Oxidative Stress in Friedreich´s Ataxia

Subjects: Others

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Friedreich´s ataxia is the commonest autosomal recessive ataxia among population of European descent. Despite the huge advances performed in the last decades, a cure still remains elusive. One of the most studied hallmarks of the disease is the increased production of oxidative stress markers in patients and models. This feature has been the motivation to develop treatments that aim to counteract such boost of free radicals and to enhance the production of antioxidant defenses.

Keywords: Friedreich´s ataxia ; Clinical Trials ; Oxidative stress ; Antioxidant therapies ; ROS scavengers ; antioxidant response ; mitochondrial metabolism ; ferroptosis

1. Introduction

Friedreich's ataxia (FRDA, OMIM no. 229300) is a rare autosomal recessive neurological disorder. The prevalence of FRDA is around 1 in 30.000. This makes FRDA the most common inherited ataxia in Europe[1]. The disease is produced due to decreased expression levels of the FXN gene that encodes for the protein frataxin[2]. Although the function of frataxin still remains obscure, it is currently widely accepted that frataxin participates ISC biosynthesis[3][4]. This hypothesis explains the deficient activity observed for many the iron-sulphur cluster (ISC) containing enzymes of the mitochondrial respiratory chain and Krebs Cycle[5][6]. Importantly, frataxin has been proposed to play a role in several additional crucial cellular processes[7][8][9][10].

2. The clinical spectrum of FRDA

The disease is characterised by the degenerative atrophy of the posterior columns of the spinal cord that it is accompanied with ataxia, sensory neuropathy, scoliosis, foot deformity, and cardiomyopathy[11]. First symptoms manifest in the puberty leading to a confinement in a wheelchair around 15 years from onset[12].

In the peripheral nervous system, the degeneration of the spinocerebellar tracks and the dorsal root ganglia (DRG) led to a peripheral sensory neuropathy along with a cerebellar and vestibular pathology. These defects will trigger the ataxia, the most common symptom in FRDA[13]. DRG neurons display a smaller size and a proliferation of satellite cells. Furthermore, the dorsal roots show a clear atrophy of large myelinated fibres[14]. Additional severe changes including loss of sensory action potentials are observed in sensory peripheral nerves[15]. All these defects impair the perception of the position, vibration, temperature, pain and light touch in the patients. Regarding the central nervous system, the major lesion lies on the age-dependent atrophy of the dentate nucleus in the cerebellum[16]. Both, grey and white matter, are also significantly diminished in the deep cerebellar nuclei and brainstem[17]. Later on, in advanced stages of the disease, speech becomes unintelligible[18].

Although FRDA is described as a neurological disorder, it should be mentioned that cardiomyopathy is the main cause of death in FRDA (around 60%) at an average age of 36.5 years[19]. Patients show cardiac wall abnormalities as well as inflammatory cells in the endomysium, attachment of monocytes to cardiomyocytes, and necrosis of heart fibres[20]. Among non-neurological feature, an increased risk of developing diabetes mellitus and glucose intolerance is strongly highlighted. Presence of insulin resistance or insulin deficiency due to pancreatic β-cell death seems to be the molecular reason[21].

Different clinical rating scales have been used to monitor and evaluate quantitatively the progression and the severity of the disease. The most important are the International Cooperative Ataxia Rating Scale (ICARS[22]), the Friedreich Ataxia Rating Scale (FARS[23] and mFARS[24]) and the Scale for the Assessment and Rating of Ataxia (SARA[25]). The isolation of the underpinning genetic cause in 1996 was pivotal to expand the clinical spectrum[26].

3. Oxidative stress markers in FRDA

The presence of iron deposits in the cardiomyocytes from patients[27] along with the toxicity induced by iron redox biology throughout the Fenton and Heber-Weiss reactions[28] strongly suggested from the very beginning that oxidative stress was a crucial element in the origin and progression of FRDA. Moreover, the defective ISC biosynthesis described in FRDA leads to an altered transport of electrons within the mitochondria that together with the concomitant surplus of free iron in the mitochondria will boost the mitochondrial ROS levels[29]. Furthermore, it has been shown that frataxin-deficient cells are unable to recruit antioxidant defences to counteract such production of ROS[30].

4. Reducing oxidative stress as a therapeutic avenue to stop FRDA progression

In this work we have summarized those therapeutic strategies whose goal is to counteract the oxidative stress induced by frataxin depletion and that have been or are being tested in clinical trials. Those trials represent the majority (60%) of all applied and ongoing approaches to improve FRDA patient´s conditions. These strategies can be divided in subgroups.

A) Direct ROS Scavengers. Most of them are small molecules that behave as free radical scavenger. Consequently, they prevent the oxidation of cellular structures[31], and improve the oxidative phosphorilation[32]. This group comprises the following compounds:

1) Coenzyme Q_{10} and idebenone. Around 2 decades ago a 4-year trials was carried on combining Coenzyme Q_{10} and Vitamin E. This long-term study revealed significant improvements in cardiac and skeletal muscle bioenergetics compared to cross-sectional data from 77 FRDA subjects. Although some features like the posture and gait symptoms continued declining, the overall progression of the disease according to ICARS score remained unchanged[33]. Similar results were obtained a couple of years later in a second trial that tested 2 doses. Interestingly, a closer analysis of the data showed a clear correlation between improvements with the therapy and decreased basal concentrations of Coenzyme Q_{10} and vitamin E in the patients[34]. Several trials have been performed with idebenone with highly variable results. Unfortunately, four randomized placebo-controlled phase-III clinical trials (NICOSIA, IONIA, MICONOS, and PROTI) did not obtain remarkable evidences on the neurological or cardiac function of idebenone in different groups of FRDA participants[35][36].

2) A0001 or alpha-tocopherol quinone. The only trial carried on with this synthetic analogue of Coenzyme Q_{10} or idebenone showed improvements in the FARS score[37]. Despite this promising results, no additional information is available.

3) EGb-761. This is a Ginkgo biloba extract. Likely because the number of participants was too small, no significant differences were found between placebo and EGb-treated individuals[38].

4) Indole-3-propionic acid or VP-20629. *VP-20629* is a result of tryptophan metabolism by gut microbiota and it is present in human plasma and cerebrospinal fluid. The compound already failed to induce significant benefits in the phase I of the study[39].

5) (+)-Epicatechin . Belongs to the family of polyphenolic flavonoids. An open-label study in 10 FRDA participants for 24 weeks was recently published and showed that it seemed to be an improvement in the cardiac function (increase in the mean left ventricle ejection fraction) but without changes in the FARS/mFARS scores[40].

6) Thiamine (also known as vitamin B1). Interestingly, thiamine deficiency is responsible for molecular and clinical alterations that highly resemble those described in FRDA[41]. Although an open-label trial reported promising improvements, no studies have continued with this avenue[42].

B) Inducers of antioxidant response. These are molecules that enhance the endogenous generation of antioxidant defenses in the cell. This group comprises the following compounds:

1) NRF2 Inducers (Omaveloxolone or RTA-408 and Resveratrol). NRF2 is a transcription factor responsible for the expression of antioxidant enzymes that share a common promoter sequence called the antioxidant response element. Interestingly, FRDA patients display reduced levels of functional NRF2 which compromises the cellular response towards oxidative insults. The trial for omaveloxolone (MOXIe) is still ongoing but the preliminary results suggests significant improvement of mFARS score after 48 weeks[43]. In case of resveratrol, an open-label clinical trial monitored the effects of 2 doses in 27 patients for 3 months. Although the high dose improved FARS and ICARS scores along with a marker of oxidative stress, it also produced gastrointestinal side effects[44]. In order to improve the tolerability, a new trial using micronized resveratrol is currently ongoing[45].

2) Enhancers of mitochondrial metabolism (Pioglitazone/Leriglitazone and Acetyl-L-carnitine (ALCAR)). Mouse models and cells derived from FRDA patients showed reduces levels of PGC-1α. This down-regulation is link to impaired mitochondrial biology, reduced fatty acid β-oxidation and lower levels of antioxidant genes[46]. This is the reason underlying the use of PPAR-γ agonists as a treatment for FRDA. Although no information is still available, pioglitazone was evaluated in a randomized, double-blind clinical trial with the objective of exploring the effects of over neurological defects[47]. The second candidate, Leriglitazone or MIN-102 is a selective metabolite of pioglitazone. The current clinical study is in the second phase and the results have not been made public yet[48]. However, this type of compounds are able to reduce cardiac fast fibres or to induce a thrombotic response[49] which might have a negative impact on the cardiovascular problems present in FRDA patients. Finally, ALCAR is an optimized version of L-carnitine with higher water solubility and bioavailability and it provides essential chemical groups for energy metabolism. The corresponding trial was conducted few years ago but results are not yet available[50].

C) Blocking ROS Production. These molecules aim to reduce the generation of free radicals attacking the source of the free radicals. This group comprises the following compounds:

1) Iron Chelators (Deferiprone). As it is widely known, free redox-active iron that might accumulate in FRDA cells will boost the generation of ROS. Among them hydroxyl radicals are of special relevance due to their ability to damage proteins, lipids and DNA. Because of this, iron chelators were tested in clinical trials very early. However, clinical trials assessing deferiprone failed to report consistent results even when combined with idebenone or riboflavin[51][52][53].

2) Inhibitors of lipid peroxidation (EPI-743 or Deuterated fatty acids). Several studies in models and samples from patients highlight a critical role for lipid metabolism in the disease[54]. Remarkably, Iron and Lipid peroxidation are the core elements of ferroptosis an iron dependent form of cell death[55]. EPI-743 or α-tocotrienol quinone inhibits 15-lipoxigenase activity, a key enzyme in the ferroptosis process[56]. A multicenter trial assessed two doses of EPI-743. The FRDA participants reported that the compound was well tolerance. Although, no statistically significant changes were observed in sight and cardiac measurements, FARS score was improved in the high-dose group. A follow-up of the study with the positive dose revealed the progression of the neurological symptoms significantly slowed down[57]. The next phase is planned to take place within the next months. dPUFAs or deuterated PUFAs are fatty acid in which hydrogen (^{1}H) is replaced by the isotope deuterium (^{2}H). Such a change strengthens the structure, reducing toxicity and increasing the resistance to lipid peroxidation[58]. A clinical trial using a deuterated homologue of linoleic acid (RT001-Retrotope) showed improvements in the cardiopulmonary exercise but only modest changes in neurological features. Currently, trials is recruiting patients for phase III[59].

5. Discussion and Conclusions

The critical analysis of all these clinical trials has revealed most of the handicaps that clinicians face when designing such trials. The first problem is that FRDA is a rare disease and thus it is extremely difficult to recruit a large number of participants. Then, the lack of a standardized methodology of data collection impacts the ability of clinicians to group the patients in the trials. Finally, the influence of epigenetic and environmental factors in the progression of the pathology is still not taken into account. Overcoming these limitations will pave the way to a personalized pharmacological treatment. Such an approach will help to reveal whether given treatments have a positive impact in FRDA patients with specific features. Nevertheless, remarkably, five different compounds have reached phase III in clinical trials. The next years are key to determine their real ability to improve significantly patient´s wellbeing.

6. Future Directions and Prospects

Identification of accurate disease biomarkers that parallel the natural history of the disease is pivotal to design solid clinical trials. Therefore, more research should be done in this sense. Furthermore, the discouraging results obtained in the clinical trials using drugs that impact the cellular redox status strongly indicate the high relevance for the disease of other pathological pathways that are not targeted by these therapies. It would be of high interest to study such pathways and implement strategies to recover them.

Many trials are based on administration of single drugs as shown in this review. Therefore, we think that it should be explored the effect of cocktails containing compatible drugs in order to test possible synergic effects of reverting simultaneously different downstream effects of frataxin deficiency.

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