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ORIGINAL PAPER

Combined Therapy with Idebenone and Deferiprone in Patients with Friedreich's Ataxia

Daniel Velasco-Sánchez · Asuncion Aracil · Raquel Montero · Ana Mas · Lorenzo Jiménez · Mar O'Callaghan · Maria Tondo · Antoni Capdevila · Josep Blanch · Rafael Artuch · Mercedes Pineda

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Abstract Iron chelators are a new therapeutical approach for patients with Friedreich's ataxia, on the basis that oxidative cell damage that occurs in these patients is due to the increasing deposits of mitochondrial iron pools. The objective of the study was to evaluate the effects of the combined therapy of idebenone and low oral doses of deferiprone on the neurological signs and cardiac function parameters. This study was designed as a prospective open-label single-arm study. Twenty Friedreich's ataxia patients were treated with idebenone (20 mg/kg/day) and deferiprone (20 mg/kg/day) for 11 months. Patients were evaluated before the start and throughout the study with the International Cooperative Ataxia Rating Scale (ICARS) scores, echocardiographic measurements and MRI (magnetic resonance imaging) techniques to asses brain iron deposits in the dentate nucleus. No significant differences were observed in total ICARS scores when comparing baseline status and the end of the study in the whole group of patients. Posture and gait scores increased significantly after 11 months of therapy (Wilcoxon's test, $p=0.04$) and kinetic function improved significantly (Wilcoxon's test, $p=0.015$). Echocardiography data showed a significant reduction of the interventricular septum thickness (Wilcoxon's test, $p=0.04$) and in the left ventricular mass index (Wilcoxon's test, $p=0.038$) after the start of the therapy. The MRI values in the dentate nucleus showed a statistically significant reduction (Wilcoxon's test $p=0.007$) between baseline conditions and after 11 months of the therapy. Combined therapy with idebenone and deferiprone in patients with FDRA indicates a stabilizing effect in neurologic dysfunctions due to an improvement in the kinetic functions, with a worsening of gait and posture scores. Heart hypertrophy parameters and iron deposits in dentate nucleus improved significantly. Combined therapy was well tolerated with mild side effects, apart from the risk of neutropenia and progressive reduction of plasma iron parameters.

Keywords Friedreich's ataxia · Iron chelator · Deferiprone · Idebenone

D. Velasco-Sánchez (✉) · L. Jiménez
Cardiology Department,
Sant Joan de Déu Hospital and the University of Barcelona,
2, Passeig Sant Joan de Déu,
08950 Esplugues, Barcelona, Spain
e-mail: daniel.velasco.sanchez@gmail.com

D. Velasco-Sánchez
Sant Joan de Déu Foundation,
39-57, Calle Santa Rosa,
08950 Esplugues, Barcelona, Spain

A. Aracil · M. O'Callaghan · M. Pineda
Neuropediatrics Department, Sant Joan de Déu Hospital,
the University of Barcelona, and Center for Biomedical Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III,
Barcelona, Spain

R. Montero · M. Tondo · R. Artuch
Biochemistry Department,
Sant Joan de Déu Hospital and CIBERER,
Barcelona, Spain

A. Mas
Pharmacy Department,
Sant Joan de Déu Hospital and the University of Barcelona,
Barcelona, Spain

A. Capdevila · J. Blanch
Radiology Department,
Sant Joan de Déu Hospital and the University of Barcelona,
Barcelona, Spain

Introduction

Friedreich's ataxia (FRDA) is a neurodegenerative disorder which represents the most common inherited ataxia in the Caucasian race, with an estimated prevalence of 1:50,000 individuals. FDRA is inherited in an autosomal recessive pattern and its mayor clinical manifestations are neurologic dysfunction, cardiomyopathy and diabetes mellitus [1–3]. The most representative clinical feature is a progressive mixed sensory and cerebellar ataxia of all four limbs and trunk that manifests as gait instability. Cerebellar dysarthria and nystamus are also commonly present. Other neurological signs that can be found are optic atrophy and neurosensorial deafness [3, 4]. Heart involvement is present in 63% of patients with FDRA [3]. The most common echocardiographic abnormality is hypertrophic cardiomyopathy which can be concentric, asymmetrical or just a thickening of the papillary muscles, although the range of abnormalities appears to be wide [5]. FDRA cardiomyopathy is often asymptomatic but at the end stages of the disease, ventricular arrhythmia is the most frequent cause of death, together with bulbar dysfunction [3].

The hypothesis that iron-mediated oxidative damage has a main pathophysiological role in FDRA has led to the use of antioxidant molecules as a possible treatment. Therapies such as idebenone have shown, in several preclinical and phase two studies, promising results, particularly in FDRA cardiomyopathy [6–16]. Moreover, studies performed in tissue culture models of FDRA with different iron chelators [17–19] as well as clinical studies in patients with FDRA have shown positive results [7]. The first attempt to remove an excess of mitochondrial iron in patients with FDRA was published by Boaddert et al. in 2007 [7]; the iron chelator employed was deferiprone (3-hydroxy-1, 2-dimethylpyridin-4-one (DFP)). DFP was chosen from among other molecules because it is able to cross the blood-brain barrier and cellular and subcellular membranes, it has the ability to enter cell organelles, it chelates the accumulated iron pools, and it transfers chelated iron to plasmatic transferrin [7, 20–26]. Doses of DFP of 20 and 30 mg/kg/day showed no differences of tolerance and efficacy but the recommended 80 mg/kg/day dose employed in thalassemic patients produced serious adverse reactions. The treatment was continued for 6 months in nine FRDA patients, and the results showed a significant improvement in the neurological signs and symptoms, especially in the younger patients. These results were in consonance with the measures of iron concentrations in the dentate nuclei made by RMI techniques that demonstrated a reduction in the iron deposits at this level. Agranulocytosis is considered the most serious side effect of deferiprone with an incidence of 0.4–2% patients per year but it's reversible after discontinuation of the drug, thought some patients may require treatment with granulocyte-colony-stimulating factor [27, 28]. Others side effects frequently associated with deferiprone are nausea, vomiting, arthralgia, arthritis, zinc deficiency and fluctuating liver functions test [29]. Side effects other than neutropenia rarely require discontinuation of therapy and they usually appear during within the first year. Although this data concerns patients with thalasemia, which are treated with higher doses of deferiprone (75 mg/kg/day or more), important attention was focused on the possible side effects of DFP, specially in haematological and iron metabolism parameters.

The objective of the present prospective open-label single-arm study was to evaluate the effects of the combined therapy of idebenone (20 mg/kg/day) and low oral doses of DFP (20 mg/kg/day) on the neurological signs and cardiac function parameters and to assess, using MRI, the effects of DFP on the brain iron deposit in a group of FRDA patients.

Materials and Methods

Patients

We prospectively studied 20 patients (age range, 8–25 years; average, 16.5 years). They were eight males (age range, 10–22 years and average, 15.6 years) and 12 females (age range, 9–26 years and average, 13.0 years) with genetic diagnosis of FDRA (range of GAA expansion size, 810–1,800; mean=1,305). Fifteen patients (75%) had previous echocardiographic signs of mild cardiomyopathy. All patients were under idebenone treatment (20 mg/kg/day) before the inclusion in the study. No consent was obtained from families to discontinue idebenone treatment and we could not asses a population of FDRA patients without idebenone treatment.

DFP was given orally (20 mg/kg/day/12 h) over a period of 11 months. Therapy was provided every 3 months by the hospital pharmacy and final drug administration relayed on parents, care-givers or patients. One patient was excluded from the study after 6 months of DFP therapy because of severe neutropenia. Exclusion criteria included iron deficiency, defined as ferritin and haemoglobin levels below the reference range for age and sex, abnormal serum transaminases greater than two times the upper limit of reference ranges in two consecutive analyses, serum creatinine outside the normal range, and history or evidence of neutropenia. Young women of childbearing age were required to produce a negative pregnancy test before inclusion in the study and had also to agree to use effective methods of contraception. Clinical DFP side effects such as vomiting, abdominal pain, diarrhoea and arthropathy were controlled as well. Written informed consent was obtained before enrolment from parents and adult patients. The study

protocol was made with the approval of the Sant Joan de Déu Hospital ethics committee and the Spanish National Medication Agency of the National Health Service.

Clinical Evaluation

Neurological evolution of our FRDA patients was evaluated using the ICARS [30]: 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, score calculations and video recording were always performed by the same investigator every 6 months.

Cardiological evaluation included a clinical examination, standard 12-lead electrocardiogram and echocardiography. Echocardiographic measurements of cardiac chambers and systolic and diastolic functions were studied using echocardiography before and after the treatment. Left ventricular end-diastolic and end-systolic diameters, fractional shortening (FS), ejection fraction (EF), septum (IVS) and posterior wall (PW) thickness and left ventricular mass index (LVMI) were measured using two-dimensional M-mode imaging according to the criteria of the Society of American Echocardiography. Mitral valve-pulsed Doppler flow (E′ wave, A′ wave and isovolumetric relaxation time (IVRT)) and Doppler tissue imagine of the mitral (Em wave, Am wave, Sm wave) and tricuspid annulus (Et wave, At wave, St wave) were taken from apical four-chamber views. All the measures were performed by the same cardiologist and echocardiographic equipment (Philips iE33).

Magnetic Resonance Imaging Measurements

Iron clusters tend to be paramagnetic and therefore cause local inhomogeneities in the magnetic field. These inhomogeneities lead to an increase in the magnetic resonance signal decay time (T2*) which is an index used to quantify magnetic resonance imaging (MRI) signal. If a homogeneous external magnetic field is assumed, then the changes in T2* mainly reflect variations in the local iron concentration in the absence of blood vessels or haemorrhages [7, 31–33]. Brain MRI examinations were performed on a 1.5 Tesla MRI instrument (SignaHD, General Electric, Milwaukee, WI, USA). A voxel encompassing the left and right nuclei (dimension 9 mm^2) was positioned in the largest section of the dentate nuclei. For each selected section, iron monitoring was performed using a single-slice multigradient echo sequence. Volume shimming and single-slice multigradient echo was repeated at the level of the putamen and thalamus nuclei. A high-resolution image of local T2* values was built and the mean value of T2* was calculated in various regions of interest (ROIs) by the same radiologist. As internal control, several circular ROIs of 11 m^2 were drawn in the white matter of the brain hemispheres where iron concentration is assumed to be low.

Biochemical Analysis

Patients were biochemically evaluated every 6 months (blood cell count, ions, glucose, insulin, C-peptide, hepatic and renal function, lipid and iron metabolism, vitamins A and E, lactic acid and idebenone concentrations). Blood samples were taken in baseline conditions and after idebenone and DFP treatment. All samples were collected in the fasting state and were measured as previously reported [25, 34]. DFP-possible chelator effect on other metals (Se, Mn, Co, Cu, Zn and Mo) was monitored every 6 months using the inductively coupled plasma mass spectrometry (ICP-MS-Agilent Technologies). Basic periodic biochemical controls were made of iron, hepatic and renal metabolism every 3 months. During the first 2 months, blood cell count was done every 10 days in order to closely monitor the risk of neutropenia or agranulocytosis.

Statistical Analysis

Wilcoxon's test was applied to compare the paired data (ICARS scores, MRI and echocardiographic data before and after the start of the therapy). Spearman's test was applied to search for correlation between the different variables of the study. Mann–Whitney U test was applied to compare values between the different groups. Statistical significance was considered as $p<0.05$. Calculations were performed with the SPSS 17.0 programme.

Results

Neurological Parameters (ICARS Score)

No significant differences were observed in total ICARS scores when comparing baseline status and the end of the study in the whole group of patients. In nine patients, the total ICARS score increased while in ten cases the score improved. When we analysed posture and gait scores, they increased significantly after 11 months of therapy (Wilcoxon's test, $p=0.04$; in five patients improved, in ten worsened and in four remained unchanged). Other kinetic function improved significantly (Wilcoxon's test, $p=0.015$; in 13 patients improved, in four worsened and in two remained stable) (Table 1, Fig. 1). These results were similar to those for patients with no wheelchair dependence ($n=14$), showing an improvement in kinetic functions (Wilcoxon's test, $p=0.045$) and a worsening in posture and gait scores (Wilcoxon's test, $p=0.045$).

Table 1 Individual results of ICARS scores in all the FDRA patients under baseline conditions and after 11 months of idebenone and DFP therapy

	Age	Total ICARS		Gait and posture		Kinetic functions		Dysarthria-speech		Oculomotor movement	
		Baseline	11 months	Baseline	11 months	Baseline	11 months	Baseline	11 months	Baseline	11 months
Patient 1	8	3.5	9	1.5	4	2	5	0	0	0	0
Patient 2	9	13	9	4	6.5	9	2.5	0	0	0	0
Patient 3	10	14.5	11.5	3	5.5	10.5	6	0.5	0	0.5	0
Patient 4	11	22	22.5	4.5	9	14	9.5	2	2.5	1.5	1.5
Patient 5	11	9	12	4	6.5	5	5.5	0	0	0	0
Patient 6	13	11.5	10	6	7	5.5	2.5	0	0	0	0.5
Patient 7	13	40	36.5	32	32	5	3.5	2.5	1	0.5	0
Patient 8	14	7.5	5	2.5	1.5	3.5	3	1.5	0.5	0	0
Patient 9	15	3	3	1	1	2	2	0	0	0	0
Patient 10	15	9.5	17	4.5	14.5	5	2.5	0	0	0	0
Patient 11	16	10	3.5	5	2.5	5	1.5	0	0	0	0
Patient 12	16	9.5	11.5	4	4	5.5	7.5	0	0	0	0
Patient 13	19	42.5	34.5	29	29	9.5	3	4	2.5	0	0
Patient 14	20	40.5	36.5	34	30	0	0	6	5	0.5	1.5
Patient 15	21	34.5	39	32	32	0	2	2.5	5	0	0
Patient 16	22	38.5	34	32.5	32	3.5	0	2.5	2	0	0
Patient 17	23	13	17	9.5	14	3.5	3	0	0	0	0
Patient 18	25	28.5	32	21	26	7.5	6	0	0	0	0
Patient 19	26	32.5	23.5	22	21	9	1.5	1	0.5	0.5	0.5
All patients (n=19)	16.5 (8–25)	19.6 (3–42.5)	19.7 (3–39)	12.9 (1–34)	15 (1–32)	6 (0–15)	3.5 (0–9.5)	1.6 (0–2.5)	1 (0–2–5)	0.8 (0–1.5)	0.2 (0–1.5)

Age is expressed in years. The results in the last line (all patients) are expressed as median (range)

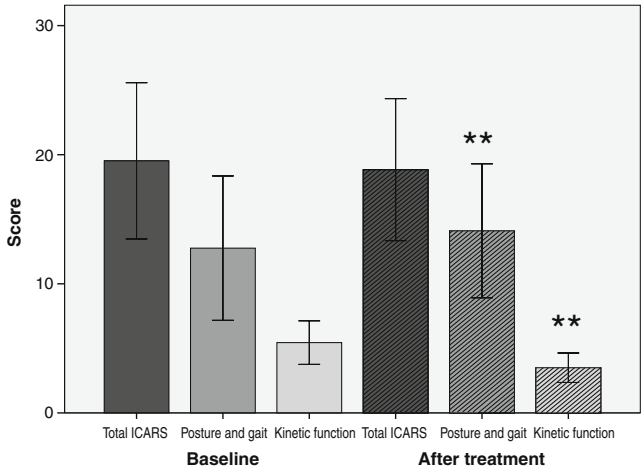

Fig. 1 ICARS scale values in all the FDRA patients under baseline conditions and after 11 months of idebenone and DFP therapy. The *boxes* represent the mean values with the *vertical lines* representing the standard error of the mean. **p value under 0.05

Echocardiografic Parameters

Echocardiogaphic data showed a significant reduction of the IVS thickness (Wilcoxon's test, p=0.04; in 11 patients decreased, in four increased and in four remained stable) and in LVMI (Wilcoxon's test, p=0.038; in 15 patients decreased and in four increased) when comparing baseline conditions and the end of the study (Table 2, Fig. 2). No other significant differences were observed in other echocardiografic parameters of heart hypertrophy, systolic (FS and EF) and diastolic functions (IVRT and E′/Em index) when comparing baseline conditions and the end of the study.

In the group of patients diagnosed with cardiomyopathy (n=15) statistical analyses showed similar results with a significant reduction of the IVS thickness (Wilcoxon's test, p=0.048) and a significant reduction of the LVMI (Wilcoxon's test, p=0.02).

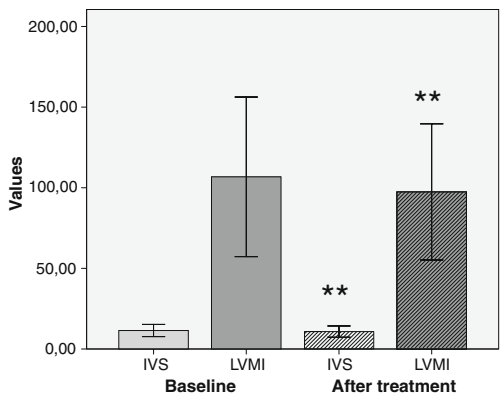

Fig. 2 Echocardiographic values of IVS and LVMI in all the FDRA patients under baseline conditions and after 11 months of combined idebenone and DFP therapy. The *boxes* represent the mean values with the *vertical lines* representing the standard error of the mean. **p value under 0.05

Brain Area Iron Levels Assessed by RMI Tools

The MRI T2* values in the dentate nucleus showed a statistically significant reduction (Wilcoxon's test p=0.007; in 14 patients decreased). No other brain areas (thalamus and putamen) underwent any significant change in T2* values.

Biochemical and Hematologic Parameters

After the treatment period, a significant decrease in serum ferritin levels was observed in all patients (Wilcoxon's test, p<0.0001), but ferritin levels decreased below the normal range for age and sex in only six patients. Significant decreased haemoglobin (Wilcoxon's test, p=0.001), hematocrite (Wilcoxon's test, p=0.003) and increased transferrin values (Wilcoxon's text, p<0.0001) were also noted.

Concerning the biochemical monitoring made from idebenone concentrations, hepatic and renal metabolism and serum concentration of Se, Mn, Co, Cu, Zn and Mo, no statistically significant differences were found between the several points of analyses (data not shown). Plasma reference values for Zn were 628–1,200 μg/L. Zn deficiency was observed in two patients (plasma Zn values of 326 and 452 μg/L) before the inclusion in the study and oral Zn supplementation was started.

Deferiprone Treatment Adverse Effects

The most frequent adverse effects were related to gastrointestinal discomfort such as nausea, vomiting and unspecific abdominal pain (25%). They all were of mild intensity, appearing the first days after the introduction of treatment and disappearing within 2 days. One patient complained of knee arthralgia which was relieved by ibuprofen within 2 days. Two patients presented neutropenia but in only one case it was severe (neutrophils account 450 cells/mm3), and therapy was interrupted definitively after 6 months of treatment. In both patients neutropenia resolved without complications after discontinuation of DFP. In the patient with mild neutropenia, there was no relapse after reintroduction of DFP.

Discussion

FDRA pathogenesis is still unclear. The first attempt to use iron chelators to remove mitochondrial iron pools together with idebenone in patients with FRDA was done by Boaddert et al., with promising results. Moreover, previous studies

Table 2 Results of echocardiographic data in all the FDRA patients, in patients with FDRA cardiomyopathy, and patients without cardiomyopathy under baseline conditions and after 11 months of combined idebenone and DFP therapy

	All patients (n=19)	FDRA cardiomyopathy (n=15)	No FDRA cardiomyopathy (n=4)
IVS baseline (mm)	11.5 (9–16)	11.47 (9–16)	8.8 (8–10)
IVS after 11 months (mm)	10.8 (8–15)	10.8 (8–15)	8.6 (8–11)
LVMI baseline	106.8 (76–172)	106.8 (76–172)	88.2 (58–102)
LVMI after 11 months	97.4 (69.8–162.1)	97.4 (69.8–162.1)	89 (65.8–115)
PW baseline (mm)	9.3 (7–12)	9.3 (7–12)	7.4 (7–8)
PW after 11 months (mm)	9.1 (7–12)	9.1 (7–12)	8 (7–9)
EF baseline (%)	72.2 (47–87)	73.1 (47–87)	69.8 (60–78)
EF after 11 months (%)	67.9 (49–78)	68.5 (49–78)	66.1 (58–70)

Results are expressed as median (range)

treating patients with idebenone indicated that antioxidant therapy with low doses (5 and 10 mg/kg/day) reduced cardiac hypertrophy, but definitive improvement in neurological and heart function has not been demonstrated [9–16]. Studies with high doses of idebenone (20 mg/kg/day) indicated a dose-dependent trend to improvement of the ICARS. When data was analyzed excluding patients who required wheelchair assistance, it showed a significant improvement in ICARS, and this improvement in the ICARS was dose dependent [6, 16–26, 35].

Other potential therapeutic approaches focused on different cellular pathophysiology pathways in FDRA are also been developed. Erythropoietin increase frataxin concentration through a posttranscriptional mechanism and is currently being test in pilot clinical trials, though its important mid and long-term side effects may limit its use [36, 37], especially in children. Pioglitazone, an oral antidiabetic drug, stimulates mitochondrial function and antioxidant response by acting on the peroxisome proliferator-activated receptor gamma pathway and it will soon be tested in clinical trials [38]. Another promising group of molecules are the histone deacetylase inhibitors. They have probed to increase frataxin expression in lymphocytes of patients with FDRA in vitro, however, many important questions still remain to be answer, specially about their effects on the transcription process of other genes [39, 40].

Limited data is available on the natural course of FRDA. The progression rate on the ICARS in untreated patients is estimated to be of 4.4–5 points per year [12, 41], but it is important to note that the population studied was older than our group (mean age 31 years), and in younger patients this rate could be even greater. Eleven months of combined therapy with high idebenone and DFP showed a stabilization of the neurological functions as the total ICARS scores remained stable, and this result was independent of patient age. In the overall group, the stabilization of the ICARS score was due to a significant recovery of kinetic functions but with a worsening of gait and posture scores. These data support the subjective reports made by parents and patients of an improvement in fine skills and manipulative dexterity. These findings can be extrapolated to those observed by Boaddert et al. where the patients exhibited improvements in fine skills and manipulative dexterity, although in his case this improvement corresponded with a modest but significant reduction of the ICARS scored in younger patients not seen in our study.

The results in the ICARS score were not influenced by the severity of the neurologic parameters, as we found the same significant results when patients with wheelchair dependence were excluded.

Although the natural history of cardiac lesions in FDRA has scarcely been reported [42], idebenone treatment has demonstrated an initial reduction in cardiac hypertrophy in FRDA patients [6–16]. This reduction is only seen, mainly, in the first years after initiation of therapy with a trend to progress over time. The echocardiographic studies with combined idebenone and DFP therapy demonstrated an improvement in the variables that measure cardiac hypertrophy (IVS and IMV) in patients with cardiomyopathy. Our results showed a decrease in the degree of heart hypertrophy which might be due to the combined therapy of idebenone and DFP. No changes were observed in diastolic or systolic cardiac function parameters. However, none of our patients had cardiac function impairment before the study and in all cases cardiac function remained within the normal reference ranges.

FDRA patients had increased T2* values in dentate nucleus measured by MRI techniques [7, 31]. The analysis of the T2* values after 11 months of idebenone and DFP treatment revealed a significant reduction with no other significant reduction in T2* values in other brain areas. These results indicated that low oral doses of DFP are able to chelate labile iron that is specifically accumulated in dentate nuclei of FDRA patients.

Combined therapy with idebenone and DFP was well tolerated with no important adverse effects, with the exception of one case of severe neutropenia that resolved

after discontinuation of the therapy, with no complications. Mild adverse gastrointestinal effects or arthralgia appeared during the first days of treatment and improved in a short period of time. The appearance of neutropenia occurred after several months of treatment and no triggering factor was found. During biochemical follow-up, patients showed a significant steady evolution to a ferropnic state with a decrease in blood iron-associated parameters which may restrict the use of DFP for prolonged periods of time. Moreover, DFP has been recently shown experimentally to be cytotoxic and inhibitory to cell aconitase activity when used for extended periods of time at concentrations that are comparable to the doses used in this study [43]. However, DFP in vitro inhibition of aconitase activity seems to recover short after cells exposure to a free DFP medium [25]. This issue raises the question of whether DFP should be administrated in alternating periods, considering moreover that Zn, an essential cofactor for Superoxide dismutase activity, might also be decreased in some cases under DFP therapy. In fact, none of our cases showed decreased Zn values during DFP therapy. In two patients, Zn supplementation was required before DFP was started, but Zn values remained within the normal range during DFP administration in all patients. The other metals studied remained within our reference values after DFP therapy.

In conclusion, combined therapy with idebenone and DFP at low doses in patients with FDRA indicates a stabilizing effect in neurologic dysfunctions due to an improvement in the kinetic functions with no effect on gait and posture. Heart hypertrophy parameters and iron deposits in dentate nucleus improved significantly. Combined therapy was well tolerated with mild side effects, excluding the risk of neutropenia which should be closely controlled. Progressive reduction of plasma iron parameters may limit long-term DFP therapy in patients with FDRA, and the question of which is the best DFP administration protocol still needs to be resolved.

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References

1. Chamberlain S, Shaw J, Rowland A, Wallis J, South S, Nakamura Y, et al. Mapping of mutation causing Friedreich's ataxia to human chromosome 9. Nature. 1988;334(6179):248–50.
2. Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science. 1996;271(5254):1423–7.
3. Opal P, Y Zoghbi H, Cruse RP. Friedreich ataxia (monograph on the Internet). Uptodate. 2008. Available at: www.uptodate.com. Accessed 21 April 2008
4. Pandolfo M. Friedreich ataxia. Semin Pediatr Neurol. 2003;10 (3):163–72.
5. Dutka DP, Donnelly JE, Nihoyannopoulos P, Oakley CM, Nunez DJ. Marked variation in the cardiomyopathy associated with Friedreich's ataxia. Heart. 1999;81(2):141–7.
6. Lodi R, Hart PE, Rajagopalan B, Taylor DJ, Crilley JG, Bradley JL, et al. Antioxidant treatment improves in vivo cardiac and skeletal muscle bioenergetics in patients with Friedreich's ataxia. Ann Neurol. 2001;49(5):590–6.
7. Boddaert N, Le Quan Sang KH, Rotig A, Leroy-Willig A, Gallet S, Brunelle F, et al. Selective iron chelation in Friedreich ataxia Biological and clinical implications. Blood. 2007;110(1):401–8.
8. Hart PE, Lodi R, Rajagopalan B, Bradley JL, Crilley JG, Turner C, et al. Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up. Arch Neurol. 2005;62(4):621–6.
9. Rustin P, Rotig A, Munnich A, Sidi D. Heart hypertrophy and function are improved by idebenone in Friedreich's ataxia. Free Radic Res. 2002;36(4):467–9.
10. Artuch R, Aracil A, Mas A, Colome C, Rissech M, Monros E, et al. Friedreich's ataxia: idebenone treatment in early stage patients. Neuropediatrics. 2002;33(4):190–3.
11. Pineda M, Arpa J, Montero R, Aracil A, Domínguez F, Galván M, et al. Idebenone treatment in paediatric and adult patients with Friedreich ataxia: long-term follow-up. Eur J Paediatr Neurol. 2008;12(6):470–5.
12. Ribaï P, Pousset F, Tanguy ML, Rivaud-Pechoux S, Le Ber I, et al. Neurological, cardiological and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow up. Arch Neurol. 2007;64(4):558–64.
13. Hausse AO, Aggoun Y, Bonnet D, Sidi D, Munnich A, Rötig A, et al. Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. Heart. 2002;87(4):346–9.
14. Mariotti C, Solari A, Torta D, Marano L, Fiorentini C, Di Donato S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. Neurology. 2003;60 (10):1676–9.
15. Rustin P, Bonnet D, Rötig A, Munnich A, Sidi D. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. Neurology. 2004;62(3):524–5.
16. Di Prospero NA, Baker A, Jeffries N, Fischbeck KH. Neurological effects of high-dose idebenone in patients with Friedreich ataxia: a randomized, placebo-controlled trial. Lancet Neurol. 2007;6(10):878–86.
17. Wong A, Yang J, Cavadini P, Gellera C, Lonnerdal B, Taroni F, et al. The Friedreich's ataxia mutation confers cellular sensitivity to oxidant stress which is rescued by chelators of iron and calcium and inhibitors of apoptosis. Hum Mol Genet. 1999;8(3):425–30.
18. Richardson DR, Mouralian C, Ponka P, Becker E. Development of potential iron chelators for the treatment of Friedreich's ataxia: ligands that mobilize mitochondrial iron. Biochim Biophys Acta. 2001;1536(2–3):133–40.
19. Richardson DR. Friedreich's ataxia: iron chelators that target the mitochondrion as a therapeutic strategy? Expert Opin Investig Drugs. 2003;12(2):235–45.
20. Breuer W, Ermers MJ, Pootrakul P, Abramov A, Hershko C, Cabantchik ZI. Desferrioxamine-chelatable iron, a component of serum non-transferrin-bound iron, used for assessing chelation therapy. Blood. 2001;97(3):792–8.
21. Waldmeier PC, Buchle AM, Steulet AF. Inhibition of catechol-O-methyltransferase (COMT) as well as tyrosine and tryptophan hydroxylase by the orally active iron chelator, 1, 2-dimethyl-3-

hydroxypyridin-4-one (L1, CP20), in rat brain in vivo. Biochem Pharmacol. 1993;45(12):2417–24.
22. Glickstein H, El RB, Link G, Breuer W, Konijn AM, Hershko C, et al. Action of chelators in iron-loaded cardiac cells: accessibility to intracellular labile iron and functional consequences. Blood. 2006;108(9):3195–203.
23. Glickstein H, El RB, Shvartsman M, Cabantchik ZI. Intracellular labile iron pools as direct targets of iron chelators: a fluorescence study of chelator action in living cells. Blood. 2005;106(9):3242–50.
24. Sohn YS, Breuer W, Munnich A, Cabantchik ZI. Redistribution of accumulated cell iron: a modality of chelation with therapeutic implications. Blood. 2008;111(3):1690–9.
25. Kakhlon O, Manning H, Breuer W, Melamed-Book N, Lu C, Cortopassi G, et al. Cell functions impaired by frataxin deficiency are restored by drug-mediated iron relocation. Blood. 2008;112 (13):5219–27.
26. Hershko CM, Link GM, Konijn AM, Cabantchik ZI. Iron chelation therapy. Curr Hematol Rep. 2005;4(2):110–6.
27. Cohen AR, Galanello R, Piga A, Dipalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol. 2000;108(2):305–12.
28. Ceci A, Baiardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V, et al. The 29 safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. Br J Haematol. 2002;118(1):330–6.
29. Al-Refaie FN, Hershko C, Hoffbrand AV, Kosaryan M, Olivieri NF, Tondury P, et al. Results of long-term deferiprone (L1) therapy: a report by the international study group on oral iron chelators. Br J Haematol. 1995;91(1):224–9.
30. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. International cooperative ataxia rating scale for pharmacological assessment of the cerebellar syndrome. J Neurol Sci. 1997;145(2):205–11.
31. Waldvogel D, van Gelderen P, Hallett M. Increased iron in the dentate nucleus of patients with Friedreich's ataxia. Ann Neurol. 1999;46(1):123–5.
32. Haacke EM, Cheng NY, House MJ, Liu Q, Neelavalli J, Ogg Rj, et al. Imaging iron stores in the brain using magnetic resonance imaging. Magn Reson Imaging. 2005;23(1):1–25.
33. Schenck JF, Zimmerman EA. High-field magnetic resonance imaging of brain iron: birth of a biomarker? NMR Biomed. 2004;17(7):433–45.
34. Artuch R, Colomé C, Vilaseca MA, Aracil A, Pineda M. Monitoring of idebenone treatment in patients with Friedreich's ataxia by high-pressure liquid chromatography with electrochemical detection. J Neurosci Methods. 2002;115(1):63–6.
35. Schulz JB, Di Prospero NA, Fischbeck K. Clinical experience with high-dose idebenone in Friedreich ataxia. J Neurol. 2009;256 Suppl 1:42–5.
36. Boesch S, Sturm B, Hering S, Goldenberg H, Poewe W, Scheiber-Mojdehkar B. Friedreich's ataxia: clinical pilot trial with recombinant human erythropoietin. Ann Neurol. 2007;62(5):521–4.
37. Boesch S, Sturm B, Hering S, Scheiber-Mojdehkar B, Steinkellner H, Goldenberg H, et al. Neurological effects of recombinant human erythropoietin in Friedreich's ataxia: a clinical pilot trial. Mov Disord. 2008;23(13):1940–4.
38. Marmolino D, Manto M, Acquaviva F, Vergara P, Ravella A, Monticelli A, et al. PGC-1alpha down-regulation affects the antioxidant response in Friedreich's ataxia. PLoS One. 2010;5 (4):e10025.
39. Herman D, Jenssen K, Burnett R, Soragni E, Perlman SL, Gottesfeld JM. Histone deacetylase inhibitors reverse gene silencing in Friedreich's ataxia. Nat Chem Biol. 2006;2(10):551–8.
40. Xu C, Soragni E, Chou CJ, Herman D, Plasterer HL, Rusche JR, et al. Chemical probes identify a role for histone deacetylase three in Friedreich's ataxia gene silencing. Chem Biol. 2009;16 (9):980–9.
41. Fahey MC, Corben L, Collins V, Churchyard AJ, Delatycki MB. How is disease progress in Friedreich's ataxia best measured? A study of four rating scales. J Neurol Neurosurg Psychiatry. 2007;78(4):411–3.
42. Meyer C, Schmid G, Görlitz S, Ernst M, Wilkens C, Wilhelms I, et al. Cardiomyopathy in Friedreich's ataxia—assessment by cardiac MRI. Mov Disord. 2007;22(11):1615–22.
43. Goncalves S, Paupe V, Dassa EP, Rustin P. Deferiprone targets aconitase: implication for Friedreich's ataxia treatment. BMC Neurol. 2008;8:20.