REVIEW

Co-enzyme Q_{10} and idebenone use in Friedreich's ataxia

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Abstract

Friedreich's ataxia is a debilitating progressive neurodegenerative disease associated with cardiomyopathy and other features. The underlying cause is a deficiency of the mitochondrial protein frataxin which causes mitochondrial iron deposition, increased oxidative stress and impaired adenosine triphosphate production. Over the last 15 years, multiple clinical trials have assessed the efficacy of antioxidant agents in this disease. This article reviews trials of the two most important agents, namely co-enzyme Q_{10} and idebenone.

Keywords: clinical trials, co-enzyme Q_{10}, Friedreich's ataxia, idebenone.

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Friedreich's ataxia (FRDA) is a rare autosomal recessive degenerative disease usually of early onset which causes progressive neurological and non-neurological features. Initial symptoms are typically gait ataxia and imbalance but can progress to include impaired upper and lower limb coordination, dysarthria, dysphagia, eye movement abnormalities, areflexia, sensory loss, and muscle weakness. Affected individuals often require aids to walking and ultimately may require a wheelchair. Non-neurological features include cardiomyopathy, diabetes mellitus, kyphoscoliosis, and foot deformities such as *pes cavus* and *talipes equinovarus* (Harding 1981; Dürr *et al.* 1996). A recent study (Giunti *et al.* 2013) showed that the annual burden of FRDA is significant and falls on the health and social care sectors, on society, on caregivers and on the individuals themselves. It has been estimated that the annual cost per person is between £11 818 and £18 774 in the United Kingdom depending on whether the cost of long-term unemployment was included.

The vast majority of affected patients have a homozygous guanine-adenine-adenine (GAA) expansion in the first intron of the *FXN* gene at chromosome 9q21.11 which causes decreased production of frataxin protein (Campuzano *et al.* 1996, 1997). Frataxin is a highly conserved protein localized to the mitochondrial matrix and associated with various aspects of iron metabolism and homeostasis, such as heme biogenesis and the formation of iron–sulfur clusters (Pandolfo and Pastore 2009). Frataxin deficiency causes mitochondrial iron accumulation (Delatycki *et al.* 1999), increased oxidative stress (Schulz *et al.* 2000; Emond *et al.* 2000; Piemonte *et al.* 2001), and impaired ATP production (Lodi *et al.* 1999). Individuals with FRDA have deficient activity of the iron–sulfur cluster-containing subunits of mitochondrial electron transport complexes I, II, and III as well as aconitase, particularly in cardiac tissue (Rötig *et al.* 1997; Bradley *et al.* 2000).

REVIEW

The biochemical reactions of the mitochondrial electron transport chain (ETC) produce reactive oxygen species (ROS) which can damage other molecules and structures such as proteins, lipids, membranes, and nucleic acids, including mitochondrial DNA (mtDNA). MtDNA is susceptible to damage by ROS because its proximity to the site of ROS production, and its absence of protective histones. As the complexes of the ETC are partially encoded in the mtDNA, its damage by ROS can further exacerbate mitochondrial dysfunction producing further ROS (Orsucci *et al.* 2011). Decreased levels of mtDNA have been found in a yeast model of FRDA (Wilson and Roof 1997). Variation in mtDNA haplogroup can influence age at onset in human subjects (Giacchetti *et al.* 2004). Increased levels of mtDNA deletions and point mutations have been found in patients with FRDA (Houshmand *et al.* 2006; Heidari *et al.* 2009).

Co–enzyme Q_{10}

Co-enzyme Q_{10} (2,3-dimethoxy-5-methyl-6-decaprenyl benzoquinone or ubiquinone) is a small lipophilic molecule present within the inner mitochondrial membrane in association with the ETC complexes, which transfers electrons between complexes I and II, and from oxidation of fatty acids and branched chain amino acids, to complex III resulting in the ultimate production of ATP (see Fig. 1). Structurally, it has a benzoquinone nucleus which is readily reduced to ubisemiquinone and ultimately to ubiquinol, as well as a 10-unit polyisoprenoid side chain conferring hydrophobicity (Orsucci *et al.* 2011; Hargreaves 2003; Lenaz *et al.* 2007) (see Fig. 2). Deficiency of co-enzyme Q_{10} can cause an early-onset ataxic syndrome responsive to supplementation with co-enzyme Q_{10} (Lamperti *et al.* 2003.

Because of its facility at undergoing redox reactions, co-enzyme Q_{10} acts as a potent antioxidant preventing oxidation of proteins, lipids, lipoproteins & DNA, and maintaining other antioxidants such as ascorbic acid and vitamin E. It is the only endogenously synthesized lipid-soluble antioxidant. It also contributes to preventing the opening of the mitochondrial membrane transition pore which permits passage of enzymes and other molecules which can contribute to the depolarization of the mitochondrial membrane potential, apoptotic events and DNA fragmentation. Co-enzyme Q_{10} may also have anti-inflammatory and anti-atherosclerotic properties (Bentinger *et al.* 2010). Co-enzyme Q_{10} links pyrimidine synthesis to the ETC by transferring electrons from the oxidation of dihydro-orotate to orotate by the flavoprotein, dihydro-orotate dehydrogenase. This enzyme form part of the pyrimidine biosynthetic pathway between glutamine and uridine mono-
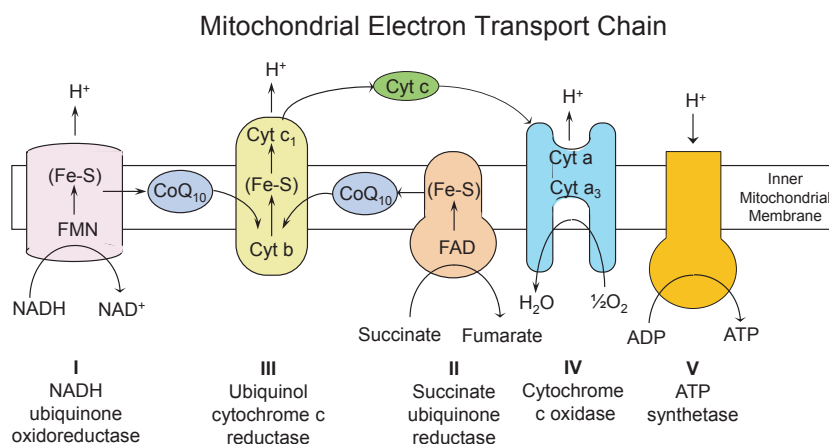
Mitochondrial Electron Transport Chain

Fig. 1 The mitochondrial electron transport chain consists of a series of complexes which undergo redox reactions, transferring electrons from donor to acceptor molecules, and generating a transmembrane proton gradient which ultimately drives the production of ATP. Complex I oxidizes NADH, the product of glycolysis, the citric acid cycle and fatty acid oxidation. Electrons are transferred via the flavoprotein FMN and an Fe-S cluster to co-enzyme Q10 which is reduced. Complex II oxidizes succinate directly from the citric acid cycle. Electrons are transferred via the flavoprotein FAD and an Fe-S cluster to co-enzyme Q10. Reduced co-enzyme Q10 (ubiquinol) from complexes I and II is the substrate for complex III, also known as the cytochrome bc1 complex. Ubiquinol is reoxidized to co-enzyme Q10 and electrons are transferred via cytochrome b, c1, an Fe-S cluster and the 'Q cycle' to the water-soluble enzyme cytochrome c which transfers the electrons to complex IV. Frataxin is thought to play a role in the biogenesis of Fe-S clusters. Idebenone probably acts by transferring electrons between complexes I and III in a similar way to co-enzyme Q10. The reduced intermediate form 2H-idebenone (idebenol) may also inhibit lipid peroxidation and its deleterious consequences (Meier and Buyse 2009; Sugiyama *et al.* 1985). ADP, Adenosine diphosphate; ATP, Adenosine triphosphate; CoQ10, Coenzyme Q10; Cyt, Cytochrome; FAD, Flavin adenosine dinucleotide; Fe-S, Iron–sulfur cluster; FMN, Flavin mononucleotide; NAD+, Nicotinamide adenine dinucleotide; NADH, Reduced nicotinamide adenine dinucleotide.
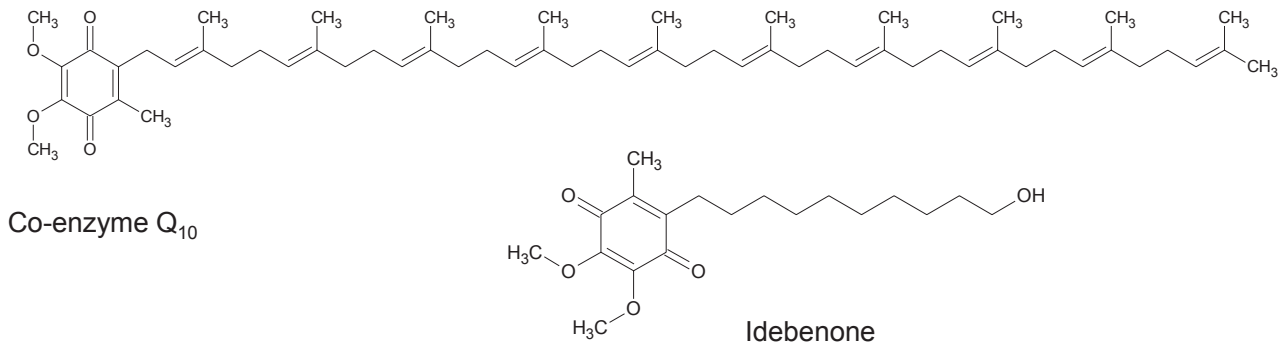
Fig. 2 Chemical structures of co-enzyme Q$_{10}$ and idebenone showing the common reducible benzoquinone nucleus and lipophilic side chains.

phosphate, and is also localized to the inner mitochondrial membrane (Evans and Guy 2004; Lenaz *et al.* 2007). It is possible that this may contribute to the decreased levels of mtDNA seen in FRDA (Bradley *et al.* 2000).

Uptake of co-enzyme Q$_{10}$ from the gut is relatively poor due to its hydrophobic nature. A single oral dose of 30 mg of oil- or granule-based co-enzyme Q$_{10}$ has only marginal effects on plasma levels. However, dose-dependent increases in plasma levels are seen up to a dose of 200 mg/day, which results in a 6.1-fold increase in plasma co-enzyme Q$_{10}$ levels (Kaikkonen *et al.* 2002). At high doses, increases in plasma co-enzyme Q$_{10}$ levels begin to plateau at a dose of around 2400 mg/day (Shults *et al.* 2004), although this may be influenced by the formulation. Attempts have therefore been made to enhance bioavailability by solubilization and other techniques (Bhagavan and Chopra 2006). The extent of co-enzyme Q$_{10}$ passage across the blood–brain barrier remains controversial. Determining this is complicated by the fact that there is endogenous synthesis of co-enzyme Q$_{10}$, and that in rodents, which have been used for distribution studies, the predominant form of co-enzyme Q found is in fact co-enzyme Q$_9$ whose ratio to co-enzyme Q$_{10}$ also varies between tissues. Oral administration of co-enzyme Q$_{10}$ in mice (Smith *et al.* 2006) and rats (Matthews *et al.* 1998; Kwong *et al.* 2002) resulted in significantly increased levels of co-enzyme Q in the brain compared to controls. When tritiated co-enzyme Q$_{10}$ was given intra-peritoneally to rats (Bentinger *et al.* 2003), it was detectable in the brain although in much lower concentrations than in liver, spleen, white blood cells, and other tissues. To our knowledge, central nervous system penetration of oral co-enzyme Q$_{10}$ has not been evaluated in humans, although CSF can be determined (Duberley *et al.* 2013).

Given its antioxidant properties and ability to facilitate electron transfer along the ETC and so increase ATP production, clinical trials of co-enzyme Q$_{10}$ were initiated (see Table 1). Lodi *et al.* (2001) treated 10 FRDA patients with 400 mg/day co-enzyme Q$_{10}$ and 2100 IU/day vitamin E for 6 months and monitored cardiac outcome by echocardiography and 31-phosphorus magnetic resonance spectroscopy, and neurological outcome by the international cooperative ataxia rating scale (ICARS). They found no consistent benefit in ICARS or echocardiographic findings but within 3 months, the cardiac phosphocreatine:ATP ratio had increased by 78% and the maximum rate of skeletal (calf) muscle mitochondrial ATP production had increased by 39% compared to baseline. The same group (Hart *et al.* 2005) continued to study these 10 patients over 4 years at the same dose and found the above parameters were maintained or moderately improved. There was no significant change in interventricular septal thickness at diastole (IVSd) or left ventricular posterior wall thickness at diastole (LVPWd) as measured by echocardiography, but there was a significant increase in fractional shortening (echocardiographic measurement that is closely related to the ejection fraction), irrespective of left ventricular hypertrophy. Over the trial period, the total ICARS score for the group did not increase (as might have been expected in a progressive condition) and there was a non-significant improvement in the kinetic subscore of the ICARS. In particular, in seven patients, these measures were better than expected compared to cross-sectional data from a comparable control group of 77 FRDA patients. This led to the idea of responders and non-responders to co-enzyme Q$_{10}$ treatment which was investigated in a larger randomized, double-blind multiple-dose study over 2 years (Cooper *et al.* 2008). In this study, 50 FRDA patients were randomized to either 600 mg/day co-enzyme Q$_{10}$ and 2100 IU/day vitamin E, or 30 mg/day co-enzyme Q$_{10}$ and 24 IU/day vitamin E. Over the study period, there was an increase in the ICARS score in both the high- and low-dose groups, but, 49% of the 43 patients who completed the 2 year trial, had better ICARS scores than expected when compared to the cross-sectional comparator group. *Post hoc* analysis revealed that the responder group had significantly lower baseline serum co-enzyme Q$_{10}$ levels, indicating that this might be a predictor for response to antioxidant therapy. To our knowledge, these are the only trials of co-enzyme Q$_{10}$ in FRDA.

Idebenone

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone) is a structural analog of co-enzyme Q_{10} with a benzoquinone nucleus and a hydroxydecyl side chain (Meier and Buyse 2009) (see Fig. 2). It was first developed and licensed in Japan for use in Alzheimer's disease and therefore has extensive clinical safety and tolerability data including extensive post-marketing data, in more than 8 million people. Physiologically, it can act as an electron carrier within the ETC (Sugiyama *et al.* 1985; Esposti *et al.* 1996) and has similar antioxidant properties to co-enzyme Q_{10} (Suno and Nagaoka 1984). Theoretically, because of its decreased molecular weight and increased water solubility, idebenone should have greater bioavailability than co-enzyme Q_{10}. To our knowledge, no direct comparative studies have been published. In rats given oral or intravenous idebenone, the drug was distributed widely with the greatest concentrations in the gut, liver, and kidney, with a smaller proportion present in brain and spinal cord. Subcellular distribution showed a significant proportion in brain mitochondria (Torii *et al.* 1985). After intravenous administration in rats, it is estimated that 0.45–0.56% of the dose distributed to the brain (Nagai *et al.* 1989). In patients with FRDA on low-dose idebenone (10 mg/kg/day), median CSF levels were 300 times lower than those in plasma, and undetectable in three of five cases (Artuch *et al.* 2004). There was no association between CSF and plasma levels. Further work needs to be undertaken to understand the distribution of co-enzyme Q_{10} and idebenone, particularly in affected tissues.

Initial human studies of idebenone in FRDA used low doses and concentrated on cardiac outcomes (see Table 1). The first preliminary study of three patients aged 11–21 years with 5 mg/kg/day idebenone for 4–9 months in an open-label study showed decreases in IVSd, LVPWd, and left ventricular mass index (LVMI) by echocardiography. The authors reported subjective improvement in strength and delicate movements such as handwriting (Rustin *et al.* 1999). Follow-up of one of these patients over 5 years showed that markers of cardiac hypertrophy had further improved until there was no evidence of cardiac dysfunction and cardiac medications were stopped (Rustin *et al.* 2004). Endomyocardial microbiopsy showed that the activity of the ETC enzymes and aconitase had largely returned to normal. The same group went on to study 40 patients with FRDA aged 4–22 years in an open-label study of idebenone at 5 mg/kg/day over 6 months (Rustin *et al.* 2002; Hausse *et al.* 2002). In this study, 48% of patients showed a more than 20% reduction in cardiac mass over the study period, and the remainder showed stable or slightly decreased cardiac mass with no patient showing an increase greater than 20%. Improvements in left ventricular outflow tract obstruction and fractional shortening were also noted in a subset of affected patients. In two patients with worsening cardiac parameters, doses up to 15 mg/kg/day were given which were said to stabilize these measures.

An early study followed biochemical markers of oxidative stress rather than clinical outcomes. Schulz *et al.* (2000) measured levels of plasma dihydroxybenzoic acid after salicylate administration – a marker of hydroxyl radical attack – and urinary 8-hydroxy-2′-deoxyguanosine (8OH2′dG) – a marker of oxidative DNA attack – in eight patients with FRDA treated open-label with 5 mg/kg/day of idebenone over 8 weeks. They found a 2.6-fold increase in normalized 8OH2′dG levels, but no change in dihydroxybenzoic acid levels compared with untreated FRDA patients and concluded that 8OH2′dG levels might be used as a biomarker in monitoring therapeutic trials in patients with FRDA.

Further early studies combined biochemical markers with clinical measures. Schöls *et al.* (2001) used 31-phosphorus magnetic resonance spectroscopy to study phosphocreatine recovery in skeletal muscle after exercise as a measure of oxidative phosphorylation, in a double-blind, placebo-controlled crossover trial in 9 ambulant FRDA patients treated with 360 mg/day of idebenone over 6 weeks. Idebenone treatment did not alter phosphocreatine recovery and almost all other measures of oxidative phosphorylation. Similarly, neurological measures including the ICARS, and cardiac parameters measured by echocardiography and electrocardiogram were unchanged. This was the only placebo-controlled study not to show an improvement in cardiac markers, which may have been because of the short duration of treatment.

Arnold *et al.* (2006), in a largely observational study of 20 FRDA patients of whom 16 were already taking 5–10 mg/kg/day of idebenone before the start of the study, recorded neurological, neurophysiological, cardiac and biochemical parameters in patients on and off treatment. For the 10 patients for which follow-up data were available (over a mean duration of 2.9 years), no deterioration in the ICARS score was seen. In this study, 63% of patients on treatment reported improvements in dysarthria, 58% in hand dexterity or handwriting, and 47% in fatigue.

A series of studies of low-dose idebenone showed improvements in cardiac measures with variable neurological results usually as secondary outcome measures. Mariotti *et al.* (2002) conducted a randomized, placebo-controlled trial of idebenone at 5 mg/kg/day in 29 patients with FRDA aged 20–31 years (14 treated). After 1 year, treated patients showed a 4.6% reduction in IVSd compared to a 5.5% increase in the placebo group. Left ventricular mass showed a 5.6% reduction in the treated group compared to a 10.7% increase in the placebo group. LVPWd decreased by 8.6% in the idebenone group and 2.4% in the placebo group (non-significant). There was no change in ejection fraction observed during the study, and the ICARS and its subscores did not show any significant changes.

Table 1 Summary of co-enzyme Q_{10} and idebenone trials

Reference	Medication	Dose	Duration	No of participants	Age range of participants[a]	Trial design	Neurological end points[a,b]	Cardiac end points[a,c]	Biomarker & other end points[a,d]	Comments
Lodi et al. 2001	(i) Co-enzyme Q_{10} + (ii) Vitamin E	(i) 400 mg/day + (ii) 2100 IU/day	6 months	10 treated; 10 controls	16–40	Open-label controlled trial	ICARS (NSC)	IVSd, LVPWd, LVMI, EF, FS (all NSC)	^{31}P-MRS: Cardiac muscle PCr:ATP (78%↑), skeletal muscle V_{max} (39%↑)	Improved cardiac bioenergetics and no worsening of cardiac or neurological end points
Hart et al. 2005	(i) Co-enzyme Q_{10} + (ii) Vitamin E	(i) 400 mg/day + (ii) 2100 IU/day	47 months	10 treated; 77 controls	16–40	Open-label controlled trial	ICARS (NSC overall, but significant deterioration in posture & gait scores, and improvement in kinetic scores)	IVSd, LVPWd (both NSC), FS (↑)	^{31}P-MRS: Cardiac muscle PCr:ATP (88%↑), skeletal muscle V_{max} (49%↑)	Sustained cardiac bioenergetics compared to previous study. No worsening of cardiac or neurological end-points. seven patients showed improvement in ICARS compared to control group
Cooper et al. 2008	(i) Co-enzyme Q_{10} + (ii) Vitamin E	High-dose: (i) 600 mg/day + (ii) 2100 IU/day; Low-dose: (i) 30 mg/day + (ii) 24 IU/day	2 years	50 treated (26 high-dose; 24 low-dose); 77 controls	10–58	Randomized, double-blind, multiple-dose-controlled trial	ICARS (Increase in ICARS in both treated group, indicating clinical deterioration); also, hand clicker test & BRAIN kinesis test (NSC)	IVSd (NSC)	–	When compared to cross-sectional data, 49% of all patients demonstrated improved ICARS scores. Post hoc analysis revealed this responder group had significantly lower baseline serum co-enzyme Q_{10} levels
Rustin et al. 1999	Idebenone	5 mg/kg/day	4–9 months	3	11–21	Open-label	Suggestion of subjective improvement in strength & delicate movements, e.g., handwriting but no change in ataxia & deep-tendon reflexes	IVSd (↓31–36%); LVPWd (↓8–20%); LVMI (↓21–32%); FS (↓ in 1 patient by 8% but ↑ by 28% & 0% in other 2); LVOO (↓ from 40 to 10 mmHg in 1 patient)	–	

Table 1. (Continued)

Reference	Medication	Dose	Duration	No of participants	Age range of participants[a]	Trial design	Neurological end points[a,b]	Cardiac end points[a,c]	Biomarker & other end points[a,d]	Comments
Rustin *et al.* 2004	Idebenone	5 mg/kg/day	5 years	1	NS	Open-label	–	Further improvement in 1 patient from above study with 'no evidence of heart dysfunction' at 5 years: IVSd (↓31%); LVPWd (↓3%); SF (↑17%); LVMI (↓28%); LVOO (↓50%)	Mitochondrial enzyme activities: complex I (↑126–147%); complex II (↑98–104%); complex III (↑31–43%); complex IV (↑19–24%); NIDH (↑9–13%); aconitase (↑10- to 13-fold)	
Rustin *et al.* 2002 Hausse *et al.* 2002	Idebenone	5 mg/kg/day	6 months	40	4–22	Open-label	–	48% showed ↓> 20% in LVMI; remainder stable or slightly ↓; no patient with ↑>20%; Improvement in LV outflow tract obstruction & FS affected subset	–	In two patients with worsening cardiac parameters, doses up to 15 mg/kg/day given which were said to stabilize these measures.
Schulz *et al.* 2000	Idebenone	5 mg/kg/day	8 weeks	8	NS	Open-label controlled trial	–	–	Normalized urinary 8OH2dG (2.6-fold ↑); plasma DHBA after salicylate (NSC)	Authors felt that urinary 8OH2dG (marker of oxidative DNA damage) may be useful in monitoring therapeutic interventions in FRDA.

Table 1. (Continued)

Reference	Medication	Dose	Duration	No of participants	Age range of participants[a]	Trial design	Neurological end points[a,b]	Cardiac end points[a,c]	Biomarker & other end points[a,d]	Comments
Schöls et al. 2001	Idebenone	360 mg/day	6 weeks	9	19–54	Double-blind placebo-controlled crossover trial	ICARS, Schoppe 'plugging' motor performance test (both NSC)	IVSd, LVPWd, FS, LVMI, LVEDD, ECG (all NSC)	^{31}P-MRS: skeletal muscle PCr recovery after exercise as measure of oxidative phosphorylation (NCS); creatinine kinase (NSC)	The only placebo-controlled study not to show improvement in cardiac markers, possibly due to short duration of study
Arnold et al. 2006	Idebenone	5–10 mg/kg/day (16 patients already taking idebenone before study)	1.6–3.5 years	20 (follow-up data available on 10)	NS	Open-label observational study	ICARS (NSC); 79% reported improvement In dysarthria (63%), hand dexterity or handwriting (58%), and fatigue (47%)	—	130% ↑ in MDA comparing those on treatment to those off	Authors interpret MDA results as showing complex I inhibition by idebenone (while it is known to stimulate complexes II & III)
Mariotti et al. 2002	Idebenone	5 mg/kg/day	12 months	14 treated; 15 controls	21–32	Randomized double-blind placebo-controlled trial	ICARS (NSC)	IVSd (treated 4.6%↓ vs. untreated 5.5%↑); LVPWd (treated 5.6%↓ vs. untreated 10.7%↑); LVM (NSC); EF (NSC)	—	Authors concluded that the absolute cardiac changes were modest, but the findings suggested that larger trials were warranted

Table 1. (Continued)

Reference	Medication	Dose	Duration	No of participants	Age range of participants[a]	Trial design	Neurological end points[a,b]	Cardiac end points[a,c]	Biomarker & other end points[a,d]	Comments
Buyse et al. 2002	Idebenone	5 mg/kg/day	12 months	8	9–27	Open-label	CAG rating scale (progressive worsening)	LVMI (16%↓); EF, FS, IVSd, LVPWd (all NSC); LSR (78%↓); LCS (67%↓); RSR (33%↓); RCS (NSC)	Erythrocyte protoporphyrin IX level (marker of iron–sulfur cluster enzyme ferrochetalase (↑ at baseline in most cases & ↓with idebenone in 5 of 6 cases)	Authors showed improvement in cardiac hypertrophy in 6 of 8 patients. Cardiac strain and strain rate imaging showed that this was preceded by early and linear improvement in cardiac function. Erythrocyte protoporphyrin IX levels were not consistently related to cardiac improvement
Ribaï et al. 2007	Idebenone	5 mg/kg/day	6 months – 7 years	88 treated; 16 controls	13–74	Open-label non-randomized controlled trial	ICARS (worsened for all patients but significantly slower deterioration in treated group: 1.93 ICARS points/year vs. 4.43)	In 61 treated patients, LVMI ↓ by 4.1 g/m²/year, LVPWd by 0.4 mm/year, EF by 1.3%/year & FS no change.	–	Authors concluded that ICARS was inappropriate for such a long-term study as neurological scores were underestimated because ceiling effects. Also, insufficient data in untreated group to calculate significance rates.
Artuch et al. 2002	Idebenone	5 mg/kg/day	12 months	9	11–19	Open-label	ICARS (49%↓) EMG, NCS, SSEP, VEP (all NSC)	IVSd, LVPWd (both NSC)	–	Patients with highest idebenone levels improved most. Authors recommended monitoring of idebenone levels in future trials

Table 1. (Continued)

Reference	Medication	Dose	Duration	No of participants	Age range of participants[a]	Trial design	Neurological end points[a,b]	Cardiac end points[a,c]	Biomarker & other end points[a,d]	Comments
Pineda et al. 2008	Idebenone	5–20 mg/kg/day (escalating doses)	3–5 years	10 children; 14 adults	8–46	Open-label	ICARS (children: NCS over study period but initial improvement, then stabilization before deterioration; adults: 31%↑)	IVSd, LVPWd, LVMI, FS, EF all NCS except ignificant worsening in FS & EF in adult cases)	Tocopherol, retinol, coenzyme Q$_{10}$, selenium, zinc, superoxide dismutase, catalase, gluthathione peroxidase & gluthathione reductase, malondialdehyde (all NCS)	Authors concluded that idebenone had stabilized cardiac and neurological dysfunction in children before puberty
Brandsema et al. 2010	Idebenone	20 mg/kg/day	1 year	7	13–18	Open-label	ICARS (NSC)	–	PedsQL, ADL (NSC in either but when element relating to physical disability excluded from PedsQL, trend toward improvement seen in emotional, social and school components)	
Velasco-Sánchez et al. 2011	(i) Idebenone (ii) Deferiprone	(i) 20 mg/kg/day (ii) 20 mg/kg/day	+11 months	20	8–26	Open-label	ICARS (NSC overall but gait & posture subscore 16%↑; kinetic subscore 47%↓)	IVSd (6.1%↓), LVMI (8.8%↓) LVPWd, FS, EF (all NCS)	Iron deposition on MRI: reduced in dentate nucleus but not thalamus or putamen	Despite adverse events involving blood dyscrasias, the authors concluded that overall this combination treatment had stabilized neurological function and improved cardiac function

Table 1. (Continued)

Reference	Medication	Dose	Duration	No of participants	Age range of participants[a]	Trial design	Neurological end points[a,b]	Cardiac end points[a,c]	Biomarker & other end points[a,d]	Comments
Di Prospero et al. 2007b	Idebenone	(i) 2.5–75 mg/kg/day (escalating doses); (ii) 60 mg/kg/day	(i) NS; (ii) 1 month	(i) 78; (ii) 15	Pediatric, adolescent & adult groups	Open-label (i) phase Ia & (ii) Ib trials	Self-reported observations: ↓ fatigue (70%); ↑ balance & stability (50%); ↑ fine motor tasks (40%); ↑ peripheral sensation (20%); ↑ general health & well-being (71%)	–	–	Phase Ia/Ib trial providing safety, tolerability & limited efficacy evidence for further higher dose idebenone trials
Di Prospero et al. 2007a Drinkard et al. 2010 (NICOSIA study)	Idebenone	(i) 5 mg/kg/day; (ii) 15 mg/kg/day; (iii) 45 mg/kg/day	6 months	27 treated; 11 placebo	9–17	Phase II randomized double-blind placebo-controlled trial	ICARS, FARS, ADL (all NSC but indication of dose-dependent improvement in ICARS by Jonckheere trend test. In patients with ICARS of 10–54, significant improvement in ICARS & dose-related improvement in all 3 scores)	Echo & cardiac MRI results (not published)	Urinary 8OH2'dG (NSC); peak oxygen consumption per unit time (VO_2) & peak work rate measured during incremental exercise testing (NSC); gene expression studies (not published)	Authors concluded that idebenone resulted in improvement in neurological function & ADL which correlated with dose, suggesting higher doses may be required for neurological effect
Lynch et al. 2010; Lagedrost et al. 2011 (IONIA study)	Idebenone	(i) 450 or 900 mg/day; (ii) 1350 or 2250 mg/day	6 months	46 treated; 24 placebo	8–18	Phase III randomized, double-blind, placebo-controlled trial	ICARS, FARS, ADL, $FACT-Z_2$ and $FACT-Z_3$ (all NSC; treated patients improved by 2.5 ICARS points & 1.6 FARS points, but placebo group also improved by 1.3 ICARS points & 0.6 FARS points)	LVMI, LVPWd, EF & ECG parameters (all NSC)	–	Authors concluded that idebenone did not significantly alter neurological Function but that larger studies of longer duration may be needed

Table 1. (Continued)

Reference	Medication	Dose	Duration	No of participants	Age range of participants[a]	Trial[a] design	Neurological end points[a,b]	Cardiac end points[a,c]	Biomarker & other end points[a,d]	Comments
Meier et al. 2012 (IONIA extension study)	Idebenone	1350 or 2250 mg/day	12 months	68 treated	8–18	Open-label extension of above study	ICARS ↑ by 1.1, but excluding posture & stance values resulted in improvement in remaining score. Combining main study & extension showed ICARS ↓ by 1.03 (3.02 for high-dose group). Similar results for FARS with high-dose group showing mean ↓ of 3.17, representing a trend toward difference when compared to placebo.	–	–	The authors concluded that the combined results of the IONIA and IONIA extension studies indicated that high-dose idebenone may stabilize overall neurological function & improve fine motor skills & speech

[a]NS, not specified; NSC, no significant change.

[b]ADL, activities of daily living; CAG, Cooperative Ataxia Group; EMG, electromyography; FACT, Friedreich's ataxia composite test (Z_2 & Z_3); FARS, Friedreich's ataxia rating scale; ICARS, International Co-operative Ataxia Rating Scale; NCS, nerve conduction studies; SSEP, somatosensory-evoked potentials; VEP, visual-evoked potentials.

[c]Echo, echocardiogram; ECG, electrocardiogram; EF, ejection fraction; FS, fractional shortening; IVSd, interventricular septal thickness at diastole; LCS, longitudinal (septal & lateral) cardiac strain; LSR, longitudinal strain rate; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVH, LV hypertrophy; LVMI, LV mass index; LVOO, LV outflow obstruction; LVPWd, LV posterior wall thickness at diastole; RCS, radial (posterior wall) cardiac strain; RSR, radial strain rate.

[d]8OH2′dG, 8-hydroxy-2′-deoxyguanosine; ADL, activities of daily living; DHBA, dihydroxybenzoic acid; MDA, malondialdehyde; MRI, magnetic resonance imaging; NIDH, nicotinamide adenine dinucleotide phosphate isocitrate dehydrogenase; ^{31}P-MRS, 31-phosphorus magnetic resonance spectroscopy; PCr, phosphocreatine; PCr:ATP, Phosphocreatine:adenosine triphosphate ratio; PedsQL, pediatric quality of life inventory; V_{max}, maximum rate of mitochondrial ATP synthesis.

Buyse *et al.* (2002) treated eight patients with FRDA and hypertrophic cardiomyopathy aged 8–27 years with 5 mg/kg/day idebenone over 12 months in an open-label study. LVMI showed a significant non-linear (early) reduction from 130 to 109 g/m^2 by the end of the study, but IVSd and LVPWd showed only non-significant reductions. Radial and longitudinal deformation properties improved significantly during the study, but ejection fraction and fractional shortening, which were normal at the start of the study, did not change during treatment. Neurological outcome was measured using the Cooperative Ataxia Group Rating Scale and showed a progressive worsening in ataxia scores. No control data were presented for comparison. The authors also measured erythrocyte protoporphyrin IX levels as a marker of the mitochondrial iron–sulfur cluster enzyme ferrochetalase which they hoped would discriminate between responders and non-responders to treatment. However, although the levels were elevated at baseline in most patients and reduced with idebenone treatment, they did not consistently relate to cardiac improvement.

Ribaï *et al.* (2007) studied 104 patients with FRDA aged 13–74 years, of whom 88 received open-label treatment with idebenone at a dose of 5 mg/kg/day over a mean period of 5 years in a non-randomized, prospective follow-up study. During this period, the total ICARS score worsened for both treated and untreated patients although with significantly slower deterioration in the treated group (1.93 ICARS points/year vs. 4.43) including subscores of posture and gait, and kinetic functions. Treated patients also deteriorated in terms of a quantitative writing task and assessment of frequency of square wave jerks by electro-oculography, although there were insufficient data in the untreated group to assess for significance. The authors felt that the neurological scores had been underestimated because of a considerable ceiling effect in the ICARS in such a long-term follow-up study. There were insufficient data in the untreated group to compare cardiological findings with the treated group over the study period, but in the 61 treated patients who were assessed at baseline, LVMI decreased by 4.1 g/m^2/year, LVPWd by 0.4 mm/year, and ejection fraction by 1.3%/year. Fractional shortening did not change significantly.

Artuch *et al.* (2002) studied nine patients with FRDA aged 11–19 years who were treated in an open-label study with 5 mg/kg/day of idebenone over 12 months. They found significant reductions in the ICARS with all patients improving in terms of fine manipulation, nystagmus, and eye movements. Only patients with low numbers of GAA repeats improved in terms of kinetic function, posture and gait. Improvement was seen within 3 months of treatment. There were no differences observed in electromyography, nerve conduction studies, somatosensory- and visual-evoked potentials, and echocardiographic measures (IVSd and LVPWd). Serum idebenone levels were measured between 3 and 12 months of the study and correlated negatively with GAA repeat number and ICARS score; in other words, more severely affected patients had lower idebenone levels. Idebenone levels correlated positively with the reduction in ICARS, indicating that those patients with the highest idebenone levels improved the most. The authors recommended monitoring of idebenone levels and further trials with higher doses.

Previous human studies had shown that idebenone was effective and tolerated up to 15 mg/kg/day (Rustin *et al.* 2002; Hausse *et al.* 2002). Animal studies of the frda/Muscle Creatine Kinase mouse model of FRDA, causing a frataxin deficiency in muscle, showed that idebenone had a dose-dependent effect on survival and life-expectancy which required up to 90 mg/kg/day of idebenone (Seznec *et al.* 2004a,b; Di Prospero *et al.* 2007b). These animals, which have a predominantly cardiac phenotype, showed reduced left ventricular mass, reduced left ventricular dilatation and stabilization of left ventricular shortening and ejection fraction. Thus, because of the promising but variable findings of smaller, shorter studies of low-dose idebenone and the paucity of adverse reactions in patients at these and higher doses, clinical trials began to use higher doses of idebenone.

Pineda *et al.* (2008) treated 24 patients with FRDA aged 8–46 years with escalating doses of idebenone from 5 to 20 mg/kg/day over 3–5 years in an open-label prospective study. In the 10 children in the study, no significant change in ICARS score was observed over the study period. In five children, the total ICARS score increased, in four it remained unchanged, and in one it improved. Most children initially improved on treatment and then stabilized for 1–2 years before deteriorating again, usually during or after puberty. No differences were observed in the gait, kinetic, or speech subscores of the ICARS in children over the study period. Among the adult participants, the total ICARS score increased for all patients, with a median increase of 12 ICARS points over 3 years. No control data were presented for comparison. In the pediatric cases, no significant differences were seen in IVSd, LVPWd, fractional shortening or ejection fraction. In the adult cases, significant deterioration was seen in fractional shortening and ejection fraction, although there was no deterioration when comparing the 20 mg/kg/day with the 10 mg/kg/day group. No significant changes were seen in IVSd, LVPWd, and LVMI. The authors concluded that idebenone had stabilized cardiac and neurological dysfunction in children before puberty.

Brandsema *et al.* (2010) studied seven patients with FRDA aged 13-18 years in a prospective, observational, open-label study over 1 year receiving 20 mg/kg/day of idebenone. The primary aim of the study was to investigate quality of life which was assessed using the Pediatric Quality of Life Inventory (PedsQL). Further measures included the ICARS and a scale of activities of daily living (ADL). There was no significant change in the PedsQL, ICARS, and ADL over the study period. No control data were presented.

Within the PedsQL only the element relating to physical abilities deteriorated which correlated with worsening ADL and when this was excluded from the PedsQL, there was a trend toward improvement in the emotional, social, and school components of quality of life.

Velasco-Sánchez *et al.* (2011) combined 20 mg/kg/day idebenone with 20 mg/kg/day of the iron-chelating agent deferiprone in an open-label study of 20 FRDA patients aged 8–26 years. Over the 11 month period of the study, there was no significant change in total ICARS score; posture and gait scores deteriorated significantly but kinetic scores improved significantly. In 9 cases, the total ICARS worsened, but in 10 cases it improved. No control data were presented. IVSd and LVMI both showed modest but significant reductions, but there were no changes in LVPWd, fractional shortening and ejection fraction. Magnetic resonance imaging measures of iron deposition in the dentate nucleus but not the thalamus or putamen, reduced significantly. The treatment was generally well tolerated with some gastrointestinal side-effects, but there were significant reductions in ferritin, hematocrit and hemoglobin levels and increased transferrin levels. Two patients became neutropenic, one of whom had to withdraw from the study. Overall, the authors concluded that this combination treatment had stabilized neurological function and improved cardiac function.

To investigate the safety, tolerability and feasibility of higher dose studies, Di Prospero *et al.* (2007b) went on to conduct an open-label, phase Ia study in 78 adult and pediatric patients with escalation of idebenone dose from 2.5 mg/kg/day to 75 mg/kg/day. All cohorts reached the maximal dose and there was no dose-limiting toxicity. All adverse events were mild except a single example of transient hyperglycemia in a diabetic patient with known poor glycemic control which was judged to be independent of the study medication. Nausea and orthostatic hypotension were reported in a small number of cases. Pharmacokinetic assessments suggested that drug availability consistently increased up to 55 mg/kg/day. Because of the success of this trial, the authors went on to undertake an open-label, phase Ib trial in 15 adult and pediatric patients using a dose of 60 mg/kg/day over 1 month. This again showed the tolerability of higher doses of idebenone with only mild adverse events including dyspepsia, loose stools, nausea, and vomiting. One subject had to discontinue the trial because of diarrhea and nausea. Self-reported observations included decreased fatigue (70%), improved balance and stability (50%), improved fine motor tasks such as handwriting (40%) and improved peripheral sensation (20%). In this study, 71% reported a subjective improvement in their general health and well-being.

As well as needing to investigate higher doses of idebenone, the field had suffered from a relative paucity of large, randomized, placebo-controlled trials. To address this deficiency, the National Institutes of Health Collaboration with Santhera in Ataxia (NICOSIA) trial was undertaken in which 48 patients with FRDA aged 9-17 years were randomized into a placebo-controlled, double-blind trial of idebenone (Di Prospero *et al.* 2007a). Eleven patients received placebo, 12 received 5 mg/kg/day, 13 received 15 mg/kg/day, and 12 received 45 mg/kg/day over a period of 6 months. The drug was well tolerated although one child on high-dose idebenone developed neutropenia which resolved after cessation of treatment. The primary outcome measure was urinary 8OH2′dG level as a marker of oxidative DNA damage, which did not change significantly with idebenone treatment. Secondary outcome measures included changes in the ICARS score, Friedreich's ataxia rating scale (FARS), and a survey of ADL. None of these showed significant differences after 6 months' treatment, but there was an indication of dose-dependent improvement in the ICARS score by the Jonckheere trend test. Because of worries of ceiling and floor effects in the ICARS score reducing the signal in wheelchair-bound and minimally affected patients, a pre-specified second analysis was undertaken on patients with an ICARS score of more than 10 and less than 54. This showed a significant improvement in the ICARS but not FARS or ADL, and suggested a dose-related improvement in all three scores. Further results demonstrated that peak oxygen consumption per unit time (VO$_2$) and peak work rate measured during incremental exercise testing showed no significant change at any dose of idebenone compared to placebo (Drinkard *et al.* 2010). Results of echocardiography, cardiac magnetic resonance imaging, gene expression studies, gait analysis, and studies of visual-motor and fine motor control have yet to be published.

However, these results warranted moving on to two larger multi-center phase III trials randomized, placebo-controlled trials of high-dose idebenone concentrating on neurological endpoints. These were the Idebenone Effects on Neurological ICARS Assessments (IONIA) study in North America and the Mitochondrial Protection with Idebenone in Cardiac or Neurological Outcome Study (MICONOS) in Europe. IONIA randomized 24 patients to placebo, 22 to medium-dose treatment (450 or 900 mg/day depending whether weight > 45 kg), and 24 to high-dose treatment (1350 or 2250 mg/day). Subjects were between 8 and 18 years of age, all were independently ambulant and had ICARS scores between 10 and 54 (Lynch *et al.* 2010). The medication was well tolerated. There were two serious adverse events (non-cardiac chest pain and idiopathic thrombocytopenic purpura), both in patients with a pre-existing history of this condition, and both of which resolved while remaining on idebenone. Gastrointestinal side-effects were again seen, largely in the high-dose group. The primary outcome measure was change in the ICARS, while secondary end-points were change in FARS, ADL, and two Friedreich's Ataxia Composite Tests (FACT-Z$_2$ and FACT-Z$_3$) including combinations of the

timed 25-foot walk, the 9-hole peg test, and the low contrast letter acuity test. During the study period, treated patients improved by 2.5 ICARS points and 1.6 FARS points, but unexpectedly the placebo group also improved by 1.3 ICARS points and 0.6 FARS points. These differences, as well as changes in FACT-Z_2 and FACT-Z_3, were not significant. Further subgroup analysis for responders and non-responders, severity, age, and disease duration, also did not reveal significant differences. LVMI, LVPWd, ejection fraction, and electrocardiogram parameters also were not significantly improved by treatment with idebenone (Lagedrost *et al.* 2011).

The most marked changes in neurological and cardiac measures were seen in the high-dose group in IONIA, and so a further 12-month open-label extension to the study was conducted (Meier *et al.* 2012). Sixty-eight pediatric patients were enrolled into the extension study from the original study including those who had originally received placebo. All received the 1350 or 2250 mg/day (according to weight). During the extension study, the mean ICARS score increased by 1.1, indicating a trend toward deterioration. However, the authors observed that the posture and stand subscores of the ICARS changed in a different direction from the eye, speech, upper and lower limb ataxia, and spiral subscores; excluding the posture and stance values resulted in a constant improvement in the remaining score. Analyzing the results for the main study and the extension together using mixed model measures showed a reduction in the ICARS by 1.03 points over the 18 months for all patients, and a significant reduction of 3.02 for the patients who received high-dose idebenone throughout. Similar results were seen for the FARS with the group receiving high-dose treatment for 18 months showing a mean reduction of 3.17 points, representing a trend toward difference when compared to placebo. The authors concluded that high-dose idebenone may offer therapeutic benefit in pediatric FRDA patients by stabilizing the overall neurological function and improving fine motor skills and speech.

MICONOS, the second of these phase III studies, was performed between April 2006 and January 2010 and recruited 232 adult and pediatric patients from 13 centers in six European countries (https://www.clinicaltrials.gov; ID: NCT00905268). Participants were studied over a 12-month period and received low-dose (180 or 360 mg/day depending whether weight > 45 kg), medium-dose treatment (450 or 900 mg/day), high-dose treatment (1350 or 2250 mg/day), or placebo. The primary end-point was change in the ICARS. Secondary end-points included change in the FARS, proportion of patients responding within ICARS, and various echocardiographic parameters. Similar to the IONIA extension, MICONOS entered a high-dose, open-label extension period lasting 2 years available to patients who had been in the original study (https://www.clinicaltrials.gov; ID: NCT00993967). This was undertaken between June 2007 and June 2012 and was estimated to recruit more than 200 patients. A proportion of patients who were still on this trial between April 2011 and July 2012, were recruited to a phase IIIb randomized, double-blind, placebo-controlled withdrawal study, called the Patient Reported Outcomes in Friedreich's Ataxia Patients After Withdrawal From Treatment With Idebenone (PROTI) study (https://www.clinicaltrials.gov; ID: NCT01303406). The primary outcome measure was patient assessment of treatment assignment (i.e., could patients tell whether they had been removed from idebenone treatment) and the secondary outcome measure, proportion of patients withdrawing from the study because of recurrence or worsening of FRDA symptoms. Although the baseline cardiological data for MICONOS (Weidemann *et al.* 2012) and combined neurological data relating to NICOSIA, IONA, and MICONOS (Metz *et al.* 2013) have been published, full clinical details are still awaited for the MICONOS, MICONOS extension, and PROTI studies. However, it has been released that MICONOS did not meet its primary endpoint (Santhera Pharmaceuticals 2010). Idebenone is currently not licensed in Europe or the United States for use in FRDA.

Conclusions

Much time and expense has been expended on clinical trials of antioxidant therapies in FRDA, but definitive answers as to efficacy remain elusive. Prescribing patterns consequently remain inconsistent and many patients currently incur significant costs in procuring antioxidant supplements privately, without robust clinical evidence. Considering the trials examined in this review, it is evident that patients should be stratified for age at onset, disease duration and level of disability. FRDA is a very slowly progressive disease and therefore minimal changes are difficult to capture. Studies should last at least 2 years for an antioxidant trial, in the absence of more sensitive markers. Many trials have required elaborate statistical maneuvers to produce significant results, but it is probably still true to state that there is greater evidence for cardiac than neurological efficacy in these agents, and greater evidence for these agents in younger and less severely disabled patients with the drug given at higher doses (600 mg/day co-enzyme Q_{10} or 2250 mg/day idebenone). While preventing cardiac complications is clearly important for survival, few patients are significantly symptomatic because of these, whereas progressive neurological disability severely impairs physical functioning, participation in society and quality of life in a large proportion of patients. It is significant that in the one study of idebenone which primarily addressed quality of life issues (Brandsema *et al.* 2010), declining functional ability had the greatest influence on quality of life. Planning future therapeutic trials, which capture this and real clinical effects, is vital. This may involve the development and use of novel

clinical assessment tools and more sensitive biomarkers. It may involve more careful patient selection to avoid diluting measured clinical outcomes by patients trapped in floor and ceiling effects. However, this can lead to subsequent problems with commissioning and prescribing authorities if efficacy is proven for only a sebset of patients.

Further work is being undertaken in improving the bioavailability, mitochondrial targeting, and efficacy of co-enzyme Q_{10} analogs. It has been shown that in rats, only 3% of orally administered co-enzyme Q_{10} is absorbed because of its hydrophobicity. In humans, ubiquinol appears to result in greater plasma levels of co-enzyme Q_{10} than ubiquinone itself, and solubilized formulations result in significantly greater uptake than non-solubilized powder-based formulations including compressed tablets, chewable tablets, powder-filled capsules, and gel capsules containing oil suspensions of the drug (Bhagavan and Chopra 2007). However, when increased plasma levels of co-enzyme Q_{10} were achieved by succinylation or acetylation of the benzoquinone group, these did not cause increased levels in brain, heart, muscle, liver, kidney, or spleen (Turunen et al. 1999).

Fash et al. (2013) produced six analogs of co-enzyme Q_{10} with different alkyl and aza side chains showing significantly improved effects over idebenone on mitochondrial oxygen consumption, mitochondrial membrane potential, suppression of ROS, and cytoprotection in glutathione-depleted cell cultures. Arce et al. (2011) modified the benzoquinone nucleus as well as the alkyl side chain producing an aza analog which protects cultured FRDA fibroblasts from oxidative stress more effectively than idebenone. The synthetic co-enzyme Q_{10} analog mitoquinone, which has a lipophilic triphenylphosphonium cation on its decyl side chain, allows high concentrations to accumulate at the inner mitochondrial membrane and probably acts as an antioxidant by its quinol form interacting with complex II (Smith and Murphy 2010). Initial evidence showing decreased levels of oxidative damage in mouse models led to two human studies in Parkinson's disease and chronic hepatitis C. The PRO-TECT study of Parkinson's disease did not show any difference in markers of disease progression between mito-quinone and placebo (Snow et al. 2010) but the CLEAR trial in chronic hepatitis C infection, in which increased levels of oxidative stress and mitochondrial damage are thought to contribute to chronic liver damage, showed a significant improvement in the liver enzyme alanine transaminase (Gane et al. 2010). No studies have yet been performed in FRDA patients.

It has been suspected that the non-prescribed use of antioxidant therapies may have confounded some previous published studies. Assessing this accurately may be very important in determining the success of future trials. Many clinicians have perceived subjectively that there are responders and non-responders to antioxidant therapies, and identi-fying these clinically or by means of biomarkers, may lead to more tailored effective treatments, and help to elucidate pathological mechanisms. Further natural history data in well-characterized large patient groups will provide greater control data and assist in calculating power for future trials: work is currently underway in major centers in Europe, North America, and Australia to address this issue. Undertaking good quality, well-planned, randomized, placebo-controlled trials is likely to involve multiple centers coordinating to recruit appropriate patients in this rare and debilitating disease. The unpublished results of completed trials are keenly awaited and will help plan future trials. Whether this will involve further antioxidant agents, remains to be seen.

Acknowledgements

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