Current and emerging treatment options in the management of Friedreich ataxia

Michelangelo Mancuso
Daniele Orsucci
Anna Choub
Gabriele Siciliano

Department of Neuroscience, Neurological Clinic, University of Pisa, Pisa, Italy

Abstract: Friedreich ataxia (FRDA) is the most common autosomal recessive ataxia. Oxidative damage within the mitochondria seems to have a key role in the disease phenotype. Therefore, FRDA treatment options have been mostly directed at antioxidant protection against mitochondrial damage. Available evidence seems to suggest that patients with FRDA should be treated with idebenone, because it is well tolerated and may reduce cardiac hypertrophy and, at higher doses, also improve neurological function, but large controlled clinical trials are still needed. Alternatively, gene-based strategies for the treatment of FRDA may involve the development of small-molecules increasing frataxin gene transcription. Animal and human studies are strongly needed to assess whether any of the potential new treatment strategies, such as iron-chelating therapies or treatment with erythropoietin or histone deacetylase inhibitors and other gene-based strategies, may translate into an effective therapy for this devastating disorder. In this review, we try to provide an answer to some questions related to current and emerging treatment options in the management of FRDA.

Keywords: frataxin, idebenone, oxidative stress

Introduction
Friedreich ataxia (FRDA, OMIM #229300) is the most common autosomal recessive ataxia among Caucasian population, and it is caused by mutations in the FXN gene (OMIM *606829), mainly an expanded GAA triplet repeat in the intron 1. Age at onset is typically 5–25 years. Sensory neurons in the dorsal root ganglia are lost initially, with secondary degeneration of the spinocerebellar tract, pyramidal tract, and dorsal columns. FRDA is, therefore, characterized by progressive gait and limb ataxia, dysarthria, loss of vibration and proprioceptive sense, areflexia, abnormal eye movements, and pyramidal signs. Involvement of the auditory sensory neurons and pathways may also be found, as in optic atrophy. Ataxia of mixed cerebellar and sensory type is the cardinal symptom. The first symptom is usually gait instability, though scoliosis may already be present when neurologic symptoms appear, and, in rare cases, hypertrophic cardiomyopathy is diagnosed before the onset of ataxia.

In patients with FRDA, voxel-based morphometry showed a symmetrical volume loss in dorsal medulla, infero-medial portions of the cerebellar hemispheres, the rostral vermis, and in the dentate region. No volume loss in cerebral hemispheres was observed. The atrophy of the cerebellum and medulla correlated with the severity of the clinical deficit and disease duration. Moreover, some magnetic resonance imaging-based studies found cerebral white matter atrophy or dysfunction.
A possible manifestation of this disease is hypertrophic cardiomyopathy, described in up to two-thirds of patients with FRDA. Ventricular arrhythmias can also occur. Later in the course of the disease, the hypertrophied heart can develop systolic dysfunction and heart failure and arrhythmias are possible causes of death in these patients. Diabetes, scoliosis, and pes cavus are other possible manifestations of FRDA. Clinical course is variable, but on average 10–15 years after onset, patients lose the ability to walk, stand, and sit without support. Age at diagnosis, which may incorporate other genetic and environmental factors, may be more important than GAA length in predicting cardiomyopathy, scoliosis, and disease progression.

In FRDA the genetic abnormality results in the deficiency of frataxin, a protein targeted to the mitochondrion. In about 98% of patients, the disease is caused by a triplet GAA expansion within the first intron of the frataxin gene on chromosome 9q13, which impedes transcription of the gene and limits protein production. The repeat expansions can range from 70 to 90 repeats (normal less than 40) to over 1,000, with inverse correlation of age at onset, severity of the disease, and associated systemic symptoms. Heterozygous carriers are clinically healthy. FRDA is the most common disease-causing triplet-repeat expansion identified so far, about 1 in 100 Europeans being a carrier. No other disease-causing triplet-repeat expansion has been recognized to date to be caused by an expansion of GAA triplets. Some patients are compound heterozygotes with the GAA expansion in one allele and one of a variety of point mutations in the other allele. The FRDA-associated expansion shows instability when transmitted from parent to child. Expansions and contractions can both be observed and are equally likely after maternal transmission, whereas contractions are most common after paternal transmission.

In this regard, FRDA resembles the other diseases associated with very large expansions in noncoding regions, including fragile X syndrome and myotonic dystrophy, and differs from the diseases that are caused by CAG repeats in coding regions, such as dominant ataxias and Huntington disease, in which size increases typically occur after paternal transmission.

FRDA pathogenetic theories and their relevance for therapeutic approaches

Although the exact physiological function of frataxin is not known, its involvement in iron–sulfur cluster biogenesis has been suggested. Frataxin iron-binding capacity is quite robust. Even when 5 of the most conserved residues from the putative iron-binding region are altered, at least 2 iron atoms per monomer can be bound. Current evidence suggests that loss of frataxin impairs mitochondrial iron handling and respiratory chain function and contributes to increased oxidative stress and cellular damage.

In a conditional knockout mouse model where frataxin was removed from the heart, transferrin receptor-1 was upregulated, resulting in increased iron uptake from transferrin. There is also marked downregulation of ferritin that is required for iron storage and decreased expression of the iron exporter, ferroportin 1, leading to decreased cellular iron efflux. The increased mitochondrial iron uptake is facilitated by upregulation of the mitochondrial iron transporter, mitoferrin 2. This stimulation of iron uptake probably attempts to rescue the deficit in mitochondrial iron metabolism that is due to downregulation of mitochondrial iron utilization (heme and iron–sulfur cluster synthesis and iron storage in mitochondrial ferritin). Therefore, increased mitochondrial iron uptake coupled with decreased utilization and release leads to mitochondrial iron-loading.

Abnormalities of the neuronal cytoskeleton due to oxidative stress and increased protein glutathionylation have been also suggested to have a potential role in FRDA. Oxidative damage within the mitochondria seems to have a key role in the disease phenotype. A combined deficiency of a Krebs-cycle enzyme, aconitase, and 3 mitochondrial respiratory-chain complexes was reported in endomyocardial biopsy samples from patients with this disorder. All 4 enzymes share iron–sulfur cluster-containing proteins that are damaged by iron overload through generation of oxygen free radicals. Using phosphorus magnetic resonance spectroscopy, Lodi et al demonstrated a maximum rate of muscle mitochondrial adenosine triphosphate (ATP) production below the normal range in all the 12 studied FRDA patients and a strong negative correlation between mitochondrial ATP production and the number of GAA repeats in the smaller allele, suggesting that FRDA is a nuclear-encoded mitochondrial disorder. Moreover, Giacchetti et al reported an influence of the mitochondrial DNA polymorphisms on the FRDA phenotype. These authors studied 99 patients with FRDA and 48 control individuals, all from southern Italy. They found that patients belonging to the haplogroup U class had a delay of 5 years in the disease onset and a lower rate of cardiomyopathy. Mitochondrial DNA polymerase (POLG) CAG repeat instability has been also proposed as a predisposing factor that, in combination with environmental risk factors, may affect age of onset and FRDA progression. For the described reasons, FRDA treatment options have been mostly directed at antioxidant protection against mitochondrial damage. Interestingly,
other studies demonstrated that in FRDA mitochondrial iron accumulation did not induce oxidative stress and that FRDA is a neurodegenerative disease not associated with oxidative damage.23

To date, no randomized controlled trial using antioxidants or any other pharmacological treatment has shown significant benefit on neurological symptoms associated FRDA.24 Moreover, the design of clinical trials in FRDA presents some problems, such as the lack of reliable biomarkers that correlate with clinical dysfunction and the rarity of the condition. Therefore, therapeutic strategies are still unclear. In this review, we try to provide an answer to some questions related to current and emerging treatment options in the management of FRDA. References for this review were identified by searches of PubMed until May 2010 with the term “Friedreich”*; articles especially considering potential therapeutic approaches were considered. Emphasis was placed on comprehensive reviews and original articles published after 1998. Other articles were identified through references from relevant articles. Only papers published in English were reviewed.

Which pharmacological agents were effective in FRDA cellular and animal models?

PPARγ agonists

A recent microarray analysis of heart and skeletal muscle in a mouse model of frataxin deficiency showed molecular evidence of increased lipogenesis in skeletal muscle, and alteration of fiber-type composition in heart, consistent with insulin resistance and cardiomyopathy, respectively.25 Since the peroxisome proliferator-activated receptor gamma (PPARγ) pathway is known to regulate both processes, dysregulation of this pathway may play a role in FRDA. PPARγ coactivator 1-alpha (PGC-1a) downregulation may contribute to the blunted antioxidant response observed in cells from FRDA patients.26 PGC-1a is a transcriptional master regulator of mitochondrial biogenesis and antioxidant responses, and can be restored by agonist pioglitazone in FRDA cells,26 suggesting a potential therapeutic approach for FRDA. Moreover, Marmolino et al27 investigated the effects of another PPARγ agonist (Azelaoyl PAF) on the frataxin protein and mRNA expression profile in human neuroblastoma cells (SKNBE) and primary fibroblasts from skin biopsies from FRDA patients and healthy controls. Azelaoyl PAF increased both messenger RNA and protein levels of intracellular frataxin in SKNBE cells and fibroblasts from FRDA patients.27

Iron chelators

Iron chelators that target the mitochrion have been proposed (ie, deferiprone).28,29 Adding the chelator deferiprone at clinical concentrations to inducibly frataxin-deficient HEK-293 cells resulted in chelation of mitochondrial labile iron, involved in oxidative stress.30 This led to restoration of impaired mitochondrial membrane and redox potentials, increased ATP production and oxygen consumption, and attenuation of mitochondrial DNA damage and reversal of hypersensitivity to apoptosis.30 On the other hand, a direct consequence of chelating mitochondrial free iron in various cell systems is a concentration and time-dependent loss of aconitase activity, which was shown to precede decreased cell proliferation.31 Therefore, if chelating excessive mitochondrial iron may be beneficial at some stage of the disease, attention should be paid to not fully deplete mitochondrial iron store.31 Li et al32 investigated the regulation of frataxin expression by iron and reported that frataxin mRNA levels decreased significantly in multiple human cell lines treated with the iron chelator desferal. In addition, frataxin mRNA and protein levels decreased in fibroblast and lymphoblast cells derived from both normal controls and from patients with FRDA.32 Lymphoblasts and fibroblasts of FRDA patients show evidence of cytosolic iron depletion, which may occur as frataxin-deficient cells overload their mitochondria with iron,32 as already discussed. Therapeutic efforts should focus on an approach that combines iron removal from mitochondria with a treatment that increases cytosolic iron levels to maximize residual frataxin expression in FRDA patients.32

Antioxidant agents

Coenzyme Q10 has been widely used for the treatment of neurodegenerative disorders, as well as its analog idebenone, which shares an identical modified parahydroxybenzoate ring with Coenzyme Q10, but has a short carbon tail. Idebenone was cytoprotective in fibroblasts from patients with FRDA.33 Because of the role of mitochondrial oxidative damage in FRDA, Jauslin et al34 compared the efficacy of mitochondria-targeted and untargeted antioxidants derived from coenzyme Q10 and from vitamin E at preventing oxidative stress-induced cell death in cultured fibroblasts from FRDA patients in which glutathione synthesis was blocked. Ubiquinones have been shown to protect mitochondria from oxidative damage, but only a small proportion of externally administered ubiquinone is taken up by mitochondria.35 Conjugation of the lipophilic triphenylphosphonium cation to a ubiquinone moiety has produced a compound, MitoQ,
which accumulates selectively into mitochondria. MitoQ passes easily through all biological membranes and, because of its positive charge, is accumulated several 100-fold within mitochondria driven by the mitochondrial membrane potential. The mitochondria-targeted antioxidant MitoQ was 800-fold more potent than the untargeted analog idebenone. The mitochondria-targeted antioxidant MitoVit E was 350-fold more potent than the water soluble analog. Therefore, targeted antioxidants may have therapeutic potential in FRDA and in other disorders involving mitochondrial oxidative damage, but have not been investigated in FRDA patients to date.

A dose-escalation trial found that idebenone was efficacious in a frataxin-deficient mouse model of FRDA. Low-dose idebenone (10 and 30 mg/kg per day) showed no benefit, whereas high-dose idebenone (90 mg/kg per day) delayed the cardiac disease onset, progression, and death of frataxin-deficient animals by 1 week.

**Gene-based strategies**

FRDA is a loss of function disorder, therefore gene-based strategies designed to increase frataxin levels could be an ideal therapy for this disease, although there are still technological limitations to their clinical applicability. Viral vectors expressing frataxin partially corrected sensitivity to oxidative stress in FRDA fibroblasts. Furthermore, in mice with a localized frataxin reduction in the brainstem functional impairment could be corrected by exposure to HSV-1 vector expressing frataxin cDNA. Other studies reported that compounds specifically targeting the GAA repeat, such as DNA sequence-specific polyamides or pentamidine, were capable of increasing frataxin transcription. The exact mechanism by which these DNA-binding compounds increase transcription through GAA repeats still needs further characterization.

**HDAC inhibitors**

Alternative gene-based strategy for the treatment of FRDA would involve the development of small-molecules increasing frataxin gene transcription. Expanded GAA repeats may silence frataxin expression inducing heterochromatin formation, and/or forming non B-DNA structures, such as triplex and sticky DNA, which block gene transcription. Therefore, possible treatments for FRDA may include drugs that facilitate chromatin opening, such as histone deacetylase (HDAC) inhibitors. Gene silencing at expanded FXN alleles is accompanied by hypoaecytlation of histones H3 and H4 and trimethylation of histone H3, observations that are consistent with a heterochromatin-mediated repression mechanism. Herman et al reported the synthesis and characterization of a class of HDAC inhibitors that reversed FXN silencing in primary lymphocytes from individuals with FRDA. These molecules directly affected the histones associated with FXN, increasing acetylation at particular lysine residues on histones H3 and H4. One compound, BML-210, showed a significant increase in frataxin message levels by approximately 2-fold. Butyric acid is another HDAC inhibitor reported to increase frataxin expression. Furthermore, compounds with pimelic diphenylamide basic structure were able to upregulate frataxin in cells from FRDA patients and in a mouse model. HDAC3 could be the likely cellular target of the pimelic diphenylamides HDAC inhibitors and the target for therapeutic intervention in FRDA. Although both the HDAC3 and HDAC1/2-specific compounds share a similar mechanism of inhibition of their target enzymes, only HDAC3-specific compounds increase frataxin gene expression and frataxin protein in cells. Rai et al treated KIKI mice (homozygous mice carrying a [GAA]230 repeat in the first intron of the mouse frataxin gene) with a novel HDAC inhibitor, compound 106, which substantially increases frataxin mRNA levels in cells from FRDA individuals. The treatment increased histone H3 and H4 acetylation in chromatin near the GAA repeat and restored wild-type frataxin levels in the nervous system and heart, as determined by quantitative reverse transcription polymerase chain reaction and semiquantitative western blot analysis. Lack of acute toxicity, normalization of frataxin levels, and of the transcription profile changes resulting from frataxin deficiency may provide support to a possible efficacy of this or related compounds in FRDA patients.

**Conclusive remarks**

In conclusion, gene-based strategies (including HDAC inhibitors), the agonist pioglitazone, iron chelators that target the mitochondrial such as deferiprone, coenzyme Q10, vitamin E (especially their mitochondria-targeted forms), and idebenone were found to be effective in FRDA cellular and animal models. Clinical studies with some of these agents are reviewed in the next paragraphs. Moreover, there is some preliminary evidence that flavin adenine dinucleotide and hemin may rescue the phenotype of frataxin deficiency in cellular and animal models, but further studies are still needed.

**Is there a role for idebenone and other antioxidants in FRDA patients? Idebenone**

The antioxidant idebenone is a short-chain benzoquinone derivative with a structure similar to coenzyme Q10 but with...
a more favorable pharmacokinetic profile. In vitro studies have shown that it acts both as an antioxidant, preventing damage to the mitochondrial membrane, and as an electron carrier, supporting mitochondrial function and ATP production. High doses of idebenone are safe and well tolerated in patients with FRDA. The idebenone half-life was relatively consistent across dose levels (2.6–21.7 hours). It exhibited dose-dependent pharmacokinetics in daily doses up to 2,250 mg. Idebenone plasma levels are thought to correlate with central nervous system concentrations because of its ability to penetrate central nervous system.

Schulz et al measured concentrations of 8-hydroxy-2′-deoxyguanosine (8OH2′dG), a marker of oxidative DNA damage, in urine and of dihydroxybenzoic acid (DHBA), a marker of hydroxyl radical attack, in plasma of 33 patients with FRDA. They found a 2.6-fold increase in normalized urinary 8OH2′dG but no change in plasma DHBA as compared with controls. Oral treatment with 5 mg/kg/day of idebenone for 8 weeks significantly decreased urinary 8OH2′dG concentrations.

Idebenone is a promising drug for treatment of FRDA. Early trials have demonstrated that low-dose idebenone (5 mg/kg per day) reduced cardiac hypertrophy (as determined by echocardiography) in the majority of patients with FRDA, with no influence upon clinical progression of the neurological disease.

Recently, a randomized, placebo-controlled trial has been conducted on 48 patients with genetically confirmed FRDA. Treatment with higher doses of idebenone (up to 45 mg/kg) was generally well tolerated and associated with improvement also in neurological function and activities of daily living in patients with FRDA. The degree of improvement correlated with the dose of idebenone, suggesting that higher doses may be necessary to have a beneficial effect on neurological function. It has been also suggested that the disease stage and patient age at which idebenone treatment is initiated may be important factors in the effectiveness of the therapy. Larger randomized trial focusing on the response to idebenone therapy of both neurological and heart symptoms are required to confirm whether an early diagnosis of FRDA can be exploited to initiate such antioxidant treatment in order to prevent the progression of this disorder.

**Other antioxidants**

To evaluate the long-term efficacy of a combined antioxidant and mitochondrial enhancement therapy on the bioenergetics and clinical course of 10 patients with FRDA, Hart et al performed an open-labeled pilot trial over 47 months with a combined coenzyme Q10 (400 mg/d) and vitamin E (2,100 IU/d) therapy. They reported a significant improvement in cardiac and skeletal muscle mitochondrial bioenergetics as assessed using phosphorus magnetic resonance spectroscopy, and heart function assessed by echocardiographic fraction shortening significantly improved. Although improved fraction shortening was reported, there was no impact upon the degree of cardiac hypertrophy evident before therapy was started. These results must be interpreted with caution because of limited patient numbers and the absence of a placebo group.

Another pilot study investigated the potential for high-dose CoQ10/vitamin E therapy to modify clinical progression in FRDA. Fifty patients were randomly divided into high-dose or low-dose CoQ10/vitamin E groups. At baseline, serum CoQ10 and vitamin E levels were significantly decreased in patients. During the trial, CoQ10 and vitamin E levels significantly increased in both groups. Serum CoQ10 level resulted to be the best predictor of a positive clinical response to CoQ10/vitamin E therapy.

**Conclusive remarks**

Overall, because of the lack of controlled studies, the variable doses used and the association with other antioxidant medications, vitamin E has not been appropriately tested in FRDA, and no conclusions can yet be drawn about its safety and efficacy in this disorder. More research is needed to identify the role of vitamin E, and of other antioxidant agents, if any, in the management of FRDA and other neurodegenerative disorders. A meta-analysis (which included 68 randomized trials with 232,606 healthy participants and patients with various diseases) reported that treatment with β-carotene, vitamin A, and vitamin E may increase all-cause mortality. Further study of causes of mortality is needed. These findings contradicts observational studies, claiming that synthetic antioxidant supplements improve health. Therefore, more research is needed to establish the real safety of such compounds, including vitamin E.

In conclusion, available evidence (Table 1) seems to suggest that patients with FRDA should be treated with idebenone, because it is well tolerated and may reduce cardiac hypertrophy and, at higher doses (up to 45 mg/kg), also improve neurological function, but large controlled clinical trials are still needed.

**Other pharmacological agents could be useful in FRDA patients?**

**Carnitine and creatine**

L-carnitine and creatine are natural compounds that may enhance cellular energy transduction. A placebo-controlled...
Table 1 Clinical trials in Friedreich ataxia

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Intervention</th>
<th>Subjects</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Prospero et al</td>
<td>Open-label, phase 1A dose-escalation trial followed by an open-label, 1-month phase 1B trial</td>
<td>Idebenone. In phase 1A, the dose was increased in 10 mg/kg increments in each successive dose group to a maximum of 75 mg/kg. In phase 1B, oral idebenone was administered at 60 mg/kg divided in 3 doses per day for 1 month</td>
<td>Phase 1A included 78 subjects with FA (24 adults, 27 adolescents, and 27 children), and phase 1B included 15 subjects with FA (5 adults, 5 adolescents, and 5 children)</td>
<td>Higher doses of idebenone led to a proportional increase in plasma levels up to 55 mg/kg per day and high-dose idebenone was well tolerated in patients with FA</td>
</tr>
<tr>
<td>Hausse et al</td>
<td>Open trial; 6 months</td>
<td>Idebenone 5 mg/kg/day</td>
<td>38 patients aged 4–22 years</td>
<td>Reduction in left ventricular mass of more than 20% in about half the patients</td>
</tr>
<tr>
<td>Mariotti et al</td>
<td>1-year, randomized, placebo-controlled trial</td>
<td>Idebenone</td>
<td>29 patients</td>
<td>Reduction of interventricular septal thickness and left ventricular mass</td>
</tr>
<tr>
<td>Di Prospero et al</td>
<td>6-month, randomized, double-blind, placebo-controlled study</td>
<td>Idebenone. The patients received placebo or 1 of 3 doses of idebenone (approximately 5, 15, and 45 mg/kg), stratified by body weight</td>
<td>48 patients, aged 9–17 years</td>
<td>Treatment with higher doses of idebenone was generally well tolerated and associated with improvement in neurological function</td>
</tr>
<tr>
<td>Hart et al</td>
<td>Open-labeled pilot trial over 47 months</td>
<td>A combined coenzyme Q10 (400 mg/d) and vitamin E (2,100 IU/d) therapy</td>
<td>10 patients</td>
<td>Improvement in cardiac and skeletal muscle bioenergetics</td>
</tr>
</tbody>
</table>

Note: The great majority of these studies must be interpreted with caution because of limited patient numbers and absence of placebo groups.

Abbreviation: FA, Friedreich ataxia.
evidence suggests that riluzole may be potentially effective as symptomatic therapy in diverse forms of cerebellar ataxia.74

Furthermore, in patients with cerebellar ataxia, coordination training improved motor performance and reduced ataxia symptoms, enabling them to achieve personally meaningful goals in everyday life.75 Rehabilitation therapies usually focus on strategies and compensatory techniques for maintaining or improving abilities to continue to participate in all environmental contexts for as long as possible.76 The benefits of physical exercise programs have been demonstrated for patients with other degenerative disabilities that include ataxia, but at present there is little evidence supporting specific physical therapy interventions that would address impairments or functional concerns in patients with FRDA.76 Patients with FRDA may improve aerobic fitness by participating in stationary cycling for 20–25 minutes at 70%–85% of their maximum heart rate.77 The plan of care should include daily attention to range of motion, including muscle length and soft-tissue extensibility, as well as maintaining independence in mobility.77

Maintaining biomechanical alignment is another important therapeutic consideration.78 Orthopedic problems such as foot deformities and scoliosis are often treated with orthoses78 or surgery79 and may result in a temporary improvement in function.78 Early intervention for biomechanical changes in the foot significantly improves alignment and thus weight bearing ability and mobility outcomes.79

Conclusion and perspectives

In conclusion, to date the best care for patients with FRDA has not been defined according to evidence-based criteria, and all efforts should be made to obtain solid standards of care, although this goal is difficult to accomplish for a rare disease.80 The first phase 2 trial of idebenone has shown dose-dependent effects on neurological scale scores in children and adolescents with FRDA.87 Large trials are needed to investigate whether all patients with FRDA can benefit from idebenone treatment, regardless of age and disease stage.80

Additional studies with animal models will be essential for an enhanced understanding of the disease pathophysiology and for the development of better therapies.81 Animal and human studies are strongly needed to assess if any of the described new treatment strategies, such as iron-chelating therapies or treatment with EPO or HDAC inhibitors and other gene-based strategies, may translate into an effective therapy for this devastating disorder.

Acknowledgment

This study was supported by Telethon Grant GUP09004.

Disclosure

The authors report no conflicts of interest in this work.

References


42. Grant L, Sun J, Xu H, Subramony SH, Chaires JB, Hebert MD. Rational selection of small molecules that increase transcription through the GAA repeats found in Friedreich’s ataxia. FEBS Lett. 2006;580(22):5399–5405.


