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FDA Approves Omaveloxolone based on Successful Moxie Trial Results for Friedreich's Ataxia - Review

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Key words: FRDA, Friedreich's Ataxia, Omaveloxolone, RTA 408, NRF2, MOXIe trail.

ABSTRACT

Introduction: In recent years, the medical community has witnessed a significant breakthrough in the treatment of Friedreich's Ataxia (FRDA), a rare and debilitating genetic disorder affecting the nervous system. This neurological condition, characterized by progressive muscle weakness, impaired coordination, and cardiomyopathy, has long posed challenges for both patients and healthcare professionals alike. However, there is newfound hope with the recent approval of Omaveloxolone by the U.S. Food and Drug Administration (FDA).

Aim of the study: This review article aims to present a detailed summary of the FDA's approval of Omaveloxolone as a therapeutic option for Friedreich's Ataxia (FRDA), focusing on the positive results obtained from the MOXIe trial. It covers various aspects of FRDA and explains how Omaveloxolone works as an activator of NRF2, a transcription factor that helps reduce oxidative stress. The MOXIe trial, which examined the safety and effectiveness of Omaveloxolone in FRDA patients, is discussed in detail, including its methodology, primary and secondary goals, and results.

Materials and methods: This review was based on available data collected in the PubMed and Google Scholar database, using the key words: FRDA, Friedreich’s Ataxia, Omaveloxolone, RTA 408, NRF2, MOXIe trail.

Conclusion: Omaveloxolone has shown significant efficacy in improving neurological function and mFARS scores compared to a placebo in the MOXIe trial. It is well-tolerated with minimal adverse events. Early intervention with Omaveloxolone offers enhanced benefits for managing Friedreich's ataxia progression.

Słowa kluczowe: FRDA, Ataksja Friedreicha, Omaweloksolon, RTA 408, NRF2, szlak MOXIe.

Friedreich's Ataxia

Friedreich's Ataxia (FRDA) is a multisystem disorder, affecting both the central and peripheral nervous systems, the musculoskeletal system, the myocardium and the endocrine pancreas. [1] The average age at which symptoms typically appear is 15.5 ± 8 years, but symptoms have been observed in individuals ranging from 8 months to 65 years of age. [2] In the overwhelming majority (90,7%) the onset of FA is neurological. The most common symptom presenting by patients is gait instability and less prevalent are clumsiness, falls, problems with hand skills, sensory loss and dysarthria. In rest of cases (9,3%), which were characterized by a non-neurological onset the most frequent symptom is scoliosis, followed by cardiomyopathy and diabetes. [3] In recent years, there has been a significant improvement in life expectancy. The most common cause of death (60%) in individuals is cardiac dysfunction, often resulting from conditions such as congestive heart failure or arrhythmia. [4]

FRDA predominantly affects Caucasians. [5] The studies that employed both clinical and molecular diagnostics yielded an average prevalence rate of 0.50 per 100,000. Conversely, the studies that relied solely on clinical diagnosis had an average prevalence rate of 1.79 per 100,000. [6]

Within Europe, there are noticeable and significant regional differences in the occurrence of FRDA. A prevalence gradient is observed, with higher rates (around 1 in 20,000) found in the southwest and west regions, such as Spain, France, and Ireland. In contrast, the north and east regions, including Scandinavia, East Germany, Austria, Czech Republic, and Russia, exhibit lower prevalence rates (1 in 250,000 or lower). [5]

Mapping of the genetic defect causing Friedreich's ataxia revealed that it is located on chromosome 9p13. [7] The vast majority, about 96%, of individuals with FRDA have a homozygous mutation characterized by an expanded guanine-adenine-adenine (GAA) repeat within the first intron of the frataxin (FXN) gene locus. [8] However, a small percentage of the remaining cases, approximately 1-3%, are linked to a compound heterozygous expansion, involving a combination of an expanded trinucleotide tract and a point mutation or deletion. In normal chromosomes, trinucleotide tracts with fewer than

about 40 repeats are commonly observed, and the pathological threshold appears to be around 70 repeats. In persons diagnosed with FRDA, the triplet numbers typically range between 600 and 900. Heterozygous carriers, who have one normal allele and one affected allele, do not exhibit symptoms of the condition and are generally healthy. The carrier rate among Europeans is estimated to be around 1 in 85. [9] The presence of expanded GAA repeats within the intron of the FXN gene results in gene silencing, leading to significantly reduced frataxin protein levels ranging from 5 to 35% compared to healthy individuals. [10, 11] In patients with neurological onset, there is a clear negative relationship between the length of GAA1-repeat and the age at which symptoms first appear. However, this correlation was not found to be significant in the group of patients with non-neurological onset. [3]

Frataxin plays a crucial role in the synthesis of iron-sulfur clusters (ISCs), which are important chemical complexes found in various respiratory chain complexes responsible for ATP production. When there is a deficiency of frataxin, the formation of ISCs is impaired, leading to the accumulation of iron within mitochondria in several areas including the dentate nucleus of the cerebellum, fibroblasts, liver, and heart. This accumulation of iron results in increased production of free radicals, oxidative stress, and ultimately leads to cellular damage and death. The progressive degeneration observed in Friedreich's Ataxia affects various regions including the dorsal root ganglia, cortical and spinocerebellar tracts, dorsal columns, gracile and cuneate nuclei, as well as the efferent cerebellar system. [2]

Omaveloxolone

Currently, the only drug approved by the FDA for use in the treatment of Friederich's ataxia is Omaveloxolone (RTA 408), semi-syntethic oleanane triterpenoid belonging to the group of nuclear factor (erytroid-derived-2)-like-2 factor (NRF2) activators. [12]

NRF2, as a transcription factor, plays a crucial role in reducing oxidative stress and minimizing its potential negative consequences. KEAP1, also known as Kelch-like ECH-associated protein 1, has been identified as a suppressor of NRF2, functioning as

part of the CULLIN 3 (CUL3)-based E3 ubiquitin ligase complex. Its main role is to target NRF2 for degradation through efficient ubiquitination under normal, non-stressful conditions. This process swiftly leads to NRF2 degradation via the proteasome pathway, keeping its activity consistently suppressed in unstressed cellular environments. However, when cells encounter oxidative or electrophilic stresses, KEAP1's ability to ubiquitinate NRF2 is compromised. Consequently, NRF2 accumulates in the nucleus and triggers the transcriptional activation of specific target genes, which encompass a range of vital enzymes involved in antioxidant defense mechanisms. [13, 14] These include superoxide dismutases (SODs), catalase, glutathione, glutathione reductase (GRed), glutathione-S-transferase (GST), glutamate-cysteine ligase catalytic subunit (GCLC), and NADH quinone oxidoreductase 1 (NQO1). [15]

The NRF2 signaling pathway is impaired in individuals with Friedreich's ataxia. By examining the impact of frataxin deficiency on NRF2 expression in a mouse model of FRDA known as FRDA YG8R hemizygous, researchers discovered a clear connection between reduced levels of frataxin and NRF2. This indicates that the decrease in FXN directly influences the levels of NRF2 expression. [16]

Omaveloxolone functions as an activator of NRF2, working to hinder the ubiquitination process of this transcription factor, enabling it to effectively activate antioxidative genes while simultaneously reducing the expression of inflammatory cytokines such as TNF-alpha and IL-6. [17]

MOXIe (RTA 408)

The MOXIe trial (NCT02255435, Reata Pharmaceuticals Inc) was conducted to evaluate the efficacy, safety, and pharmacodynamics of Omaveloxolone in the treatment of patients with FRDA between 2015 and 2024. [18] The research consists of two sections with placebo control, as well as an open-label extension for participants who finished either part 1 or part 2. [19] The initial stage of the MOXIe trail consists of a randomized, placebo-controlled, double-blind, dose-escalation research that enrolled 69 individuals. Its primary objective is to evaluate the safety of RTA 408 at different doses. The subsequent phase involves a randomized, placebo-controlled, double-blind,

parallel-group examination (enlisted 103 participants). Here, the focus is on assessing both the safety and effectiveness of Omaveloxolone at a specific dose of 150 mg. Following the completion of either Part 1 or Part 2, the extension phase of the study will assess the long-term safety and tolerability of RTA 408 in eligible patients with Friedreich's ataxia. [17, 18, 19, 20] The ongoing open-label extension phase of the study included 149 patients, which accounted for approximately 87% of the participants from either Part 1 or Part 2. [19]

Individuals were considered eligible for enrollment in the trial if they met the following criteria: confirmation of a genetic diagnosis of FRDA, a modified Friedreich's Ataxia Rating Scale (mFARS) score ranging from 20 to 80, and an age between 16 and 40. [18] The mFARS is an all-encompassing assessment tool used to measure the severity and progression of Friedreich's Ataxia. It includes four components: bulbar function (scoring up to 5 points), upper limb coordination (36 points), lower limb coordination (16 points), and upright stability (36 points). The maximum score on the mFARS is 93, with lower scores indicating better functional status. [21] Participants who did not meet specific criteria, including uncontrolled diabetes, elevated B-type natriuretic peptide levels, a history of significant heart disease, active infections (including HIV or hepatitis), substance abuse, or abnormal clinical hematology or biochemistry, were excluded from the trial. The enrolled individuals were required to abstain from consuming any additional antioxidant supplements for a minimum of two weeks before the initial evaluation. [18]

During Part 1 of the MOXIe Study, participants underwent randomization into a 3:1 ratio of RTA 408 and placebo. Various doses of Omaveloxolone, ranging from 2.5 mg to 300 mg once-daily, were tested. 69 participants were enrolled with an average age of 25.6 years at the start of the reasearch. The primary measure focused on the peak work achieved during maximal exercise testing. Secondary outcomes included the evaluation of clinical measures using the mFARS scores at 4 and 12 weeks, as well as the assessment of the SF-36 Health Survey Update score, Fatigue Severity Scale score, 9-hole peg test, timed 25-foot walk test, low-contrast letter visual acuity test, peak oxygen utilization during maximal exercise testing, and laboratory testing.

Overall, RTA 408 treatment did not show a statistically significant difference in peak workload compared to placebo or baseline. In contrast, Omaveloxolone significantly improved mFARS scores in a dose-dependent manner. The highest improvement was seen with a dosage of 160 mg, resulting in an average improvement of 3.8 points in mFARS compared to the baseline and a 2.3-point improvement compared to the placebo group.

Regarding predictive factors, it was found that the absence of pes cavus (high-arched feet) was linked to a more significant enhancement in mFARS scores. This improvement included a placebo-adjusted change in mFARS of 4.4 points specifically in patients without pes cavus who were administered RTA 408 at a dosage of 160 mg/day. However, the age of symptom onset, patient's age, duration of the disease, length of GAA1 repeat, and length of GAA2 repeat did not show any correlation with the improvements observed in mFARS scores.

In terms of its safety profile, Omaveloxolone was generally well tolerated, and only one participant discontinued the treatment due to a skin rash at a daily dose of 40 mg. The most frequently reported adverse event was a mild upper respiratory infection, which affected 40% of patients in the treatment group. Two serious adverse effects were observed, but they were not deemed to be associated with the study drug. A few individuals showed elevations in ALT and AST levels. Nevertheless, these increases were not accompanied by any indications or symptoms of liver damage, such as elevated direct bilirubin, reduced albumin levels, or changes in total protein. These isolated changes in liver enzymes are anticipated as a result of the pharmacological effects of NRF2 activation.

The study observed a dose-dependent increase in the expression of NRF2 transcriptional target proteins and markers. Ferritin and gamma-glutamyl transferase (GGT) levels increased compared to the baseline when RTA 408 was administered at doses of 80 mg/day or higher. Both aspartate aminotransferase (AST) and creatinine kinase (CK) displayed a rise that correlated with the dosage, specifically between 80 mg and 160 mg with reduced improvement at 300 mg/day. [17]

The second phase of the MOXIe trial aimed at evaluating the safety and efficacy of Omaveloxolone using change from baseline in mFARS after 48 weeks of treatment as the primary endpoint. Patients were allocated randomly in equal numbers to either receive a placebo or a daily dose of 150mg omaveloxolone. The randomization process took into account the presence or absence of pes cavus, a foot deformity, which was identified as a relevant factor in a previous study. Additionally, patients with severe pes cavus, indicating a specific subtype of FRDA with slightly distinct clinical characteristics, were included in the study but limited to 20% of the total participants enrolled Additionally, secondary outcome measures such as PGIC, CGIC, 9-HPT, T25-FW, frequency of falls, peak work during maximal exercise testing, and FA-ADL scores were assessed at week 48 compared to the baseline. Throughout the study, vital signs, electrocardiograms, and the occurrence and severity of adverse events were recorded at each visit. Echocardiograms were conducted during the screening process, as well as at weeks 24 and 48. In part 2 of the study, treatment with Omaveloxolone showed substantial enhancements in neurological function compared to placebo after 48 weeks of treatment. Patients who received omaveloxolone experienced an average decrease of -1.55 ± 0.69 points in mFARS at week 48 from baseline. In contrast, patients who received placebo showed an average increase of 0.85 ± 0.64 points in mFARS, resulting in a difference of -2.40 ± 0.96 points between the treatment groups. This improvement is particularly important in terms of upright stability, as it reflects key clinical milestones in Friedreich's Ataxia, including the loss of ambulation. The findings of part 2 are consistent with those of part 1 in terms of the timing and magnitude of enhancement with omaveloxolone treatment. Similar to part 1, patients with pes cavus showed a lesser degree of improvement in mFARS compared to those without pes cavus. Additionally, younger subjects and those with longer GAA repeat lengths showed a stronger response to omaveloxolone treatment, suggesting that RTA 408 targets the most severe biochemical abnormalities in FRDA and may address deficits in individuals with more severe or rapidly progressing disease.

Patients who were randomly assigned to receive Omaveloxolone exhibited notable advancements in FA-ADL scores that were statistically significant compared to those who received a placebo. However, there were no significant differences between the

treatment groups in terms of other secondary measures. Similar to previous studies, RTA 408 was generally well tolerated in this study, with only a few cases of discontinuation or serious adverse events. Importantly, Omaveloxolone did not raise blood pressure or have negative effects on various cardiac parameters, such as ventricular heart rate, QTcF, wall thicknesses, or ejection fraction, which are particularly relevant in FRDA patients with cardiomyopathy. Treatment with RTA 408 did lead to temporary and reversible increases in aminotransferases and GGT, but these changes were not indicative of liver damage. Instead, they were consistent with the activation of NRF2, a process that increases glutathione synthesis enzymes and mitochondrial bioenergetics, representing a proper physiological response to NRF2 activation. FRDA patients receiving Omaveloxolone also experienced improvements in eGFR and total bilirubin levels, even though their baseline levels were already within the normal range. Furthermore, adverse events were not linked to the observed treatment efficacy; they tended to occur within the first 12 weeks of therapy initiation, while the positive effects of RTA 408 on mFARS were observed after week 24. [20]

Participants who successfully completed the 48-week treatment period and the 52-week follow-up safety visit in the MOXIe part 2 trial were eligible to participate in the open-label extension study. In this study, there were two groups: the "omaveloxolone-omaveloxolone" group consisted of individuals who were initially randomized to receive RTA 408 in MOXIe part 2 and continued with RTA 408 in the open-label extension, while the "placebo-omaveloxolone" group included those who initially received a placebo in part 2 but started treatment with Omaveloxolone in the extension study. Therefore, the individuals in the placebo-omaveloxolone group began RTA 408 treatment 52 weeks after those in the omaveloxolone-omaveloxolone group. All participants in the open-label extension received a daily dose of 150 mg of the drug. Throughout the extension study, subjects underwent mFARS assessments on day 1 and every 24 weeks during treatment.

The main objective was to compare the difference between the initial placebo and initial RTA 408 groups during the "delayed-start period" with the difference between the initial Omaveloxolone and placebo groups during the "placebo controlled period."

The findings from the delayed-start analyses demonstrate a consistent positive impact of RTA 408 therapy on the progression of the disease. Individuals who initially received Omaveloxolone during the double-blind placebo-controlled period (Part 2) maintained a sustained benefit that was not achieved by those who initially received a placebo but started RTA 408 treatment in the extension study. This suggests that starting Omaveloxolone intervention earlier provides an advantage.

Furthermore, patients who were previously randomized to RTA 408 in the double-blind period continued to experience a slower progression of the disease, as measured by mFARS, even after more than 2.5 years of treatment in the extension study. The delayed-start analysis also indicates that the improvement in neurological function persists to some extent with ongoing therapy, indicating that initiating Omaveloxolone treatment earlier may offer greater benefits compared to delayed treatment in this particular study population. The duration of the delayed-start period, which was 72 weeks for the primary analysis, allowed individuals in the delayed-start group sufficient time to experience the potential symptomatic effects of omaveloxolone, as the maximum effects of RTA 4078 on individuals in the placebo-controlled Part 2 occurred at week 24. The long-term safety profile of omaveloxolone in the extension study was comparable to what was observed in Parts 1 and 2, and overall, RTA 408 was well tolerated in the extension study. Serious adverse events were reported in 13 patients (8.7%), but the investigator determined that these events were unrelated to the study drug. While there was an increased occurrence of upper respiratory infections in Part 1 of MOXIe, this was not clearly observed in Part 2 or the extension cohort. The most commonly reported treatment-related adverse events were elevated alanine aminotransferase levels and coronavirus infection. Notably, the elevations in aminotransferase levels did not coincide with increases in total bilirubin, and none of the participants met the criteria for Hy's law, which indicates severe drug-induced liver injury. [19]

Conclusion

Recent research endeavors focusing on Friedreich's ataxia have unveiled the integral role played by frataxin deficiency and its consequent impact on the depletion of the transcription factor NRF2. Consequently, efforts have been directed towards developing

therapeutic approaches that target the oxidative stress environment caused by FXN deficiency.

The MOXIe trial highlighted the significant efficacy of Omaveloxolone in improving mFARS scores and neurological function compared to a placebo in the treatment of FRDA. Throughout the trial, RTA 408 exhibited good tolerability, with minimal instances of discontinuation or serious adverse events. Notably, commencing treatment at an earlier stage offered enhanced benefits, suggesting the potential advantage of early intervention with Omaveloxolone in managing the progression of Friedreich's Ataxia.

While the approval of Omaveloxlone marks a noteworthy milestone in the management of FRDA, it is imperative to acknowledge the need for further investigations to comprehensively understand the long-term effects of RTA 408 in Friedreich's ataxia patients. These forthcoming studies, conducted over an extended duration, will provide valuable insights into the lasting impact and sustainability of the observed improvements associated with Omaveloxolone. Additionally, they will contribute to a holistic understanding of how this treatment influences the overall quality of life for individuals living with FRDA.

Supplementary Materials

Not applicable.

Author Contributions

Study conception and design: KK. and JK.; data collection: K.K., J.K., K.N., M.J. (Maciej Jędrak), M.J.(Maciej Józefiak) and P.S.; analysis and interpretation of results: K.K., J.K., K.N., M.J. (Maciej Jędrak), M.J.(Maciej Józefiak) and P.S.; writing—original draft preparation: K.K., J.K., K.N., M.J. (Maciej Jędrak), M.J.(Maciej Józefiak) and P.S.; writing—review and editing: K.K.; project administration: K.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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