

# Heart Hypertrophy and Function Are Improved by Idebenone in Friedreich's Ataxia

PIERRE RUSTIN<sup>a,\*</sup>, AGNÈS RÖTIG<sup>a</sup>, ARNOLD MUNNICH<sup>a</sup> and DANIEL SIDI<sup>b</sup>

<sup>a</sup>Unité de Recherches sur les Handicaps Génétiques de l'Enfant (INSERM U393), Hôpital Necker-Enfants Malades, 149, rue de Sèvres, 75015 Paris, France; <sup>b</sup>Service de Cardiologie Pédiatrique, Hôpital Necker-Enfants Malades, 149, rue de Sèvres, 75015 Paris, France

Accepted by Professor H. Sies

(Received 26 April 2001; In revised form 24 September 2001)

Friedreich's ataxia (FRDA) is a neuro-degenerative disease causing limb and gait ataxia and hypertrophic cardiomyopathy. It results from a triplet expansion in the first intron of the frataxin gene encoding a mitochondrial protein of yet unknown function. Cells with low frataxin content display generalized deficiency of mitochondrial iron-sulfur cluster-containing proteins, which presumably denotes overproduction of superoxide radicals in these organelles. Idebenone, a short-chain quinone, may act as a potent free radical scavenger protecting mitochondria against oxidative stress. We therefore carried out an open trial of idebenone (oral supplementation; 5 mg/kg/day) in a large series of FRDA patients and followed their left ventricular mass and function. Consistent and definitive worsening being observed in the natural course of the disease and cardiac hypertrophy having no chance of spontaneous reversal and to be subject to a placebo effect, the patient's heart status before and after the treatment was used to unambiguously establish the effect of the drug. After six months, heart ultrasound revealed more than 20% reduction of left ventricular mass in about half of the patients ( $p < 0.001$ ) and no significant change in the other half. Since any measurable reversion of this pathogenic trait is highly significant, this demonstrates the efficiency of idebenone in controlling heart hypertrophy in FRDA. Owing to the absence of side effects of the drug, idebenone (up to 15 mg/kg/day) should be prescribed for FRDA patients continuously as early as possible.

**Keywords:** Ataxia; Idebenone; Hypertrophic cardiomyopathy; Frataxin

## INTRODUCTION

Friedreich's ataxia (FRDA), the most common autosomal recessive ataxia (1/30,000 live births), also triggers a severe hypertrophy of the myocardium. This disease is the consequence of a GAA repeat expansion within the first intron of the frataxin gene.<sup>[1]</sup> The frataxin protein localizes at the mitochondrial inner membrane, and its absence results in a mitochondrial iron overload<sup>[2,3]</sup> and a generalized deficiency of iron-sulfur cluster-containing proteins (i.e. respiratory chain complexes I, II, and III, and aconitases) in endomyocardial biopsies of FRDA patients.<sup>[4]</sup> A similar iron-sulfur cluster-containing protein deficiency has been recently observed in the heart muscle of conditional frataxin-knockout mice.<sup>[5]</sup> While it remains to be established which of iron or superoxides are the primary factors involved in the loss of iron-sulfur cluster-containing protein activity, a vicious cycle between those is currently admitted to cause the iron-sulfur cluster-containing protein deficiency as these are exquisitely sensitive to superoxide radicals (Fig. 1). Idebenone, a short-chain quinone acting as an antioxidant, protects *in vitro* iron-sulfur cluster-containing proteins from radicals derived from Fenton chemistry.<sup>[6]</sup> We have performed an open trial of idebenone in 40 FRDA

\*Corresponding author. Tel.: +33-1-44-38-15-84. Fax: +33-1-47-34-85-14. E-mail: rustin@necker.fr.

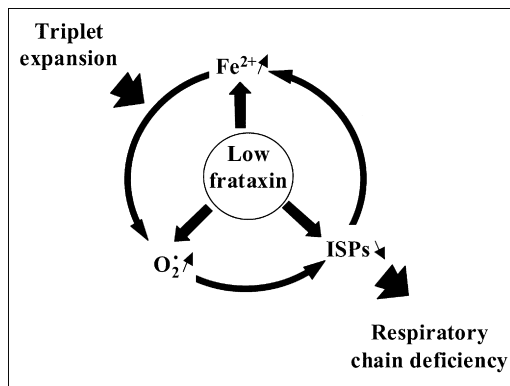


FIGURE 1 Friedreich's ataxia: the consequences of a loss of function of frataxin.

patients studying their left ventricular mass and function.

## PATIENTS AND METHODS

### Patients

A series of 40 FRDA patients, with a large GAA expansion in the first intron of the frataxin gene, aged 4–22 years (21 boys, 19 girls) were included in this study with the informed consent of their parents. Asymmetric hypertrophic cardiomyopathy was observed in 10 patients and the concentric form in all the other patients with hypertrophic cardiomyopathy. No patient presented a dilated cardiomyopathy. The patients were given idebenone orally (5 mg/kg daily during meals) over a period of six months.

### Methods

Heart ultrasound parameters were recorded immediately before and after six months of oral

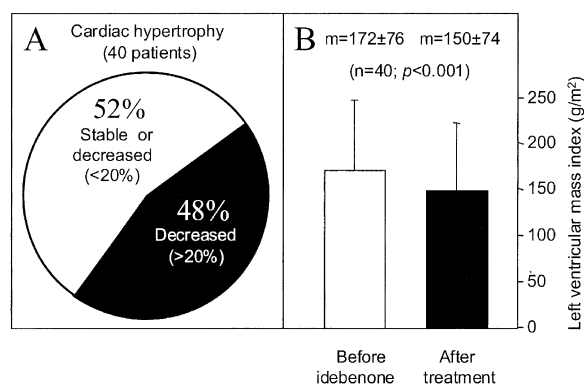


FIGURE 2 The effect of idebenone oral treatment (5 mg/kg/day) on the heart left ventricular mass index in Friedreich's ataxia. (A): Percent of patients with stable or decreased left ventricular mass index (LVMI). Only changes exceeding 20% of the LVMI were considered as significant. (B): *t*-tests analysis of the differences in LVMI before and after six months of idebenone administration in 40 patients with Friedreich's ataxia. LVMI was measured as described under "Patients and Methods."

idebenone. For each patient, the same ultrasonographer assessed left ventricular function using the same ultrasonographer (Accuson XP 128, Mountain View, CA, USA). Shortening fraction, septal thickness and left ventricular posterior wall thickness were measured in the M-mode, on parasternal, longitudinal, and transversal views. A *t*-test (two group comparison; SIGMASTAT statistical software) was used to analyze the differences in heart measurements before and after six months of idebenone administration.

## RESULTS

After six months of idebenone, more than 20% reduction of the left ventricular mass was observed in about half of the 40 patients (Fig. 2A). This reduction of the left ventricular mass index was highly significant (Fig. 2B;  $p < 0.001$ ). Cardiac hypertrophy was largely stabilized in the other half and in none of them did the hypertrophy significantly increase (more than 20%) over the six-month trial period.

A left ventricular outflow tract obstruction was initially noted in two of the 40 patients. It was decreased after six months of idebenone administration and  $\beta$ -blockers could be discontinued (the gradient pressure fell from 60 and 40 mm Hg to 30 and 10 mm Hg, based on Doppler flow velocity).

The shortening fraction improved in five of the six children with reduced shortening fraction (six among 40 patients) given idebenone (11–26%; mean  $\pm$  1SD =  $33 \pm 3$ ). However it continued to deteriorate in one patient (26–11%). Owing to the innocuousness of the drug, the patient was given 10 mg/kg/day idebenone for an additional six month period. A reestablishment of its initial shortening fraction value (11–24%; initial 26%)

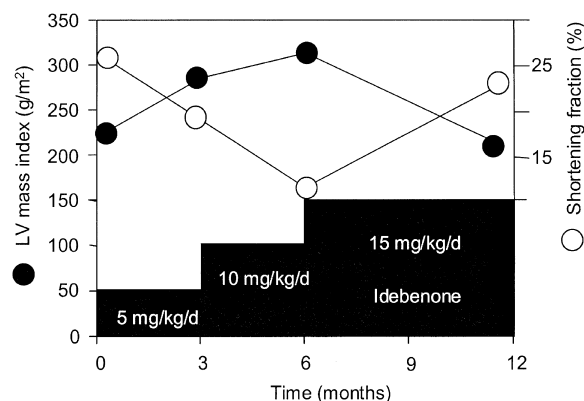


FIGURE 3 Changes in left ventricular mass index and shortening fraction in the heart of a patient with Friedreich's ataxia given increasing oral doses of idebenone. Oral treatment was successively increased from 5, 10 to 15 mg/kg/day ultimately resulting in a significant decrease of LVMI and increased shortening fraction.

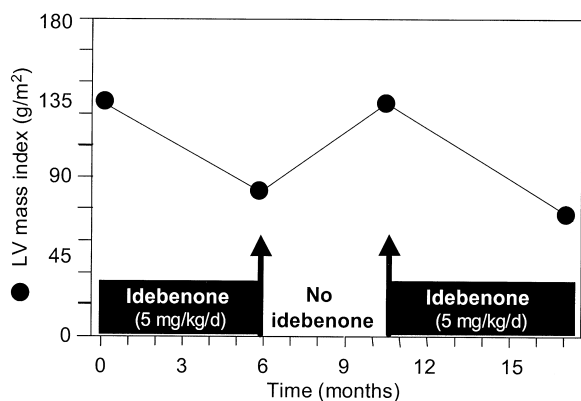


FIGURE 4 The effect of idebenone treatment interruption and resumption on heart left ventricular mass index in a Friedreich's ataxia patient. Idebenone oral supplementation was erroneously interrupted for a four-month-period, after an initial treatment that resulted in a significant LVMI decrease which was recovered upon treatment resumption.

together with a decrease of the left ventricular mass index ( $392-210 \text{ g/m}^2$ ;  $-46\%$ ) was noticed thereafter. A decrease in heart hypertrophy was finally obtained in another patient only after increasing idebenone dosage to  $15 \text{ mg/kg/day}$  without noticeable side effect (Fig. 3). Two patients had an improvement of the shortening fraction not associated with any significant change in myocardial mass.

One patient, whose cardiac hypertrophy significantly responded to the treatment, had his treatment erroneously interrupted for a short period and his cardiac hypertrophy readily worsened (Fig. 4). Upon resumption of idebenone oral supplementation, heart hypertrophy decreased again. This strongly supported the causal effect of idebenone in reducing heart hypertrophy in FRDA.

## DISCUSSION

The exact function of frataxin is not yet fully established, however it is now recognized that the lack of frataxin triggers iron-sulfur cluster-containing protein deficiency related to iron- and/or superoxide-triggered Fenton chemistry. This appears to cause cardiac hypertrophy presumably through a mechanism that resembles cardiac myocyte hypertrophy triggered *in vitro* by the inhibition of the cytosolic copper-zinc superoxide dismutase.<sup>[7]</sup> The involvement of superoxides in the development of

cardiac hypertrophy in FRDA was an incentive to test the effect of idebenone in a series of 40 patients. The above data, confirming our preliminary report,<sup>[6]</sup> establish the indisputable effect of idebenone on the heart hypertrophy in about half of the FRDA patients.

The heterogeneity of the response between patients remains to be elucidated, as is the natural course of the disease. However, besides inter-individual variation in absorption and metabolism of the drug, it should be borne in mind that FRDA is a progressive disease that could result in increased damages to mitochondria, some of which might be irreversible.

In conclusion, FRDA patients should be given idebenone at onset of hypertrophic cardiomyopathy. If idebenone possesses a preventive action, it could even be given *prior* to heart involvement. The fact that the progressive course of the disease might reflect progressive damages to an increasing number of mitochondrial components (non iron-sulfur cluster-containing proteins mtDNA, as observed in yeast mutant deleted for the frataxin gene homologue, for example), some of which are possibly irreversible, is also an incentive to give idebenone to patients as early as possible.

## References

- [1] Campuzano, V., Montermini, L., Molto, M.D., *et al.*, (1996) "Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion", *Science* **271**, 1423-1427.
- [2] Babcock, M., de Silva, D., Oaks, R., *et al.*, (1997) "Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin", *Science* **276**, 1709-1712.
- [3] Foury, F. and Cazzalini, O. (1997) "Deletion of the yeast homologue of the human gene associated with Friedreich's ataxia elicits iron accumulation in mitochondria", *FEBS Lett.* **411**, 373-377.
- [4] Rötig, A., de Lonlay, P., Chretien, D., *et al.*, (1997) "Aconitase and mitochondrial iron-sulphur protein deficiency in Friedreich ataxia", *Nat. Genet.* **17**, 215-217.
- [5] Puccio, H., Simon, D., Cossée, M., *et al.*, (2001) "Mouse models for Friedreich ataxia exhibit cardiomyopathy, sensory nerve defect and Fe-S enzyme deficiency followed by intramitochondrial iron deposits", *Nat. Genet.* **27**, 181-186.
- [6] Rustin, P., von Kleist-Retzow, J.C., Chantrel-Groussard, K., *et al.*, (1999) "Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study", *Lancet* **354**, 477-479.
- [7] Siwik, D.A., Tzortzis, J.D., Pimental, D.R., *et al.*, (1999) "Inhibition of copper-zinc superoxide dismutase induces cell growth, hypertrophic phenotype, and apoptosis in neonatal rat cardiac myocytes *in vitro*", *Circ. Res.* **85**, 147-153.

Copyright of Free Radical Research is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.