, laboratory data, patient histories, physical examinations, and any adverse experience reports. These will be filed in a dedicated filing cabinet at each center organized by patient code number. Drug dispensing logs will be kept to record the total amount of medication received from and returned to the site. Completed informed consent forms from each subject will be available in the subject's file and verified for proper documentation.

Reporting obligations

The site investigators will be responsible for insuring that all blank data spaces on each CRF are filled in. The statistician, along with the coordinating center, will notify each investigator of any missing data. All completed CRFs are to be reviewed by the site investigator. Changes/additions to data entered on original case report forms must be made with a single line drawn through the error, so as to leave the error still legible. The correction will be entered in black ink, with the date and the initial of the person making the correction. All data entry for a visit will be completed by site personnel within 5 business days of the visit date. If all expected CRFs are not entered within 5 days of the end of the allowable window for the visit the data system will generate an email reminder to the site.

9. Stopping Guidelines

Premature discontinuation, protocol violation, loss to follow-up

All attempts will be made to enhance patient compliance. Early withdrawal may occur for any of the following reasons:

- Patient requests;
- Investigator decides that it is in the patient's interest
- Serious adverse event that is probably related to study medication
- Significant protocol violation occurs
- Breaking of the blind

If the patient withdraws early, termination evaluations will be completed and the patient will be encouraged to continue with scheduled visits. If a patient is unable to return to the center, a phone call will be made to the patient. In the event of a loss to follow-up, information about the patient will be sought from the family or family physician.

Study discontinuation

The DSMB can recommend to the sponsor / study PI that the study to be terminated at any time . Reasons for terminating the study may include the following:

- Incidence or severity of AEs indicates a potential health hazard to study subjects
- Study enrollment is unsatisfactory
- Data recording is inaccurate or incomplete.

Code break procedures

Each site will receive documentation to break the randomization code if needed. The site investigators will not have access to the randomization codes. An individual at each site (who is not involved in this study) will be identified to receive the unblinding codes. This person at the study site will get sealed envelopes that can be opened only in the case of a dire medical emergency requiring knowledge of treatment assignment. It should be emphasized that this step should only be taken if absolutely necessary, that we anticipate that most of these situations can be handled simply by suspending study medication, and that code breaks will occur very rarely in this trial.

Mazen Dimachkie, MD or Michael Hanna, MD will be notified prior to unblinding if at all possible to make absolutely sure that the situation cannot be handled any other way (e.g., by simply suspending study medication. If this is not possible, then one of the above listed investigators must be notified at the first possible moment.

For most emergencies that would cause a subject to be discontinued from the study, cessation of the study drug is usually sufficient. In most cases, the identity of the study drug would not change the course of the subject's emergency treatment. In the rare instance where establishing the identity of the study drug is vital for safe emergency treatment of the subject, the investigator after communicating with the safety monitor will have the authority to ask the research pharmacy to un-blind the code for that subject only. If the safety monitor is unavailable, the investigator may proceed with unblinding if it is in the best interest of the subject.

A data and safety monitoring board (DSMB) will be established for this study as well as an independent medical monitor. If the AE rate leading to discontinuation of the study is >25%, the medical monitor will immediately draw these events to the attention of the DSMB. In other words, if more than 38 participants have an adverse event considered by the PI to be probably related to the study medication and that leads the local PI to discontinue the medication in that subject, then the DSMB would recommend to the overall study PI that the study be temporarily halted. The DSMB will then determine if it is safe for the study to proceed. AEs SAEs and completion of data entry will be assessed by the DSMB.

10. Data and safety monitoring plan

Medical Monitor

An independent neurologist or rheumatologist will serve as the medical monitor. This person will be picked prior to the beginning of the study. The medical monitor will be responsible for independent

review of the safety laboratory tests and adverse events will be responsible for monitoring the real-time reporting of Serious Adverse Events, will review laboratory reports and adverse events monthly, or more frequently as needed. The medical monitor will be blinded to treatment assignment. If the safety monitor has concerns regarding the safety data, they may notify the DSMB. The safety monitor may request additional or clarifying information from the coordinating center of the treating physician. The safety monitor will prepare a report to present to the DSMB prior to their meetings.

Data and Safety Monitoring Board (DSMB)

A DSMB will be established through the University of Kansas Medical Center Office of Compliance. The DSMB will meet every six months by phone to review recruitment, adverse events, and serious adverse events. They will meet with the study statistician prior to the meetings to review the event reports and identify any issues that need to be addressed. The DSMB is comprised of a clinical trialist, two IBM specialists, and a statistician. An IBM specialist will head the DSMB. The members of the DSMB are not located at the University of Kansas Medical Center.

Data and Safety Monitoring Executive Committee (DSM-EC)

Administrative support of DSMB is through the Office of Compliance at the University of Kansas Medical Center. The scope of the DSM-EC is to provide multi-disciplinary, independent oversight of research studies. The DSM-EC will arrange the conference calls and will prepare minutes of the DSMB meetings.

Protocol Adherence

The study PI will work closely with principal investigators at all other sites to ensure adherence of the protocol by the study sites and study data integrity. The principal investigator will be responsible for communicating with all sites to ensure smooth conduct of the study and prompt data submission. The principal investigator will coordinate e-mail and conference call communications and work with the data coordinator to prepare monthly reports from each site indicating the status of the study and problems that might arise. Serious adverse events will be reported immediately to the principal investigator and reviewed promptly by the safety monitor.

Based upon our previous experience in managing multicenter studies of neuromuscular disorders at KUMC, we will again assemble a communications and computing infrastructure and technical staff to ensure the success of this study. We will use strategies for intra- and inter-site communication, data entry, storage, management, and analysis similar to those we have previously used and currently use. We will have several ways to ensure adequate communication between the data center and the individual clinical sites. Telephone, fax, and electronic mail will be the primary modes of inter- and intra-site communication for investigators and study staff. The existing infrastructure at each site includes sophisticated telephone networks, voice messaging systems, fax machines and Ethernet connections to the Internet to support this strategy. All study computers at the data center and each of the clinical sites will be password protected, and kept in locked offices. The evaluators performing the monthly studies will complete a CRF after each visit. The principal investigator/study coordinator will be responsible for dispensing and accounting for all study medication. The principal investigator at each study site is responsible for all aspects of the study at the site. The investigator agrees to cooperate fully with monitors.

Monitoring Plan

The University of Kansas Medical Center Monitoring division will monitor all sites. This will consist of remote monitoring. Sites will send in their source documents as the first subject enters the study and

periodically anytime throughout the study. The University of Kansas Medical Center Monitoring division personnel in collaboration with the MSG Data Coordinating Center will verify accuracy of data entered on RedCap.

Data Storage and Backup

Original paper CRFs will be stored at each of the clinical sites in double locked storage. Electronic data at the data center will be backed up daily. Frequent checks of backup integrity will be conducted. In the event of a loss or corruption of records at any one site, data can be reconstructed.

References:

1. Jackson CE, Barohn RJ, Gronseth G, Pandya S, Herbelin L; Muscle Study Group. Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. Muscle Nerve. 2008 Apr;37(4):473-6
2. Rider LG, Werth VP, Huber AM, Alexanderson H, Rao AP, Ruperto N, Herbelin L, Barohn R, Isenberg D, Miller FW. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S118-57
3. Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. JNNP. 2009;80(10):1060-1068
4. Engel WK, and Askanas, V. Inclusion-body myositis: Clinical, diagnostic, and pathologic aspects. Neurology. 2006; 66(Suppl 1): S20-S29
5. Amato AA, Barohn RJ. Inflammatory myopathies. Neurol. Clin. N. Amer. 1997; 15: 615-648.
6. Amato AA, Gronseth GS, Jackson CE, Wolf GI, Katz JS, Bryan WW, Barohn RJ. Inclusion body myositis—clinical and pathological boundaries. Ann. Neurol. 1996; 40: 581-586.
7. Griggs RC, Askanas V, DiMauro S, Engel A, Karpati G, Mendell JR, et al. Inclusion body myositis and myopathies. Annals of Neurology 1995; 38: 705-713.
8. Rabi Tawil, MD, and Robert C. Griggs, MD. Inclusion body myositis. Curr Opin Rheumatol 2002, 14:653–657
9. Amato AA, Barohn RJ. Inclusion body myositis: old and new concepts. JNNP 2009;80(10):1186-93.
10. Dimachkie MM. Idiopathic inflammatory myopathies. J Neuroimmunol. 2011 Feb;231(1-2):32-42.
11. Dimachkie MM and Barohn RJ. Inclusion Body Myositis. Curr Neurol Neurosci Rep. 2013 Jan;13(1):321
12. *Dimachkie MM, Barohn RJ. Inclusion body myositis* in Neuromuscular Therapy: From Bench to Bedside*. Semin Neurol. 2012Jul;32(3):237-45.*
13. *Machado P, Dimachkie MM, Barohn RJ. Sporadic Inclusion Body Myositis: new insights and potential therapy. Curr Opin Neurol 2014; Oct 27:591-8.*
14. *Barohn RJ and Dimachkie MM. Inclusion Body Myositis. Neurol Clin 2014; Aug;32:629-646.*
15. Invited contribution, Dimachkie MM, Barohn RJ, Idiopathic Inflammatory Myopathies, ABIM Internal Medicine Boards Review, Epub version is also on Kindle and Nook, Ragavendra R Baliga Editor, 2012.
16. Engel WK, and Askanas, V. Inclusion-body myositis: Clinical, diagnostic, and pathologic aspects. Neurology. 2006; 66(Suppl 1): S20-S29.
17. Mastalgia FL, Garlepp MJ, Phillips BA, Zilko PJ. Inflammatory myopathies: clinical, diagnostic, and therapeutic aspects. Muscle and Nerve. 2003; 27: 407-425.
18. Phillips BA, Cala LA, Thickbroom GW, Melsom A, Zilko PJ, Mastalgia FL. Patterns of muscle involvement in inclusion body myositis: clinical and magnetic resonance imaging study. Muscle and Nerve. 2001; 24: 1526-1534.
19. Dimachkie MM, Barohn RJ. Idiopathic inflammatory myopathies. *Front Neurol/Neurosci. 2009;26:126-46.*
20. GriggsRC. The current status of treatment for inclusion-body myositis. Neurology. 2006; 66(Suppl 1): S30-S32.
21. Rose MR, McDermott, MP, Thornton CA, Palenski C, Martens WB, Griggs RC. A prospective natural history study of inclusion body myositis: implications for clinical trials. Neurology 2001;57:548-550.
22. Muscle Study Group. Randomized pilot trial of betaINF1a (Avonex) in patients with inclusion body myositis. Neurology 2001;57:1566-1570.
23. Muscle Study Group. Randomized pilot trial of high-dose betaINF-1a in patients with inclusion body myositis. Neurology 2004;63:718-720.
24. Benveniste O, Guiguet M, Freebody J, et al. Long-term observational study of sporadic inclusion body myositis. Brain 2011;134 (Pt 11):3176–3184.

25. Estephan B, Barohn RJ, Dimachkie MM et al. Sporadic IBM: a Case Cohort. Journal of Clinical Neuromuscular Disease. 2011; 12(3):18-19
26. Salajegheh M, Pinkus JL, Taylor JP, et al. Sarcoplasmic redistribution of nuclear TDP-43 in inclusion body myositis. Muscle Nerve 2009;40(1):19–31.
27. Subourg O, Wanschitz J, Maisonobe T, et al. Diagnositic value of markers of muscule degeneration in sporadic inclusion body myositis. Acta Myol. 2011 30;103-8.
28. Askanas V, Engel WK. Molecular Pathology and Pathogenesis of Inclusion-Body Myositis. Microscopy Research and Technique. 2005; 67: 114-120.
29. Askanas V, Engel WK, Nogalska. Sporadic inclusion-body myositis: A degenerative muscle disease associated with aging, impaired muscle protein homeostasis and abnormal mitophagy. Biochim Biophys Acta. 2014 Sep 18. [Epub ahead of print]
30. Askanas V, Engel WK. Inclusion-bodymyositis: amyodegenerative conformational disorder associated with Abeta, protein misfolding, and proteasome inhibition. Neurology 2006;66(2, Suppl 1):S39–S48.
31. Ozturk A, McFerrin J, Engel WK, Askanas V. HSP70 chaperone machinery in sporadic inclusion-body myositis muscle fibers. Neurology. 2004; 62: 168.
32. Fratta P, Engel WK, McFerrin J, Davies KJA, Lin SW, Askanas V. Proteosome inhibition and aggresome formation in sporadic inclusion-body myositis and in amyloid-B precursor protein-overexpressing cultured human muscle fibers. Am J Pathology. 2005; 167(2): 517-526.
33. Engel WK, and Askanas, V. Inclusion-body myositis: Clinical, diagnostic, and pathologic aspects. Neurology. 2006; 66(Suppl 1): S20-S29.
34. Forloni G, Terreni L, Bertani I et al. Protein misfolding in Alzheimer's and Parkinson's disease: genetics and molecular mechanisms. Neurobiol Aging. 2002;23:957-976.
35. Hartl F, Hayer-Hartl M. Molecular chaperones in the cytosol: from nacent chain to folded protein. Science. 2002;295:1852-1858.
36. Sherman MY, Goldberg AL. Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative diseases. Neuron 2001; 29(1): 15-32.
37. Kieran D, Kalmar B, Dick JR et al. Treatment with Arimoclomol, a coinducer of heat shock proteins, delays disease progression in ALS mice. Nat Med. 2004;10:402-405.
38. Oldfors A, Moslemi AR, Jonasson M, Ohlsson M, Kollberg G, Lindberg C. Mitochondrial abnormalities in inclusion-body myositis. Neurology. 2006; 66(Suppl 1): S49-S55.
39. Oldfors A, Moslemi AR, Fyhr IM, Holme E, Larsson NG, Lindberg C. Mitochondrial DNA deletions in muscle fibers in inclusion body myositis. J Neuropathol Exp Neurol. 1995; 54: 581-587.
40. Ahmed, M., Miller, A., Hanna, M.G. & Greensmith, L. Investigating the effects of pharmacological up-regulation of the heat shock response in an in-vitro model of sporadic inclusion body myositis. *Neuromuscular Disorders* **22**, S26-S26 (2012).
41. Miller, A., Ahmed, M., Hanna, M.G. & Greensmith, L. Developing New Therapeutic Strategies for Inclusion Body Myositis. *Journal of Neurology Neurosurgery and Psychiatry* **83**(2012).
42. Machado, P, et al. Protein homeostasis manipulation: a potential experimental therapy for inclusion body myositis.
43. Ahmed M, Miller A, Herbelin L, He J, Noel J, Wang Y, McVey AL, Pasnoor M, Gallagher P, Statland J, Lu C-H, Kalmar B, Brady S, Sethi H, Samandouras G, Parton M, Holton J, Hanna MG, Richard J. Barohn RJ, Dimachkie MM* & Linda Greensmith.* Targeting protein homeostasis as a novel therapeutic approach in Sporadic Inclusion Body Myositis. Nature Medicine. Submitted.
44. Cudkowicz ME, Shefner JM, Simpson E, Grasso D, Yu H, Zhang H, Shui A, Schoenfeld D, Brown RH, Wieland S, Barber JR; Northeast ALS Consortium. Muscle Nerve. 2008 Jul;38(1):837-44
45. Barohn RJ, Jackson C, Pandya S, Gronseth G, Herbelin L, The Muscle Study Group (MSG). Inclusion body myositis functional rating scale. *Neurology* 2007;68 (Suppl. 1):A361.
46. Morrow JM, Ramdharry GR, Machado P, Burns T, Amato A, Barohn R, Phillips L, Seyedsadjadi R, Joshi A, Dimachkie M, Gwathmey K, Herbelin L, Solorzano G, Hanna M. RASCH ANALYSIS OF THE IBMFRS. Muscle & Nerve. Volume 48, Issue Supplement S1, S2-3, 2013.
47. Wang Y, He J, McVey AL, Pasnoor M, Gallagher P, Herbelin L, Statland J, Miller A, Greensmith L, Machado M, Hanna M, Barohn RJ, Dimachkie MM. Twelve-month Change of IBMFRS in the Arimocolomol Inclusion Body Myositis Pilot Study. Poster 7.255 at the American Academy of Neurology annual Meeting April 26 2012 at 5 pm, New Orleans.

48. Hilton-Jones, D., Hanna M. et al. International Workshop on Inclusion Body Myositis held at the Institute of Myology, Paris, on 29 May 2009. Neuromuscular disorders: 2010;20, 142-147.
49. Benveniste O, Hilton-Jones D., Hanna M, et al. International Workshop on Inclusion Body Myositis held at the Institute of Myology, Paris, on 29 May 2009. Neuromuscul Disord. 2010 Jun;20(6):414-21
50. Barohn RJ, Amato AA. Inclusion body myositis. Curr Treat Options in Neurol. 2000;2:7-12.
51. Barohn RJ, Amato AA, Sahenk Z, Kissel JT, Mendell JR. Inclusion body myositis: explanation for poor response to immunosuppressive therapy. Neurology 1995;45:1302-1304.
52. Rose MR, Group EIW. 188th ENMC International Workshop: Inclusion Body Myositis, 2-4 December 2011, Naarden, The Netherlands. Neuromuscular disorders: NMD. 2013 Dec; 23(12):1044-1055
53. FSH-DY Group. A prospective, quantitative study of the natural history of facioscapulohumeral muscular dystrophy (FSHD): implications for therapeutic trials. Neurology 1997; 48:38-46.
54. Personius KE, Pandya S, King WM, Tawil R, McDermott MP and FSH-DYGroup. Facioscapulohumeral muscular dystrophy natural history study: standardization of testing procedures and reliability of measurements. Phys Ther 1994; 74:253-263.
55. Tawil R, McDermott M, Pandya S, King W, Kissel JT, Mendell JR, Griggs RC, and The FSH-DY Group. A pilot trial of prednisone in facioscapulohumeral dystrophy (FSHD). Neurology 1997;48:46-9.
56. Kissel JT, McDermott MP, Mendell JR, et al: Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumerol muscular dystrophy. Neurology 2001;57:1434-1440
57. Kissel JT, Mendell JR, Griggs RC, McDermott M, Tawil R, and The FSH-DY group. Open-label clinical trial of albuterol in facioscapulohumeral muscular dystrophy. Neurology 1998;50:1402-6.
58. Fenichel G, Pestronk A, Florence J, RobisonV, Hemelt V. A beneficial effect of oxandrolone in the treatment of Duchenne muscular dystrophy: a pilot study. Neurology 1997;48:1225-6.
59. Fenichel GM, Griggs RC, Kissel JT, et al. A randomized efficacy and safety trial of oxandrolone in the treatment of Duchenne dystrophy. Neurology 2001;56:1075-1079.
60. Mendell JR, Kissel JT, Amato AA, et al. Randomized, double-blind, one-year trial of myoblast transfer in Duchenne muscular dystrophy. N Engl J Med 1995;333:832-8.
61. Mendell JR, Moxley RT, Griggs RC, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. N Engl J Med 1989;320:1592-7
62. Brooke MH, Griggs RC, Mendell JR, et al. Clinical trial in Duchenne dystrophy. I. Design of the protocol. Muscle and Nerve 1981; 4:186-197.
63. Griggs RC, Moxley RT, Mendell JR et al. Duchenne dystrophy: Randomized controlled trial of prednisone (18 months) and azathioprine (12 months). Neurology, 1993;43:520-527.
64. Muscle Study Group. A randomized pilot trial of etanercept in dermatomyosisits. Ann Neurol 2011. Sep;70(3):427-436.
65. Lowes LP, Alfano L, Viollet L, Rosales XQ, Sahenk Z, Kaspar BK, Clark KR, Flanigan KM, Mendell JR, McDermott MP.Knee extensor strength exhibits potential to predict function in sporadic inclusion-body myositis.Muscle Nerve. 2012 Feb;45(2):163-8.
66. Fries JF, Spitz PW, et al. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23(2): 137-45.
67. Fries JF, Spitz PW, et al. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982;9(5): 789-93.
68. Bohannon RW. Reference values for the Timed Up and Go Test: A Descriptive Meta-Analysis. Journal of Geriatric Physical Therapy, 2006;29(2):64-8.
69. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the timed up & go test. Phys Ther. 2000;80:896-903.
70. Kristensen MT, Foss NB, Kehlet H. Timed "Up and Go" Test as a predictor of falls within 6 months after hip fracture surgery. Phys Ther. 2007.87(1):24-30.
71. Rutkove SB, Parker RA, Nardin RA, Connolly CE, Felice KJ, Raynor EM. A pilot randomized trial of oxandrolone in inclusion body myositis. Neurology 2002;58(7):1081–1087.
72. van der Ploeg AT, Barohn R, Carlson L, Clemens PR, Hopkin RJ, Kishnani PS, Laforêt P, Morgan C, Nations S, Pestronk A, Plotkin H, , Sims KB, Tsao E. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. Molecular genetics and metabolism. 2012 Nov;107(3):456-461.
73. Molenberghs G, Thijs H, Jansen I, Beunckens C, Kenward MG, Mallincdrodt C, Carroll RJ. Analyzing incomplete longitudinal clinical trial data. Biostatistics 2004; 5:445-464.

74. Molenberghs G, Kenward MG. Missing Data in Clinical Studies. Chichester, UK: John Wiley and Sons, 2007.

Appendix A

European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria 2011			
Diagnostic sub-group	**Clinico-pathologically defined IBM**	**Clinically defined IBM**	**Probable IBM**
Clinical features			
Duration of weakness > 12 months	X	X	X
Age at onset > 45 years	X	X	X
Creatine kinase ≤ 15x ULN	X	X	X
FF weakness > SA weakness ***AND/OR*** KE weakness ≥ HF weakness	X	-	-
FF weakness > SA weakness ***AND*** KE weakness ≥ HF weakness	-	X	-
FF weakness > SA weakness ***OR*** KE weakness ≥ HF weakness	-	-	X
Pathological features			
Endomysial inflammatory infiltrate	X	≥1, but not all of the 4 pathological features	≥1, but not all of the 4 pathological features
Rimmed vacuoles	X		
Protein accumulation* or 15-18nm filaments	X		
Up-regulation of MHC Class I	-		
*Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). FF, Finger flexion; HF, Hip flexion; KE, Knee extension; SA, Shoulder abduction; MHC Class I, Major histocompatibility complex class I; ULN = Upper limit of normal.			

Review Group: FDA Orphan Products Development Ad Hoc Panel Review

Investigator: Mazen Dimachkie
Degree: MD
Position: Professor
Organization: University of Kansas Medical Center
City, State: Kansas City, KS
Requested Start Date: 11/01/2015

Project Title: Phase 2 Study of Arimoclomol for the Treatment of Sporadic Inclusion Body Myositis

Recommendation: Approval **Priority Score: 118**
Special Note: Human Subjects

Project Year	Total Costs Requested
01	$394,501
02	$391,250
03	$399,300
04	$397,836

R01 FD004809-01-A2 Dimachkie, M

RESUME AND SUMMARY OF DISCUSSION:
This resubmission proposes a Phase 2 multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of arimoclomol in 150 adults with inclusion body myositis. The strengths of the proposal include the strong scientific rationale, the study design, expertise of the investigators, and the available resources and environment. Although a weakness remains in that clinical benefit has not been demonstrated with this type of product in other diseases, the concerns raised in previous reviews have been addressed. The reviewers recommended approval of this application with high enthusiasm.

DESCRIPTION (provided by applicant):
Sporadic inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy presenting after age 50 years. It presents with chronic insidious proximal leg and distal arm asymmetric muscle weakness. Muscle histopathology reveals endomysial inflammatory exudates surrounding and invading non-necrotic muscle fibers, oftentimes accompanied by rimmed vacuoles and inclusions. Unlike polymyositis and dermatomyositis, patients with IBM do not improve with therapy; at present there is no effective treatment for IBM. The histopathological features and lack of response to immunotherapies has led many experts in the field to believe that IBM is primarily a degenerative disorder of muscle with secondary inflammation. A randomized controlled pilot study in 24 IBM subjects has been completed. Eighteen subjects received oral arimoclomol 100 mg three times daily (TID) for four months and 8 were on placebo. Arimoclomol increases heatshock proteins and may prevent protein misfolding. The investigators reported that arimoclomol was safe and the IBM functional rating scale (IBMFRS) decline at 1 year was less in the arimoclomol group compared to placebo with the p-value approaching significance. The proposed study is a twenty month, randomized, placebo-controlled Phase 2 study of arimoclomol in 150 IBM subjects. The primary aim is to assess the efficacy and safety of arimoclomol (200 mg TID). The primary efficacy endpoint is the IBMFRS. Secondary efficacy outcomes will include different measures of strength

and function: manual muscle testing (MMT), maximum voluntary isometric contraction (MVICT) of quadriceps and grip, modified timed up and go (mTUG), 6 minute walk test with 2 minute distance captured, grip and pinch test; a general physical function measure: Health Assessment Questionnaire (HAQ- DI); a Health-Related Quality of Life (HRQoL) measure using SF36. Safety laboratory and adverse events will be collected.

CRITIQUE 1:
Strengths:

- The overall significance of the proposal is high, particularly in view of the lack not only of an effective therapy for IBM but its relative lack of study in view of its prevalence and disability. There is also inherent and general scientific value for a treatment trial for IBM in view of the widespread interest in neurologic diseases where protein misfolding and aggregation have been implicated in the pathogenesis. That the previous unsuccessful treatment trials were based on an earlier less accurate view of the disease as primarily inflammatory in nature, also adds to the significance of the proposed trial.
- The study drug arimoclomol has a mechanism of action, that of induction of molecular chaperone expression that is of long standing interest as a treatment for diseases associated with pathogenic proteins. Data is also shown supporting a second mechanism of action, that of reduced sequestration of molecular chaperones in conditions where they are already induced and a benefit in a novel cellular model of IBM created by the investigators involved in the current proposal.
- The investigators also present efficacy data from a murine model of familial IBM with mutations of the valosin containing protein, where a significant level of prevention of loss of grip strength and tetanic force was seen. Prevention of histopathologic changes in these mice was also seen with treatment.
- Preclinical data is summarized from multiple species with a wide range of dosing, supporting safety and tolerance of the drug at the proposed dose. This conclusion is supported by Phase 1 data in normal volunteers and in amyotrophic lateral sclerosis (ALS) patients, where it appears that there is reasonable tolerance of this drug but at this point its efficacy remains uncertain.
- The investigators have also completed a 24 patient pilot study validating the patient scale for IBM. This open label study also supports the rationale for the current proposed study. The change in dose from 100 mg to 200mg TID is also justified. Trends seen in this small study, although not statistically significant, also justify further evaluation in a larger population and with a higher dose.
- The study design is reasonable and the use of the patient report scale, muscle strength and functional activities as outcome measures are well justified considering the limitations of variable and relatively slow rate of progressive worsening in the study population.
- The investigators have addressed the comments of the previous review reasonably well such as: 1) documenting support for supply of drug for the study, 2) justification of the use of the IBMFRS as the primary outcome measure, and 3) cost concerns regarding surrogate laboratory outcome measure-although magnetic resonance imaging (MRI) changes would in particular strengthen the study design, they are not essential to the core study and they will seek other funding to do this in the future, and 4) concerns regarding the adequacy of the sample size and the duration of the study to detect

changes in outcome measurements have been addressed and the study design has been lengthened to 20 months. This raised concern regarding long-term tolerance, but there is supporting evidence from the ALS trial that beyond one year as open label this product continues to have good tolerance.

Weaknesses:

- Arimoclomol is one of many drugs that have extended the lifetime of mice expressing mutant SOD1. However the validity of this model is clearly open to questions since none of these compounds have shown clinical benefit in ALS, with arimoclomol still under study.

The investigative team is highly expert in this population and the appropriate group to execute this study. They have extensive preclinical and clinical experience with both IBM and arimoclomol and are the source of the vast majority of data justifying the study. The Principal Investigator (PI), Dr. Dimachkie, is an experienced neuromuscular specialist. He has participated in many clinical trials of neuromuscular disease, where he has been PI on several of these studies. Dr. Dimachkie has several directly relevant publications to the goals of the study. The Co-Investigator, Dr. Barohn, is a leader in neuromuscular clinical research. The University of Kansas Medical Center has clearly sufficient facilities and patient resources for the goals of the study. The consortium sites will allow for fulfillment of recruitment goals.

In summary, this proposal has been significantly revised and has the potential to be a landmark study for this field.

CRITIQUE 2:
The reviewer agreed with the previous comments and added that this would be a very important trial in IBM not just for developing a possible treatment, but because of the general paucity of trials studying this disease which is one of the more common rare neuromuscular disorders. In addition, the IBMFRS, a validated outcome that this group has validated itself and is based on the revised ALS Functional Rating Scale (ALSFRSR) which has been the primary outcome for ALS clinical trials for the last decade, and a number of secondary efficacy outcomes will be measured. The outcomes are excellent, the investigators are excellent, the scientific rationale is very sound, and they have addressed the concerns of the previous review so approval is recommended.

CRITIQUE 3:
The application is impressive and the two previous reviews are excellent.

CRITIQUE 4:
There are no other concerns.

INVESTIGATORS:
The investigators appear to be well qualified to conduct this study.

RESOURCES AND ENVIRONMENT:
The resources and environment appear adequate to conduct this study.

BUDGET:
The budget appears appropriate and well justified to conduct this study.

MONITORING AND HUMAN SUBJECTS PROTECTION:
The rights and welfare of human subjects and monitoring appear to be adequate.

OPD RECOMMENDATION:
OPD concurs with the recommendations of the review panel.

MRI of a Poet's Brain

Vernon Rowe, MD
vrowe@neurokc.com

In this image
of your brain
I see each curve
in the corpus callosum,
curlicues of gyri,
folding of fissures,
sinuous sulci,
mammillary bodies,
arcuate fasciculus,
angular gyrus,
tracts and nuclei,
BOLD blood flow,
eyes and ears,
tongue and pharynx--
but not a single
syllable of
one
tiny
poem.

This poem was included in Sea Creatures, 1995, by Vernon Rowe, M.D.

Remembrance

Elizabeth Snow Rowe, PhD, MBA
erowe@neurokc.com

In a snow-filled Kansas pasture,
the sun sparkles on the covered ground,
framed by stream and wooded hill.
Leafless silhouetted trees
make blue shadows on the snow.
Like Grandma Snow's painting of
a Connecticut woods, my father's favorite.
She gave it to him when he was dying.

Included in Sailing Downwind by Elizabeth Snow Rowe

27 Crossroads

A full-length play

By Walter Anderson

waltersound@mac.com

ii.

"They say that kid Robert Johnson disappeared for quite a spell. When he came back, he could play the guitar better than anybody else. They say he made a deal with the Devil down at the Crossroads. When you make that deal, you might not make it past 27"

-Anonymous Bluesman

iv.

ACT I

SCENE 1

Blues music from a solitary guitar plays to reveal a 27 YEAR OLD BLACK MAN in a natty pinstripe suit, sitting alone in a grotty, FILTHY LONDON FLAT. He stops playing.

MAN

Good Evening Ladies and Gentlemen, and welcome to the show. If you like the Blues, you came to the right place. If not, there's still time to ask for a refund at the front door. Good luck with that. In the cotton fields where I'm from, there's a nearby Indian tribe that believes that when you say a dead person's name, you bring them back to life. Perhaps only briefly. But, when you play their music, strum it just so, well, that's a whole 'nother thing altogether... You're gonna hear some music here, but mostly there'll be a bunch of skinny white kids talkin' bout it. Four of them are my "flat mates" as they say around here, and they are a lazy lot. Allow me to introduce these no good Nankers, they'll all be here pretty soon-

(Sound cue- WW2 WARNING SIREN blares)

SCENE 2

The SOUND of WW2 bombers as they drop a load overwhelm and SHAKE a DARTFORD HOSPITAL NURSERY WARD. THREE NURSES are non plussed as they tend to HALF DOZEN BABIES.

HEAD NURSE

Caught in the crossfire for the third time this shift! Mr. Churchill is not making Britain Great again as promised, I'm afraid.

(she struggles to bottle feed baby)

HEAD NURSE
Funny Ears here refuses to take a drop. He’s the skinniest one here-

(a nearby baby starts a CRYING FIT and all three nurses react)

HEAD NURSE
He just won’t shut up, that one, will he? That baby with the big lips is the loudest one I’ve ever heard, I swear!

(all three drop what they’re doing to fuss over him)

SCENE 3

We’re in a posh CHELTENHAM DOCTOR’S OFFICE with 8 year old BLONDE LEWIS JONES JR., his PARENTS and a PEDIATRICIAN. The child sits APART from his parents, withdrawn and staring at the floor.

DOCTOR
Your son has a condition known as asthma.

(The parents are somewhat staggered)

DOCTOR
It’s a lifelong condition, but yet very manageable with the right therapies.

LEWIS JONES SR.
(Resigned acceptance)
Well, it won’t keep him out of Oxford. Or even Cambridge. Perhaps this will help keep him less... distracted.

(Lewis Jr. remains withdrawn)

LOUISA JONES
What therapies should we be doing? Which are the best? Cost is not an issue; we have a telephone and a motorcar-

DOCTOR
I will give you an inhaler which will quell these short fits. Long term, we would strongly endorse a musical instrument to strengthen his lungs. A clarinet often works well-

LOUISA JONES
Well, my side of the family is very musically talented.

LEWIS JONES SR.
And most of them are on the dole. Music didn't get the doctor this nice office, did it?

DOCTOR
You work at over the Cheltenham Aeronautical Research Institute I understand, Mr. Jones?

LEWIS JONES SR.
Actually yes, I'm head of the Airworthiness Department. Jet engines. Hurricanes, Spitfires and the like.

DOCTOR
Wow. Impressive.

LEWIS JONES SR.
Well, first in flight, we like to say.

(Sound cue- a lone woodwind instrument)

SCENE 4

In a WORKING CLASS FLAT in Dartford a skinny, smallish for his age, 10 yr old RICKY is playing a tune on his SAXAPHONE almost as big as him, surrounded by mother DORIS and her SIX SISTERS. A GUITAR is MOUNTED LIKE A TROPHY high up and way out of his reach on a wall. They all dote over him as he finishes the lick.

(his aunts clap and cheer,)

AUNT #1
That was SO wonderful! Yet another Dupree to the center stage!

DORIS
Ha! You don’t know the half of it! Should I tell them?

RICKY
(protesting)
No Mum, please...

(excitement mounts)

OTHERS
What?? TELL US!

DORIS
Well, he’s been one of three boys selected for choir at a special service at Westminster Abbey...

(the room quiets)

DORIS
My son singing to a Royal Audience, the Queen herself!

(The room erupts and Ricky gets smothered by the women. Doris goes offstage briefly, reappearing with the ridiculous effeminate FLUFFY COSTUME Ricky is to wear. He puts up a weak fight as they dress him like a Barbie doll.)

AUNT #2
Do you think his grandpa will let him, you know, on the account of this?

(the commotion halts; all eyes go to the GUITAR MOUNTED ON THE WALL)

DORIS
Well, Dad is pretty firm about him mastering at least three instruments before that thing comes down off the wall. But if this singing goes well...

(cue Skiffle song)

SCENE 5

A few blocks away in an UPGRADED FLAT a same aged, but much taller MIKE performs karaoke style to this tune with a hairbrush microphone from a spinning 45. His mum EVA sits with younger brother CHRIS in her lap. Across the room his PE teacher father JOE dressed in track suit and WHISTLE around neck, views the spectacle disapprovingly with crossed arms. This kid's moves are pretty good for someone his age. The song ends, Mum puts down Chris to hug Mike-

EVA
(ecstatically)
Smashing! Where in ever did you get such natural rhythm I'll never know!

MIKE
Well you ain't seen nothing yet, ladies and gentlemen-

(He motions to little Chris to change the record, who puts on a LITTLE RICHARD song, Mike jumps and spins. Joe BLOWS THE WHISTLE and halts everything. Needle off the record-

JOE
(yelling)
That's it! This is finished- there will be NO jungle music in this household, as long as I'm here! This does not qualify as fitness on any level, young man! Give me thirty press ups, right now!

(A wet blanket on the party, Mike drops to the floor and dutifully complies.)

SCENE 6

Cheltenham Grammar School, stately and traditional. Louise and Lewis Sr. have been summoned to HEADMASTER STERN'S OFFICE. They sit opposite his desk, on separate chairs.

HEADMASTER STERN

No, Mrs. Jones, your son has done nothing wrong. Yet. In fact, his marks are quite good, near the top in most of his courses. That is the concern, that there is this trend-

LEWIS JONES

Trend? What trend?

HEADMASTER STERN

With your son and with some others. I would use the word defiance, but perhaps that is a strong word at this point. It is 1956 after all, and we realize Britain is blazing a new path into the future. Certainly no one is more aware of this than you, Mr. Jones. Those new Rolls Royce jet engines of yours are the stuff of Space.

LEWIS JONES SR.

Thank you, but I cannot discuss a classified topic any further, obviously...

HEADMASTER STERN

At your factory there is of course a system in place. There is a structure of levels. Of order. Our society relies on it, too. We must be better prepared for that next war. This is Cheltenham Grammar, not a Tech School. At prestigious institutions like this one, it is imperative that along with providing a basic starting point for all the noble disciplines, we also send our students on with a sense of Order. They will lead our future. Our cousins across the pond have a completely different way of doing things. More experimental. Less order. We'll see how that works. Some of their music that has snaked it's way over here is encouraging of bad behavior-

LOUISA JONES

(interrupting)

Pardon, but what does all this have to do with our boy?

HEADMASTER STERN
Part of our responsibility here, Mrs. Jones, is to monitor the social well being of all our students. Your son has had his slips here and there, not entirely unusual. His asthma problem has caused him to drop out of varsity sports, which is a school point of pride, but, he has channeled his talents into many musical instruments and mastered them. Including the guitar. In fact, apparently young Mr. Jones has been playing at times in a rather unsavory jazz and blues place across town. During school hours. I don't know if you were aware-

LOUISA JONES
Blue Place?

HEADMASTER STERN
He's had several absences attributed to doctor's appointments, are you aware of those as well?

(the parents exchange a look, Stern opens a folder)

HEADMASTER STERN
Here's a recent comment from one of his councilors: "Lewis Jones Jr. is clever, but needs careful handling. There is a reckless potential there." Then there is this. From our girl's school. It has been noted that one of the students has taken a leave of absence. There is a disturbing account that one of our students has gotten one of theirs into "trouble." Your son's name has come up.

(The Jones are stunned)

SCENE 7

Tech Schoolboy Ricky comes running round the corner into a DARTFORD BACK ALLEY, books on his back. He stops, out of breath. VOICES offstage yell back and forth. Ricky eyes a LARGE ASHCAN and hides behind it. A BULLY student comes from the direction Ricky did, a BIGGER BULLY emerges from the other end of the alley.

BULLY #1

Okay sister boy, you are a trapped rat now. You'd best come out, or we give you twice the usual!

(they continue searching)

BULLY#2

We can smell your perfume, the same crap you slathered on for the Queen...

(Ricky emerges from hiding, with a black eye from a previous beating)

RICKY

(digging into pockets)

Here's 2p, it's all I have.

(Bully #1 snatches the coin and SLAMS Ricky into the ashcans violently. He slowly rises back up.)

BULLY #1

It would be a lot easier on all of us if you would simply present this to us earlier in the day, Monkey Ears. A time saver.

(He gut punches Ricky, who doubles over on the ground.)

BULLY#2

Aw, you should show a little more compassion, mate! Our classmate here has been demoted from Choir, on account his lovely girlish voice has cracked in puberty. Cruel, such a shame. Imagine, all that practice and field trips to London down the drain! Insult AND injury indeed. And speaking of demotion, all that time away has caused all the Choir Trophy boys to stay back a year!

(The bullies share a big laugh. Ricky curls into a big hedgehog ball. The bullies are about to leave.)

BULLY #1
(sniffing in Rich's direction)
All this heavy breathing has revealed a familiar scent. Black Courant Chewies. My fave!

(Ricky quickly removes a candy box from his bag and tosses before they do further damage, curling quickly back up. A Bully grabs his book bag and dumps the remaining contents on ground, then tosses the bag.)

BULLY#2
On top of everything else, he has an "honesty" problem as well. A total disaster.

(He shakes his head and gives Ricky a swift hard kick in the arse. Ricky yells. The bullies chuckle and exit. Staying curled up until he's sure they're gone, he gets up, gathers his things, and heads off.)

SCENE 8

Inside Ricky's family flat, Grandpa Gus and mum Doris await his return from school. Gus is stringing a VIOLIN and sipping his TEA.

GRANDPA GUS
I don't know Doris, I don't have a lot experience with adolescent boys. I had seven daughters for chrissakes. Eight, counting your mum. What does Bert have to say in all this?

DORIS
(upset)
Bert is always at work. Even when he's here, which is late every damn night, he's on about the factory. Then on weekend, he's off to the tennis club. He takes him along, and then makes him chase all the errant balls the whole day. He almost got electrocuted on the rail tracks last Saturday.

On top of getting sacked from choir the day before. And now it’s likely he’ll have to repeat a year!

(Doris is about to breakdown, but pulls it together as she HEARS RICKY at the front door.)

DORIS
Hey there, handsome! How was your day? Your Grandpa came-

(A beaten Ricky blows through the lounge straight out the back without acknowledging anyone. He SLAMS the backdoor.)

DORIS
Crap. He’s gotten his arse kicked, again. He’s such a wuss. I’ve had it with those hooligans, I’ll get with their mums. Now he’s off to his tent for the rest of the day.

GRANDPA GUS
The tent I got for him?

(Behind the actors,(who are oblivious to this), the mounted GUITAR STARTS TO SPIN, slowly at first.)

DORIS
(sarcastically)
Yes, thanks by the way. He’s pitched it out back, and just retreats back to it for hours upon end, doing God knows what in there. He’s taken a turn for the dark, that one, I tell you.

(a few beats)

DORIS
(losing it)
You go talk to him!

(THE GUITAR STOPS ABRUPTLY. She exits. Gus’s gaze follows her out, then his attention shifts to the mounted guitar, curiously. He notices it is now OFF TILT.

He walks over to it, now focused on it pensively. He gets a chair, and instead of straightening it, he TAKES IT OFF THE WALL and exits out the back door.)

SCENE 9

The backyard of the flat is in the ugly part of Dartford town, still pockmarked with the LEFTOVER WAR RUBBLE. A smallish RED TENT is pitched amongst the STACKS of rotten TOMATO CRATES from the green grocer shop on the bottom floor of the flat. Gus looks at the tent, which GLOWS from light inside. He starts to play an OLD BLUES TUNE. Ricky emerges slowly from the tent, like a charmed snake.

GRANDPA GUS
(finishing the riff)
I came over to re thread the violin, but I can see this needs some tending to-

RICKY
I thought it was not to be touched-

(It’s the same guitar from the opening scene)

GRANDPA GUS
It wasn’t, It’s kind of a special one I paid a bit up for. It’s from the States. The South.

(Rich just stares at it.)

GRANDPA GUS
I know I’ve been keeping it from you. Waiting for the right time. You’ve gotten decent on all the others, so, I think the time has come for this.

I will caution you, the problem with this damn thing is once you pick it up, all the others won't interest you so much. You'll ignore them. That I know first hand.

(He hands the guitar over to Ricky, who runs his hands over the curves like a teenage boy discovering the opposite sex for the first time.)

GRANDPA GUS

...Okay, there are three basic chords, learn them and you can build ten thousand songs, just like those Cambridge science guys showed us you can make a dinosaur or a beetle from just four proteins...

(The kid has the guitar now as the lesson commences.)

MUSIC CUE

SCENE 10

A KITCHEN at an American Air Force base near Dartford. JOSE, a two striper enlisted black man is washing up and singing along to a record amongst STACKS OF UNWASHED DISHES. JOE and MIKE enter.

JOE

Jose, turn that noise off! Please- you know that's not allowed!

JOSE

(shutting off music)

I'm so sorry sir. I completely forgot, sir, my mistake.

JOE

I'm doing a rock climbing seminar over at the gymnasium, the BBC is here to see it. If they like it, they're going to put it on the telly.

JOSE

(impressed)

No kidding, television?

JOE
Yes! And Mike here could very well be one of the youth demonstrators.

JOSE
Mike?

(Mike nods enthusiastically.)

JOSE
A television star right here In my kitchen, my lord.

JOE
Well I’m off, I’ll be back round half six. Put him to work, Jose.

(Joe EXITS)

JOSE
Ok, rock climbing star, you know the drill. Wash three stacks, get a cheeseburger.

(Mike rushes over to the grill. Jose playfully stops him.)

JOSE
After, not before.

(Mike dons some RUBBER GLOVES and dives in. The LIGHTS DIM TO BLACK for a few moments, and then FADES UP with MUSIC PLAYING as we rejoin the scene in the NOW TIDY KITCHEN. (the scene resumes with JOSE PLAYED BY THE ACTOR FROM SCENE 1.) Jose is dancing to a record, there are SEVERAL RARE BLUES RECORDS spread out on the table. Mike is in heaven, eating the CHEESEBURGER, studying JOSE’S MOVES and simultaneously drooling over the album covers. The SONG ENDS.)

MIKE
Fantastic! Who was that?

JOSE
That there is Howlin’ Wolf.

He grabs the album cover and hands it to Mike.

MIKE
Such a cool name. Where did you get all these?

JOSE
Brought some over. Sent home for most of em. Chess Records in Chicago.

(Picks up an album, points to the back corner.)

JOSE
The address is right here.

(Hands to Mike.)

JOSE
Tell you what. I loan you a few, you wear the shit out of em, learn em, then bring em back next time. I’ll give you a few more. Kinda like a library.

MIKE
Oh my god, are you kidding? My Pops-

JOSE
Don’t you worry bout that. I got you covered.

(Jose looks over to the door perceptively, then scoops up all the music and disappears into the background, just as JOE ENTERS.)

JOE
(Triumphantly)
Ha Ha Ha, sealed the deal! And you my son, are set to be the main Youth Demonstrator for the entire telecast! To be seen in Scotland, Wales and Ireland as well!

(Mike is excited too, and Jose re enters with a neat BUNDLE under his arm.)

JOSE
Man, that is something else, sir. And to think, I got to witness the whole thing, right here. Well done, sir.

JOE
Thank you so much, Jose, for minding Mike. C'mon Mike, we've got a lot to do

(Heading to the door)

JOSE
Oh Mike, here's that stuff-

JOE
(somewhat suspicious, intercepting the package)
What's all this?

JOSE
Some old uniforms I was gonna toss out. Mike said he wanted them.

(Jose extends hand to Mike, they SHAKE.)

JOSE
Thanks Mike, you're more help than you know. You have a great kid here, sir.

JOE
So kind of you Jose. Those kids will wear anything, I suppose. Thank you, Jose.

JOSE
My pleasure Mr. Jagger. My pleasure indeed.

SCENE 11

The same alley where Ricky got his ass kicked. He's a little bigger now, and more confident. He goes by a different name from now on. The bullies have him cornered.

RICKY (NOW KEITH)
Hey fellas, I was looking for you-

BULLY #1
No kidding, imagine your luck. Give over Monkey Boy.

KEITH
I've been meaning to introduce you to my new mate Nigel.

(ENTER NIGEL, a MASSIVE upperclassmen Rugby player. He's got a RUGBY BALL under his arm. The bullies freeze in their tracks.)

KEITH
Nigel here has a bit of a fancy for my cousin Kate, and we're on the way over to her house for an introduction and the like. He's first team second row on our varsity, and they happen to be recruiting for fall. I have been telling, kind of bragging, actually, about your boys' ...athleticism.

BULLY #1
...Well, I'm not into sport so much.

The other bully shakes his head.

NIGEL
It's really quite basic, mates. Let me demonstrate.

(The prospective players start to back off.)

BULLY#2
That won't be necessary. We're not interested.

NIGEL
Here, you're on the attacking side-

(He tosses ball to Bully #2, who catches it but stands limply.)

NIGEL
Now, Keith and I are defenders. The basic tackle:

(He smashes the bully to the ground with a BONE CRUSHING TACKLE.

The other one bolts, but not before Keith can BOOT HIM IN THE ASS. The former bully writhes on the ground.)

KEITH

I’m sorry Nige, I guess I was wrong. Maybe they don’t have the makeup after all.

NIGEL

Well, if you lads change your minds, I’ll have eyes on you.

(The ruggers exit.)

END ACT I

ACT II

SCENE 1

TBD Cheltenham exterior. Blonde teenager LEWIS BRIAN JONES JR. is holding court to THREE CUTE UNIFORMED SCHOOLGIRLS. He's got his SCHOOL BLAZER tied irreverently around his waist, and a GUITAR slung over his shoulder. He's come out of his shell, maybe too far. The girls giggle-

BRIAN JONES
What do you say we get out of these silly prison rags and head over to the clubhouse? I've got a new tune to show off.

SCHOOLGIRL #1
(Teasing)
Tune, or show off a new outfit? You are such the peacock Jones.

BRIAN
I do detest uniforms of any kind. It's like you're in the army. When you're not even.

SCHOOLGIRL #2
Well if you get in that band you talk about, they'll make you wear one. And the same haircut.

BRIAN
Bollocks they will. I'd quit them straight away.

SCHOOLGIRL #2
Such the rebel. So James Dean. But only blonde!

(She musses his hair)

BRIAN
No really, it's like they're preparing us all to work in some giant sooty gray factory in Leceister.

(mimicking factory workers)

BRIAN
"Hey Earnie, here's another bolt. Cheers mate, I'll give it to Earnie Number Two, he'll put a nut on it. Then let's do it like six hundred and sixty-six more times. We'll have us a pint at the pub across the way with all the other Earnies after the end whistle." ...If you stay at it for twenty years grinding away, they'll promote you to Supervisor Earnie... To all that, I politely say, no thank-you.

(The girls giggle at his funny voices)

BRIAN
What is it you lovely ladies see yourselves doing after all this?

SCHOOLGIRL #2
Easy. I love horses, so probably I'll be a veterinarian or the like.

SCHOOLGIRL #1
I'm already set up to have a chair in my aunt's hair salon. I simply can't get there soon enough. I love everything about styling.

BRIAN
Really?, And what would you do with mine?

(she touches his hair)

SCHOOLGIRL #1
First you grow it long, like those Liverpool boys, then you fluff it all up, by frequent shampooing...What kind of music is your band going to play?

BRIAN
The Delta Blues for sure. Muddy Waters, Elmore James, Leadbelly, Howlin' Wolf. Robert Johnson, they all copied him. He died at age 27. They say he made a deal with the Devil so he could play better than anyone else.

SCHOOLGIRL #2
Wonderfully colorful names. Would you make that same deal if you could?

(He swings his guitar around, runs his fingers over the strings for effect, and waits a beat.)

BRIAN
...In a Mississippi minute ma'am, in a Mississippi minute...

(They laugh at his attempt at a southern accent)

SCHOOLGIRL #2
With what name?, You'd have to get a better stage name!

BRIAN
You have a point. Lewis Brian Jones Jr. Sounds much too nice. And too English. I'd change it up a bit. "Elmo Lewis" has a ring to it...

(The girls give their approval. His attention shifts to Girl #3, who has remained quiet so far. She's far the fairest, and he likes the cut of her jib.)

BRIAN
And you Diane, what is your dream job?

SCHOOLGIRL #3
It's Denise, first of all. Secondly, it's not really a job I'm after, I'll just continue modeling, until I meet that fabulously rich entertainer and we move to the Antilles and make babies...

BRIAN
Sounds to me the best plan of all.

SCHOOLGIRL #1
Speaking of babies, did you hear about that girl who got preggers over at Brian's sister school? Put it up for adoption, she did-

(The conversation tacks in the opposite direction, and he slows his roll.)

SCHOOLGIRL #2
They just can't keep their knickers on over there, can they? Which classmate is it?

(she looks his way- awkward pause would be an understatement)

BRIAN
(A little shaken)
Have heard nothing about that. Probably just one of those nasty fake stories that get around-

SCHOOLGIRL #1
Well, whoever is responsible for it ought to do the decent thing and fess up. Probably one of those Rugby players- they're always putting their hands all over everything...
(Changing subject)
OK, we're off girls, let's drop by my aunt's on the way back, she's got this fab new curling iron...

(They start to go, Denise wants to stay back)

DENISE
I've got to head over to High Street way to pick up some things at the Post Office- go ahead without me.

(The other two stop, exchange a look)

SCHOOLGIRL #2
Are you sure? We can go that way tomorrow-

DENISE
Thanks. I'm okay.

(the two girls exit)

BRIAN
(back in the game)
I'm going that way too. Let's cut across the park, it's longer but prettier. I'll play you the new tune as we walk....Denise...such a poetic musical name. Are you named for someone in the family?

(As they EXIT)

SCENE 2

Waikiki Clubhouse, a Cheltenham makeshift repurposed space for small music and pub food. ALEX KORNER and her JAZZ/BLUES BAND have just finished a set. The audience is clearing out as elder U.S. BLUESMAN BROWNIE MCGEE meticulously wraps his gear. Brian has been sitting in on guitar.

ALEX KORNER
Thanks for sitting in short notice, Brian. Spot on, as usual. Your dedication is really paying off. Brian, this is Brownie-

BRIAN
(Awe not worn off yet)
Yes I know. Such a pleasure to meet you, Sir. Thanks for tolerating me tagging along, sir.

(Alex heads over to the bar.)

BROWNIE
They even call me Sir around here. White joints that pay you to play AND they serve you. I could get use to this shit. You ain’t bad for young white boy. Just got one thing to say...

(Brian is all ears)

BROWNIE
Which way is the free food?

(Alex motions them over to a table near the bar, Brownie makes a beeline and Brian peruses. They sit. Brownie takes a big swig of his PINT GLASS)

BROWNIE
Damn that is tasty! What do you call this kind?

BRIAN
It’s a bitter.

BROWNIE
On account of I'll be bitter if they don't pour me another one!

(He nods approval to the barkeep)

BROWNIE
We usually take it colder, but it got more flavor like this. How long you been knowin' Miss Korner, boy?

ALEX
Brian hasn't missed a show since we've started coming through here. He's a rising talent, that one.

BROWNIE
Here's your first test kid, order me something off this.

(hands menu to Brian)

BROWNIE
My eyes wearin' out, can't read shit no more. I been told English food is shitty and the beer is warm. This beer ain't cold; But it is cool. What y'all got close to ribs?

BRIAN
Try the steak and kidney pie, they do a good one.

BROWNIE
A pie made with a kidney. Damn. Get me some fries with that. "Chips", right?. I know 'bout that. Say, which way is the head in here? I gotta wash up.

ALEX
The loo is that way, Brownie-

(She motions, he goes off)

BRIAN
Well, I guess he's not too interested in my playing.

ALEX
That old guy is interested in two things, his guitar and food.

(The barkeep drops off the extra beer)

ALEX
Okay, three things...I've got some great news, Brian, but first I want to hear about you. How'd the testing go? What's up with your parents?

BRIAN
(somewhat deflated)
Not quite sure what the word "parent" actually means at this point. I think my exams were...underwhelming. Lewis has dropped the idea of me becoming the UK's foremost rocket scientist, and is now trying to push me in the direction of Optometry School. He says at the very least I can fit people with glasses...

ALEX
You should stick with your schooling, Brian.

BRIAN
I'm done with that. I'm a Bluesman now.

ALEX
There's no great future in the Blues, Brian. Not a lot of cash there. It's Elvis versus Buddy for the big money.

BRIAN
Well that's funny, coming from you...So what's the good news?

ALEX
Bobby and I have finally got the Liquor License we've been waiting forever for. We open up "Korner Jazz n' Blues" in West London next week. My Blues Incorporated group will be the house band.

BRIAN
Oh, so it's good enough for you, apparently!

ALEX
We sell booze, Brian. Music makes people thirsty.

(Brian starts to gather his things, BROWNIE'S FOOD is delivered to the table. Brownie emerges from the back, he is now PLAYED BY THE ACTOR FROM ACT I, SC I.)

BROWNIE
Leaving so soon Mr. Jones? The fun starts when the show ends.

BRIAN
I have another gig to be at, sir. It was nice playing with you.

(Brownie extends his hand. They SHAKE hands.)

BROWNIE
Stay the course, Brian, you've got the touch.

(Brian EXITS.)

SCENE 3

The Jagger Duplex now in a nicer part of Dartford. Upgrade. Eva Jagger is in the lounge area, drumming her fingers and sitting across from the FRONT DOOR in anticipation. Joe is dressed in a flashy track suit, gathering up ATHLETIC EQUIPMENT for work.

JOE
For god sakes Eva, go do something else, like in the garden. When the mail comes, it comes. You're not going to speed it up-

EVA
He's thirty-five minutes late. Again.

JOE
I'm telling you, the college acceptance notifications have just started to come out. It could be days. He's already got two admissions.

EVA
But not the big one. Do you know what that would mean?

(he stops what he's doing)

JOE
The London School of Economics. Admission to The Big Boys Club. That would be something for a Jagger.

EVA
Rockefeller went there. John F. Kennedy. He could do politics!

JOE
Or something useful...Anyways they'll probably just deliver a box of those stupid jungle records he squanders his money on.

EVA
It's his money, Joe. My god, that boy must have had thirty jobs by now. All favorable reviews. That looks good on an application.

JOE
Not to mention a member of nearly all the sports teams at school, in addition to all the American ones on the Base.

EVA
Along with the top marks in nearly all required categories. They'd be crazy not to take him...You know he's going by "Mick" now, all the boys in his band call him that-

JOE
Yes, "The Blue Boys" they call themselves. Well, all that will just become a weekend hobby in someone's garage when he goes off to university. The longish hair, the excessively tight pants, all those childish things will go away-

(NOISE at front door, then a KNOCK. Eva jumps up and rushes to door.)

MAILMAN
Morning Mrs. Jagger- I've got another box from Chess Records Chicago, U.S.A and 3 letters. Good day!

EVA
Thanks Cecil!

(She can't shut the door and put down the BOX fast enough.)

EVA
There it is! There it is!

(She waves a letter in the air)

JOE
Let me see that.

(He examines)

JOE
Yes this is it. L.S.E.

(They both just stand there.)

EVA
He’s not home for four more hours...

JOE
Yes, I know...

(As if on cue, the steam kettle in the kitchen WHISTLES LOUDLY. They look at each other for beat.)

EVA
That would be sooo wrong of us-

(They both dash JUST OUT OF VIEW to the KITCHEN. We hear SOUNDS and AD LIBS indicating the steaming open of the letter. Then ELATED YELLS from both. Touchdown!)

SCENE 4

Dartford Tech Headmaster’s Office. Keith Richard’s Exit Interview.

(Lanky teen Keith Richards lounges outside the door of Headmaster Crunge’s office, chewing gum and drawing in his SKETCHBOOK. LOUD YELLING is heard.

The DOOR BOLTS OPEN and HEADMASTER CRUNGE flushes a DELINQUENT STUDENT out.

HEADMASTER CRUNGE
That’s it! We’re done! If you should EVER set foot on the grounds of Dartford Tech again, the police shall be notified and you will be hauled off!

(Crunge turns to Keith, the delinquent boy FLIPS THE BIRD at Keith as he exits.)

HEADMASTER CRUNGE
Richards, you’re next.

(The two enter the office, Crunge is now composed.)

HEADMASTER CRUNGE
Please, be seated.

(Crunge pulls a FOLDER from a STACK on his desk.)

HEADMASTER CRUNGE
Well, the mastermind himself. I must say, after an illustrious and decorated tenure at this school, you managed to go out with quite a bang. Cutting out with your mates on the LAST possible day and getting expelled is an act of sheer genius. Enlighten me; What was going through that pensive head of yours?

KEITH
(straightening up a bit)
Well, sir, being that as it was the last day, and that most of it was to be taken up by a meaningless assembly mostly designed for underclassmen, I, rather we, thought we’d have a smoke. Not wanting to cause any disturbance, we ventured barely off campus, apparently. Intending to return to the festivities, we unfortunately got distracted-

HEADMASTER CRUNGE
(interrupting)
Let’s pause there. Smoking is prohibited in the bylaws. Leaving campus without permission is grounds for dismissal.

Period. “Barely off campus” happens to be a pub on the High Street of the next village over.

KEITH
Well, sir, It’s not exactly as it might appear. There was an element of misinformation-

HEADMASTER CRUNGE
Just stop, Richards. Expulsion from Dartford Tech has been recommended. I am in the midst of that decision, taking your record into consideration. Let’s review some of your highlights:

(opening folder)

HEADMASTER CRUNGE
Seventeen absences excused by parental notes with likely unauthentic signatures. Twenty-one reports of violence or fisticuffs.

KEITH
Most of those I didn’t start, I was the victim.

HEADMASTER CRUNGE
Let’s move on to extracurricular activities. The Eagle Scouts.

KEITH
Learned a lot, knots and such.

HEADMASTER CRUNGE
Fantastic. Should take you far. After you rose through the ranks to Beaver Patrol, it’s cited here that you instigated some whiskey drinking on an overnight which resulted in a broken bone.

KEITH
I think it was bourbon, actually.

HEADMASTER CRUNGE
(slamming file down)
Our school crest is emblazoned with the image of an Oak Sapling; Not a regal symbol, but one emphasizing development a solid potential. You, Richards, are a weed. A tumbleweed at that.

KEITH
...A weed is resilient, and a tumbleweed shows mobility. Change or die. Darwin, right?

HEADMASTER CRUNGE
(fully lathered)
I've spoken to your father Bert. He tells me you spend most of your time strumming a guitar and/or playing records. He seems to think the quicker you join the work force, the better. I concur. It will be my recommendation that you be declared eligible for the Labor Exchange...But someone has stepped in on your behalf, inexplicably...Mrs. Mountjoy, our Art Instructor. She seems to think you have some kind of "talent" and is willing to send Admission Approval for you to attend The Sidcup School for the Arts.

(Keith perks up.)

HEADMASTER CRUNGE
I will go on record to protest it as complete waste of education resources, but will reluctantly give you a piece of paper acknowledging the fact that you did your time here. It is NOT a diploma.

(He takes a PAPER from Keith's file folder and shoves it across the desk.)

HEADMASTER CRUNGE
Please do me the favor of not reproducing any offspring that are of age to attend this institution until I am fully in retirement. Now go away-

(Keith pops up and grabs the paper)

KEITH
Suitable for framing. Thanks for the years of nurturing support, sir.

(Keith exits into the waiting area past the NEXT VICTIM to an ASHCAN. He stops, takes the WAD OF GUM out of his mouth, puts in the paper, forms a ball and TOSSES it into the can, and EXITS.

SCENE 5

The Jones Residence in a bucolic Cheltenham. The home has CHRISTMAS DECORATIONS. Brian and a BOOTS CHEMIST COWORKER approach the gate with their BLUE SMOCKS showing under their jackets, guitar slung over Brian's shoulder.

BRIAN
(stopping at gate)
I'm just gonna pop in, spread some holiday cheer and get a fiver off Lewis. Sure you don't want to come in for a minute?

BOOTS CO WORKER
No, I was never a favorite of his- I'll catch up with you over at Waikiki.

BRIAN
(to self)
You are not alone there, mate.

BOOTS CO WORKER
(exiting)
Be sure to say Happy Christmas to everyone!

(Brian OPENS GATE and heads to the front door. He stops there and notices a PILE OF BELONGINGS. There's a LETTER TAPED to the top of the pile. Brian slowly walks over, picks up an item, recognizing the things as his. Sitting on a TRUNK, he OPENS THE LETTER reads the note.)

As the LIGHTS DIM on the MAIN SET, a spotlight illuminates ONLY LEWIS JONES, SR. on a FAR SIDE OF THE STAGE.

LEWIS JONES SR.
You are disowned. You’re no longer our son. You gave up on your scholarship, you gave up your education, your career, everything else that was planned for you. Go to London to be a bum and hang out, and be with people like those derelict musicians. We’re on holiday. When we return, be gone. Enclosed is a cheque for 200 pounds. Don’t ever knock on our door again.

The SPOTLIGHT goes DARK as the LIGHTS ON THE MAIN STAGE FADE UP. Brian soaks up the last bit for a beat or two, and jumps to his feet.

BRIAN
(Yelling for all to hear)
HAPPY FUCKING CHRISTMAS EVERYONE!

(A LIGHT goes on NEXT DOOR.)

END ACT II

ACT III

SCENE 1

Cheltenham Train Station. Brian's TRUNK AND BAGS lean up against CLASSIC RED PHONE BOOTH as he feeds coins.

BRIAN
I'd like the number for a Robert or Alexis Korner in West London please, that's Korner with a K... Yes, Ealing would be it. Thank you so much, Happy New Year to you too, cheers.

(He hangs up, dials)

BRIAN
Hello, Bobby? This is Brian Jones. Yes, the blonde one. Happy New Year!...Great to hear your voice, been a bit...Yes, everything's great. Is Alex there? Just wanted to wish her- Sure, I can wait...She's not. OK. So how's the new Club getting on?...Fantastic! Say, chance has me in the area today, how about I come by and check it out? She'll be at the Club later? What's the address again? I think I've lost it... Magic, will I see you there?... Great, cheers Bobby.

(He writes on his hand)

BRIAN
I'm super close by. Great- I'll stop by, and I'll bring my gitty, see you soon.

(He hangs up, quickly gathers his belongings and hustles over to the TRACKS.)

SOUND CUE: TRAIN SOUND FX (WELLS UP, THEN DOWN DURING SET CHANGE)

SCENE 2

Dartford Train Platform. MICK JAGGER waits for the northbound London train on BENCH, completely absorbed in an ECONOMICS TEXTBOOK. Next to him is a daypack and a small STACK OF UNOPENED ALBUMS. FIVE Newly ARRIVING PASSENGERS pass by, amongst them KEITH RICHARDS, who stops abruptly in his tracks, pissing off the GUY behind him who bumps him.

KEITH
Mike. Mike Jagger.

(He walks towards him.)

MICK
(looking up)
Yeah what?

KEITH
It’s Keith. Keith Richards from Primary school.

MICK
(feigning recognition)
Oh, hey Keith, great to see you.

KEITH
Is that your Chuck Berry record? I have the same one. That’s the only other one I’ve ever seen. Can I have a look?

MICK
(slightly annoyed)
Yeah, I guess. Okay.

(hands to Keith)

KEITH
(examining)
It’s brand new, never been played. It’s beautiful. Mine’s scratched to shit and doesn’t have a back. Damn. Well, you’ll absolutely fall in love with it.

(He hands it back, starts to leave)

MICK
Do you play?

KEITH
Yes, quite a bit, in fact.

MICK
What kind of stuff?

KEITH
That kind of stuff. I can play every track on that album, top to bottom. It’s pretty basic, really.

MICK
(now interested)
Do you have a minute? Here, have a seat...

(He moves his pack)

KEITH
(sitting)
You heading north?

MICK
Yeah. LSE, First year. This shit is really dense, but I seem to be hanging in there.

(puts book away)

KEITH
I’m just back from Sidcup.

MICK
The Art school? How do like it? Must be lots of tail running around down there-

KEITH
Not as much as you’d think. The School? There’s more talking about art than actually doing it... Say Mike, Do you think I could have a look at the rest of those records?

MICK
(glancing at watch)
Looks like my train is late. Yeah, sure.

(He hands the stack over. Keith cant't believe his eyes.)

KEITH
Holy shit! Wow. I didn't know these even existed! Where did you get these?

MICK
Chicago. Chess Records. Sent away two months ago. Just arrived, haven't had the time to spin them yet.

As the boys have been talking, a black man in the uniform of a BRITISH RAIL OFFICIAL has approached a giant INFORMATION BOARD in the BACKGROUND. Next to a panel that reads 14:27 KINGS CROSS, LONDON he slides in a panel that reads CANCELLED in BIG RED LETTERS. A VOICE comes over a PA SPEAKER.

PA SPEAKER
MAY I HAVE YOUR ATTENTION, PLEASE. DUE TO ENGINE BREAKDOWN THE SCHEDULED 14:27 SERVICE TO KING'S CROSS STATION IS NOW CANCELLED. THE NEXT SCHEDULED TRAIN WILL ARRIVE AT 17:40 ON THE NORTHBOUND PLATFORM.

MICK
Shit. Just my luck... Say Keith, wanna help me kill some time and flip these discs over at my parent's house?

KEITH
Well, I was just gonna knock you over the head, grab them and run, but yeah, let's do that instead.

(The two gather their stuff.)

MICK
By the way, against my wishes, I'm "Mick" now, not "Mike."

KEITH
You and every other bloke born Michael in England.

(The now familiar looking BR Official at the Information Board turns and tracks their EXIT, grinning.)

SCENE 3

Korner Jazz n' Blues, London, located under the Ealing Tube Station. After hours, Brian helps owners BOBBY KORNER and wife/musician Alex wrap up the aftermath after a performance. TWO OTHERS assist in the chores.

ALEX

Well, if you ask me, Davies is really starting to milk those harmonica solos a little too much. The next one, I swear I'm gonna put my guitar down and slip out back for a smoke.

(Bobby is at the till counting cash)

BOBBY KORNER

Well I beg to differ. The kids love it when he gets all sweaty and worked up like a wild man. It exhausts me too, and I'm not even particularly paying that much attention. Two minutes after he's done our lager sales are spiking...Not bad, we cleared over 300 again.

(The crew finishes up and gathers by the front door.)

ALEX

Hey Brian, c'mon let's go home. You played great, once again, by the way-

BRIAN

If it's all right, I'd like to stay behind and work on a bit I'm not happy with. Go on, I'll lock up.

(Bobby and Alex share a look)

ALEX

That's twice this week. You need rest too, kid.

BRIAN
I swear, twenty minutes, tops.

ALEX
Suit yourself. Bobby will leave a light on for you.

They all exit. Brian sets up a RECORD PLAYER, playing along with a particular section that has a RIFF he is trying to duplicate. He stops the record and starts over. He tries twice more without success. He slumps down in frustration.

THE STAGE LIGHTS DIM TO BLACK FOR A FEW SECONDS, THEN COME BACK UP.

An hour or so later, sleeves rolled up and THREE EMPTY BEER BOTTLES nearby, Brian tries again, unsuccessfully. He CURSES. In a fit of anger, he coils as if to smash his guitar on a BEAM, stopping himself just short of completing the task. Again he slumps down.

AGAIN THE LIGHTS DIM TO FULL BLACK, THEN COME BACK UP.

Brian is now SLEEPING on THREE CHAIRS he has lined up. We HEAR the record is SKIPPING on the player. Near his head on a lone chair is a LIQUOR BOTTLE WITH A LONG NECK. On it’s own, the BOTTLE FALLS TO THE FLOOR, waking Brian up. He swears, gets up and scrambles over to the bar and returns with a RAG to mop up the mess, picks up the BROKEN PIECES and puts them in a TRASHCAN. He starts to tidy up and goes to put away the record. HE STOPS...He looks back at the trashcan. He briskly walks over and pulls out the BOTTLENECK. It’s a fairly clean break.

He rifles through a DRAWER an pulls out a KNIFE GRINDING STONE. He smooths out the bottom on the neck, blowing the DUST off. He returns the record player. He slips the TUBE ON HIS FINGER. He holds it up to the light and it SHIMMERS. He puts the needle on and plays the lick again. He picks up his guitar, slowly. He PLAYS THE LICK. Spot on. He let's out a TRIUMPHANT YELL.

SCENE 4

The Garage at the Jagger residence repurposed as a studio. Mick, Keith and THREE BLUE BOYS finish up a BLUES COVER SONG.

(Mick dashes over to a REEL TO REEL PORTABLE RECORDER and turns it off.)

MICK
That's it, that makes five numbers.

KEITH
Okay, now what do we do.

BLUE BOY #1
Easy, we just have to figure out how to put this (picks up TAPE REEL) On this (picks up VINYL).

MICK
Not to worry boneheads, Sir Mick has a four step plan. First we get it to the guy who is in position to get it to a slightly bigger guy who has a hook up with the guy who works for the Big Guy.

(#2 packing up gear)

BLUE BOY #2
Brilliant. Phone us when you get to step three.

KEITH
You may want to consider labeling that reel with another Band name-

MICK
What’s wrong with Little Boy Blue and the Blue Boys? It’s got a ring, it says what we do-

KEITH
Sounds a bit swishy to me. A little too much “blowing” going on there. Maybe something with motion, energy. Something you can actually fit on a marquee...Anyways, back to Step One. Who’s the guy?

MICK
Female, actually. Alexis Korner of Blues Incorporated. She and her husband just opened the first Jazz and Blues joint that does R&B in London. I had a great phone conversation with her yesterday. She said to give her a demo. I said we had one. Now we do.

BLUE BOY #1
You going to post it to her?

MICK
I’m going to hand it to her. Tonight. No time like the present. Who wants to tag along?

(The boys all MUTTER AD LIBS about having other plans, as they finish wrapping up their gear.)

MICK
(Dangling CAR KEYS)
That coupe in the driveway is mine tonight. Got room for one more!

BLUE BOY #2
There’s a young bloke in her band that plays Slide, I hear.

KEITH
(suddenly interested)
Slide guitar?

BLUE BOY #2
Yeah, calls himself "Elmo Lewis." He's got blonde hair. Blonde Elmo Lewis. Sounds like an oxymoron.

BLUE BOY #1
More like half that; The moron part.

(The others laugh, except Keith.)

KEITH
Hey Mick, I'll run up there with you.

SCENE 5

Korner Jazz n' Blues Club. LOUD APPLAUSE from an AUDIENCE (20-25) as Alex and BLUES INCORPERATED finish their last set of the night. Mick and Keith sit at a SMALL TABLE away from the stage.

ALEX
(into stage mic)
Thank you. Thank you so much. That was "Dust My Broom", and that was Elmo Lewis over there, doing all the sweeping!

(She gestures to Brian, the applause gets LOUDER and some of the audience STAND. Brian takes a bow.)

ALEX
Well that's it everybody. The last train out upstairs is at 20 after. Goodnight all!

(Some of the crowd start for the exit, others go for last call at the bar. Mick, TAPE BOX in hand, and Keith make their way to the stage.)

MICK
Alex!... Alex!

(She turns from another band member.)

MICK
It’s Mick- we spoke on the phone yesterday. You were amazing. Even better than your records!

ALEX
Oh Mick, right, the one from LSE, right?

MICK
Yes, we were in the area, recording, thought we’d pop by. This is Keith Richards, my lead guitarist.

(They politely exchange greetings.)

ALEX
Mick says you were so good on guitar, it caused him to pack it in and switch to vocals. Would you two like a beer on the house while we wrap it up?

MICK
Actually we’ve got a gig to go to-

ALEX
What’s still open at this hour?

MICK
It’s a private thing, you know, VIP’s and all. We’re not supposed to say- Oh, here’s that demo you asked for.

(Alex accepts the box)

ALEX
Great. We do a Semi Pro night on Tuesdays. If we like your stuff, we’ll call you.

MICK
Super. Our number is on the back. Thanks again, Alex.

ALEX
Hold on-

(To Brian)

ALEX
Hey Elmo, come over here for a minute-

(Brian heads over)

ALEX
This is Mick and, sorry, what was it again?

KEITH
Keith. Richards.

(As they shake hands)

ALEX
They’re part of the-

MICK
Little Boy Blue and The Blue Boys.

BRIAN
Great. Blew as in, which one of you blew the other one?

(Keith tries to contain a “told you so” laugh.)

ALEX
Sorry, Elmo here has tended bar on Open Mic Stand Up one too many times.

(She goes off, tape in hand)

KEITH
Hey, really dug the Robert Johnson, man. That slide is cool.

BRIAN
Thanks. What’s your muse?

KEITH
Him, all the others that came after. It’s a long list-

BRIAN
Tell me about it- Did she tell you about Semi Pro night?

MICK
She mentioned it as a possibility.

BRIAN
You play with a pro, they get the dough. You guys split a semi doughnut... Hey, gotta go, cheers.

(He goes off, Keith and Mick head out the other way)

MICK
Okay, so maybe we reconsider the name thing.

SCENE 6

102 Edith Grove. A three storey flat in Chelsea. Brian, NEWSPAPER in hand, RINGS the buzzer. He rings twice more, starts walking away. The door flies open, revealing JAMES PHELGE (will be "JIMMY FUDGE"), a chubby 20 year old. He's wearing only tight white UNDERPANTS.

FUDGE
(pissed off)
Yeah, what do you want?

BRIAN
Oh, sorry. Didn't intend to disturb, just inquiring about an advert for "Flatmates Wanted." Must be the wrong place.

FUDGE
You got the right, place.

BRIAN
Oh. "2 Bedrooms, Lounge, common Loo. Phone?"

FUDGE
Yep, that's it.

BRIAN
Right. Well, suppose I could have a look?

FUDGE
Maybe. First things first. There's a process. Application. Hold on.

(Fudge dashes UPSTAIRS. Brian waits patiently.Fudge RETURNS, PEN AND PAPER in hand, still only in underpants.)

FUDGE
Name, Surname first.

BRIAN
Uh, Jones. Brian Jones. Look, I can come back...

FUDGE
Occupation?

BRIAN
I’m an assistant barkeep and musician. Paid musician.

FUDGE
(writing)
Hmm. Average wages per week?

BRIAN
The ad says 10 quid a week. I can do that. It also said Nankers need not apply.

FUDGE
I’ll explain that in the next Phase. Issues with previous tenants. We can now proceed to Inspection. Any questions so far?

BRIAN
Uh yes. The question mark by the word “phone.” Is there a phone in the flat?

FUDGE
Well, not as such.

(He motions to a NEARBY RED PHONEBOOTH.)

FUDGE
That’s it over there. On a still night you can hear it ring. The last guy here discovered if you clicked the cradle a certain way you could make free calls. I could never duplicate that, however.

(motioning up the stairs)
This way, Mr. Jones

(Brian makes note of the phone and the two go up the stairs.)

SCENE 7

Dartford Train Platform. Mick and Keith are sitting on the bench, waiting for the train to their respective schools. Mick is reading a MUSIC PUBLICATION, Keith is working out some fingering on his GUITAR.

MICK
The problem with a manager in the music business is the main thing they "manage" to manage is to sort out how to screw you out of everything. The Contract Structuring they're allowed to write is absolutely criminal. My Statistical Analysis professor estimates-

KEITH
(interrupts)
Do you reckon cows ever get bored?

MICK
What?

KEITH
When you see a pack of them out the train window. They just chew grass, walk around a bit, have a shit. They've got to be thinking of something. Imagining something.

MICK
(still reading)
What they're thinking of is that fine long-horned stallion of a bull, kicking the stall to get at them...Hey, listen to this Wanted Ad: "Forming a Rhythm & Blues Band. Need vocals, Harmonica and Guitar. Be willing to rehearse. Plenty of interesting work."

KEITH
That's definitely interesting.

MICK
Yeah, and get this. The address is the Korner Club under Ealing Station. It’s from that guy who played that amazing slide.

KEITH
Him? He was kind of a dick. But yeah, he’s really good.

MICK
It’s just an audition to play with him, not live with him.

(The boys get up with the SOUND OF THE APPROACHING TRAIN.)

SCENE 8

Korner Club. Bobby and Alex Korner are stocking and setting up the bar, Brian is nearby helping.

BOBBY
That Edith Grove is a great location. Chelsea is near enough to everything. There’s tons of gigs over that way. And you’ll always have our place to sack out when you’re near here.

ALEX
And don’t think twice about leaving my band. You’ll always have that spot. You’re so ready to take the wheel.

(Brian still wipes the same table. Somethings bothering him.)

BRIAN
Thanks so much. Both of you.

ALEX
(fully concerned)
Is something wrong, Brian? Tell me.

BRIAN
Something I need to get off my chest...Back in Cheltenham...there’s this girl...

ALEX
Brian, I know about that schoolgirl. I know about the adoption. Is that what this is about?

BRIAN
(still struggling)
Well, yes...and...

(Alex puts her hands on his shoulders.)

ALEX
Look. That’s all in your rear view mirror now, Okay? You’re going forward now.

(Brian nods. Something’s still not right.)

ALEX
I know music is everything to you now. But it’s not the most important thing, Okay?

BRIAN
Okay.

(Alex steers in a positive direction.)

ALEX
Right. Your auditions; Do you want do them here on Sunday mornings? Otherwise Thursday nights you could use the back room area-

BRIAN
(lightening up)
Thanks, but there’s a place down a ways from Edith, the Bricklayer’s Lodge. They’ve got a room upstairs for a few quid.

ALEX
Cool. Everybody will chip in. I saw your list. There’s some decent talent. Ian Stewart, solid piano. Plus, he owns a moving van. Don’t worry about rhythm boys too much. My drummer Charlie will come sniffing when there’s any kind of money whatsoever. You may want to invite Wyman at some point.

I hear he’s jerry rigged a PA and turned it into a room rattling bass. Those kids who show up on Tuesdays, the Dartford Duo. There’s a spark there-

SCENE 9

Outside Edith Grove. Near the door is a sign that reads KINDLY FUCK OFF NANKERS. Mick and Keith, music gear in hand, ring the buzzer. The DOOR OPENS ALMOST IMMEDIATLY. Fudge is dressed as before, only he has another pair COVERING HIS FACE like a mask, as well.

FUDGE
Can I help you?

KEITH
Is Elmo here?

FUDGE
Who’s Elmo?

MICK
Brian. Brian Jones. We’re here to see him. We’re musicians.

FUDGE
How do I know you are who you say you are?

KEITH
We didn’t say who we are.

FUDGE
Look. Don’t get smart with me. I’ve seen the list.

(Mick puts out his hand, then thinks better of it.)

MICK
I’m Mick, this is Keith. We’re here for the audition.

FUDGE
Why didn’t you say that in the first place, then?

KEITH
We did.

FUDGE
No you didn’t. Look here fellas, I’m Brian’s flatmate. I can’t just go letting any Nanker past the door who says he knows some bloke named Elmo, can I? Can’t you read the sign?

KEITH
The one that says “Fuck off Nankers?”

FUDGE
No, the one that says the audition has been moved round the corner to the Bricklayer’s Lodge.

(He steps out on the porch, surveying.)

FUDGE
Shit- somebody must have nicked it. More likely than that, Brian probably forgot to put it up. I spent the better part of the morning making him a nice detailed map with fancy arrows- Brian’s a bit forgetful-

KEITH
Sorry to interrupt, but could we just get the address?

FUDGE
Look, it’s really quite simple. Left down to King’s Road, go right. Three doors down. Sorry, don’t have all day, lads, Okay? I’ve something on the burner.

(He slams the door.)

MICK
Well there’s two minutes we’ll never get back. It was like being trapped in a BBC comedy sketch.

KEITH
(As they EXIT right.)
Do you have the feeling this whole thing is a complete waste of time, like me?

SCENE 10

A ROOM ABOVE the Bricklayer's Lodge Public House. There's a TABLE to one side with TWO DOZEN BLUES ALBUMS and a PORTABLE TELEPHONE. The BAND has just finished up a number, SWEATY from playing for a while. IAN STEWART is behind a STANDUP PIANO dressed like a TYROLIAN MOUNTAIN CLIMBER. Mick sits on a stool, microphone in hand. Brian and Keith stand next to each other. A BASS PLAYER and a DRUMMER with his KIT are off to the side. MANY PINT GLASSES filled to various levels decorate the room.

BRIAN
Okay, we've got that one halfway decent, thank you Ian, for sorting out the whole middle part. Let's have a piss break, I've got to check in with the office.

(He heads over to the TABLE and DIALS A NUMBER, the others have a smoke, etc. A BLACK BAR KEEP ENTERS barely noticeable in the BACKGROUND tidying up the mess. Keith goes over to Mick.)

KEITH
Shit, I can barely keep up with him.

MICK
Yeah, I noticed. Not a bad thing, right? You're always talking about that guitar weaving thing-

KEITH
What's with the piano. I mean he's super good, but Lederhosen? Do you think he's gonna have us yodeling at some point?

(Brian can be heard from the table.)

BRIAN
Hold on Bobby, give a minute-
(covering mouthpiece)
Hey boys- Blues Incorporated just got a booking for a BBC live broadcast. They're asking if I, that would be we, want their Saturday spot in the line-up. Ian?

IAN
Are you kidding? No fucking way. We're a whole postal code away from being ready.

BRIAN
Yeah Bobby, of course we'll take it.

(The others surround the table, except for Ian.)

BRIAN
Yes. Hold on, let me check with the boys.
(covering mouthpiece again)
They need a band name for the Union paperwork. Any suggestions?

(Crickets. He motions to Keith to give him a PARTICULAR ALBUM.)

BRIAN
Yeah, that Muddy.

(He flips it over to the backside, fingering a LINE.)

BRIAN
Got a pen? (beat) The Rollin' Stones. R O L L I N apostrophe. Yes, Stones like a rock.

(All the others show their approval, except for Ian.)

BRIAN
They need an address for the ledger. Should I give them the Edith Grove?

MICK
No fucking way. If someone smashes something up, you, slash we, get the billing. Make something up.

BRIAN
Nice, LSE boy, I knew that would come in handy-

(Keith hands him ANOTHER ALBUM.)

BRIAN
(finding something)
Put the band's address as Crossroads. Number 27.

(They others contain laughs.)

BRIAN
London SW 19. There is no 19? (pauses) Sorry, meant 15. One pint too many. Hey, my love to Alex... Cheers.

(He hangs up, the room buzzes with energy.)

IAN
That's like the worst band name I've ever heard of, but it's your party, Brian.

BRIAN
I don't remember hearing anything from the piano when I asked, Debbie Downer.

MICK
Hey, It's a working title. Like a place holder. It's not like we're stuck with it for fifty years.

BRIAN
You two are gonna need a place to stay, everybody else lives here. As Ian optimistically points out, we've got a shit ton of rehearsing ahead. You can stay at my place, there's plenty of room.

KEITH
What about Sergeant Underpants?

MICK
We met your flatmate on the way over; You sure he's okay with this?

BRIAN
Jimmy's harmless. But you may have to fill out an application.

END OF ACT III

ACT IV

SCENE 1

2 AM outside Edith Grove. Keith, Mick and Brian are on the landing with their BELONGINGS. Move In Day. Or night.

(Brian pats his pockets, can't seem to find the key.)

BRIAN
Shit, I totally recall grabbing it on the way out.

(He RATTLES the door knob.)

MICK
Is there a back way?

BRIAN
We're on the middle floor. Windows are too high. Tried it.

KEITH
(calmly)
Check your inside jacket pocket.

(He does, pulling out some stuff, his asthma SPRAYER, slide TUBE, a KEY. He tries the key, but it DOESN'T WORK.)

BRIAN
Bollocks, grabbed the wrong one.

KEITH
May I?

(Keith tries it a couple times then gives it back. He KNEELS and inspects the hole briefly and produces a PICK from a pocket. He POPS OPEN the door.)

KEITH
A leftover from my misspent youth.

(The boys gather up their stuff and head up. There's SUDDEN SWEARING and BAGS TUMBLING as they scramble back OUT amidst a YELLOW STREAM. Someone on the landing is PEEING on them, with plenty of ammunition.)

BRIAN
FUDGE ARE YOU FUCKING KIDDING ME? YOU FUCKING WANKER!

(They're soaked, but do sense the humor. Kinda. LIGHTS go on.)

SCENE 2

Inside the DUMPY FLAT, the boys are toweling off. Sargent Underpants is in his usual attire.

FUDGE
Put yourself in my position. Voices wake you up, you hear the lock being fiddled with multiple times. There's been reports of break in's of late.

BRIAN
I can see your concern. Thieves have heard about your valuable Perry Como record collection, waiting to pounce at just the right time...

FUDGE
Hey, that '78 is extremely rare.

BRIAN
And why do you think that is? They've all been tossed out...Just don't fucking do this anymore, Okay?

FUDGE
Got it. Not to belabor the point, but lacking a proper weapon, it was quite resourceful. And effective.

BRIAN
Okay, enough said, moving past. Mick and Keith here are going to be staying here for a few days, maybe longer. If it works out, maybe we could split the rent four ways, reducing our cash flow issues by half.

FUDGE
Wow. This is kind of awkward. Maybe you could have brought up this proposal in a more discreet setting.

BRIAN
Apologies, my mistake. Just trying to put the application process on a faster track. Shall we give her a go?

FUDGE
Yeah, I guess that would be okay, the tryout thing. We'll have to tweak the floor plan a bit.
(getting up)
The loo on the landing you're already acquainted with. Let's start with a tour of the kitchen facilities.

(He heads to the MESSY kitchen, pausing to SPIT ON THE WALL. Keith and Mick LOOK at Brian, who SHRUGS.)

SCENE 3

The Same. Day. Keith and Brian are fiddling with their GUITARS and sipping TEA, Mick has his head in an ECONOMICS BOOK. Fudge ENTERS, fully dressed for work.

FUDGE
All right gentlemen, I'm off to the print shop, on the afternoon shift now.

MICK
(barely recognizing)
Who the fuck is that?

FUDGE
This is work mode Jimmy. As in job. As in something you Nankers don't have.

BRIAN
As in off you go, Earnie. Have a nice day, luv.

KEITH
What's the difference between a "Nanker" and a "wanker"?

FUDGE
Ha. Figures you wouldn't know. A Nanker is one who goes to Wanker School, only he's dropped out because he's a total nitwit.

(He makes the FULL NANKER FACE.)

FUDGE
An "Earnie" is just your average working slob, a brainless lemming who follows all the others just trying to earn enough for some bangers n' mash. Brian here has just used the term in a sentence. Only I'm not one. A sentence with Nanker might be: I hope you two Nankers have moved out by the time I get back from work.

(He makes the Nanker face again and EXITS.)

MICK
I get it. That's why he runs around in dirty underpants. He's desperately trying to not become an Earnie. It's like a Superman costume sans the cape.

KEITH
Yeah, that actually makes sense. Kinda.

BRIAN
It scares people away. All the neighbors think he's a whack job and totally avoid him.

MICK
(getting up)
Well, I've an afternoon class, campus is conveniently close by, thankfully.

(He starts to get dressed.)

KEITH
...Speaking of classes and dropping out, I've decided to quit Sidcup.

MICK
What? That’s a drastic step. We’ve done like three gigs-

KEITH
All Sidcup leads to is some wanker coffee fetcher job at the J. Walter Thompson Agency. If you’re lucky, you get to draw up some soap advert of a housewife exclaiming how white her hubby’s shirts came out in the wash. Or some fancy bloke bragging about his brand of cigarettes. I’m sorry, but there’s little or no satisfaction there. Not to mention it’s starting to seriously interfere with my drinking and guitar research. I think my colleague here would concur.

BRIAN
At the risk of providing a bad example, it seems to work for me.

MICK
Well I’m a firm believer in the notion of keeping a foot in both places until you’re absolutely certain it’s safe to jump. All these classes will pay off one way or the other at some point, either way.

KEITH
I’ve made a pact with my guitar. I’m gonna follow her wherever she may lead. At least for now...(to Brian) C’mon let’s work on that handoff again...

(They get back to it as Mick collects his books and EXITS.)

SCENE 4

The KITCHEN AREA of the flat. UNWASHED POTS AND PANS are PILED HIGH in the sink. Fudge is STANDING on a chair, DRAWING a CIRCLE around an area he has previously spit (”gobbed”) and labeling it, apparently. Keith ENTERS.

KEITH
What the fuck are you doing?

(He puts a kettle on for coffee.)

FUDGE
Tradition. If you gob one really good and it sticks, it gets a name, like a classified hurricane. This one is Green Humphrey.

(pointing around)
That one over there is Bloody Morris. In the front room hangs Brown Sugar.

KEITH
You're disgusting.

FUDGE
I've noted you're not exactly afflicted by the Anal Retentive Syndrome either. How about channeling some of that excess energy into the washing up?

KEITH
All right you depraved Nanker. I'll knock this out twice as fast as you ever could.

(Keith dives in. This is gonna take forever. He shoves a GREASE PACKED FRYING PAN at Fudge.)

KEITH
You do that one.

(Fudge accepts the task, but doesn't have much success. Frustrated, he OPENS A WINDOW AND TOSSES OUT THE PAN.)

FUDGE
That pan was really starting to piss me off. Plus, it's supposed to rain really hard tonight-

(Keith admires the thinking and the both of them laugh as they TOSS THE REMAINDER of the pans into the backyard.)

SCENE 5

The Same, next day. The Kitchen is COMPLETELY TIDY with the pots and pans NEATLY STACKED. Brian is having a coffee. Keith ENTERS.

(He looks around, confused.)

KEITH
I'd thank you, but I know it's outside the realm of possibility. Who did all this?

(Fudge ENTERS.)

BRIAN
I thought you two did.

FUDGE
We started to, but didn't quite see it through to completion.

KEITH
(concerned)
Shit. You don't suppose it was the landlord's wife who scooped them up from the backyard?

BRIAN
Backyard? Look, if she did anything at all, believe me we'd have heard about it long before now.

FUDGE
Maybe Jagger did 'em. He's the clean one.

KEITH
(yelling)
Mick, come in here!

ENTER Mick.

MICK
Yeah what?

KEITH
Did you clean up the kitchen?

MICK
Not directly, but yes. Priscilla, the nurse from downstairs said she found those all over the backyard. She washed 'em all up and them brought them up. I helped stack. She tidied up while I sang her a song with her name in it. You have no idea how hard it is to fit the name Priscilla gracefully into a verse.

BRIAN
See, I'm telling you; Music is like currency.

KEITH
Cool. Thought it was the landlord's wife.

MICK
Speaking of whom, he's due to come round today for rent. Give it to me now and I'll run it by his shop on my way out. Maybe we can avoid him barging in, again, in the midst of a compromising position. Brian.

FUDGE
Getting paid today, I'll have it tonight.

KEITH
Spent my last bit on our new gitty strings-

BRIAN
Skinned.

MICK
Right. Being the only one with a checking account, I'll write a check which is bound to bounce as high as an overhead smash at Wimbledon.

(Mick has pulled out his CHECKBOOK.)

KEITH
While you're at it, can I get one too?

MICK
Sure. How much would make you happy, Mr. Richards?

KEITH
(calculating)
A nice round one million pounds.

(Mick writes a check, Slaps it on the TABLE. Keith picks it up.)

KEITH
"Pay the Bearer One Million Pounds"

(They all laugh, Keith slaps the check down.)

FUDGE
Damn, wouldn't that be nice though.

MICK
Hey don't laugh, I read somewhere that over in the States, California I think, someone presented one just like that, and the bank accidentally cashed it-

(There's a BEAT, then the OTHER THREE DIVE to get the check, shoving and wrestling. Mick enjoys the last laugh.)

SCENE 6

Outside the flat, the band, including Ian, BILL WYMAN and CHARLIE WATTS are bringing MUSIC GEAR out of the flat and staging it by the curb. Ian and Brian are standing STAGE RIGHT, next to the PHONE BOX.

BRIAN
Can you front me a shilling? I'm gonna book us for a session.

IAN
(reaching into pocket)
You really think you and the Three Chord Wonders are ready for that?

BRIAN
Nothing ventured nothing gained.

(Ian gets distracted by gear activity.) Brian POCKETS THE COIN and CLICKS THE PHONE CRADLE 4 TIMES IN SEQUENCE. He gets DIAL TONE and dials a number.)

BRIAN
Hello, this is Brian Jones, we spoke earlier, I'd like to go ahead and book that slot on Friday if it's still available...It is? Magic, you're the best, luv...Method of payment?

(LOOKS at Mick, who's bringing gear down)
That would be by cheque, please...You don't take cheques from musicians?... I see, no problem, I don't blame you. Got it, cash only. Right then, see you Friday!

(Ian returns.)

IAN
I saw that. Give me my 10p back.

(Busted, he RETURNS the coin.)

IAN
How'd you do that?

BRIAN
(makes sure others can't hear)
Easy, just click the cradle three quarter beats and one half beat. Free calls forever...Don't tell the others, It's a steady source of income.

CHARLIE WATTS
Hey Ian! Get the bloody van, we're gonna be late-

(As he exits STAGE LEFT.)

IAN
Is it my fault you have to park two blocks away every damn where you go in Chelsea?

BILL WYMAN
Hey, why does your stairway reek of piss?

KEITH
(LOOKING at Fudge)
It’s part of our security system.

(Brian looks at the phone HESITANTLY and DIALS ANOTHER NUMBER.)

BRIAN
Hey Bobby! It’s Brian...Yeah, all is good, on our way to a gig as we speak. Can I speak to Alex?...Yeah sure, I’ll hold.

(He looks out at the others, then SHUTS THE DOOR OF THE PHONE BOX.)

SCENE 7

All four are back in the flat. A MICROPHONE DANGLES underneath the center light.

BRIAN
Okay, so I’ve got some great news and some not so great news. Which first?

MICK
Why do I get the feeling that the Less Than Great news is going to involve me writing a cheque?...

BRIAN
The excellent news is I was able to book Glyn Johns to mix 5 songs for us tomorrow. I pulled some favors and got a super low rate. Gentlemen, we’re gonna be on vinyl.

(The others are impressed.)

MICK
Well done. So what’s the special rate?

BRIAN
Fifty. You guys split it up; That’s a tenner each.

MICK
For all six band members it’s eight pounds thirty three and a third. That’s not too bad.

KEITH
Much too good to pass on. We gotta figure out a way. Probably won’t take a cheque from the likes of us.

FUDGE
I’ll do a share.

BRIAN
Aw, cheers, Jimmy.

FUDGE
Look, I’m just trying get rid of these guys as soon as possible. So what’s the bad part?

BRIAN
The bad part is I’m not sure we’ll be welcomed at the Korner Club for a while. Alex is pissed at me. It involves my past.

(Silence.)

BRIAN
I had to tell her about (GIRL A) and the kid.

MICK
Wait a minute, I thought it was (GIRL B) with the kid?

BRIAN
Well, yeah, there’s her too...

FUDGE
Including your school girl episode that makes THREE!

(Brian nods. The boys are taken aback.)

KEITH
Christ Brian, you’ve knocked up enough for the entire band! You’ve used up our entire allotment. Wow. Prolific. This is why I sleep with my guitar. You should try it-

FUDGE
Pan the mythological half goat Flute playing bird magnet god didn’t bag as many by age 20!

MICK
And you’ve just now told Alex?

BRIAN
I tried to tell her before, but there was a lot of other stuff going on.

(Silence Again.)

FUDGE
Crap... This is like in a Shakespeare play, in Act 4, when all the bad shit happens...Well the good news/bad news thing here is, in the final act, you either get crowned King, or, it all ends in a double suicide...

(The others give him a deadpan look.)

FUDGE
Hey guys, you weren't the only one's who went to school.

SCENE 8

Outside the flat. DORIS and GRANDPA GUS have arrived with freshly folded laundry in a LAUNDRY BAG and a freshly REPAIRED GUITAR. They RING the bell.

DORIS
This time no fiddling around; Last time you took 20 minutes.

GRANDPA GUS
I had to fix two guitars! I thought it went pretty fast-

DORIS
Bill's going to circle the cab around the block twice, then scoop us-

GRANDPA GUS
Good thing you have a...friend, who owns his own taxi cab, else we'd be broke.

(She gives him stern look)

DORIS
Bill's been extremely kind. Be nice to him.

(Footsteps are heard, the DOOR OPENS and Keith ENTERS.)

KEITH

Mum! Gramps!

(Hugs and kisses all around. Gus presents the REPAIRED GUITAR.)

KEITH

Looks like the day I bought it! And fresh laundry! You guys are the absolute best! C’mon up and say hello to the lads-

(Keith bounds UP THE STAIRS with his booty. Mum and Gus follow as she gives him the CUT SIGN as they DISAPPEAR. GREETINGS AND VOICES OF ALL SIX ACTORS ARE HEARD, PUNCTUATED BY DORIS.)

DORIS

(Just offstage)

Sorry, got to go! Cab waiting!

Doris and Gus RE ENTER from the stairway, Gus with a new SOILED LAUNDRY BAG, ANOTHER BROKEN GUITAR, and HOLDING HIS NOSE. They walk to the curb.

DORIS

I’ll never enter that pigsty again if I can avoid it.

GRANDPA GUS

My god, going up and down that staircase is akin to walking through the men’s latrine at Wembley!

DORIS

...I’ve never seen that odd boy in anything else but his underwear... What’s his name again?

GRANDPA GUS

They call him Fudge, and I’m not going to ask why. Just another fine product of our British educational system. We can really churn them out.

DORIS
There’s Bill coming up now- The broken guitar can ride up front, but that foul smelling bag goes in the boot.

SCENE 9

Inside the flat, almost bedtime. Mick is exercising, Keith is fingering his guitar, and Fudge is doing God knows what. BOUNDING FOOTSTEPS come from the stairwell and the DOOR FLINGS OPEN.

(Brian ENTERS out of breath, PACKAGE IN HAND, RIPPING IT OPEN.)

BRIAN
Here it is! It’s still warm from the pressing-

(He HOLDS UP a plain white ALBUM JACKET for all to see. The others stop what they are doing and SURROUND him as if they are seeing a newborn for the first time.)

MICK
Let’s spin that baby right now-

(He GRABS the record and goes towards the turntable. Keith INTERCEPTS IT.)

KEITH
Wait a minute. Let’s savor this for a moment. This is like our first born-.

(He carefully handles the record as he REMOVES IT from the jacket. He HOLDS IT UP TO THE LIGHT.)

KEITH
Do you see that virgin groove? It will never look the same again. It’s one long line, from beginning to end, cut by a diamond. Every microscopic hill and valley is carved by our instruments and voices.

(He hands it carefully to Brian.)

BRIAN
It is a thing of beauty. There is a lot of sweat and blood on those tracks.

(He hands it to Fudge.)

FUDGE
Looks like a record to me.

(He hands it back to Mick, who carefully puts it back in the jacket.)

MICK
Keith is right. We can’t hog this moment. The rest of the band needs to be present. At the very least we should phone them and tell them. Give them a call, Brian-

BRIAN
Agreed. All for one; One for all. Anybody got any coins?

FUDGE
Oh, you don’t need any coins anymore! All you have to do is tap the cradle four times; Three quick ones then one long one, then you get dial tone!

BRIAN
Wait, what? How did you-

FUDGE
Charlie told us. He and Wyman made a shitload of calls. Ian showed them how. It works every time!

(Mick and Keith chime in to confirm)

BRIAN
(Exiting)
No secrets in a band.

(He EXITS to stairwell)

FUDGE
While we’re waiting, I’ll put some music on.

(He rifles through a NEARBY STACK.)

FUDGE
By the way, has anybody seen my Perry Como records lately? Keith?

Keith and Mick fight off grins.

KEITH
Can’t say I have. Not a massive fan of his.

FUDGE
That’s funny, because the nurses downstairs said they found some records in the backyard. Said they had to bin them because they were so badly warped by the sun... Strange that someone would toss them there in that manner... Why would anybody do something like that, Mick?

MICK
There’s no accounting for taste and such. That couple in the flat above us are a bit “off”, wouldn’t you say, Keith?

KEITH
I’ve noticed. The Offer couple. They always seem to be arguing. Throwing things around...

(Brian RE ENTERS)

BRIAN
Wyman and Charlie said they could swing by tomorrow. Ian said he doesn’t care one way or the other; He already knows as he was there. If the three of us say yes, then we have a majority-

MICK
Yeah. I don’t know, man. Now I feel guilty. What say you, Keith?

KEITH
Shit. Put it on me then. I want to hear that thing right this second too, but, like you say, this is a precedent setting moment. If we’re gonna run like a pack, then we eat as a pack.

MICK
Well, I guess that settles it, then. We go to bed, and the six of us play it tomorrow...

(The all stare at the record for a beat, then peel off each to their OWN BED. They all prepare for sleep in their OWN WAY. Each glancing over at the RECORD PLAYER. The LIGHTS GO OFF and the STAGE GOES DARK. Then-

(Keith's VOICE)

KEITH
OKAY, FUCK IT! LET'S PLAY IT!

(The LIGHTS SNAP BACK ON and ALL FOUR SCRAMBLE OVER to the record player hastily putting THE RECORD on. We HEAR a few introductory NEEDLE CRACKLES...)

SCENE 10

The Same, weeks later. Brian is POLISHING HIS BOOTS while sitting on HIS BED. Mick is studying, Keith is walking around eating out of a CAN OF BEANS. Fudge is in BED, sleeping.

BRIAN
It's a really good record, I mean the vocals may be a little too much in the foreground and some other minor issues. But it's been almost a month now, and we can't hardly get any one of those tracks to get any radio play.

MICK
It does help if you've got a record label who's got DeeJays all over the UK on the payroll. That's what got the Beatles over to the States. I mean look at them... And the vocals are perfectly balanced, by the way.

BRIAN
Screw those arseholes and their bouncy Buddy Holly music. The Labels just want to put you in a uniform, give you all the same cute haircut, like a bunch of cuddly Teddy Bears. (Mimics) She loves you, yeah, yeah, yeah-

KEITH
(eating beans)
The difference is, people sing along with that shit. When we play in a club, people get off their asses and move. Unfortunately that's hard to see on a radio...

(To Brian)

KEITH
Hey, you know you're spilling that polish all over the place.

BRIAN
(taking notice)
Shit! How do I clean that stuff out!

MICK
(nose still in book)
There's a bottle of kerosene on the heater. Use a rag to get it out.

Brian fetches the KEROSENE and a RAG from the kitchen. He RUBS the stain.

BRIAN
You're right, but this reeks to high heaven-

(He puts KEROSENE BOTTLE down on the corner of the bed, and rubs some more. The bottle FALLS spilling ALL OVER the bed.)

BRIAN
Crap! I'm an idiot!

KEITH
You bloody Nanker! The whole place is gonna stink to high heaven!

(Keith RIPS THE COVERS OFF THE BED, goes in the kitchen, and tosses the covers OUT THE WINDOW.)

BRIAN
(frustrated)
I hate this fucking place. We're nowhere closer. Have we hit the peak? It sure doesn't feel like it. I say we give it three more months, and if nothing happens by then, we try something else.

MICK
That is, if we have the resources to stretch it to that long.

(The doldrums start to set in. Keith COMES from kitchen with THREE BEERS.)

KEITH
(trying to lighten the sobriety)
Relax lads. Put a hold on the doom and gloom. Let's have us a libation or two and discuss these matters further.

(They all TAKE A BEER BOTTLE saying "cheers". Fudge starts to SNORE.)

KEITH
I mean what kind of bluesman worth his salt turns around after a couple of potholes on the road? Keep rollin' up Highway 61, right?

(Fudge's snoring gets LOUDER. Keith THROWS something at him, which works for the moment.)

BRIAN
Why not just dump some water on him-

KEITH
Too easy. The Dartford Dragon would do the trick.

MICK
(laughing)
Now that would do it. But no...

BRIAN
What’s the Dartford Dragon?

(The snoring STARTS UP AGAIN. Keith STANDS UP.)

MICK
No Keith, No.

(Brian is now fully intrigued. The snoring continues)

KEITH
Can you hand me that box of matches, please, Mr. Jagger?

(Mick shakes his head as he reluctantly hands him the BOX OF MATCHES. Keith walks over to the snoring Fudge.)

KEITH
Ladies and Gentlemen, may I present to you, for your viewing pleasure, The Dartford Dragon-

(Keith DROPS HIS PANTS and CROUCHES, his butt close the source of the snoring. Keith STRIKES A MATCH.)

KEITH
Drumroll, please.

(Brian obliges, DRUMMING ON THE TABLE. Keith moves the match behind as he LET’S OUT A HUGE FART, WAKING UP Fudge who IMMEDIATLY BITES KEITH’S ASS. Keith YELLS, falling away and DROPS THE MATCH.)

KEITH
That little shit took a bite out of my ass! God damn!

(Mick and Brian are laughing their asses off. Brian notices the RUG IS SMOKING. Keith, still in some pain takes no notice.

FUDGE
(now fully awake)
What the fuck are you Nankers doing?

Brian heroically rushes over, picks up the SMOKING THROW RUG, runs into the kitchen and THROWS IT OUT THE STILL OPEN WINDOW.

KEITH
(over the pain for the moment)
Did you just toss that out the window?

BRIAN
Of course, why?

(All four turn to the WINDOW, which, as if on cue FLICKERS WITH A BRIGHT ORANGE LIGHT.)

END ACT IV

ACT V

SCENE 1

A POSH PRIVATE VIP BAR in a major London Music Venue. A DOZEN well dressed heavy hitters enjoy NICE COCKTAILS. Through a SIDE DOOR ENTERS THE FAB FOUR, followed by a FEW ENTOURAGE. It's a quick break between sets, and they've come to slam a quick one.

(The four approach the bar, where the BARKEEP already has their drinks prepared. They stand.)

JOHN

I thought Ringo was a goner for sure; Those two birds dashed right past me like I was in their way. If the one didn't trip over my cable they'd have ripped him right out of his drum kit!

PAUL

Trip? I saw you lasso her feet! Nice one. Whipped it around like a champion fly fisherman. Good thing she didn't fall off the stage.

JOHN

Yeah, can you imagine the press?...So where are we clubbing after? Anybody hear of anything half way decent?- I can't bear one more joint with yet another copycat outfit. It's like mushrooms popping up everywhere after a spring rain.

(A DAPPER BLACK MAN who has been sitting next to John with his BACK TURNED, SPINS on his BARSTOOL. We know this guy. Politesse, wealth and taste.)

DAPPER MAN

I'm sorry for eavesdropping, but if you guys are looking for a joint that's really jumpin', I know of a place.

JOHN
I’m sorry sir, have we met? I’m sure I’ve seen you before, right?

DAPPER MAN
Maybe. Would have been a while back. Used to play guitar, the Blues. I’m long retired and in a different line of work. More lucrative, as they say...Anyways, you guys gotta get back on stage, so I’ll make it quick; The name of the place is The Crawdaddy, it’s up Richmond way. The band up there is pretty good.

The boys slam the remainder of their drinks, and head back to the side door.

JOHN
I’m sorry sir, I didn’t catch your name-

DAPPER MAN
Legba. People call me Papa.

(Papa EXTENDS HIS HAND. THEY SHAKE.)

JOHN
I’m John. Thanks for the tip, Papa-

DAPPER MAN
Completely my pleasure.

(An entourage member HURRIES John out the door.)

SCENE 2

The Crawdaddy Club. The Stones are FINISHING UP the second encore, Mick STRUTTING AND MOVIN’ like he does. The room is filled with SWEATY KIDS who are MOVING TOO. As the song ends, the room ERUPTS INTO A STANDING OVATION.

MICK
(Into the mic)
I’m sorry, they’re telling me absolutely no more! If we start it up again, they bring in the cops! Goodnight all! Be safe! ...Or not.

(The crowd HISSES AND BOOS, but slowly complies. ALEX APPROACHES the stage as the crowd starts to filter out, giving Brian a HUG.)

ALEX
Clearly you guys have outgrown the Korner! This place is twice the size. C’mon, I wanna introduce you to some guys you may know of-

(In a CORNER, a GROUP OF 6 FANS CLEAR OUT, REVEALING THE FAB FOUR, cooly LEANING UP AGAINST THE WALL.)

MICK
Yeah, we heard they were here-

(They approach the corner.)

ALEX
Rollin’ Stones, meet the Beatles.

(The ten exchange greetings awkwardly, ADLIBS abound as they complete the process.)

PAUL
They told us it would get a bit hot and sweaty in here. Wow. You really got em moving. Almost jumped out there myself. Well done-

MICK
Cheers. Our motto is, if they’re not drenched at the end, we probably screwed something up.

JOHN
Dig the playlist. Do you ever try any of your own stuff?

BRIAN
Talked about it, but mostly we cover the proven stuff with our own spin-

RINGO
(interrupting)
I'm sorry boys, but I'm parched. How's about we continue all this in wetter conditions?

KEITH
Shit, nothing open anywhere at this hour. What do you say we commandeer a couple of cases and bottles from the bar and head over to our place? Chelsea's not too far for you, is it?-

JOHN
Yeah. We're not done yet, right guys? (to his crew) It's either we get some drinks, or just settle it all and square off with a fight right here. Mop Tops versus Bad Boys. Superman versus Batman-
(laughter)
Since you've got a two man advantage, we'll just have to settle for outdrinking you.

KEITH
Challenge accepted; onward to Edith Grove.

SCENE 3

The flat. All the furniture is PUSHED ASIDE and they've got a rager going, ALL TEN band members and SIX CUTE GIRLS. And of course, Fudge in his obligatory underpants.

(Paul, Keith, Brian and John surround the TABLE WITH THE RECORD PLAYER and TWO DOZEN RECORDS, which they thumb over.)

PAUL
Explain something to me, Keith. Why do you open an umbrella, then enter the building?

(He looks at Fudge, who’s DANCING with one of the girls.)

KEITH
For whatever cause, there’s a pipe that sometimes sprays a leak over the stairs late at night, for some reason-

PAUL
Get the landlord to hire a plumber. While he’s in there, it smells like you have a loose sewage pipe, too.

(Brian gives a record to John. Mick has come over.)

JOHN
Put on another Jimmy Reed? We’ve just done two sides. Got any other Wolf’s?

BRIAN
What’s wrong with Jimmy Reed. I thought you said you like his cadence?

JOHN
I do, but let’s go somewhere else for a minute.

BRIAN
(annoyed)
Oh, like some Buddy Holly? Something really bouncy...

JOHN
Okay, I see where you’re going with this. What I meant earlier, was that you guys are so much more than just a cover band. In a way, I would really like to go your path. I mean, we want to hold your hand, while your style can sing about spending the night...

KEITH
Yeah, you’re right. Celebrate the taboos. The Blues element allows you to be happy and sad, both at the same time.

PAUL
Write about the stuff around you. I mean look at all this- Talk about your wants, your needs-

MICK
When did you start writing on your own?

PAUL
Just like you, we were a cover band for too long over in Hamburg. One night we just took the next step, wrote our own ditty. It was just okay. But it opened the door.

JOHN
Your lot has been too long in Hamburg. Blend those Blues in with your own songs. Time to jump-

(Fudge yells above the music from across the room)

FUDGE
Hey Keith! Ringo and George here don’t know what a Dartford Dragon is! Why don’t you come over and show them!

(Mick and Keith laugh.)

PAUL
Dartford Dragon?

KEITH
You really don’t want to know.

SCENE 4

Outside the flat, dawn breaking. John and George wait for a cab. Fudge is having a smoke, now wearing a JACKET.

GEORGE
Bloody hell! I’ve got to be at the BBC in 45 minutes!

JOHN
You’re kidding! Management booked that?

GEORGE
That stupid song competition show. I’m a judge, with some lame muckity muck from Decca Records.

JOHN
That sod? He’s an idiot. We’ll have to jerk his chain...Hey Fudge, give us a smoke for the road...

(Fudge passes two cigarettes.)

JOHN
Cheers. So tell me again why it smells like piss out here?

FUDGE
Wolves and defendant dogs have been successfully using it for like 15,000 years. It’s two fold; First, it establishes domination over intruders. It’s like they smell your piss and go away. Statement. This is my territory. Best you keep moving along, mate. When you piss on top of another dog’s piss, you’re making a challenge. We’re just staking this territory to the Stones... The other part of it is for navigation purposes. Like a marker. I can find my way to the front door in total darkness. Simply put, deep down, we’re all just dogs, really...

(The LIGHTS OF THE CAB pass over)

GEORGE
(waving)
That’s us now-

(John hesitates.)

JOHN
Hold the cab, I’ll be right there.

(George EXITS. John walks over to the building, turns his back to us, UNZIPS and PEES. He zips up.)

JOHN
Until we meet again, Mr. Jimmy.

(Fudge waves them off. Keith comes BOUNDING DOWN THE STAIRS and out the door.)

KEITH
Where’d they go? I wanted to see them off-

FUDGE
They all just left...Lennon just took a long piss, right over there.

KEITH
What? Let me guess; You went on about that dog piss theory of yours, did you?

FUDGE
Yep. He was rather defiant in his manner. He seemed to have a particular spot in mind.

KEITH
That bloody Nanker.

(Keith goes over to the spot, and PEES. When he's finished, Fudge does the SAME.)

FUDGE
Stone's Territory. Just making sure.

KEITH
It's a punctuation mark. We're gonna be moving on to a better place, soon, my friend. I can feel it.

FUDGE
Like uptown?

KEITH
No. Like way further. Like Jamaica.

FUDGE
Now how exactly is it you get to Jamaica from here?

(Keith holds the DOOR OPEN for Fudge, who EXITS UP)

KEITH
Easy. Just follow the line.

(He follows Fudge, and EXITS.)

SCENE 5

The SET of the show BRITAIN'S NEXT STAR.

George and DICK ROWE of Decca Records are in MAKE UP CHAIRS preparing to go on camera as guest judges. TWO HAIR AND MAKE UP LADIES get them ready. CREW MEMBERS scurry about with CAMERAS AND LIGHTS.

GEORGE
Perform your magic ladies. It’s a good thing these black and white cameras won’t show the red in my eyes-

DICK
Yet another all nighter? Ah, to be young again. You do have a reputation to maintain. Just another day at the office, eh?

GEORGE
Answering the call of duty, sir. Someone has to do it.

DICK
Your lot should be well chuffed. You’ve paid your dues. I, on the other hand am headed to the polar opposite. I will go down in history as the idiot who turned down the Beatles. Decca Records took a pass on The Fab Four. Our rivals immediately scooped you, of course. I instead recommended David Dunwoody and the Druids.

GEORGE
Who?

DICK
Exactly. I’m sure I’ll be sacked at month’s end, out competing for a position at some fledgeling outfit just starting up. From the top of the mountain all the way down to the bottom.

GEORGE
...Well Dick, today is your lucky day. We saw a new band last night. They set the house on fire. They’re playing at a club at the Station Hotel. They’re called The Rollin’ Stones-

(An ASSISTANT DIRECTOR INTERRUPTS)

ASSISTANT DIRECTOR
Gentlemen, this way, please-

There is a LONGER PAUSE than usual, as CHEERY THEME MUSIC wells up-

SCENE 6

The set of ABC's SHINDIG!. May 1965. The show is IN PROGRESS. The Rolling Stones are now in full glory. COLORFULLY dressed white teenaged extras surround the band, dancing for THE THREE FLOOR CAMERAS. Host JIMMY O'NEIL approaches the MINI STAGE.

O'NEIL
America, a big hand for England's latest hit makers- The Rolling Stones!

(Two CREW MEMBERS HOLD UP SIGNS saying "Applause!" towards the audience.)

O'NEIL
The band has made a special request. Brian?

BRIAN
We started because we wanted to play rhythm and blues, and Howlin' Wolf was one of our idols-

O'NEIL
Mick, anything you'd like to add?

(Brian grabs the mic back)

BRIAN
It's about time we shut up and we put Howlin' Wolf on the stage!

O'NEIL
Ladies and Gentlemen, Charles Burnett! A.K.A. The Howlin' Wolf!

(He ENTERS. IT'S THE SAME ACTOR from Act 1, Scene 1.

He APPROACHES THE MIC, EVERYBODY SITS AROUND HIM. He has a HARMONICA. A SPOTLIGHT HITS HIM.)

HOWLIN' WOLF
Before we go any further, I wanna thank these kids. The Rolling Stones, Ladies and Gentlemen. And all the other British kids that are making this Invasion, by breathing new life back into the music us old timers played, and puttin' some that light back on us.

The SURROUNDING LIGHTS HAVE DIMMED. ONLY WOLF is in the NARROWING SPOT.

HOWLIN' WOLF
One of those ole' songs is 'bout a young kid who is forced to make a life choice. He takes the road with music on it. It's called Crossroads, and it goes like this:

(It goes BLACK. The FINAL CURTAIN DROPS.)

THE END