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Use of Idebenone for the Treatment of Leber's Hereditary Optic Neuropathy: Review of the Evidence

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Abstract

Leber's hereditary optic neuropathy (LHON) is one of the most frequent mitochondrial disorders. It is caused by mutations in genes of the mitochondrial DNA coding for subunits of the respiratory chain and leads to severe bilateral vision loss, from which spontaneous recovery is infrequent. Retinal ganglion cells show a selective vulnerability to mitochondrial dysfunction in LHON. Idebenone is the first medication approved for LHON. It is a short-chain benzoquinone, which is an analogue of coenzyme Q10, but with distinct properties and mechanisms of action. Idebenone is a potent antioxidant and inhibitor of lipid peroxidation. Importantly, it facilitates electron flux directly to complex III, bypassing the dysfunctional complex I of the mitochondrial respiratory chain, thereby increasing adenosine triphosphate (ATP) production. In the Rescue of Hereditary Optic Disease Outpatient Study (RHODOS) randomized placebo-controlled clinical trial, 85 patients with LHON were enrolled, in the first 5 years after symptom onset, and randomized to either idebenone 900 mg/d for 6 months or placebo. Idebenone was well tolerated, and although the prespecified primary end point (best recovery in visual acuity [VA]) did not reach statistical significance, all secondary end points (change in best VA, change of VA of best eye at baseline, and change of VA in all eyes) showed a trend toward visual recovery in favor of idebenone. An increasing body of evidence shows that idebenone is effective and safe for the treatment of patients with LHON, including a large retrospective open-label study, several case reports and case series, an expanded access program, and ongoing post-authorization clinical studies. Here, we review the literature on idebenone for the treatment of patients with LHON.

Keywords

LHON, complex I, respiratory chain, oxidative phosphorylation, Leber's hereditary optic neuropathy, Leber optic atrophy, Leber disease, idebenone, mitochondrial disease

Introduction

Leber's hereditary optic neuropathy (LHON, MIM 535000) is a rare disease, yet one of the most frequent mitochondrial disorders, with an estimated prevalence of 1:31 000.[1] It is caused by mutations in the mitochondrial DNA (mtDNA), leading to acute or subacute bilateral visual loss, usually in young adults, most frequently males.

The pathophysiology of LHON involves selective dysfunction of retinal ganglion cells and later apoptosis of these cells. The primary mtDNA mutations causing LHON are m.11778G>A in the MT-*ND4* gene,[2] m.3460G>A in the MT-*ND1* gene,[3] and m.14484T>C in the MT-*ND6* gene,[4] and all involve subunits of the complex I of the mitochondrial respiratory chain, leading to reduced adenosine triphosphate (ATP) production[5] and increased free radical production.[6]

Idebenone is a synthetic short-chain benzoquinone. Being a less hydrophobic analogue of coenzyme Q10, it can cross mitochondrial membranes. The mechanisms of action of idebenone

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include stimulation of ATP formation, antioxidant capacity, scavenging of free radicals, protecting against lipid peroxidation,[7] and bypassing the dysfunctional complex I of the mitochondrial respiratory chain.[8] Idebenone can thereby improve the bioenergetic production by the respiratory chain in the presence of a mitochondrial complex I defect.[8,9]

An increasing body of published evidence indicates that idebenone is effective and safe for the treatment of patients with LHON.[10] A randomized placebo-controlled trial[11] and a large multicenter expanded access program (EAP) provided evidence for efficacy and favorable side effect profile of idebenone for the treatment of patients with LHON. This added to the evidence from case reports and small case series, reviewed in Table 1,[12-21] and one large retrospective open-label study.[22] With the sum of the available evidence, idebenone was approved in September 2015 in the European Union for the treatment of visual impairment in adolescent (12 years and older) and adult patients with LHON.[23,24]

Recently, idebenone was also found in a phase III randomized clinical trial (RCT) to significantly reduce the loss of respiratory function in patients with Duchenne muscular dystrophy.[25] Here, we review the evidence from the literature and our own experience in the use of idebenone in patients with LHON.

Methods

Relevant medical literature was searched on idebenone use in LHON. The bibliographic review was performed using the PubMed, MEDLINE databases. The search terms used were "Idebenone" plus "LHON", "Leber's" or "Leber". Also reviewed were bibliographies of relevant literature and the European Medicines Agency (EMA) 2015 report on idebenone (EMA/480039/2015).[23]

Idebenone: Rationale for Use in LHON

Idebenone is a compound first synthesized in the 1980s in Japan, found to improve mitochondrial respiratory and phosphorylating activities in rat brain mitochondria.[26]

In 1988, the first mutation of the mtDNA causative of LHON was found in position m.11778G>A.[2] Later, the other two primary mutations, m.3460G>A[3] and m.14484T>C,[4] were found, all of which lead to dysfunction of complex I of the respiratory chain. This was the rationale to using idebenone as a treatment for patients with LHON.

Studies of Idebenone for the Treatment of Patients With LHON

The first published case report of idebenone use in LHON is from 1992 and describes a 10-year-old boy with LHON caused by the m.11778G>A mutation, who was treated with idebenone 90 mg/d for 1 year. Some recovery of visual acuity (VA) was noted after 1 month of treatment, and a recovery to normal VA of 6/6 bilaterally was documented 4 months after starting treatment.[12] This case report suggested that idebenone has therapeutic potential for the treatment of LHON, but the probability of spontaneous improvement of a 10-year-old child with LHON is higher than for patients with the habitual age at onset in the second and third decades of life.[27] No definite conclusion on efficacy was therefore possible.

An increasing body of evidence from case reports and case series followed, further suggesting that idebenone has therapeutic potential for the treatment of LHON. From 1995 to 2016, 37 papers were published in PubMed with the keywords "Idebenone" and "LHON" or "Leber" or "Leber's." Table 1 summarizes the results of published case reports of the use of idebenone in patients with LHON.

The published case reports of patients with LHON treated with idebenone are heterogeneous. Several factors need to be taken into account when interpreting the outcome of treatment,[28-31] including underlying mtDNA mutation; age at onset of symptoms; time delay from first symptom to treatment start; duration of treatment; daily doses of idebenone; whether the patient had LHON, LHON-plus, or Harding's disease; and duration of follow-up. For example, in some case reports where no effect of idebenone is reported, the follow-up time was too short to allow any robust conclusion.

The data were suggestive enough to justify performing a multicenter placebo-controlled double-blinded RCT. The results of this multicenter RCT to assess efficacy, safety, and tolerability of the treatment with idebenone in LHON were published in 2011.[11] In this phase III RCT, called "Rescue of Hereditary Optic Disease Outpatient Study" (RHODOS; NCT00747487), 85 patients were enrolled with LHON caused by one of the three primary LHON mutations, in the first 5 years after symptom onset. Patients were assigned in a 2:1 randomization ratio to take either idebenone 900 mg/d for 6 months or placebo.[11] This has been so far the only RCT of idebenone in LHON. Although the prespecified primary end point (best recovery in VA) did not reach statistical significance in the intention-to-treat population, it could be shown in post-hoc analyses that the group of affected individuals with discordant VAs (defined as a difference of >0.2 log of the minimum angle of resolution (logMAR) between the 2 eyes) were more likely to benefit from idebenone, and all secondary end points (change in best VA, change in VA of best eye at baseline, change in VA in all eyes) showed a trend toward visual recovery in favor of idebenone.[11] For patients with "off-chart" VA in both eyes at baseline, 7 of 25 in the idebenone group and 0 of 13 in the placebo group could at 6-month follow-up read at least one full line in the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 1 m.[11] In the RHODOS study, a daily dose of 900 mg/d of idebenone was found to be safe, with no significant drug-related adverse events (AEs).[11]

In the follow-up study "RHODOS Follow-up Single-visit study" (NCT 01421381), 60 patients who had been enrolled in RHODOS (39 of whom had taken idebenone) were reevaluated in one follow-up visit, performed 30 months (median) after the last visit in RHODOS. It could be shown that, for the patients who benefited from the 6-month treatment with

Table 1. Data from Case Reports of Use of Idebenone in LHON (1992-2016).

Authors	No. of Patients Treated, Diagnosis	Age (years), Gender	LHON-Mutation	Country/ Ethnicity	Duration of Symptoms at IDE Start (months)	Daily IDE Dose	Duration of Treatment (months)	VA at Baseline Before Treatment	VA at Last Follow-Up
Mashima et al, 1992[12]	1, LHON	10, M	m.11778	Japan	Unknown, acute phase	90 mg	12	6/90 bil.	at 4 months, OD 6/6; at 7 months, full recovery, OD/OS 6/6
Cortelli et, 1997 al[13]	1, LHON + MS-like	31, M	m.11778	Italy	84; 2 weeks after spastic paraparesis	135-405 mg	12	NA	at 6 days, significant recovery of spastic paraparesis. No change in VA
Carelli et al, 1998[14]	1, LHON	24, M	m.14484	Italy, North African	3	270 mg	12	OD 20/200, OS 8/200	at 12 months, 20/20 bil.
Mashima et al, 2000[15]	14, LHON	NA	m.11778, 11; m.3460, 1; m.14484, 2	Japan	NA	180 mg	≥ 12	NA	Faster rate of visual recovery compared to untreated eyes
Carelli et al, 2001[16]	1, LHON + myoclonus	19, M	m.11778	Italy	10	270 mg	11	OD 1/50, OS CF 40 cm	at 11 months, no recovery
	one, LHON + MS-like + myoclonus	45, M	m.11778	Italy	3	450 mg 3 months, then 675 mg 3 months	6	OD HM, OS 3/10	at 3 months, OD 1/50, OS 1/20; @ 6 months, 1/20 bil.
Barnils et al, 2007[17]	2, LHON	30, M and 19, F	m.11778	NA	NA	270 mg	12	NA	at 12 months, no recovery
Sabet-Peyman et al, 2012[18]	1, LHON	31, F	m.11778	United States	2.5	900 mg	9	20/200 bil.	at 9 months, 20/25 bil.; near-total resolution of VF abn
Cheng et al, 2014[19]	1, LHON	15, M	m.11778	China	11	900 mg	6	OD 1/60, OS 2/60	at 6 months, no VA change
Eckenweiler et al, 2015[20]	1, LHON	16, M	m.14487	Germany	3.5	900 mg	≥ 12	logMAR OD 0.90; OS 1.36	logMAR OD 0.10; OS 0.16
Catarino et al, 2016[21]	1, LHON	75, F	m.11778 and m.14484	Germany	9	900 mg	≥ 12	NLP bil.	at 9 months, HM bil

Abbreviations: bil., bilateral; F, female; HM, hand motion; LHON, Leber's Hereditary Optic Neuropathy; logMAR, log of the minimum angle of resolution; M, male; MS, multiple sclerosis; NLP, no light perception; VA, visual acuity.

Table 2. Clinical Studies of Idebenone in LHON.

Authors	Name of Study	Clinicaltrials.gov Study ID	Type of Study	Number of Patients Treated/ Total Number	Study Design	Study Results
Klopstock et al, 2011[11]	RHODOS	NCT00747487	Multicenter randomized placebo-controlled double-blinded clinical trial	53/85 (only 3 major LHON mutations)	6 months IDE 900 mg/d versus placebo; 2:1 randomization ratio; VA at baseline and at 6 months	Primary end point (best recovery in VA) not statistical significant; secondary end points trend in favor of IDE
Klopstock et al, 2013[32]	RHODOS-OFU	NCT01421381	Follow-up study after RHODOS	39/60 (only 3 major LHON mutations)	VA in 1 follow-up visit, performed 30 months (median) after last visit in RHODOS	VA stable or slight improvement for patients who benefited from IDE at 6 months
Rudolph et al, 2013[33]	NA	NA	Retrospective analysis of color vision in RHODOS	28/39 (only 3 major LHON mutations)	Color vision in patients who took IDE for 6 months compared to placebo	Significant improvement in tritan color vision compared to placebo; trend for improvement in protan color vision
Carelli et al, 2011[22]	NA	NA	Retrospective open-label study	44/103 (only 3 major LHON mutations)	IDE 270 mg/d initially and later 540-675 mg vs no treatment; VA at each visit, follow-up 5 years	Proportion of patients or eyes with visual recovery higher for IDE group
Klopstock et al, 2016[34]	EAP	NA	EAP	112/112 (any LHON mutation)	IDE 900 mg/d; VA every 3 months	Proportion of patients with visual recovery or stabilization higher for IDE group

Abbreviations: EAP, Expanded access program; IDE, Idebenone; NA, not available/ not applicable; RHODOS, Rescue of Hereditary Optic Disease Outpatient Study; RHODOS-OFU, RHODOS Follow-up Single-visit study; VA, visual acuity.

idebenone, the beneficial effect persisted. The VAs were either stable or had some slight improvement since the 6-month follow-up visit in RHODOS.[32] Five of the 7 patients, who were "off-chart" at baseline and had improved at 6 months, also maintained this improvement in the follow-up visit.[32] In summary, the beneficial effect from the treatment with idebenone 900 mg/d for 6 months continued to be present despite discontinuation of therapy.

The effect of idebenone on color vision was analyzed in a group of 39 patients with LHON enrolled in the RHODOS study, 28 of whom had taken idebenone, at baseline and at 6-month follow-up. The treated group had a significant improvement in tritan color vision when compared to the placebo group and also showed a trend for improvement in protan color vision. This benefit was more evident for patients with discordant VAs at baseline, defined as difference of >0.2 logMAR between the 2 eyes.[33]

In a large open-label retrospective study, 103 patients with LHON carrying a primary mtDNA LHON mutation were followed up for at least 5 years. Forty-four of these patients were treated with idebenone within 1 year after visual loss in the second eye, with a dose of 270 mg/d initially and later 540 to 675 mg. The proportion of patients or eyes with visual recovery, defined as gain of at least 2 lines on Snellen acuity or a change from "off-chart" to "on-chart," was higher for the group treated with idebenone compared to the untreated group.[22]

Taken together, the data from the RHODOS study and from this retrospective study suggest that treatment with idebenone, when started early, increases the probability of visual recovery in LHON and may change the natural history of the disease. Table 2 summarizes these data.

A large multicenter EAP for the treatment of patients with LHON with idebenone, started within the first 12 months after symptom onset, was performed from November 2011 to September 2015, with the objective to further evaluate the efficacy and safety of idebenone in LHON.[34] In 36 participating medical centers worldwide, patients with a recent diagnosis of LHON were enrolled and given idebenone 900 mg/d orally. The safety data confirmed the good tolerability of idebenone. The efficacy data used for comparison were data from the medical literature on natural history in LHON (Table 3) and data from a case record survey (CRS) of a cohort of patients with LHON who had not been treated with idebenone.[42] The results of this EAP are currently being analyzed (manuscript in preparation).

Safety and Tolerability of Idebenone in LHON

Based on the data from the RHODOS clinical trial, from the literature, and the authors' clinical experience, including the EAP of the use of idebenone in LHON (manuscript in preparation), oral idebenone, 300 mg 3 times daily, is usually well

Table 3. Rates of Spontaneous Visual Recovery in LHON.

LHON Primary mtDNA Mutation	Rates of Spontaneous Visual Recovery	Authors
m.11778G>A	4%-23%	Harding et al,[35] Newman et al,[36] Lam et al[37]
m.14484T>C	37%-71%	Johns et al,[38] Mcmillan et al,[39] Spruijt et al[40]
m.3460G>A	15%-25%	Harding et al,[35] Spruijt et al,[40] Johns et al[41]

tolerated and reported side effects are rare. In the RHODOS clinical trial, AEs were reported in 89% for the idebenone group versus 87% in the placebo group.[11] The most frequently reported side effects included nasopharyngitis (25.5%), headache (23.6%), and cough (10.9%), more frequent in the idebenone group than in the placebo group. Dizziness was also reported at a higher incidence in patients receiving idebenone (5.5%) than in the placebo group (0%). Minor gastrointestinal events such as diarrhea (9.1%), nausea/vomiting (7.3%), and abdominal pain (5.5%) did not require discontinuation of treatment. Only 2 patients experienced a severe AE in the RHODOS trial: one patient had a severe headache, considered not related to the treatment, and one had abnormal liver function test results, which occurred after 35 days of treatment and led to discontinuation of treatment and was considered possibly related to the treatment with idebenone.[11]

Discussion

Idebenone is the first drug approved for the treatment of patients with LHON. Treatment with idebenone has been shown to be effective, safe, and well tolerated.

In a 2016 international expert consensus meeting on the use of idebenone in LHON, it was recommended that patients with LHON should be treated, if within 1 year from symptoms affecting the second eye, with idebenone 3 × 300 mg/d, for at least 1 year, and treatment should be continued in responders until a 1-year plateau is reached (Carelli et al. in press).

There are, however, several questions to be answered, which warrant further clinical research.

1. Ideal duration of treatment. A longer treatment period with idebenone may offer additional therapeutic benefit and could lead to a significant recovery of vision, even if patients have established disease and severe vision loss at treatment onset.[32] In a large retrospective study, determinants of better prognosis for visual recovery were early initiation of treatment and a more prolonged treatment course.[22] The mean time to recovery was about 17 months after starting treatment with idebenone.[15,22]
2. Maximum time window from symptom onset to starting treatment with idebenone. The therapy with idebenone is likely to have most impact when started early,[32] since retinal ganglion cell loss is still minimal in the early phase of disease.[22] Currently, there is no robust evidence to support the use of idebenone in patients with long-standing visual loss, and this warrants further research.
3. Leber's Hereditary Optic Neuropathy may become symptomatic in children under 10 years[27] and also in patients with late-onset LHON,[43] who are more prone to multiple comorbidities and polymedication. For both groups of patients, robust data are needed on the use of idebenone. Published data on the treatment of children with LHON with idebenone, or older people, consist mainly on case reports.[12,21]
4. A biomarker for predicting drug response to treatment with idebenone is currently not available and will still require further research.
5. No studies have been performed on the use of idebenone as prophylaxis in asymptomatic mutation carriers of an LHON mutation.
6. Anecdotal data on idebenone use in patients with LHON-plus[16,44,45] have been published but are insufficient to evaluate a possible effect of idebenone on extraocular manifestations. The same applies to the effect of idebenone in patients with LHON + multiple sclerosis (MS)-like disease ("Harding disease").[46] One patient with LHON and MS-like disease was reported by Carelli et al,[16] whose VA improved after 6 months of treatment with idebenone. Regarding the possible effect on new-onset extra-neurological features, a 31-year-old male patient was reported, who had improvement in spastic paraparesis, which had begun 1 week before starting idebenone, and no effect on vision loss, which had begun 7 years before.[13]
7. Mitochondrial DNA copy number and mitochondrial biogenesis have been shown to be associated with incomplete penetrance in LHON, with high mtDNA content being associated with unaffected LHON mutation carriers.[47,48] The mtDNA copy number may be a determinant of conversion to disease in LHON mutation carriers, and influencing mitochondrial biogenesis has been suggested as a potential therapeutic strategy to be further evaluated.[49] It has been recently shown that under specific circumstances, idebenone may have an effect on mitochondrial biogenesis,[50] but further research is warranted to further elucidate this.

Next Steps of Research of Use of Idebenone in LHON

There are currently ongoing phase IV post-authorization research studies to evaluate the long-term efficacy and safety of the treatment with idebenone (Raxone®) in patients with LHON.

The LEROS Study ("External Natural History-Controlled Open-Label Intervention Study to Assess the Efficacy and Safety of Long-term Treatment with Raxone in LHON Patients") is an open-label interventional study of the use of

idebenone for patients with LHON up to 5 years after clinical onset (NCT02774005).

As a control group for the LEROS study, data are being collected in a CRS study ("Historical Case Record Survey of Visual Acuity Data from Patients with LHON"), which is an observational retrospective study of a cohort of patients with LHON who had not been treated with idebenone.

Further, a non-interventional study is ongoing, the PAROS study, "Post-Authorisation Safety Study with Raxone in LHON Patients" (NCT02771379), which aims to evaluate the long-term safety profile and long-term effectiveness of idebenone in the treatment of patients with LHON when used under conditions of routine clinical care.

Supportive Management of Patients With LHON

The treatment of patients with LHON also entails supportive management, including visual aids and rehabilitation, avoidance of environmental risk factors, such as smoking and excess alcohol consumption, and early recognition and treatment of psychiatric comorbidities, such as reactive depression.

Other Treatments for LHON Currently Being Tested in Phase III Clinical Trials

There are currently ongoing phase III clinical trials to assess the efficacy and safety of gene therapy of a single intravitreal injection of a viral vector (adeno-associated virus) transporting the wild-type *ND4* gene, in patients with LHON caused by the mutation m.11778G>A, in the first year after symptom onset. Randomized, double-masked, sham-controlled, pivotal clinical trials are ongoing to evaluate the efficacy of a single intravitreal injection of GS010 (rAAV2-*ND4*) in patients affected by LHON due to the m.11778G>A mutation, in the first 6 months after the first symptom (GS-LHON-CLIN-03A, RESCUE) study (NCT02652767) or between 6 and 12 months after the first symptom (GS-LHON-CLIN-03B, REVERSE) study (NCT02652780).

Declaration of Conflicting Interests

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