Available online at www.sciencedirect.com
ScienceDirect
journal homepage: http://www.elsevier.com/locate/pjnns

Review article

Progress in the treatment of Friedreich ataxia

Q1 Geneieve Tai [a], Louise A. Corben [a,b,c], Eppie M. Yiu [a,c,d], Sarah C. Milne [a,b], Martin B. Delatycki [a,b,c,e,*]

[a] Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, Parkville, Victoria 3052, Australia
[b] School of Psychological Science, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria 3168, Australia
[c] Department of Paediatrics, University of Melbourne, Parkville, Victoria 3052, Australia
[d] Department of Neurology, Royal Children's Hospital, Parkville, Victoria 3052, Australia
[e] Victorian Clinical Genetics Services, Parkville, Victoria 3052, Australia

ARTICLE INFO

Article history:
Received 30 January 2018
Accepted 12 February 2018
Available online xxx

Keywords:
Friedreich ataxia
Therapy
Rehabilitation
Gene therapy

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.

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

* *Corresponding author at*: Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, Flemington Rd, Parkville, Victoria 3052, Australia.
E-mail address: martin.delatycki@vcgs.org.au (M.B. Delatycki).
https://doi.org/10.1016/j.pjnns.2018.02.003
0028-3843/

Please cite this article in press as: Tai G, et al. Progress in the treatment of Friedreich ataxia. Neurol Neurochir Pol (2018), https://doi.org/10.1016/j.pjnns.2018.02.003

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 (≤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

Please cite this article in press as: Tai G, et al. Progress in the treatment of Friedreich ataxia. Neurol Neurochir Pol (2018), https://doi.org/10.1016/j.pjnns.2018.02.003