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Clinical experience with high-dose idebenone in Friedreich ataxia

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Abstract

Several reports in the literature describe the effects of low-dose (5 mg/kg/day) idebenone in significantly reducing cardiac hypertrophy in patients with Friedreich ataxia. However, the effects of idebenone on neurological function have not been reliably determined in these studies; when neurological parameters were reported, results were often inconclusive, usually because of subject heterogeneity and lack of adequate statistical power. In two of these studies, some patients showed beneficial effects of idebenone on their cardiomyopathy only when the dose was increased, prompting the systematic investigation of higher doses of idebenone. Following a phase 1 dose escalation study, a phase 2 tolerability and efficacy trial with low, intermediate, and high doses of idebenone was conducted. The results suggested that treatment with intermediate- and high-dose idebenone had beneficial effects on neurological symptoms. On the basis of these results, two phase 3 trials have been initiated, one in the United States with young ambulatory patients and one in Europe without limits on age and disease severity.

Keywords

Friedreich ataxia; idebenone; rare disorders; clinical trials; cardiomyopathy; neurologic; ICARS; FARS; oxidative stress

Introduction

Friedreich ataxia (FRDA) is a progressive, multi-system, degenerative disorder caused by a reduction in levels of frataxin in the body [1]. FRDA causes a progressive neurological

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syndrome characterised by gait and limb ataxia, dysarthria, areflexia, loss of vibratory and position sense, and weakness of proximal and distal muscles [2]. Non-neurological features may include hypertrophic cardiomyopathy, scoliosis, and diabetes mellitus. Fibroblasts and muscle cells of patients with FRDA and model systems of FRDA show a loss of iron-sulphur cluster proteins, which include the respiratory chain complexes I, II, and III and aconitase [1]. This loss results in reduced adenosine triphosphate (ATP) generation, which has been demonstrated in the heart and skeletal muscle of patients with FRDA through the use of magnetic resonance spectroscopy [3]. Furthermore, FRDA affects the way mitochondria handle iron, leading to the accumulation of iron in mitochondria and, consequently, the formation of reactive oxygen species via the Fenton reaction [1]. An increase in markers of oxidative stress has been measured in blood and urine samples of patients with FRDA [4, 5].

Use of Idebenone in FRDA

Clinical studies with idebenone at 5 mg/kg and 10 mg/kg per day

Idebenone is a short-chain benzoquinone structurally related to co-enzyme Q10, whose properties as a potent anti-oxidant and electron carrier make it an appealing potential treatment for FRDA. Initial clinical studies with idebenone in FRDA were carried out with a dosage of 5 mg/kg/day. Only two of these studies were double-blind and placebo-controlled [6, 7]; all the others were open-label trials. These investigations consistently demonstrated a reduction in cardiac hypertrophy, as measured by echocardiography, in most idebenone-treated patients [6-12]. Only the shortest trial (1.5 months versus 4–84 months for the other studies) failed to show any benefit of treatment [7]. Two trials that evaluated cardiac function in addition to heart size showed that some functional improvement accompanied the reduction in cardiac hypertrophy [8, 9]. In contrast, 61 patients in one study [11] presented a worsening rather than an improvement of the ejection fraction, despite significant reductions in left ventricular mass. It should be noted, however, that this study involved the longest follow-up of idebenone-treated patients; therefore, some significant disease progression probably occurred in this cohort, which may have outweighed any positive effect of treatment.

Data on the effects of idebenone treatment on neurological symptoms have been less robust, and interpretation of results has been limited, in most cases, by the open-label design of the trials. Earlier studies reported an improvement in motor skills with idebenone treatment [12, 13], and other trials reported an improvement in the International Cooperative Ataxia Rating Scale (ICARS) score [13, 14]. ICARS improvement also was reported in children, but not in adults [10]. In a large cohort of patients (N = 88), investigators reported a slowing of disease progression with idebenone treatment [11]. FRDA progression, measured as an increase in ICARS score per year, was 1.9 points in idebenone-treated patients versus 4.4 points in untreated patients. However, this was a retrospective, open-label study, so these results should be interpreted with caution.

Safety and tolerability of high-dose idebenone in patients with FRDA

In the open-label studies and in the two randomised, placebo-controlled trials discussed above, most patients were treated with idebenone 5 mg/kg/day. In an animal model of FRDA with frataxin deficiency in heart and striated muscle, which leads to a lethal cardiomyopathy, idebenone was not effective at 10 mg/kg/day; showed a trend toward efficacy at 30 mg/kg; and significantly delayed disease onset, slowed progression, and extended survival at 90 mg/kg/day [15]. Furthermore, in three of the above clinical trials, patients who failed to respond to an initial dose of idebenone 5 mg/kg/day subsequently responded to higher doses of idebenone at 10 mg/kg/day [9, 16] and 20 mg/kg/day [10]. These findings therefore suggested that greater efficacy could be achieved at higher idebenone doses. To investigate the safety and tolerability of increasing doses of idebenone, an open-label, phase 1A, dose-escalation trial in 78 patients with FRDA was conducted, followed by an open-label, 1-month phase 1B trial in 15 patients with FRDA [17]. These studies included separate cohorts of adults, adolescents, and children. In the dose-escalation trial, no dose-limiting toxicity was observed up to the maximum dose tested (75 mg/kg). Plasma levels of total idebenone were found to increase in proportion to the drug dose up to 55 mg/kg. In the open-label 1-month trial, 14 of 15 patients with FRDA tolerated idebenone at a dosage of 60 mg/kg/day. One child experienced mild nausea and diarrhoea during the second day of idebenone administration. The medication was stopped with resolution of symptoms. Two weeks later, the child was re-challenged with idebenone; symptoms recurred, and the medication was discontinued. Furthermore, four self-limited adverse events (AEs) were reported with mild gastrointestinal complaints, including dyspepsia, loose stool, nausea, and vomiting. No serious AE occurred. No significant changes in vital signs, physical examination findings, haematology or chemistry blood values, or electrocardiograms were noted.

The time taken to reach maximum plasma concentration averaged about 2 hours. The mean terminal half-life of total idebenone following administration of 60 mg/kg/day ranged from 9.4 hours in children to 12.7 hours in adults.

Neurological effects of high-dose idebenone in patients with FRDA

As was discussed earlier, previous studies indicated that low-dosage idebenone (5 mg/kg/day) reduces cardiac hypertrophy, but definite improvement in neurological and heart functions had not been shown. Based on the pharmacokinetic data and on the encouraging safety and tolerability information gathered in the phase 1A and 1B studies, a phase 2, 6-month, randomised, double-blind, placebo-controlled trial that tested higher doses of idebenone was conducted in 48 patients, aged 9–17 years, with genetically confirmed FRDA. The randomisation assignment was stratified by weight (≤ 45 kg or > 45 kg) to maintain the dose range and by the shorter *GAA* repeat length (≤ 800 or > 800) to control for disease progression. Patients were randomised to one of four treatment arms: (i) placebo, (ii) low idebenone dose of 180 mg per day (≤ 45 kg body weight) or 360 mg per day (> 45 kg) corresponding to 4–8 mg/kg/day (commonly referred to as 5 mg/kg/day), (iii) intermediate dose of 450 mg per day (≤ 45 kg) or 900 mg per day (> 45 kg) corresponding to 10–20 mg/kg/day (commonly referred to as 15 mg/kg/day), and (iv) high dose of 1350 mg per day (≤ 45 kg) or 2250 mg per day (> 45 kg) corresponding to 30–50 mg/kg/day (commonly

referred to as 45 mg/kg/day). Because no quantitative data on disease progression were available at the time of study initiation, and because the duration of the study was considered too short to anticipate significant effects on neurological progression, urinary 8-hydroxy-2′-deoxyguanosine (8OH2′dG), a marker of oxidative DNA damage, was selected as the primary end point. This choice was prompted by an earlier open-label phase 2 study that showed elevated urinary 8OH2′dG concentrations in patients with FRDA compared with healthy controls, which decreased significantly ($P < 0.05$) with treatment with low-dose idebenone [5]. Secondary end points included changes in ICARS, Friedreich Ataxia Rating Scale (FARS), and Activities of Daily Living (ADL) scores. Other exploratory end points included measures of cardiac morphology and function (systolic and diastolic), biomarker analysis, alteration in gene expression, and functional tests such as gait analysis, measurements of force control, and exercise capacity. Data on these end points have not yet been published.

In general, the treatment was well tolerated, with no difference in the number of AEs among the four groups. One child receiving high-dose idebenone developed neutropenia after 6 months, which resolved after discontinuation of treatment. No re-exposure occurred. In contrast to the earlier study [5], the concentrations of uri-nary 8OH2′dG in patients with FRDA were not different from those in healthy control subjects. After 6 months of treatment, urinary 8OH2′dG was lower in all groups, with no significant difference noted among treatment groups in a co-variate analysis, even though the average decrease was 40 % in patients treated with high-dose idebenone versus 20 % in patients receiving placebo. Thus, the study failed to achieve statistical significance in its primary end point [18]. Because the two batches of samples (baseline versus 6 months of treatment) were analysed separately, a batch effect was possible. Examination of other markers of oxidative stress (i. e., lipid peroxidation) revealed a range of values, some of which were outside the normal range; however, the FRDA group mean fell within the normal range, with no significant differences among treatment groups after 6 months (unpublished results).

Although an overall analysis did not show a significant difference in ICARS, FARS, or ADL total scores, a statistical test for trend (Jonckheere) indicated dose-dependent improvement in ICARS. A second, pre-specified analysis, excluding patients who required wheelchair assistance, showed a significant improvement in ICARS and a dose-dependent improvement in ICARS, FARS, and ADL with idebenone treatment. For these functional scales, the data indicated that neither placebo nor low-dose idebenone had an effect, whereas intermediate and high doses of idebenone significantly improved the scores, with little difference observed among the latter two groups. In the pre-specified analysis, scores in the intermediate-dose and high-dose groups improved by approximately 4.3 and 5.8 points, respectively, on the ICARS scale and by 5.2 and 5.1 points on the FARS [18].

Limited data are available on the natural course of the disease. The progression rate per year on the ICARS in untreated patients only recently has been investigated. Two separate groups estimated the progression rate as approximately 4.4–5 points per year on the ICARS [11, 19]. It is important to note that the populations in these studies were older (mean ages, 30 (11) and 32 (19) years) than those in the phase 2 idebenone study (mean age, 13 years) and may have been declining at a different rate. An investigation of progression based in part on

FARS showed a decline of up to 9 points per year, although this study added the ADL score to the FARS, so this number may be somewhat inflated [19]. Of course, the use of either of these scales may be limited by their lack of linearity. In the phase 2 study, ICARS appeared to have a ceiling effect, which also was observed in another study [11]. Despite these limitations, it appears that, in the phase 2 study, 6 months of treatment with intermediate- or high-dose idebenone not only prevented progression of the functional deficit in ambulatory subjects, but also led to an improvement comparable to the loss previously noted at 1 year of disease progression.

Open Questions

Phase 2 trial data support the hypothesis that treatment with intermediate- and high-dose idebenone provides neurological benefit and improves ADL in a subset of patients with FRDA. Low doses of idebenone may not be beneficial with regard to neurological signs and symptoms. Although these data are derived from one small, single-centre study in children and adolescents, they are promising. Nevertheless, these effects have to be confirmed in additional independent studies that also should address the following open questions:

- **i.** Is treatment with high-dose idebenone safe when continued for longer than 6 months?
- **ii.** Do patients older than 18 years also benefit from treatment with intermediate- and high-dose idebenone?
- **iii.** Are the effects of intermediate- and high-dose idebenone treatment symptomatic, or is there an effect on long-term disease progression?
- **iv.** Do all patients benefit from idebenone, or are the effects dependent on disease stage?
- **v.** Does pre-symptomatic treatment of genetically identified at-risk subjects delay or prevent disease onset?
- **vi.** Can the symptomatic (and protective) effects be reproduced in a larger sample in a multi-centre study?

Currently, phase 3 trials are being conducted in Europe (MICONOS trial) and the United States (IONIA trial) to answer these questions. In the European trial, which aims to recruit 204 patients, ambulatory and wheelchair-bound patients older than 8 years are eligible; all patients are randomised to receive placebo or low-, intermediate-, or high-dose idebenone treatment and to be followed for 12 months. In the U.S. trial, a minimum of 51 ambulatory patients aged 8–17 years will be randomised to placebo or intermediate- or high-dose idebenone treatment and followed for 6 months. In both studies, ICARS is the primary outcome measure. After completion of the randomised treatment period, patients enrolled in either study will be invited to participate in an open-label extension study with high-dose idebenone.

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