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ACMG THERAPEUTICS BULLETIN

Omaveloxolone approved for patients aged 16 years and older with Friedreich ataxia (FRDA): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Friedreich ataxia (FRDA) is a genetic disorder caused by biallelic pathogenic variants in the *FXN* gene[1] encoding the frataxin protein. Frataxin is involved in several key pathways of mitochondrial function, particularly in iron homeostasis and the assembly of iron-sulfur complexes, which are involved in a wide range of cellular processes including respiration, replication, DNA repair, and translation. Frataxin has also been implicated in cellular antioxidant defenses dependent on Nrf2 activation.[2] FRDA involves slowly progressive neurologic dysfunction, including weakness, sensory loss, ataxia, and spasticity. Other frequently observed features include cardiomyopathy and diabetes.[3]

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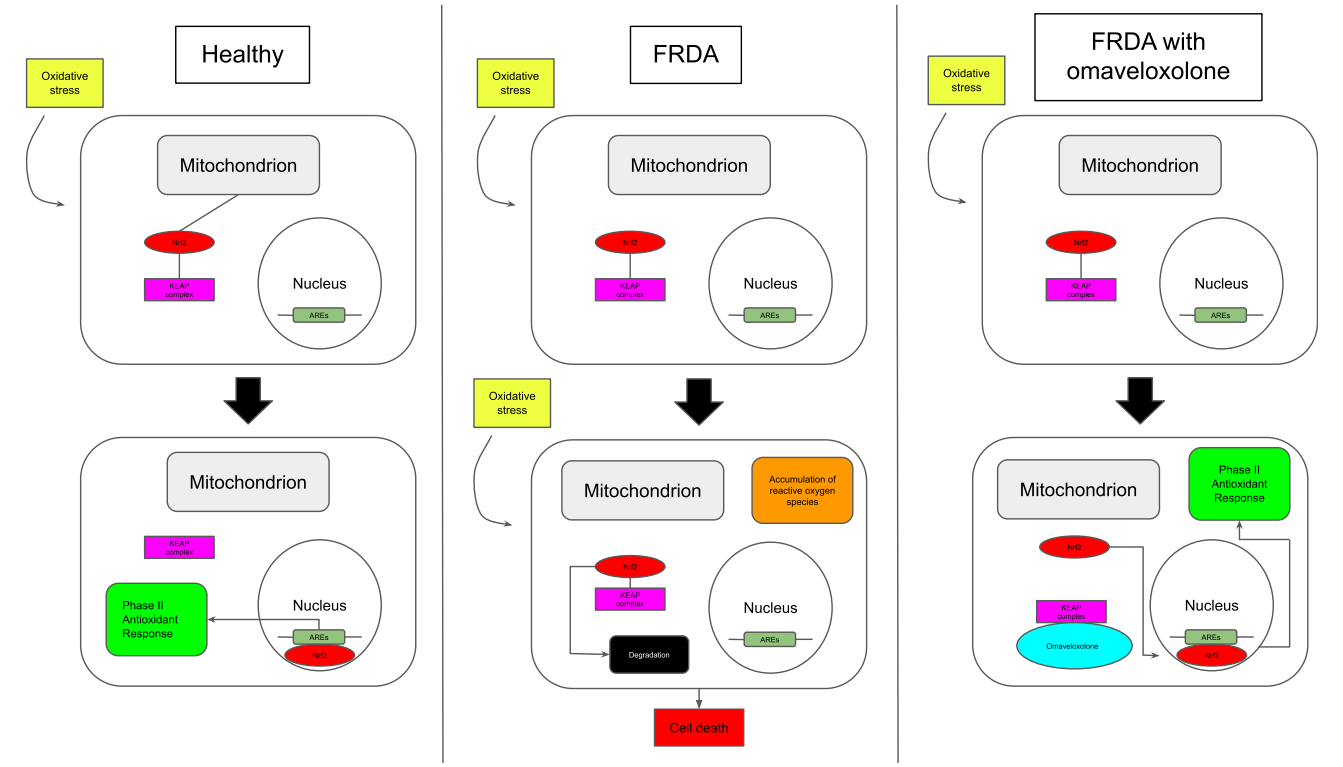

Figure 1 Simplified mechanism of action for omaveloxolone.

Management and Treatment

Consensus guidelines for management of FRDA were published by an international work group in 2014 with evidence-based grading.[3] Management involves active treatment of spasticity; monitoring and bracing for scoliosis; physical, occupational and speech therapy; and audiometry. Guidelines also suggest surveillance for diabetes mellitus as well as cardiomyopathy and arrhythmias. Before 2023, there were no US Food and Drug Administration (FDA)-approved therapies with evidence for improvement in neurological function, quality of life, or cardiac function in FRDA.[3] Past trials of idebenone, luvadaxistat, erythropoietin, deferiprone, interferon gamma-1b, and CoQ10 have not demonstrated clinical benefit.[4]

Newly Approved Therapy

Indication and approved treatment population

Omaveloxolone (trade name: SKYCLARYS) is a Nrf2 activator that increases cellular resilience to oxidative stress that has been FDA approved for patients with FRDA who are 16 years and older. Omaveloxolone received orphan drug, fast track, priority review, and rare pediatric disease designations. Omaveloxolone is a semisynthetic triterpenoid administered orally once daily.

Mechanism of action

Omaveloxolone activates Nrf2, a regulator of oxidative stress response genes involved in FRDA (Figure 1). Nrf2 is normally suppressed by KEAP1, which targets it for degradation. Oxidative stresses disrupt KEAP1 interaction with Nrf2, allowing Nrf2 to activate expression of antioxidant enzymes. This leads to restoration of redox balance. In FRDA, Nrf2 is degraded prematurely. Omaveloxolone prevents ubiquitination of Nrf2, resulting in increased expression of antioxidant genes. Therefore, FRDA neurons exhibit hypersensitivity to oxidative stress, resulting in neuronal dysfunction and death.[2,5]

Outcomes and efficacy

The MOXIe study (RTA 408 Capsules in Patients with FRDA) was a double-anonymized randomized placebo-controlled phase 2 trial. Part 1 was a study of 69 patients showing dose-dependent improvement of neurological function using the modified Friedreich's Ataxia Rating Scale (mFARS).[6,7] Part 2 included 103 patients, 51 of whom received 150 mg omaveloxolone daily.[8] The primary

outcome was mFARS score at 48 weeks. Omaveloxolone led to an improvement of −2.40 points compared with placebo ($P = 0.014$), as well as improvement from baseline (−1.55, 95% CI [−2.93 to −0.18]).[8] The treatment effect remained significant after 72 weeks of open-label extension.[9] No difference was observed in cardiopulmonary function at 12 weeks.[6]

Adverse effects and toxicity

Adverse reactions among patients treated with omaveloxolone included upper respiratory infections, headache, diarrhea, mild increases in liver aminotransferases, nausea, arthralgia, and fatigue. Patients with laboratory evidence of liver inflammation did not show symptoms of acute liver injury. There are no boxed warnings for omaveloxolone.

Additional Considerations

No other clinical trials are ongoing currently for omaveloxolone. As of the time of this writing, multiple other clinical trials are in the early stages. Agents under investigation include rosuvastatin, methylprednisolone, micronized resveratrol, nicotinamide, artesunate, etravirine, and several novel biologics (www.clinicaltrials.gov). Among these, research is preliminary, and results are not yet available.[10]

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Conflict of Interest

The authors declare no conflicts of interest.

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