Updates from the fray: rational off-label and over-the-counter prescribing in amyotrophic lateral sclerosis

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Keywords: *Amyotrophic lateral sclerosis, clinical trials, review, off-label prescribing*

ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a terminal condition, which is increasing in incidence. Therapeutic interventions have enjoyed limited success. However, research is progressing, with some promising drug candidates emerging. Patients cannot always wait for the results of large trials. The general practitioner has a central role in management of ALS.

Objective: To review and summarise available evidence evaluating the disease-modifying and life-extending potential of approved medications available off-label or over the counter. To inform doctors and patients of updates in the field and assist their decision-making.

Method: A literature search was conducted of PubMed, UpToDate and Google Scholar from 1st January 2010 until 1st July 2020. Search terms were "amyotrophic lateral sclerosis", "motor neuron(e) disease", "clinical trial", and "treatment", with review articles and clinical trial results evaluated by the author for safety and efficacy. Only literature investigating medications already approved for use in Australia was included.

Discussion: Four experimental candidates were deemed to have a reasonable likelihood of efficacy, and doses/routes of administration were clarified. Possibilities for novel therapies were outlined, and the importance of research support was highlighted.

Introduction

A 65-year-old woman presented to her general practitioner (GP) with foot drop. Neurological examination and neurophysiological studies confirmed sporadic amyotrophic lateral sclerosis (ALS), a terminal condition. Two Australian patients receive this diagnosis daily (1). She was offered standard treatment, including riluzole and medications to relieve symptoms. She sought further therapeutic options in concert with her treating team, but found no clear source of research updates.

Aim

Advances in ALS have been limited. There is some optimism at present, which has not been widely reported. This article presents news of current research into potentially useful disease-modifying and life-extending treatments for this condition, to inform GPs and patients. In particular, evidence for off-label prescribing of approved medications, and over-the-counter medications/supplements, is examined. While robust randomised controlled trials with hundreds of participants provide the strongest evidence of efficacy, ALS patients often cannot wait for these results. There is therefore more freedom applied to the therapies discussed, following demonstration of an adequate safety profile. However, medications are still assessed with reference to available evidence. This article does not outline ongoing clinical trials, as these are changing rapidly. Also, it does not focus on standard treatment, which is covered elsewhere (2).

The treatments discussed in this paper are experimental. This information must be handled with caution and used only in consultation with a neurologist. No assurance is offered that use of these medications for this condition is safe or appropriate for any particular patient. Off-label prescribing remains the responsibility of the prescriber, and treatments should be added in a stepwise fashion to allow observation of benefit and/or side effects. Clinicians should be aware of the limitations of trials with small patient numbers (for example, Phase II trials), even if they show a statistically significant effect. [Lithium (3) and dexpramipexole (4), though initially promising in ALS, were shown to be ineffective in trials with larger patient numbers.]

Method

A literature search was conducted of PubMed, UpToDate and Google Scholar from 1st January 2010 until 1st July 2020. Search terms were "amyotrophic lateral sclerosis", "motor neuron(e) disease", "clinical trial", and "treatment", with review articles and clinical trial results filtered out for closer assessment. Patient-oriented ALS news websites and social media were also consulted to locate relevant sources. All literature was reviewed by the author, with interventions evaluated for safety and efficacy. Only literature investigating medications already approved for use in Australia was included. Pertinent findings were summarised.

Results

- Abacavir/dolutegravir/lamivudine (The Lighthouse Trial)

The role of retroviruses in the pathogenesis of ALS was first suspected following reports of Human Immunodeficiency Virus (HIV) patients presenting with ALS-like symptoms, as well as research demonstrating increased levels of the reverse transcriptase enzyme in ALS patients' serum (5). A search for the causal agent has led to human endogenous retroviruses (HERVs), whose genetic sequences are believed to have become incorporated into the human genome over millions of years (6). One virus, HERV-K, may be responsible for the increased enzyme activity (7).

Abacavir 600mg/dolutegravir 50mg/lamivudine 300mg (marketed as "Triumeq") is a medication used to treat HIV patients. It is highly effective against HERV-K, and easily penetrates the blood-brain barrier. An HLA-B*5701 blood test must be negative prior to administration of any medicine containing abacavir. A 24-week, open-label, Phase IIA trial of Triumeq was commenced in Australia in late 2016 (8). This trial found a decrease in the slope of clinical progression based on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) of around 30%, as well as an effect on biomarkers. The lack of blinding and placebo control were mitigated in part by a 10-week, pre-treatment observation period against which to compare clinical decline.

The trial dose was 1 tablet daily, with no safety concerns or interactions with co-administered riluzole noted. The Lighthouse Trial has now progressed to Phase III.

- Curcumin (ALSUntangled)

Professor Richard Bedlack and the Duke ALS Clinic have made great contributions to this field. Among their projects is "ALSUntangled", which analyses possible alternative and off-label treatments based on several criteria, creating a comprehensive review for each candidate (9). Many treatments examined by the group have received equivocal assessments. One of the more promising is curcumin. Researchers deduced four plausible mechanisms of action involving neuroinflammation, protein aggregation, oxidative stress and the faecal microbiome.

They also identified some positive case reports, as well as three pre-clinical and two clinical studies showing a beneficial effect. All five studies have limitations and are difficult to interpret (10). In this setting, planning for a trial of Integrative Therapeutics' "Theracurmin HP" formulation, at 90mg oral twice daily, is underway at Duke University. This product was chosen on the basis of previous encouraging research in neurodegeneration (11).

Among other proposed treatments, the group posits some value from carnitine supplements. This is again based on feasible mechanisms, laboratory evidence, and a limited clinical trial showing a positive effect. They suggest a theoretical benefit of 1g three times daily of oral acetyl-L-carnitine (12). Some common alternative therapies for ALS (vitamin E, coQ10 and creatine) have poor evidence and might better be avoided (9).

Another project, "ALS Reversals", aims to document and understand rare cases of patients who experience disease remission (13). It has produced intriguing work relating to potential treatments, but has not yet achieved a significant victory.

- Sodium phenylbutyrate/tauroursodeoxycholic acid (The CENTAUR Trial)

Sodium phenylbutyrate was initially approved for use in urea cycle disorders, based on its activity as an ammonia scavenger (14). It is approved in Australia for this indication, as granules for oral administration – however it does not appear readily available. Other mechanisms of sodium phenylbutyrate include ameliorating endoplasmic reticulum stress from misfolded protein accumulation by acting as a chemical chaperone (15), and promoting appropriate transcription by inhibiting histone deacetylase (16). These processes are of interest in neurodegeneration, and the molecule shows some pre-clinical efficacy (16, 17).

Tauroursodeoxycholic acid is a bile acid which has a demonstrated role in some cholestatic liver diseases. It has antiapoptotic actions, likely related to reduced mitochondrial dysfunction. Various studies have documented the role of bile acids in neuroprotection (18). One randomised controlled trial in ALS showed mixed effects (19), and another demonstrated statistically significant slowing of the ALSFRS-R slope (20).

A proprietary combination of these two compounds has been marketed as "AMX0035" by Amylyx Pharmaceuticals Inc. They recruited 137 patients and completed a 24-week Phase II randomised controlled trial in 2019. Results demonstrate statistically significant slowing of disease progression measured by the ALSFRS-R (21). Secondary outcomes included muscle strength, slow vital capacity, and survival. Secondary outcomes were not statistically

significant between groups – although they generally favoured AMX0035. All-cause mortality was evaluated at 35 months, indicating a survival benefit of 6.5 months among participants in the active group (22).

The trial dose was oral sodium phenylbutyrate 3g and tauroursodeoxycholic acid 1g, both twice daily. The researchers plan to move towards regulatory approval.

- Methylcobalamin

Methylcobalamin is an active form of vitamin B_{12} which has demonstrated neuroprotective effects in vitro and in vivo (23, 24). The importance of vitamin B_{12} for neural function is clear, and deficiency can manifest as central or peripheral nervous system pathology. Methylcobalamin reduces homocysteine levels, inhibiting neuronal degeneration (25).

Interest in high-dose methylcobalamin gained momentum in 1998 with the publishing of the first human trial, which demonstrated a statistically significant increase in compound muscle action potential amplitudes among the treated group over 28 days (25). Subsequent trials have yielded some positive results, the most significant of which was a Phase II/III randomised controlled trial of 373 patients over 3 years (26).

Population-wide results of this trial were negative. Among participants who were diagnosed within 12 months of symptom onset, ALSFRS-R decline was reduced and time to death or full ventilatory support was prolonged in post-hoc analysis. The greatest effect was seen with intramuscular methylcobalamin 50mg twice a week. Investigators have sought to confirm these results in a subsequent trial (27).

- Other possibilities

Mild functional benefits were observed in a Phase II trial of tamoxifen 40mg oral daily (28), and a Phase I trial using trimetazidine to modulate ALS hypermetabolism is planned (29). Masitinib, which is approved for treatment of mast cell tumours in dogs, showed a positive effect on ALS progression at 4.5mg/kg oral daily in a Phase II/III trial (30).

Outside the realm of off-label and over-the-counter therapeutics, encouraging clinical trial results for novel compounds and biological interventions have been published. These include mesenchymal stem cell-neurotrophic factor cells (31), autologous regulatory T-lymphocyte infusions (32), CuATSM (33 p. 280), reldesemtiv (34), and others. These (and any) preliminary findings should be interpreted with appropriate caution. To find clinical trials recruiting volunteers, patients should ask their neurologist or Motor Neurone Disease Australia.

Conclusion

This article hopes to provide some direction for the compassionate and inquisitive GP. Patients often have more access to GPs than specialists, and they are an integral source of information and support. GPs may also have the important role of reducing the diagnostic delay (35). As a co-ordinator of care for ALS patients, GP awareness of ongoing scientific inquiry is invaluable. This patient group needs the best chance of asserting control over their disease process.

Historically, many ALS clinical trials protocols have faced design flaws. Some features, including poor outcome measures, lack of blinding and inadequate statistical power, persist in many trials (36). This is clear from the current review. However, recent paradigm shifts have begun to align modern trials with best practice. Watertight clinical trial design is crucial, as it allows for more reliable conclusions to be drawn from earlier data – thereby enabling faster transmission of information to patients (36). A new focus on patient-centered trials is welcome – but validity of results must remain the priority.

Whether current experimental prescribing is ultimately demonstrated to be efficacious in large trials remains to be seen. Regardless, patients may attend appointments equipped with knowledge of research, seeking clarification and guidance. ALS patient groups are increasingly engaged with research, perhaps aided by desperation (37). The informed GP will be familiar with the field, and able to discuss options and temper expectations.

The prognosis and morbidity of ALS necessitate urgent and zealous support of research, and the hastening of approval processes. Drug candidates are frequently stuck in clinical trials for a decade or more, which is highly regrettable. As the incidence increases (38), so does the importance of taking up arms against what the Fight MND Foundation calls “The Beast”.

Acknowledgements

Professor Saxby Pridmore, for his suggestions. Clinical researchers, including Professor Julian Gold, Professor Richard Bedlack, Professor Stanley Appel, and Assistant Professor Sabrina Paganoni, for their kindness and contributions. Dr Mary Pridmore, for her joie de vivre.

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