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Review article

Progress in the treatment of Friedreich ataxia

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ABSTRACT

Friedreich ataxia (FRDA) is a progressive neurological disorder affecting approximately 1 in 29,000 individuals of European descent. At present, there is no approved pharmacological treatment for this condition however research into treatment of FRDA has advanced considerably over the last two decades since the genetic cause was identified. Current proposed treatment strategies include decreasing oxidative stress, increasing cellular frataxin, improving mitochondrial function as well as modulating frataxin controlled metabolic pathways. Genetic and cell based therapies also hold great promise. Finally, physical therapies are being explored as a means of maximising function in those affected by FRDA.

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1. Friedreich ataxia

Friedreich ataxia (FRDA) is the most common of the inherited ataxias with a prevalence of approximately 1 in 29,000 individuals [1,2]. In 96% of affected individuals a homozygous GAA triplet repeat expansion in intron 1 of the *FXN* gene is the cause of FRDA. The remainder are compound heterozygotes, with a GAA expansion in one allele and a point mutation/deletion/insertion in the other [3,4]. *FXN* encodes frataxin, a mitochondrial protein involved in iron metabolism including iron–sulphur cluster synthesis.

The main clinical features of FRDA include gait and limb ataxia, dysarthria, areflexia, extensor plantar responses, posterior column dysfunction, cardiomyopathy and scoliosis [4,5]. The average age of onset of symptoms is 10–15 years but can be considerably earlier or later. The requirement for the use of a wheelchair is on average 15 years after symptom onset [6].

At present, there is no approved pharmacological treatment for this progressive condition [7]. However, research into potential pharmacological treatment for FRDA has advanced considerably in the past two decades with many potential therapeutic agents proposed to delay disease progression and

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address clinical symptoms, currently undergoing clinical trial evaluation [8,9].

2. Neurological rating scales

One of the main challenges of measuring the progression of FRDA, and therefore to measure the benefit of any therapy, is the clinical variability and heterogeneity of this slowly progressive disorder. As effective therapeutic agents are likely to delay disease progression, it is imperative that measures used to detect clinically significant changes are accurate [7].

Neurological function in FRDA is assessed using a range of rating scales that are administered by trained clinicians. The most common of these scales is the Friedreich Ataxia Rating Scale (FARS) [10]. The International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA) are two other widely used neurological rating scales [11,12].

The FARS [10] is a clinical rating scale specific to FRDA. This scale consists of three subscales measuring ataxia, activities of daily living, and a neurological examination, and has good inter-rater reliability indicating the degree to which raters provide consistent estimates of the same behaviour is high [10]. The ICARS [11] is comprised of four subscales measuring posture and gait, kinetic function, speech and oculomotor function, and has high inter-rater reliability [13]. The SARA is the most recently developed tool in the rating of FRDA. This scale encompasses eight items evaluating gait, stance, sitting, speech, and limb kinetic function [12]. The use of the SARA is increasing due to its ease and speed of administration, especially when compared to the FARS and ICARS.

While rating scales provide a good indicator of disease progression, they can be biased as they depend on administration by clinicians. This can result in reduced sensitivity and reliability [7,14]. Functional composites have therefore been designed to measure disease severity in FRDA. The composite most widely used in the evaluation of FRDA is the Friedreich Ataxia Functional Composite (FAFC). This composite comprises the 25-foot walk test, the 9-hole peg test and the Sloan low contrast letter acuity test [14]. Whilst functional composites are considered more objective, are easier to administer, and have good inter- and intra-rater reliability, they suffer from significant ceiling effects which reduce sensitivity in those individuals with more severe disease [15].

3. Pharmacological therapies in FRDA (Table 1)

3.1. *Therapies that decrease oxidative stress and enhance mitochondrial function*

3.1.1. *Idebenone*

Mitochondrial dysfunction and oxidative tissue damage are contributors to the pathology of FRDA [16,17]. The use of antioxidants has thus been explored as a potential therapy for the treatment of this condition.

Idebenone, an antioxidant and a synthetic analogue of coenzyme Q_{10} [18], has been studied as a potential treatment for both the neurological and cardiac aspects of FRDA since 1999. Despite the fact it is generally well-tolerated and safe in terms of adverse effects [19], results from studies have been inconclusive [20–29]. Early studies used low-dose idebenone at 5 mg/kg/day [21–23] however higher doses of idebenone have increasingly become used in clinical trials as these doses may be required to demonstrate efficacy. Several open-label low-dose (5 mg/kg/day) idebenone trials showed improved echocardiographic parameters in people treated with idebenone that was maintained for up to five years [21–23], as well as improved neurological symptoms in children as demonstrated by the ICARS after three and six months [26].

In contrast, the four randomised double-blind placebo-controlled trials that have been published have not demonstrated robust evidence in terms of the benefits of idebenone on neurological or cardiac function. Only modest changes in cardiac function were found in a year-long randomised placebo controlled trial of 5 mg/kg/day of idebenone in 29 individuals with FRDA. There were some significant improvements (reduced interventricular septal thickness and left ventricular mass) in the intervention compared to the placebo group but there was no change reported in ejection fraction [25].

The placebo-controlled NICOSIA (National Institutes of Health Collaboration With Santhera in Ataxia) study of 48 children over six months demonstrated no significant effect on urinary 8-hydroxy-2′-deoxyguanosine (8OHdG), the primary endpoint, or a change in FARS or ICARS (secondary endpoints) [27]. However, a dose-dependent (5 mg/kg/day, 15 mg/kg/day and 45 mg/kg/day) improvement in the ICARS was reported, indicating that higher doses could have potential neurological benefit [27].

A phase 3 double-blind placebo-controlled study (IONIA: Idebenone Effects on Neurological ICARS Assessments) was conducted in 70 paediatric participants over six months with individuals administered either low (450 or 900 mg) or high dose (1350 or 2250 mg) idebenone per day, depending on body weight ($\leq$ or $>$ 45 kg) [28,29]. The IONIA study demonstrated no reduction in left ventricular hypertrophy nor any improvement in cardiac function. There was no significant change in neurological function as measured by the FARS or ICARS [28,29].

The 12-month MICONOS (Mitochondrial Protection with Idebenone In Cardiac Or Neurological Outcome Study) study enrolled 232 mainly adult participants who received low, medium, or high-dose idebenone [30]. No significant difference in ICARS score between participants receiving treatment and placebo were detected. There was also no difference observed between the treatment and placebo groups in the cardiac endpoints [30].

Despite these conflicting results, many individuals with FRDA continue the use of idebenone as it is readily accessible and has few adverse effects [20]. Neutropenia is reported as a rare but significant adverse event and should be monitored for, particularly in individuals on high-dose idebenone [27,31].

3.1.2. *Coenzyme Q_{10}*

Coenzyme Q_{10} is another antioxidant agent that has been studied in the treatment of FRDA. An open-label study showed an improvement in cardiac and skeletal muscle bioenergetics

Table 1 – Summary of pharmacological therapies in FRDA.

Pharmaceutical name	Proposed mechanism	Stage of development	Study outcomes
Therapies that decrease oxidative stress and enhance mitochondrial function			
Idebenone	Antioxidant properties, prevents damage to mitochondrial membrane and supports mitochondrial function	Randomised double-blind placebo-controlled studies	Results have been inconclusive with modest improvements seen in some studies but not others; unlikely to be approved as a treatment for FRDA
Coenzyme Q_{10}	Improves cellular bioenergetics, decreases oxidative stress, improves mitochondrial function	Randomised double-blind two dose study	No benefit found in high *vs* low dose therapy
A0001	Antioxidant, chemically similar to but more potent than idebenone and coenzyme Q_{10}	Randomised double-blind placebo-controlled study	No difference in primary endpoint (Disposition Index) however a dose-dependent improvement was found in the FARS score
EPI-743	Similar to A0001 – improves mitochondrial function and prevents oxidative stress	Randomised double-blind placebo-controlled study, followed by open-label study	No difference in primary endpoint (low contrast visual acuity assessment) however improvement found in FARS neurological scale (low dose *vs* placebo)
Omaveloxolone (RTA 408)	Nrf2 activator – reduces intracellular oxidative stress and mitochondrial damage, increases mitochondrial respiration and biogenesis	Randomised double-blind placebo-controlled study	Study is currently underway
RT001	Deuterised polyunsaturated fatty acid (dPUFA) – reduces oxidative stress in mitochondria therefore increasing ATP production	Randomised double-blind study	Primary safety, tolerability, pharmacodynamic endpoints met; full results to be published
Thiamine (vitamin B1)	Involved in energy metabolism, oxidative stress and potentially neuroprotective	Open-label study	Improvement found in SARA scores, return of deep tendon reflexes reported in 57% of participants
Pioglitazone	PPARγ agonist – increases frataxin protein levels, anti-oxidant properties	Proof of concept study	Full results to be published
L-Carnitine and creatine	Involved in fatty acid transport in mitochondria, alters levels of membrane proteins in cerebellar mitochondria therefore reducing oxidative stress	Randomised placebo-controlled crossover study, followed by open-label study	No differences in ICARS scores or echocardiographic measures in treatment group compared to the placebo group; open-label study is ongoing
Anti-inflammatory therapy			
Methylprednisolone	A steroid that has anti-inflammatory properties, may alter oxidative damage caused by frataxin deficiency	Open-label study	Study is currently underway
Iron chelators			
Deferiprone	Iron chelator – removes surplus iron therefore decreasing oxidative stress and cellular damage	Randomised double-blind placebo-controlled study	No differences in FARS scores; participants on higher doses found to have greater progression in FARS score than the placebo group.
Frataxin level modifiers			
Erythropoietin	Increases frataxin levels by a post translation mechanism	Randomised double-blind placebo-controlled study	No difference in frataxin levels or SARA scores between treatment and placebo group
Carbamylated erythropoietin	A modified form of EPO that has minimal erythropoietic properties	Randomised placebo-controlled study	No improvements in frataxin levels, FARS or SARA scores
Ubiquitin competitors	Blocks ubiquination of frataxin therefore increasing intracellular frataxin levels	Animal studies	Studies are currently underway
CTI-1601	Delivery system (trans-activator transcription, TAT) that transports synthetic frataxin directly into mitochondria	Animal studies	Mean lifespan in mice increased by 53%, improvement shown in cardiac function; given orphan drug designation and currently being developed as a treatment.

Agents that increase FRDA gene expression			
RG2833	An HDAC inhibitor, increases histone acetylation resulting in increased frataxin levels	Randomised double-blind placebo-controlled study	Increased FXN gene expression reported however toxic metabolites found indicating safety concerns
Nicotinamide	An HDAC inhibitor, increases histone acetylation resulting in increased frataxin levels	Open-label dose-escalation study	Upregulation in frataxin expression found however no improvements in clinical measures; randomised, double-blind placebo-controlled study is planned.
Interferon gamma	Cytokine that that increases frataxin mRNA and protein	Randomised, double blind placebo-controlled study	No difference in primary endpoint (modified FARS score) found when compared to placebo
Resveratrol	Natural phenol and antioxidant, increases *FXN* gene expression	Open-label study	Improvement found in oxidative stress marker, FARS, ICARS, hearing and speech outcome measures however little change in primary endpoint (PBMC frataxin levels); randomised placebo-controlled study is planned.
Granulocyte-colony stimulating factor and stem cell factor	Cytokines with neuroprotective effects, increases frataxin levels and reduces inflammation	Animal studies	Improvement shown in motor coordination and locomotor activity in mouse models

using a combination of 400 mg/day of coenzyme Q_{10} and 2100 IU/day vitamin E in a study of 10 individuals with FRDA. After three months of treatment, the maximum rate of skeletal muscle mitochondrial ATP production increased to 139% of baseline values [32]. An open-label extension study demonstrated significant improvement in cardiac and skeletal muscle energy metabolism that was maintained throughout a study period of 47 months [33]. A two-year double-blind randomised study of high and low dose coenzyme Q_{10} and vitamin E, without a placebo group, was conducted to ascertain the potential of these agents to modify clinical progression in FRDA [34]. There was no difference in ICARS scores, the primary outcome measure, between the high (600 mg/day of coenzyme Q_{10} and 2100 IU/day of vitamin E) and low dose (30 mg/day coenzyme Q_{10} and 24 IU/day vitamin E) groups indicating that high dose therapy provided no additional benefit when compared to low dose therapy [34].

3.1.3. *A0001*

Another antioxidant that has undergone clinical testing is A0001 (α-tocopherylquinone) which is structurally similar to coenzyme Q_{10} and idebenone. It is more potent than these two agents and was therefore proposed to be more efficacious [35]. The primary endpoint of a double-blind randomised placebo-controlled trial of 31 adults was the Disposition Index, a widely used measure of beta-cell function that deteriorates before diabetes mellitus development. Participants on this four-week study received placebo, low-dose A0001 (510 mg/day), or a high-dose A0001 (750 mg/day). There was no statistical difference in the Disposition Index between individuals receiving A0001 and the placebo group, however a dose dependent improvement in the FARS score was noted [36].

3.1.4. *EPI-743*

Following on from A0001, EPI-743 (α-tocotrienolquinone) was subsequently developed as a potent antioxidant with the aim of treating inherited mitochondrial respiratory chain disorders by improving mitochondrial function. EPI-743 is reported to be one to ten thousand fold more potent than coenzyme Q_{10} and idebenone in preventing oxidative stress in fibroblast assays [37,38]. EPI-743 has been tested in individuals with mitochondrial diseases including Leigh Syndrome and Leber Hereditary Optic Neuropathy with clinical improvement demonstrated without serious adverse events [39,40].

A six-month placebo-controlled multicentre study of EPI-743 in 63 adults with FRDA was conducted [41]. Participants received placebo, 600 mg/day EPI-743 or 1200 mg/day EPI-743. This was then followed by an 18-month open-label extension study where all participants received EPI-743 therapy. The primary endpoint of low contrast visual acuity assessment was not met, however an improvement in the neurological examination subscale of the FARS was found in participants administered low-dose EPI-743 when compared to the placebo group ($p = 0.047$) at 6 months. Treatment over 18 months demonstrated significant improvement in neurological outcomes, and treatment was found to be well tolerated [41]. EPI-743, at 1200 mg/day, has also been tested in people with FRDA who are compound heterozygous for a *FXN* GAA repeat expansion and a point mutation in an 18-month open-label study [42]. There were significant improvements in neurological function as assessed by the FARS indicating potential benefit in this subgroup of individuals.

3.1.5. *Nuclear factor erythroid-derived 2-related factor 2 (Nrf2) activators*

Nuclear factor erythroid-derived 2-related factor 2 (Nrf2) function is deficient in FRDA [43], with Nrf2 deficiency leading to faulty mitochondrial fatty acid oxidation and ATP production [44]. Nrf2 activation is hypothesised to increase mitochondrial respiration and biogenesis [45], reduce intracellular oxidative stress, and repair mitochondria damage [46]. RTA 408 (Omaveloxolone) is an Nrf2 activator that is currently being

studied in a phase 2 double-blind placebo-controlled study comparing 150 mg/day RTA 408 to placebo (https://clinicaltrials.gov/ct2/show/NCT02255435).

3.1.6. RT001 (dPUFA)

Polyunsaturated fatty acids (PUFAs) are fatty acids that are essential to the structure and function of lipid membranes. PUFAs are prone to oxidative injury and it has been postulated that this damage can lead to mitochondrial dysfunction [47]. By replacing hydrogen molecules with a hydrogen isotope known as deuterium, PUFAs can be strengthened and, in the process, protect the cells from oxidative damage. RT001 is a deuterised PUFA (dPUFA) which has been tested in 18 individuals with FRDA in a randomised double-blind study. The study was conducted over 28 days with participants administered 1.8 g or 9 g per day of RT001 or an RT001 comparator. All primary safety, tolerability and pharmacodynamics endpoints of the study were reportedly met [48]. Full results have not been published.

3.1.7. Thiamine

Thiamine (vitamin B1) has recently been proposed as a therapy for FRDA. Thiamine is important in central and peripheral nervous system functioning. Thiamine also plays a role in oxidative stress and is potentially neuroprotective [49–51]. An open-label study reported improved neurological function in 34 individuals with FRDA administered 100 mg thiamine intramuscularly every three to five days for three months [52]. An open-label study of 100 mg thiamine twice weekly for up to 24 months in 34 individuals with FRDA was therefore conducted [53]. There were no reported serious adverse events. The investigators found an improvement in SARA scores (mean score at baseline was 26.6 ± 7.7 compared to 21.5 ± 6.2 at the final visit, $p < 0.02$) and reported the return of deep tendon reflexes in 57% of the study participants after three months of treatment. Swallowing difficulties were reduced in over 60% of individuals who reported this morbidity.

3.1.8. PGC-1α modulation

The down-regulation of the peroxisome proliferator activated receptor gamma (PPARγ) coactivator 1α (PGC-1α) has been shown to inhibit the antioxidant response in FRDA [54]. It is postulated that this effect can be restored by PPARγ agonists [55]. Pioglitazone is a PPARγ agonist that is commonly used in the treatment of type II diabetes [54]. A proof of concept study exploring the effects of pioglitazone in FRDA over two years has been completed (https://www.clinicaltrials.gov/ct2/show/NCT00811681), with participants receiving pioglitazone at a starting dose of 15 mg/day and up to 45 mg/day. Results have not been published.

3.1.9. L-Carnitine and creatine

L-Carnitine and creatine have been trialled in 16 individuals with FRDA in a placebo-controlled crossover setting [56]. The two compounds are thought to improve cellular energy transduction, with L-carnitine in particular thought to enhance mitochondrial function in FRDA. Participants were administered 3 g per day of L-carnitine and 6.75 g per day of creatine over four months. While both compounds were found to be well tolerated, no significant changes were found in ICARS scores or echocardiographic measures when compared to placebo [56]. Mitochondrial ATP production improved compared to baseline ($p < 0.03$). An open label study in which individuals with FRDA are administered 2 g/day of acetyl-L-carnitine over 24 months is ongoing. Outcome measures are both cardiac and neurological (https://www.clinicaltrials.gov/ct2/show/NCT01921868).

3.2. Anti-inflammatory therapy

3.2.1. Methylprednisolone

It is suggested that the anti-inflammatory properties of steroids may play a role in altering oxidative damage caused by frataxin deficiency. A case report of two individuals with FRDA and nephrotic syndrome suggested a link between the two conditions. One of these individuals reported improvement of neurological symptoms after being treated with corticosteroids [57]. As a result of this initial finding, an open-label trial exploring the safety and efficacy of methylprednisolone treatment in FRDA is underway. Participants are receiving six cycles of a reducing dose of oral methylprednisolone for 6 days, followed by 22 days without medication prior to the next cycle (https://www.clinicaltrials.gov/ct2/show/NCT02424435).

3.3. Iron chelators

3.3.1. Deferiprone

Deficiency in frataxin leads to an imbalance in cellular iron homeostasis [58]. Excess mitochondrial iron has been identified as a result [59,60]. Iron accumulation in the dentate nuclei of individuals with FRDA has been reported, leading to oxidative stress and cell death [61–63].

Deferiprone is an iron chelator that is used to treat iron overload in several conditions including hemoglobinopathies [62]. It was first studied in nine adolescents with FRDA in a six-month open label study of 20–30 mg/kg per day of deferiprone [64]. A decrease in iron accumulation in the dentate nucleus assessed by MRI was reported (relaxation rate R2* in dentate nuclei reduced from $18.3 + 1.7\ s^{-1}$ to $15.7 \pm 0.7\ s^{-1}$ ($p < 0.002$)) after six months of treatment. Small neurological improvements were noted, with ICARS scores reduced by 10% in the youngest participants [64]. Reduced reactive oxygen species (ROS) damage to mitochondrial proteins in cells treated with deferiprone was reported [65], but of concern, the activity of aconitase, an iron–sulphur protein involved in iron homeostasis [66], was reduced in fibroblasts obtained from individuals with FRDA following *in vitro* treatment with deferiprone [67].

A subsequent six-month double-blind, randomised, placebo-controlled study assessed the safety and tolerability of deferiprone at 20, 40, and 60 mg/kg/day in 72 individuals aged 7–35 affected by FRDA [68]. Individuals treated with 20 mg/kg/day of deferiprone did not demonstrate significant changes in FARS scores however those on 40 mg/kg/day were found to have a significant deterioration in FARS and ICARS scores compared to those on placebo. Individuals treated with 20 mg/kg/day and 40 mg/kg/day had a decline in LVMI compared to those in the placebo group. Deferiprone at 20 mg/kg/day showed an acceptable safety profile however there were safety concerns in doses of 40 and 60 mg/kg/day, with reports of

worsening ataxia. This was demonstrated early in two individuals taking 60 mg/kg/day however the deterioration in individuals administered 40 mg/kg/day was only shown during analysis of efficacy data at 6 months [68].

3.4. *Frataxin level modifiers*

3.4.1. *Erythropoietin*

Erythropoietin (EPO), a hormone that stimulates red blood cell production [8], has been shown to increase frataxin levels *in vitro* [69]. One study found that recombinant human erythropoietin (rhuEPO) increased frataxin levels in primary lymphocytes from individuals with FRDA as well as in various other cell types, including neuronal and cardiac cells [69]. An open-label clinical pilot study was conducted to ascertain the role of rhuEPO on frataxin levels in 12 individuals affected by FRDA [70]. Significant increase in frataxin levels was reported after eight weeks of treatment with 5000 IU of rhuEPO ($p < 0.01$). No significant neurological improvements, as measured by the SARA, were reported [70]. A six-month open label study was then performed where eight individuals with FRDA received 2000 IU of rhuEPO three times a week [71]. Modest neurological benefit was shown, with improvements in the FARS and SARA demonstrated. There was a 24% overall increase in frataxin levels ($p = 0.017$) and a reduction in urinary 8-hydroxydeoxyguanosine ($p = 0.012$), a marker of oxidative stress. A randomised placebo-controlled trial of 16 individuals with FRDA was undertaken over six months [72]. Treatment consisted of 20,000 IU rhuEPO administered intravenously every three weeks, 40,000 IU every three weeks and 40,000 IU every two weeks. While the therapy was well tolerated, there was no significant change in any outcome measure including frataxin levels and SARA scores. There are concerns about the extended use of rhuEPO as it can increase red blood cell production and lead to an increased risk of cardiovascular events [73].

Carbamylated erythropoietin (CEPO) is a form of modified EPO that has minimal erythropoietic properties [74]. The safety and tolerability of this agent was tested in a randomised placebo-controlled trial of 36 people with FRDA. While the drug was well tolerated, which fulfilled its primary endpoint of safety and tolerability, there were no significant improvements found in secondary outcome measures including frataxin levels in peripheral blood mononuclear cells (PBMCs), FARS and SARA scores [74].

3.4.2. *Ubiquitin competitors*

It has been determined that the ubiquitin-proteasome system (UPS) controls frataxin stability [75] leading to development of a therapeutic approach aimed at preventing the degradation of frataxin [76]. RNF126 has been identified as the frataxin E3 ligase that promotes frataxin ubiquitination and degradation. Inhibition of RNF126 is therefore another potential therapeutic strategy for FRDA [77]. Further studies exploring this therapeutic approach are being planned.

3.4.3. *TAT-frataxin*

Payne and colleagues have developed an innovative delivery system named trans-activator transcription (TAT) to transport synthetic frataxin directly into the mitochondria of mouse models of FRDA homozygous for a conditional deletion of the *FXN* gene [78]. Mean lifespan in these mice was increased by 53%, with improvement also shown in cardiac function, including increased heart rate, and improved diastolic function [78]. TAT-Frataxin (now known as CTI-1601) has since been given orphan drug designation and is currently being developed as a treatment for FRDA [79].

3.5. *Agents that increase FRDA gene expression*

3.5.1. *Histone deacetylase inhibitors*

Histone deacetylase (HDAC) inhibitors reduce epigenetic silencing of genes by reverting chromatin to an open and active state for gene transcription. In FRDA, specific classes of HDAC inhibitors have been found to increase histone acetylation and restore frataxin to normal levels in the central nervous system and heart of FRDA mouse models [80–82]. It has been shown that a HDAC inhibitor was able to restore frataxin to normal levels in the central nervous system and heart of mouse models [83–85]. RG2833, a synthetic HDAC inhibitor, was tested in an *in vitro* human FRDA neuronal cell model derived from patient induced pluripotent stem cells to study its efficacy in modulating *FXN* gene expression [85]. Findings revealed an increase in *FXN* mRNA levels and frataxin protein. A phase 1 clinical trial of RG2833 in 20 adults with FRDA was conducted to determine safety and efficacy. The study comprised four cohorts – two of the cohorts were open label in design with single 30–120 mg doses, while the other two were enrolled to randomised, double-blind, placebo-controlled crossover studies. In the latter two cohorts, participants received either a single 180 mg dose or placebo, or two 120 mg doses or placebo. RG2833 was well tolerated and was found to increase *FXN* gene expression in circulating lymphocytes in all but one participant. Upregulation of *FXN* mRNA levels in participants on the highest three doses (120 mg, 180 mg and 240 mg) was demonstrated, with an average induction of 1.5–1.6 fold shown within 24 h of therapy administration. While RG2833 was well tolerated, potentially toxic metabolites of the compound were detected making it unsuitable for further testing. Additional compounds are currently being identified as potential candidates for clinical trials [86,87].

Nicotinamide (Vitamin B3) is a HDAC inhibitor that has been studied in FRDA. It has good bioavailability and has been shown to pass through the blood brain barrier [88]. In an open-label dose-escalation study, ten individuals with FRDA were treated with doses of up to 8 g/day of oral nicotinamide [89]. While generally well tolerated, three subjects demonstrated abnormal liver function test results after taking high doses of nicotinamide that resolved after the dose was reduced. Daily dosing at 3.5–6 g demonstrated a significant upregulation of frataxin expression ($p < 0.0001$). There were no significant improvements in clinical measures [89]. A randomised, placebo-controlled, double-blinded study investigating the efficacy of high dose nicotinamide in FRDA (NICOFA) over two years is planned [90].

3.5.2. *Interferon gamma*

Interferon gamma (IFNγ) is a cytokine that contributes to iron metabolism and immune responses. It was shown to increase

frataxin mRNA and protein content in cell lines derived from individuals with FRDA [91]. Treatment with IFNγ was also shown to increase frataxin levels in neurons from the dorsal root ganglia and prevents neuronal degeneration as well as preventing neurological dysfunction in a FRDA mouse model [91]. An open-label study of IFNγ in 12 children with FRDA was conducted [92]. The dose of IFNγ administered subcutaneously three times per week was increased from 10 to 50 μg/m^2 during the first four weeks and then remained at 50 μg/m^2 for the remaining eight weeks. There was a significant improvement seen in FARS scores ($p = 0.0078$), however no other significant changes were observed in the patient reported scales. Change in frataxin levels in PBMCs and buccal cells did not reach significance [92].

A phase 2 clinical trial testing the safety and efficacy of IFNγ in nine adults over four weeks found modest but non-significant increases in frataxin levels in PBMCs [93]. There was no significant change in the SARA score. A phase 3 multicentre randomised placebo-controlled trial of IFNγ in FRDA has been completed (STEADFAST study) and the primary endpoint, change in the modified FARS score, was not met at 26 weeks when compared to placebo [94].

3.5.3. *Resveratrol*

Resveratrol is a naturally occurring polyphenol with postulated antioxidant and neuroprotective benefits. Resveratrol was found to increase frataxin expression in FRDA cell and mouse models [95]. An open-label 12 week study of 24 individuals with FRDA (12 receiving 1 g resveratrol daily and 12 receiving 5 g resveratrol daily) showed possible clinical benefit in the high dose group as measured by FARS, ICARS, a hearing outcome measure and a speech outcome measure [96]. While little change was noted in PBMC frataxin protein levels (the primary outcome measure), high dose resveratrol also resulted in an improvement in an oxidative stress marker, plasma F2-isoprostanes. A randomised placebo-controlled trial is planned [96].

3.5.4. *Granulocyte-colony stimulating factor and stem cell factor*

Granulocyte-colony stimulating factor (G-CSF) and stem cell factor (SCF) are cytokines whose neuroprotective effects have been explored in a humanised murine model of FRDA [97]. After six months of treatment with monthly subcutaneous infusions of G-CSF and SCF (200 μg/kg), frataxin levels were found to have increased [97]. Improvement was also shown with motor coordination and locomotor activity, along with increase in neural stem cell numbers and reduction in inflammation. Treatment with G-CSF and SCF therefore look promising however studies in individuals in FRDA will need to be conducted to determine safety and efficacy.

4. Gene therapy

Gene replacement therapy is another avenue of treatment that is being studied and is perhaps the most promising in terms of correcting frataxin loss in FRDA [98]. There are a number of strategies for gene correction and cellular targets that are currently being explored [99]. Perdomini and colleagues used Mck-Cre-Fxn$^{L3/L}$-mice, a conditional cardiac and skeletal muscle *FXN* knockout model, and treated the mice with intravenously administered adeno-associated virus rh10 vector expressing human *FXN* [100]. They found that cardiomyopathy onset was averted in these mice. When the treatment was administered to mice after the onset of cardiac disease, cardiomyopathy was completely reversed, establishing the potential of gene therapy in the treatment of cardiac disease in FRDA.

In another study, zinc finger nucleases were used to excise the *FXN* GAA expansion repeat on one allele of cells derived from individuals with FRDA. This excision lead to an increase in *FXN* mRNA and protein expression [101].

Appropriate and adequate systemic delivery to target cells, immunogenicity of vectors, and safety concerns are common challenges related to gene therapy approaches. Thorough examination and assessment of vectors in FRDA disease models will be imperative to ensure efficacy and safety prior to human trials [99].

5. Rehabilitation

While the search for effective therapeutic agents is ongoing, rehabilitation has long been the foundation of managing physical symptoms and ambulation decline in individuals with FRDA [102,103]. Despite this, there have been few clinical studies that have evaluated rehabilitation interventions in FRDA [104].

An intensive coordinative training programme that consisted of a four-week course of three one-hour sessions each week was conducted on 16 individuals with degenerative cerebellar disorders (3 with FRDA) [103]. Exercises in the programme included static balance, dynamic balance, whole-body movements for trunk-limb coordination, falling prevention and strategies and movements to treat and prevent contracture. A significant reduction in the SARA score was demonstrated for all subjects indicating short-term improvements in motor performance was achieved. However individuals with cerebellar ataxia were found to have greater improvements when compared to those with an afferent form of ataxia, which included the individuals with FRDA [103]. One year after intervention and using a home exercise training schedule, a significant reduction of ataxia symptoms as measured by the SARA was found specifically in the group with cerebellar ataxias. In the group with afferent ataxia, including FRDA, the reductions in ataxia symptoms were less significant compared to the cerebellar group and the benefits did not persist long-term [105].

A retrospective study demonstrated that inpatient rehabilitation specific to FRDA was effective in improving or preventing decline in function for people with the condition as measured using the Functional Independence Measure (FIM) which is an indicator of an individual's ability to perform activities of daily living [102]. FIM scores were found to improve significantly by a mean of 8.5 points during inpatient rehabilitation and continued to improve by a mean of 2.0 points following rehabilitation. These results indicate that inpatient rehabilitation is beneficial in preventing decline in function in individuals with FRDA [102].

More recently, a randomised controlled trial was conducted, examining the effects of a six-week rehabilitation programme specifically for individuals with FRDA [106]. The prescribed rehabilitation programme was individualised and the study compared an intervention (six weeks of rehabilitation followed by a six-week home exercise programme) group to a control group (no intervention for six weeks followed by six weeks of rehabilitation then a six-week home exercise programme). The intervention portion of the programme was conducted three times a week and consisted of two to three hours of physiotherapy, supervised gym exercises and aquatic physiotherapy. This study showed improvements in function following short-term rehabilitation in FRDA. While there was no significant difference in the FIM score between the intervention and control groups, a significant change in the body movement subscale of the Friedreich Ataxia Impact Scale (FAIS), a patient reported outcome measure, revealed a significant improvement in health and wellbeing in the intervention group compared to controls ($p = 0.003$). There was a significant within-group improvement in the motor domain of the FIM for the interventional group whereas there was no such change in the control group. The home exercise programme was not effective in terms of sustaining frequency of exercise performance and maintaining the results achieved during rehabilitation. While the authors concluded that rehabilitation can play a role in improving health and wellbeing in individuals with FRDA, a main limitation was the size of the study, and therefore a larger, adequately powered study is required to enable definitive conclusions to be drawn.

In addition to physical rehabilitation, further evidence is required to establish the efficacy of occupational therapy and speech pathology on improving function in FRDA. A review of the effects of interventions for speech disorder in adults and children in FRDA and other hereditary ataxias found insufficient and low quality evidence to determine the effectiveness of any treatment for speech disorders [107]. There is currently no published evidence on occupational therapy intervention.

6. Conclusion

FRDA is a slowly progressive neurological disorder for which there is currently no treatment proven to modify the natural history of the disorder. The exploration for therapeutic agents has advanced rapidly in the last few decades, with various pharmacological agents at different stages of development. The Friedreich's Ataxia Research Alliance (FARA) provides a comprehensive outline of current therapeutic agents with a treatment pipeline (http://www.curefa.org/pipeline). At this time, no study has successfully achieved its stated endpoint and studies examining the same compounds are generally inconclusive or conflicting. Several issues play a role in this lack of success including the short length of trials, the responsiveness of tools used to measure disease progression in studies as well as the heterogeneity of the populations studied. It is suggested that studies should target individuals with FRDA in the early stages of the disease as change is greatest in this group [108,109]. Further work is needed to increase the availability of sensitive and responsive outcome measures that ensures the inclusion in clinical trials of all individuals with FRDA across the disease trajectory. Research into gene therapy holds the most promise in the treatment of this condition however safety and logistic issues will need to be addressed [8,98].

Conflict of interest

None declared.

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REFERENCES

[1] Delatycki M, Williamson R, Forrest S. Friedreich ataxia: an overview. J Med Genet 2000;37(1):1–8.
[2] Cossee M, Schmitt M, Campuzano V, Reutenauer L, Moutou C, Mandel JL, et al. Evolution of the Friedreich's ataxia trinucleotide repeat expansion: founder effect and premutations. Proc Natl Acad Sci U S A 1997;94(14):7452–7.
[3] Campuzano V, Montermini L, Molto M, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271:1423–7.
[4] Durr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med 1996;335(16):1169–75.
[5] Filla A, De Michele G, Cavalcanti F, Pianese L, Monticelli A, Campanella G, et al. The relationship between trinucleotide (GAA) repeat length and clinical features in Friedreich ataxia. Am J Hum Genet 1996;59(3):554–60.
[6] Klockgether T, Ludtke R, Kramer B, Abele M, Burk K, Schols L, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain 1998;121(Pt 4):589–600.
[7] Delatycki M. Evaluating the progression of Friedreich ataxia and its treatment. J Neurol 2009;256(Suppl. 1):36–41.
[8] Aranca TV, Jones TM, Shaw JD, Staffetti JS, Ashizawa T, Kuo S-H, et al. Emerging therapies in Friedreich's ataxia. Neurodegener Disease Manag 2016;6(1):49–65.
[9] Bürk K. Friedreich Ataxia: current status and future prospects. Cerebell Ataxias 2017;4:4.
[10] Subramony SH, May W, Lynch DR, Gomez CM, Fischbeck KH, Hallett M, et al. Measuring Friedreich ataxia: interrater reliability of a neurologic rating scale. Neurology 2005;64(7):1261–2.
[11] Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, 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 1997;145(2):205–11.

[12] Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006;66(11):1717–20.
[13] Storey E, Tuck K, Hester R, Hughes A, Churchyard A. Inter-rater reliability of the International Cooperative Ataxia Rating Scale (ICARS). Movem Disord 2004;19(2):190–2.
[14] Lynch DR, Farmer JM, Wilson RL, Balcer LJ. Performance measures in Friedreich ataxia: potential utility as clinical outcome tools. Movem Disord 2005;20(7):777–82.
[15] Tai G, Yiu EM, Delatycki MB, Corben LA. How does performance of the Friedreich Ataxia Functional Composite compare to rating scales? J Neurol 2017;264 (8):1768–76.
[16] Parkinson MH, Schulz JB, Giunti P. Co-enzyme Q10 and idebenone use in Friedreich's ataxia. J Neurochem 2013;126(Suppl. 1):125–41.
[17] Armstrong J, Khdour O, Hecht S. Does oxidative stress contribute to the pathology of Friedreich's ataxia?. A radical question. FASEB J 2010;24(7):2152–63.
[18] Gillis JC, Benefield P, McTavish D. Idebenone: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in age-related cognitive disorders. Drugs Aging 1994;5(2):133–52.
[19] Rustin P, von Kleist-Retzow J-C, Chantrel-Groussard K, Sidi D, Munnich A, Rötig A. Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study. Lancet 1999;354(9177):477–9.
[20] Kearney M, Orrell RW, Fahey M, Pandolfo M. Antioxidants and other pharmacological treatments for Friedreich ataxia. Cochr Datab Syst Rev 2009;(4):CD007791.
[21] Hausse AO, Aggoun Y, Bonnet D, Sidi D, Munnich A, Rotig A, et al. Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. Heart 2002;87(4):346–9.
[22] Buyse G, Mertens L, Di Salvo G, Matthijs I, Weidemann F, Eyskens B, et al. Idebenone treatment in Friedreich's ataxia. Neurology 2003;60(10):1679–81.
[23] Pineda M, Arpa J, Montero R, Aracil A, Dominguez F, Galvan M, et al. Idebenone treatment in paediatric and adult patients with Friedreich ataxia: long-term follow-up. Eur J Paediatr Neurol 2008;12(6):470–5.
[24] Schols L, Vorgerd M, Schillings M, Skipka G, Zange J. Idebenone in patients with Friedreich ataxia. Neurosci Lett 2001;306(3):169–72.
[25] 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 2003;60(10):1676–9.
[26] Artuch R, Aracil A, Mas A, Colome C, Rissech M, Monros E, et al. Friedreich's ataxia: idebenone treatment in early stage patients. Neuropediatrics 2002;33(4):190–3.
[27] Di Prospero 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 2007;6(10):878–86.
[28] Lynch DR, Perlman SL, Meier T. A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. Archiv Neurol 2010;67(8):941–7.
[29] Lagedrost SJ, Sutton MSJ, Cohen MS, Satou GM, Kaufman BD, Perlman SL, et al. Idebenone in Friedreich ataxia cardiomyopathy – results from a 6-month phase III study (IONIA). Am Heart J 2011;161(3):639–45.
[30] Santhera's MICONOS Trial with catena in Friedreich's ataxia misses primary endpoint. Available from: https://lacaf.org/en/santhera-trial-with-catena-in-friedreich-ataxia-misses-primary-endpoint/.
[31] Schulz JB, Di Prospero NA, Fischbeck K. Clinical experience with high-dose idebenone in Friedreich ataxia. J Neurol 2009;256(Suppl. 1):42–5.
[32] Lodi R, Hart PE, Rajagopalan B, Taylor DJ, Crilley JG, Bradley JL, et al. Antioxidant treatment improves in vivo cardiac and skeletal muscle bioenergetics in patients with Friedreich's ataxia. Ann Neurol 2001;49(5):590–6.
[33] Hart PE, Lodi R, Rajagopalan B, Bradley JL, Crilley JG, Turner C, et al. Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up. Archiv Neurol 2005;62(4): 621–6.
[34] Cooper J, Korlipara L, Hart P, Bradley J, Schapira A. Coenzyme Q10 and vitamin E deficiency in Friedreich's ataxia: predictor of efficacy of vitamin E and coenzyme Q10 therapy. Eur J Neurol 2008;15(12):1371–9.
[35] Hawi A, Heald S, Sciascia T. Use of an adaptive study design in single ascending-dose pharmacokinetics of A0001 (α-tocopherylquinone) in healthy male subjects. J Clin Pharmacol 2012;52(1):65–77.
[36] Lynch D, Willi S, Wilson R, Cotticelli M, Brigatti K, Deutsch E, et al. A0001 in Friedreich ataxia: biochemical characterization and effects in a clinical trial. Movem Disord 2012;27(8):1026–33.
[37] Shrader WD, Amagata A, Barnes A, Enns GM, Hinman A, Jankowski O, et al. α-Tocotrienol quinone modulates oxidative stress response and the biochemistry of aging. Bioorg Med Chem Lett 2011;21(12):3693–8.
[38] Enns GM, Kinsman SL, Perlman SL, Spicer KM, Abdenur JE, Cohen BH, et al. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. Mol Genet Metab 2012;105(1):91–102.
[39] Sadun AA, Chicani CF, Ross-Cisneros FN, Barboni P, Thoolen M, Shrader WD, et al. Effect of EPI-743 on the clinical course of the mitochondrial disease leber hereditary optic neuropathy. Archiv Neurol 2012;69(3): 331–8.
[40] Martinelli D, Catteruccia M, Piemonte F, Pastore A, Tozzi G, Dionisi-Vici C, et al. EPI-743 reverses the progression of the pediatric mitochondrial disease—genetically defined Leigh syndrome. Mol Genet Metab 2012;107(3):383–8.
[41] Zesiewicz T, Perlman S, Sullivan K, Huang Y, Salemi J, Klein M, et al. EPI-743 (alpha-tocotrienol quinone) demonstrates long-term improvement in neurological function and disease progression in Friedreich's ataxia. Neurology 2017;88(16 Suppl.).
[42] Sullivan K, Freeman M, Shaw J, Gooch C, Huang Y, Klein M, et al. EPI-743 for Friedreich's ataxia patients with point mutations (P5.388). Neurology 2016;86(16 Suppl.).
[43] Paupe V, Dassa EP, Goncalves S, Auchère F, Lönn M, Holmgren A, et al. Impaired nuclear Nrf2 translocation undermines the oxidative stress response in Friedreich ataxia. PLOS ONE 2009;4(1):e4253.
[44] Holmström KM, Kostov RV, Dinkova-Kostova AT. The multifaceted role of Nrf2 in mitochondrial function. Curr Opin Toxicol 2016;1:80–91.
[45] Shin S, Wakabayashi J, Yates MS, Wakabayashi N, Dolan PM, Aja S, et al. Role of Nrf2 in prevention of high-fat diet-induced obesity by synthetic triterpenoid CDDO-imidazolide. Eur J Pharmacol 2009;620(1–3):138–44.
[46] Abeti R, Uzun E, Renganathan I, Honda T, Pook MA, Giunti P. Targeting lipid peroxidation and mitochondrial imbalance in Friedreich's ataxia. Pharmacol Res 2015;99 (Suppl. C):344–50.
[47] Cotticelli MG, Crabbe AM, Wilson RB, Shchepinov MS. Insights into the role of oxidative stress in the pathology of Friedreich ataxia using peroxidation resistant polyunsaturated fatty acids. Redox Biol 2013;1(1):398–404.
[48] Retrotope announces Phase I/II Clinical Trial results of RT001 in treatment of Friedreich's ataxia. Available from: https://static1.squarespace.com/static/549af14ae4b004237f7bb71a/t/57dd7786f7e0ab741930775f/1474131955350/PR+Retrotope+Phase+1+Results.pdf.

[49] Jhala SS, Hazell AS. Modeling neurodegenerative disease pathophysiology in thiamine deficiency: consequences of impaired oxidative metabolism. Neurochem Int 2011;58 (3):248–60.
[50] Mkrtchyan G, Aleshin V, Parkhomenko Y, Kaehne T, Luigi Di Salvo M, Parroni A, et al. Molecular mechanisms of the non-coenzyme action of thiamin in brain: biochemical, structural and pathway analysis. Scient Rep 2015;5:12583.
[51] Gibson GE, Blass JP. Thiamine-dependent processes and treatment strategies in neurodegeneration. Antioxid Red Signal 2007;9(10):1605–20.
[52] Costantini A, Giorgi R, D'Agostino S, Pala MI. High-dose thiamine improves the symptoms of Friedreich's ataxia. BMJ Case Rep 2013;2013.
[53] Costantini A, Laureti T, Pala MI, Colangeli M, Cavalieri S, Pozzi E, et al. Long-term treatment with thiamine as possible medical therapy for Friedreich ataxia. J Neurol 2016;263(11):2170–8.
[54] Marmolino D, Manto M, Acquaviva F, Vergara P, Ravella A, Monticelli A, et al. PGC-1alpha down-regulation affects the antioxidant response in Friedreich's ataxia. PLOS ONE 2010;5(4):e10025.
[55] Coppola G, Marmolino D, Lu D, Wang Q, Cnop M, Rai M, et al. Functional genomic analysis of frataxin deficiency reveals tissue-specific alterations and identifies the PPARγ pathway as a therapeutic target in Friedreich's ataxia. Hum Mol Genet 2009;18(13):2452–61.
[56] Schöls L, Zange J, Abele M, Schillings M, Skipka G, Kuntz-Hehner S, et al. L-Carnitine and creatine in Friedreich's ataxia. A randomized, placebo-controlled crossover trial. J Neural Transm 2005;112(6):789–96.
[57] Shinnick JE, Isaacs CJ, Vivaldi S, Schadt K, Lynch DR. Friedreich ataxia and nephrotic syndrome: a series of two patients. BMC Neurol 2016;16:3.
[58] Waldvogel D, Peter Van Gelderen MH. Increased iron in the dentate nucleus of patients with Friedreich's ataxia. Ann Neurol 1999;46(1):123–5.
[59] Babcock M, de Silva D, Oaks R, Davis-Kaplan S, Jiralerspong S, Montermini L, et al. Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin. Science 1997;276(5319):1709–12.
[60] Delatycki MB, Camakaris J, Brooks H, Evans-Whipp T, Thorburn DR, Williamson R, et al. Direct evidence that mitochondrial iron accumulation occurs in Friedreich ataxia. Ann Neurol 1999;45(5):673–5.
[61] Schenck JF, Zimmerman EA. High-field magnetic resonance imaging of brain iron: birth of a biomarker? NMR Biomed 2004;17(7):433–45.
[62] Pandolfo M, Hausmann L. Deferiprone for the treatment of Friedreich's ataxia. J Neurochem 2013;126:142–6.
[63] Richardson T, Kelly H, Yu A, JW S. Therapeutic strategies in Friedreich's ataxia. Brain Res 2013;1514:91–7.
[64] Boddaert N, Le Quan Sang KH, Rotig A, Leroy-Willig A, Gallet S, Brunelle F, et al. Selective iron chelation in Friedreich ataxia: biologic and clinical implications. Blood 2007;110(1):401–8.
[65] Kakhlon O, Manning H, Breuer W, Melamed-Book N, Lu C, Cortopassi G, et al. Cell functions impaired by frataxin deficiency are restored by drug-mediated iron relocation. Blood 2008;112(13):5219–27.
[66] Rotig A, de Lonlay P, Chretien D, Foury F, Koenig M, Sidi D, et al. Aconitase and mitochondrial iron–sulphur protein deficiency in Friedreich ataxia. Nature Genet 1997;17 (2):215–7.
[67] Goncalves S, Paupe V, Dassa E, Rustin P. Deferiprone targets aconitase: implication for Friedreich's ataxia treatment. BMC Neurol 2008;8(1):20.
[68] Pandolfo M, Arpa J, Delatycki MB, Le Quan Sang KH, Mariotti C, Munnich A, et al. Deferiprone in Friedreich ataxia: a 6-month randomized controlled trial. Ann Neurol 2014;76(4):509–21.
[69] Sturm B, Stupphann D, Kaun C, Boesch S, Schranzhofer M, Wojta J, et al. Recombinant human erythropoietin: effects on frataxin expression in vitro. Eur J Clin Invest 2005;35 (11):711–7.
[70] Boesch S, Sturm B, Hering S, Goldenberg H, Poewe W, Scheiber-Mojdehkar B. Friedreich's ataxia: clinical pilot trial with recombinant human erythropoietin. Ann Neurol 2007;62(5):521–4.
[71] Boesch S, Sturm B, Hering S, Scheiber-Mojdehkar B, Steinkellner H, Goldenberg H, et al. Neurological effects of recombinant human erythropoietin in Friedreich's ataxia: a clinical pilot trial. Movem Disord 2008;23(13):1940–4.
[72] Mariotti C, Fancellu R, Caldarazzo S, Nanetti L, Di Bella D, Plumari M, et al. Erythropoietin in Friedreich ataxia: no effect on frataxin in a randomized controlled trial. Movem Disord 2012;27(3):446–9.
[73] Mariotti C, Nachbauer W, Panzeri M, Poewe W, Taroni F, Boesch S. Erythropoietin in Friedreich ataxia. J Neurochem 2013;126:80–7.
[74] Boesch S, Nachbauer W, Mariotti C, Sacca F, Filla A, Klockgether T, et al. Safety and tolerability of carbamylated erythropoietin in Friedreich's ataxia. Movem Disord 2014;29(7):935–9.
[75] Rufini A, Fortuni S, Arcuri G, Condò I, Serio D, Incani O, et al. Preventing the ubiquitin–proteasome-dependent degradation of frataxin, the protein defective in Friedreich's ataxia. Hum Mol Genet 2011;20(7):1253–61.
[76] Rufini A, Cavallo F, Condò I, Fortuni S, De Martino G, Incani O, et al. Highly specific ubiquitin-competing molecules effectively promote frataxin accumulation and partially rescue the aconitase defect in Friedreich ataxia cells. Neurobiol Disease 2015;75(Suppl. C):91–9.
[77] Benini M, Fortuni S, Condò I, Alfedi G, Malisan F, Toschi N, et al. E3 ligase RNF126 directly ubiquitinates frataxin, promoting its degradation: identification of a potential therapeutic target for Friedreich ataxia. Cell Rep 2017;18 (8):2007–17.
[78] Vyas PM, Tomamichel WJ, Pride PM, Babbey CM, Wang Q, Mercier J, et al. A TAT–frataxin fusion protein increases lifespan and cardiac function in a conditional Friedreich's ataxia mouse model. Hum Mol Genet 2012;21(6):1230–47.
[79] Chondrial announces FDA orphan drug designation for CTI-1601, a novel investigational technology for the treatment of Friedreich's ataxia. Available from: https://chondrialtherapeutics.com/chondrial-announces-fda-orphan-drug-designation-cti-1601-novel-investigational-technology-treatment-friedreichs-ataxia/.
[80] Di Prospero NA, Fischbeck KH. Therapeutics development for triplet repeat expansion diseases. Nature Rev Genet 2005;6:756.
[81] Kazantsev AG, Thompson LM. Therapeutic application of histone deacetylase inhibitors for central nervous system disorders. Nature Rev Drug Discov 2008;7(10):854–68.
[82] Gottesfeld JM, Rusche JR, Pandolfo M. Increasing Frataxin gene expression with histone deacetylase inhibitors as a therapeutic approach for Friedreich's ataxia. J Neurochem 2013;126(Suppl. 1):147–54.
[83] Rai M, Soragni E, Jenssen K, Burnett R, Herman D, Coppola G, et al. HDAC inhibitors correct frataxin deficiency in a Friedreich ataxia mouse model. PLOS ONE 2008;3(4):e1958.
[84] Herman D, Jenssen K, Burnett R, Soragni E, Perlman SL, Gottesfeld JM. Histone deacetylase inhibitors reverse gene silencing in Friedreich's ataxia. Nature Chem Biol 2006;2 (10):551–8.
[85] Soragni E, Miao W, Iudicello M, Jacoby D, De Mercanti S, Clerico M, et al. Epigenetic therapy for Friedreich ataxia. Ann Neurol 2014;76(4):489–508.

[86] Soragni E, Gottesfeld JM. Translating HDAC inhibitors in Friedrich's ataxia. Exp Opin Orphan Drugs 2016;4(9): 961–70.
[87] BioMarin highlights breadth of innovative development pipeline at R&D day on October 18th in New York. Available from: http://investors.biomarin.com/2017-10-18-BioMarin-Highlights-Breadth-of-Innovative-Development-Pipeline-at-R-D-Day-on-October-18th-in-New-York.
[88] Hoane MR, Kaplan SA, Ellis AL. The effects of nicotinamide on apoptosis and blood–brain barrier breakdown following traumatic brain injury. Brain Res 2006;1125(1):185–93.
[89] Libri V, Yandim C, Athanasopoulos S, Loyse N, Natisvili T, Law PP, et al. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. Lancet 2014;384(9942):504–13.
[90] NICOFA: nicotinamide for the treatment of Friedreich ataxia. Available from: http://www.orpha.net/consor/cgi-bin//ResearchTrials_Networks.php?lng=EN&data_id=119998&title=NICOFA—Nicotinamide-for-the-treatment-of-Friedreich-ataxia&search=Directory_Institutions_Simple.
[91] Tomassini B, Arcuri G, Fortuni S, Sandi C, Ezzatizadeh V, Casali C, et al. Interferon gamma upregulates frataxin and corrects the functional deficits in a Friedreich ataxia model. Hum Mol Genet 2012;21(13):2855–61.
[92] Seyer L, Greeley N, Foerster D, Strawser C, Gelbard S, Dong Y, et al. Open-label pilot study of interferon gamma-1b in Friedreich ataxia. Acta Neurol Scand 2015;132(1):7–15.
[93] Marcotulli C, Fortuni S, Arcuri G, Tomassini B, Leonardi L, Pierelli F, et al. GIFT-1, a phase IIa clinical trial to test the safety and efficacy of IFNγ administration in FRDA patients. Neurol Sci 2016;37(3):361–4.
[94] Horizon Pharma: horizon pharma plc announces topline results from phase 3 study of ACTIMMUNE® (interferon gamma-1b) in Friedreich's ataxia. Available from: http://ir.horizon-pharma.com/news-releases/news-release-details/horizon-pharma-plc-announces-topline-results-phase-3-study.
[95] Li L, Voullaire L, Sandi C, Pook MA, Ioannou PA, Delatycki MB, et al. Pharmacological screening using an FXN-EGFP cellular genomic reporter assay for the therapy of Friedreich ataxia. PLOS ONE 2013;8(2):e55940.
[96] Yiu EM, Tai G, Peverill RE, Lee KJ, Croft KD, Mori TA, et al. An open-label trial in Friedreich ataxia suggests clinical benefit with high-dose resveratrol, without effect on frataxin levels. J Neurol 2015;262(5):1344–53.
[97] Kemp KC, Cerminara N, Hares K, Redondo J, Cook AJ, Haynes HR, et al. Cytokine therapy-mediated neuroprotection in a Friedreich's ataxia mouse model. Ann Neurol 2017;81(2):212–26.
[98] Strawser C, Schadt K, Hauser L, McCormick A, Wells M, Larkindale J, et al. Pharmacological therapeutics in Friedreich ataxia: the present state. Exp Rev Neurotherapeut 2017;17(9):895–907.
[99] Evans-Galea M, Pebay A, Dottori M, Corben L, Hwee Ong S, Lockhart JP, et al. Cell and gene therapy for Friedreich ataxia: progress to date. Hum Gene Ther 2014;25(8):684–93.
[100] Perdomini M, Belbellaa B, Monassier L, Reutenauer L, Messaddeq N, Cartier N, et al. Prevention and reversal of severe mitochondrial cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia. Nature Med 2014;20(5):542–7.
[101] Li Y, Polak U, Bhalla AD, Rozwadowska N, Butler JS, Lynch DR, et al. Excision of expanded GAA repeats alleviates the molecular phenotype of Friedreich's ataxia. Mol Therap 2015;23(6):1055–65.
[102] Milne SC, Campagna EJ, Corben LA, Delatycki MB, Teo K, Churchyard AJ, et al. Retrospective study of the effects of inpatient rehabilitation on improving and maintaining functional independence in people with Friedreich ataxia. Archiv Phys Med Rehabilit 2012;93(10):1860–3.
[103] Ilg W, Synofzik M, Brötz D, Burkard S, Giese MA, Schöls L. Intensive coordinative training improves motor performance in degenerative cerebellar disease. Neurology 2009;73(22):1823–30.
[104] Milne SC, Corben LA, Georgiou-Karistianis N, Delatycki MB, Yiu EM. Rehabilitation for individuals with genetic degenerative ataxia: a systematic review. Neurorehab Neural Rep 2017;31(7):609–22.
[105] Ilg W, Brötz D, Burkard S, Giese MA, Schöls L, Synofzik M. Long-term effects of coordinative training in degenerative cerebellar disease. Movem Disord 2010;25(13):2239–46.
[106] Milne SC, Corben LA, Roberts M, Murphy A, Tai G, Georgiou-Karistianis N, et al. Can rehabilitation improve the health and well-being in Friedreich's ataxia: a randomized controlled trial? Clin Rehabilit 2017 [Epub ahead of print].
[107] Vogel AP, Folker J, Poole ML. Treatment for speech disorder in Friedreich ataxia and other hereditary ataxia syndromes. Cochr Database Syst Rev)2014;(10).
[108] Friedman LS, Farmer JM, Perlman S, Wilmot G, Gomez CM, Bushara KO, et al. Measuring the rate of progression in Friedreich ataxia: implications for clinical trial design. Movem Disord 2010;25(4):426–32.
[109] Patel M, Isaacs CJ, Seyer L, Brigatti KW, Gelbard S, Strawser C, et al. Progression of Friedreich ataxia: quantitative characterization over 5 years. Ann Clin Trans Neurol 2016;3(9):684–94.