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# Friedreich's Ataxia: Idebenone Treatment in Early Stage Patients

Original Article

## Abstract

**Background:** Antioxidant therapy has been applied to Friedreich's ataxia patients. We assessed the effect of idebenone treatment in patients with Friedreich's ataxia.

**Methods:** Design: open-label trial. Nine Friedreich's ataxia patients (age range 11–19 years) were treated with idebenone (5 mg/kg/day). Patients were evaluated before the start of the therapy and throughout one year of treatment by International Cooperative Ataxia Rating Scales (ICARS) scores, neurophysiological investigations and echocardiographic measurements. Serum idebenone concentrations were measured by HPLC with electrochemical detection. The number of GAA repeats at the frataxin gene was analyzed by PCR.

**Results:** Serum idebenone concentrations ranged between 0.04–0.37 µmol/L. Significantly positive correlation was observed between idebenone values and the percentage of difference between the ICARS scores before and 12 months after the start of the therapy ($r = 0.883$; $p = 0.002$). Significant reduction was observed comparing the ICARS scores in baseline conditions and after 3 months of treatment ($p = 0.017$). No differences were observed in echocardiographic measurements after the start of the therapy.

**Conclusions:** Cerebellar improvement was notable in mild patients after the first 3 months of therapy. Idebenone treatment at early stages of the disease seems to reduce the progression of cerebellar manifestations. Further blind trials with a greater number of patients and higher doses are needed to fully assess the therapeutic potential of idebenone in Friedreich's ataxia.

**Key words**
Friedreich's Ataxia · Idebenone Treatment · Hypertrophic Cardiomyopathy · FRDA Gene · GAA Trinucleotide Repeat

## Introduction

Friedreich's ataxia (FRDA; OMIM 229 300) is an autosomal recessive disorder involving the central and peripheral nervous system [3]. Essential diagnostic criteria have been defined [5] related to neurological involvement. Other common signs are hypertrophic cardiomyopathy, nystagmus, optic atrophy, deafness and diabetes mellitus or glucose intolerance [10]. Friedreich's ataxia is caused by mutations at the FRDA gene, coding frataxin. Most mutations are intronic GAA repeat expansions, causing a defective synthesis of frataxin [2]. Clinical variability in FRDA has been related to the size of the expanded alleles [9]; milder forms of the disease are associated with shorter expansions of the smaller allele.

Frataxin is located at the inner mitochondrial membrane. Its function is still unknown, although frataxin deficiency has been related to defective mitochondrial iron homeostasis and respiration, and increased sensitivity to oxidative stress [7,11]. Antioxidant therapy with ubiquinone and tocopherol has been applied to FRDA patients [8] with a resulting improvement in cardiac and skeletal muscle bioenergetics, although neurological and echocardiographic benefits could not be demonstrated after 6 months of therapy.

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Treatment with idebenone, a quinone analogue, has also been applied to FRDA patients, resulting in a protection of heart muscle iron-induced damage [12] and a decreased left-ventricular mass index after 4–9 months of therapy [13]. These results have recently been questioned by Schöls et al [14], who did not observe improvements either in muscle bioenergetics studied by $^{31}P$ magnetic resonance or in clinical scores and cardiomyopathy.

Our aim was to assess the neurological and cardiological status in nine patients with FRDA in baseline conditions and after 3, 6 and 12 months of idebenone treatment, and to evaluate the results of idebenone monitoring.

## Materials and Methods

### Subjects

Nine patients (5 males and 4 females; age range 11–19 years; median 14 years) with clinical diagnosis and genetic confirmation of FRDA, treated with idebenone at 5 mg/kg/day p.o. divided in three doses, for a 12 month period. No side effects were observed after 12 months of idebenone treatment. The study was carried out in accordance with the Helsinki Declaration of 1964, as last revised in Edinburgh in 2000, and was approved by the Ethics Committee of the Hospital Sant Joan de Déu.

### Clinical evaluation

Patients were evaluated before the start of the therapy and throughout one year of treatment, every 3 months. Assessment of cerebellar ataxia was performed with the International Cooperative Ataxia Rating Scale (ICARS) [15]: posture and gait (0–34 points), kinetic functions and limb co-ordination (0–52 points), dysarthria-speech (0–8 points) and oculomotor movement disorders (0–6 points). Higher scores indicate a more severe disease. Neurophysiological investigations (electromyography [EMG], nerve conduction velocity [NCV], somatosensory and visual evoked potentials) were performed before beginning and 12 months after the start of idebenone therapy. The muscles tested in EMG studies were the anterior tibialis and the first interosseous dorsalis. The nerves tested in NCV studies were the median nerve in the upper limbs and the peroneal and sural nerves in the lower limbs. In motor nerves, we evaluated the distal latency, conduction motor velocity and compound muscle action potential. In the sensory nerves, we evaluated the conduction sensory velocity and the amplitude of the sensory potential. Somatosensory evoked potentials were measured in the median nerve in accord with the guidelines of the International Federation of Clinical Neurophysiology. Neurological evaluation and score calculations were always performed by the same investigator. Echocardiographic assessment: septum thickness and posterior wall thickness were calculated by 2 D and M-mode imaging before and after 6 and 12 months of idebenone therapy using a Sonolayer SSH 140 A (Toshiba, Japan).

### Idebenone determination

Serum samples from patients were collected in the fasting state (at 3, 6 and 12 months), before the oral doses (10 hours after the last dose), immediately centrifuged and stored protected from light at –70 °C until the moment of the analysis. Serum idebenone concentrations were analyzed by HPLC (Series 200, Perkin-Elmer, Norwalk, CT, USA) with electrochemical detection (Coulochem II, ESA, Chelmsford, MA, USA), according to a previously reported procedure [1]. Briefly, idebenone was extracted from 50 µL of serum and separated in a Nucleosil C18 column (5 µm, 25 × 0.4 cm, Teknokroma), mobile phase (80/20 methanol/MiliQ-water containing 20 mmol/L of 95% lithium perchlorate). Quantitation was performed by electrochemical detection with a model 5010 analytical cell (ESA). The first electrode was attached at –400 mV, while the analytical electrode voltage was +200 mV.

### Genetic analysis

DNA from peripheral lymphocytes was obtained by standard phenol extraction and ethanol precipitation. The GAA repeat at the first intron of the FRDA gene was amplified by PCR and the number of repeats were measured on agarose gels, as previously described [9].

### Statistical analysis

Wilcoxon test was applied to compare paired data (ICARS and echocardiographic data before and after treatment). Spearman test was applied to search for correlations between serum idebenone concentrations, the clinical data and the number of GAA repeats of the smaller allele. Statistical significance was considered as $p < 0.05$. Calculations were performed with the SPSS.10.0 program.

## Results

Patient details (age, disease duration, number of repeats of the smaller allele) and clinical and biochemical data before and after 12 months of idebenone therapy, are reported in Table **1**. After the start of the therapy, the median of idebenone concentrations at 3, 6 and 12 months ranged between 0.04–0.37 µmol/L.

Significantly negative correlations were observed between serum idebenone concentrations and the number of GAA repeats ($r = -0.736$; $p = 0.024$), and the ICARS score after 12 months of treatment ($r = -0.817$; $p = 0.007$). Significantly positive correlation was observed between idebenone values and the percentage of difference between the ICARS scores before and 12 months after the start of the therapy ($r = 0.883$; $p = 0.002$). The number of GAA repeats correlated with the ICARS scores in baseline conditions ($r = 0.828$; $p = 0.006$). Significant reduction was observed comparing the ICARS scores in baseline conditions and after 3, 6 and 12 months of treatment (Wilcoxon test: $p = 0.017$, $p = 0.012$ and $p = 0.007$, respectively), as well as comparing the scores between 3 and 6 months of therapy ($p = 0.011$). No differences were observed in echocardiographic measurements and neurophysiological investigations before and 12 months after the start of the therapy.

Considering the ICARS scale in categories, all patients improved in fine manipulation, nystagmus and eye movements (Table **2**). Results of kinetic function, posture and gait improved only in patients with the lowest number of GAA repeats.

## Discussion

We describe a group of nine FRDA patients, younger than those of other reported series [8,14], after 1 year of idebenone treatment.

Table 1 ICARS and echocardiographic data and serum idebenone concentrations from nine FRDA patients before and after one year of idebenone treatment. Idebenone concentrations are reported as the median of the 3, 6 and 12 months' monitoring values, except for patient 9

| | Disease evolution | GAA repeat | Serum idebenone | ICARS score | | | | | Echocardiography (thickness in mm) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Septum | | Posterior wall | |
| Pt. (age) | (years) | number | (μmol/L) | 0 | 3 | 6 | 12 | 0 → 12* | 0 | 12 months | 0 | 12 months |
| 1 (14) | 5 | 650 | 0.27 | 19 | 11 | 7 | 5 | 73 | 10.7 | 10.8 | 12.7 | 10.7 |
| 2 (17) | 5 | 790 | 0.06 | 40 | 31 | 27 | 26 | 35 | 11.5 | 11 | 13 | 11.5 |
| 3 (11) | 1 | 680 | 0.37 | 17 | 6 | 3 | 3 | 82 | 9.5 | 11 | 9.5 | 11.5 |
| 4 (12) | 5 | 830 | 0.05 | 53 | 51 | 48 | 47 | 11 | 12.7 | 12 | 12.8 | 13 |
| 5 (14) | 3 | 650 | 0.29 | 25 | 17 | 10 | 10 | 60 | 8.4 | 8.7 | 9.8 | 8.4 |
| 6 (16) | 4 | 600 | 0.35 | 8 | 3 | 2 | 2 | 75 | 9.6 | 9 | 9.7 | 9.2 |
| 7 (11) | 4 | 710 | 0.28 | 18 | 10 | 4 | 4 | 78 | 9.4 | 9.3 | 9 | 9.1 |
| 8 (19) | 9 | 750 | 0.04 | 42 | 42 | 36 | 36 | 14 | 8.8 | 9 | 9.1 | 9.1 |
| 9 (18) | 7 | 610 | 0.09 | 63 | – | – | 51 | 19 | 9 | 9.7 | 9.8 | 9.9 |

*0 → 12: Difference between ICARS scores at 0 and 12 months expressed as %.

Table 2 Division of ICARS scores from nine FRDA patients before and after 6 and 12 months of idebenone treatment

| | | Gait and posture | | | Kinetic function | | | Speech disorders | | | Oculomotor disorders | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | (Age) | 0 | 6 | 12 | 0 | 6 | 12 | 0 | 6 | 12 | 0 | 6 | 12 |
| 1 | (14) | 8 | 4 | 3 | 9 | 3 | 2 | 0 | 0 | 0 | 2 | 0 | 0 |
| 2 | (17) | 23 | 20 | 20 | 13 | 5 | 5 | 2 | 1 | 1 | 2 | 1 | 0 |
| 3 | (11) | 7 | 2 | 2 | 8 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| 4 | (12) | 32 | 31 | 30 | 16 | 14 | 14 | 3 | 2 | 2 | 2 | 1 | 1 |
| 5 | (14) | 9 | 5 | 5 | 13 | 4 | 4 | 2 | 1 | 1 | 1 | 0 | 0 |
| 6 | (16) | 2 | 1 | 1 | 5 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| 7 | (11) | 5 | 1 | 1 | 11 | 3 | 3 | 1 | 0 | 0 | 1 | 0 | 0 |
| 8 | (19) | 26 | 26 | 26 | 12 | 8 | 8 | 2 | 1 | 1 | 2 | 1 | 1 |
| 9 | (18) | 33 | – | 32 | 23 | – | 14 | 3 | – | 2 | 4 | – | 3 |

* Number of months after the start of idebenone treatment (0 is the baseline).

Moreover, we report the results of idebenone monitoring which, to our knowledge, has not been previously determined for FRDA patients. Interestingly, the serum idebenone concentrations correlated negatively with both the number of GAA repeats at the FRDA gene and the ICARS score, and positively with the percentage of differences between the ICARS scores before and after 12 months of therapy. Furthermore, the greater the number of repeats, the lower were the serum idebenone concentrations observed and the lesser the modification in the ICARS scores after one year of treatment. These findings suggest that the most severely affected patients would need higher doses of idebenone to achieve serum concentrations similar to those of the more mildly affected patients. However, pharmacokinetic parameters for idebenone have scarcely been reported, and the age, sex, hepatic metabolism, renal clearance, intestinal absorption and body mass index might influence serum idebenone concentrations. Therefore, the correlation between the GAA length and serum idebenone might be due to differences in pharmacokinetic parameters among the nine patients. The positive correlation observed between the percentage of the differences between the ICARS scores at 0 and 12 months and serum idebenone concentrations suggest that cerebellar improvement in FRDA patients after treatment might be related to the residual idebenone amounts detected just before the oral doses.

The improvement in ICARS scores was statistically significant at 3 and 6 months after the start of the therapy, although it was more notable in the milder patients, with a lower number of GAA repeats (see Table 1). It is important to note that the oculomotor disorders improved in all patients, while gait and posture scores only improved in the milder patients. Therefore, the reduction in cerebellar scores was not of clinical significance in posture and gait. However, improvement in oculomotor disorders and fine motor skills allowed patients to write again with a ballpoint pen instead of a computer, or to read without fatigue. This improvement was related to a better quality of life documented by the parents. All these data support the hypothesis that idebenone treatment would be useful to prevent the progression of the cerebellar signs of FRDA patients after at least 3 months of therapy, especially when applied in young patients

with a mild phenotype. Our data differ from those reported by Schöls et al [14], who did not observe a neurological improvement after idebenone therapy, although the age range of their population was higher than that of our group of patients, and the duration of idebenone treatment was limited to 6 weeks. Other authors who did not report a clinical benefit after antioxidant therapy [8] also studied an older population with greater disability than our patients.

Although a blind trial would have been ideal to assess the therapeutic effect of idebenone, the present study is an open-label trial. The low number of patients in our series, and the great clinical and genetic variability, complicated the design of a blind study with a placebo approach. We cannot rule out the possibility that some of the improvements in ICARS scores during treatment may be due to the training of the patients. In fact, the retest reliability of the ICARS scores may be decisive in learning if the improvement is due solely to idebenone and not to the influence of training. However, we should take into account that some of the neurological manifestations of our patients (nystagmus and saccadic ocular movements, which disappeared in most cases) are not readily trainable.

According to other authors [14] idebenone did not improve cardiomyopathy (evaluated as septum and posterior wall thickness). We should take into account that most of our patients did not present with severe cardiomyopathy before the start of the therapy, and only 3 cases (numbers 1, 2 and 4) presented with a mild cardiac involvement. Therefore, although idebenone does not seem to reduce cardiomyopathy, at least in our patients under the described protocol, the non-evolution of cardiomyopathy in our series might be considered as a positive sign. However, a longer follow-up is needed to clearly assess the therapeutic effect of idebenone on cardiomyopathy in FRDA. We did not observe the relationship between the number of GAA repeats and cardiomyopathy that has been suggested by other authors [6]. Probably the low number of patients and the normal septum thickness of almost all of them account for the lack of correlation observed in the present study.

Other antioxidants might be associated with idebenone for FRDA treatment. Lodi et al [8] reported an improvement in cardiac and heart muscle bioenergetics after tocopherol and ubiquinone therapy, although the clinical benefits could not be demonstrated. In our experience, serum tocopherol concentrations were always in the normal range in our patients (data not shown), although its supplementation might be considered, together with an increment of idebenone doses. The higher diffusion toward tissues of idebenone compared to ubiquinone [4] would support its application in FRDA, especially to improve cerebellar signs and symptoms.

In conclusion, idebenone monitoring should be performed to correlate concentrations with the clinical data. Cerebellar improvement is notable, especially in milder patients after the first 6 months of therapy. Pharmacokinetic parameters of idebenone should be investigated to learn if patients with a greater number of repeats might need higher doses of idebenone. Further blind trials with a greater number of patients and higher doses are advisable to fully assess the therapeutic potential of idebenone in Friedreich's ataxia.


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