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Clinical outcomes of treatment with idebenone in Leber's hereditary optic neuropathy in the Netherlands: A national cohort study

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ABSTRACT.

Purpose: **The purpose of the study was to present results from a national Dutch cohort of patients with Leber's Hereditary Optic Neuropathy (LHON) treated with idebenone.**

Methods: **The multicentre, open-label, retrospective evaluation of the long-term outcome of idebenone treatment of Dutch LHON patients on visual function and on thickness of the retinal ganglion cell layer. Patients included in the analysis had a confirmed mutation in their mitochondrial DNA encoding either of the seven subunits of complex I, had a reported loss of vision in at least one eye and had a follow-up of more than 6 months after their treatment was started. Control visits involved routine clinical examinations of visual function and retinal structure at (1) the start of treatment, (2) nadir (time of lowest visual acuity), (3) the time of recovery (if any), (4) the time of termination of treatment and (5) more than 6 months after termination of the treatment.**

Results: **Data from 72 patients were analysed. Treatment duration was 23.8 ± 14.4 (mean ± SD) months. A positive response, *that is* either a clinically relevant recovery (CRR) or a clinically relevant stabilization (CRS), occurred in 53% and 11% of the patients, respectively. The magnitude of CRR was 0.41 ± 1.54 logMAR. CRR of visual acuity is associated with recovery of colour discrimination. The thickness of both the ganglion cell complex (GCC) and the retinal nerve fibre layer (RNFL) is irreversibly reduced.**

Conclusion: **Our results confirm that idebenone may help to restore or maintain visual function. Whether this effect will persist is still unknown. Thinning of retinal neural tissue appears to be permanent.**

Key words: complex I deficiency – ganglion cells – LHON – mitochondrial hereditary disease – retina

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Introduction

Leber's Hereditary Optic Neuropathy (LHON) is a rare, maternally inherited disease. It is characterized by an, initially, subacute loss in vision (visual acuity and colour vision) in one eye while the fellow eye becomes similarly involved, usually within a couple of months (Hwang *et al.* 2017). Ultimately, vision generally, and irreversibly, deteriorates. Mutations in the mitochondrial DNA (mtDNA) can disturb the oxidative phosphorylation (Carelli *et al.* 2004). With the mtDNA encoding complex I (nicotinamide adenine dinucleotide-ubiquinone oxidoreductase) involved, adenosine triphosphate (ATP) synthesis is hampered, and the production of oxygen-free radicals is increased causing dysfunction of the retinal ganglion cells (Gueven 2014) leading to opticopathy.

It has been suggested that although their functionality is suppressed, retinal ganglion cells can retain their viability for a prolonged period of time (Howell 1998). With the proper medication to restore ganglion cell function, this would provide a therapeutic window for the recovery of vision. Idebenone is thought to facilitate the electron transfer from complex I to complex III and, thereby, to restore ATP production (Lyseng-Williamson 2016). A randomized clinical trial presented evidence that idebenone, in particular in patients

with a dissimilar visual acuity in their eyes at baseline, can be beneficial to preserve and/or restore vision (Klopstock *et al*. 2011). In 2015, the European Medicines Agency granted marketing authorization for the treatment of LHON with idebenone (Raxone®, Santhera Pharmaceuticals GmbH, Germany) under the condition of additional monitoring. With this medication available, however, the therapeutic window should not be lost by a delay of diagnosis (van Everdingen *et al*. 2021).

In 2017, a consensus conference was held to address therapeutic issues that remained unclear, such as management and response assessment strategies (Carelli *et al*. 2017). Since then, the previously reported beneficial effect of idebenone on recovery and preservation of vision (Klopstock *et al*. 2011) has been confirmed by two other studies:

the real-world expanded access programme (EAP) in a mainly Western setting (Catarino *et al*. 2020) and a Japanese prospective, interventional study (Ishikawa *et al*. 2021). We present the results on visual acuity, colour discrimination and retinal neuronal layer thickness from a Dutch, nationwide, cohort of LHON patients who were treated with idebenone for some period of time since its introduction between 2014 and 2021.

Methods

All records of Dutch patients with LHON (*i.e*. patients with a confirmed complex I mutation) who were treated with idebenone (Raxone®, Santhera Pharmaceuticals GmbH, Germany) were retrospectively analysed. The Dutch Medical Research Involving Humans Act (WMO) does not apply to this type of study and, as confirmed by the Ethical Committee, official medical ethical approval was not required. This study adhered to the tenets of the Declaration of Helsinki.

Health authorities in the Netherlands, have designated three hospitals where LHON patients may be treated with idebenone. Patients eligible for treatment are referred by their ophthalmologist to one of these centres. In accordance with Dutch guidelines, treatment should be started during the subacute (<6 months from onset) or dynamic (6–12 months) phase of LHON and adhered to for at least 15 months, with control visits every 3 months. Idebenone was prescribed at 900 mg/day (3 × 300 mg) for all patients (two children starting at 3 × 150 mg excepted). For our analysis, data were used that had been acquired at the following moments during follow-up (*cf*. Catarino *et al*. 2020): (1) at baseline (BL), *that is* at the start of treatment, (2) at nadir (time of lowest visual acuity), (3) at the time of vision recovery (see below for its criteria), (4) at the termination of treatment (LTV) and (5) at a post-treatment visit (PTV), *that is* 6–18 months after termination.

Best corrected visual acuity (BCVA) was usually measured with Early Treatment Diabetic Retinopathy (ETDRS) charts (logMAR); when BCVA was measured otherwise, values were converted to logMAR for analysis. Colour discrimination was examined by means of pseudoisochromatic Hardy Rand Rittler (HRR) plates (Red-Green score: 0–20, Blue Yellow score: 0–8; a higer score indicating better colour vision); foveal threshold was determined with the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA) with either the 30–2 or 10–2 test field. Optical coherence tomography (OCT) was used to assess the thickness of retinal neural layers; depending on the type of OCT that was used, the (average of the perifoveal field of the) Ganglion cell complex (GCC; Canon HS100) and/or of the (TSNIT average of the) retinal nerve fibre layer (RNFL; Canon HS100 or Spectralis Heidelberg Engineering) were measured.

Data were analysed either per patient (*i.e*. based on the patient's best eye) or per eye. For the evaluation of BCVA outcome, the same criteria were applied as the ones used in a previous study of the effect of idebenone (Catarino *et al*. 2020), with clinically relevant stabilization (CRS) defined as a patient having a BCVA of <1.0 logMAR in at least one eye at baseline which is maintained in that eye until the last visit and clinically relevant recovery (CRR) as an improvement, relative to nadir, from off-chart (*i.e*. >1.68 logMAR) to on-chart 1.60 logMAR or better or by an (on-chart) improvement of at least 0.20 logMAR.

Statistical calculations and the preparation of graphs were performed using Excel (Microsoft Office 2010) or SPSS (IBM-SPSS Statistics, version 25). The time interval from the start of treatment (BL) to CRR was used to construct a cumulative incidence plot.

Results

In this retrospective study, 78 patients recently diagnosed with LHON were eligible for analysis. The medical records from this nationwide cohort were retrieved and evaluated with the earliest treatment dating from 2014 (Santhera Pharmaceuticals' compassionate use programme) and a data cut-off of October 2021. One patient was excluded from the analysis because no mutation had been detected at any nucleotide position in the mtDNA encoding for either of the seven subunits of complex I, another patient was excluded because no treatment was prescribed, and four more patients were excluded due to the absence of sufficient follow-up data (<6 months after treatment start). Otherwise, no other exclusion criteria were applied. Of the 72 patients remaining, 38 (53%) had the m.11778G > A mutation (ND4 of Complex I) and 26 (36%) the m.14484 T > C mutation (ND6). Furthermore, the following mutations were identified: m.3460G > A (ND1), $n = 3$; m.14596A > T (ND6), $n = 3$ (one of whom in combination with m.11696G > A (ND4)); m.14500A > T (ND6), $n = 1$ and 13513G > A (ND5), $n = 1$[1].

Table 1 summarizes the demographic characteristics and visual function of our study population at baseline. The mean time interval between onset in the first and second affected eye was 2.6 ± 4.4 months. Treatment duration ranged from 0.4 to 63.6 months. The treatment of one patient was interrupted for a period of 6 months, three (11778G > A) patients terminated their treatment in favour of gene therapy.

Clinically relevant stabilization of visual acuity

At baseline, 37 patients had a BCVA better than 1.0 logMAR (Table 1) in their best eye. Only eight of these (Table 2) had a CRS in accordance with its strict definition that this should be maintained in that eye (see Methods). Another eight patients (Table 3) had a BCVA better than 1.0 logMAR

Table 1. Demographic characteristics and baseline (start of treatment) visual function by mutation, with visual function outcome based on the patient's best eye.

	All	11778G > A	14 484 T > C	miscellaneous
Patients in analysis	72/72 (100%)	38/72 (53%)	26/72 (36%)	8/72 (11%)
Gender male	53/72 (74%)	30/38 (79%)	17/26 (65%)	6/8 (75%)
Age (years)	33.0 ± 21.6 (5–77)	36.0 ± 21.1 (5–77)	33.7 ± 23.6 (12–77)	16.6 ± 4.9 (9–23)
<12	5/72 (7%)	4/38 (11%)	0/26 (0%)	1/8 (13%)
12–17	20/72 (28%)	6/38 (16%)	11/26 (42%)	3/8 (38%)
18–64	37/72 (51%)	23/38 (61%)	10/26 (38%)	4/8 (50%)
>65	10/72 (14%)	5/38(13%)	5/26 (19%)	0/8 (0%)
Onset – baseline (months)*	5.4 ± 7.3 (0.0–42.6)	5.5 ± 6.9 (0.0–35.8)	5.9 ± 8.6 (0.4–42.6)	3.1 ± 3.9 (0.3–12.5)
Treatment duration (months)	23.8 ± 14.4 (0.4–63.6)	21.2 ± 12.5 (0.4–63.6)	28.7 ± 17.3 (3.9–61.0)	20.3 ± 7.4 (10.9–34.3)
BCVA (logMar)	0.83 ± 0.59 (−0.16–1.80)	0.92 ± 0.62 (−0.16–1.80)	0.69 ± 0.53 (−0.12–1.80)	0.89 ± 0.57 (−0.10–1.80)
≥1.0	35/72 (49%)	20/38 (53%)	12/26 (46%)	3/8 (38%)
<1.0	37/72 (51%)	18/38 (47%)	14/26 (54%)	5/8 (62%)
HRR-RG score	11.8 ± 7.4	13.8 ± 7.2	11.0 ± 7.5	6.5 ± 4.4
HRR-BY score	6.3 ± 3.0	6.6 ± 2.9	5.9 ± 3.3	7.3 ± 1.5
[# patients]	[45]	[20]	[21]	[4]
foveal threshold (dB)	18.9 ± 13.7 (0–39)	17.2 ± 15.3 (0–39)	20.5 ± 12.0 (0–36)	20.0 ± 14.2 (0–36)
[# patients]	[60]	[29]	[25]	[6]

Values are presented either as *n* (%) or as mean ± SD (range).
For colour discrimination and foveal threshold: number of patients in square brackets.
* Time interval between onset in the earliest affected eye and the start of treatment.

Table 2. Patients with a clinically relevant stabili

Subject's mutation(s)	BCVA (logMar) baseline	BCVA (logMar) last visit
14 484 T > C	−0.12	−0.20
14 484 T > C	0.30	0.18
14 484 T > C	0.08	−0.26
14 484 T > C	0.38	0.30
11778G > A	0.12	−0.06
11778G > A	0.08	0.02
14596A > T & 11696G > A	0.80	0.50
13513G > A	0.42	−0.08

Baseline is at the start of treatment, last visit is at the termination of treatment.
BCVA = best corrected visual acuity, is reported for the eye that was patient's best at baseline.

Table 3. Patients with a BCVA < 1.0 logMAR at baseline AND at the most recent visit.

Subject's mutation	BCVA (logMar) baseline	BCVA (logMar) most recent visit
14 484 T > C	0.80	0.06
14 484 T > C	0.08	0.04
14 484 T > C	0.70	−0.16
14 484 T > C	0.32	0.80
14 484 T > C	−0.08	0.30
11778G > A	0.70	0.70
11778G > A	0.80	0.42
14596A > T	0.78	0.64

BCVA = best corrected visual acuity, is reported for the patient's best eye at the time of the visit.

in at least one of their eyes at the most recent visit; this, however, was either in the contralateral eye and/or after a temporary loss of vision in the eye with initial vision better than 1.0 logMAR.

Clinically relevant recovery of visual acuity

Clinically relevant recovery was observed in 40 (56%) patients (Table 4) or 78 (54%) eyes. In 5 of these subjects, vision had deteriorated again at their final visit by more than 0.2 logMAR (2 of them with a residual improvement relative to nadir of 0.2 logMAR or more, and 3 others with a remaining improvement that was smaller).

In Fig. 1, the cumulative distribution of CRR events is shown both per patient (56%) and per eye (54%). In one patient (both eyes), CRR was observed 15 months after treatment was stopped (the treatment lasting only 12 days); another patient (right eye) had a sudden CRR 24 months after termination of treatment. When these cases are excluded from the analysis of Fig. 1, the cumulative CRR incidence becomes 53% by patient and 52% by eye respectively.

Figure 2 shows the development over time of the mean visual acuity in those patients experiencing a CRR. It can be observed (*cf.* means and their confidence intervals) that after a statistically significant improvement of BCVA from nadir to CRR (corresponding to four lines on the ETDRS chart), a further statistically significant improvement (three lines) occurs from CRR to last treatment visit.

Visual function of the study population in general

In Fig. 3, the distribution of three categories of BCVA (*i.e.* off-chart,

Table 4. Clinically relevant recovery.

	All	11778G > A	14 484 T > C	Miscellaneous
Patients with a CRR*	40/72 (56%)	18/38 (47%)	19/26 (73%)	3/8 (38%)
Time from nadir to CRR (months)	8.5 ± 6.1 (0.8–34.7)	8.8 ± 7.8 (0.8–34.7)	8.6 ± 4.4 (3.0–17.1)	5.6 ± 5.1 (1.0–11.2)
BCVA gain from nadir to CRR (logMar)	0.41 ± 0.32 (0.10–1.54)	0.40 ± 0.25 (0.10–0.98)	0.44 ± 0.40 (0.20–1.54)	0.31 ± 0.07 (0.24–0.38)
BCVA gain from nadir to LTV (logMar)	0.68 ± 0.57 (0.00–1.94)	0.52 ± 0.46 (0.04–1.36)	0.79 ± 0.66 (0.00–1.94)	0.78 ± 0.50 (0.34–1.32)

Values are presented as *n* (%) or as mean ± SD (range).
* In two (11778G > A) patients CRR occurred after termination of the treatment; in five cases CRR was followed by a deterioration of vision of more than 0.20 logMAR (14 484 T > C: 3; 11778G > A: 2).

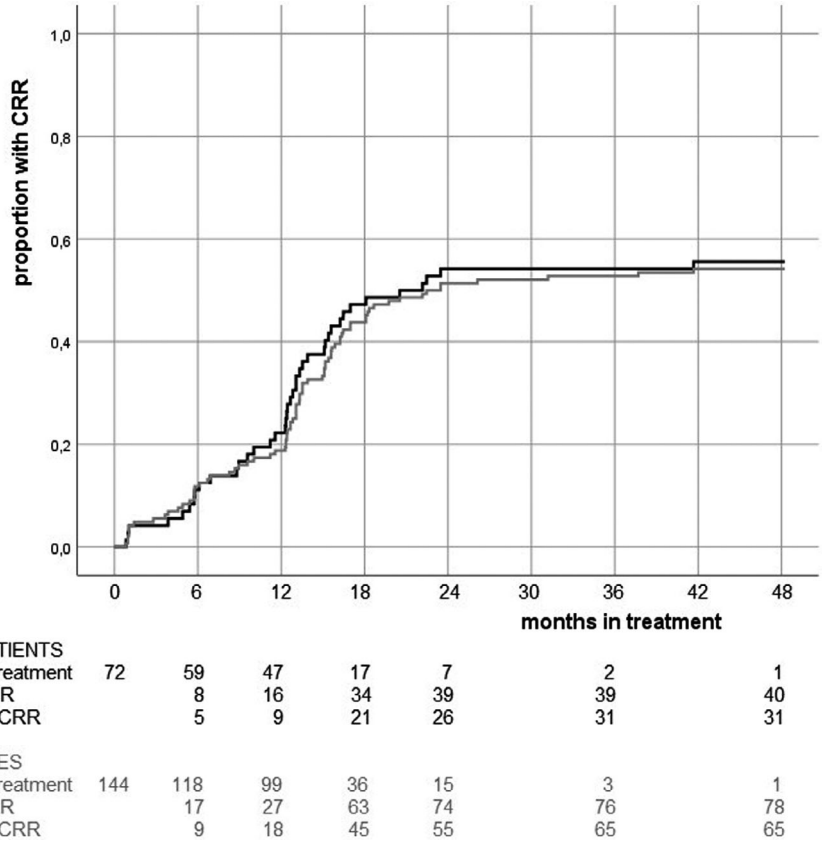

Fig. 1. Cumulative distribution of events of clinically relevant recovery (time from baseline).

1.00–1.68 logMAR and better than 1.0 logMAR) is shown at baseline ($n = 71$), at nadir ($n = 69$) and at the last visit during treatment ($n = 70$). The shift observed for BCVA categories is associated with changes in foveal threshold (from visual field measurements) and colour discrimination (Table 5). In general, red-green discrimination appears to be more affected than blue-yellow discrimination and its recovery worse. Statistically significant improvements, from nadir, of both types of colour discrimination and foveal threshold were observed in patients with a CRR only.

Ganglion cell complex and retinal nerve fibre layer

The reduction in the thickness of both retinal neural constituents is illustrated in Figs. 4 and 5. In both graphs, the thickness distribution in a healthy population is indicated along with the ordinate (from the Premarket notification Canon OCT, 2019). From BL to LTV, GCC thickness is reduced by about 20%. After an initial swelling of the RNFL (*cf.* the thicknes at BL with that of a healthy population), thickness decreases with almost 40% at LTV.

Discussion

Since the introduction of Raxone® for the treatment of LHON in the Netherlands in 2014, and until 2020, 72 patients were treated with this medication (with treatment duration ranging from less than a month to more than 5 years) and monitored for its efficacy. On average, this would corresponds with 12 newly treated patients annually, implying (on a population of 17 million) an incidence of $7{\cdot}10^{-7}$. Although converting prevalence to incidence (or the reverse) is far from straightforward, this figure does not appear to be incompatible with the Dutch prevalence of vision loss due to LHON which was estimated to be 1:39 000 (Spruijt *et al.* 2006): with an approximated average disease duration of 40 years, an incidence of $6{\cdot}10^{-7}$ can be inferred.

Analysis of the data collected during this study demonstrates a beneficial effect which is in agreement with previous findings (Klopstock *et al.* 2011, Catarino *et al.* 2020). The results of the present study must be evaluated in the context of what is known about the natural history of LHON. Unfortunately, publications on natural history are not entirely consistent: patient populations differ, some patients used idebenone while others did not, the frequency and type of assessments varies and, sometimes, the data analysed (partially) coincide.

Recently, two reports were published on the natural course of LHON in relatively large cohorts of 83 patients (Silva *et al.* 2018) and 44 patients (Yu-Wai-Man*et al.* 2022) respectively. In the former study, with collated data from 11 centres, 18% of the patients had a vision better than 1.0 logMAR at their last visit. In the latter study, with half of the patients using idebenone,

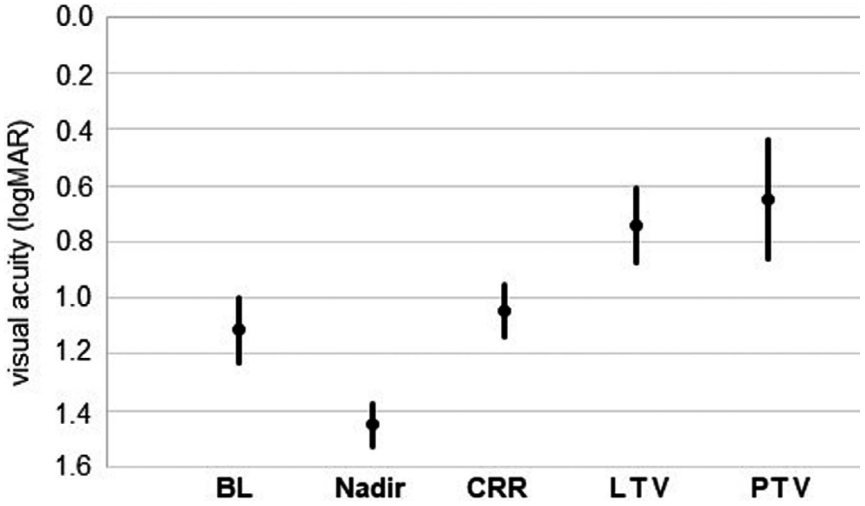

Fig. 2. BCVA of eyes with a CRR. Mean values are shown at baseline (BL, $n = 78$), nadir ($n = 78$), at the time of CRR ($n = 71$), at the last visit during treatment ($n = 76$) and at a post-treatment visit (PTV, $n = 25$). Error bars represent the 95% CI. The contralateral eyes of seven patients with CRS showing recovery at the LTV or the PTV (total: 71 + 7 = 78 eyes) are included in this graph.

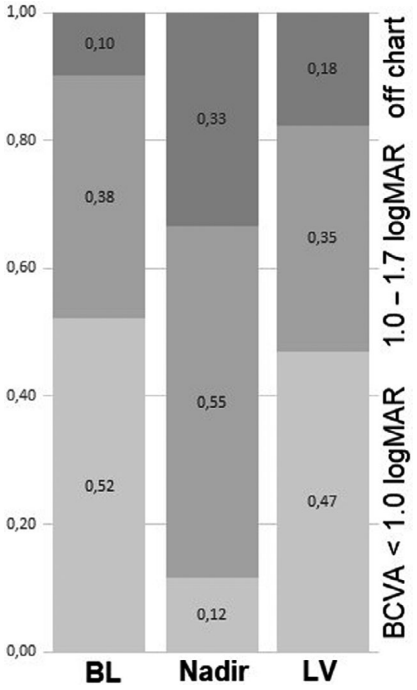

Fig. 3. Shift of patients across three categories of BCVA: off-chart (dark grey), 1.00–1.68 logMAR (grey) and better than 1.0 logMAR (light grey).

that proportion was 24%. From a meta-analysis, conducted for m.11778G > A patients only (Newman *et al.* 2020), it was concluded that, at best, about 14% of the them (100/695) 'recovered some vision' (with definitions of recovery varying among studies). A randomized clinical trial (Newman *et al.* 2021), comparing gene therapy with natural history data originating from various studies (some of which were also evaluated in the meta-analysis mentioned above (Newman *et al.* 2020)) shows that 27% of the 408 external control eyes had a visual acuity better than 1.3 logMAR at the last observation and that 28% (36/127) experienced an improvement of 0.3 logMAR or more.

In the present study, 49% (34/70) of the patients had a vision better than 1.0 logMAR at their last visit (*i.e.* after 23.8 ± 14.4 months). Eight patients had a CRS while 40 experienced a CRR (Fig. 1). Two patients had an improvement of vision long after treatment was terminated, and three had a CRR that did not last until the final visit; without these five subjects, 60% (43/72) of our patients might be considered to have benefited from the treatment with idebenone. In the EAP study (Catarino *et al.* 2020), 32% of the patients had a vision of better than 1.0 logMAR at the last observation, 12 patients had a CRS and 40 had a CRR, implying an overall benefit of 60% (52/87). A Japanese prospective, interventional study observed a proportion of 26% of patients with a vision better than 1.0 logMAR at the end of the trial (Ishikawa *et al.* 2021).

The proportions of patients with a vision better than 1.0 logMAR at their last visit appears to be substantially different among these three studies (49%, 32% and 26%). This may, at least partially, be explained by the different proportions of m.11778G > A patients that were included in the analysis: 53% in our study population, 62% in the EAP study, and 95% in the Japanese study. The general notion that the 11778G > A mutation is associated with a poor visual outcome is also supported by comparing subgroups from our study: the proportion of patients with a BCVA better than 1.0 logMAR at their LTV was 31% (11/36; m.11778), 65% (17/26; m.14484) and 75% (6/8; miscellaneous mutations) respectively (X^2-test, $p = 0.007$). Support for this conjecture can also be found in the different magnitudes of recovery. At the last observation of the EAP study, visual acuity gain was 0.52 ± 0.39 logMAR for patients with a m.11778 mutation versus 1.12 ± 0.40 logMAR for those with a m.14484 mutation (Table 3 of Catarino *et al.* 2020). In the present study, this difference was less prominent: 0.52 ± 0.46 versus 0.79 ± 0.66 logMAR (Table 4).

In spite of the poor consistency among studies of the efficacy of idebenone treatment for LHON and among natural history studies, it is concluded that treatment may enhance the proportion of patients with some degree of (maintained or recovered) visual

Table 5. Colour vision and foveal threshold (mean ± SD) of the patient's best eye at the time of baseline, nadir and last visit. (RG score: 0–20, BY score: 0–8). P-values: Wilcoxon signed rank test for nadir versus last visit.

CRR	BL	Nadir	LTV	p
Colour vision RG	11.4 ± 7.9	5.2 ± 6.3	13.1 ± 4.9	<0.001
Colour vision BY	5.6 ± 3.5	4.0 ± 3.6	7.6 ± 1.2	0.003
Foveal threshold	15.6 ± 13.9	6.5 ± 11.1	15.5 ± 13.0	0.036
No CRR				
Colour vision RG	12.3 ± 6.8	5.6 ± 7.1	7.2 ± 8.1	0.60
Colour vision BY	7.2 ± 2.1	3.8 ± 3.4	4.7 ± 3.4	0.58
Foveal threshold	23.4 ± 12.4	11.8 ± 15.0	13.7 ± 16.2	0.09

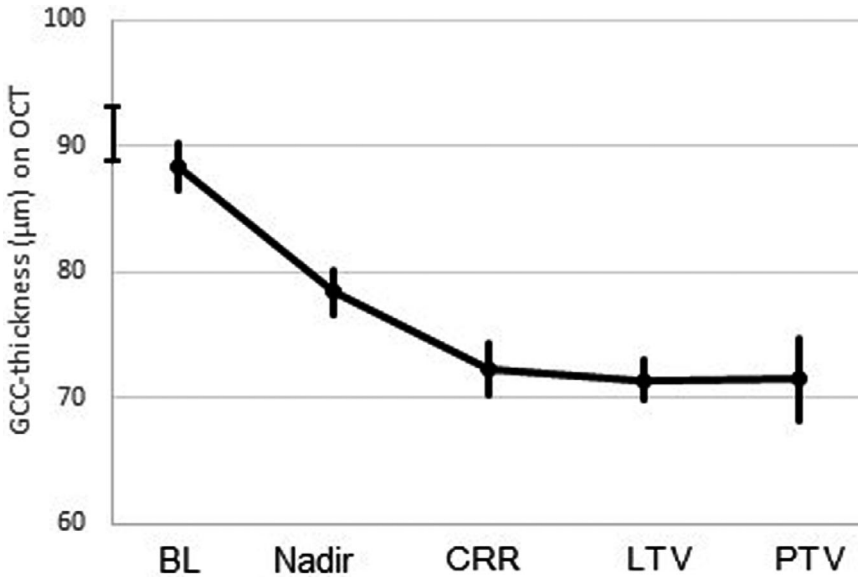

Fig. 4. Average thickness of the perifoveal ganglion cell complex (GCC) of all eyes during follow-up. Error bars indicate the 95% confidence interval of the mean. Along the ordinate, the distribution in the normal, healthy population is indicated (see text). Number of eyes by visit: BL, 109; Nadir, 111; CRR, 69; LTV, 100; PTV, 26.

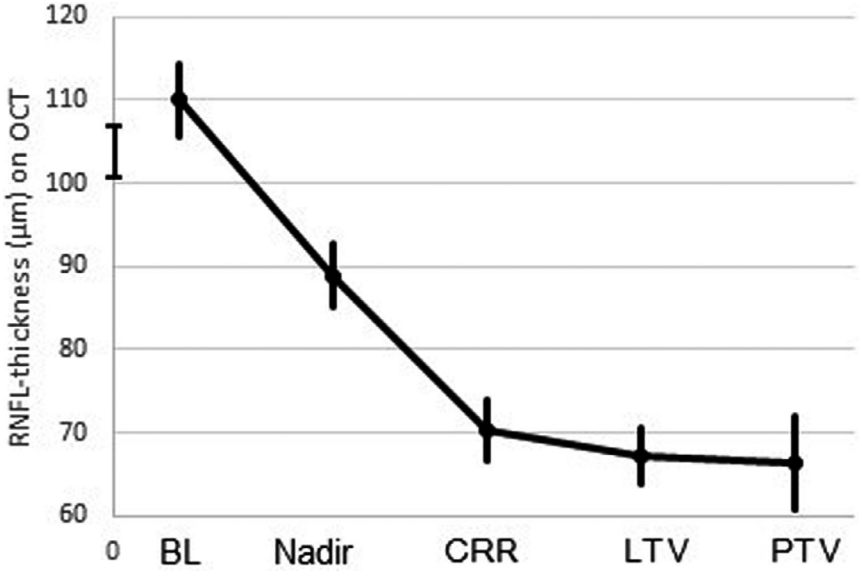

Fig. 5. Average thickness of the peripappillary retinal nerve fibre layer (RNFL) of all eyes during follow-up. Error bars indicate the 95% confidence interval of the mean. Along the ordinate, the distribution in the normal, healthy population is indicated (see text). Number of eyes by visit: BL, 125; Nadir, 119; CRR, 76; LTV, 115; PTV, 31.

function. This beneficial effect is also reflected in the other functional outcomes: foveal threshold of visual fields (which is closely related to BCVA, see for instance Flaxel et al. 2007) and colour discrimination (Table 5). After an initial, and significant, decline of GCC and RNFL thickness, thinning of neuronal tissue levels off. The conversion of LHON has been associated with an initial swelling of the RNFL (see Fig. 5) followed by an irreversible decrease in its thickness (Hedges *et al.* 2016; Hwang *et al.* 2017; Wang *et al.* 2021). A thickness decline of the GCC (Fig. 4) was also noticed before (Botelho et al. 2021; Ishikawa *et al.* 2021). Whether these structural changes have any bearing on the prognosis of visual function, or whether the beneficial effect of idebenone will be preserved over a longer period of time, remains, as yet, to be elucidated.

Note

[1]In some populations, mutation 3460G > A is fairly common (*e.g.* Catarino *et al.* 2020); mutations 14596A > T and 11696G > A (de Vries *et al.* 1996), and mutation 13513G > A (Krylova *et al.* 2020) have also been identified before in LHON patients.

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