Clinical trials in Leber hereditary optic neuropathy: outcomes and opportunities

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Purpose of review
Leber hereditary optic neuropathy (LHON) is a mitochondrial DNA disease characterised by sequential bilateral vision loss due to loss of retinal ganglion cells. The purpose of this review is to provide an update on the results of recent clinical trials for LHON, focusing on studies of idebenone and lenadogene nolparvovec gene therapy.

Recent findings
Evidence from three clinical studies (RHODOS, RHODOS-OFU, and LEROS) suggest that idebenone should be started early and continued for at least 24 months. Treatment effect varies according to the stage of LHON and the underlying mutation. Favourable outcomes are associated with the m.11778G>A mutation and chronic eyes with the m.14484T>C mutation. Caution should be taken in subacute/dynamic eyes with the m.3460G>A mutation, due to possible clinical worsening with idebenone. Compared to eyes from an external natural history cohort, pooled data from four clinical studies (RESCUE, REVERSE, RESTORE and REFLECT) show that a single intravitreal injection of lenadogene nolparvovec can result in sustained bilateral visual improvement in m.11778G>A LHON patients aged ≥15 years when treated within 1 year of onset. Although the treatment effect is modest, the final visual acuity of treated patients (~1.2 logMAR) significantly differs from the published natural history of LHON and the treatment benefit is more pronounced than the effect of idebenone alone in patients with the m.11778G>A mutation.

Summary
There is increasing evidence for the potential therapeutic benefit of idebenone and lenadogene nolparvovec gene therapy.

Keywords
allotopic expression, clinical trial, gene therapy, idebenone, Leber hereditary optic neuropathy

INTRODUCTION

Leber hereditary optic neuropathy (LHON) is a rare, maternally inherited mitochondrial disease associated with severe sequential bilateral vision loss due to loss of retinal ganglion cells (RGC) [1▪]. Globally, 90% of cases of LHON are caused by three mutations in mitochondrial DNA (mtDNA): m.3460G>A in *MT-ND1*, m.11778G>A in *MT-ND4*, and m.14484T>C in *MT-ND6*. Most individuals carrying a causative-mutation remain asymptomatic, with 4–32% of female patients and 18–51% of male patients at risk of experiencing vision loss [1▪,2], although recent studies have reported expression rates at the lower levels of these ranges. Age of onset in most cases of LHON occur between 15 and 35 years of age, with 90% occurring by the age of 50 years.

The risk of developing vision loss is related to genetic and environmental factors [1▪]. The three most common mutations of LHON involve genes encoding subunits of complex I, the first enzyme of the mitochondrial respiratory chain. Dysfunctional complex I results in defective oxidative phosphorylation and increased production of reactive oxygen species [3,4]. Normal cellular functions are disrupted leading to increased mitochondrial genome instability, disrupted Ca^{2+} homeostasis, and release of factors signalling cellular apoptosis. Environmental

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Curr Opin Neurol 2025, 38:79–86
DOI:10.1097/WCO.0000000000001343

KEY POINTS

- The clinical presentation of Leber hereditary optic neuropathy (LHON) can be classified into three stages from time of onset of vision loss: subacute (0–6 months), dynamic (6–12 months) and chronic (>12 months).
- Best corrected visual acuity has been the primary outcome measure used in all clinical trials for LHON, with a range of predefined trial endpoints including a 0.3 logMAR improvement or responder rates by outcome criteria.
- The results of clinical trials for idebenone suggest that idebenone should be started early and continued for at least 24 months, especially in patients with the m.11778G>A mutation.
- The use of idebenone in subacute or dynamic LHON due to the m.3460G>A mutation may be associated with clinical worsening.
- A single intravitreal injection of lenadogene nolparvovec delivered in the first 12 months of vision loss can result in sustained bilateral visual improvement in patients with the m.11778G>A mutation aged at least 15 years.

metabolic stressors such as smoking also alter the balance between mitochondrial biogenesis and mitochondrial selective autophagy, and are considered potential triggers of conversion to symptomatic disease [4,5].

Identification of the mitochondrial basis of LHON and the mechanisms leading to vision loss has accelerated the therapeutic delivery pipeline [6▪]. Very few treatments for LHON have reached the late stages of drug development and even fewer are available in clinical practice. The aim of this review is to provide an update on the results of recent clinical trials for LHON. To date, only idebenone and gene therapy have been studied at the level of multiple large-scale clinical trials. We firstly summarise the clinical presentation of LHON, outline trial measures and endpoints, and then discuss the results of recent trials.

CLINICAL PRESENTATION OF LEBER HEREDITARY OPTIC NEUROPATHY

The presentation of LHON can be classified into three stages from the time of onset of vision loss [7]. In the subacute stage (0–6 months after onset), affected individuals experience painless vision loss in one or both eyes, typically beginning with blurring or clouding of vision centrally, accompanied by impaired colour vision. Visual field defects are typically central or caecocentral. On funduscopic examination, the optic disc may appear hyperemic, with pseudo-edema and peripapillary telangiectasias. Visual acuity may be mildly reduced initially but declines severely to 6/60 or less, reaching a nadir three to six months after onset [8,9]. In 50–75% of patients, the second eye is affected weeks to months after the first eye.

In the dynamic stage (6–12 months after onset), visual acuity tends to stabilise. In most cases, visual acuity is worse than 3/60, fulfilling the criteria for legal blindness in most countries. Vision may spontaneously improve at this stage. However, this is variable and depends on the underlying mtDNA mutation and age of onset, with the m.14484T>C mutation and childhood onset (≤12 years) portending a better visual prognosis [10,11]. The m.11778G>A mutation, accounting for 70% of cases, is associated with a poor visual prognosis and a low probability of spontaneous improvement [8]. Although this improvement is frequently described as "recovery" in the literature, this is a misnomer. Most patients with LHON remain significantly visually impaired with visual acuity of 6/60 or less and poor quality of life [12,13]. By 12 months after onset of vision loss (chronic stage), clinical measures of visual function tend to plateau.

TRIAL MEASURES AND ENDPOINTS

Clinical trials for LHON have used the Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) as the primary outcome measure. Other measures such as visual fields, optical coherence tomography, visual electrophysiology, and assessment of vision-related quality of life have also been conducted. In this review we will focus on BCVA.

Conforming to FDA guidance regarding acceptable primary endpoints for clinical trials [14], the primary endpoint for gene therapy studies has been a 3-line improvement in BCVA (equivalent to –0.3 Logarithm of minimum angle of resolution (logMAR) or +15 ETDRS letters). Efficacy has also been evaluated by different outcome criteria, especially in clinical trials of idebenone, specifically the rate of participants experiencing a clinically relevant benefit (CRB), clinically relevant stabilisation (CRS), clinically relevant recovery (CRR), or clinically relevant worsening (CRW) of BCVA (Table 1).

When analysing longitudinal changes in BCVA, the rate of spontaneous improvement as part of the natural history of LHON needs to be considered. In the largest prospective longitudinal study of the natural history of LHON, 44 affected individuals carrying the m.11778G>A mutation were evaluated every six months for up to 36 months [9]. Excluding

Table 1. Definitions of responder outcomes used in clinical trials of Leber hereditary optic neuropathy

Outcome	Definition
Clinically relevant benefit (CRB)	Composite measure of all eyes attaining CRS or CRR
Clinically relevant stabilisation (CRS)	Maintenance of BCVA <1.0 logMAR at baseline until follow-up
Clinically relevant recovery (CRR)	Improvement of BCVA from off-chart at baseline to on-chart at follow-up, with at least 5 ETDRS letters read; or if BCVA was on-chart at baseline, improvement by at least 10 ETDRS letters (–0.2 logMAR) at follow-up
Clinically relevant worsening (CRW)	Worsening of BCVA from on-chart at baseline to off-chart at follow-up; or worsening of BCVA by at least 10 ETDRS letters (+0.2 logMAR) at follow-up
Off-chart vision	Inability to read any letters of the ETDRS chart, equivalent to >1.68 logMAR
On-chart vision	The ability to read at least a single ETDRS letter, equivalent to ≤1.6 logMAR

BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; logMAR, Logarithm of minimum angle of resolution.

participants aged < 15 years, the rate of improvement, defined as an improvement of +15 ETDRS letters, was 11% (8/72) of eyes and 14% (5/36) of participants. A systematic review and meta-analysis, which combined visual function information from 695 patients with the m.11778G>A mutation from 15 studies, also found that meaningful visual recovery (≥0.3 logMAR improvement) occurred in 11.3% (23/204) of patients aged ≥15 years [8].

IDEBENONE

Idebenone is a synthetic hydrosoluble analogue of co-enzyme Q10 that shuttles electrons in the mitochondrial respiratory chain directly to complex III, thereby bypassing complex I and II [15]. In preclinical studies, idebenone partially restores cellular ATP levels under conditions of impaired complex I function [16]. Idebenone is the only licensed treatment for LHON, having been approved by the European Medicines Agency (EMA) in 2015 based on cumulative evidence from the clinical trial RHODOS (Rescue of Hereditary Optic Disease Outpatient Study) [17], its extension study RHODOS-OFU (RHODOS observational follow-up study) [18], and real-world data from an industry-sponsored expanded access programme [19]. A separate clinical trial, LEROS (Study to Assess the Efficacy and Safety of Raxone in LHON Patients) [20▪▪], was published in March 2024.

RHODOS and RHODOS-OFU

RHODOS was a multicentre double-blind, randomised, placebo-controlled trial [17]. Eighty-five LHON participants within 5 years of vision loss and harbouring known mtDNA mutations were randomised to receive idebenone (300 mg three times a day) or placebo for 24 weeks. At week 24, idebenone was associated with better BCVA than placebo in the intention-to-treat population. However, the primary endpoint of difference in best recovery in BCVA did not reach statistical significance (–0.064 logMAR; $P = 0.291$).

In RHODOS-OFU, participants of RHODOS were assessed a median of 30 months after they had discontinued idebenone and placebo [18]. The mean difference in best recovery of BCVA between treatment groups from baseline of RHODOS to the RHODOS–OFU visit was −0.158 logMAR (+7 ETDRS letters, $P = 0.086$), in favour of idebenone. Most of the improvement in the idebenone group was observed between week 24 of RHODOS and RHODOS-OFU, whereas the trajectory in BCVA of the placebo group did not change in the same period. Improvement in BCVA was primarily confined to patients who were treated within a year of onset of vision loss.

LEROS

Following RHODOS, a real-world study using data from an expanded access programme showed the potential benefit of maintaining idebenone therapy for 24 months in patients with subacute or dynamic LHON [19]. To confirm these findings, LEROS, an open-label, natural history-controlled study, was developed with guidance from the EMA to assess the safety and efficacy of idebenone over a treatment period of 24 months [20▪▪]. A total of 199 patients with one of the three common LHON mutations commenced idebenone within five years of symptom onset. The primary endpoint was the proportion of eyes experiencing a CRB of BCVA.

Overall, LEROS met its primary endpoint. In subacute/dynamic eyes, the rate of CRB following 12 months of treatment was 42.3% in treated eyes compared to 20.7% of control eyes from an external natural history cohort matched for duration of vision loss ($P = 0.002$). The treatment effect was

primarily driven by CRS; after 12 months of treatment, subacute/dynamic eyes improved from 1.29 logMAR at baseline to 1.20 logMAR, whereas control eyes worsened from 1.26 logMAR to 1.32 logMAR (relative improvement of –0.12 logMAR or +6 ETDRS letters in favour of idebenone; $P = 0.03$). After 24 months of treatment, CRB was maintained in the treatment group 52.9% vs. 36.0% ($P = 0.003$). However, no significant difference in the magnitude of improvement in BCVA between the two groups was detected.

In chronic LHON, the rate of CRB after 12 and 24 months of treatment was also significantly higher in idebenone-treated eyes compared to control eyes (50.3% vs. 38.6% eyes at 12 months, $P = 0.009$; and 49.1% vs. 37.6% eyes at 24 months, $P = 0.02$). In contrast to subacute/dynamic LHON, CRB was primarily driven by CRR in chronic LHON; after 12 months of treatment, chronic LHON eyes improved from 1.16 logMAR at baseline to 1.11 logMAR. Control eyes worsened from 1.11 logMAR to 1.21 logMAR at 12 months (relative improvement of –0.10 logMAR or +5 ETDRS letters in favour of idebenone, $P = 0.004$). Chronic eyes treated for 24 months also improved from 1.20 logMAR at baseline to 1.07 logMAR, whereas control eyes worsened from 1.18 logMAR to 1.24 logMAR (relative improvement of –0.17 logMAR or +8 ETDRS letters in favour of idebenone, $P < 0.001$).

Sub-analyses of results by mtDNA mutation, revealed that m.11778G>A eyes treated with idebenone exhibited a significant improvement compared to control eyes at all time points and stages of disease. Subacute/dynamic m.11778G>A eyes treated with idebenone experienced a relative improvement of +16 ETDRS letters compared to control eyes at 12 and 24 months, while chronic eyes treated with idebenone experienced a relative improvement of +5 ETDRS letters compared to control eyes at both time points. In m.3460G>A eyes treated with idebenone, a significant worsening of subacute/dynamic eyes after 24 months of treatment was observed (relative worsening of 0.53 logMAR or –26 ETDRS letters; $P = 0.001$), with most subacute/dynamic eyes worsening from on- to off-chart. In m.14484T>C eyes treated with idebenone, a significant improvement in chronic eyes after 24 months treatment was observed (relative improvement of –0.52 logMAR or +26 ETDRS letters in favour of idebenone; $P < 0.001$).

Idebenone – summary and recommendations

Taken together, the results of RHODOS, RHODOS-OFU, LEROS and real-world studies (not discussed in this review) provide evidence for the safety and potential therapeutic benefit of idebenone in LHON, particularly for those with the m.11778G>A mutation. The drug is well tolerated, with mostly mild adverse effects including headache, cold symptoms, diarrhoea, and nausea [19,20▪▪].

Idebenone should be started early [7]. The treatment effect is primarily a CRS of BCVA in the first 12 months, with an increased likelihood of CRR with longer treatment duration from 12 to 24 months [20▪▪]. In m.14484T>C eyes, idebenone is associated with a favourable outcome, particularly for chronic eyes treated for 24 months. Due to the small sample size, the rates of CRW in subacute/dynamic m.3460G>A eyes treated with idebenone should be interpreted with caution. Subacute/dynamic patients with the m.3460G>A mutation should be advised about the possible risk of BCVA worsening with idebenone, which may be related to polymorphisms in the *NQO1* gene encoding NAD(P)H oxidoreductase 1 [15].

GENE THERAPY

Due to the relatively impervious double-membrane structure of the mitochondria, conventional viral vectors used in gene therapy are as of yet unable to transfer exogenous genes into the mitochondrial genome. Current approaches to gene therapy in LHON utilise the technique of allotopic expression, which involves expression of the mitochondrial gene in the cell nucleus and import of the gene product into the mitochondria with the aid of a mitochondrial targeting sequence (Fig. 1). Gene therapy products for the m.11778G>A mutation have been developed by several groups [3], with the first human trial of gene therapy conducted in 2011 in Wuhan, China [21]. We will focus on trials for lenadogene nolparvovec, also known as GS010 or LUMEVOQ, the only gene therapy product for the m.11778G>A mutation that has been investigated as part of four phase 3 studies with peer-reviewed published results (RESCUE, REVERSE, RESTORE, and REFLECT).

RESCUE, REVERSE and RESTORE

RESCUE (NCT02652767) [22] and REVERSE (NCT02652780) [23] were randomised, double-masked, sham-controlled clinical trials evaluating the efficacy of a single intravitreal injection of lenadogene nolparvovec (9×10^{10} viral genomes/eye) in subacute (RESCUE) or dynamic (REVERSE) LHON patients with the m.11778G>A mutation. Participants were followed for 96 weeks after treatment, and then invited to participate in an extension study

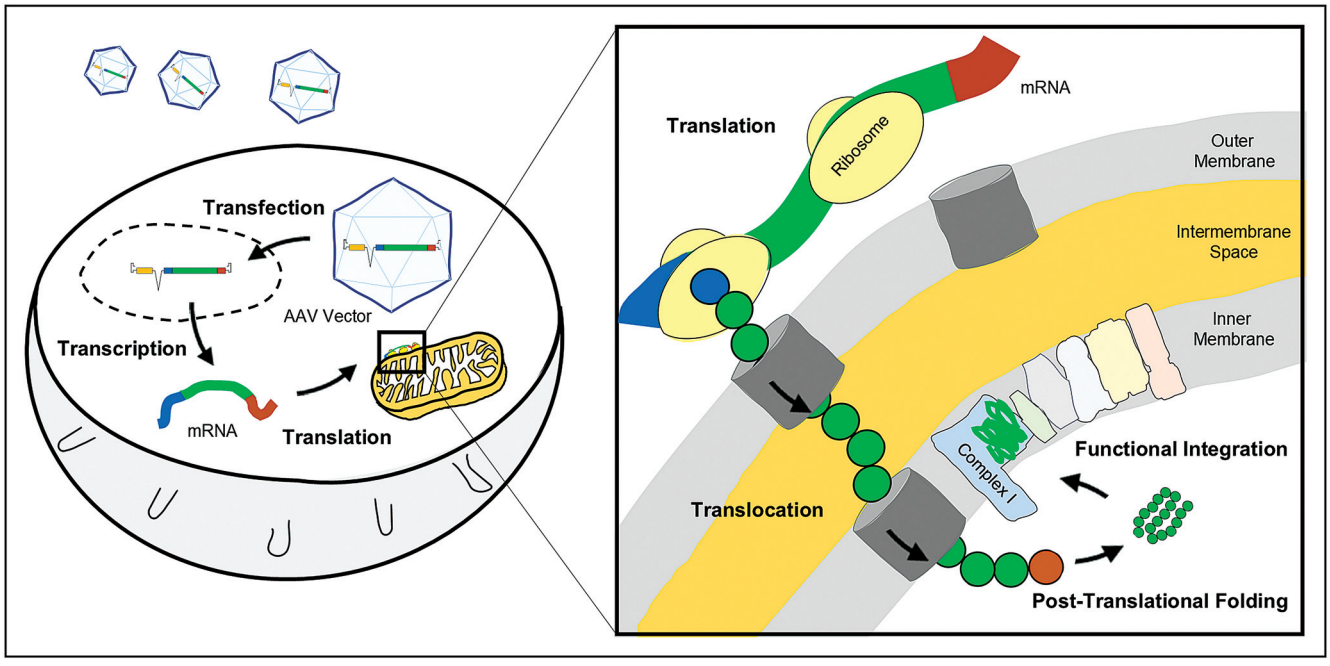

FIGURE 1. Gene therapy for Leber hereditary optic neuropathy (LHON) using the technique of allotopic expression. The gene therapy vector contains the replacement mitochondrial *ND4* gene modified according to the nuclear code. This nuclear-encoded version of *ND4* is fused to two mitochondrial targeting sequences (MTS) and a promoter is inserted for more efficient expression. The gene therapy vector is packaged into an adeno-associated virus (AAV), usually serotype 2, which is delivered to the retinal ganglion cells by intravitreal injection. The AAV transfects the retinal ganglion cells, delivering the gene therapy product into the nucleus, where it remains in an episomal state. From here, the inserted gene sequence undergoes transcription to messenger RNA (mRNA) and, with the aid of the MTS, it is directed to mitochondrial ribosomes on the external surface of the mitochondrial outer membrane, where gene translation occurs. As it is being synthesised, the newly translated ND4 protein is translocated across the two mitochondrial membranes into the mitochondrial matrix aided by the MTS. Finally, the imported ND4 subunit undergoes posttranslational folding before being integrated within complex I, restoring its function.

for a follow-up of five years after treatment (RESTORE; NCT03406104) [24]. Initially designed so that each participant would be their own control with one treated eye and one sham-treated eye, RESCUE and REVERSE did not meet their primary endpoint, a clinically significant difference of 0.3 logMAR between treated and sham-treated eyes at 48 weeks.

Participants in both studies experienced bilateral visual improvement. The difference of change in BCVA from baseline to week 48 between treated and sham-treated eyes was –0.01 logMAR ($P = .89$) and –0.007 logMAR ($P = .89$) in RESCUE and REVERSE, respectively [22,23]. In postmortem ocular analysis of two RESCUE participants, successful gene transfection of RGCs was found in both eyes [25]. The underlying mechanisms were investigated in nonhuman primates and hypothesised to be the result of transneuronal spread by synaptic transfer mechanisms via preserved RGC axons in the optic nerve and chiasm [23].

REFLECT

REFLECT (NCT03293524) [26▪▪] was a randomised, double-masked, placebo-controlled clinical trial evaluating the efficacy and safety of bilateral intravitreal injection of lenadogene nolparvovec in subacute/dynamic LHON patients with the m.11778G>A mutation. Ninety-eight participants received lenadogene nolparvovec in their first affected eye and were randomised to receive either lenadogene nolparvovec or placebo in their second affected eye. The primary endpoint, the difference in change from baseline of BCVA in the treated vs. placebo-treated second affected eye at 1.5 years, was not met due to bilateral improvement of BCVA in both groups (mean difference in change of BCVA –0.05 logMAR, $P = 0.61$).

Lenadogene nolparvovec gene therapy vs. natural history cohort

The results of the four phase 3 studies were pooled and compared to a natural history cohort consisting

of 208 matched patients from 11 natural history studies [27▪▪]. A locally estimated scatterplot smoothing (LOESS), nonparametric, local regression model was used to explore evolution of BCVA in treated and natural history eyes (Fig. 2), with each patient's eyes considered independently. Eyes receiving sham- or placebo-treated were considered exposed to gene therapy across all studies and were pooled in the treated group for analysis.

Treated eyes had better BCVA than natural history eyes at all time points, with the largest mean difference observed at 48 months after vision loss. At month 48, mean BCVA for treated eyes and natural history eyes were 1.23 logMAR [95% confidence

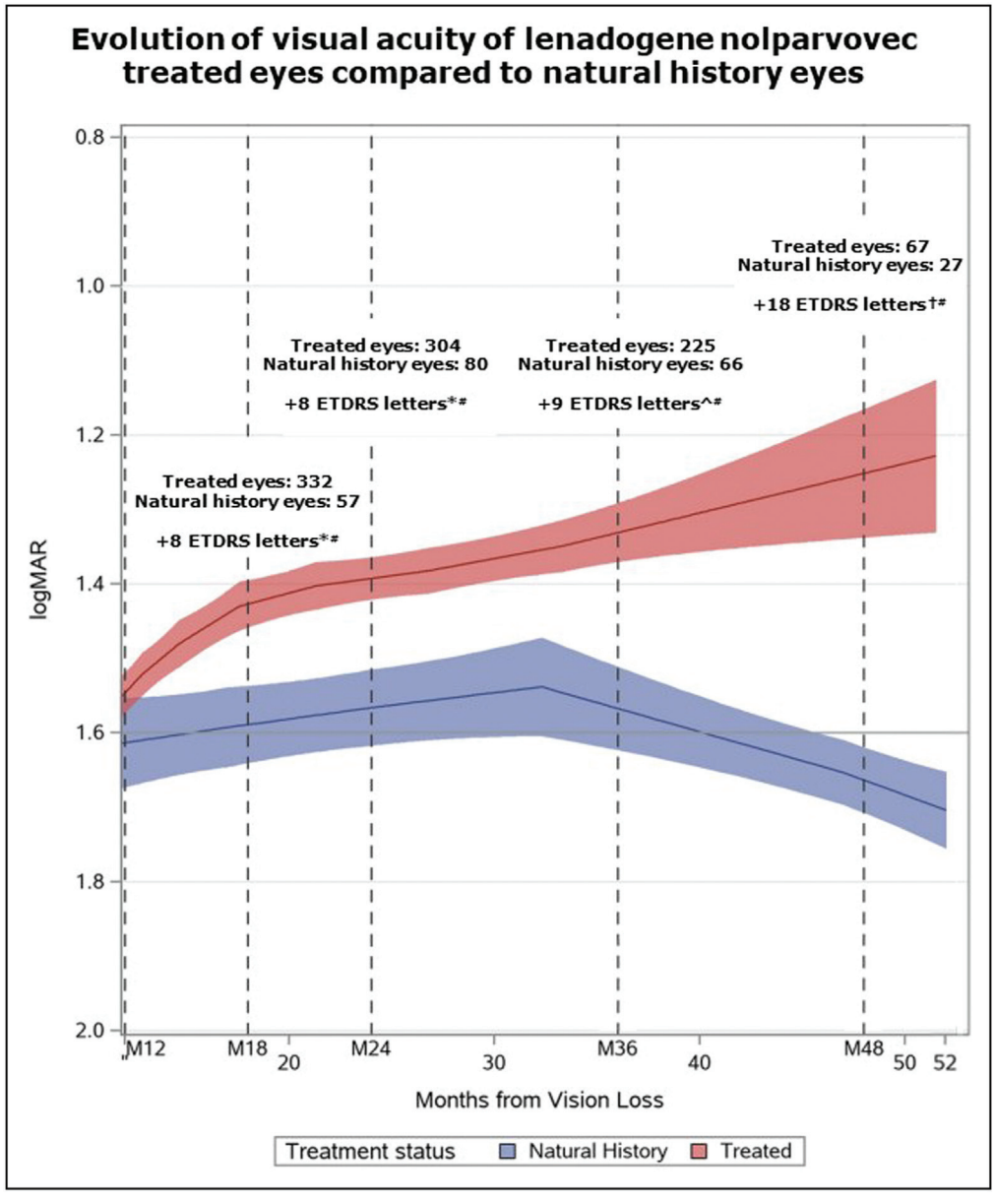

FIGURE 2. Evolution of visual acuity of lenadogene nolparvovec-treated eyes compared to natural history eyes. The evolution of visual acuities from 12 months after onset of vision loss for lenadogene nolparvovec-treated eyes ($n = 348$) and natural history eyes ($n = 408$) estimated by locally estimated scatterplot smoothing (LOESS) regression (solid line) with 95% confidence interval around the fitted curve (shaded area). Visual acuity of natural history eyes plateaued around 1.6 logMAR up to 36 months after vision loss, followed by a slow decline off-chart. Lenadogene nolparvovec-treated eyes showed a progressive, continuous sustained improvement between 12 and 52 months after vision loss, with BCVA remaining on-chart for the duration of follow-up. Mean differences in visual acuity at months 18, 24, 36 and 48 were estimated by a mixed-model analysis of covariance (ANCOVA) demonstrating a significant difference in favour of lenadogene nolparvovec-treated eyes [$*P = 0.03$; $^P = 0.02$; $†P < 0.01$; and # Kruskal–Wallis test, $P < 0.01$). Adapted from Carelli *et al.* [27▪▪], with permission.

interval (CI): 1.13, 1.34] and 1.59 logMAR (95% CI: 1.41, 1.76), respectively (mean difference: –0.352; 95% CI: –0.554, –0.149; $P < .01$). Almost 90% (60/67) of treated eyes were on-chart (logMAR $\leq$ 1.6) compared to 48.1% (13/27) of natural history eyes at month 48 ($P < 0.01$). At last follow-up (up to 3.9 years posttreatment), the mean effect estimate adjusted for gender, ethnicity, age at onset of vision loss, and duration of follow-up, was –0.43 logMAR (+21.5 ETDRS letters) ($P < 0.0001$). Most treated eyes were on-chart (76.1%, 265/348) at last observation, compared to natural history eyes (44.4%, 181/408) ($P < 0.01$). Bilateral treatment with lenadogene nolparvovec was associated with a larger treatment effect, including more eyes on-chart at last observation: 79.2% bilaterally treated patients, 67.0% of unilaterally treated patients, and 44.4% of natural history patients ($P < 0.01$).

Lenadogene nolparvovec gene therapy – summary and recommendations

The results of the phase 3 studies show that a single intravitreal injection of lenadogene nolparvovec can result in sustained bilateral visual improvement. The results of the phase 3 studies only provide evidence for treating individuals with subacute or dynamic LHON due to the m.11778G>A mutation who are at least 15 years old. The best timing of treatment within the first year following disease onset remains unclear, although the better outcomes in REVERSE suggest counterintuitively that delay in administration of gene therapy to after at least 6 months from onset is preferable. Further studies are required to determine whether lenadogene nolparvovec is also beneficial for chronic LHON.

CONCLUSION

Considerable progress has been made to advance the therapeutic pipeline for LHON, with idebenone and lenadogene nolparvovec gene therapy the focus of several later phase clinical studies in recent years. The treatment effect of idebenone and lenadogene nolparvovec is modest, with final mean BCVA in the range of ~1.2 logMAR. However, this significantly differs from the published natural history of LHON in which spontaneous improvement occurs in <20%. Gene therapy could be transformative for people with the m.11778G>A mutation within 12 months of vision loss. Patients with chronic LHON and those with other mtDNA mutations represent a significant unmet need. Evidence from clinical studies of idebenone indicate that these patients may stand to benefit from extended idebenone therapy (24 months). Although idebenone is considered a 'mutation-independent' treatment, the treatment effect is not consistent across all mtDNA mutations, with possible worsening associated with early treatment of the m.3460G>A mutation as highlighted in the LEROS study.

Acknowledgements

B.S.C. is supported by a Senior Clinical Research Fellowship (2433 SCF) from the New Zealand Neurological Foundation.

Financial support and sponsorship

N.J.N. is a consultant for GenSight Biologics, Santhera/Chiesi, Neurophth and Stoke Therapeutics. No funding was received for this article.

Conflicts of interest

There are no conflicts of interest.

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This is the largest longitudinal study comparing visual outcomes in patients receiving lenadogene nolparvovec (pooled from four phase 3 studies) versus an external matched natural history cohort of individuals with LHON due to the m.11778G>A mutation.