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LETTER TO THE EDITOR

Idebenone in Friedreich ataxia and Leber's hereditary optic neuropathy: close mechanisms, similar therapy?

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Sir,

In 1999, we reported in a preliminary study that idebenone (Mnesis) decreased heart hypertrophy in three young patients with Friedreich ataxia, possibly with slight improvement in delicate movements (Rustin *et al.*, 1999*b*). In the vast majority of patients with Friedreich ataxia, an abnormal GAA expansion is found in the first intron of the frataxin (*FXN*) gene impairing transcription of the gene (Campuzano *et al.*, 1996). The resulting loss of function of the mitochondria-targeted frataxin protein leads to a deficiency of the mitochondrial iron-sulphur containing proteins (ISP), including complexes I, II and III of the respiratory chain in the heart of the patients (Rotig *et al.*, 1997). Defect of the ISP was shown to cause an iron-dependent oxidative stress which could be controlled *in vitro* by reduced idebenone (Rustin *et al.*, 1999*a*). *In vivo*, idebenone can be reduced by respiratory chain and/or NQO1 (NADH quinone oxidoreductase) activity (Haefeli *et al.*, 2011). Following the preliminary report of idebenone efficacy to counteract heart hypertrophy in Friedreich ataxia, the drug was tested in a number of open or double-blinded trials (Table 1). Leaving aside single case reports, 13 studies trialling idebenone in Friedreich ataxia have been published including five double-blinded studies, one of these being 6 weeks long (presumably too short to possibly observe any significant neurological improvement). Noteworthy, a 1 year long doubled-blind study (MICONOS), enrolling a large number of patients (232 adults), ended in 2010 but could not be listed here in the absence of any factual report. However, it was publicized by the trial initiators that, if the safety of idebenone could be confirmed, the trial missed its primary end point (mean change of the neurological condition as estimated by the International Cooperative Ataxia Rating Scale). Of the four double-blinded studies that lasted more than 3 months, two reported improvements in some aspects of the neurological condition for drug-receiving patients as compared with placebo groups, albeit without reaching statistical values (Table 1). Heart hypertrophy was significantly decreased according to one of these studies, stabilized when present for another, and without improvement for the others. Of the eight open trials, three of the six documenting cardiac changes reported decreased hypertrophy without neurological improvement, except for a stable neurological condition in 10 young patients as opposed to worsening in 14 adults. Yet despite these studies, there is no clear consensus on the benefits of idebenone therapy for patients with Friedreich ataxia. Nevertheless, being essentially harmless idebenone has been, and is still, given to many patients with Friedreich ataxia all over the world.

Such was the situation for idebenone in Friedreich ataxia when the European Medicines Agency authorized marketing of idebenone (Raxone®) in September 2015 for the treatment of visual impairment in adolescent and adult

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Table 1 Fifteen years of idebenone trials in Friedreich ataxia

	Number of patient	Duration	Cardiac outcome	Neurological outcome	Other	Comments	Reference
Double-blind trials							
2010, 2011 IONA	70	6 mo	No cardiac improvement	ICARS score improved 2.5 points (placebo 1.3); FARS improved 1.6 points (placebo declined 0.6)		Not statistically significant	Lynch *et al.*, 2010; Lagedrost *et al.*, 2011
2009	35	5 y	No change when hypertrophy initially present, no protection when initially absent	No protection		Suggestion of heart hypertrophy stabilization	Rinaldi *et al.*, 2009
2007, 2010	48	6 mo		Improvement modulated by idebenone dosage	Idebenone did not increase exercise capacity	First suggestion that idebenone dosage might change trial outcomes	Di Prospero *et al.*, 2007; Drinkard *et al.*, 2011
2003	29	1 y	Significant reduction of ventricular hypertrophy	No improvement of neurologic condition		A first double-blind trial demonstrating decreased cardiac hypertrophy	Mariotti *et al.*, 2003
2001	9	6 w	No improvement	No improvement		A very short trial	Schols *et al.*, 2001
Open trials							
2012 IONA-E	68	12 mo	No information	Limited ICARS and FARS score changes −1 and +2.2 points, respectively. Improved fine motor skills and speech noticed		Open-label extension of the double-blind IONA trial. No major effect of idebenone except for fine motor skills and speech	Meier *et al.*, 2012
2010	7	1 y	No information	No improvement	Trend toward improved total, emotional, social, and school components of quality of life scores (not statistically significant)	Aspects seldom studied in reported trials	Brandsema *et al.*, 2010
2008	24	3-5 y	Stable heart conditionfor 5 y	Stable condition in young patients (n = 10) but progression of neurological dysfunction in adults (n = 14)		Prevention of cardiomyopathy in patients with Friedreich ataxia, effect on the neurological condition in paediatric population	Pineda *et al.*, 2008
2007	88	5 y	Left ventricular mass index decreased but ejection fraction too	No effects on the neurological condition		No relationship between hypertrophy decrease and heart function	Ribai *et al.*, 2007
2003	8	1 y	Significant reduction of heart hypertrophy and improved cardiac function in 6 of the 8 patients	No effect on the ataxia		Differential cardiac and neurological effects	Buyse *et al.*, 2003
2002	38	6 mo	Reduced hypertrophy (>20%) in 44% of patients	No information		Evidence for individual response to the drug	Hausse *et al.*, 2002
2002	9	1 y	No improvement	Reduction of the progression of cerebellar manifestations (ICARS score)		Significant effect in patients at early stage of the Friedreich ataxia disease	Artuch *et al.*, 2002
1999	3	4 mo	Decreased heart hypertrophy	Strength and delicate movements (e.g. handwriting) improved, according to parents and teachers		The first proposal to use idebenone in Friedreich ataxia	Rustin *et al.*, 1999*a*

ICARS = International Cooperative Ataxia Rating Scale; FARS = Friedreich Ataxia Rating Scale.

patients with Leber's hereditary optic neuropathy (LHON), another mitochondrial disorder. In this instance, this decision was taken mainly based on the results from a trial revealing that a subset of idebenone-treated LHON patients were responders whereas the trial missed the endpoint when the whole population of LHON patients was considered (responders plus non-responders) (Klopstock *et al.*, 2013). The deficiency of respiratory chain in this rare condition mostly results from mutations in mitochondrial DNA genes encoding complex I of the respiratory chain (Wallace *et al.*, 1988). In typical cases, it leads to a rapid, profound and permanent blindness in otherwise healthy patients, while in the related LHON plus affection mostly originating from mitochondrial DNA mutations as well the blindness associates neurological and cardiac impairments (Finsterer *et al.*, 2002; Gropman *et al.*, 2004; Paquay *et al.*, 2014). Remarkably, the blindness described in some of the patients with Friedreich ataxia with acute visual impairment (2 of 26 patients) was reported to mimic the sudden loss of central vision typically observed in LHON (Fortuna *et al.*, 2009). This comes as no surprise as these two diseases share common pathomechanisms chiefly involving mitochondrial respiratory chain, especially complex I. Sharing close mechanisms and some common clinical features (i.e. acute visual loss when present in Friedreich ataxia), the two diseases should be partially sensitive to similar drug therapies. However, for legal and/or marketing reasons, recent idebenone authorization for LHON resulted in some patients with Friedreich ataxia having difficulty obtaining it. So far the occurrence of potential responders to idebenone in Friedreich ataxia has not been rigorously examined, but in view of the data obtained in LHON, defining a subgroup of therapy-responder patients appears a reasonable objective for next trials in this (and other) rare disease. Moreover the similarity in the response to idebenone of these two mitochondrial disorders, which requires further confirmation, suggests that other patients affected by diseases involving at some point a mitochondrial respiratory chain defect, especially involving complex I, may benefit from idebenone therapy even if they exhibit symptoms not restricted to the eye.

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