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Original article

Idebenone treatment in paediatric and adult patients with Friedreich ataxia: Long-term follow-up

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ABSTRACT

Background: Antioxidant therapy is a new therapeutical approach for patients with Friedreich ataxia.
Aims: To assess the effectiveness of long-term idebenone treatment in Friedreich ataxia patients.
Methods: An open-labelled prospective study. Ten paediatric patients (age range 8–18 years) and 14 adults (age range 18–46 years) with genetic diagnosis of Friedreich ataxia were treated with idebenone (5–20 mg/kg/day) for 3–5 years. Neurological evolution was evaluated using the International Cooperative Ataxia Rating Scale (ICARS), and cardiological outcomes using echocardiography.
Results: In paediatric patients, no significant differences were observed in ICARS scores and echocardiographic measurements when comparing baseline status and after 5 years of follow-up. Concerning adult cases, ICARS scores showed a significant increase in neurological dysfunctions during 3 years of therapy (Wilcoxon test, $p = 0.005$), while echocardiographic measurements remained unchanged.
Conclusions: Our results indicate that longer-term idebenone treatment prevented progression of cardiomyopathy in both paediatric and adult patients, whereas its stabilizing effect on neurological dysfunction was present only in the paediatric

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population, mainly before puberty. This suggests that the age at which idebenone treatment is initiated may be an important factor in the effectiveness of the therapy.

1. Introduction

Friedreich's ataxia (FRDA; OMIM 229300) is an autosomal recessive disorder involving central and peripheral nervous system (progressive gait and limb ataxia, absence of deep tendon reflexes).[1,2] Other signs that appear are hypertrophic cardiomyopathy, diabetes mellitus and optic atrophy.[3] In most patients, FRDA is caused by homozygous expansions of the GAA triplet in intron 1, resulting in reduced levels of frataxin expression.[4] Frataxin function is not fully understood, although it has been associated with mitochondrial iron accumulation and increased sensitivity to oxidative stress,[5] and more recently, with the function of mitochondrial respiratory chain.[6]

Idebenone therapy has been applied in FRDA patients since it was demonstrated that it may improve cardiac and neurological functions.[7–10] Recently, a 6-month double-blind, placebo-controlled trial with idebenone was carried out in 48 FRDA patients, resulting in a neurological improvement in those patients treated with the highest idebenone doses.[11] The largest open-labelled prospective survey with idebenone demonstrated a worsening of International Cooperative Ataxia Rating Scale (ICARS) scores in patients under idebenone therapy (similar to FRDA patients without idebenone) and an improvement in some echocardiographic measurements.[12]

Our aim was to assess the effectiveness of long-term idebenone treatment on neurological and cardiac dysfunction in paediatric and adult FRDA patients, and to monitor idebenone therapy and antioxidant status over the course of the evolution of the disease.

2. Materials and methods

2.1. Patients

We studied 10 paediatric patients prospectively (4 males and 6 females; age range 8–18 years; average 14 years) with genetic diagnosis of FRDA (size of GAA repeat expansion range 582–830), and 14 adults (7 males and 7 females; age range 18–46 years; average: 29 years: repeat expansion range 600–1115) before and after the start of the therapy. Paediatric patients were clinically and biochemically evaluated every 3 months for 3–5 years, while adults were studied once per year for 3 years. We could not assess a population of FRDA patients without idebenone therapy during the same period. The study protocol was approved by the ethics committees of the Hospital Universitario La Paz and Hospital Sant Joan de Déu. Written informed consent was obtained from parents and adult patients.

Paediatric patients started with 5 mg/kg/day of idebenone (18 months) and doses were increased to 10 mg (during the last 3 years and 6 months of the study: maximal daily dosage was 650 mg of idebenone). Adults started with 5 mg/kg/day (1 year) and idebenone doses were increased to 10 (1 year) and to 20 mg/kg/day (in the last year of follow-up: maximal daily dosage was 1400 mg of idebenone). Idebenone (Takeda-Italy) doses were administered orally three times per day.

2.2. Clinical evaluation

Neurological evolution of our FRDA patients was evaluated using the ICARS[13]: posture and gait (0–34 points), kinetic functions (0–52 points), dysarthria–speech (0–8 points) and oculomotor movement disorders (0–6 points). Higher scores indicate a more severe disease (maximum score = 100 points). Neurological evaluations and score calculations were always performed by the same investigator. Video recording of the paediatric patients was made every 6 months. Cardiological outcome was studied by echocardiography once per year: fractional shortening (FS), ejection fraction (EF), septum (SP) and posterior wall (PW) thickness and left ventricular mass index (LVMI) were calculated by a two-dimensional and M-Mode imaging (Sonolayer SSH 140A, Toshiba, Japan).

2.3. Biochemical analysis

Blood samples were taken in baseline conditions and after the idebenone treatment (every 3 months for 5 years in paediatric patients and once per year for 3 years in adult patients). All samples were collected in the fasting state (and after 10–12 h from the last oral idebenone doses) and stored at −80 °C prior to the analysis.

Plasma idebenone concentrations were determined by reverse-phase high-pressure liquid chromatography (HPLC, Waters, MA, USA) with electrochemical detection (Coulochem II, ESA, MA, USA), as previously reported.[14] Other antioxidants (tocopherol, retinol, coenzyme Q10, selenium, zinc, antioxidant enzymes in erythrocytes (superoxide dismutase, catalase, gluthathione peroxidase and gluthathione reductase)) and oxidative damage markers (plasma malondialdehyde) were measured as previously reported.[14,15]

2.4. Statistical analysis

Wilcoxon test was applied to compare the paired data (ICARS scores and echocardiographic data before and after the start of the therapy). Spearman test was applied to search for correlation between the different variables of the study. Statistical significance was considered as $p<0.05$. Calculations were performed with the SPSS 11.0 programme.