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LETTER TO THE EDITOR

Idebenone treatment in patients with *OPA1*-mutant dominant optic atrophy

Piero Barboni,[1,2] Maria Lucia Valentino,[2,3] Chiara La Morgia,[2,3] Michele Carbonelli,[1] Giacomo Savini,[4] Annamaria De Negri,[5] Francesca Simonelli,[6] Federico Sadun,[7] Leonardo Caporali,[2,3] Alessandra Maresca,[2,3] Rocco Liguori,[2,3] Agostino Baruzzi,[2,3] Massimo Zeviani[8] and Valerio Carelli[2,3]

1 Studio Oculistico d'Azeglio, Via d'Azeglio 5, 40123 Bologna, Italy
2 Department of Biomedical and NeuroMotor Sciences, University of Bologna, Via Ugo Foscolo 7, 40123 Bologna, Italy
3 IRCCS, Istituto delle Scienze Neurologiche, Via Ugo Foscolo 7, 40123 Bologna, Italy
4 IRCCS Fondazione Bietti, Via Livenza 3, 00198 Roma, Italy
5 Azienda Ospedaliera San Camillo-Forlanini, Via Portuense 332A, 00151 Roma, Italy
6 Department of Ophthalmology, Second University of Naples, Via S. Pansini 5, 80131 Naples, Italy
7 Ospedale San Giovanni Evangelista, Via A. Parrozzani 3, 00019 Tivoli, Italy
8 IRCCS Istituto Besta, via Temolo 4, 20126 Milano, Italy

Correspondence to: Valerio Carelli, MD, PhD,
IRCCS Istituto delle Scienze Neurologiche di Bologna,
Department of Biomedical and NeuroMotor Sciences,
University of Bologna,
Via Ugo Foscolo 7,
40123 Bologna, Italy
E-mail: valerio.carelli@unibo.it

Sir, Last year we reported our experience on idebenone therapy in patients with Leber's hereditary optic neuropathy (Carelli *et al*., 2011), presenting results similar with those obtained by the Rescue of Hereditary Optic Disease Outpatient Study (Klopstock *et al*., 2011). We now report, for the first time, on the administration of idebenone in seven consecutive patients with dominant optic atrophy carrying *OPA1* mutations in an open-label trial.

Dominant optic atrophy is one of the most frequent hereditary optic neuropathies, characterized by degeneration of retinal ganglion cells leading to loss of central vision, and is currently considered untreatable (Carelli *et al*., 2004; Yu-Wai-Man *et al*., 2011). The majority of patients with dominant optic atrophy carry heterozygous mutations in the *OPA1* gene (Alexander *et al*., 2000; Delettre *et al*., 2000), which encodes for a mitochondrial dynamin-like GTPase mainly involved in fusion of the mitochondrial inner membrane, control of apoptosis and maintenance of mitochondrial DNA and oxidative phosphorylation (Landes *et al*., 2010).

Clinical expression of dominant optic atrophy is mostly limited to optic neuropathy with variable severity (Carelli *et al*., 2004; Yu-Wai-Man *et al*., 2011), ranging from severe congenital optic atrophy to mild cases (Barboni *et al*., 2010). Visual loss affects central vision with colour perception defects and temporal optic disc atrophy because of early involvement of the papillomacular bundle. The natural history of dominant optic atrophy is a relentless and slowly progressive visual loss, which may stabilize usually without spontaneous recovery of vision (Kjer, 1959; Votruba *et al*., 1998; Carelli *et al*., 2004; Yu-Wai-Man *et al*., 2011). A subgroup of patients presents a multi-system disease, defined as dominant optic atrophy 'plus', involving the central and peripheral nervous system and skeletal muscle (Yu-Wai-Man *et al*., 2010).

We previously documented that *OPA1* mutations leading to haploinsufficiency induce defective complex I-driven ATP synthesis (Zanna *et al*., 2008), suggesting a common pathogenic mechanism with Leber's hereditary optic neuropathy, a mitochondrial optic neuropathy due to mutations in mitochondrial DNA-encoded complex I subunits (Carelli *et al*., 2009). Thus, we prospectively enrolled and treated with idebenone (Mnesis, Takeda Italia, 45 mg capsules) seven consecutive patients with dominant optic atrophy with *OPA1* haploinsufficiency mutations, under the off-label regulations in Italy (Table 1). For this pilot study, we obtained the informed consent of the patients and the approval of the internal review board at the University of Bologna. Daily dosage was

Table 1 Demographic and genetic data of patients treated with idebenone

Patient	Gender	Age	Idebenone dosage (mg/day)	*OPA1* mutations	
1	M	43	1000	c.984+3 A>T	Splice defect
2	M	41	540	c.2708_11delTTAG	p.V903GfsX3
3	M	10	270	c.2815 delC	p.L939fs
4	F	12	270	c.112_129del18 + c.992 T>C	p.38delRSIYHS + p.L331P
5	F	24	540	c.2708_11delTTAG	p.V903GfsX3
6	M	47	675	c.2708_11delTTAG	p.V903GfsX3
7	F	24	675	c.2708_11delTTAG	p.V903GfsX3

Table 2 Ophtalmological data of dominant optic atrophy patients at baseline and after treatment with idebenone

Patient	Subjective recovery	Visual acuity						Colour vision		Visual field threshold (MD)			
		Baseline		First follow-up (7.4 ± 1.1 months)		Second follow-up (16.4 ± 4.3 months)		Baseline	Second follow-up	Baseline		Second follow-up	
		OD	OS	OD	OS	OD	OS			OD	OS	OD	OS
1	No	0.06	0.08	0.06	0.08	0.06	0.08	1/15	1/15	−21.93	−10.56	−18.48	−13.64
2	No	0.05	0.05	0.05	0.05	0.1	0.05	1/15	3/15	−13.96	−17.36	−17.41	−18.93
3	Yes	0.5	0.5	0.5	0.5	0.5	0.5	2/15	15/15	−6.97	5.73	−4.53	−4.92
4	Yes	0.16	0.1	0.32	0.2	0.32	0.2	15/15	15/15	−4.39	−4.15	−2.5	−2.99
5	Yes	0.32	0.2	0.4	0.32	0.4	0.32	15/15	15/15	−2.71	−4.21	−2	−2.78
6	Yes	0.32	0.5	0.5	0.63	0.63	0.63	10/15	15/15	−1.19	−2.64	−1.33	−0.16
7	Yes	0.16	0.16	0.2	0.2	0.2	0.2	2/15	10/15	−4.16	−5.77	−3.71	−4.84

MD = mean deviation; OD = right eye; OS = left eye.

270 mg in children, and ranged between 540 and 675 mg in adults. One patient received 1000 mg/day of a different brand (Idebenone Smart Powders, 500 mg capsules). Patients were treated and followed for at least 1 year.

All patients underwent ophthalmological examination, including visual acuity measurement (in decimals), Humphrey quantitative visual field testing, colour test (by Ishihara plates) and retinal nerve fibre layer thickness and optic disc area measurements by optical coherence tomography, as previously reported (Savini *et al*., 2010, 2012). Patients were examined at baseline, at ~7 months (mean ± standard deviation: 7.4 ± 4.1 months) and after at least 1 year (mean ± standard deviation: 16.4 ± 4.3 months) from start of idebenone treatment. Visual acuity before baseline was retrospectively retrieved from clinical charts.

Kolmogorov–Smirnov test showed a normal distribution of the data. Repeated-measures ANOVA, along with Tukey–Kramer multiple comparisons test, was used for baseline and post-treatment measurements comparison. Statistical significance was assumed for *P*-value <0.05.

Demographic and genetic data are summarized in Table 1, whereas clinical results on therapeutic follow-up are shown in Table 2. Overall, mean visual acuity (± standard deviation) improved in both eyes at the last evaluation compared with baseline. In OD (right eye), visual acuity increased from 0.22 ± 0.16 to 0.29 ± 0.19 at the first follow-up and to 0.31 ± 0.21 at the second follow-up (ANOVA, $P = 0.034$), with a statistically significant difference ($P < 0.05$) only between baseline and the second follow-up. In OS (left eye), visual acuity increased from 0.23 ± 0.19 to 0.28 ± 0.21 at the first follow-up and 0.28 ± 0.21 at the second follow-up (ANOVA, $P = 0.014$), with a statistically significant difference ($P < 0.05$) between baseline and both follow-up.

Five patients (mean age: 23 ± 15 years) reported bilateral subjective improvement of visual function. A gain in visual acuity was measured bilaterally in four of these five patients, whereas Patient 3 showed only improvement in colour discrimination (Table 2). All five patients showed improvement of the Humphrey quantitative visual field mean defect (Table 2 and Fig. 1), although this was statistically significant only in the left eye. The mean defect improved in the right eye from −3.9 ± 2.1 to −2.8 ± 1.3 dB at the second follow-up ($P = 0.087$) and in the left eye from −4.5 ± 1.3 to −3.1 ± 1.9 dB ($P = 0.010$). The other two patients (mean age: 42 ± 1 years) did not report any subjective improvement, but objective measurements showed improvement of some visual functions, such as visual field in Patient 1, and visual acuity and colour discrimination in Patient 2.

According to the clinical charts all patients had a childhood onset of visual impairment. However, a more precise temporal definition of onset was difficult. Visual acuity before baseline had progressively declined in the five patients who experienced visual improvement with therapy: from 0.4 ± 0.18 to 0.29 ± 0.14 in the right eye and from 0.42 ± 0.18 to 0.29 ± 0.19 in the left eye (mean interval of time between measurement and baseline: 2.4 ± 0.9 years). The two patients without visual improvement had no visual acuity decline before baseline, possibly because their visual acuity loss had been already severe since infancy.

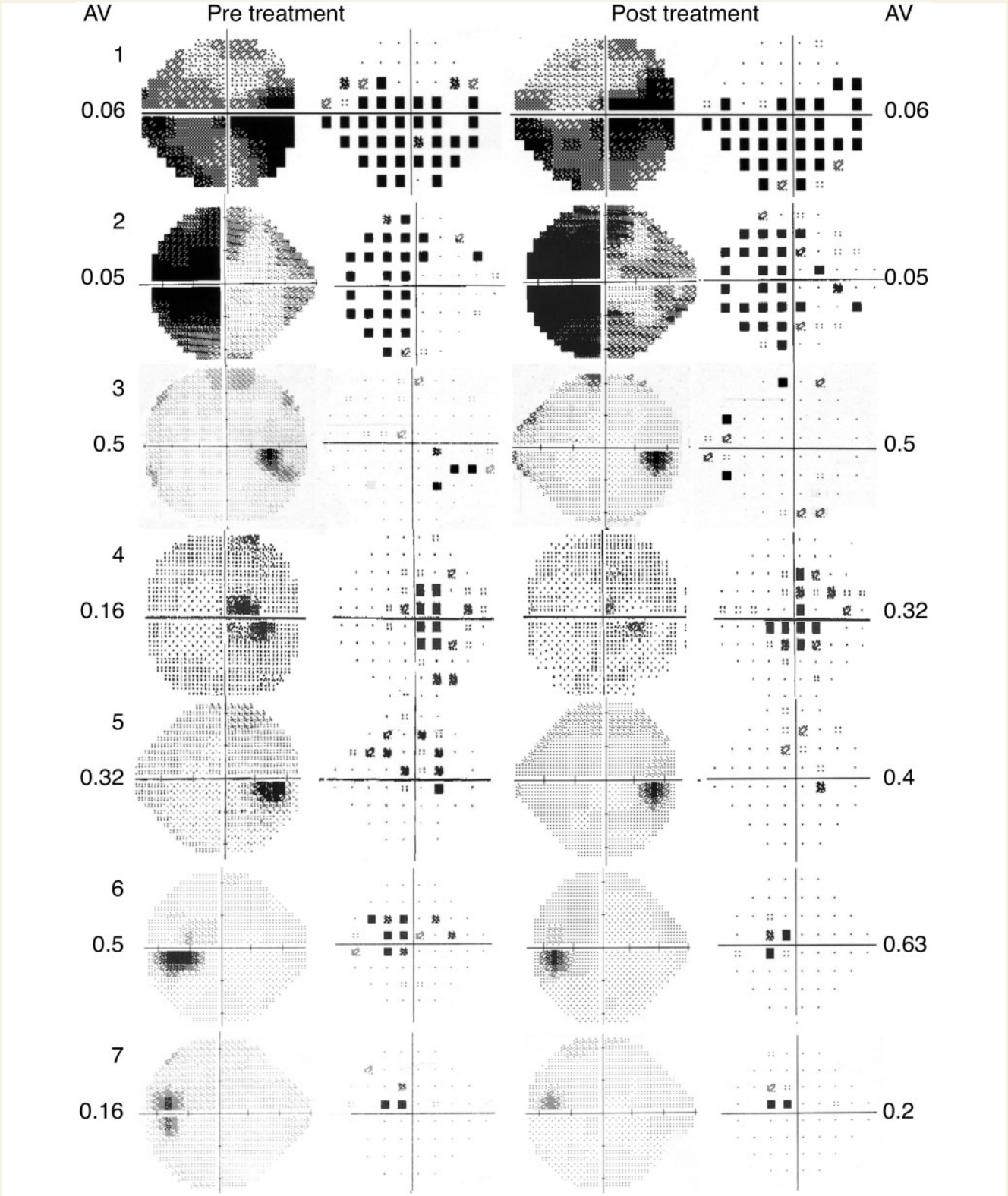

Figure 1 Full threshold visual fields (greyscale and total deviation) and visual acuity of the seven patients, described in Tables 1 and 2, before and after 1 year of therapy.

Mean retinal nerve fibre layer thickness did not change from baseline (right eye: 62.2 ± 4.5 μm) to last examination (63.3 ± 6.0 μm, $P > 0.05$). The baseline retinal nerve fibre layer thickness was lower in patients that did not recover (58.0 ± 9.9 in right eye and 60.5 ± 6.4 in left eye) compared with those who recovered visual functions (65.2 ± 5.3 in right eye and 65.4 ± 6.5 in left eye). Moreover, optic nerve head analysis showed that the optic disc area was larger in patients who recovered vision (1.9 ± 0.4 in right eye and 1.8 ± 0.2 in left eye versus 1.5 ± 0.1 in right eye and 1.6 ± 0.1 in left eye).

This pilot open trial on patients with *OPA1*-mutant dominant optic atrophy documents, for the first time, the occurrence of some improvement of visual function after idebenone treatment. We observed improvement of colour vision, shrinkage of the central scotoma at Humphrey quantitative visual field and increase of visual acuity in five of seven idebenone-treated patients. Older patients with worst baseline visual acuity and Humphrey quantitative visual field, associated with thinner retinal nerve fibre layer and smaller optic disc, failed to achieve visual improvement with therapy. The improvement of visual function occurred after at least 6 months of idebenone administration and, in two cases, was further consolidated after 1 year of therapy. Three of the four patients carrying the recurrent c.2708_11delTTAG microdeletion displayed the best recovery of visual function among the seven treated. The fourth patient, carrying the same mutation, did not subjectively perceive any change in his vision, but showed small improvement of visual acuity and colour vision.

Idebenone was recently shown to ameliorate visual function in patients with Leber's hereditary optic neuropathy (Carelli *et al*., 2011; Klopstock *et al*., 2011), promoting recovery of visual acuity after the profound loss of central vision that follows the acute phase. Idebenone is a benzoquinone that directly transfers electrons to complex III, bypassing complex I (Geromel *et al*., 2002; Haefeli *et al*., 2011). Idebenone also has anti-oxidant properties (Geromel *et al*., 2002), which may correct increased production of reactive oxygen species, a well-established consequence of complex I dysfunction (Carelli *et al*., 2004, 2009). Studies on a model of *OPA1*-mutant *Drosophila* showed increased production of reactive oxygen species and partial rescue of the clinical phenotype by treatment with anti-oxidants, further supporting the use of idebenone in patients with *OPA1*-mutant dominant optic atrophy (Yarosh *et al*., 2008).

Albeit encouraging, this study has limitations. First, the cohort of patients is small. Second, idebenone was given at different dosages. Third, improvement of visual functions was based on intra-individual comparisons between baseline and ~1 year follow-up, rather than being compared with an untreated group. However, the clinical history of dominant optic atrophy in our patients, before idebenone treatment, showed a mean visual acuity decline in five cases and no progression in the two most severe cases, demonstrating the absence of spontaneous visual recovery in these patients. To the best of our knowledge, only one reported patient, with a unique *OPA1* mutation affecting exon 5b and a subacute Leber's hereditary optic neuropathy-like optic neuropathy, experienced recovery of visual function (Cornille *et al*., 2008). In a recently reported large case series of Australian patients with dominant optic atrophy, a few of them apparently presented some visual improvement (Cohn *et al*., 2008). The authors of this study cast doubt that this could merely reflect the limits of retrospective collection of patients.

In conclusion, although preliminary, the results of this study are encouraging, documenting some improvement of visual function in patients with dominant optic atrophy after idebenone therapy. Double-blind, placebo-controlled and randomized trial with idebenone in dominant optic atrophy will be necessary to consolidate these results.

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