Idebenone treatment in Leber's hereditary optic neuropathy

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Abstract

Objective: Idebenone has been proposed as a therapeutic option in Leber's hereditary optic neuropathy (LHON). This study evaluated idebenone efficacy in a large cohort of LHON treated patients.

Methods: We retrospectively evaluated 103 LHON patients defined by the presence of a primary mtDNA mutation, 44 treated with idebenone (270-675 mg/day) within one year after disease onset and 59 untreated, which were followed for at least five years. For all patients we analyzed age of disease onset, time lapse between loss of visual acuity in the eyes, time between disease onset and start of therapy, time between disease onset and recovery of visual acuity, average therapy dosage, therapy duration and visual acuity of best and worst eye at last evaluation. Recovery of visual acuity was defined as a gain of at least two lines on Snellen charts or a change from "off chart" to "on chart".

Results: This study shows an increase in the frequency of visual recovery in treated compared to untreated patients, which is significant for patients carrying the 11778/ND4 mutation. Recovery of vision was significantly associated with earlier and longer therapy administration. Moreover, in six patients treated very early, before visual loss in the second eye, idebenone significantly delayed the involvement of the second eye.

Conclusions: Idebenone treatment has beneficial effects in LHON patients with the 11778/ND4 mutation by increasing the frequency of visual recovery. Early treatment may modify the natural history of the disease.

Introduction

Leber's hereditary optic neuropathy (LHON) is the most frequent mitochondrial disorder associated in 90% of cases with one of three mitochondrial DNA (mtDNA) point mutations affecting ND subunits of complex I at positions11778/ND4, 3460/ND1 and 14484/ND6.[1-3]

The natural history of the disease includes a subclinical stage characterized by fundus oculi, color vision and retinal nerve fiber layer thickness abnormalities, which may remain so throughout life.[4-6] In about 50% of males and 10% of females these subclinical abnormalities convert to an acute phase characterized by rapid loss of central vision, which reaches the nadir in six months and stabilizes by the end of the first year from onset.[2,3,7,8] After the first year the patients enter a chronic phase, which may show a further very slow progression. A few patients, most frequently carrying the 14484/ND6 mutation or any mutation but with early onset, recover spontaneously some visual acuity,[2,3] mostly within the first five years after onset.[9]

The biochemical basis of LHON suggests a combination of defective complex I-driven ATP synthesis, increase in reactive oxygen species production and lowered threshold for apoptosis.[10-12] In 1992 Mashima reported remission of LHON after idebenone treatment[13] and additional anecdotal reports suggested a possible therapeutic use of this benzoquinone,[14-16] by exploiting its antioxidant properties and its potential for bypassing the complex I defect.[17]

We have been extensively using idebenone as the only therapeutic option for LHON patients. The present study retrospectively evaluates its effectiveness in promoting recovery of visual acuity.

Materials and methods

At the Department of Neurological Sciences of the University of Bologna we have currently diagnosed 219 LHON patients from 115 pedigrees carrying one of the three common mutations at positions 11778/ND4, 3460/ND1 and 14484/ND6. Idebenone is approved in Italy since early 1990s for treatment of dementia of both neurodegenerative and vascular etiology. Over the past 10 years we treated a large group of our LHON patients with idebenone (Mnesis®, Takeda Italia Farmaceutici, 270-675 mg/day), under the regulation for "off-label" drug administration and after patient's informed consent. Four more idebenone-treated (450-600 mg/day) patients, who obtained the drug through internet websites on voluntary basis, were monitored (AAS and DA) at the Doheny Eye Institute, University of Southern California (Los Angeles, CA). To evaluate retrospectively the efficacy of idebenone therapy we reviewed all these cases with approval for the study by the internal institutional review board. Based on available ophthalmologic documentation, we included 44 patients (37 males), either treated within one year after the onset of visual acuity loss in the second eye (N=38) or treated before the involvement of the second eye ("in-between-eyes"; N=6), defining the entire group as early treatment (ET). Thirty had the 11778/ND4, eight the 3460/ND1 and six the 14484/ND6 mutation. We compared the frequency of spontaneous recovery of visual acuity in idebenone treated patients with 59 untreated patients (40 males) for whom we had ophthalmological evaluations for at least five or more years after onset; this group was defined as non-treated (NT). Of these 43 had the 11778/ND4, ten the 3460/ND1 and six the 14484/ND6 mutation. Recovery of visual acuity was counted for patients/eyes with a gain of at least two lines on Snellen charts or a change from "off chart" to "on chart", as previously established.[18]

We excluded subjects with disease onset before 10 years of age (childhood cases), because of their well-established benign prognosis.[2,3,19] For all patients we retrieved: age of disease onset, time lapse between loss of visual acuity in the eyes, time between disease onset and start of therapy, time between disease onset and recovery of visual acuity, average therapy dosage, and therapy duration. Furthermore, we evaluated all available longitudinal assessments of visual acuity and for statistical analysis we considered only visual acuity of best and worst eye at last evaluation. The interval between loss of vision in the eyes was evaluated only for the patients with asynchronous onset of symptoms, which were 56% for 11778/ND4, 50% for 3460/ND1 and 67% for 14484/ND6 mutation, having excluded three outliers (time lapse of 23, 180 and 504 months respectively).

The difference in the frequency of visual recovery between ET and NT patients/eyes was assessed by Fisher exact test ($p<0.05$). An analysis of variance (ANOVA) was used for comparisons of continuous variables between more than two groups followed by post-hoc comparison (Bonferroni), whereas comparison between two groups was performed by t-test ($p<0.05$). A logistic regression was used to investigate the effect of genetic, demographic, clinical and therapeutic parameters (mutation type, gender, age at onset, therapy/no therapy, time between disease onset and start of therapy, average therapy dosage, therapy duration) on visual recovery. A linear multiple regression was used to investigate the effect of the same parameters on interval between disease onset and onset of visual recovery. In both analyses a forward stepwise method was applied to obtain a significant model in which all included variables had a p-value <0.05.

Results

The clinical data for all patients combined and separately for the 11778/ND4 patients are summarized in Table 1. Considering that in many cases only one eye recovered visual acuity, we considered both number of patients and number of eyes recovering vision. The proportion of patients or eyes with visual recovery was higher for ET patients compared to NT patients, but the difference was not significant, considering all mutations together. Patients recovering vision had better final visual acuity compared to patients without recovery ($p<0.001$). Among the ET patients the duration of therapy was significantly longer for patients recovering vision ($p=0.024$). Furthermore, among the patients recovering vision, the ET group had a trend towards an earlier onset of recovery and the NT group tended to have a younger age at disease onset.

Upon stratification by mutation we found that in the 11778/ND4 patients (n= 73) the frequency of visual recovery was significantly higher in ET patients ($p=0.045$) or ET eyes ($p=0.017$), which also had trends for earlier onset of recovery and longer duration of therapy. Concerning the 3460/ND1 and 14484/ND6 mutations, the number of patients available was too low for a meaningful statistical analysis (18 and 12 respectively). As expected,[2,3] the 14484/ND6 patients had a high rate of visual recovery whereas the 3460/ND1 patients did not seem to be influenced by therapy (supplementary Table 1).

In the six patients treated “in-between-eyes”, the time separating the involvement of the two eyes was significantly longer compared to patients treated after the second eye or the untreated group ($p=0.045$) (Fig 1). However, all the second eyes became eventually affected and three out of six had 0.05 final visual acuity. In these latter eyes, two had this final visual outcome after visual loss progression and one after recovery from the nadir.

Regression analysis performed for all mutations (Table 2) showed that visual recovery was significantly associated with the 14484/ND6 mutation independently from

therapy (p=0.03), whereas idebenone therapy was significantly associated with visual recovery in the 11778/ND4 patients (p=0.039). In the ET group, considering all mutations, we found a significant association between duration of therapy and visual recovery (p=0.031), and between start of therapy and timing of visual recovery (p=0.024), the latter being maintained also in the 11778/ND4 patients (p=0.046).

Discussion

This retrospective evaluation of our large cohort of LHON patients treated with idebenone shows, compared to untreated patients, an increased frequency of recovery of visual acuity, which is significant for the 11778/ND4 subgroup. The patients who started therapy at the early stage of monocular disease had a significant delay in the involvement of the second eye. The untreated patients that spontaneously recovered visual acuity tended to have younger age at onset, as previously reported.[2,3] Considering all mutations together, there was a trend for earlier onset of visual recovery in treated patients compared to untreated, which is in agreement with similar findings previously reported by Mashima and colleagues.[13] Furthermore, treated patients recovering vision had a significantly longer therapy duration than those that failed to recover and earlier start of therapy correlated with earlier onset of visual recovery.

Within the limits intrinsic to a retrospective study, these results suggest a therapeutic efficacy of idebenone in increasing the frequency of recovery after the acute phase, which was significant for the 11778/ND4 patients. None of the six patients treated "in-between-eyes" had the second eye spared by the pathology, but they had a delayed onset. The final visual outcome of these early-treated eyes did not stand out for being more benign, even if we cannot extrapolate from the available data how they possibly diverged from the natural history of the disease. It is also evident that within the treated group, only a proportion of patients responded to treatment. Among the different parameters evaluated, the longer duration of therapy correlated with responsiveness; likewise, earlier treatment promoted earlier recovery. Mutation stratification indicates a different propensity to respond, the 11778/ND4 patients being good responders, the 3460/ND1 poor responders, whereas the recovery of 14484/ND6 patients is independent from treatment.

LHON remission after idebenone therapy has been difficult to interpret in single case reports,[13-15] given the possibility of a spontaneous recovery of visual acuity.[2,3,9,18] Our study took into consideration a large cohort of untreated patients with different mutations, thus allowing an estimate of the frequency of spontaneous visual recovery, which was essentially similar to previously published rates.[2,3,9,18]

The mechanism of visual recovery in LHON remains poorly understood. We have previously described histologically a segmental loss of myelin in spared axons and occasional evidence of remyelination.[2] A recent murine model of rotenone-induced optic neuropathy also showed that myelin damage is a phenomenon integral to the morphological events characterizing the axonal neurodegeneration, with evidence of demyelinated axons.[20] We propose that the subset of segmentally demyelinated dysfunctional axons represents the anatomical substrate for recovery of visual acuity through re-modeling of myelin, which may revert the fate of neurodegeneration.[2]

We conclude that early and prolonged idebenone treatment of acute LHON patients may improve significantly the frequency of visual recovery and possibly change the natural history of the disease. Despite the retrospective nature of this study, our results indicate that idebenone administration may be indicated in LHON patients, in complete absence of any other therapeutic option at present. Carefully designed prospective double-blind placebo-controlled trials are needed to firmly establish the efficacy of idebenone therapy in LHON, by using the main metrics of visual fields and optic coherence tomography added to that of visual acuity.

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Figure legend

Figure 1

Comparison of the interval between asynchronous disease onset in the 1st and the 2nd eye in ET (in-between-eyes), ET (after the 2nd eye) and NT patients.

X-axis indicated the three groups and Y-axis the time lapse in months between the involvement of the 1st and the 2nd eye. Asterisk (*) indicates p=0.045.

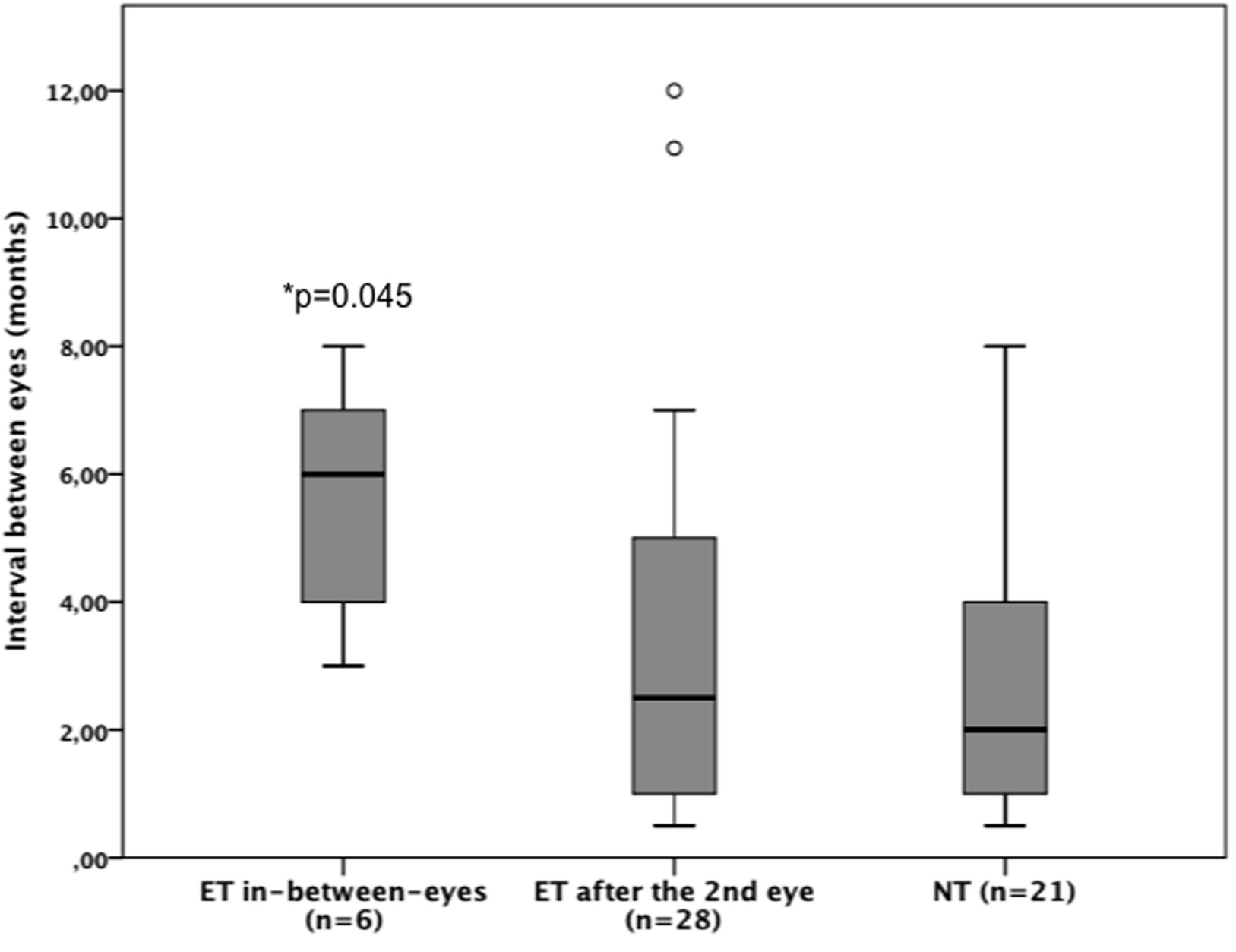
TABLE 1. Clinical data

All mutations	ET		NT		
	Recovery	**Not recovery**	**Recovery**	**Not recovery**	
N. patients	20 (16 males)	24 (21 males)	19 (13 males)	40 (27 males)	
Recovery (patients, %)	45.5		32.2		p=0.219
N. eyes	35/88	53/88	37/118	81/118	
Recovery (eyes, %)	39.8		31.4		p=0.238
Age at onset (years)	26.0 ± 13.9	26.5 ± 11.7	20.4 ± 8.0	27.0 ± 10.3	p=0.178
Interval of disease onset between eyes (n=58/103) (months)	3.7 ± 2.9	3.8 ± 3.1	1.8 ± 0.8	2.9 ± 2.3	p=0.402
Interval onset-therapy (months)	6.1 ± 4.1	5.3 ± 4.0			p=0.509
Interval onset-recovery (months)	17.0 ± 7.7		25.0 ± 18.9		p=0.089
Therapy average dosage (mg/day)	346.8 ± 141.9	400.3 ± 137.7			p=0.228
Therapy duration (months)	50.2 ± 29.9	32.4 ± 20.4			**p=0.024**
VA-Best Eye	0.515 ± 0.410	0.056 ± 0.202	0.726 ± 0.336	0.041 ± 0.111	**p <0.001**
VA-Worst Eye	0.348 ± 0.389	0.015 ± 0.015	0.379 ± 0.343	0.027 ± 0.064	
***post-hoc* pairwise comparisons**	*	*			*p <0.001
		*	*		*p <0.001
			*	*	*p <0.001
	*			*	*p <0.001
11778/ND4	**ET**		**NT**		
	Recovery	**Not recovery**	**Recovery**	**Not recovery**	
N. patients	14 (11 males)	16 (14 males)	10 (7 males)	33 (24 males)	
Recovery (patients, %)	47		23		**p=0.045**
N. eyes 11778	25/60	35/60	19/86	67/86	
Recovery (eyes, %)	41.7		22.1		**p=0.017**
Age at onset (years)	29.5 ± 15.3	25.8 ± 12.6	24.8 ± 8.8	27.8 ± 9.8	p=0.727
Interval of disease onset between eyes (n=41/73) (months)	4.6 ± 3.2	3.9 ± 2.7	1.8 ± 1.3	2.9 ± 2.3	p=0.241
Interval onset-therapy (months)	7.1 ± 4.4	5.4 ± 3.9			p=0.281
Interval onset-recovery (months)	17.2 ± 7.8		27.7 ± 22.5		p=0.185
Therapy dosage (mg/day)	352.5 ± 149.7	408.1 ± 142.3			p=0.332
Therapy duration (months)	49.2 ± 29.8	33.4 ± 22.8			p=0.110
VA-Best Eye	0.422 ± 0.407	0.015 ± 0.015	0.648 ± 0.381	0.033 ± 0.103	**p<0.001**
***post-hoc* pairwise comparisons**	*	*			*p <0.001
		*	*		*p <0.001
			*	*	*p <0.001
	*			*	*p <0.001
VA-Worst Eye	0.232 ± 0.291	0.012 ± 0.012	0.316 ± 0.374	0.017 ± 0.022	**p<0.001**
***post-hoc* pairwise comparisons**	*	*			*p =0.011
		*	*		*p=0.001
			*	*	*p<0.001
	*			*	*p=0.003

TABLE 2. Regression analysis

Sample studied	Significantly associated independent variables	Dependent variables	Significance
Whole group[A]	14484/ND6	Visual recovery	p=0.03
11778/ND4 patients[A]	Idebenone therapy	Visual recovery	p=0.039
ET group (all mutations)[A]	Duration of therapy	Visual recovery	p=0.031*
ET group (all mutations)[B]	Start of therapy	Timing of visual recovery	p=0.024[#]
ET group (11778/ND4 patients)[B]	Start of therapy	Timing of visual recovery	p=0.046[#]

A=logistic regression model; B=linear multiple regression model; in both analyses a forward stepwise method was applied to obtain a significant model in which all included variables had a p-value <0.05; *=longer duration of therapy was associated with visual recovery; [#]=earlier start of therapy was associated with earlier visual recovery.


Interval between eyes (months)
12,00
10,00
8,00
6,00
4,00
2,00
,00
*p=0.045
ET in-between-eyes (n=6)
ET after the 2nd eye (n=28)
NT (n=21)