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REVIEW

Orphan Drugs In Development For The Treatment Of Friedreich's Ataxia: Focus On Omaveloxolone

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Abstract: Friedreich's Ataxia (FRDA) is a devastating and progressive ataxia, marked by mitochondrial dysfunction and oxidative stress. Nrf2 activators such as omaveloxolone (Omav) modulate antioxidative mechanisms, and thus may be viable therapeutic agents in FRDA.

Keywords: FRDA, omaveloxolone, Nrf2 activators, oxidative stress, Omav

Introduction

Friedreich's Ataxia (FRDA) is an autosomal recessive and progressive neurodegenerative disease that leads to ataxia, incoordination, cardiomyopathy, diabetes, and scoliosis.[1] While it is a rare disease, with a measured prevalence of approximately 2 to 4 affected/100,000 people,[2] it is estimated that 1 in 100 people carry the FXN gene.[3] FRDA is most common in inhabitants of or descendants from Western Europe.[4] The mean age of symptomatic onset is 15.5 ± 8 years, but the presentation of symptoms has been noted from individuals aged 8 months to 65 years.[2,4] This variability in age of onset is dependent on the length of the GAA1 expansion, as well as other genetic and environmental factors.[5]

FRDA can be genetically attributed to the homozygous expansion of the guanine-adenine-adenine (GAA) triplet within the first intron of the frataxin gene (FXN) in over 90% of patients. A direct relationship has been identified between the length of the triplet expansion and the severity of the expressed phenotype; those patients with longer repeats demonstrate earlier onset, faster disease progression, and more serious symptomatic presentation. The GAA expansion effectively silences the frataxin gene, and thereby diminishes frataxin production to 5–20% of levels of an unaffected individual.[2,4,6]

Frataxin plays a pivotal role in the formation of iron-sulfur clusters (ISCs), chemical aggregates found in several respiratory chain complexes that direct ATP production. Frataxin deficiency prevents formation of ISCs, resulting in mitochondrial iron accumulation in the dentate nucleus of the cerebellum, fibroblasts, liver, and heart, increased free radicals, oxidative stress, and ultimately cell damage and death.[4,6–8] The progressive degeneration found in FRDA affects the dorsal root ganglia, cortical and spinocerebellar tracts, dorsal columns, gracile and cuneate nuclei, and the efferent cerebellar system.[4]

While not all forms of FRDA present similarly, the cardinal symptoms of the disease include limb and gait ataxia, diminished or absent reflexes, sensory peripheral neuropathy, and dysarthria. Patients exhibit metabolic disorders, skeletal deformations, and cardiomyopathy, the latter being the leading cause of death in individuals suffering

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from FRDA. The progressive nature of the disease often leaves many patients wheelchair bound and lacking self-care abilities.[1,6]

Therapies aimed at alleviating the effects of FRDA are crucial in helping to ameliorate the devastating symptoms associated with the disease and to slow its progression. Several investigations have been conducted to assess the efficacy of proposed therapies, such as idebenone—to treat the cardiac complications of FRDA– and RT001. However, these studies have failed to provide significant and certain results about the benefits for FRDA.[9–11] There are currently no Food and Drug Administration (FDA)-approved therapies for FRDA.

FRDA has been designated an orphan disease, a label ascribed to conditions that affect less than 200,000 people in the United States. Uncommon diseases, like FRDA, are fraught with challenges, including delayed or incorrect diagnosis, limited access to effective drugs, and often exorbitant costs for the few treatments that do exist. The passage of the Congressional Act (Orphan Drug Act, 1983) motivated development of these "orphan drugs" for rare diseases.[12] In the specific case of FRDA, the proliferation of orphan drugs in recent years has been crucial for continued treatment of this devastating disease. This review will examine one such orphan drug, omaveloxolone (Omav).

Omaveloxolone (Omav)

Omav belongs to a specific class of drugs known as nuclear factor erythroid 2-related factor 2 Nrf2 activators. Nrf2 is a transcription factor that plays an important role in protecting cells against oxidative stress; Nrf2 signaling is abnormal in FRDA patients. One pre-clinical study using an FRDA YG8R hemizygous mouse model demonstrated that frataxin deficiency—the notable and common abnormality in FRDA—leads to decreased expression of Nrf2 in dorsal root ganglia,[13] resulting in a mitigated response to oxidative stress. Nrf2 activation has also been shown to increase mitochondrial function in FRDA-derived cells.[14] Omav prevents the ubiquitination of Nrf2 and its subsequent degradation. As a result, it restores Nrf2 levels and permits downstream effects to activate target genes which suppress oxidative stress and inflammation and promote normalized cellular metabolism.[15]

MOXIe (RTA 408)

The MOXIe trial (NCT02255435, Reata Pharmaceuticals Inc) was conducted to assess the safety and efficacy of Omav in patients with FRDA between 2015 and 2017.[15] The trial was a multicenter, double blind, randomized, placebo-controlled Phase 2/3 clinical trial in FRDA patients. Participants were deemed eligible to enter the trial if they had a genetically confirmed diagnosis of FRDA, a modified Friedreich's Ataxia Rating Scale (mFARS) score between 10 and 80 and were age 16 to 40. "mFARS" is an abbreviated form of the FARS, or the Friedreich's Ataxia Rating Scale for clinical assessment of symptoms. Participants were also eligible if they were able to participate in maximal exercise testing: riding an exercise ergometer at 60 rpm for 3 mins without resistance. The exclusion criteria included uncontrolled diabetes (hemoglobin A1c over 11.0), BNP over 200pg/mL, significant cardiac disease, or active infection. The participants were prohibited from taking any other antioxidant supplements at least two weeks prior to the baseline assessment.[15]

The trial was divided into two parts. Part I consisted of a randomized, placebo-controlled, double blind, dose escalation study to assess the safety of multiple oral doses of Omav. Study participants were randomized into a 3:1 ratio of Omav and placebo, and several different doses ranging from 5 mg to 300 mg once-daily were tested. The primary outcome was peak work that was attained during maximal exercise test performance. Secondary outcomes included clinical outcome measures using the "mFARS" scores at 4 and 12 weeks, as well as the timed 25-foot walk, 9 hole peg test, low contrast vision tests, and laboratory testing.[16]

Part 2 of the study enrolled 69 patients; average age upon study entry was 25.6 years and the average age at diagnosis was 15.3 years. Overall, Omav did not improve the peak work load relative to baseline. However, several clinical sites noted that patients with pes cavus could not reach the peak muscle exhaustion due to foot pain. When study data was analyzed in patients without pes cavus, there was an increased peak workload of 6.5 watts at Week 12 compared to baseline ($p = 0.002$). An increase of 4.3 watts was found compared to placebo in this group, although the changes were not statistically significant. In regard to secondary endpoints, Omav improved mFARS scores in a dose dependent manner. When comparing dosages, the highest improvement was seen at 160 mg which showed an average of 3.8 points improvement in mFARS compared to baseline ($p<0.001$) and 2.3 points improvement in mFARS compared to the placebo group. Placebo corrected changes neared statistical significance ($p=0.06$) and were equivalent to approximately one year of progression.[15,17]

Dose-dependent induction of Nrf2 transcriptional target proteins and markers were observed in the study. Ferritin and gamma-glutamyl transferase (GGT) increased from baseline at doses of Omav 80 mg/day or higher. Aspartate aminotransferase (AST) and creatinine kinase (CK), markers of cellular energy metabolism and mitochondrial function, also increased in a dose-dependent manner between 80 mg to 160 mg. Interestingly, a decrease in response at higher concentrations of 300 mg/day was observed. The reason for this phenomenon is unclear and possibly due to negative feedback regulation of the redox system.[15,17]

In regard to safety, Omav was well tolerated with only one discontinuation due to a skin rash at a dose of 40 mg/day. The most common adverse event was mild upper respiratory infection, affecting 21 patients (40%) of the treatment group. Other adverse events include headache, nausea, and arthralgia. Two serious adverse effects were noted, but not considered related to study drug; one person experienced benzodiazepine withdrawal and another suffered from a third degree burn. In terms of prognostic factors, an absence of pes cavus was associated with greater improvement in mFARS scores compared to both baseline and to placebo. However, the age of onset, disease duration, length of GAA repeat, sex, ambulation assist type, or prior scoliosis surgery did not influence the clinical outcome.[15,17]

The second phase of the MOXIe trial is currently ongoing, and consists of a randomized, placebo-controlled, double-blind, parallel-group study aimed at evaluating the safety and efficacy of Omav using change from baseline in mFARS after 48 weeks of treatment as the primary endpoint. Randomized in a 1:1 ratio, subjects either receive the placebo or a 150 mg dose of Omav. Phase 1 demonstrated that a dosage of 160 mg/day was the most efficacious; however, this dosage required multiple capsule administrations. In order to reduce the number of capsules and ease the means of administration, a dosage of 150 mg/day was chosen for Part 2 of the trial, rather than 160 mg/day. Secondary endpoints include the change in peak workload during periodic maximal exercise bike tests for 12 weeks, activities of daily living scale (ADL), the 25-foot timed walk test, the 9-hole peg test, the frequency of falls, and SF-36 scores are tested. An open label extension is currently available for patients who have completed either the first or second portion of the study. This portion of the trial seeks to evaluate the long-term tolerability of Omav at a constant dose of 150 mg.[17]

Transaminase Levels With Omav Use

There are demonstrated increases in transaminase levels—aspartate transaminase (AST) and alanine transaminase (ALT)–with the use of Omav. The increase in transaminases was noted to be dose dependent with levels increasing at lower dosages and reaching their highest point at a dose of 160 mg. It was noted that 12% of subjects treated with Omav experienced increases in their AST and ALT levels compared to 0% of subjects treated with the placebo. The mechanism by which Omav elevates aminotransferases appears to relate to its pharmacologic actions. ALT and AST play a critical role in glucose metabolism, providing energy to cells by catalyzing the reversible transfer of amino groups between alanine and α-ketoglutarate to form pyruvate and glutamate.[18] Thus, the increase in ALT and AST seen with Omav may reflect improvements in glucose metabolism. Moreover, genetic manipulation of Nrf2 has been shown to regulate the induction of aminotransferase genes and the serum activity of ALT and AST. In mice, Nrf2 activity has been shown to directly correlate with aminotransferase enzyme activity. Mice that lack Nrf2 have lower serum concentrations of ALT and AST than do wild-type and genetically-activated Nrf2 (Keap1-knockdown) animals.[19,20] Omav also increases ALT and AST mRNA levels in cell lines derived from non-hepatic tissues, supporting the concept that aminotransferase levels are influenced by Nrf2 status and that transient increases in aminotransferases with Omav may be related to the pharmacology of the drug and not due to intrinsic liver toxicity. Notably, the increases in ALT and AST with Omav are not associated with increases in total bilirubin, and therefore not consistent with signs of hepatotoxicity, which include increased levels of bilirubin, albumin, and overall protein.[15,17] Clinical assessment of the patient to ascertain true hepatic disease is important, including jaundice, ascites, fatigue, nausea, and vomiting.

Other Nrf2 Activators

Other members of the class of Nrf2 activators, such as sulforaphane (SFN) and dimethyl fumarate (DMF), have also been studied for potential positive effects on FRDA.[14] SFN is a naturally occurring Nrf2 activator noted for its anti-inflammatory mechanisms and ability to quickly cross the blood-brain-barrier. DMF, another Nrf2 activator that efficiently crosses the blood-brain-barrier, is an approved treatment for Multiple Sclerosis. In a recent 2017 in-vitro study, the molecules were evaluated for their potential neuroprotective effects on frataxin-silenced neurons. Both DMF and SFN exhibited significant upregulation of Nrf2 and its associated target genes. This was evidenced by tremendous increases in Nrf2 mRNA levels and Nrf2-regulated phase 2 enzymes. Both SFN and DMF effectively reverse oxidative stress buildup and function to protect the neurons from the neurodegenerative phenotype in frataxin deficient cells.[21]

Nrf2 activators mechanism of action make them a viable option in the treatment of many diseases associated with oxidative stress in addition to FRDA, including several neurodegenerative diseases. Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) have all been linked to abnormalities in the Nrf2 pathway.[22]

Conclusion

Investigations into the pathological mechanisms of FRDA have revealed the central role of frataxin deficiency and the subsequent lack of transcription factor Nrf2. Consequently, the Nrf2 activators discussed here as well as the several treatments in development focus on reversing the oxidative stress environment caused by frataxin deficiency. While the discussed orphan drugs show promise in the treatment of FRDA, further investigations must be conducted in order to ensure the efficacy and safety of such drugs, as well as to determine even more therapeutic options.

Clinical trials in a rare disease such as FRDA have resulted in negative or inconclusive results, despite their testing of promising molecules and well-defined targets. Despite our knowledge of the genetic cause of FRDA, the disease is often heterogenous in terms of clinical symptoms, and clinical outcome measures and scales may carry inherent subjectivity. Objective measures, such as cardiopulmonary exercise testing, and the development of biomarkers, would provide more objective study of drug efficacy.

Disclosure

Dr Zesiewicz has received personal compensation for serving on the advisory boards of Boston Scientific, Reata Pharmaceuticals, Inc, and Steminent Biotherapeutics. Dr Zesiewicz has received personal compensation as senior editor for Neurodegenerative Disease Management and as a consultant for Steminent Biotherapeutics. Dr Zesiewicz has received royalty payments as co-inventor of varenicline for treating imbalance (patent number 9463190) and nonataxic imbalance (patent number 9782404). Dr Zesiewicz has received research/grant support as principal investigator/investigator for studies from AbbVie Inc, Biogen, Biohaven Pharmaceutics, Boston Scientific, Bukwang Pharmaceuticals Co, Ltd, Cala Health, Inc, Cavion, Friedreich's Ataxia Research Alliance, Houston Methodist Research Institute, National Institutes of Health (READISCA U01), Retrotope Inc, and Takeda Development Center Americas, Inc. Dr. Meyer is an employee of Reata Pharmaceuticals, Inc. The authors report no other conflicts of interest in this work.

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