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REVIEW

A Milestone in the Treatment of Ataxias: Approval of Omaveloxolone for Friedreich Ataxia

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Abstract

The exciting news about the US FDA approval of omaveloxolone as the first-ever drug to be approved for an inherited ataxia is welcome news for patients and families that deal with this devastating disease as well as for health care providers and investigators with an interest in this and other rare diseases. This event is the culmination of long and fruitful collaboration between patients, their families, clinicians, laboratory researchers, patient advocacy organizations, industry, and regulatory agencies. The process has generated intense discussion about outcome measures, biomarkers, trial design, and the nature of approval process for such diseases. It also has brought hope and enthusiasm for increasingly better therapies for genetic diseases in general.

Keywords Friedreich ataxia · Omaveloxolone · Clinical trial · Nrf 2 · Drug approval

The approval of omaveloxolone by the US FDA as the first-ever approved therapy for Friedreich ataxia (FRDA) is a landmark event that will be applauded not only by patients and families affected by this disabling disease, but also by the numerous clinicians who encounter these patients. In addition, the larger community of providers caring for ataxias and other rare neurological disorders should welcome this benchmark as it provides a paradigm for similar achievements in other disorders. It illustrates the relatively rapid progress that can be achieved in monogenic disorders with the approval occurring 27 years after the identification of a GAA repeat expansion as the cause of FRDA [1]. It also testifies to the effectiveness of the tremendous collaborations between bench work scientists, industry, regulatory agencies, and clinicians knitted together by committed patient support organizations that continue to push the envelope for better treatments for FRDA and envision the hope that one day we will be able to prevent or at least significantly postpone the onset and reduce the severity of FRDA and similar diseases.

The road to this event started immediately after the gene was identified with the recognition of the mitochondrial iron regulatory function of a yeast homolog, *Yfh1* and subsequent work documenting a major role for frataxin in the synthesis of key iron-sulfur cluster moieties needed as components of the electron transport chain and other enzymes [2, 3]. Frataxin deficiency caused by the GAA repeat expansion in the *FXN* gene leads to impairments in these molecules, energy failure, and excess oxidative stress in vitro aggravated by possible iron overload in mitochondria [3]. The findings also led to concepts that can be generalizable to many similar diseases. Gene mutations lead to perturbations of several downstream cellular pathways some of which may be meaningful therapeutic targets but evolving biotechnology also can increasingly aim to manipulate the gene itself in several ways. One might speculate that such "proximal" targeting may be more effective than manipulating downstream events. Advances in knowledge related to pathogenesis of FRDA were paralleled by studies documenting the variable natural history of FRDA by collaborative efforts in the USA, Australia, and Europe [4, 5] and the development of clinical outcome measures.

In the case of FRDA, given the strong evidence for electron transport chain dysfunction, oxidative stress, and the possible role of iron overload, initial trials involved known

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anti-oxidant molecules including potential components of electron transport chain such as idebenone and CoQ 10 and also reactive oxygen species scavengers such as epicatechins [6–8]. Other trials have involved agents such as RT 001 [9] and vatiquinone that may lessen lipid peroxidation and ferroptosis. Iron chelation with deferiprone is another strategy to redistribute iron and lessen oxidative stress [10]. These studies have generally not shown significant benefits, perhaps because they each attack only a small part of the overall pathophysiology.

The observation that the nuclear erythroid 2-related factor (Nrf 2) signaling pathway is paradoxically defective in FRDA cells led to the current work with omaveloxolone [11]. Nrf 2 is a transcription factor that drives the synthesis of many anti-oxidant defense molecules such as reduced glutathione, superoxide dismutase, and NAD(P)H:quinone oxidoreductase 1. Defective translocation of Nrf 2 to the cell nucleus in the context of excess oxidative stress contributes to impaired oxidative defense mechanisms in FRDA [12]. Omaveloxolone impairs the destruction of Nrf 2, allowing rescue of cellular models of FRDA [13]. An initial dose ranging study documented the safety of the drug but also allowed the choice of the mFARS as a primary outcome measure and identified the dose of 150 mg per day as having the best possible effect [14]. The pivotal phase 2 placebo-controlled study randomized a total of 103 patients into placebo and omaveloxolone arms for 48 weeks followed by an open label phase that is still ongoing. At the end of 48 weeks, there was a significant difference of 2.40 in the total mFARS score between the 2 groups, with the treated arm having a score of 1.55 below the baseline value, reflecting an improvement and the placebo arm being 0.55 points above the baseline score [15]. Patients aged 16 to 18 had a greater effect and there was a trend for improvement in many other outcome measures including the activities of daily living score and patient global impression. Additional analyses including data from open label extension comparing the patients who had been converted to the active drug at the end of the 48-week period with those that had already been treated in the earlier phase as well as a comparison of the treated subjects with selected "controls" from a natural history data base using propensity matching continue to support a favorable response to this drug [16]. The findings lead to the hope that long-term effects of this drug may postpone key milestone events and better preservation of quality of life. Adverse events from the drug were mild to moderate intensity and included elevation of liver enzymes and mild GI symptoms but the majority of subjects (98%) continued in the open label phase.

The approval of this drug for FRDA by the FDA is indeed exciting for not only the patients and families but also for clinical providers that care for chronic neurological conditions and rare genetic diseases and it is estimated that close to 10,000 FRDA subjects may be eligible for the currently approved age range. Thus, patients over 16 years of age with molecularly proven FRDA should all be eligible with the caveat that younger patients may have a better response. The study documents the idea that key downstream events may be real therapeutic targets. Despite large efforts by US and European consortia, the currently available clinical outcome measures have a reputation for having high variability and poor sensitivity, but such a measure did perform sufficiently well as a primary outcome measure in this study. The main limitations of the study did not reflect the outcome measures, but more the inability to link such changes in outcome measures to clinically meaningful events. There is need for more reliable and sensitive measures and biomarkers and while these remain challenging to develop, many efforts are on way including MRI measures of neural structures, quantitative measures of motor dysfunction and speech and estimation of frataxin, and other biochemical measures. Each of these measures will need to be understood in the context of how they reflect inherent clinical meaning to patients. Such advancements will be needed urgently as several novel strategies directed at the mutation itself are at the threshold of trials including protein replacement, synthetic transcription elongation factors, epigenetic modulation, oligonucleotides, and vector-based gene delivery. As a multitude of trials enter the field, there is need for clinical and biomarker measures that can reduce sample sizes needed to document an effect. The potential for many such interventions to have better efficacy on disease course may also allow for smaller samples.

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Data availability No original data is being reported in this manuscript and none is available.

Declarations

Ethical Approval This paper is an invited editorial comment and does not report any original human or animal research. No ethical committee approval was needed for this work.

Competing Interests Both the authors of this work were investigators in the pharmaceutical trials being commented on. They received research support from Reata Pharmaceuticals to conduct the trials and also participated in advisory board meetings for the company. DL did not receive compensation for his advisory board participation. There are no non-financial interests to report.

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