Title

Emerging therapies in Friedreichs ataxia.

Journal

Neurodegenerative Disease Management, 6(1)

Authors

Aranca, Tanya
Jones, Tracy
Shaw, Jessica
et al.

Publication Date

2016

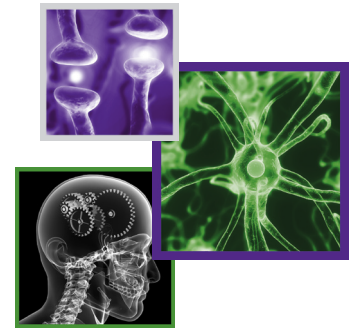
DOI

10.2217/nmt.15.73

Peer reviewed

REVIEW

Neurodegenerative Disease Management



Emerging therapies in Friedreich's ataxia

Tanya V Aranca[1], Tracy M Jones[1], Jessica D Shaw[1], Joseph S Staffetti[1], Tetsuo Ashizawa[3], Sheng-Han Kuo[4], Brent L Fogel[5], George R Wilmot[6], Susan L Perlman[7], Chiadi U Onyike[8], Sarah H Ying[9,10,11] & Theresa A Zesiewicz*[,1,2]

Friedreich's ataxia (FRDA) is an inherited, progressive neurodegenerative disease that typically affects teenagers and young adults. Therapeutic strategies and disease insight have expanded rapidly over recent years, leading to hope for the FRDA population. There is currently no US FDA-approved treatment for FRDA, but advances in research of its pathogenesis have led to clinical trials of potential treatments. This article reviews emerging therapies and discusses future perspectives, including the need for more precise measures for detecting changes in neurologic symptoms as well as a disease-modifying agent.

First draft submitted: 10 August 2015; Accepted for publication: 14 December 2015; Published online: 19 January 2016

Practice points

- Friedreich's ataxia is an inherited neurodegenerative disease, for which there is currently no US FDA-approved treatment.
- Therapeutic strategies and disease insight have expanded rapidly over recent years, providing new opportunities for disease relief.
- Advances in the study of disease mechanisms have been translated into clinical trials of potential treatments.
- Homogenous populations in clinical trials and the use of technologically advanced measures will advance the capacity to test promising treatments.
- Research in gene therapy provides a promising outlook in the future treatment of Friedreich's ataxia.

[1]University of South Florida Ataxia Research Center, Department of Neurology, FL, USA
[2]James A. Haley Veterans' Hospital, FL, USA
[3]McKnight Brain Institute, University of Florida Department of Neurology, FL, USA
[4]Department of Neurology, Columbia University, NY, USA
[5]Department of Neurology, Neurogenetics Program, David Geffen School of Medicine, University of California, CA, USA
[6]Department of Neurology, Emory University, GA, USA
[7]Ataxia and Huntington Disease Center of Excellence, University of California, CA, US
[8]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University school of Medicine MD, USA
[9]Department of Neurology, Johns Hopkins University School of Medicine, MD, USA
[10]Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, MD, USA
[11]Department of Ophthalmology, Johns Hopkins University School of Medicine, MD, USA
*Author for correspondence: Tel.: +1 813 974 5909; Fax: +1 813 974 8032; tzesiewi@health.usf.edu

Future Medicine part of fsg

KEYWORDS
• antioxidants
• erythropoietin • FRDA
• Friedreich's ataxia • HDAC
• iron

Background

Friedreich's ataxia (FRDA) is the most common autosomal recessive form of ataxia. It has a prevalence of approximately 1.7–4.7/100,000 [1] in most parts of the world, except for East Asia (China, Japan, Korea and Southeast Asia), sub-Saharan Africa, and Amerindians where the disease has never been reported in the indigenous populations [2].

FRDA is caused by an unstable triplet (intronic GAA) repeat expansion in *FXN* that results in reduced transcription of a nuclear-encoded *FXN* gene and, thereby, a decreased production of the mitochondrial protein frataxin. The deficiency of frataxin results in abnormal mitochondrial respiration, increased free-radical production [1], and intramitochondrial iron accumulation in the heart, liver, dentate nucleus of the cerebellum, and fibroblasts. The age of symptom onset and length of GAA repeats are correlated, with greater repeats indicative of earlier onset of symptoms and more severe presentation [3]. The mean age of onset of FRDA is 15 years, with most cases developing before age 25 [1].

The disorder is characterized by progressive gait and limb ataxia, dysarthria, cardiomyopathy, diabetes, abnormal proprioception and vibratory sense, and loss of reflexes [1–5], with a slowly progressive course that culminates in reliance on hands-on assistance for self-care and wheelchair dependence. Nursing and rehabilitative interventions are the mainstays of treatment, as there are no curative therapies. However, research on pharmacologic treatments for FRDA has advanced significantly in the past decade. Potential agents such as antioxidants, frataxin-inducing agents (histone deacetylase (HDAC) inhibitors and interferon gamma), and gene therapy are currently under investigation **(Table 1)**.

FRDA clinical rating scales

Standardized rating scales are used to quantify and evaluate the severity and progression of FRDA [6–11]. The most commonly used are the International Cooperative Ataxia Rating Scale (ICARS), the Scale for the Assessment and Rating of Ataxia (SARA) and the Friedreich's Ataxia Rating Scale (FARS). A variety of other scales that measure functionality and quality of life are commonly used in the evaluation of Friedreich's ataxia including the Inventory of Non-Ataxia Signs (INAS), the Spinocerebellar Ataxia Functional Index (SCAFI), the neurocognitive phonemic verbal fluency test, Friedreich Ataxia Impact Scale, and the EQ-5D [6–8]. The ICARS has a range of 0–100 points and while it evaluates posture and gait, limb coordination, speech disorder, and oculomotor dysfunction, it is weighted in favor of kinetic function – which accounts for more than half the points. The ICARS has been validated in numerous studies of FRDA and spinocerebellar ataxia (SCA) [9].

The SARA score ranges from 0–40 and consists of eight items evaluating gait, stance, sitting, speech, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide. Limb coordination items are rated independently for the patient's left and right sides and the two scores averaged. The SARA has been validated in studies and is most often used when evaluating SCA and other ataxias that have a predominance of cerebellar symptoms [10].

The FARS, developed specifically for evaluating FRDA patients and consists four main sections: functional staging, activities of daily living subscale (ADLs), neurological exam, and quantitative timed activities. The functional staging section of the FARS examines patient mobility, and the ADLs section assesses ability to complete daily tasks such as speaking, dressing, and walking. The neurological exam targets specific areas impacted by FRDA including bulbar function, upper limb coordination, lower limb coordination, peripheral nerve, upright stability and gait functions. The quantitative timed activities include the 25-foot walk, 9-hole peg test, and PATA speech rate. Studies have demonstrated the validity of the FARS in the evaluation of FRDA patients [10,11].

Treatment of FRDA: medications

• Decrease oxidative stress &/or increase mitochondrial function

Medications that have been tested or are currently being studied in FRDA patients include: idebenone (Raxone®/Catena®; Santhera Pharmaceuticals, Switzerland), coenzyme Q10, vitamin E, A0001, Vincerinone® (EPI-743), OX1®, resveratrol, L-acetylcarnitine, RTA-408 and dPufas. Furthermore, because FRDA is characterized by mitochondrial respiratory chain dysfunction and oxidative stress, patients may benefit from therapies that inhibit free radical formation.

Idebenone

Idebenone (Raxone/Catena), an analogue of coenzyme Q10, is an antioxidant and a

Table 1. Studies of pharmaceutical treatments in Friedreich's ataxia population.

Intervention	Sample size	Treatment duration	Year	Findings		Study (Year)	Ref.
				Cardiac	Neurologic		
Medications that decrease oxidative stress and/or increase mitochondrial function							
Idebenone							
Idebenone 450 or 1350 mg/d (if body weight ≤45 kg at baseline) or 900 or 2250 mg/d (if body weight >45 kg at baseline)	70	6 months	2012	No significant decrease in left ventricular (LV) hypertrophy or improvement cardiac function		Lagedrost *et al.*	[13]
First treatment arm: 450 idebenone per day (if body weight ≤45 kg) or 900 mg (if body weight >45 kg)	70	6 months	2010		Idebenone did not significantly improve the neurological status of pediatric patients with Friedreich ataxia compared with placebo (450 or 900 mg, p = 0.19 and 1350 or 2250 mg, p = 0. 63)	Lynch *et al.*	[14]
Second treatment arm: 1350 or 2250 mg of idebenone per day							
Idebenone 5 mg/kg of body weight per day	38	6 months	2002	Reduction in LV mass of more than 20% was reported in about half of subjects (p < 0.001)		Hausse *et al.*	[15]
Idebenone 5mg/kg/day	29	12 months	2003	Interventricular septal (IVS) thickness reduced by 4.3% (p = 0.05) at 6 months and 4.6% (p = 0.004) at 12 months in the idebenone group versus an increase of 3.2% at 6 months and 5.5% at 12 months in the placebo group	No statistically significant changes in the ICARS scores of these patients during this time	Mariotti *et al.*	[16]
Idebenone 5–20 mg/kg/day	24	3–5 years	2008	No significant changes in echocardiographic measurements	No significant changes in ICARS scores measures in pediatric patients after 5 years of follow up; adult ICARS scores showed a significant increase in neurological dysfunctions during 3 years of therapy (p = 0.005)	Pineda *et al.*	[17]
Idebenone 180–2250 mg/day based on body weight divided into low, intermediate and high doses	48	6 months	2007		Analysis on patients with ICARS scores between 10 and 54 at baseline found a significant improvement in the total ICARS (p = 0.01). Patients who received higher doses had more significant improvement in their total ICARS (p = 0.03); however this was not true for their total FARS (p = 0.14) and ADL scores (p = 0.16)	DiProspero *et al.*	[18]
Idebenone 5 mg/kg/day in three doses, maximum of 300 mg/day	8	12 months	2003	Findings showed a reduction of the LV mass index of approximately 20% in six of eight patients (p = 0.03)	Despite idebenone treatment, there was an increase in total ataxia scores (p = 0.039 at 8 months, p = 0.016 at 12 months)	Buyse *et al.*	[80]

Table 1. Studies of pharmaceutical treatments in Friedreich's ataxia population (cont.).

Intervention	Sample size	Treatment duration	Year	Findings		Study (Year)	Ref.
				Cardiac	Neurologic		
Idebenone 5 mg/kg daily, in three doses	3	4–9 months	1999	Decrease in left-ventricular mass (LVM) index occurred in all 3 patients. Patient 1 LVM decreased from, 145 g at baseline to 114 g after 9 months of treatment. Patient 2 LVM decreased from 215 g at baseline to 151 g after 4 months of treatment. Patient 3 LVM decrease from 408 g at baseline to 279 g after 4 months of treatment		Rustin *et al.*	[81]
Coenzyme Q10							
Coenzyme Q10 (dose of 400 mg/day) and vitamin E (dose of 2100 IU/day)	10	6 months	2001	No consistent benefits in echocardiographic testing	No consistent benefits in neurological testing, the maximum rate of skeletal muscle mitochondrial ATP production increased to 139% ($p = 0.01$) of baseline values following 3 months of testing	Lodi *et al.*	[19]
Coenzyme Q10 (dose of 400 mg/day) and vitamin E (dose of 2100 IU/day)	77	47 months	2005	Significant improvements in cardiac and skeletal muscle bioenergetics that was maintained over 47 months	Total ICARS scores did not worsen over the trial period; however posture and gait scores worsened significantly ($p < 0.02$)	Hart *et al.*	[20]
Low-dose coenzyme Q10 (30 mg/day) and a high-dose coenzyme Q10 (600 mg/day) and vitamin E (2100 IU/day)	50	2 years	2008		At baseline serum CoQ10 and vitamin E levels were significantly decreased in the FRDA patients ($p < 0.001$). During the trial CoQ10 and vitamin E levels significantly increased in both groups ($p < 0.01$). No significant differences in the ICARS scores from either treatment ; however this data was not reported in study results	Cooper *et al.*	[21]
A0001							
A001 170 mg or 250 mg/day	31	4 weeks	2012		No significant changes in the Disposition Index between the drug and placebo groups; however, significant and dose-dependent improvement in the total FARS after 28 days of treatment	Lynch *et al.*	[22]
Resveratol							
Resveratrol 1g or 5 g/day	24	12 weeks	2015		No changes in peripheral blood mononuclear cell frataxin levels in either dose group; however, improvement in the total FARS score (-3.4 points) in patients taking high dose resveratrol was seen after the 12 week treatment	Yiu *et al.*	[24]
L-Carnitine							
3 g/d L-carnitine and 6.75 g/d creatine	16	4 months	2005		No significant improvements of neurological deficits or ICARS scores	Schöls *et al.*	[25]

Table 1. Studies of pharmaceutical treatments in Friedreich's ataxia population (cont.).

Intervention	Sample size	Treatment duration	Year	Findings		Study (Year)	Ref.
				Cardiac	Neurologic		
L-acetylcarnitine 1000 mg	24 (11 with FRDA)	6 months	2000		Improvement in overall coordination for FRDA participants at both month 3 ($p < 0.04$) and month 6 ($p < 0.03$)	Sorbi *et al.*	[27]
Iron chelators							
Deferiprone							
Deferiprone 20, 40, or 60 mg/kg/day	72	6 months	2014		Deferiprone was well tolerated at 20 mg/kg/day. The 60 mg/kg/day dose was discontinued due to worsening ataxia in 2 patients. There were no significant changes in the FARS in the 20 mg/kg/day group, and a worsening of the FARS patients who received 40 mg/kg/day	Pandolfo *et al.*	[33]
Combined idebenone (20 mg/kg/day) and deferiprone (20 mg/kg/day)	20	11 months	2011	Significant reduction of the interventricular septum thickness ($p = 0.04$) and left ventricular mass index ($p = 0.038$)	The MRI values in the dentate nucleus showed a statistically significant reduction ($p = 0.007$). No significant differences were observed in total ICARS scores. Posture and gait scores increased significantly ($p = 0.04$). Kinetic function improved significantly (Wilcoxon's test, $p = 0.015$)	Velasco-Sanchez *et al.*	[35]
Deferiprone 20–30 mg/kg/day	9	6 months	2007		Reduced MRI H-relaxation rates R2* in dentate nuclei and proportionally to the initial R2* ($r = 0.90$)	Boddaert *et al.*	[82]
Frataxin stabilizers, enhancers, and replacement							
Erythropoietin							
5,000 units recombinant human erythropoietin three times weekly	12	8 weeks	2007		Significant increase in frataxin levels in isolated lymphocytes after 8 weeks ($p < 0.01$). All patients showed a reduction of oxidative stress markers	Boesch *et al.*	[42]
Carbamylated EPO (CEPO) 325 ug three times a week up to 6 doses	36	Up to 103 days after baseline	2014		CEPO was found to be safe and well tolerated, neither frataxin levels in blood and buccal samples nor ataxia ratings (SARA, FARS, and CGI-I/S) differed between the drug and placebo groups	Boesch *et al.*	[43]
Erythropoietin 20,000 IU every 3 weeks, 40,000 IU every 3 weeks, or 40,000 IU every 2 weeks	16	6 months	2012		No significant clinical, or biochemical outcomes with EPO use. SARA score, $p = 0.19$, LV PW thickness $p = 0.19$, IVS thickness $p = 0.68$ frataxin level $p = 0.16$	Mariotti *et al.*	[44]
Neurotrophic factors							
Insulin/insulin-like growth factor 1 (IGF-1)							
IGF-1 therapy with 50 μg/kg twice a day subcutaneously	5	12 months	2014	The echocardiograms of these patients remained normal	The annual worsening rate (AWR) of the SARA score in the study patients was -0.4+/-0.83(CI 95%) whereas the AWR for the control group was 2.05+/-1.23 (CI 95%)	Rufini *et al.*	[45]

Table 1. Studies of pharmaceutical treatments in Friedreich's ataxia population (cont.).

Intervention	Sample size	Treatment duration	Year	Findings		Study (Year)	Ref.
				Cardiac	Neurologic		
Agents that increase FRDA gene expression							
Nicotinamide							
Nicotinamide (Vitamin B3) 2–8 g	10	61 days	2014		Dose-response proportional change in FXN from baseline to 8 h after dose ($p = 0.0004$). Significant upregulation of FXN expression in peripheral blood mononuclear cells. No significant improvements were observed in clinical rating scales	Libri *et al.*	[49]
Interferon gamma							
Interferon gamma 10 mcg/m^2 3 times weekly then titrated up to 50 mcg/m^2 over 4 weeks	12	12 weeks	2014		Results showed significant improvement in the total FARS score ($p = 0.0078$) with the upper limb coordination subscale improving approximately 3.5 points ($p = 0.02$); however, frataxin levels in RBC, peripheral blood mononuclear cells and platelets did not significantly improve	Seyer *et al.*	[55]
Triple therapy							
Triple therapy with deferiprone (5–25 mg/kg/day), idebenone (10–20 mg/kg/day) and riboflavin (10–15 mg/kg/day)	13	15–45 months	2014	LVMI decrease by 6.5 g/m2 in the 1st year of the study (not significant), but increased to basal value at the end of the second year. LVEF remained stable in all patients except three	There was statistically significant worsening of the SARA score from the fourth quarter of the study. The AWR of the SARA score, however, was 0.96% (CI 95%) on average in study participants whereas the theoretical AWR was 2.05+/-1.23 indicating a slowing in the progression of FRDA with the use of triple therapy	Arpa *et al.*	[56]
Ddarbepoetin alfa (150 μg every 2–3 weeks), idebenone (10–20 mg/kg/day TID), and riboflavin (10–15 mg/kg/day TID) for 32+/-19.4 months	11	4 years	2013	The LVMI and LVEF showed nonsignificant decrease during the 4 years of study treatment. LVMI decreased between 8.3 and 21.8 g/m^2 and LVEF decreased between 3.6 and 7.5%. Triple therapy yielded cardiac stability in participants during the four years of treatment	The mean AWR of the SARA score for study participants at 24 months was -1.42+/-0.51 whereas theoretical AWR is 2.05+/-1.23 in the general FRDA population. This appears to indicate a decreased rate of neurological progression in study participants	Arpa *et al.*	[57]
Miscellaneous medications							
Physostigmine							
Physostigmine 3 mg daily, then titrated up to 8 mg/daily over a 3-week period	21 (10 with FRDA)	12 months	1981		13 patients, 'responders', had improvement in their 'tests of ataxia' scores as a group while on physostigmine in comparison to placebo group ($p < 0.025$)	Kark *et al.*	[61]

Table 1. Studies of pharmaceutical treatments in Friedreich's ataxia population (cont.).

Intervention	Sample size	Treatment duration	Year	Findings		Study (Year)	Ref.
				Cardiac	Neurologic		
Riluzole							
Riluzole 100 mg daily	40 (3 with FRDA)	8 weeks	2010		Approximately 68% of participants who received riluzole experienced a decrease of 5 points or greater in their ICARS score, two of these participants had FRDA	Ristori *et al.*	[62]
Riluzole 50 mg twice daily	60 (28 with FRDA	12 months	2015		There was a significant decrease in SARA scores of 14 of the 28 patients on treatment when compared with the placebo group (OR 8·00, 95% CI 1·95–32·83; p = 0·002)	Romano *et al.*	[63]
Amantadine							
Amantadine 1 mg per pound of weight for subject to a max dose of 100 mg three times daily	16	Single dose treatment	1988		The total disability score improved by an average of 29.5% ($p < 0.0005$) after the single dose treatment when compared with the preadministration of amantadine; however, the effects of gradually dissipated over 4 h	Peterson *et al.*	[69]
Amantadine hydrochloride 100 mg	14 (12 with FRDA)	4 weeks	1993		No significant changes found according to treatment time, i.e., basal score, first treatment, second treatment, (chi-square = 5.29; df = 3) or study treatment (chi-square = 2.46; df = 3)	Filla *et al.*	[70]

potent-free radical scavenger [12]. Study results regarding treatment of FRDA with idebenone have been inconclusive. In a 6 month randomized, double-blind, controlled study, 70 pediatric patients were divided in to three groups. Patients in Group A received either 450 mg/d (if body weight ≤45 kg at baseline) or 900 mg/d (if body weight >45 kg at baseline), group B received 1,350 mg/d (if ≤45 kg) or 2,250 mg/d (if >45 kg), and group C received placebo. All patients were evaluated with echocardiography, EKGs, and the ICARS. The study did not find a significant decrease in left ventricular (LV) hypertrophy or improvement cardiac function [13]. Idebenone also had no significant effect on the neurologic status of the patients in the study [14]. However, several variables could have influenced these negative results. The study included only ambulatory children, and this highly selected population may not have included individuals with significant heart disease. Furthermore, while echocardiography is the most common method for evaluating FRDA patients, strain rate and cardiac magnetic resonance imaging (MRI) would have been more sensitive in detecting changes in cardiac function, LV size and mass for patients in this short-term study. However, cardiac MRI is not yet practical for large studies due to cost inefficiency and a lack of uniformity across sites.

Conversely, two short-term follow-up trials reported a significant reduction of interventricular septal (IVS) thickness and LV mass, as well as a reduction of cardiac hypertrophy in subjects taking idebenone [15,16]. These studies consisted of small sample sizes, and found idebenone to be well tolerated, with only one subject in either of the studies developing tachycardia while on the drug [16]. The first study was an open label trial that included 38 patients, ages 4–22 years, who were administered oral idebenone 5 mg/kg/day. Cardiac status was evaluated via ultrasound both before the initial administration of the medication and after 6 months of therapy. A reduction in LV mass of more than 20% was reported in about half of subjects ($p < 0.001$) [15]. The next

short-term trial was a randomized, placebo controlled 1-year trial that consisted of 29 patients receiving idebenone 5 mg/kg/day or placebo [16]. Cardiac ultrasound measured IVS thickness and LV mass at baseline, 6 months, and 12 months. IVS thickness was reduced by 4.3% ($p = 0.05$) at 6 months and 4.6% ($p = 0.004$) at 12 months in the idebenone group versus an increase of 3.2% at 6 months and 5.5% at 12 months in the placebo group. There were no statistically significant changes in the ICARS scores of these patients during this time [16].

The effect of idebenone on the neurological progression of FRDA has been evaluated in several clinical trials. In one open label study, 10 pediatric patients and 14 adult patients with FRDA received treatment with 5–20 mg/kg idebenone daily for 3–5 years [17]. There were no significant changes in the ICARS after 5 years of follow-up, suggesting disease stabilizing effects, although there was a statistically significant increase ($p \leq 0.005$) in the total ICARS in adult patients when compared with measurements taken 3 years earlier [17]. A double-blind study randomized 48 FRDA (ages 9–17) patients to receive idebenone (5 mg/kg, 15 mg/kg or 45 mg/kg/day) or placebo for 6 months [18]. No significant changes in the total ICARS, total FARS, or activity of daily living scores were reported. Due to limitations of the rating scale in evaluating wheelchair bound patients, study data may have been skewed and consequently, a secondary analysis was performed on data from patients with initial ICARS scores between 10 and 54. A significant improvement in the total ICARS was found ($p = 0.01$). Further evaluation of the data from the secondary analysis suggested a dose dependent result; patients who received higher doses of idebenone were found to have a more significant improvement in their total ICARS ($p = 0.03$), although this was not true for their total FARS ($p = 0.14$) and ADL scores ($p = 0.16$). One subject experienced neutropenia while on a high dose (45 mg/kg of idebenone) after 6 months. This resolved after discontinuation of treatment [18].

Additional antioxidants

Several small trials have evaluated the effect of *coenzyme Q10* and *vitamin E* in FRDA patients. In one study, 10 FRDA patients received coenzyme Q10 (dose of 400 mg/day) and vitamin E (dose of 2,100 IU/day) for 6 months [19]. Although the study failed to find any consistent benefits in neurological and echocardiographic testing, the maximum rate of skeletal muscle mitochondrial ATP production increased to 139% ($p = 0.01$) of baseline values following 3 months of testing [19]. Another open label study tested the long-term efficacy of antioxidant agents (coenzyme Q10, dose of 400 mg/day and vitamin E, dose of 2,100 IU/d) in FRDA patients for 47 months [20]. The study found significant improvements in cardiac and skeletal muscle bioenergetics. Conversely, a third study that compared low-dose coenzyme Q10 (30 mg/d) to high-dose coenzyme Q10 (600 mg/d) and vitamin E (2,100 IU/day) for 2 years found no differences in the ICARS scores from treatment [21].

A0001 (α-tocopheryl quinone, Edison Pharmaceuticals) is a potent antioxidant evaluated in 31 adult FRDA patients in a double-blind, placebo-controlled pilot trial [22]. The primary endpoint was the Disposition Index [22], a measure of 'diabetic tendency', and the secondary study measure the FARS. Following 4 weeks of therapy, there were no significant changes in the Disposition Index between the drug and placebo groups. However, there was a significant and dose-dependent improvement in the total FARS. Patients in the low-dose A0001 group improved by 4.9 points, while patients in the high dose group improved by 6.1 points ($p < 0.01$). A related compound, *EPI-743* (*Vincerinone*® Edison Pharmaceuticals) was developed to treat life-threatening diseases that involve the mitochondrial respiratory chain such as Leber Hereditary Optic Neuropathy (LHON). It is currently being tested in a Phase II 6 month, double-blind, placebo-controlled trial with an open label extension phase in 60 adult FRDA patients (www.clinicaltrials.gov/ct2/show/NCT01962363). Another potent antioxidant, indole-3-propionic acid (SHP622, Shire Pharmaceuticals [formerly VP20629®]), is also currently being evaluated in adults with FRDA in a Phase I, multidose, multicenter trial (www.clinicaltrials.gov/ct2/show/NCT01898884).

Resveratrol is a natural phenol and an antioxidant that has been found to increase *Fxn* gene expression in FRDA animal models [23]. An open-label study evaluated the effect of resveratrol in two doses (1 g and 5 g daily) on peripheral blood mononuclear cell (PBMC) frataxin levels in 24 FRDA patients for 12 weeks [24]. While there were no changes in PBMC frataxin levels in either dosage group at study endpoint, there

was improvement in the total FARS score (-3.4 points) in patients taking high dose resveratrol ($p = 0.036$).

L-acetylcarnitine is a derivative of L-carnitine, a substance involved in fatty acid transport into the mitochondria [25]. Preclinical studies suggest L-acetylcarnitine can alter the levels of membrane proteins in the cerebellar mitochondria and thus may reduce oxidative stress [26]. One double-blind, placebo-controlled, crossover study investigated 24 patients with various degenerative ataxias, including 11 patients with confirmed FRDA, 10 patients with idiopathic late onset cerebellar ataxia (ILOCA), 2 patients with SCA2 and 1 patient with SCA1. Subjects received either 1,000 mg L-acetylcarnitine or placebo twice daily for 6 months, followed by a 1-month washout period and crossover to the alternate therapy for another 6 months [27]. No side effects were reported. The study utilized a modified ataxia rating scale (ARS) validated in 47 patients [28]. The scale assessed six domains: cranial nerves, coordination, tone, reflexes, peripheral signs, and evaluation of muscle strength [29]. A significant treatment effect ($p < 0.007$) on muscle tone at 6 months was observed. Improvement in overall coordination was also observed at month 3 ($p < 0.04$) and month 6 ($p < 0.03$) [27]. Conversely, another double-blind randomized, placebo-controlled, triple-crossover trial, investigating the effect of 3 g/d L-carnitine, 6.75 g/d creatine, in 16 ambulatory patients with FRDA found no significant improvements in neurological deficits or ICARS scores [25].

Deuterated polyunsaturated fatty acids (D-PUFAs)

Studies of both mouse and human FRSA fibroblasts showed potential benefits of D-PUFAs in the reduction of oxidative stress [30]. One agent, RT001, is currently in Phase I/II study as a potential treatment in FRDA (www.clinicaltrials.gov/ct2/show/NCT02445794). RT001 is deuterated linoleic acid that is chemically altered to enable its entry into the cell where it has the potential to reduce oxidative stress in the mitochondria and increase ATP production [31,32].

• Iron chelators

FRDA is characterized by a deficiency in frataxin, an important component in the assembly of iron-sulfur clusters, with resultant mitochondrial iron accumulation [33]. The potential role of iron chelation has been considered as treatment for FRDA, but many potential chelators have been hampered by poor permeability in biological membranes [33].

Deferiprone

Deferiprone is an orally administered iron chelator with good permeability that has been tested treatment of FRDA. One double-blind, placebo-controlled study randomized 72 FRDA patients to receive deferiprone 20, 40, or 60 mg/kg/day or placebo for 6 months [34]. The primary objective was to determine the safety of deferiprone, and secondary measures included the FARS. Deferiprone was well tolerated at 20 mg/kg/day, while the 60 mg/kg/day dose was discontinued due to worsening ataxia in 2 patients. One patient on deferiprone 20 mg/kg/day also experienced reversible neutropenia. There were no significant changes in the FARS in the 20 mg/kg/day group, and worsening was observed in those patients who received 40 mg/kg/day. An open label study conducted over 11 months tested a combination of deferiprone and idebenone (20 mg/kg/day, respectively) [35]. While there were no significant improvements in the ICARS, a reduction in intraventricular septum thickness as well as left ventricular mass index was reported ($p = 0.04$ and $p = 0.038$, respectively) [35].

• Modulators of frataxin-controlled metabolic pathways

Apoptosis occurs in FRDA due to reactive oxygen species (ROS) in the mitochondria of the neuronal, cardiac, and beta cells. This oxidative stress is caused by a lack of frataxin and decreased production of iron–sulphur (Fe–S) clusters leading to reduced activation of Fe–S enzymes and increased iron levels. The excessive iron in the mitochondria reacts with the ROS resulting in cellular destruction [36].

Incretin analogs

Incretin analogs have been found to reduce oxidative stress and increase cAMP production in beta cells lacking frataxin. Results were produced in both rat and human islet cells and two human iPS neurons. Specifically, glucagon-like peptide 1 (GLP-1) and forskolin were found to reduce cell death, normalize free radical production and increase frataxin by 1.5-2 fold [37]. In a similar study of β-cells, analogs of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) have been found *in vitro* to partially

protect frataxin-deficient islet cells from apoptosis [38]. These compounds have not yet been tested in human FRDA patients.

Pioglitazone

Peroxisome proliferator activated receptor (PPAR)-γ agonists, including rosiglitazone and pioglitazone, are used to treat diabetes, but may potentially be effective in treating FRDA. One PPAR-γ agonist, Azelaoyl PAF, has been found to increase *FXN* mRNA expression and frataxin protein in primary fibroblasts from FRDA patients and healthy controls [39]. PPAR agonists may potentially treat FRDA by increasing frataxin levels and through antioxidative properties [40]. A Phase III efficacy trial of pioglitazone has been completed (www.clinicaltrials.gov/ct2/show/NCT00811681).

Nuclear factor erythroid-derived 2-related factor 2 (Nrf2) activators

Studies of fibroblasts have shown that the GAA repeats in the *FXN* gene inhibit Nrf2 in patients with FRDA, allowing oxidative mechanisms to predominate [30,40]. Therefore, the development of pharmaceuticals to activate Nrf2 will reduce intracellular oxidative stress and damage to the mitochondria in FRDA patients [30]. One such therapy, RTA 408, is in a Phase II trial (www.clinicaltrials.gov/ct2/show/NCT02255435).

• Frataxin stabilizers, enhancers & replacement

Erythropoietin

Erythropoietin (EPO) is a hormone that controls erythropoiesis, or red blood cell production. Recombinant human erythropoietin has been found to increase frataxin in cellular models [41]. An open-label study in 12 FRDA patients who received 5,000 units of recombinant human erythropoietin administered subcutaneously three times weekly reported a significant increase in frataxin levels in isolated lymphocytes after 8 weeks ($p < 0.01$) [42]. However, several additional clinical trials have failed to report improvement in clinical outcomes with EPO testing. One double-blind, placebo-controlled trial evaluated the safety and tolerability of carbamylated EPO (CEPO) in 36 ambulatory FRDA patients with > 400 GAA repeats [43]. Patients were randomized to receive CEPO (325 mg three times a week) or placebo for a total of six doses. While CEPO was found to be safe and well tolerated, neither frataxin levels nor ataxia ratings differed between the drug and placebo groups. No adverse events occurred in the CEPO group compared with the placebo group. Similarly, in another 6 month, randomized placebo-controlled, double-blind, study that assessed the safety and efficacy of EPO in increasing frataxin levels in 16 adult FRDA patients, there were no significant clinical, or biochemical outcomes with EPO use [44].

Ubiquitin competitors

Ubiquitin competitors are in the discovery phase of development in the treatment of FRDA. Frataxin degradation is controlled by the ubiquitin–proteasome system. By blocking ubiquitination of frataxin, intracellular frataxin levels increase. A ubiquitin competing molecule, NSC620299, decreased frataxin degradation within the cell; however, further study must be completed on the effect within the mitochondria. Ubiquitin competitors show potential promise as treatment of FRDA [45].

Neurotrophic factors

• Insulin/insulin-like growth factor 1 (IGF-1)

IGF-1 is a polypeptide hormone that is important to central nervous system cell proliferation and death, metabolism, and homeostasis. Neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and spinocerebellar ataxia were thought to be caused in part by malfunction in the insulin-like system and, therefore, IGF-1 has been studied in these disease states. Currently, IGF-1 is being evaluated as a potential treatment in FRDA due to its neuroprotective qualities in Purkinje cells. A total of 5 genetically confirmed FRDA patients with normal ventricular function participated in a 12-month open label study evaluating the safety, tolerability, and efficacy of IGF-1 therapy. Participants received 50 ug/kg twice a day subcutaneously. IGF-1 was well tolerated by study participants. Efficacy was determined by changes in SARA scores from baseline to end of study (assessed quarterly) and changes in echocardiogram from baseline to end of study. The annual worsening rate (AWR) of the SARA score in the study patients was -0.4+/-0.83(CI 95%) whereas the AWR for the control group was 2.05+/-1.23 (CI 95%). Echocardiograms of these patients remained normal. The main limitation of this study was its small sample

size, but results indicated improvement or slowing of the progression of FRDA symptoms [46].

Agents that increase FRDA gene expression

Epigenetic silencing of a gene can occur due to its closeness to heterochromatin, or highly condensed DNA. The expanded GAA repeats in FRDA lead to heterochromatin formation, resulting in gene silencing and reduced transcription of *FXN* mRNA [47,48].

• HDAC Inhibitors

Histone deacetylase (HDAC) inhibitors could potentially restore affected genes to normal function, by increasing histone acetylation on the *FXN* gene. Studies have shown that HDAC inhibitors increase *FXN* in cellular and animal models [49,50] and increase *FXN* mRNA in FRDA lymphocytes [50]. One HDAC inhibitor, the pimelic 2-aminobenzamide, has been identified as an inducer of *FXN* gene expression and frataxin protein [51]. Pimelic 2-aminobenzamide also upregulates *FXN* expression in patient-induced pluripotent stem cells and in animal models [52].

An open-label study evaluated the effect of nicotinamide (Vitamin B3), a drug with HDAC properties, in 10 FRDA patients who were 18 years of age and older. Patients were treated with single doses of nicotinamide in first phase of the study, daily doses of 2–8 g of oral nicotinamide for 5 days in the second phase, and were treated for an additional 8 weeks in the third phase of the study [49]. The primary study outcome was upregulation of *FXN* expression; secondary outcomes included using chromatin immunoprecipitation on peripheral blood mononuclear cells to detect differences in chromatin structure in the *FXN* gene, and assessment clinical rating scales, including the SARA, the spinocerebellar ataxia functional index (SCAFI) [53], and the speech intelligibility test [49]. Nicotinamide was generally well tolerated, with the main side effect being mild and reversible nausea. However, three out of ten patients had abnormal results from liver function tests when taking high doses (mild to moderate in two patients and severe in one patient) that resolved with a reduction in nicotinamide dose. In the first phase, there was a dose-response proportional change in frataxin from baseline to 8 h after dose ($p = 0{\cdot}0004$) although the dose of 8 g is much higher than the recommended daily dose. Further analysis suggested that 3.8 g of nicotinamide would cause a 1.5-times increase, and 7.5 g, a doubling of frataxin. There was a significant upregulation of *FXN* expression with repeated daily ingestion of 3.5–6 g, as well as changes in chromatin structure. No significant improvements were observed in clinical rating scales at end point compared with baseline, however.

• Interferon gamma

Interferon gamma is a medication that is used in chronic granulomatous disease (CGD) and malignant osteopetrosis. The medication mimics the action of interferon gamma that is naturally occurring in the body by regulating nearly all phases of the immune and inflammatory response. Its effects mediate the activation and differentiation of T-cells, B-cells, macrophages, and NK cells. It is a cytokine that is involved in iron metabolism and immune response. Interferon gamma has shown to stimulate frataxin production by increasing transcription of the *FXN* gene in both cell and animal models of FRDA [54]. In one open label study, 12 pediatric patients with FRDA received 10 mcg/m^2 interferon gamma via subcutaneous injection three times weekly then titrated up to 50 mcg/m^2 over 4 weeks, and maintained for 8 weeks. For this study, the primary outcome measure was frataxin level in whole blood; however, secondary measures included frataxin levels in platelets, PBMC, RBC and buccal cells. Additionally, neurological progression was assessed via FARS. Interferon gamma was generally well tolerated with only two patients reporting severe flu-like symptoms. Side effects resolved with a 10 mcg/m^2 reduction of dose. Results showed significant improvement in the total FARS score ($p = 0.0078$) with the upper limb coordination subscale improving approximately 3.5 points ($p = 0.02$). Surprisingly, despite these positive findings, frataxin levels did not significantly improve for patients [55]. Interferon gamma is currently being studied in a human Phase III clinical trial and appears to be the most promising new therapy currently in clinical development.

Combination therapy

The treatment of FRDA currently focuses on monotherapy to treat a particular pathway or symptom of thedisease. Several studies, however, focus on triple or combination therapy to combat multiple pathways in FRDA patients. Triple therapy with deferiprone (5–25 mg/kg/day), idebenone (10–20 mg/kg/day) and riboflavin

(10–15 mg/kg/day) was evaluated via open-label study in 13 patients with FRDA and normal cardiac function over 15–45 months. The efficacy of treatment was evaluated through change in SARA score from baseline and change in baseline in echocardiogram. While triple therapy was generally well tolerated, four patients were removed from the study to due to deferiprone-induced, low ferritin levels. There was statistically significant worsening of the SARA score from the fourth quarter of the study. The AWR of the SARA score, however, was 0.96% (CI 95%) on average in study participants whereas the theoretical AWR was 2.05+/-1.23 indicating a slowing in the progression of FRDA with the use of triple therapy. LVMI decrease by 6.5 g/m^2 in the 1st year of the study (not significant), but increased to basal value at the end of the 2nd year. LVEF remained stable in all patients except three [56].

A second open-label study of triple therapy included 11 FRDA patients with no known history of cardiomyopathy were given darbepoetin alfa (150 μg every 2–3 weeks), idebenone (10–20 mg/kg/day TID), and riboflavin (10–15 mg/kg/day TID) for 32+/-19.4 months. The effect of treatment was evaluated via change in SARA score from baseline and change in cardiac function from baseline using echocardiogram. The therapy was generally well tolerated with no AEs reported. Two patients withdrew from the study at 3 months due to hemoglobin levels above 15.5 g/dl. The SARA score showed no statistically significant improvement in participants during the first 24 months of the study. Nevertheless, the mean AWR of the SARA score for study participants at 24 months was -1.42+/-0.51 whereas theoretical AWR is 2.05+/-1.23 in the general FRDA population. This appears to indicate a decreased rate of neurological progression in study participants. The LVMI and LVEF showed nonsignificant decrease during the 4 years of study treatment. LVMI decreased between 8.3 and 21.8 g/m^2 and LVEF decreased between 3.6 and 7.5%. Triple therapy yielded cardiac stability in participants during the 4 years of treatment [57].

The initial results of triple, or combination therapy show potential promise for FRDA patients. Triple therapy slowed neurological progression of FRDA and provided cardiac benefits to participants. Whether the efficacy of triple therapy is greater than monotherapy, requires further double-blind, placebo-controlled studies.

Miscellaneous medications

• Physostigmine

Physostigmine is US FDA approved for use in anticholinergic toxicity and has been studied as a treatment in Alzheimer's disease and cerebellar ataxia [58,59]. The rationale for evaluating physostigmine in ataxia, including FRDA, is its inhibition of acetylcholinesterase, which prolongs central and peripheral effects of acetylcholine [60]. A double blind, placebo-controlled, crossover study investigated the effects of oral physostigmine on ataxic symptoms in 21 patients with various hereditary ataxias (10 patients with FRDA) over four consecutive 3-month phases [61]. Patients were initially treated with physostigmine 3 mg daily and were then titrated up to 8 mg/daily over a 3-week period, and maintained at that dose for the remainder of the treatment phase. One 9-year old patient reported nausea, which resolved after the dosage was reduced by half. Evaluators assessed patients for nystagmus, dysmetria, conversational speech, repetitive speech, lingual movements, upper and lower limb coordination, posture, stance, and gait in a standardized 'scale'. Overall, 13 patients saw improvement in symptom scores while on physostigmine in comparison to placebo ($p < 0.025$) [61]. The authors did not provide specifics on the types of ataxias that responded to physostigmine, but stated that the drug appeared to have impacts on dysmetria, dysrhythmia and speed of movement.

• Riluzole

Riluzole is currently used in the treatment of amyotrophic lateral sclerosis (ALS) and demonstrated positive effects on ataxia patients in one clinical trial [62]. It has been proposed that the mechanism of action may relate to the small conductance calcium-activated potassium channels that appear to regulate excitability in neurons found within deep cerebellar nuclei [64,65]. Abnormal, rapid firing of these neurons may contribute to ataxia, and it may be that riluzole reduces this hyperexcitability [62,66]. The efficacy of riluzole in ameliorating FRDA has not been examined in a focused trial; however, FRDA patients were included in a clinical study of various ataxias that showed mixed results [62]. In this double-blind placebo controlled trial, a sample of 40 patients with various cerebellar ataxias (eight of whom had FRDA) were randomly assigned to the riluzole 100 mg daily or placebo arm for 8 weeks [62]. The primary end point of the study

was a decrease in the ICARS score of 5 points or more at 4 and 8 weeks compared with baseline. About 68% of the participants who received riluzole experienced a decrease of 5 points or greater in their ICARS score. However, only one of the three FRDA patients in the riluzole group experienced a reduction of 5 or greater points in the ICARS score at 8 weeks, while another FRDA patient had an increase of 1 point in the ICARS at 8 weeks. One of the FRDA patients treated with placebo also had 5 points decrease in ICARS scores at 8 weeks. Two patients who received riluzole were observed to have a slight increase of alanine aminotransferase levels (<1.5 times above normal limit). Liver function tests in patients taking riluzole should be monitored once per month for 3 months, once every 3 months for the following 9 months, and intermittently thereafter [62]. Further study is necessary to determine whether riluzole has any benefit in patients with FRDA.

• Varenicline

Varenicline (Chantix®, Pfizer Inc.), an alpha4 beta2 nicotinic partial agonist, has been demonstrated to have some clinical benefit in spinocerebellar type 3 (Machado Joseph) patients [67]. However, a Phase II trial to study the effect of varenicline in FRDA patients [68] was discontinued early due to concerns of safety in FRDA patients, several of whom reported worsening balance.

• Amantadine

Amantadine is an antiviral medication that is used to treat dyskinesia in Parkinson's disease and tardive dyskinesia arising from chronic neuroleptic therapy. An open-label study involving 16 FRDA patients investigated the effects of amantadine using the Functional Ataxia Scoring Scale (FASS), which evaluates ocular movements, lingual movements, upper limb coordination, lower limb coordination, posture and gait [69]. Two blinded evaluators scored unedited video recordings, cassette recordings of speech and writing samples of each patient. An average of the raters' individual scores were used to calculate a total disability score for each patient both before and 1 h after the administration of amantadine syrup 1 mg per pound of patient body weight up to 100 mg. The 1-h postadministration TDS improved by an average of 29.5% ($p < 0.0005$) when compared with the preadministration TDS; however, the effects of amantadine gradually dissipated over 4 h. Patients who were less functionally disabled at baseline were found to have the best response to the treatment, and those without signs of congestive heart failure (n = 13) continued amantadine treatment beyond the single dose. The initial drug trial dosage for each patient was increased every 6 weeks to tolerance (max dose = 100 mg TID). While no cardiac side effects were encountered, hallucinations, constipation, livedo reticularis, and difficulty concentrating were reported [69].

A double-blind cross-over study investigated the effects of amantadine hydrochloride in 12 patients with FRDA and 2 patients with autosomal dominant cerebellar ataxia. Patients were randomly assigned to a placebo–amantadine or amantadine–placebo treatment sequence that included a 2-week interval between treatments. Manual dexterity and writing assessments were videotaped at baseline and 90 min after administration of 100 mg amantadine or placebo. Three blinded evaluators used the FASS to independently score the videos, finding no treatment effects [70].

Rehabilitation therapy

Rehabilitation therapy is a cornerstone of present-day ataxia therapy and there is evidence that physical therapy improves symptoms of cerebellar degeneration in the short-term and that, with continued exercise, benefits can be maintained long-term. A study involving 16 patients with degenerative cerebellar disease, 3 of whom had FRDA, assessed the effectiveness of a 4-week intensive coordination-training program [71]. Subjects were assessed with the ICARS, SARA, individual goal attainment scores and quantitative movement analysis 8 weeks prior to treatment, immediately before, directly after, and 8 weeks after training. Improvement was evident for patients after rehabilitation intervention. Furthermore, patients with ataxia due to degeneration of the afferent pathways, including those with FRDA, had significant improvement in the SARA ($p < 0.026$), ICARS ($p < 0.027$) and Berg Balance scores ($p < 0.03$) [71]. In a follow-up study, these subjects were instructed to continue exercises at home for 1 year to evaluate long-term effects of rehabilitation therapy. Due to disease progression, subjects experienced a decline of motor function and an increase of ataxia symptoms after 1 year; however, the results implied long-term rehabilitation therapy impedes the natural

disease progression, allowing patients to retain motor function and coordination longer than they otherwise would have [72].

Additionally, because FRDA begins in adolescence, videogame therapy provides a novel treatment tool for these patients. Physiotherapy exercises complemented by whole-body and coordinative training on commercially available videogame technology have been found to be beneficial for both early onset and advanced, multisystem degenerative ataxia patients [73–75]. Videogame-based training involves motivational reward incentives and stimulating exercise environments. This training incorporates interactive exercises within dynamic environments that can stimulate and train patients' real-world activities and anticipatory coordination capacities [73]. And additional advantage of video game therapy for progressed ataxia patients with mobility impairments is the elimination of the burden of travel because the exercises can be performed in the home.

Gene therapy

Research in gene replacement therapy is another treatment under development. One study investigated the use of gene therapy in a conditional mouse model with complete *Fxn* deletion in cardiac and skeletal muscle (Mck-Cre-Fxn $^{L3/L-}$ mice). The mice received adeno-associated virus rh10 vector expressing human *FXN* intravenously. The treatment fully prevented cardiomyopathy in the mouse models. Additionally, the treatment was also given to the mice after the onset of heart failure. The late administration of the therapy completely reversed cardiomyopathy in the mice at the functional, cellular, and molecular levels [76].

A second genetic study used zinc finger nucleases (ZFNs) to excise the GAA expansion repeat on one allele of FRDA patient cells. The study was performed on FRDA patient derived lymphoblast, fibroblasts, and iPSCs. Excision was performed on only one allele because gene silencing occurs in patients that are homozygous for GAA repeats. The excision of the GAA repeats lead to increase *FXN* mRNA and protein expression in lymphoblasts, fibroblasts, and iPSCs derived neuronal cells. Also noted in iPSC derived neuronal cells were correction of the FRDA biomarker signature and increased aconitase activity and ATP levels [77].

Another genetic study considered the effect of R loops, an RNA/DNA hybrid that forms on repeat expansions of the *FXN* gene in FRDA. The R loops are resistant to degradation and silence the expression of the *FXN* gene. This inhibition of the *FXN* gene in turn leads to the formation of heterochromatin and oxidative stress. Therapies that target R loops are a potential treatment in FRDA [78].

The effects of *FXN* deletion have also been examined in yeast strains. One strain expressing single scaffold protein, M107I Isu 1, in cells with *FXN* deletion facilitated Fe-S cluster formation in the mitochondria although at a lower rate than normal. Thus M107I Isu1 is viewed as having potential for FRDA treatment [79].

Conclusion

Our understanding of the mechanism of FRDA has lead us to identify frataxin deficiency as the primary cause of the disease, and the replacement of frataxin is a critical mechanism-based therapy. In addition, the monitoring peripheral frataxin levels have become an important biomarker for treatment development. Both HDAC inhibitors and interferon gamma show potential as frataxin enhancement therapies and thus could hold promise in future treatment for FRDA. The Freidreich's Ataxia Research Alliance has compiled a research pipeline at [82] which provides the most current state of preclinical and clinical research in FRDA.

Rehabilitative and pharmacologic interventions may offer FRDA patients symptom relief. However the extent of benefit from pharmaceutical agents is unclear, as studies investigating the treatment of FRDA have often provided inconclusive and contradicting results arising from inhomogeneity in trial populations, and conflicting rates of improvement in the placebo arms. In older studies, nonvalidated measures were used. Future studies can be expected to evaluate treatments in homogenous populations. The use and development of model clinical instruments and technologies such as computerized gait monitoring, speech evaluation, and imaging along with molecular indices adds precision and new avenues for capturing ataxic symptoms and physiologic functions. Thereby, resulting in more precise and extended measurement of disease progression and therapeutic effects. There is currently no FDA-approved disease-modifying agent to correct FRDA at the genetic or cellular level, and development of such an agent is crucial to treat this disease.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Klockgether T. Parkinsonism & related disorders. Ataxias. *Pakinsonism Relat. Disord.* 13, S391–S394 (2007).

2 Labuda M, Labuda D, Miranda C *et al.* Unique origin and specific ethnic distribution of the Friedreich ataxia GAA expansion. *Neurology* 54, 2322–2324 (2000).

3 Filla A, Michele G, Cavalcanti F *et al.* The relationship between trinucleotide (GAA) repeat length and clinical features in Friedreich ataxia. *Am. J. Hum. Genet.* 59, 554–560 (1996).

4 Manto M, Marmolino D. Cerebellar ataxias. *Curr. Opin. Neurol.* 22, 419–429 (2009).

5 Dürr A, Cossee M, Agid Y *et al.* Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N. Engl. J. Med.* 335, 1169–1175 (1996).

6 Saute JAM, Donis KC, Serrano-Munuera C *et al.* Ataxia rating scales – psychometric profiles, natural history and their application in clinical trials. *Cerebellum* 11, 488–504 (2012).

•• **This is a comprehensive review of ataxia rating scales where the scales are systematically reviewed and critiqued.**

7 Reetz K, Dogan I, Costa AS *et al.* Bilogical and clinical characteristics of the European Friedreich's ataxia consortium for translational studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol.* 14(2), 174–182 (2015).

8 Cano SJ, Riazi A, Schapira AH *et al.* Friedreich's ataxia impact scale: a new measure striving to provide the flexibility required by today's studies. *Mov. Disord.* 24(7), 984–992 (2009).

9 Trouillas P, Takayanagi T, Hallett M *et al.* International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. *J. Neurol. Sci.* 145, 205–211 (1997).

10 Bürk K, Schulz S, Schulz J. Monitoring progression in Friedreich ataxia (FRDA): the use of clinical scales. *J. Neurochem.* 126(Suppl. 1), 118–124 (2013).

11 Subramony SH, May W, Lynch D *et al.* Measuring Friedreich ataxia: interrater reliability of a neurologic rating scale. *Neurology* 64, 1261–1262 (2005).

12 Gillis JC, Benefield P, McTavish D. Idebenone: a review of its pharmacodynamics and pharmacokinetic properties, and therapeutic use in age-related cognitive disorders. *Drugs Aging* 5, 133–152 (1994).

13 Lagedrost S, Sutton M, Cohen M *et al.* Idebenone in Friedreich ataxia cardiomyopathy-results from a 6-month Phase III study (IONIA). *Am. Heart J.* 161, 639–645 (2011).

14 Lynch DR, Perlman SL, Meier T. A phase 3 double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. *Arch. Neurol.* 67(8), 941–947 (2010).

15 Hausse AO, Aggoun Y, Bonnet D *et al.* Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *Heart.* 87, 346–349 (2002).

16 Mariotti C, Solari A, Torta D, Marano L, Fiorentini C, Di Donato S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 60(10), 1676–1679 (2003).

17 Pineda M, Arpa J, Montero R *et al.* Idebenone treatment in pediatric and adult patients with Friedreich ataxia: long-term follow-up. *Eur. J. Paediatr. Neurol.* 12, 470–475. (2008).

18 DiProspero NA, Baker A, Jeffries N, Fischbeck KH. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. *Lancet Neurol.* 6, 878–886 (2007).

19 Lodi R, Hart PE, Rajagopalan B *et al.* Antioxidant treatment improves *in vivo* cardiac and skeletal muscle bioenergetics in patients with ataxia. *Ann. Neurol.* 49(5), 590–596 (2001).

20 Hart P, Lodi R, Rajagopalan B *et al.* Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up. *Arch. Neurol.* 62(4), 621–626 (2005).

21 Cooper JM, Kolipara LV, Hart PE, Bradley JL, Schapira AH. Coenzyme Q10 and vitamin E deficiency in Friedreich's ataxia: predictor of efficiency of vitamin E and coenzyme Q10 therapy. *Eur. J. Neurol.* 15(12), 1371–1379 (2008).

22 Lynch DR, Willi SM, Wilson RB *et al.* A0001 in Friedreich ataxia: biochemical characterization and effects in a clinical trial. *Mov. Disord.* 27(8), 1026–1033 (2012).

23 Li L, Voullaire L, Sandi C *et al.* Pharmacological screening using an FXN-EGFP cellular genomic reporter assay for the therapy of Friedreich ataxia. *PLoS ONE* 8(2), e55910 (2013).

24 Yiu EM, Tai G, Peverill RE *et al.* An open-label trial in Friedreich ataxia suggest clinical benefit with high-dose resveratrol, without effect on frataxin levels. *J. Neurol.* 262(5), 1344–1353 (2015).

25 Schöls L, Zange J, Abele M *et al.* L-Carnitine and creatine in Friedreich's ataxia, A randomized, placebo-controlled crossover trial. *J. Neural. Transm.* 112, 789–796 (2005).

26 Villa RF, Turpeenoja L, Benzi G, Giuffrida Stella AM. Action of actylcarnitine on age-dependent modifications of mitochondrial membrane proteins from rat cerebellum. *Neurochem. Res.* 13(10), 909–916 (1988).

27 Sorbi S, Forleo P, Fani C, Piacentini S. Double-blind, crossover, placebo-controlled clinical trial with L-acetylcarnitine in patients with degenerative cerebellar ataxia. *Clin. Neuropharmacol.* 23(2), 114–118 (2000).

28 Pourcher E, Barbeau A. Field testing of an ataxia scoring and staging system. *Can. J. Neurol. Sci.* 7, 339–344 (1980).

29 Angel RW. The rebound phenomenon of Gordon Holmes. *Arch. Neurol.* 34(4), 250 (1977).

30 Albeti R, Uzun E, Renganathan I *et al.* Targeting lipid peroxidation and mitochondrial I mbalance in Friedreich's ataxia. *Pharmacol. Res.* 99, 344–350 (2015).

31 Hill S, Lamberson CR, Xu L, To R *et al.* Small amounts of isotopereinforced polyunsaturated fatty acids suppress lipid autoxidation. *Free Radic. Biol. Med.* 53(4), 893–906 (2012).

32 Lamberson CR, Xu L, Muchalski H *et al.* Unusual kinetic isotope effects of deuterium reinforced polyunsaturated clinical features fatty acids in tocopherol-mediated free radical chain oxidations. *J. Am. Chem. Soc.* 136(3), 838–41 (2014).

33 Pandolfo M, Hausmann L. Deferiprone for the treatment of Friedreich's ataxia. *J. Neurochem.* 126(1), 142–146 (2013).

34 Pandolfo M, Arpa J, Delatycki MD *et al.* Deferiprone in Friedreich ataxia: a 6-month randomized controlled trial. *Ann. Neurol.* 76(4), 509–521 (2014).

35 Velasco-Sanchez D, Aracil A, Montero R *et al.* Combined therapy with idebenone and deferiprone in patients with Friedreich's ataxia. *Cerebellum* 10(1), 1–8 (2011).

36 Pandolfo M, Igoillo-Esteve M, Hu A *et al.* Study of beta cells and neurons indicate incretin analogs as potential therapeutics for Friedreich's ataxia. *Neurology* 84(14), Suppl. S32.005 (2015).

37 Igoillo-Esteve M, Gurgul-Convey E, Hu A *et al.* Unveiling a common mechanism of apoptosis in β-cells and neurons in Friedreich's ataxia. *Hum. Mol. Genet.* 24(8), 2274–2286 (2015).

38 Cnop M, Igoillo-Esteve M, Rai M *et al.* Central role and mechanism of β-cell dysfunction and death in Friedreich ataxia-associated diabetes. *Ann. Neurol.* 72(6), 971–982 (2012).

39 Marmolino D, Fabio Pinelli M *et al.* PPAR-γ agonist azelaoyl PAF Increases frataxin protein and mRNA expression. New implications for the Friedreich ataxia therapy. *Cerebellum* 8, 98–103 (2009).

40 Paupe V, Dassa EP, Goncalves S *et al.* Impaired nuclear Nrf2 translocation undermines the oxidative stress response in Friedreich ataxia. *PLoS ONE* 4, 4253–4264 (2009).

41 Sturm B, Stupphann D, KAUN C *et al.* Recombinant human erythropoietin: effects on frataxin expression *in vitro*. *Eur. J. Clin. Invest.* 35(11), 711–717 (2005).

42 Boesch S, Strum B, Hering S, Goldenberg H, Poeve W, Scheiber-Mojdehkar B. Friedreich ataxia: clinical pilot trial with recombinant human erythropoietin. *Ann. Neurol.* 62(5), 521–524 (2007).

43 Boesch S, Nachnauer W, Mariotti C *et al.* Safety and tolerability of carbamylated erythropoietin in Friedreich ataxia. *Mov. Disord.* 29(7), 935–939 (2014).

44 Mariotti C, Francellu R, Caldarazzo S *et al.* Erythropoietin in Friedreich ataxia: no effect on frataxin in a randomized controlled trial. *Mov. Disord.* (27)3, 446–449 (2012).

45 Rufini A, Fortuni S, Arcuri G *et al.* Preventing the ubiquitin-proteasome-dependent degradation of frataxin, the protein defective in Friedreich's ataxia. *Hum. Mol. Genet.* 20(7), 1253–1261 (2011).

46 Sanz-Gallego I, Torres-Aleman I, Arpa J. IGF-1 in Friedreich's ataxia – proof-of-concept trial. *Cerebellum Ataxias.* 1(10), doi:10.1186/2053–8871–1–10 (2014).

47 Gottesfeld JM, Rusche JR, Pandolfo M. Increasing frataxin gene expression with histone deacetylase inhibitors as a therapeutic approach for Friedreich ataxia. *J. Neurochem.* 126(10), 147–154 (2013).

48 Silva AM, Brown JM, Buckle VJ, Wade-Martins R, Lufino MM. Expended GAA repeats impair FXN gene expression and reposition the FXN locus to the nuclear lamina in single cells. *Hum. Mol. Genet.* 24(12), 3457–3471 (2015).

49 Libri V, Yandim C, Athanasopoulos S *et al.* Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich ataxia: an exploratory, open-label, dose escalation study. *Lancet* 384, 504–513 (2014).

50 Herman D, Jenssen K, Burnett R *et al.* Histine deacetylase inhibitors reverse gene silencing in Friedreich's ataxia. *Nat. Chem. Biol.* 2(10), 551–558 (2006).

51 Gottesfeld JM, Rusche JR, Pandolfo M. Increasing frataxin gene expression with histone deacetylase inhibitors as a therapeutic approach for Friedreich ataxia. *J. Neurochem.* 126(1), 147–154 (2013).

•• **An in-depth review of HDAC inhibitors, their effectiveness and the prospect of future clinical studies.**

52 Rai M, Soragni E, Jenssen K *et al.* HDAC inhibitors correct frataxin deficiency in a Friedreich mouse model. *PLoS ONE* 3(4), e1958 (2008).

53 Schmitz-Hubsch T, Giunti P, Stephenson DA *et al.* SCA Functional Index: a useful compound performance measure for spinocerebellar ataxia. *Neurology* 71, 486–492 (2008).

54 Tomassini B, Arcuri G, Fortuni S *et al.* Interferon gamma upregulates frataxin and corrects the functional deficits in a Friedreich ataxia model. *Hum. Mol. Genet.* 21, 2855–2861 (2012).

• **Provides detailed information on Interferon gamma and its potential as an effective treatment of Friedreich's ataxia.**

55 Seyer L, Greeley N, Foerster D *et al.* Open-label pilot study of interferon gamma-1b in Friedreich ataxia. *Acta Neurol. Scand.* 132(1), 7–15 (2015).

56 Arpa J, Sanz-Gallego I, Rodriguez-de-Rivera FJ *et al.* Triple therapy with deferiprone, idebenone and riboflavin in Friedreich's ataxia – open-label trial. *Acta. Neurol. Scand.* 129, 32–40 (2014).

57 Arpa J, Sanz-Gallego I, Rodriguez-de-Rivera FJ *et al.* Triple therapy with darbepoetin alfa, idebenone, and riboflavin in Friedreich's ataxia: an open-label trial. *Cerebellum* 12, 713–720 (2013).

58 Coelho F, Birks J. Physostigmine for Alzheimer's disease. *Cochrane Databse Syst. Rev.* 2, CD001499 (2001).

59 Wessel k, Langenberger K, Nitschke M *et al.* Double-blind crossover study with physostigimine in patients with degenerative cerebellar disease. *Arch. Neurol.* 54(4), 397–400 (1997).

60 Rodriguez-Budelli M, Kark RAP, Blass JP, Spence MA. Action of physostigmine on inherited ataxia. *Adv. Neurol.* 21, 195–204 (1978).

61 Kark RAP, Budelli MMR, Wachsner R. Double-blind, triple-crossover trial of low doses of oral physostigmine in inherited ataxias. *Neurology* 31, 288–292 (1981).

62 Ristori G, Romano S, Visconti A *et al.* Riluzole in cerebellar ataxia. *Neurology* 74, 839–845 (2010).

63 Romano S, Coarelli G, Marcotulli C *et al.* Riluzole in patients with hereditary cerebellar ataxia: a randomized, double-blind, placebo-controlled trial. *Lancet Neurol.* 14, 985–991 (2015).

64 Alviña K, Khodakhah K. Selective regulation of spontaneous activity of neurons if the deep cerebellar nuclei by N-type calcium channels in juvenile rats. *J. Physiol.* 10, 2523–2538 (2008).

65 Feng S, Jaeger D. The role of SK calcium-dependent potassium currents on regulating the activity of deep cerebellar nucleus neurons: a dynamic clamp study. *Cerebellum* 7(4), 542–543 (2008).

66 Cao YJ, Dreixler JC, Couey JJ, Houamed KM. Modulation of recombinant and native neuronal SK channels by the neuroprotective drug riluzole. *Eur. J. Pharmacol.* 449, 47–54 (2002).

67 Zesiewicz T, Greenstein PE, Sullivan KL *et al.* A randomized trail varenicline (Chantix) for the treatment of spinocerebellar ataxia type 3. *Neurology* 78(8), 545–550 (2012).

68 Clinical Trials Database. Identifier: NCT00803868 https://clinicaltrials.gov/ct2/show/NCT00803868

69 Peterson PL, Saad J, Nigro MA. The treatment of Friedeich's ataxia with amantadine. *Neurology* 38, 1478–1480 (1988).

70 Filla A, De Michele G, Orefice G *et al.* A double-blind cross-over trial of amantadine hydrochloride in Friedreich's ataxia. *Can. J. Neurol. Sci.* 20, 52–55 (1993).

71 Ilg W, Synofzik M, Brötz D, Burkard S, Giese MA, Schöls L. Intensive coordinative training improves motor performance in degenerative cerebellar disease. *Neurology* 73, 1823–1830 (2009).

72 Ilg W, Synofzik M, Brötz D, Burkard S, Giese MA, Schöls L. Long-term effects of coordinative training in degenerative cerebellar disease. *Movm. Disord.* 25, 2239–2246 (2010).

73 Synofzik M, Ilg W. Motor training in degenerative spinocerebellar disease: Ataxia-specific improvements by intensive physiotherapy and exergames. *Biomed. Res. Int.* doi:10.1155/2014/583507 (2014).

74 Ilg W, Schatton C, Schicks j *et al.* Video game-based coordinative training improves ataxia in children with degenerative ataxia. *Neurology* 79(20), 2056–2060 (2012).

75 Synofzik M, Schatton C, Giese M *et al.* Videogame-based coordinative training can improve advanced, multisystemic early-onset ataxia. *J. Neurol.* 260(10), 2656–2658 (2013).

76 Perdomini M, Belbellaa B, Monassier L *et al.* Prevention and reversal of severe mitochondiral cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia. *Nat. Med.* 20, 542–547 (2014).

•• **Provides information on promising research in gene therapy for treating cardiomyopathy in the Friedreich's ataxia population.**

77 Li Y, Polak U, Bhalla AD *et al.* Excision of expanded GAA repeats alleviates the molecular phenotype of Friedreich's ataxia. *Mol. Ther.* 23(6), 1055–1065 (2015).

78 Groh M, Lufino MMP, Wade-Martins R *et al.* R-loops associated with triplet repeat expansion promote gene silencing in Friedreich ataxia and fragile X syndrome. *PLOS Genetics* 10(5), 1–13 (2014).

79 Yoon H, Knight SAB, Pandey A *et al.* Frataxin-bypassin Isu1: characterization of the bypass activity in cells and mitochondria. *Biochem. J.* 459(1), 71–81 (2014).

80 Buyse G, Mertens L, Di Salvo G *et al.* Idebenone treatment in Friedreich ataxia: neurological, cardiac and biochemical monitoring. *Neurology* 60(10), 1679–1681 (2003).

81 Rustin P, vonKliest-Retzow JC, Chantrel-Groussard K *et al.* Effect of idebenone on cardiomyopathy in Friedreich ataxia: a preliminary study. *Lancet* 354(9177), 477–479 (1999).

82 Boddaert N, Le Quan Sang KH, Rötig A *et al.* Antioxidant treatment of patients with Friedreich ataxia: four year follow up. *Arch. Neurol.* 62(4), 621–626 (2005).

83 The Friedreich's Ataxia Treatment Pipeline is a visual tool for communicating the progress of research and development on lead therapeutic candidates. www.curefa.org/pipeline