

Neuromuscular junction disorders

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MG is an Autoimmune Disorder

Figure 1

Myasthenia Gravis is an Autoimmune Disease

- Simpson (1960)
 - Speculation Based on: Assoc. with Other AI Diseases; Thymus Abnormalities, Fluctuating Course, Transient Neonatal MG
- Lindstrom lab (1973)
 - EAMG
 - Passive Transfer Rabbit –to–Rabbit
- Appel lab (1974)
 - AChR-Ab Found in MG Pts
- Toyka et al (1977)
 - Passive Transfer Man-to-Mouse
- Engel et al
 - IgG and C3 at NMJ in MG (1977)
 - MAC at NMJ in MG (1987)
- Vincent lab (2002)
 - MuSK Ab to muscle specific tyrosine kinase
- Higuchi et. al. (2011); Pevzner et. al. (2012); Zhang et. al. (2012)
 - LRP4 Antibodies

Autoimmune Response to Acetylcholine Receptor

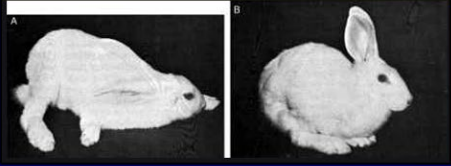
Jim Patrick¹, Jon Lindstrom¹
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Science 25 May 1973;
 Vol. 180, Issue 4088, pp. 871-872
 DOI: 10.1126/science.180.4088.871

Abstract

Injection of rabbits with acetylcholine receptor highly purified from the electric organ of Electrophorus electricus emulsified in complete Freund's adjuvant resulted in the production precipitating antibody to acetylcholine receptor. After the second injection of antigen, the animals developed the flaccid paralysis and abnormal electromyographs characteristic of neuromuscular blockade. Treatment with the anticholinesterases edrophonium or neostigmine dramatically alleviated the paralysis and the fatigue seen in electromyography.

Patrick J, Lindstrom J. Autoimmune response to Acetylcholine Receptor. Science 1973; 180:871-2



The concept that myasthenia gravis (MG) is autoimmune is relatively recent given how long we have known about the disease. It was speculated that MG was an autoimmune disease in 1960 by Dr. Simpson (Figure 1). His speculation was based on several observations that included the association of MG with other autoimmune diseases, thymus gland abnormalities, fluctuating course, and transient neonatal MG where infants born to MG mothers are weak at birth and then improved gradually. The real proof did not emerge until the early 1970s. In 1973 Dr. Jon Lindstrom, in his laboratory in California, produced the first experimental allergic MG model in rabbits. His group was able to passively transfer myasthenia from rabbit to rabbit. Dr. Stanley Appel was part of the team at Duke in 1974 that was first able to identify acetylcholine receptor antibodies (AChR-Ab) in MG patients. A couple of years later, Dr. Klaus Toyka and his team in Germany were able to passively transfer these antibodies from human to mouse (Figure 2).

Figure 2

Important Publications on MG Pathophysiology

Acetylcholine Receptor Antibodies in Myasthenia Gravis

Appel SH, Almon RR, Levy N, Drachman DB, Griffin DE, et al. N Engl J Med 1975; 293:760-761.

This article has no abstract; the first 100 words appear below.

RECENT studies suggest the involvement of the acetylcholine receptor and the immune system in the pathogenesis of the neuromuscular disorder, myasthenia gravis.^{1,2,3,4,5} Patrick and Lindstrom⁶ produced an experimental myasthenic-like syndrome in rabbits by inoculation of acetylcholine receptors purified from electric eel. Using the high affinity cholinergic antagonist, alpha bungarum Fabmrough et al.⁷ demonstrated an apparent reduction in the number of available acetylcholine receptors in muscle biopsies from myasthenic patients. Our own laboratory demonstrated the presence in myasthenic patients of a circulating globulin that blocked the binding of ¹²⁵I labeled alpha-bungarotoxin to the acetylcholine receptor extracted from denervated rat skeletal muscle.⁸ The

October 9, 1975
N Engl J Med 1975; 293:760-761
DOI: 10.1056/NEJM197510092931508

ACHR Abs

Myasthenia Gravis — Study of Humoral Immune Mechanisms by Passive Transfer to Mice

Authors: Klaus V. Toyka, M.D., Daniel B. Drachman, M.D., Diane E. Griffin, M.D., Ph.D., Alan Pestronk, M.D., Jerry A. Winkelstein, M.D., Kenneth H. Fischbeck, Jr., M.D., and Ing Kao, M.D., Ph.D. Author Info & Affiliations
Published January 20, 1977 | N Engl J Med 1977;296:125-131 | DOI: 10.1056/NEJM197701202960301
VOL. 296, NO. 3

Abstract

To study the role of humoral factors in the pathogenesis of myasthenia gravis, we employed passive transfer of human serum fractions to mice. Immunoglobulins from 16 patients with myasthenia gravis were injected into mice daily for one to 14 days. Typical myasthenic features of reduction in amplitude of miniature end-plate potentials (mean change more than 50 per cent, P<0.0005) or reduction in acetylcholine receptors at neuromuscular junctions (mean change more than 50 per cent, P<0.0005) (or both) were produced by immunoglobulin from 15 of the 16 patients. Some mice showed weakness or decremental responses to repetitive nerve stimulation as well. The active fraction was identified as IgG by three different purification methods. Its effect was enhanced by the third component (C3) of the complement system, but the fifth component (C5) had no effect. These data suggest that the pathogenesis of myasthenia gravis often involves an antibody-mediated autoimmune attack on the acetylcholine receptors of the neuromuscular junction. (N Engl J Med 296:125-131, 1977)

Passive Transfer

Appel SH, Almon RR, Levy N. Acetylcholine Receptor Antibodies in Myasthenia Gravis. N Engl J Med 1975; 293:760-761. Toyka KV, Drachman DB, Griffith DE, et al. Myasthenia gravis. Study of humoral immune mechanisms by passive transfer to mice. N Engl J Med 1977; 296:125-130

In 1977 at the Mayo Clinic, Dr. Andrew Engel and his team made the initial observations that in addition to the autoimmune antibodies, complement was important in MG pathophysiology at the neuromuscular junction. Our group was able to demonstrate complement elevation in the plasma of MG patients. The complement elevation was higher when the disease was more severe. The finding that complement was important in the development of MG ultimately led to the use of complement inhibitors for the treatment of MG (Figure 3).

Figure 3

Complement and MG

Mayo Clin Proc. 1977 May;52(5):267-80.

Immune complexes (IgG and C₃) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations

A G Engel, E H Lambert, F M Howard
PMID: 870771

1977

Abstract

Although there is strong evidence that myasthenia gravis (MG) is caused by an autoimmune reaction to the nicotinic postsynaptic acetylcholine receptor (AChR) protein, immune complexes have never been directly demonstrated at the end-plate by immunocytochemistry or immunoelectron microscopy. Staphylococcal protein A (which binds to the Fc region of human IgG subclasses 1, 2, and 4) and rabbit anti-human C₃ conjugated with peroxidase were used for the ultrastructural (2 patients) and light microscopic (12 patients) localization of IgG and C₃, respectively, at MG end-plates. Both IgG and C₃ were localized on segments of the postsynaptic membrane and fragments of degenerating junctional folds in the synaptic space. In nonmyasthenic control patients no immune complexes were evident at the end-plate. As judged by morphometric analysis of electron micrographs, the immune complexes were more abundant in the less severely affected MG patients than in the more severely affected ones. A linear correlation was demonstrated between the length of the postsynaptic membrane binding immune complexes and the amplitude of the miniature end-plate potential. The less intense reaction for immune complexes in the more severely affected MG patients can be attributed to the smaller quantity of AChR remaining at their end-plates. The findings provide unambiguous evidence for a destructive auto-immune reaction involving the postsynaptic membrane in MG. Immunopharmacologic blockade of AChR and IgG-induced modulation of AChR may also contribute to the AChR deficiency at the MG end-plates.

Engel AG, Lambert EH, Howard FM. Immune complexes (IgG and C₃) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations. *Mayo Clin Proc.* 1977 May;52(5):267-80.

Ultrastructural Localization of the Terminal and Lytic Ninth Complement Component (C9) at the Motor End-plate in Myasthenia Gravis

KO SAHASHI, M.D., ANDREW G. ENGEL, M.D., EDWARD H. LAMBERT, M.D., PH.D., AND FRANK M. HOWARD, JR., M.D. (Rochester, Minnesota)

Abstract. The terminal and lytic complement component (C9) was localized at the motor end-plate in acquired autoimmune myasthenia gravis (MG) by the immunoperoxidase method, with adequate preservation of fine structure and negligible background staining. C9 was localized on short segments of the postsynaptic membrane, on degenerated fragments of the junctional folds shed into the synaptic space, and on disintegrating junctional folds. An inverse relationship was noted between the structural integrity of the junctional folds and the abundance of C9 at a given end-plate region. Destruction of junctional folds by complement may induce relocation of the nerve terminal and increase regions on the muscle fiber. Destruction of junctional folds may also induce formation of the immune attack complex in the synaptic space. The findings suggest that antibody-dependent modulation of the receptor. In certain disorders other than autoimmune MG, pathological mechanisms other than complement-mediated lysis may affect the structural integrity of the postsynaptic region.

1980

Sahashi K, Engel AG, Lambert EH, Howard FM Jr. Ultrastructural localization of the terminal and lytic ninth complement component (C9) at the motor end-plate in myasthenia gravis. *J Neuropathol Exp Neurol.* 1980 Mar;39(2):160-72.

Soluble terminal complement components in human myasthenia gravis

Richard J. Barohn, Robin L. Brey

1993

Abstract

The loss of membrane acetylcholine receptor (AChR) leading to muscle weakness and impaired neuromuscular transmission in human myasthenia gravis (MG) is in part due to the loss of AChR from the postsynaptic membrane. This has been supported by the demonstration of AChR antibodies in the serum of MG patients. We evaluated for evidence of soluble terminal complement components in the serum of 42 MG patients from healthy controls. Absence of soluble terminal complement components (SC5b-9) in 42 (55%) at one or more time points was observed. Multiple samples were obtained from 10 patients with deterioration in some, but not all. There was no clear distinction between the presence of AChR antibody levels and complement-mediated muscle weakness. The presence of SC5b-9 in MG, but also demonstrated in other autoimmune disorders, correlate with disease activity.

Fig. 1. SC5b-9 levels in myasthenia gravis patients grouped by clinical grade.

Barohn RJ, Brey RL. Soluble terminal complement components in human myasthenia gravis. *Clin Neurol Neurosurg.* 1993 Dec;95(4):285-90.

The next big scientific breakthrough was in 1999 when Doctors Vanda Lennon and Edward Lambert discovered that the Lambert-Eaton myasthenic syndrome was due to antibodies directed against the presynaptic voltage-gated calcium channels at the neuromuscular junction. In 2001 Dr. Angela Vincent's lab in Oxford, England discovered antibodies directed against the muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction in patients with MG who did not have AChR antibodies. In 2011 and 2012 several labs found low-density lipoprotein receptor-related protein 4 (LRP4) antibodies in a portion of MG patients who were seronegative to both AChR and MuSK. While there are other antibodies that are still being pursued in research labs, these three are now commercially available--AChR, MuSK, and LRP4.

Figure 4

Important Publications: NMJ Antibodies

1999

2001

2012

Lennon VA, Lambert EH. Autoantibodies Bind Solubilized Calcium Channel- α -Conotoxin Complexes From Small Cell Lung Carcinoma: A Diagnostic Aid for Lambert-Eaton Myasthenic Syndrome. *Mayo Clinic Proc* 1989; 64:1498

Mayo Clinic Proceedings
Volume 64, Issue 12, December 1989, Pages 1498-1504

Autoantibodies Bind Solubilized Calcium Channel- α -Conotoxin Complexes From Small Cell Lung Carcinoma: A Diagnostic Aid for Lambert-Eaton Myasthenic Syndrome
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Available online 13 December 2012.

Ca++ Abs

[https://doi.org/10.1016/S0025-4196\(12\)61370-7](https://doi.org/10.1016/S0025-4196(12)61370-7)

Serum autoantibodies found by radioimmunoassay in 27 of 52 patients with the Lambert-Eaton myasthenic syndrome (LES) bound specifically to a soluble α -conotoxin binding component of a voltage-gated Ca^{2+} channel (VGCC) complex extracted from small cell lung carcinoma (SCLC). These antibodies were not found in 43 control patients with other neurologic diseases, including myasthenia gravis, peripheral neuropathies, and amyotrophic lateral sclerosis, or in 9 patients with endocrine autoimmunity, but they were found in 2 of 21 control patients with SCLC without a history of LES, 1 of whom had severe autonomic neuropathy. Seropositivity was more frequent in patients with LES who had evidence of a primary lung cancer (10%) than in those with other neoplasms or without evidence of cancer (30%). Antigens extracted from SCLC tumor lines derived from patients with and without LES and from a human neuroblastoma line yielded results that were highly correlated. A control extract of colonic carcinoma (derived from a patient with LES) yielded negative results. The data implicate a tumor-associated VGCC as the autoimmunogenic stimulus in a subset of patients with a current neoplasia. *Proc Natl Acad Sci U S A* 1989; 86:1498-1502.

Hoch W, McConville J, Helms S, et al. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* 2001; 7:365-368

Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies
W Hoch¹, J McConville, S Helms, J Newsom-Davis, A Melmis, A Vincent

Affiliations: 1 expand
PMID: 11231638 DOI: 10.1038/85520

MuSK Abs

Abstract
Myasthenia gravis (MG) is an antibody-mediated autoimmune disease of the neuromuscular junction. In approximately 80% of patients, auto-antibodies to the muscle nicotinic acetylcholine receptor (AChR) are present. These antibodies cause loss of AChR numbers and function, and lead to failure of neuromuscular transmission with muscle weakness. The pathogenic mechanisms acting in the 20% of patients with generalized MG who are seronegative for AChR-antibodies (AChR-Ab) have not been elucidated, but there is evidence that they also have an antibody-mediated disorder, with the antibodies directed towards another, previously unidentified muscle-surface-membrane target. Here we show that 70% of AChR-Ab-seronegative MG patients, but not AChR-Ab-seropositive MG patients, have serum auto-antibodies against the muscle-specific receptor tyrosine kinase, MuSK. MuSK mediates the agrin-induced clustering of AChRs during synapse formation, and is also expressed at the mature neuromuscular junction. The MuSK antibodies were specific for the extracellular domains of MuSK expressed in transfected COS7 cells and strongly inhibited MuSK function in cultured myotubes. Our results indicate the involvement of MuSK antibodies in the pathogenesis of AChR-Ab-seronegative MG, thus defining two immunologically distinct forms of the disease. Measurement of MuSK antibodies will substantially aid diagnosis and clinical management.

Zhang B, Tziartos JS, Belizemi M, et al. Autoantibodies to Lipoprotein-Related Protein 4 in Patients With Double-Seronegative Myasthenia Gravis. *Arch Neurol* 2012; 69:445-451.

Autoantibodies to Lipoprotein-Related Protein 4 in Patients With Double-Seronegative Myasthenia Gravis
Bin Zhang, PhD, John S. Tziartos, MD, PhD, Maria Belizemi, PhD, Samir Raghav, PhD, Beverly Baskour, BS, Richard J. Lewis, MD, Wen-Cheng Sheng, PhD, Robert F. Ludke, MD, Scotten J. Tzartos, PhD, Lou Mei, PhD

LRP4 Abs

Objectives: To determine whether lipoprotein-related protein 4 (LRP4), a newly identified agrin that is essential for neuromuscular formation, and to establish whether such antibodies in MG pathogenesis.

Design: Serum samples from patients with MG with known status of serum antibodies to the acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) and serum samples from control subjects (healthy individuals and individuals with other diseases) were tested for antibodies to LRP4. Serum samples with such antibodies were tested to determine whether they had the ability to inhibit LRP4 function in the neuromuscular junction.

Setting: Serum samples were collected at the Hellenic Pasteur Institute and Wayne State University. Samples were tested for LRP4 autoantibodies at Georgia Health Sciences University. Other immunoreactivities of the samples were tested at the Hellenic Pasteur Institute, Athens, Greece, or processed through University Laboratories of the Detroit Medical Center, Michigan.

Patients: The study included 117 patients with MG, 76 patients with other neurologic or psychiatric diseases, and 45 healthy control subjects.

LRP4 antibodies were detected in 11 of 16 MG without detectable anti-AChR or anti-MuSK (double seronegative) and in 1 of 16 non-MG anti-AChR antibodies but with antibodies, but they were not detected in patients with anti-AChR antibodies. No antibodies and only 2 of the 76 control patients with neurologic disease had anti-LRP4 antibodies. Serum samples from patients with MG with anti-LRP4 antibodies were able to inhibit the LRP4-agrin interaction and/or AChR clustering in muscle cells.

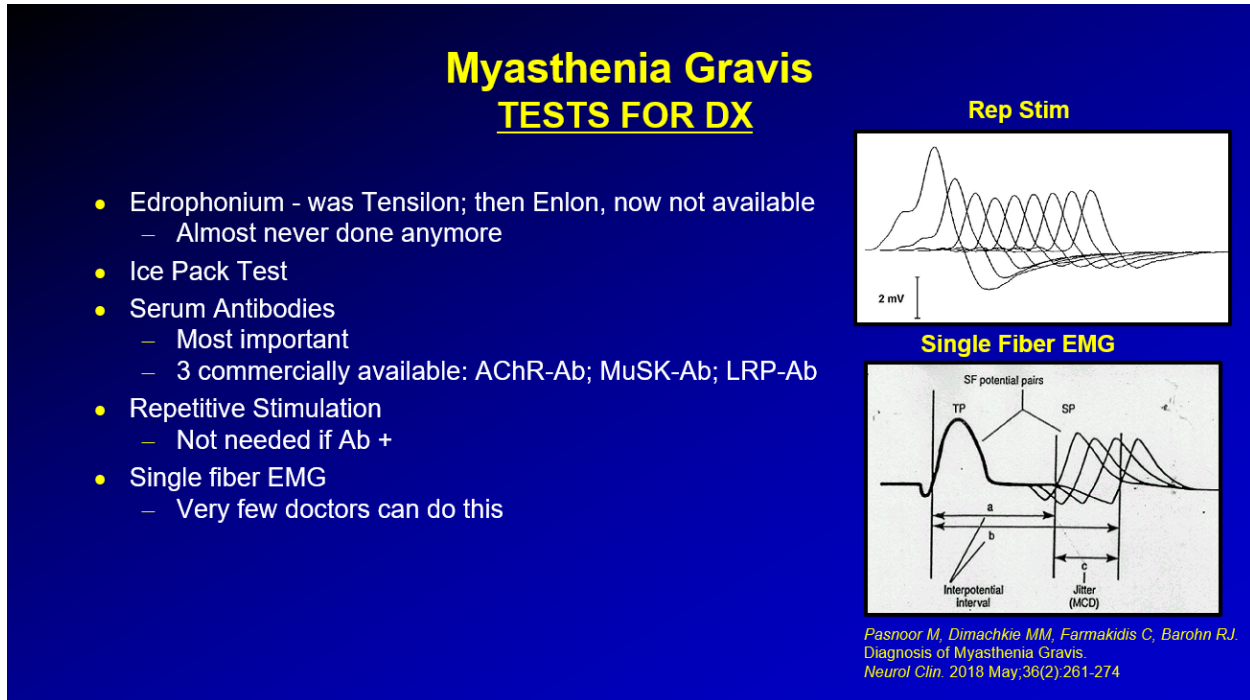
Conclusions: Anti-LRP4 antibodies were detected in the serum of approximately 9.2% of patients with double seronegative MG. This frequency is intermediate compared with 2 recent studies showing anti-LRP4 antibodies in 2% and 30% of patients with double-seronegative MG from different geographic locations. Together, these observations indicate that LRP4 is another autoantigen in patients with MG, and anti-LRP4 autoantibodies may be pathogenic through different immunopathogenic processes.

Arch Neurol. 2012;69(4):445-451. Published online December 12, 2011. doi:10.1001/archneurol.2011.2193

Diagnosis of MG

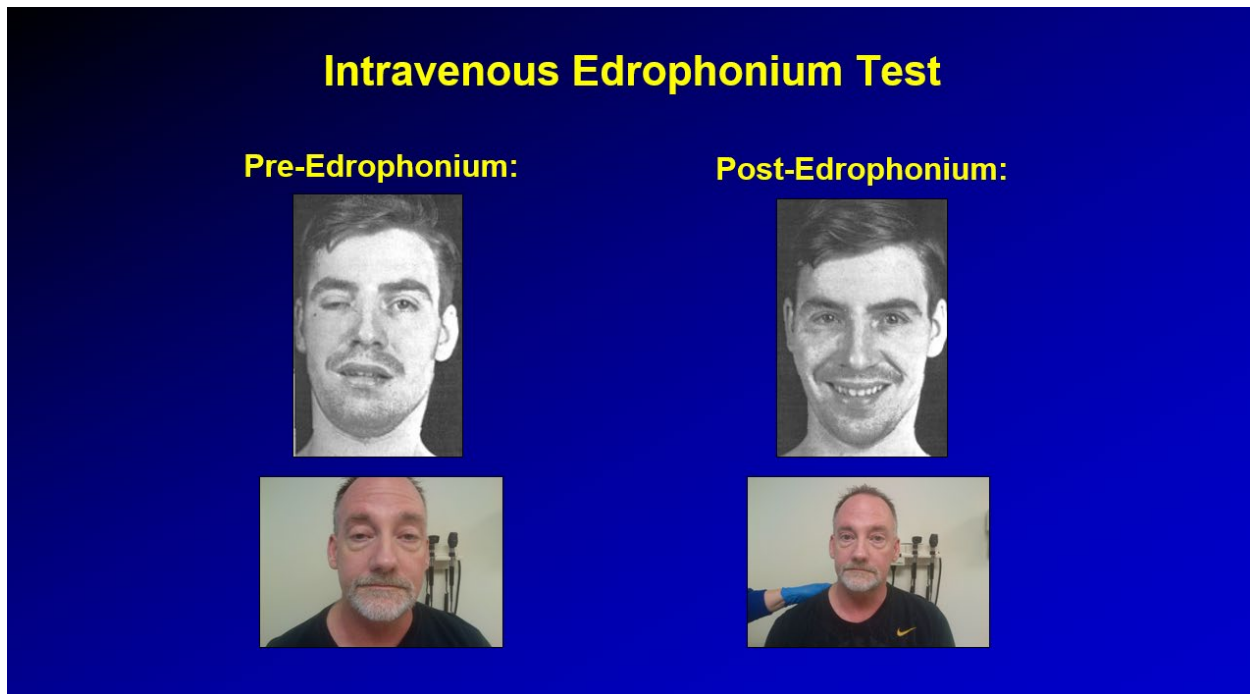
Edrophonium-chloride, previously known by the trade names Tensilon and Enlon, was developed in the mid-1950s to diagnose MG (Figure 5).

Figure 5



By injecting intravenously this acetylcholinesterase inhibitor, some symptoms and signs of MG could be improved or reversed, especially ptosis (Figure 6).

Figure 6



However, since 2018 edrophonium is no longer available in the United States. We hope that one day a drug company will bring edrophonium back on the market because we believe it is useful in the diagnosis of MG in both inpatient and outpatient settings when patients first present with symptoms and signs. In the absence of the ability to do edrophonium tests, an ice pack test can be performed by putting ice wrapped in a plastic bag over a patient's ptotic eye to see if the lid raises. This is not as effective as an edrophonium test. The pharmacologic basis for the ice pack test is that cold temperature slows down the activity of the enzyme acetylcholinesterase thus increasing the availability of the neurotransmitter acetylcholine at the neuromuscular junction to effect neuromuscular transmission. Serum antibodies are the most important diagnostic test and as mentioned above, there are now three commercially available serum antibodies: antibodies to AChR, MuSK, and LRP4. Repetitive stimulation is still a useful test to demonstrate neuromuscular junction pathophysiology. Figure 3 shows an example of an abnormal decremental response of an ulnar-innervated hand muscle when the

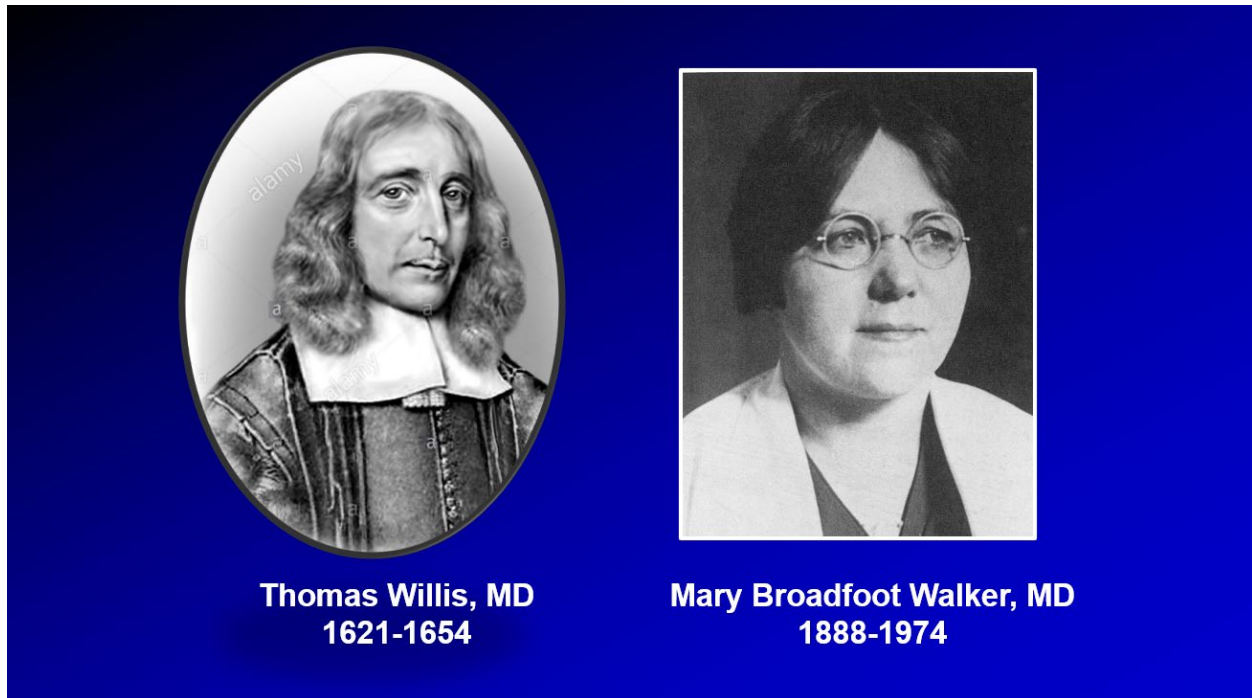
ulnar nerve was stimulated at 2 Hertz. In a patient who has the typical presentation of MG symptoms and signs, a positive antibody test to these components of the neuromuscular junction lessens the need to do repetitive stimulation as the diagnosis has already been confirmed.

Single fiber electromyography (EMG) is also a useful test to demonstrate neuromuscular junction dysfunction (Figure 3). It is more sensitive than repetitive stimulation. Single fiber EMG is most often used to document evidence of neuromuscular junction dysfunction in antibody-negative patients.

However, single fiber EMG is a difficult test to perform that requires training and special equipment and it is not available at many medical centers.

Two historic figures that led to our understanding and treatment of MG

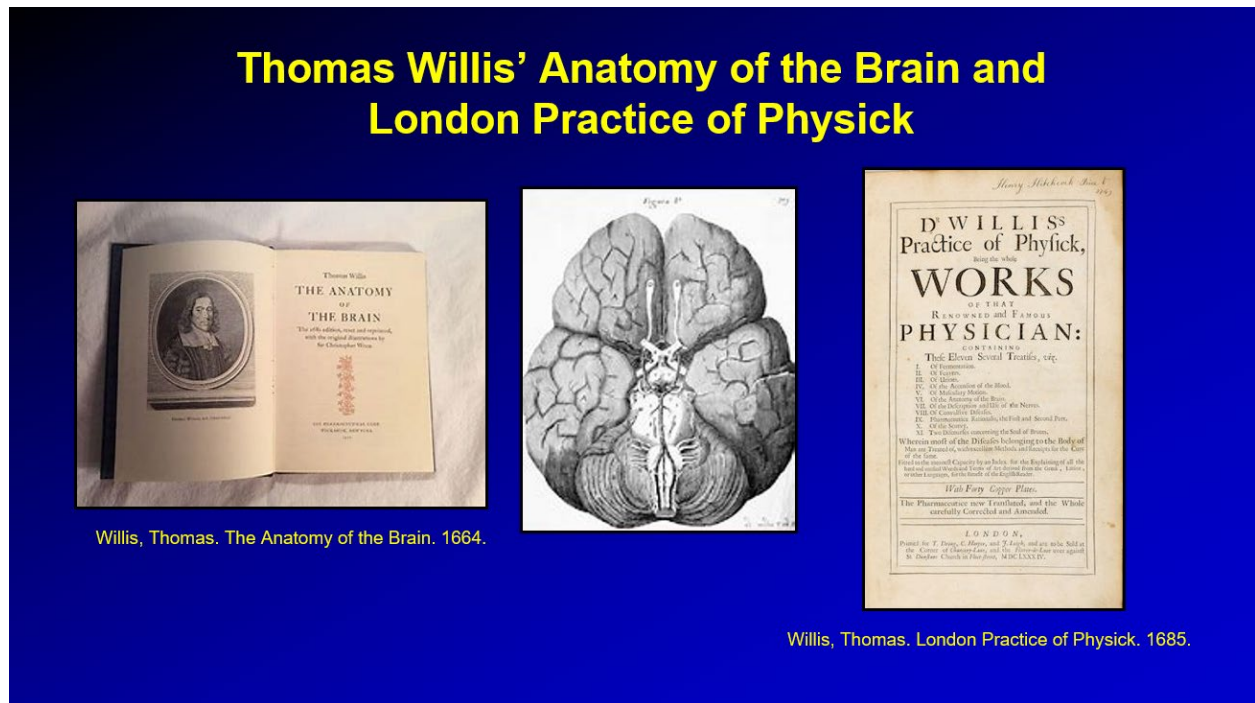
Figure 7



Who are these two individuals in Figure 7? The man on the left is Thomas Willis who was an important physician who practiced in England in the 1600s. He was primarily famous for publishing on the anatomy of the brain and describing the vasculature at its base which we now call the circle of Willis. He also was the first physician to describe the clinical features of MG in one of the many books that he published. ‘De Anima Brutorum’, published by Willis in London in 1672 and written in Latin, described patients who were well in the morning and fatigued toward noon and were unable to speak for a long time. This book was then translated into English in 1685 under the title ‘The London Practice of Physick’:

“in the morning [they] are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing, before noon the stock of Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot” (Figure 8).

Figure 8

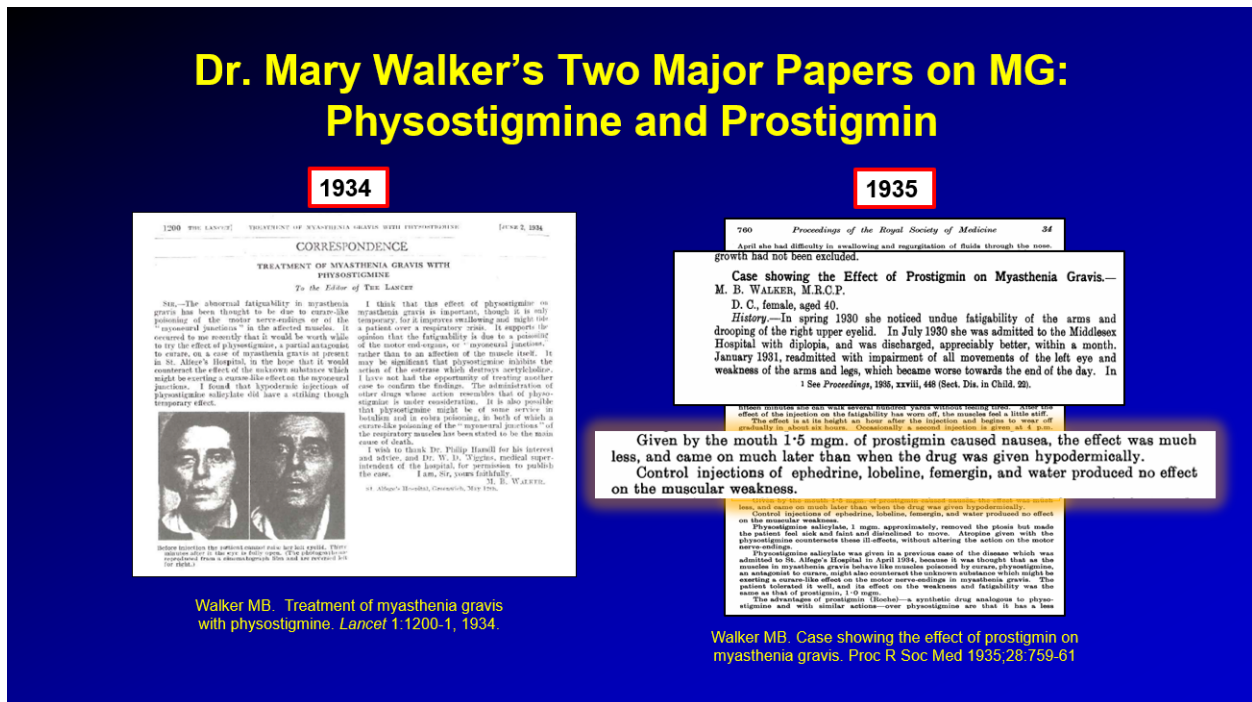


Willis, Thomas. The Anatomy of the Brain. 1664.

Willis, Thomas. London Practice of Physick. 1685.

The woman may not be as well known to many of you but she's one of the heroes in MG history and her name is Mary Broadfoot Walker. Dr. Walker first demonstrated that physostigmine and prostigmin were effective in treating MG. She published two papers, one in 1934 and one in 1935, that showed this beneficial effect.

Figure 9



Walker MB. Treatment of myasthenia gravis with physostigmine. *Lancet* 1:1200-1, 1934.

Walker MB. Case showing the effect of prostigmin on myasthenia gravis. *Proc R Soc Med* 1935;28:759-61

She saw similarities between the symptoms and signs of MG and curare intoxication. Curare poisoning was being treated with physostigmine, and based on this knowledge, she decided to use these drugs to treat MG-and it worked! This was a landmark discovery in the history of medicine. In the 1935 paper, she injected not only prostigmin (also known as neostigmine) but then injected water placebo and showed that the placebo did not work (see highlighted area in Figure 9). The observations of Dr. Walker were the biggest breakthrough in the treatment of MG in the early half of the last century. The next major observation in the treatment of MG regarded the thymus gland. For years cases of MG had been observed with enlarged thymus glands or thymic tumors. In the 1930s and 40s thymectomy began being used for thymomatous and non-thymomatous MG by Dr. Alfred Blalock and others, and they reported improvement in the status of the patients (Figure 10).

Figure 10

Treatment of MG and Decades Introduced

| YEAR | TREATMENT |
|-----------------|---|
| 1930's | Neostigmine & Physostigmine |
| 1930's & 40's | Thymectomy |
| 1950's | Mechanical ventilation, Edrophonium chloride & Pyridostigmine Bromide |
| 1960's & 70's | Corticosteroids, Plasmapheresis Azathioprine |
| 1980's | Cyclosporine |
| 1980's & 90's | Intravenous immune globulin |
| 1990's & 2000's | Mycophenolate mofetil |
| 2000's | Rituximab (RITUXAN®) |
| 2017 | Eculizumab (SOLIRIS®) |
| 2021 | Efgartigimod (VYGART®) |
| 2022 | Ravulizumab (ULTOMIRIS®) |
| 2023 | Rozanolixizumab (RYSTIGGO®) Zilucoplan (ZILBRYSQ®) Efgartigimod SQ (Hytrulo SQ) |

To increase Acetylcholine

- Cholinesterase Inhibitors
 - Pyridostigmine (Mestinon)
 - Prostigmin (Neostigmine)

To inhibit immune response

- Immunosuppressive Therapies
- Surgery
 - Thymectomy

A major advance in the treatment of MG occurred in the 1950s when mechanical ventilators became available. As mentioned, edrophonium chloride became available in the 1950s, and then pyridostigmine bromide, which goes by the trade name of Mestinon, was developed in the mid-1950s and largely replaced the use of prostigmin (Neostigmine) due to fewer side effects. Pyridostigmine (Mestinon) became the first FDA-approved drug for MG in 1955. Corticosteroids and plasmapheresis were introduced in the 1970s. However, there were many reports in which ACTH was used for MG beginning in the 1950s which was really the first attempt of using corticosteroids for MG. The late 1960s and early 1970s ushered in an era of using drugs that were developed to prevent organ transplant rejection in autoimmune diseases such as MG. The first was azathioprine and the next was cyclosporine, and finally mycophenolate mofetil. In the 1980s and 90s, intravenous immune globulin (IVIG) began being used for MG.

Around 20 years ago, rituximab was first introduced as MG therapy. All of the above medications were approved for other disease states and were off label for MG. Finally, in 2017 the first FDA-approved

immunotherapy for MG was introduced-eculizumab--and subsequently several other drugs have been FDA-approved for MG, most notably efgartigimod in 2021.

Course of Disease and Patterns of Presentation

Figure 11

Myasthenia Gravis

COURSE

- About 80 % present with eye symptoms: double vision or eye droop (MP5-eyeball pattern)
- However, only 15% remain ocular at 3 yrs.
- Other presentations: MP6 (neck) ; MP7 (bulbar) ; MP1 (limb girdle); MP2 (distal) MP9 (periodic)
- Mortality:
 - Prior to 1960: 30%
 - Now: < 1%
 - Why: Due to mechanical ventilation and prednisone & other therapies
- We now expect most patients to improve and some to go into remission.
- Prednisone is essential in the management of most MG patients especially early in the course.

The course of MG is well known. Eighty percent are present with the ocular symptoms of either double vision or a droopy eyelid. This is the MP5 eyeball pattern discussed in the pattern recognition lecture published previously. However, only 15% of patients remain purely ocular at three years of disease duration. Other presentations include the MP6 neck drop pattern, the MP7 bulbar pattern, occasionally the MP1 limb-girdle pattern, and sometimes the MP2 distal pattern. Because many patients state that they get weaker with exercise, the MP9 pattern should be added to this list. Prior to all of the treatments that were just mentioned, MG was indeed a grave disease. The mortality rate prior to 1960 was 30%. However with our current therapies, the mortality rate should be well below 1%. Patients should not die of MG. When this does occur, it is usually due to complications from one or more of the therapies such as an overwhelming infection. The dramatic reduction in the mortality rate

in the 1960s and 1970s was most likely due to the introduction of mechanical ventilation and corticosteroids, but certainly other therapies played a role as well.

Time to Effectiveness of Each Therapeutic Modality

How long does it take these individual therapies to have a clinical effect? First it should be recognized that not all of these therapies will be effective in every patient. If they are effective, the time of onset to the improvement ranges from minutes to months depending on the therapy.

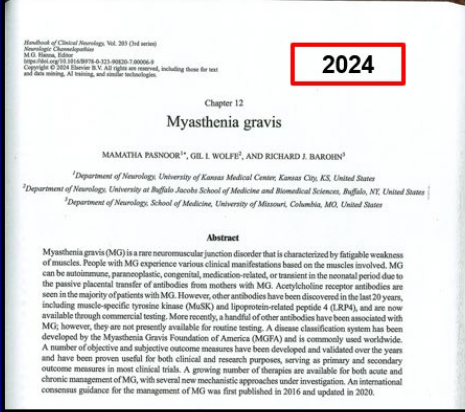
Figure 12

Treatment of Myasthenia Gravis

Typical Time to Clinical Effect After Initiating Therapy

| THERAPY | TIME |
|----------------|-----------------|
| Pyridostigmine | Minutes |
| Plasmapheresis | 1-14 days |
| IVIg | 1-14 days |
| Prednisone | 2-8 weeks |
| Eculizumab | 2-8 weeks |
| Efgartigimod | 2-8 weeks |
| Cyclosporine | 2-6 months |
| Methotrexate | 2-6 months |
| Mycophenylate | 2-6 months |
| Azathioprine | 12-18 months |
| Rituximab | months |
| Thymectomy | months to years |

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Pyridostigmine works in a matter of minutes. Plasmapheresis and IVIG work in days. Prednisone and eculizumab work in 2 to 8 weeks. Cyclosporine, methotrexate, and mycophenolate mofetil, if they are going to have an effect, only start showing benefit after two to six months, sometimes longer. On the other hand, azathioprine, which does have an effect on MG, does not have an effect for 12 to 18 months. Rituximab, if it is effective, may take several months. Thymectomy surprisingly also seems to have an effect within several months.

Annual Cost of Individual Therapies

Figure 13

Annual Cost of Therapy for Myasthenia Gravis

| INTERVENTION | REGIMEN | APPROX. ANNUAL COST |
|-------------------------------|--|---------------------|
| Pyridostigmine | 60 mg tid | \$1,000 |
| Prednisone | 20 mg qod | \$12 |
| Azathioprine | 150 mg qd | \$2,200 |
| Mycophenolate | 1000 mg bid | \$6,500 |
| Cyclosporine | 150 mg bid | \$6,800 |
| Methotrexate | 20 mg/ week | \$400 |
| IVIg | 12 gm / kg total dose | \$83,000-\$98,000 |
| Plasma exchange | 36 exchanges | \$40,000 |
| Eculizumab (Soliris) | IV every other week | \$500,000 |
| Efgartigimod (Vyvgart) | IV weekly & 1 mo. | \$200,000 |
| Ravulizumab (Ultomiris) | IV every 8 weeks | \$400,000 |
| Rozanolixizumab (Rystiggo SC) | Weekly for 6 weeks, repeated after 6 weeks | \$290,400 |
| Zilucoplan (Zilbrysq) | Daily SC if they are between 56 and 77 kg | \$380,000 |
| Efgartigimod SQ (Hytrulo SQ) | Weekly for 4 weeks, repeated after 4 weeks, just like IV | \$315,460 |

The cost of these drugs ranges from very inexpensive to staggeringly expensive and that is shown in Figure 13. If you can get prednisone for a dollar a month at your local Walmart, then the cost is \$12 a year. After that, the drugs get increasingly more expensive. Methotrexate, which has been around since the 1950s, is relatively inexpensive compared to other oral immunosuppressive agents. On the other hand, IVIG and plasmapheresis have a large price tag. But the new biologics that either inhibit complement or Fc receptors are even more costly.

Published Studies on Therapy for MG

Figure 14

Published Studies on Therapy for MG

- Prior to 2000, most have been non-controlled, non-randomized, non-blinded
- Many simply observational/anecdotal
- Rare controlled, randomized, blinded trials
- But, since 2000 there were many randomized controlled trials!
- Note: All Rx meds for MG are “off-label” re FDA except pyridostigmine
 - Until: Eculizimab (Soliris®)
Efgartigimod (Vyvgart®)

Prior to 2000 most MG studies were uncontrolled, nonrandomized, and unblinded with a few exceptions. There were many observational and anecdotal studies, particularly around thymectomy and prednisone. However, since 2000 there have been many published randomized controlled trials. We are currently in an exciting age of innovation regarding the treatment of MG. The list of FDA approved drugs in the biologic era continues to expand and now includes eculizumab, efgartigimod intravenous (IV), ravulizumab, rozanolixizumab, zilucoplan, and subcutaneous (SQ) efgartigimod.

MG Activities of Daily Living Scale

Figure 15

MG-ADL

| Grade | 0 | 1 | 2 | 3 | Score |
|---|--------|--|---|----------------------------------|---------------------|
| Talking | Normal | Intermittent slurring or nasal speech | Constant slurring or nasal, but can be understood | Difficult to understand speech | |
| Chewing | Normal | Fatigue with solid food | Fatigue with soft food | Gastric tube | |
| Swallowing | Normal | Rare episode of choking | Frequent choking necessitating changes in diet | Gastric tube | |
| Breathing | Normal | Shortness of breath with exertion | Shortness of breath at rest | Ventilator dependence | |
| Impairment of ability to brush teeth or comb hair | None | Extra effort, but no rest periods needed | Rest periods needed | Cannot do one of these functions | |
| Impairment of ability to arise from a chair | None | Mild, sometimes uses arms | Moderate, always uses arms | Severe, requires assistance | |
| Double vision | None | Occurs, but not daily | Daily, but not constant | Constant | |
| Eyelid droop | None | Occurs, but not daily | Daily, but not constant | Constant | |
| | | | | | Total Score: |

1999

Myasthenia gravis activities of daily living profile

Article abstract—The authors have developed an MG activities of daily living (ADL) profile (MG-ADL)—a simple eight-question survey of MG symptoms. In 254 consecutive encounters with established MG patients, the authors compared scores from the MG-ADL to the quantitative MG score (QMG)—a standardized, reliable scale used in clinical trials. The mean MG-ADL score was 4.09 ± 3.63. The mean QMG score was 10.00 ± 5.76. Pearson's correlation coefficient was 0.593 ($p < 0.001$). The MG-ADL is an easy-to-administer survey of MG that correlates well with the QMG and can serve as a secondary efficacy measurement in clinical trials.

NEUROLOGY 1999;52:1487-1489

G.L. Wolfe, MD, L. Herbelin, R. Eddy, S.P. Nations, MD, R. Foster, PhD, W.W. Bryan, MD, and R.J. Barohn, MD

A number of grading systems have been developed to assess the degree of disease severity in MG and to monitor the response to therapy in clinical trials. Modified versions of Osserman's classification are the most widely utilized, but have limitations from a clinical trial standpoint. These include vague descriptions of severity, a limited number of grades, and in some cases an ambiguity for responses. Because of these shortcomings, investigators have developed quantitative MG scoring systems (QMGs). Tinsell et al.¹ used a 13-item QMG as the primary outcome measure in a double-blind, placebo-controlled trial demonstrating that pyridostigmine is effective in MG. We recently determined that a modified version of Tinsell's QMG has high inter-rater reliability in MG patients and normal control subjects.²

Increasing emphasis has been placed on scales that measure how neurologic disease impacts ADL and quality of life.³ We have developed a simple MG activities of daily living profile (MG-ADL) to assess the severity of MG symptoms. This eight-question survey is an expanded version of symptom-based test items from Tinsell's scoring system and can be administered with patient instruction in less than 10 minutes. During this study we investigated the correlation between the MG-ADL and the QMG.

Methods. The MG-ADL and QMG scores were determined in 254 consecutive encounters with established MG patients. All MG patients were followed in our neuromuscular clinic and were diagnosed according to accepted clinical, electrophysiologic, and serologic standards.⁴

A trained technician (L.H.) performed the QMG, and asked the questions and recorded the responses for the MG-ADL. The QMG consists of 13 objective items (Figure 1), each scored from 0 (normal) to 3 (most severe). Total QMG scores range from 0 to 39. The MG-ADL is an eight-question survey of symptom severity, with each response graded from 0 (normal) to 3 (most severe). Two questions concern ocular: three ophthalmologic, one respiratory, and two extremity functions (Figure 2). Quantitative MG-ADL scores range from 0 to 24.

The two scales were completed during the same patient encounter. Pearson's correlation coefficient was used to assess statistically the relationship between the two grading systems.

Results. A total of 254 MG patients (99 women, 155 men) were evaluated. Of the 254 consecutive encounters, 98 were repeat examinations. The mean MG-ADL score was 4.09 (SD, 3.63, range, 0 to 18). The mean QMG score was 10.00 (SD, 5.76, range, 0 to 27). Pearson's correlation coefficient was 0.593 ($p < 0.001$). The 95% CI was 0.507 to 0.685.

Copyright © 1999 by the American Academy of Neurology. 1487

Wolfe GL, Herbelin L, Nations SP, et al. Myasthenia gravis activities of daily living profile. *Neurology* 1999; 52:1487-1489

If you are going to be taking care of MG patients, then it is important to know about the MG activities of daily living scale MG-ADL which our team developed at University of Texas Southwestern in the 1990s. This scale was developed for research purposes, but it should now be routinely used to monitor the progress of MG patients. It is a very simple scale to use. A medical assistant can ask the patient the questions or the patient can fill it out on their own. In the office setting when a patient is first put in the waiting or the examination room, the MG-ADL can be completed. Therefore, when the physician walks in the exam room to begin the encounter the MG-ADL scale will have already been completed. The advantage of obtaining an MG-ADL at each clinic visit is that you have a quantitative score of the severity of the MG.

It is strongly encouraged that the MG-ADL be done routinely as a standard of care every time a MG patient is seen whether or not it is in a general neurologist's office or a tertiary care neuromuscular clinic.

Pyridostigmine


Pyridostigmine is the first-line treatment for MG. It also goes by the trade name Mestinon. The most important caveat with pyridostigmine is not expecting from or using it too much. If the patient is on 60mg three or four times a day and they are still symptomatic then it is time to go on to immunosuppressive therapy.

There is no need to increase the dose to 120mg every two or three or four hours. All this will do is cause more side effects such as increased bowel movements and sweating, and it will not improve the MG symptoms or signs any more than the effect of 60mg three or four times a day. Generic pyridostigmine is now available and it is just as effective as the trade drug. It is less expensive.

Figure 16

Pyridostigmine (Mestinon)

- 1st Line treatment for MG
- Don't Expect or Use Too Much
 - **60 mg three or four times a day**
- If need more than this, immunosuppressive therapy is needed
- Generic now available
- Time-release form-180 mg-used infrequently
- Anticholinergic Meds Useful for GI Side Effects:
 - Hyoscyamine Sulfate 0.125 mg (Levsin/Anaspaz)



Neurol Clin. 2018 May;36(2):311-337

There is also a version called Mestinon Time Span which is a time release formulation. In general, we prefer not to use this formulation, as it gives a large pyridostigmine dose and absorption is erratic.

However some patients take the time release tablet at bedtime presumably so they have fewer MG symptoms in the morning. Therefore, if a patient insists on using the time release capsule and believes they are benefiting we will agree with their decision as in these instances the patient is usually correct.

If the patient does have loose stools on pyridostigmine, it should be treated with a muscarinic anticholinergic agent such as hyoscyne sulfate 0.125mg that is taken with each pyridostigmine dose up to three times a day.

Percy Lavon Julian was a chemist who started his career at DePauw University and he and his team synthesized physostigmine.

Figure 17

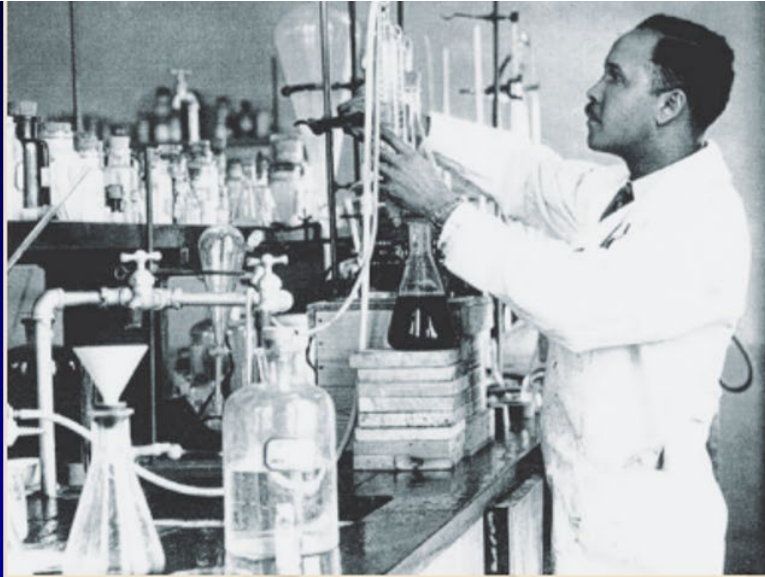
What Did Percy Lavon Julian do for MG?

1935-

- Synthesized physostigmine
- Previously extracted naturally from Calabar bean

1950-

- Synthesized cortisol from soybean extracts previously from adrenal glands



Percy Julian in the laboratory at DePauw during his tenure as a research fellow. Julian directed qualified DePauw chemistry seniors in fundamental research. In a span of 4 years, 11 senior papers from DePauw students were published in the *Journal of the American Chemical Society*.

Prior to that, physostigmine had to be extracted naturally from Calabar beans which was the source of the drugs that Mary Walker used.

The use of corticosteroids for MG

The synthesis of acetylcholinesterase inhibitors by Dr. Julian's team was a huge breakthrough in MG.

For this reason alone, he should be considered a hero in our understanding and treatment of MG.

However, he should perhaps be even better remembered for the discovery in the 1950s in which his team synthesized cortisol from soybean extracts.

Previously cortisol had to be extracted from adrenal glands. His technique revolutionized the use of corticosteroids for many diseases.

Figure 18

Prednisone Rx for MG

- High Dose
 - 60 to 100 mg/day x 2 weeks
 - Then 60 to 100 mg qod until much better
 - Then taper 5 mg q 2 wks.
 - Requires initial inpatient admission
- No randomized trial of prednisone in general MG, but it works!
- Probably most effective drug for MG
 - Even given potential side effects
- Low / Slow Approach
 - Seybold & Drachman 1974
 - Gradual increase to avoid initial worsening
 - 10 mg/day; increase by 10 mg q 5-7 days
 - Then switch to qod
- In-between Approach
 - Mycophenolate trial protocol
 - Pred 20 mg/day

BENEFIT FROM ALTERNATE-DAY PREDNISONE IN MYASTHENIA GRAVIS
JOHN R. WARMOLTS, M.D., AND W. KING ENGEL, M.D.

Abstract Five adults with myasthenia gravis of varying severity and duration were treated with long-term, high-dose (100 mg), alternate-day oral prednisone. Improvement in muscle function appeared 24 to 72 hours after the initiation of therapy and has been maintained from day 17 to 13 months. Complete remission of symptoms was obtained in one patient in four months and has been maintained for 13 months.

Case Reports
Case 1 (NHS 87-287): A 44-year-old man had had mild ocular and limb muscle weakness for 8 years. Loss of consciousness after a dose of valproic acid and urinary incontinence led to admission to the hospital. He had a 10-month history of weight loss, increasing hunger and excessive sweating and tachycardia. He had severe orthostatic hypotension and had been treated with a variety of drugs, including anticholinergics, antihypertensives, and antidiarrheals. He had a 10-month history of weight loss, increasing hunger and excessive sweating and tachycardia. He had severe orthostatic hypotension and had been treated with a variety of drugs, including anticholinergics, antihypertensives, and antidiarrheals.

Case 2 (NHS 88-752): A 19-year-old girl, with 7 months of fluctuating ocular weakness and fatigability of her muscles, had had limb muscle weakness and weakness of her respiratory muscles and had been treated with a variety of drugs, including anticholinergics, antihypertensives, and antidiarrheals.

EFFICACY OF PREDNISONE FOR THE TREATMENT OF OCULAR MYASTHENIA (EPITOME): A RANDOMIZED, CONTROLLED TRIAL
MICHAEL BENATAR, MD, PhD, MICHAEL P. HADENOTT, PhD, DONALD R. SANDERS, MD, DR. I. WOLFE, MD, RICHARD J. SANDSON, MD, RICHARD J. NORDA, MD, MICHAEL HEHR, MD, VERA JESU, MD, RAND KATZBERG, MD, HABI FARUQ, MD, AND THE MUSCLE STUDY GROUP (MSG)

Abstract Introduction: In this study we evaluated the safety, efficacy, and effect of prednisone in patients with ocular myasthenia gravis (OMG). Objective: To evaluate the efficacy of prednisone in patients with ocular myasthenia gravis (OMG). Design: Randomized, controlled trial. Setting: A tertiary care center. Participants: Patients with OMG who were able to participate in a randomized, controlled trial. Interventions: Patients were randomized to receive either prednisone (60 mg/day for 2 weeks, then tapered to 5 mg/day) or placebo. Measurements and Main Results: The primary endpoint was the proportion of patients who achieved a 50% or greater improvement in the primary endpoint (P=0.001). Secondary endpoints included the proportion of patients who achieved a 75% or greater improvement in the primary endpoint (P=0.001), the proportion of patients who achieved a 100% improvement in the primary endpoint (P=0.001), and the proportion of patients who achieved a 100% improvement in the primary endpoint (P=0.001).

Planned 88 patients
11 randomized (6 pred/5 plac)
Up to 60 mg/day
Failure to reach remission
 – 100% PLAC
 – 17% PRED
NNT 1.2

Warmolts, Engel. 1972;17-20

Benatar et al. Muscle Nerve. 2016; 53(3)363-9.

While high-dose prednisone therapy is used to treat MG, it has been observed that if you put a generalized MG patient on high-dose prednisone therapy (60 to 100 mg a day), a small percentage of patients will have transient worsening during the first week of therapy.

Therefore, when an MG patient is placed on 60 to 100 mg a day of prednisone this should be done when they are in a hospital setting, and this usually is when they are in crisis on a ventilator or experiencing severe worsening that requires hospitalization. When starting prednisone as an outpatient, what has been used for decades is the go-low and slow escalation approach developed by Drs. Marjorie Seybold and Dan Drachman in the 1970s. In this approach, the patients start on 10 mg a day of prednisone, and every week you increase by 10 mg up to the target dose that you wish to reach. At some point, the patient can be switched to every other day to reduce the side effects. A third approach came out of our experience performing the Muscle Study Group mycophenolate mofetil trial

66

in MG. During that trial all new MG patients were placed immediately on 20 mg a day of prednisone and either mycophenolate mofetil or placebo.

We learned in this study that a patient can be put immediately on prednisone of 20 mg a day and a benefit could be achieved without increasing the dose in many patients.

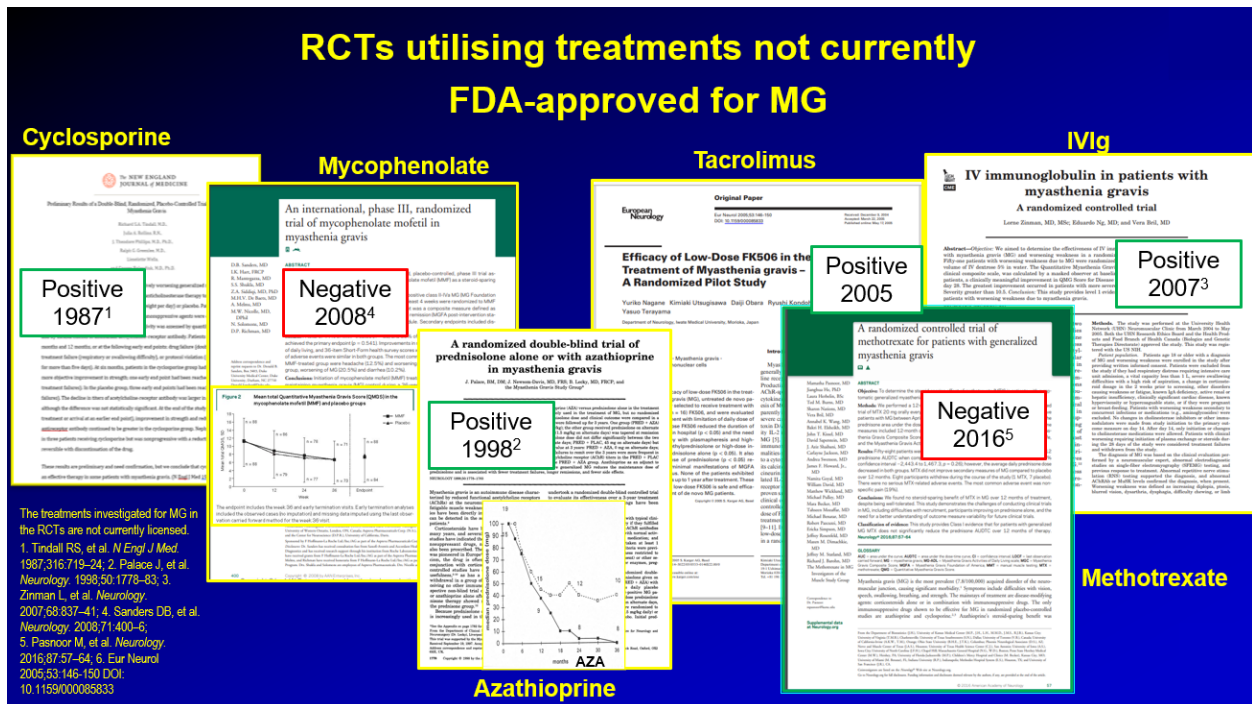
There are no randomized controlled trials of oral prednisone for generalized MG, but we all know from years of using the drug in MG that it is effective. We do have a small randomized controlled trial in ocular MG that was led by Dr. Michael Benatar and showed a dramatic effect of prednisone compared to a placebo in ocular MG patients (Figure 18). Essentially all of the ocular patients on prednisone got better but none of the patients on placebo improved.

The first paper that used high-dose prednisone in MG was authored by Drs. John Warmolts and King Engel at the NIH in 1972, and this was another landmark paper in the history of MG (Figure 18). The MG patients they reported improved dramatically even though this was not a placebo-controlled trial.

Other non-FDA approved immunosuppressive drugs for MG

Between the 1970s until the advent of the new biologic drugs a number of immunosuppressive drugs have been used to treat MG patients with varying degrees of success. A number of randomized control trials with these drugs have been performed and published (Figure 19).

Figure 19



Azathioprine (Imuran)

Azathioprine is effective in MG, but the problem with the drug is that it does not have an effect for at least a year and does not have its maximal effect for 18 months after it is started (Figure 20).

Therefore, it is not a drug that is used to improve MG patient symptoms in the near term.

Azathioprine is used to decrease patient dependency on prednisone in the long term.

In general, we do not believe that a generalized MG patient and also an ocular MG patient can be managed without initially using prednisone. You can occasionally avoid prednisone in a small number of patients but generally, you have to use immunosuppressive therapy in the form of corticosteroids to see an initial improvement in a MG patient. Our view on this may change over time but currently, we use prednisone in all of our generalized MG patients once they get the maximum benefit from pyridostigmine. But we place greater emphasis now on trying to reduce prednisone to lower doses as

quickly and safely as possible with the help of other therapies as part of the goal of limiting corticosteroid-related side effects.

Figure 20

Azathioprine (Imuran) Rx for MG

- Purine analog - blocks DNA/RNA synthesis and cell proliferation
- Response is slow - up to 18 months
- Dose: Begin 50 mg/day x 1 week, Then, 2-3 mg/kg/day
- **Typical dose 150 mg/day (single dose)**
- Toxicity
 - Systemic “flu-like” reaction
 - Leukopenia
 - Hepatotoxicity
- Monthly CBC/LFTs
- We do not use Thiopurine Methyltransferase (TPMT) test

- High dropout (34 to 18)
- Take at least a year to have an effect

A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis

J. Palace, BM, DM, J. Newsom-Davis, MD, FRB, B. Locky, MD, FRCP, and the Myasthenia Gravis Study Group*

Article abstract—We compared prednisolone (PRED) and azathioprine (AZA) versus prednisolone alone in the treatment of MG. Prednisolone alone or combined with azathioprine is widely used in the treatment of MG, but no randomized placebo-controlled comparative trial data are available. The prednisolone dose and clinical outcome were compared in a multicenter randomized double-blind study of 34 MG patients who were followed up for 3 years. One group (PRED + AZA) received prednisolone on alternate days plus azathioprine 1.5 mg/kg, the other group received prednisolone on alternate days plus placebo (PRED + PLAC). Initial high-dose prednisolone (1.5 mg/kg on alternate days) was tapered at discretion to the minimal dose required to maintain remission. The prednisolone dose did not differ significantly between the two groups at 1 year (median values: PRED + AZA, 27.5 mg on alternate days; PRED + PLAC, 43 mg on alternate days) but was reduced at 2 and 3 years in the PRED + AZA group (median value at 3 years: PRED + AZA, 9 mg on alternate days; PRED + PLAC, 40 mg on alternate days).

Palace J et al. Neurology 1998; 50 (6) 602-605

| Months | Placebo (%) | AZA (%) |
|--------|-------------|---------|
| 0 | 100 | 100 |
| 6 | 90 | 90 |
| 12 | 75 | 75 |
| 18 | 60 | 60 |
| 24 | 50 | 40 |
| 30 | 45 | 30 |
| 36 | 40 | 10 |

p = 0.02 at 24 mo.

Cyclosporine and tacrolimus

The next drug after azathioprine that we began using as cyclosporine, again off label. Cyclosporine, like azathioprine, was first developed to suppress the immune system on patients undergoing organ transplantation. There were two cyclosporine randomized controlled trials for MG performed at University of Texas Southwestern, showing that cyclosporine was effective in improving patients with MG compared to placebo (Figure 21).

Figure 21

Cyclosporine in MG

- Selective/reversible on T-cells
 - Inhibit IL-2 and interferon γ
 - Inhibits cytotoxic/express supp T_s
- 1987 - CSA Effective in non-immunosuppressed MG
 - 20 patients
- 1993 - CSA Effective in Steroid-Dep MG
 - 39 patients
- QMG - Primary End-Point
- In 1993 Study:
 - Mean Dec QMG 3.5 in CSA
 - Mean Dec QMG 0 in Placebo
- Sandoz industry study: results never released
- **Dose-100 mg tabs; usually 1 tab twice a day**
- Check monthly kidney function and CSA blood level

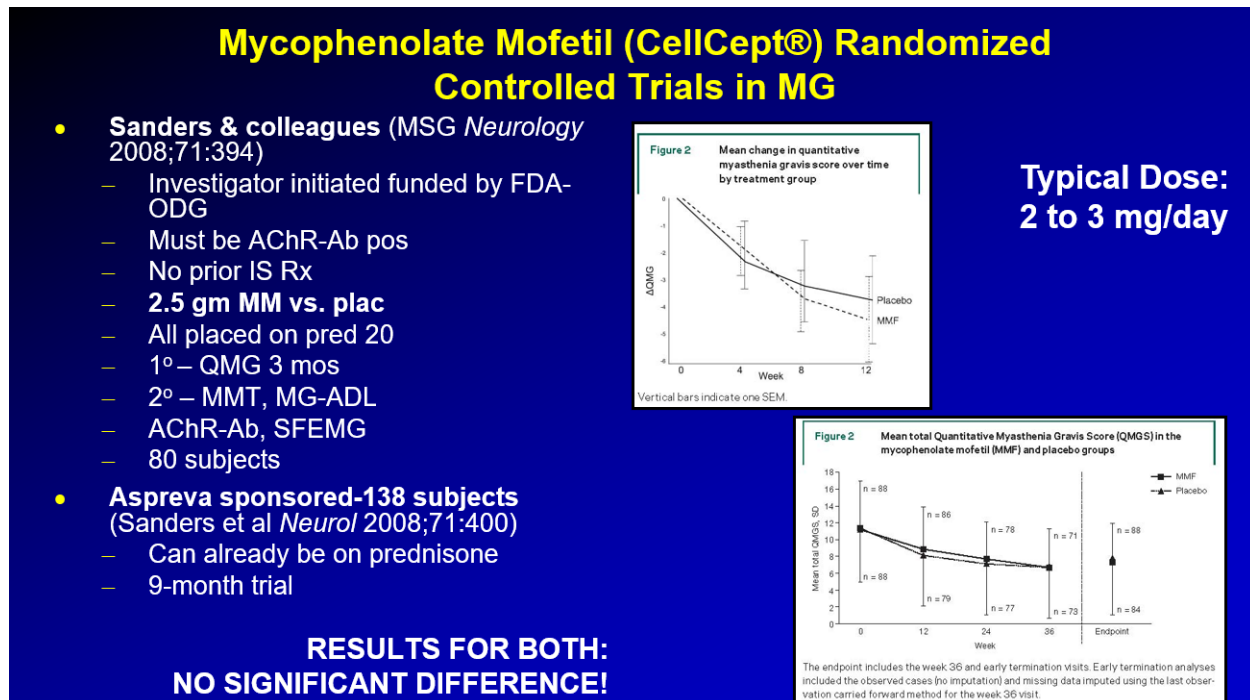
Tindall et al 1987 & 1993

Therefore, in the mid and late 1980s and into the 1990s some of us were using a lot of cyclosporine for our MG patients. When it has an effect, this seems to occur in two to four months. Compared to others, it is a somewhat challenging drug to use because you have to monitor renal side effects, blood pressure and drug interactions very closely.

Mycophenolate Mofetil

Many of us stopped using cyclosporine as often in MG when the drug mycophenolate mofetil (CellCept) became available, primarily because it had fewer side effects and was easier to monitor (Figure 22).

Figure 22



While mycophenolate mofetil is still used by many neurologists to treat MG, there have been two very good randomized controlled trials of mycophenolate mofetil in MG compared to a placebo. Both studies were negative; there was no hint of positivity at all in either study. So while this has dampened our enthusiasm for mycophenolate mofetil, it does not mean that we never use mycophenolate mofetil in MG, but in some clinics, it has lost its placement as a second-line drug for MG.

Methotrexate

When we had the results of the negative mycophenolate mofetil trials we then searched for another oral drug to test in MG, and we turned to the very old compound methotrexate which was originally developed in the 1940s for cancer treatment.

Figure 23

Phase II Trial of Methotrexate in MG

Barohn and Muscle Study Group

FDA OPD R01 FD003538/IND #101,306

- A randomized, double-blind, placebo-controlled study
- 50 patients
 - 25 receiving MTX; 20mg/week
 - 25 receiving placebo/12 mo. study
- Hypothesis – adding MTX therapy will improve the MG manifestations so that prednisone dose can be reduced and clinical measures of MG severity will improve
- The primary measure of efficacy will be the 9-month prednisone area under the curve
- Secondary: QMG, MG ADL, MG Comp, MG QOL15
- 20 sites – KUMC, UTSW, UTSCSA, UC-Irvine, OSU, U. North Carolina, U. Virginia, UCSF – Fresno, U. Miami, U. Indiana, MGH, CPMC, U. Iowa, Toronto, Phoenix, Methodist, NM Center Houston, Penn State, U. Florida, U. Toronto
- Conclusion: no difference in pred. dose, but trend in MG ADL/ QMG**
- Considering new trial with subcutaneous dosing**

Oral Dose: 15 to 20mg/week

Monthly CBC, LFTs

Pasnoor et al. *Neurology* 2016;87:57-64

A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis

2016

ABSTRACT

Objective: To determine the steroid-sparing effect of methotrexate (MTX) in patients with seronegative generalized myasthenia gravis (MG).

Methods: We performed a 12-month, multicenter, randomized, double-blind, placebo-controlled trial of MTX (15 to 20 mg weekly) versus weekly oral prednisone (10 to 20 mg) in 50 seronegative patients with MG between April 2010 and August 2014. The primary outcome measure was the prednisone area under the curve (AUC) over 12 months. Secondary outcome measures included 12-month changes of the Quantitative Myasthenia Gravis Score, the Myasthenia Gravis Composite Score, Manual Muscle Testing, the Myasthenia Gravis Quality of Life, and the Myasthenia Gravis Activities of Daily Living.

Results: Fifty-eight patients were screened and 50 received MTX. MTX did not reduce the month 8-12 prednisone AUC (when compared to placebo) (MTX = 4883.0 mg, 95% confidence interval = 2342.4 to 7423.2; p = 0.20). However, the average daily prednisone dose decreased in both groups. MTX did not improve secondary measures of MG compared to placebo over 12 months. Eight participants withdrew during the course of the study. MTX was tolerated. There were no serious MTX-related adverse events. The most common adverse event was non-serious diarrhea.

Conclusions: We found no steroid-sparing benefit of MTX in MG over 12 months of treatment, despite being well tolerated. This study demonstrates the challenges of conducting clinical trials in MG, including difficulties with recruitment, patient adherence on prednisone alone, and the need for a better understanding of outcome measure variability for future clinical trials.

Classification of evidence: This study provides Class I evidence that for patients with seronegative MG, MTX does not significantly reduce the prednisone AUC over 12 months of therapy. [NCT01481874](#)

KEY WORDS: Myasthenia gravis, methotrexate, prednisone, randomized controlled trial, steroid-sparing effect

DISCUSSION: The objective of this study was to determine the steroid-sparing effect of methotrexate (MTX) in patients with seronegative generalized myasthenia gravis (MG). We performed a 12-month, multicenter, randomized, double-blind, placebo-controlled trial of MTX (15 to 20 mg weekly) versus weekly oral prednisone (10 to 20 mg) in 50 seronegative patients with MG between April 2010 and August 2014. The primary outcome measure was the prednisone area under the curve (AUC) over 12 months. Secondary outcome measures included 12-month changes of the Quantitative Myasthenia Gravis Score, the Myasthenia Gravis Composite Score, Manual Muscle Testing, the Myasthenia Gravis Quality of Life, and the Myasthenia Gravis Activities of Daily Living. Results: Fifty-eight patients were screened and 50 received MTX. MTX did not reduce the month 8-12 prednisone AUC (when compared to placebo) (MTX = 4883.0 mg, 95% confidence interval = 2342.4 to 7423.2; p = 0.20). However, the average daily prednisone dose decreased in both groups. MTX did not improve secondary measures of MG compared to placebo over 12 months. Eight participants withdrew during the course of the study. MTX was tolerated. There were no serious MTX-related adverse events. The most common adverse event was non-serious diarrhea. Conclusions: We found no steroid-sparing benefit of MTX in MG over 12 months of treatment, despite being well tolerated. This study demonstrates the challenges of conducting clinical trials in MG, including difficulties with recruitment, patient adherence on prednisone alone, and the need for a better understanding of outcome measure variability for future clinical trials. Classification of evidence: This study provides Class I evidence that for patients with seronegative MG, MTX does not significantly reduce the prednisone AUC over 12 months of therapy. NCT01481874

Many of us have been using methotrexate for years for dermatomyositis and polymyositis and we were comfortable using it. We thought that it could be effective in MG. We and others had anecdotal experience of MG patients improving on methotrexate. Our team designed a trial, randomizing patients to methotrexate versus placebo. It was a one-year trial in which patients received methotrexate 20 mg or placebo once a week. In this trial we used oral methotrexate, but subcutaneous methotrexate is also an option and probably produces higher blood levels and may be more effective.

In the research trial, we enrolled 50 patients at 20 sites in the US and Canada. We made a decision to use as our primary endpoint the cumulative prednisone dose the patient received during the trial. Our secondary endpoints were the MG-ADL score described earlier and the quantitative MG (QMG) score, an objective measure of strength.

To our disappointment, the study was negative using our primary endpoint of prednisone dose. In other words, patients on methotrexate did not have lower prednisone requirements than those on placebo.

On the other hand, our secondary endpoints were very close to nearing statistical significance. We believe that if we would have chosen the MG-ADL score as our primary endpoint we would have had a better chance of demonstrating that methotrexate was effective in MG. Many of us still believe that methotrexate is effective in some MG patients. In the future we hope to investigate further the use of methotrexate in MG and perhaps to use the subcutaneous delivery method.


Intravenous Immunoglobulin (IVIg)

The MG community began using IVIG for MG in the 1990s. This was about the same time we began using IVIG for Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), and dermatomyositis. IVIG is still not FDA-approved for MG. There has been one well-designed randomized control trial from Canada which showed IVIG was more effective than placebo in MG patients (Figure 24).

Figure 24

IV Immunoglobulin in Patients with Myasthenia Gravis

- 51 pts IVIg vs. placebo
- QMG: Sig dif at day 14 ($p=0.047$)
- Persisted at day 28
- Change in
 - IVIg: -2.54
 - Placebo: -0.89
- Post intervention status at day 14
 - IVIg imp 25%
 - Placebo imp 6%
- RNS/SFEMG-no sig diff
- Meriggioli editorial:
 - Getting enough “bang for the buck”



The Canadians Save the Day!

IV immunoglobulin in patients with myasthenia gravis
A randomized controlled trial

Lorne Zinman, MD, MSc; Eduardo Ng, MD, and Vera Bril, MD

Abstract—Objective: We aimed to determine the effectiveness of IV immunoglobulin (IVIg) in the treatment of patients with myasthenia gravis (MG) and worsening weakness in a randomized, placebo-controlled, masked study. **Methods:** Fifty-one patients with worsening weakness due to MG were randomized to infusion with 2 g/kg of IVIg or an equivalent volume of IV dextrose 5% in water. The Quantitative Myasthenia Gravis (QMG) Score for Disease Severity, a validated clinical composite score, was calculated by a masked observer at baseline and days 14 and 28. **Results:** In IVIg-treated patients, a clinically meaningful improvement in QMG Score for Disease Severity was observed at day 14 and persisted at day 28. The greatest improvement occurred in patients with more severe disease as defined by a QMG Score for Disease Severity greater than 10.5. **Conclusion:** This study provides level 1 evidence for the effectiveness of IV immunoglobulin in patients with worsening weakness due to myasthenia gravis.

NEUROLOGY 2007;68:837-841

Acquired myasthenia gravis (MG) is mediated by two autoantibodies: acetylcholine receptor antibodies (AChRAB) and antibodies to muscle-specific tyrosine kinase (MuSK).^{1,2} AChRAB lead to clinical weakness by blocking and accelerating degradation of acetylcholine receptors, thus impairing neuromuscular transmission,^{3,4} but it is unknown if MuSK behave in the same fashion. Successful treatment of MG requires attenuation or elimination of the aberrant immune process using immunosuppressive medications and immunomodulation therapy.^{5,6} IV immunoglobulin (IVIg) is an immunomodulatory treatment commonly used in patients with MG with a clinical exacerbation requiring a rapid improvement in strength, who are intolerant of or fail immunosuppressive therapy or who live in centers lacking plasma exchange facilities,^{7,8,9} but the efficacy of IVIg in these patients is controversial.^{10,11} The most recent Cochrane Review concluded that there is insufficient evidence from randomized, controlled trials to determine if IVIg treatment improves functional outcome in patients with chronic MG.¹² Therefore, we sought to determine the effectiveness of IVIg vs placebo in patients with MG in an appropriately powered, double-masked, randomized, controlled clinical trial.

Methods. The study was performed at the University Health Network (UHN) Neuroimmunology Clinic from March 2003 to May 2005. Both the UHN Research Ethics Board and the Health Product and Food Branch of Health Canada, (Hilgates and Genetic Therapies Directorate) approved the study. This study was registered with the US NIH.

Patient population. Patients age 18 or older with a diagnosis of MG and worsening weakness were enrolled in the study after providing written informed consent. Patients were excluded from the study if they had respiratory distress requiring intensive care with admission, a vital capacity less than 1 L, severe swallowing difficulties with a high risk of aspiration, a change in corticosteroid dosage in the 2 weeks prior to screening, other disorders causing weakness or fatigue, known high delirium, active renal or hepatic insufficiency, clinically significant cardiac disease, known hypersensitivity or hypercoagulable state, or if they were pregnant or breast-feeding. Patients with worsening weakness secondary to noncurrent infections or medications (e.g., aminoglycosides) were excluded. No changes in cholinesterase inhibitors or other immunomodulators were made from study initiation to the primary outcome measure on day 14. After day 14, only initiation or changes to cholinesterase medications were allowed. Patients with clinical worsening requiring initiation of plasma exchange or steroids during the 28 days of the study were considered treatment failures and withdrawn from the study.

The diagnosis of MG was based on the clinical evaluation performed by a neuroimmunologist, abnormal electrophysiological studies on single-fiber electromyography (SFEMG) testing, and previous response to treatment. Abnormal repetitive nerve stimulation (RNS) testing supported the diagnosis, when present. Abnormal AChRAB or MuSK levels confirmed the diagnosis, when present. Worsening weakness was defined as increasing fatigue, ptosis, blurred vision, dysarthria, dysphagia, difficulty chewing, or limb

Zinman, Eduardo, Bril *Neurology* 2007; 68:837-881

Figure 24 shows a very important article for you to know about. This is the results of the research trials which showed that IVIG is more effective than placebo in a well-designed randomized control trial. It is the best information available to make the case to insurance companies when you are trying to convince them to cover the cost of IVIG in a MG patient. The use of IVIG for MG is similar to the dosing used in CIDP. There is a 2 gram per kilogram loading dose followed by monthly doses of one gram per kilogram. The biggest mistake we have observed by practitioners using IVIG is that they do not continue the chronic maintenance therapy monthly after the loading dose. We recommend monthly maintenance therapy continue for six months and then the patient may be reevaluated to see if the drug has been effective and if it needs to be continued. Usually if the drug has been effective it does need to be continued for even a longer period of time and stopping the drug will often result in a relapse of symptoms.

Plasmapheresis

Plasmapheresis is a technique in which antibodies are removed from the patient's body by removing their plasma. If the patient's plasma contains harmful antibodies such as those directed against the AChR or MuSK causing MG, then removing the antibodies can result in improvement of MG symptoms and signs.

Figure 25

Plasmapheresis

- Directly removes humoral factors such as autoantibodies, immune complexes, complement and other nonspecific inflammatory mediators
- Remove 3-6 liters of plasma over several hours. Replace with albumin or purified protein fraction (PPF).
- Indications for MG:
 - Crises (on ventilator)
 - Pre-thymectomy
 - Severe MG (not in crises) when initiating or increasing oral immunosuppressive drugs
 - Chronic Rx

Neurol Clin. 2018 May;36(2):311-337

Each plasmapheresis treatment removes 3 to 6 liters of plasma over several hours. Plasmapheresis is most often used in MG when a patient is in crisis and on a ventilator or if the patient is nearly in crisis but not yet on a ventilator, and they are admitted to the hospital for a course of plasmapheresis to avoid further worsening. Occasionally we use plasmapheresis prior to a thymectomy to make the patient stronger in preparation for surgery. However, in the modern era it is less common to use plasmapheresis preoperatively because we try to optimize the patient's status using prednisone and other drugs before the thymectomy.

When we admit the patient for plasmapheresis this generally involves 5 to 10 courses of plasmapheresis over 10 to 20 days. During this time there are other MG medications that are optimized so that when the patient is discharged they will not have to be readmitted when the effect of the plasmapheresis wears off after a few weeks. There are a very small number of patients who require chronic plasmapheresis once or twice a month, particularly MG patients with MuSK antibodies.

We still prefer to use plasmapheresis for our patients in crisis on a ventilator rather than IVIG. We believe plasmapheresis is probably more effective than IVIG in the crisis situation but there is really no comparative effectiveness data on this topic. If your hospital has the ability and experience to use plasmapheresis when an MG patient is in crisis, we would suggest that course of therapy. However, if you are in a hospital that does not have access to plasmapheresis, then loading a patient with IVIG is another option (Figure 26).

Figure 26

**MG Crises
Rx Caveats**

- Begin plasmapheresis ASAP
 - Minimum of 5 exchanges
- Increase steroids to high dose
 - Solumedrol 60 to 100 mg/IV/Day
- Stop pyridostigmine
- Usually on ventilation at least 5 to 7 days

Neurol Clin. 2018 May;36(2):311-337

A minimum of five plasmapheresis treatments should be performed, but usually if a patient is in crisis they will require more and perhaps up to ten. The plasmaphereses are usually performed every other day to allow time for the patient's clotting factors to reaccumulate between exchanges.

While the patient is on the ventilator, corticosteroids should be given in the form of Solu-Medrol IV up to 60 to 100mg a day. Also, while the patient is on a ventilator, one should stop the pyridostigmine, as it will cause excessive oral secretions and complicate airway management. Pyridostigmine does not have

a role in MG crisis. You can restart the pyridostigmine orally when they are extubated and taking oral medications. A myasthenic patient is generally on a ventilator for at least five to seven days in the intensive care unit (ICU).

If the ICU doctors are advocating taking the patient off the ventilator after two to three days when they seem to be improving, there is a need to convince them that the patient needs to be rested on a ventilator for at least five to seven days before attempting extubation.


MG, thymoma, and thymectomy

Thymoma occurs in 15% of MG patients. The reason a chest CT is obtained on all new MG patients, both ocular and generalized, is to search for thymoma. The chest CT is not performed to look for so-called thymic hyperplasia which is a judgement call by the radiologist and can frequently be overinterpreted. The only reason to obtain a chest CT in a MG patient is to look for a thymoma. While a routine chest x-ray can occasionally show a thymoma it is usually only revealed once the thymoma has grown to a large size as shown in Figure 27.

Figure 27

MG and Thymoma

- 15% of MG patients
- Mostly in MG patients > 30 years
- Reason for chest CT in all new MG patients
- If Thymoma patient, thymectomy has to be done.
 - But still have to treat MG with medication
 - Taking out thymectomy often doesn't stop MG symptoms



A.M. Priola, S.M. Priola / *Clinical Radiology* 69 (2014) e230-e235

The chest CT is used to demonstrate the presence of a thymoma in its early stages. Figure 27 shows a thymoma visualized on a chest CT. If a thymoma is identified it is mandatory to do a thymectomy as soon as possible. Before the thymectomy is performed the patient should be put on pyridostigmine, and usually they need to also start prednisone and other drugs to improve their status and stabilize them prior to the thymectomy.

Thymoma is a mandatory reason to have a thymectomy. Thymectomy is also done for MG patients as a form of therapy if they do not have thymoma. This is called non-thymomatous MG and is the most common form of MG. A decision to do a thymectomy is not based on the chest CT in a non-thymomatous patient but based on data discussed below.

Until recently we did not have a randomized controlled trial of thymectomy in MG; now we do.

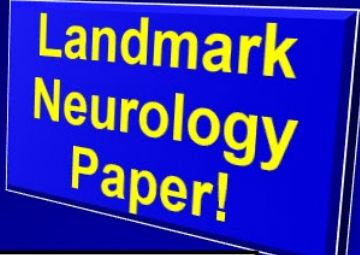
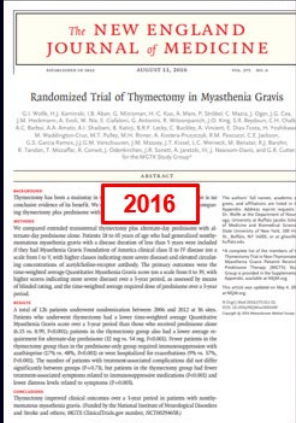
This is another landmark neurology publication, similar to the initial paper describing plasmapheresis treatment for Guillain-Barré syndrome. We consider both to be landmarks in neuromuscular

neurology publications as the result of large multicenter trials that led to a consensus and really changed how we managed patients.

Figure 28

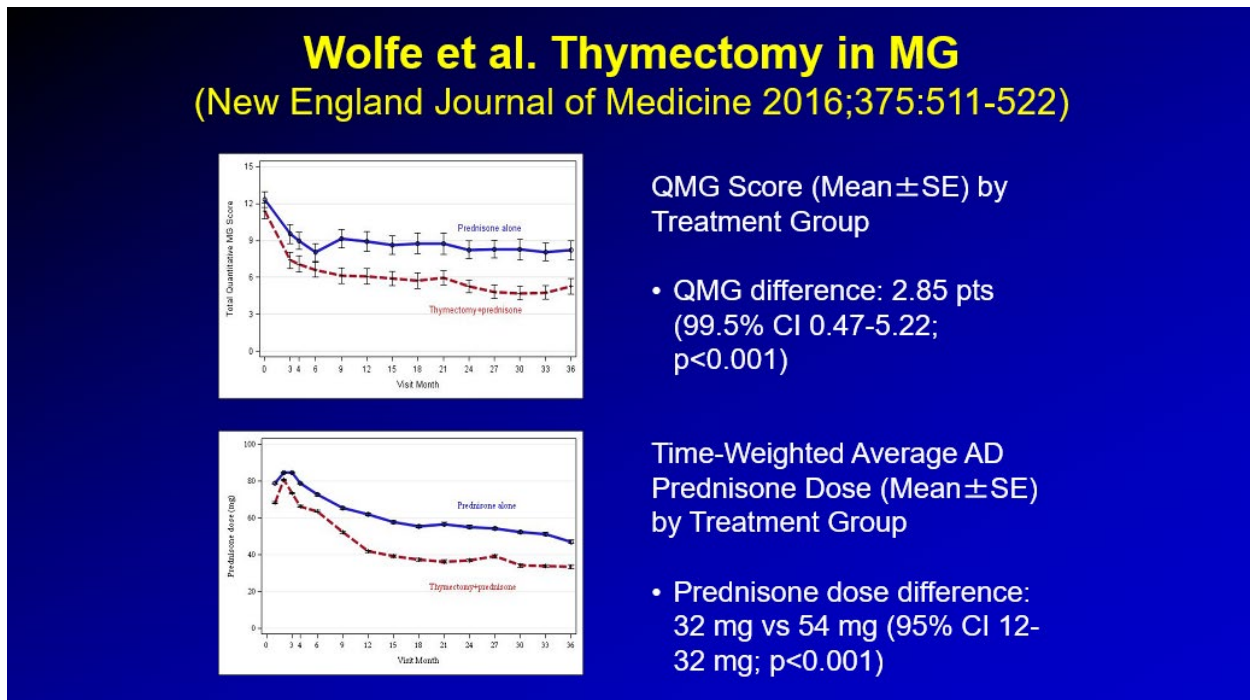
Randomized Blinded Trial of Thymectomy for MG

- Newsom-Davis, Wolfe, Cutter, Kaminski, Jaretski
- Randomized/controlled NIH trial
- REQ – gen, AChR Ab+
- All pts go on prednisone
- All get transsternal thymectomy
- Blinded evaluations
- OUTCOME: Pred dose and QMG at 3 yrs
- QUESTION: Do THY pts do better than pred alone?
- Difficult/slow enrollment but enrollment complete (# 126 patients)
 - Most subjects outside USA
- Wolfe G, et al. *NEJM* 2016;375:511-522

In this international trial, the MG community came together and enrolled over 100 patients and randomized them to either thymectomy or medical treatment. All patients were put on a prednisone-dose protocol and when the patients improved the prednisone was tapered per standardized protocol. What this important study showed was that at four months we can start seeing that patients who receive a thymectomy had a lower prednisone daily dose and also had a lower QMG score indicating improved MG (Figure 29). This data held up in a follow-up study of the same population at five years. Therefore, we now have a controlled trial of thymectomy in MG and to the surprise of many, the study was dramatically positive.

Figure 29




When you advise patients regarding whether or not they want to have a thymectomy, you do need to tell them that the response may not be immediate and that there's no guarantee that the thymectomy will result in an improvement, even though the study showed that overall patients who get a thymectomy are more likely to improve (Figure 30).

Figure 30

Thymectomy for MG Summary

- Now a Controlled Trial Exists! Positive study!
- But Response May Not be Immediate
 - Measured in Months to Years
- No Guarantee of Improvement
- Numerous Procedures
- Thymoma is an absolute indication
- Not rec for:
 - Ocular
 - MUSK+ or LRP+ MG
 - Triple antibody negative MG
 - Very young children
 - Greater than 60, or, ? > 70, or ? > 80
 - (Depends on how old the Rx treating neurologist is!)



The type of procedure that is done for a thymectomy is variable. In the study that we just referred to all patients received identical extended transsternal thymectomies. However, transsternal thymectomies are not done very often today in the age of robotic surgery, so most patients now receive robotic or minimally invasive thymectomy surgery. We do not believe that there is ever going to be a comparative effectiveness research study comparing the various types of thymectomy.

We do not routinely recommend thymectomy for triple antibody-negative MG, but again this is somewhat debatable. We do not do thymectomies in young children who are under the age of two.


Over the years there has been a belief that you should not do thymectomies in someone who is elderly.

But the question is what is the upper age at which you would not do a thymectomy and the answer is not known. In the thymectomy study, patients were allowed to be enrolled up to age 65. But if an MG patient is a healthy 73 year-old should they get a thymectomy? We simply do not know the answer based on data and therefore the decision is left to the physician and the patient.

Complement inhibitors in MG

As we mentioned earlier in this presentation, Dr. Andrew Engel and the group at Mayo Clinic first showed how important the role of complement was at the neuromuscular junction in MG (Figure 3). These early pivotal papers were published in the 1970s and 1980s. As mentioned earlier, one of us (Dr. Barohn) performed a study in the 1990s that measured serum terminal complement levels in MG patients and was able to show that not only were they elevated but the magnitude of increase correlated with disease severity. The recognition of the role of complement in MG ultimately led to the pharmaceutical development industry having an interest in trying complement inhibitors as a therapy for MG. Eculizumab had previously been FDA approved for paroxysmal nocturnal hemoglobinuria (PNH) and hemolytic uremic syndrome (HUS). The pharmaceutical company that developed eculizumab for PNH and HUS then performed phase 2 and phase 3 trials for MG.

Figure 31



2017

Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

Summary

Background Complement is likely to have a role in refractory generalised myasthenia gravis, but no approved therapies specifically target this system. Results from a phase 2 study suggested that eculizumab, a terminal complement inhibitor, produced clinically meaningful improvements in patients with anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis. We further assessed the efficacy and safety of eculizumab in this patient population in a phase 3 trial.

Methods We did a phase 3, randomised, double-blind, placebo-controlled, multicentre study (REGAIN) in 76 hospitals and specialised clinics in 27 countries across North America, Latin America, Europe, and Asia. Eligible patients were aged at least 18 years, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 3 or more, Myasthenia Gravis Foundation of America (MGFA) class II-IV disease, no evidence against botulinum toxin, and previous treatment with at least two immunosuppressive therapies or one immunosuppressive therapy and three intravenous immunoglobulins or plasma exchange for 12 months without complete control. Patients with a history of thrombosis or recent myeloma, thrombocytopenia within 12 months before screening, or use of intravenous immunoglobulin or plasma exchange within 4 weeks before randomisation, or rituximab within 6 months before screening, were excluded. We randomly assigned participants (1:1) to either intravenous eculizumab or intravenous matched placebo for 26 weeks. Dosing for eculizumab was 900 mg on day 1 and at weeks 1, 5, and 9; 1200 mg at week 4; and 1500 mg every second week thereafter as maintenance dosing. Randomisation was done centrally with an interactive voice or web response system with patients stratified to one of four groups based on MGFA disease classification. Where possible, patients were maintained on existing myasthenia gravis therapies and steroid modification was allowed at the study physician's discretion. Patients, investigators, staff, and outcome assessors were masked to treatment assignment. The primary efficacy endpoint was the change from baseline to week 26 in MG-ADL total score measured by worst-task (MG-ADL). The effect population set was defined as all patients who were assigned to treatment groups who received at least one dose of study drug, had a valid baseline MG-ADL assessment, and at least one postbaseline MG-ADL assessment. The safety analyses included all randomly assigned patients who received eculizumab or placebo. This trial is registered with ClinicalTrials.gov, number NCT01997273.

Findings Between April 30, 2014, and Feb 19, 2016, we randomly assigned and treated 121 patients, 62 with eculizumab and 59 with placebo. The primary analysis showed no significant difference between eculizumab and placebo (least-squares mean rank Se = [13.8 + 5] vs [14.3 + 5], rank-based treatment difference = 11.7, 95% CI -24.3 to 6.9, p = 0.809). By death or cause of discontinuation, patients received during the study. The most common adverse events in both groups were headache and upper respiratory tract infection (see [24]) for both events in the eculizumab group and 12 (20%) for both in the placebo group. Rash/serious rash was reported by six (10%) patients in the eculizumab group and 15 (25%) in the placebo group. Six (10%) patients in the eculizumab group and 11 (19%) in the placebo group reported serious events.

Interpretation The change in the MG-ADL score was not statistically significant between eculizumab and placebo, as measured by the worst-task analysis. Eculizumab was well tolerated. The use of a worst-task analysis of approach proved to be an important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result. Further research into the role of complement is needed.

Funding Alexion Pharmaceuticals.

Introduction Refractory generalised myasthenia gravis is a chronic, debilitating, rare disorder of severe muscle weakness resulting from autoantibody-mediated destruction of the neuromuscular junction. Patients with refractory generalised myasthenia gravis, representing

Eculizumab Phase 3 Trial MG Study REGAIN

- Intravenous complement inhibitor
- 62 eculizumab pts/63 placebo
- Rx: weekly IV x 4 weeks then every 2 weeks x 26 weeks
- Primary outcome measure – MGADL change from baseline
- Secondary outcome measures – QMG, MG Composite, MG QOL

Howard JF, et. al. Safety and Efficacy of Eculizumab in Anti-acetylcholine Receptor Antibody-Positive Refractory Generalised Myasthenia Gravis (REGAIN): a phase 3, randomized, double-blind, placebo-controlled, multicenter study. *Lancet Neurol.* 2017;16(12):976-986.

These trials were successful and showed that patients who received intravenous complement inhibitors had improved MG-ADL scores, and other secondary outcome measures including QMG score. Many believe that the development of complement inhibitors for MG is the biggest breakthrough in MG therapy over the last 50 years. This drug is now FDA-approved under the trade name Soliris. The labeling indication says it is indicated for the treatment of adult patients with AChR antibody positive generalized MG. However, the labeling indication approved by the FDA perhaps may be too wide and currently the neuromuscular community uses eculizumab therapy for generalized MG patients that still have persistent signs on immunosuppressive therapy or when immunosuppressive therapy has previously failed.

Figure 32

Eculizumab for Generalized MG

- Eculizumab trade name: Soliris®
- Indicated for the treatment of adult patients with generalized Myasthenia Gravis who are acetylcholine receptor (AChR) antibody positive.
- My Rec: For Generalized MG with persistent symptoms and signs on immunosuppressive therapy
- Given via IV infusion. Recommend dosage regimen:
 - 900mg weekly for first 4 weeks
 - 1200mg for 5th dose 1 week later
 - **1200mg every 2 weeks thereafter**
- Requires meningococcal vaccination prior to starting therapy.

Before a patient receives eculizumab they need to have completed a full meningococcal vaccination regimen.

For the first month, eculizumab is administered weekly and after that, the infusions are given every two weeks. These can be done either in an outpatient hospital setting or at home.

After the release of eculizumab the same pharmaceutical company released ravulizumab (tradename Ultomiris). The major advantage of ravulizumab is that it can be administered every 8 weeks intravenously (Figure 33). Figure 33 shows the recommended loading and maintenance doses for ravulizumab. More recently, zilucoplan (Zilbrysq), another complement inhibitor, was FDA approved (Figure 13). The advantage of zilucoplan is that the drug is self-administered subcutaneously as a quick injection daily. Immunization guidelines for meningococcus have been recently updated by the Advisory Committee on Immunization Practices (ACIP) and should be closely followed for patient safety. In addition to meningococcus vaccination, clinicians should be aware that the late 2024 ACIP

recommendation is not to start complement inhibitors until after a full immunization series with 3 doses of the meningococcus B vaccine which takes 6 months, or in patients who cannot wait for 6 months, they should receive antibiotic prophylaxis. The 2024 ACIP recommendations state: “Persons on complement inhibitor therapy likely remain at substantially increased risk for meningococcal disease, even if they are fully vaccinated or taking antimicrobial prophylaxis...Persons not up to date with meningococcal vaccinations for whom urgent complement inhibitor therapy is indicated should be provided antimicrobial prophylaxis. Few data are available to guide decision-making regarding the optimal duration of antimicrobial prophylaxis; therefore, the duration of prophylaxis should be determined based on clinical judgment. Providers could consider treating patients with antimicrobial prophylaxis for the duration of complement inhibitor treatment.”

Figure 33

Ravulizumab (Ultomiris)

NEJM Evid 2022; 1 (5)

- New complement inhibitor
- FDA approved in 2022
- Every 8 weeks IV

Dosing

| | <u>Weight</u> | <u>Load</u> | <u>Maintenance</u> |
|--|---------------|-------------|--------------------|
| 1. New Patients | | | |
| Load | | | |
| 1 st maintenance | 40 to <60 kg | 2,400 mg | 3,000 mg |
| Dose day 15 | 60 to <100 kg | 2,700 mg | 3,300 mg |
| Then every 8 weeks | >100 kg | 3,000 mg | 3,600 mg |
| 2. Switching from Eculizumab | | | |
| Loading dose 2 weeks after last Eculizumab | | | |
| Then every 8 weeks | | | |

Rituximab in MG

Rituximab was developed as a treatment for hematologic tumors because it eliminates B-lymphocytes. Due to this action, rituximab was applied to MG and other autoimmune diseases. It is generally believed that rituximab is very effective for patients with MUSK MG even though a randomized controlled trial has never been done in this rare patient population.

We all believe rituximab probably works for most MG patients, but MUSK MG is so rare that a randomized controlled trial may never be performed.

Many in the MG community believe that rituximab is effective in AChR-Ab positive MG based on anecdotal experience. This led to a randomized controlled trial in MG with rituximab in MG and generalized AChR antibody MG (Figure 34).

To our disappointment, the study was negative and did not show any steroid sparing effect compared to placebo.

Figure 34

Rituximab For AChR-Ab Positive Myasthenia Gravis

2021

- Rituximab depletes B-cells that make antibodies
- Study PI – R. Nowack (Yale)
- CoPIs – J. Goldstein, M. Dimachkie, R. Barohn
- Funded by NeuroNext/NIH
- 50 pts; 1:1 randomization
- Subjects enrolled 2014-2016
- Last patient finished April 2017
- Rituximab dose for trial: 375 mg/m² IV weekly x 4 Repeat in 6 months
- Results AAN 2018: Negative study! No difference in Prednisone dose, QMG, MG-ADL, other 2 end points. Publication pending.
- But, Rituximab probably works in MuSK MG-all case reports

Neurology Dec 2021; 98(4):e376-e389

Moore recently, a rituximab study out of Sweden suggested that there might be a benefit in recent onset AChR antibody positive MG.

Fc receptor blockers

Another new class of drugs that has shown to be effective in MG is neonatal Fc receptor blockers.

Efgartigimod decreases the level of all IgG that a human produces through blocking the FcRn receptor (Figure 35). This novel mechanism of action promotes intracellular lysosomal degradation of IgG. The FcRn is critical for maintaining IgG through rescuing IgG from lysosomal degradation and allowing it to exit the cells after entry as part of normal IgG recycling. Therefore, by blocking the FcRn receptorendogenous IgG levels decrease.

A phase 3 trial with this drug in MG was positive and led to FDA approval. As mentioned above, the generic name for the drug is efgartigimod with the tradename Vyvgart (Figure 13). The intravenous

preparation of this drug is on average given as 4 weekly cycles followed by a break for about 4 weeks, but this is also dependent on the patient’s response to therapy. Recently a subcutaneous preparation for this drug has also been FDA approved, efgartigimod SQ, with tradename Vyvgart Hytrulo SQ, as well as another subcutaneous FcRn blocking agent, rozanolixizumab (Rystiggo).

Figure 35

IgG Regulation Through FcRn Blocking: A Novel Mechanism for the Treatment of Myasthenia Gravis

Neonatal Fc Receptor (FcRn) – Critical for maintaining IgG through rescuing from lysosomal degradation.

FcRn blocking agents prevent, reduction of IgG, including IgG autoantibodies

2021

Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial

Howard JF, Smith AG, Taylor TH, Green DM, et al. *Lancet* 2021; 397:165-176.

Summary

Background There is an unmet need for treatment options for generalised myasthenia gravis that are effective, targeted, well tolerated and can be used in a broad population of patients. We aimed to assess the safety and efficacy of efgartigimod (MG-ADL) in a broad population of patients with generalised myasthenia gravis.

Methods ADAPT was a randomised, double-blind, placebo-controlled, phase 3 trial done at 16 international academic and community centres in 11 countries in North America, Europe, and Japan. Patients aged at least 18 years with generalised myasthenia gravis were eligible to participate in the study, regardless of anti-acetylcholine receptor antibody status, if they had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 1 (50% non-responders), and were on a stable dose of at least one treatment for generalised myasthenia gravis. Patients were randomly assigned by interactive response technology (1:1) to efgartigimod (19 mg/kg or matching placebo), administered as four infusions per cycle (two infusions per week), repeated as needed depending on clinical response or response from 4 weeks after initiation of the previous cycle. Patients, investigators, and clinical staff were all blind to treatment allocation. The primary endpoint was proportion of anti-acetylcholine receptor antibody-positive patients who were MG-ADL responders (≥2-point MG-ADL improvement sustained for ≥4 weeks) in the first treatment cycle. The primary analysis was done in the randomised-intention-to-treat population of all anti-acetylcholine receptor antibody-positive patients who had a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment. The safety analysis included all randomly assigned patients who received at least one dose or part dose of efgartigimod or placebo. This trial is registered at ClinicalTrials.gov (NCT04005650), an open-label register for ongoing RCTs (NCT04005650).

Findings Between Sept 5, 2018, and Nov 20, 2020, 167 patients (81 in the efgartigimod group and 86 in the placebo group) were enrolled, randomly assigned, and treated. 128 (77%) were anti-acetylcholine receptor antibody positive. Of these patients, most of those in the efgartigimod group were MG-ADL responders (≥2-point MG-ADL to total 4 due to the efgartigimod group (91 [70%] of 130) with an odds ratio of 4.95 (95% CI 2.3–11.1, p=0.0004) (31 [77%] of 40 patients in the placebo group had a total 4 due to the placebo group). 41 (31%) in the efgartigimod group had treatment-emergent adverse events, most being respiratory infections. Efgartigimod (19 mg/kg) and matching placebo (19 mg/kg) were given to 167 patients in the efgartigimod group and 86 patients in the placebo group had a mean disease severity. These patients in each treatment group (9%) discontinued treatment during the study. There were no deaths.

Interpretation Efgartigimod was well tolerated and efficacious in patients with generalised myasthenia gravis. The individualised dosing based on clinical response was a unique feature of ADAPT, and translation to fixed-patient with longer term safety and efficacy data will be further informed by the ongoing open-label extension.

Funding agencies

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Introduction

Generalised myasthenia gravis is a rare, chronic, autoimmune disease that causes debilitating and potentially life-threatening muscle weakness affecting ocular, oropharyngeal, respiratory, and limb muscles. It is caused by autoantibodies against acetylcholine receptor (AChR) and/or muscle-specific tyrosine kinase (MuSK) and functionally important receptor-related proteins (e.g. *LRP4*). A small proportion of patients have no identifiable antibodies. These autoantibodies exert a direct

Efgartigimod Phase 3 Trial in MG

- RCT weekly infusions
- MG-ADL responders
 - 44165 (68%) efgartigimod
 - 19164 (30%) placebo
- Howard JF et al. *Lancet Neurology* 2021; 20:526-536
- FDA approved Dec 2021: Vyvgart

Treatment recommendations for MG

Figure 36

| Myasthenia Gravis | |
|---|---|
| My Rx Recommendations - prior to 2007 | Rx Recommendations – 2025 |
| <ul style="list-style-type: none"> • 1st Line: Tensilon Mestinon Prednisone Thymectomy ? | <ul style="list-style-type: none"> • 1st Line: Pyridostigmine Prednisone Thymectomy ! YES |
| <ul style="list-style-type: none"> • 2nd Line: Azathioprine Mycophenolate Mofetil Cyclosporine | <ul style="list-style-type: none"> • 2nd Line: Azathioprine Cyclosporine/Tacrolimus IVIg |
| <ul style="list-style-type: none"> • 3rd Line: IVIg Plasmapheresis | <ul style="list-style-type: none"> • 3rd Line: Plasmapheresis Complement inhibitors: Eculizumab (Soliris®) Ravulizumab (ULTOMIRIS®) Zilucoplan (Zilbrysq®) FcRn receptor blockers: Efgartigimod (Vyvgart®) Rozanolixizumab (Rystiggo SC®) Efgartigimod SQ (Hytrulo SQ®) |
| | <ul style="list-style-type: none"> • 4th Line: Methotrexate Mycophenolate Mofetil Rituximab |

Figure 36 shows what our recommendations for MG were in 2007 compared to what they are now in 2024. This figure shows us how far we have come in the field of MG.

The first line treatment is pyridostigmine and we now have a generic form.

Prednisone is still the first line immunosuppressive treatment. Thymectomy is also a first line treatment, but usually patients are stabilized first on prednisone.

Second line treatment consists of traditional immunosuppressive drugs that have shown to be positive in randomized controlled trials: azathioprine, tacrolimus, and IVIG although all are off label.

Third line treatment is plasmapheresis, and the new class of FDA approved drugs that either suppress complement or the FcRn receptor blockers.

The fourth line category includes drugs that still have not been shown to be effective in randomized controlled trials such as methotrexate, mycophenolate mofetil, and rituximab.

These drugs may work in selected patients, but they are in the fourth line category as the randomized controlled trials with these drugs so far have been negative. Now, there is extensive discussion among the physicians and patients in the MG community whether the complement inhibitor and FcRn receptor blocking drugs can be used as first or second line therapy. In many instances this is now being done but the practice is somewhat restricted because often insurance companies require that at least two traditional immunosuppressive drugs have been used before one of these new classes of drugs can be tried. We suspect that over time as more data accumulates the newer drugs will be used as first and second line therapy.

Emerging Therapies

Chimeric antigen receptors T (CAR-T) cell therapy has revolutionized the care of patients with many advanced malignancies. CAR-T therapies and other related advanced cell therapy approaches are in clinical trials for autoimmune neuromuscular diseases, including MG. The antigenic targets of CAR-T are either the B-cell maturation antigen (BCMA, a marker of plasmablasts and plasma cells) or the CD19 surface cell marker (expressed on plasmablasts and earlier B-cell lineage cells). The goals are to reset the immune system targeting BCMA⁺ or CD19⁺ cells, to revert to a naïve B-cell phenotype and to impact pathogenic autoantibody production. Steps in these studies include leukapheresis to remove white blood cells from the patient, cell manufacturing (for T-cell enrichment, followed by virus-based transfection of enriched T cells, then cell expansion), and finally by reinfusion under a controlled setting into the patient. Therefore, this autologous approach requires close collaboration and care coordination between neurology, oncology and cell therapy to manage these complex studies. This is to closely monitor for any adverse event such as cytokine-release syndrome and for immune effector cell-associated neurotoxicity syndrome. The aim from these studies is to assess whether these approaches are safe in MG and ultimately whether patients can reach prolonged drug-free disease remission.

Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LEMS) basically comes in two categories: those patients that have cancer and those who do not have cancer.

The cancer patients are usually older men and the non-cancer patients are generally younger women, although of course there are many exceptions.

Both groups have voltage gated calcium channel antibodies in the blood that are directed against the presynaptic terminals and prohibit the release of acetylcholine into the synaptic cleft. The detection of voltage gated calcium channel antibodies is not specific for LEMS. The diagnosis of LEMS requires electrophysiologic confirmation. This can be done even before the voltage gated calcium channel antibody results are obtained.

Figure 37

LEMS

Malignancy/Non-malignancy Assoc.

- LEMS more common in men - 4.7:1 M:F
- Overall 50% have a malignancy
 - 75% Males
 - 25% Females
- Tumor usually small-cell lung CA
- 3% small cell lung CA pts develop LEMS
 - LEMS can proceed tumor detection by many months
- Most young women: non-malignant
- Most old men: malignant

Voltage-Gated Ca⁺⁺ Channel Ab's

- 85% of patients
 - Cancer: 98%
 - No cancer: 90%

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Electrophysiological evidence is obtained via nerve conduction studies when one can show a dramatic increment in the size of the compound muscle action potential either by doing a brief 10 seconds of exercise or by performing 50 Hertz repetitive stimulation.

The treatment of LEMS is twofold: there is symptomatic treatment and there is immunosuppressive treatment. The symptomatic treatment involves giving 3,4 diaminopyridine (Figure 38).

Figure 38

LEMS – Rx Pharmacologic

- 3,4-Diaminopyridine
 - Blocks outward K^+ efflux
 - Increase duration of presynaptic action potential
 - Indirectly prolongs activation of VGCC and increases Ca^{++} entry
 - 10-20 mg tid to qid improves strength
 - Get through:
 - Catalyst FDA approved 2018 for adults: Firdapse® (amifampridine)
 - 10mg tabs
 - Jacobus- Now FDA approved 2019 for pediatric use

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3,4-Diaminopyridine blocks the outward potassium efflux and increases the duration of the presynaptic action potential and thereby indirectly prolongs the activation of voltage gated calcium channels and increases calcium entry.

In essence, it increases the presynaptic release of acetylcholine vesicles into the neuromuscular junction.

This is very effective symptomatic treatment for LEMS patients and improves their strength.

The typical dose is 10 to 20 mg three to four times a day.

There were two FDA-approved forms: one is by Catalyst, and it is called Firdapse; the other was made by Jacobus, but that drug is no longer on the market. In the past we could obtain 3,4-diaminopyridine through compounding pharmacy but this is no longer an option now that an FDA-approved drug exists. Even when you put a patient on 3,4-diaminopyridine you usually still have to treat them with immunosuppressive treatment for LEMS and this involves the same traditional drugs that we use in MG (Figure 39).

Figure 39

**LEMS – Rx
Immunosuppressive**

- Prednisone
- Azathioprine
- Mycophenolate
- Cyclosporine
- Plasmapheresis
- IVIg – only published placebo-controlled study in LEMS

– Bain PG, Motomura M, Newsom-Davis J, et al. *Neurology* 1996;47(3):678-683.

In general, we do not believe that LEMS can be treated without prednisone. Other traditional immunosuppressive treatments can be used including azathioprine, mycophenolate mofetil and cyclosporine. Plasmapheresis and IVIg are also effective in LEMS.

Amazingly there is a placebo-controlled trial of IVIG in LEMS done by the British in the 1990s which showed a positive benefit of the drug compared to placebo.

Therefore, there are a number of treatment options. The bottom line is even if patients have cancer, you as the treating neurologist have to treat LEMS with 3,4-diaminopyridine because treating the cancer alone will not improve the weakness from LEMS.

Many of the patients who have small cell cancers and LEMS will die in a matter of months. Therefore, the goal of the neurologist is to keep them as strong as possible as long as possible so they can enjoy the remaining days that they have.

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