Current and Emerging Therapies for Leber Hereditary Optic Neuropathy

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Leber hereditary optic neuropathy (LHON) is the most common primary mitochondrial DNA disorder, presenting typically as a sequential, painless, subacute, optic neuropathy in young males. Despite the very limited therapeutic options in LHON, recent developments involving novel pharmacological agents and emerging gene therapy interventions have shown promising results for improved visual outcomes. A synthetic analogue of coenzyme Q (idebenone) is the most common medical treatment in LHON. In a multicentre, double-blind randomized, placebo-controlled clinical trial (Rescue of Hereditary Optic Disease Outpatient Study [RHODOS]), a dose of 900 mg/day of idebenone for 24 weeks was found to be well tolerated and safe. In a follow-up study (RHODOS-OFU), the visual acuity of 70% of patients enrolled in RHODOS was reassessed 30 months after discontinuation of idebenone. Results from this study suggested that visual acuity continued to improve even after discontinuation of the drug. Gene therapy has recently emerged as a potential treatment for LHON. RESCUE and REVERSE were two phase III clinical trials of viral-mediated gene therapy using lenadogene nolparvovec intravitreal injections in patients with early-stage LHON. Results in these trials have shown long-term safety and bilateral visual acuity improvement after unilateral intravitreal injections at 96 weeks, and sustained visual improvement after 3 years of treatment. The most recent phase III clinical trial in LHON (REFLECT) has shown significant improvement of vision after bilateral intravitreal injections of lenadogene nolparvovec compared with unilateral injections. These promising results suggest that, in the near future, LHON might become the first mitochondrial disorder to benefit from gene therapy.

Keywords

Gene therapy, hereditary optic neuropathy, idebenone, leber hereditary optic neuropathy, mesenchymal stem cell transplantation, mitochondrial diseases, optic atrophy

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Leber hereditary optic neuropathy (LHON) is a mitochondrially inherited optic nerve disease characterized by bilateral (sequential or simultaneous), subacute, painless central vision loss.[1] LHON was first described in 1871 by the German ophthalmologist Theodor Leber.[2] However, it was not until 1988 that the mitochondrial mutation was discovered by Wallace et al.[3]

LHON is the most common hereditary mitochondrial optic neuropathy. Several primary mitochondrial DNA (mtDNA) mutations may affect the respiratory chain complex I function leading to retinal ganglion cell loss in LHON.[4] The prevalence of LHON is 1 in 27,000 in Northeast England and 1 in 45,000 in Europeans. There is a male predominance in LHON, with males being affected in up to 90% of all cases. The typical age of LHON ranges between 15 and 35 years.[5]

Three mitochondrial mutations account for approximately 95% of all LHON cases (m14484T>C, m3460G>A and m11778G>A). Of these, the m11778G>A mutation is the most common.[6] With regards to visual prognosis, studies have shown that up to 25% of patients carrying the m11778G>A and the m3460G>A mutations are more likely to experience spontaneous full recovery of vision, and those with the m14484T<C mutation have overall better prognosis, with a 37–60% likelihood of visual recovery.[7,8]

There has been suggestion of a link between LHON and multiple sclerosis, referred to as 'Harding's disease'.[9] Although this association is most likely due to chance alone, it proposes that optic neuropathy could be immunologically mediated and that susceptibility to multiple sclerosis might be related to mutations in mitochondrial genes. Patients with Harding's disease have an overlap in clinical and molecular features of both disease processes: patients are more likely to be female, present with painless vision loss that persists, and experience more than two visual events.[9,10] Further studies to clarify the association between LHON and multiple sclerosis are warranted.

Interestingly, autosomal gene mutations encoding for mitochondrial proteins can produce non-mtDNA-associated LHON cases. In contrast to mitochondrial LHON, these pedigrees can follow autosomal dominant, autosomal recessive or X-linked inheritance patterns.[7,11] In those with an autosomal recessive pattern of inheritance, the DNAJC30 c.152.A>G;p.(Tyr51Cys) variant

is the most common variant followed by c.610G>T;p.(Glu204) and c230_232del;p(His77del).[12,13] In addition, these patients are more likely to have an earlier onset of the disease but good visual prognosis.[12,13] Patients testing negative for the typical LHON mtDNA mutations should be screened for the whole mtDNA genome.[11]

Although there is no cure for LHON, lifestyle modifications are often recommended, including suppression of tobacco and alcohol use.[14] Several promising treatment options have emerged recently including novel pharmacological agents, such as idebenone (Raxone®; Santhera Pharmaceuticals, Pratteln, Switzerland), mesenchymal stem cell (MSC) treatment and gene therapy. In this article, we review a few of these new therapies for LHON and the results of recent pivotal clinical trials.

Methods

A literature search of PubMed was conducted using the following keywords: Leber hereditary optic neuropathy, LHON, mitochondrial inherited neuropathy, gene therapy, idebenone, mesenchymal stem cell, mitochondrial disease. We aimed to identify English and non-English language articles published between 2016 and 2022. We also considered it important to add four anecdotal references from previous years that are relevant for description of the genetic basis, pathophysiology, demographics and clinical manifestations of LHON.

Treatment

The treatment options for LHON can be divided into mutation-specific therapies and mutation-independent therapies. Among the mutation-specific therapies that have been studied, we can include gene therapy with allotopic expression and gene therapy with mitochondrially targeted adeno-associated virus (AAV). Mutation-independent options are antioxidants (idebenone, coenzyme Q10 and vatiquinone).[15]

Idebenone

Idebenone is a short-chain, hydrosoluble, synthetic analogue of ubiquinone that includes coenzyme Q10 and acts as an electron shuttle between complex I and II of the electron transport chain, thus generating adenosine triphosphate.[14] In 2011, Klopstock et al. reported on a 24-week multicentre, double-blind, randomized, placebo-controlled trial, the Rescue of Hereditary Optic Disease Outpatient Study (RHODOS), in 85 patients with LHON carrying m14484T>C, m3460G>A, m11778G>A or other mtDNA mutations, in an effort to evaluate the efficacy and tolerability of oral idebenone at 900 mg/day versus placebo.[16] The results of RHODOS suggested that although patients on idebenone did not improve their visual acuity compared with those on placebo, there was trend in favour of idebenone upon analysis of visual acuity changes of the best eye and of both eyes after excluding patients carrying the m14484T>C mutation, as this mutation increases the likelihood of spontaneous recovery.[14] Patients with LHON and discordant best corrected visual acuities (BCVAs) at baseline were also more likely to benefit from idebenone.[15] Furthermore, a follow-up study (RHODOS-OFU) was performed years later in 70% of patients originally enrolled in the RHODOS trial.[17] Visual acuity was reassessed 30 months after discontinuation of idebenone. Results demonstrated that visual acuity in patients treated with idebenone, continued to improve even after discontinuation of the drug.[17] In general, the drug was considered safe and well tolerated, and patients treated at early stages had better long-term functional and structural outcomes , as depicted on optical coherence tomography studies of the retinal ganglion cell layer.[18,19] In 2015, idebenone received approval from the European Medicines Agency for the treatment of LHON in both adult and paediatric populations at 900 mg/day in patients presenting with disease duration of not more than 5 years.[19] An open-label phase IV interventional study (LEROS) is currently assessing the long-term efficacy and safety of treatment with idebenone for up to 24 months in patients with chronic disease, with vision loss of 1–5 years since onset.[20]

Furthermore, a study from Catarino et al. described the real-world clinical experience with idebenone in the treatment of LHON.[21] This was an open-label, multicentre, retrospective, non-controlled analysis of long-term visual acuity and safety in patients treated with the standard dose of 900 mg/day. The average treatment duration was 25.6 months. Visual recovery of seven lines in the Early Treatment Diabetic Retinopathy Study (ETDRS) chart was seen in 46% of patients.[21] Overall, patients tolerated the treatment well and most adverse events were classified as minor.[21]

Of note, apart from idebenone, other molecules have been investigated in LHON, including alpha-tocotrienol quinone (EPI-743), which has a powerful antioxidant and neuroprotective effect, as well as elamipretide (MTP-131; topical ophthalmic solution) and naphthoquinones, which are thought to slow the disease progression, allowing better visual prognosis.[22]

Mesenchymal stem cell therapy

In the past few years, MSC therapy has been proposed as a new treatment strategy for LHON.[23] The Stem Cell Ophthalmology Treatment Study (SCOTS), an open-label, non-randomized, efficacy clinical trial conducted by Weiss et al., utilized bone marrow-derived stem cells for treating optic nerve and retinal diseases.[24] Five patients were enrolled in the study and received the treatment. The authors suggested that LHON-affected patients on MSC can experience visual gain of up to 35 letters on the ETDRS, but also improvement of visual field parameters and retinal nerve fibre layer thickness.[24] No serious complications were seen, but more prospective studies are warranted to support these findings.[24,25]

Gene therapy

Considering the unique anatomy and function of the eye, gene therapy has demonstrated a growing potential for the treatment of various ocular diseases. Additionally, the location of the eye makes it an easily accessible route for delivering the genetic material through either intravitreal injection or ocular surgery. Thus far, two vector-based gene replacement treatments have been approved by the United States Food and Drug Administration: voretigene-neparvovec, which is an AAV-2 approved product for Leber congenital amaurosis type 2 (*RPE65* gene mutations), and onasemnogene abeparvovec, which is an AAV-9-based product for treating spinal muscular atrophy (type 1, *SMN1* gene).[25]

In LHON, the gene is delivered to the nucleus of the retinal ganglion cells using allotopic expression, which refers to the functional relocation of mitochondrial genes into the nucleus and then import of the gene-encoded polypeptide from the cytoplasm into the mitochondria.[26] The goal is to produce a fully functional mitochondrial ND4 protein.

Several clinical trials have assessed the safety and efficacy of gene therapy for LHON. RESCUE and REVERSE were randomized, double-blind, sham-controlled, multicentre phase III clinical trials that included patients carrying the m11778G>A mutation.[27] The duration of vision loss was <6 months in the RESCUE trial and >6 months to 1 year in the REVERSE trial. All 39 patients in RESCUE and all 37 patients in REVERSE received an intravitreal injection with lenadogene nolparvovec. Patients in both studies were administered gene therapy in one eye and a sham injection in the other eye. Over the 96-week follow-up period, treated eyes showed mean improvement of BCVA of +15 letters; surprisingly, there was also

an improvement of +13 letters in the sham-treated eyes. The bilateral improvement was attributed to transfer of the viral vector DNA from the treated eye to the fellow non-treated eye. It was assumed that transfer of the DNA was achieved though the optic chiasm.[19,27]

A total of 61 patients who completed REVERSE and RESCUE were enrolled in the RESTORE study and continued a follow-up of 4.3 years after treatment.[28] This prolonged follow-up showed progressive and sustained improvement of BCVA up to 52 months after the onset of vision loss. RESTORE demonstrated that the effect of lenadogene nolparvovec on BCVA and vision-related quality of life seen at 2 years after treatment in RESCUE and RESTORE, was maintained at 3 years after treatment.[28–30]

REVEAL was an open-label, single-centre, dose-escalation study that evaluated the safety and tolerability of lenadogene nolparvovec in patients with LHON for up to 5 years following a single intravitreal injection.[31] This study revealed that gene therapy was well tolerated in terms of immune response, adverse effects and biodissemination. After unilateral injections, a transient mild increase in AAV-2 neutralizing antibodies titres was reported, which was not dose dependent. In terms of biodissemination, this study demonstrated that some tear samples were positive for the promoter up to 1 week after the intravitreal injection, but none were positive after 2 weeks. Blood samples detected mild levels of lenadogene nolparvovec in a few patients, and all urine samples were negative. No unexpected adverse events or severe adverse events occurred during the 5-year follow-up. However, the authors found that anterior chamber inflammation and vitritis were dose limiting and successfully treated with topical steroids.[29,30] Interestingly, the brain biopsy (performed during a tumour excision) of a patient who was included in the REVERSE clinical trial, did not show any evidence of lenadogene nolparvovec, 3 years after intravitreal gene therapy.[31]

REFLECT is the most recent randomized, double-blind, placebo-controlled phase III clinical trial for the treatment of LHON in patients with confirmed m11778G>A mutation.[32] This study aimed to investigate the efficacy and safety of mutation-dependent allotopic treatment using bilateral injections of lenadogene nolparvovec versus unilateral injections. The study included 98 patients, with recent vision loss (less than 1 year) in one or both eyes. Forty-eight patients were randomly allocated to bilateral treatment and 50 to unilateral treatment (second affected eye injected with placebo). Patients who underwent bilateral treatment had a statistically significant improvement in mean BCVA from baseline and at the nadir at 1.5 years, which was maintained at 2 years, compared with those in the group receiving unilateral treatment. Patients with bilateral gene therapy had better average final BCVA (+6 letters) compared with those receiving unilateral treatment. Although BCVA also improved in the placebo-treated eyes, this was consistent with the previous report of contralateral effect of a unilateral injection of lenadogene nolparvovec, reported in RESCUE and REVERSE. Very mild intraocular inflammation was reported in 70.7% of lenadogene nolparvovec-treated eyes versus 10.2% of placebo-treated eyes. Overall, the gene therapy was well tolerated, and no systemic adverse events were reported. Results in this trial suggest a dose effect with bilateral injection of lenadogene nolparvovec.[32,33]

A recent study[34] analysed pooled results from 174 patients with LHON carrying the m11778G>A mutation who were treated with lenadogene nolparvovec in four studies (REVERSE, RESCUE, RESTORE and REFLECT),[19,27,28,32] comparing them with the spontaneous evolution in a control group of 208 matched patients with LHON (from 11 natural history studies). BCVA data were collected from the study inclusion to week 96 after treatment in the REVERSE and RESCUE studies, from study inclusion to year 1.5 after treatment in the REFLECT study, and from week 96 after treatment to the last available observation in the RESTORE study. Natural history patients were adjusted for age and LHON genotype to match those of treated patients. For relevant comparison with treated patients, the authors included patients who matched the inclusion criteria for REVERSE, RESCUE and REFLECT. The authors compared visual outcomes between treated eyes and natural history eyes at 12, 18, 24, 36 and 48 months after vision loss. Natural history patients were slightly younger than treated patients (23.5 years versus 29.0 years; $p<0.01$) and in both cohorts most patients were male (81%). Results showed that eyes treated with lenadogene nolparvovec had better visual acuity at all time points when compared with natural history eyes. In addition, patients with LHON carrying the m11778G>A mutation who were treated with lenadogene nolparvovec, had sustained visual acuity improvement compared with the spontaneous evolution of vision in matched natural history controls. In the treated group, the mean improvement in BCVA was +15 letters versus those in the natural history group. After adjustment of confounding variables such as sex, age of onset, ethnicity and duration of follow-up, the estimated mean improvement in visual acuity versus natural history was +21.5 letters. The treatment effect was long-lasting up to the last visual acuity value.[34]

Another team has recently reported the results of a phase I clinical trial, performed in a single institution, which aimed to assess the safety of gene therapy in patients with m11778G>A LHON mutation, by measuring visual acuity and assessing adverse events.[35] A total of 28 patients were included: 11 had bilateral vision loss >1 year, nine had bilateral vision loss <1 year and eight had unilateral vision loss.[35] A unilateral intravitreal injection of lenadogene nolparvovec was administered in the worse eye of patients with bilateral vision loss and in the better eye of patients with unilateral vision loss, and followed for a mean of 2 years. BCVA was compared with a prospective natural history cohort study.[36] Results of the study showed that uveitis was seen in 29% of patients, and was the only adverse effect that was dose related. Similarly to the findings in RESCUE and REVERSE, this study found that improvement of at least 15 letters in BCVA occurred in both treated and fellow eyes. However, it is very important to note that all patients with unilateral vision loss, in whom visual acuity was 20/40 or better, lost at least 15 letters during the first year after receiving gene therapy. Results in this study were limited by the small number of included patients, absence of randomization and no placebo-controlled arm, which will be necessary in the future to discriminate true therapeutic effect from the natural history of the disease.[37]

Discussion

LHON is the most common maternally inherited optic neuropathy. Patients with LHON develop permanent bilateral central vision loss. Although a small proportion of patients recover some vision spontaneously (mainly if associated with the m14484T>C mutation), most patients develop significant permanent bilateral vision loss.

In the USA, current treatment options remain limited. Thus, patients are mainly treated conservatively, with avoidance of environmental toxins, alcohol and tobacco use. In Europe, however, idebenone is already approved and available for the treatment of children and adults. Nevertheless, ongoing clinical trials are still in the process of determining the safety profile and long-term efficacy of this therapy.[20]

Attempts to provide efficacious treatment options for patients with LHON have been made with MSC therapy. The efficacy and safety of

this treatment are still under investigation and studies currently lack sufficient evidence and statistical power; furthermore, although no serious complications have been reported in previous trials, prospective studies are warranted to support these findings.

As technology evolves, emerging therapies targeting the defective gene in the mitochondria have been developed. Gene therapy trials in LHON, with lenadogene nolparvovec, have reported clinically significant visual benefits compared with the natural history of the disease. This promising treatment option is still under investigation and has not yet been approved for the treatment of LHON. However, favourable results reported by several ongoing and previous clinical trials are encouraging, and this could make LHON the first mitochondrial disorder to be treated with gene therapy.

Conclusion

Various emergent therapies are currently being assessed in LHON. Antioxidants such as idebenone might be beneficial when offered at early stages; gene therapy using lenadogene nolparvovec seems to provide some evidence of short- and long-term benefit in visual acuity, at least in patients carrying the m11778G>A mutation. Although the favourable results of gene therapy in LHON are only mild, we are still at an early stage; there is reasonable hope that this treatment may become an available option in the near future. ❑

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