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Review article

Meta-analysis of treatment outcomes for patients with m.11778G>A *MT-ND4* Leber hereditary optic neuropathy

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ABSTRACT

Our aim was to assess the visual outcomes of patients with Leber hereditary optic neuropathy (LHON) harboring the m.11778G>A *MT-ND4* mutation who had no treatment (natural history) or received idebenone or lenadogene nolparvovec. Efficacy outcomes included clinically relevant recovery (CRR) from nadir and final best-corrected visual acuity (BCVA). For the natural history and idebenone groups, we performed a systematic review of the literature and available clinical/regulatory reports. For the lenadogene nolparvovec group, all data from phase 3 studies were included. The overall effect and its 95 % confidence interval (CI) were estimated using a random effects model. For each meta-analysis, patients had a mean age of approximately 30 years at vision loss and were mostly (≥78 %) men. The CRR from nadir [95 % CI] at eye level was 17 % [7 %; 30 %] (n=316 eyes), 31 % [24 %; 40 %] (n=313) and 59 % [54 %; 64 %] (n=348) in untreated, idebenone-treated and lenadogene nolparvovec-treated patients, respectively. This gradient of efficacy was also observed with CRR at the patient level and final BCVA. There was a gradient of efficacy in all assessed visual outcomes, more marked for CRR than for final BCVA, with lenadogene nolparvovec gene therapy superior to idebenone treatment, and both superior to the natural history of the disease.

1. Introduction

Leber hereditary optic neuropathy (LHON) is a blinding maternally-inherited mitochondrial disease that in 90 % of cases results from 1 of 3 mitochondrial DNA (mtDNA) mutations, m.3460G>A in *MT-ND1*, m.11778G>A in *MT-ND4* or m.14484T>C in *MT-ND6*.[6,58] The mitochondrial proteins ND1, ND4 and ND6 are subunits of complex I of the mitochondrial respiratory chain and their alteration by their respective missense mutation leads to alterations in ATP synthesis and increased production of reactive oxygen species, ultimately causing loss of the

Abbreviations: AAV2, adeno-associated virus serotype 2; BCVA, best-corrected visual acuity; CI, confidence interval; CRR, clinically relevant recovery; LHON, Leber hereditary optic neuropathy; LogMAR, logarithm of the minimum angle of resolution; MtDNA, mitochondrial DNA; SD, standard deviation.

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particularly vulnerable retinal ganglion cells.[61] Clinically, LHON typically manifests as a subacute, painless loss of central vision with sequential or coincident bilateral involvement. LHON affects both genders of all ages, but occurs most often in young male adults who are otherwise healthy.[6,61] Spontaneous visual recovery is rare, but possible, with mitochondrial genotype and age at onset of vision loss being 2 key prognostic factors for visual outcome.[60] Patients harboring the m.11778G>A mutation, the most frequent of the 3 common mutations, have a poor rate of spontaneous recovery (reported between 14 % and 20 %),[33,55,60] and patients aged 12 years or less at the onset of the disease are more likely to recover than older patients.[1,28,60] The rate of spontaneous recovery in *MT-ND4* patients at least 15 years of age at the time of vision loss is poor and usually partial and has been estimated at 11 %.[33] Therefore, in most cases, LHON *MT-ND4* patients experience a severe and chronic reduction in visual acuity in both eyes, which seriously affects their quality of life.[9,24]

Treatment options have been limited, mostly focusing on avoiding potential precipitating factors such as tobacco and prescribing low vision aids. Currently, the only approved treatment for LHON is idebenone (Raxone, Chiesi Farmaceutici S.p.A, Italy), a synthetic analog of coenzyme Q_{10} with antioxidant properties. Based on the results of the prospective, double-masked, placebo-controlled, randomized RHODOS study, evaluating the efficacy and safety of a 6-month regimen of 900 mg/day of idebenone in 85 patients with LHON from all 3 common mtDNA mutations within 5 years after disease onset,[25] idebenone was approved to treat LHON in adolescents and adults in the European Union and in Israel;[63] however, there has yet to be approval of idebenone by medicine agencies in other countries, including the United States.

Another approach to treat LHON is to use gene therapy to compensate for the mitochondrial defect. To date, only intravitreal gene therapy to restore the activity of the dysfunctional ND4 protein caused by the severe and most common causative m.11778G>A *MT-ND4* mutation has been performed, and only in a few centers around the world.[10,20] Designed using the allotopic expression technique,[19] lenadogene nolparvovec is a novel, not yet approved, gene therapy product composed of a recombinant adeno-associated virus serotype 2 (AAV2) vector and a wild-type *ND4* transgene flagged with a mitochondrial transport sequence. Intravitreal injection of lenadogene nolparvovec allows transfer of the wild-type *MT-ND4* gene into retinal ganglion cells, which then transcribe ND4 mRNA in the nucleus. The mitochondrial targeting sequence enables delivery of the ND4 protein translated from mRNA by ribosomes on the surface of mitochondria, leading to wild-type ND4 import and restoration of mitochondrial function.[10] Since 2014, the clinical development program of lenadogene nolparvovec has been ongoing and includes one phase 1/2B study (REVEAL, completed[51]) and 3 randomized phase 3 studies (RESCUE, completed[36]; REVERSE, completed[59]; REFLECT, ongoing[37]) with a long-term follow-up phase 3 study for RESCUE and REVERSE, named RESTORE (completed)[2].

In all these gene therapy studies, administration of a single unilateral injection of lenadogene nolparvovec resulted in a reproducible increase in visual acuity in both eyes beyond what would be expected from the natural history of the disease. This unexpected contralateral effect of gene therapy raises difficulties in interpreting the real effect of treatment in the absence of a control arm of untreated patients in clinical studies. Therefore, an indirect comparison approach between visual acuity data from all phase 3 studies of lenadogene nolparvovec and an external control group of untreated (*i.e.*, natural history) patients was performed.[7,35] This analysis demonstrated that patients treated with lenadogene nolparvovec showed a clinically significant and consistent improvement in their best-corrected visual acuity (BCVA) across all 3 efficacy studies, achieving a degree of response that has not been demonstrated in any of the natural history studies of LHON.[7] With 3 phase 3 studies and approval for use in early access programs, lenadogene nolparvovec is a promising new therapeutic option for patients with *MT-ND4* LHON.

To date, there has been no comparison of the efficacy of LHON treatments (approved or in development) on visual outcomes in the *MT-ND4* LHON patient population. The aim of this study was to perform a meta-analysis of 2 efficacy outcomes of interest, the visual recovery rate (clinically relevant recovery [CRR] from nadir) and final BCVA, in patients with LHON due to the m.11778G>A *MT-ND4* mutation, and to indirectly compare 3 subgroups of patients, those with the natural course of the disease, those who received idebenone, and those who were treated with lenadogene nolparvovec gene therapy.

2. Methods

2.1. Outcomes of interest

The 2 visual outcomes of interest were the clinically relevant recovery (CRR) from nadir and final BCVA in logarithm of the minimum angle of resolution (LogMAR). CRR from nadir was defined as follows: for patients with 'on-chart' BCVA at nadir, an improvement of at least 0.2 LogMAR and for patients with 'off-chart' BCVA at nadir, a switch to 'on-chart' (equivalent to at least 1.6 LogMAR).

2.2. Selection of studies

2.2.1. Sources of data

Three sources of studies were considered: a natural history pool of 11 studies previously used as an external group for an indirect comparison analysis with lenadogene nolparvovec,[7,35] a systematic review of the literature, and a review of the unpublished available LHON reports from Chiesi Pharmaceuticals. The number of selected studies for natural history subgroup, idebenone subgroup and lenadogene nolparvovec subgroup are presented in Figure 1. Table 1 shows the characteristics of the selected studies.

2.2.2. Natural history studies

The natural history pool included studies with individual patient data (already established for indirect comparison analyses).[7,35] A study was considered eligible if it contained longitudinal BCVA with at least 3 data points by eye allowing CRR evaluation, or data on final BCVA. The CRR from nadir was evaluated in each eligible study at the eye level (each eye considered separately) and at the patient level (recovery in at least one eye) based on individual BCVA data. In these studies, patients were aged 15 years or more at onset. Two studies out of 11 were eligible for the meta-analysis of CRR from nadir, while all 11 studies could be included in the final BCVA analysis (Figure 1).

To be as comprehensive as possible in our data acquisition, natural history studies containing aggregate data were also considered for inclusion. Aggregate data from studies from the systematic review of the literature and the review of available unpublished reports on the natural history of LHON were included if *MT-ND4* LHON patient aggregate data included visual outcomes of interest: final BCVA and/or CRR from nadir assessable at the patient level and/or at eye level. The selection of studies did not consider the patient age at onset of vision loss. For the meta-analyses of CRR from nadir and final BCVA, 3 and 2 studies with aggregate data were eligible, respectively (Figure 1).

All eligible studies were included in the meta-analyses, regardless of whether the outcomes of interest were available in aggregate or individual form. A total of 5 and 13 studies were selected for the meta-analyses of CRR from nadir and final BCVA, respectively.

It should be noted, however, that the Lam 2014 study[17,27], included in the CRR and final BCVA meta-analyses, and the Stephenson 2022 study[49], included in the final BCVA analysis, both included some patients treated with idebenone (15/44 and 20/36, respectively). These idebenone-treated patients could not be excluded from the natural history subgroup and included in the idebenone subgroup because these two publications did not individually identify the patients taking idebenone.[17,49]

A list of the natural history studies excluded and the reasons for their

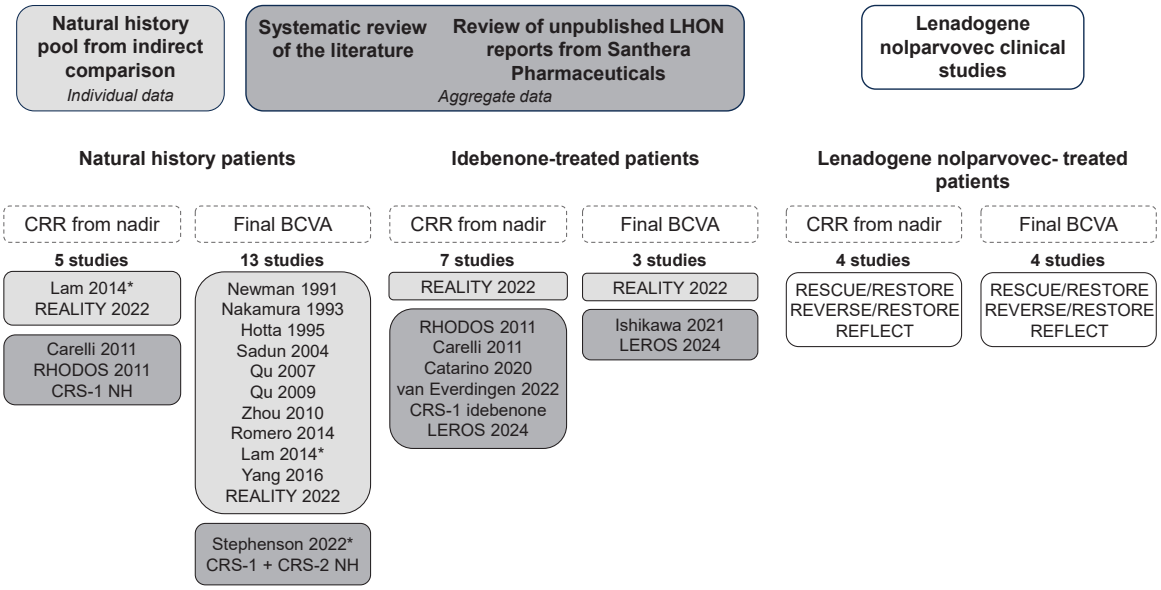

Fig. 1. Number of studies selected for each patient subgroup and efficacy outcome of interest. *The study included some patients treated with idebenone.

non-eligibility are shown in Table 2.

2.2.3. Studies of idebenone-treated patients

Idebenone studies including individual patient data were first evaluated. A study was considered eligible if it contained patient level data for both idebenone status and final BCVA or longitudinal BCVA with at least 3 data points by eye allowing for CRR evaluation. Individual idebenone patient data were available in only 1 study (REALITY[60]) which was eligible for the assessment of CRR from nadir and final BCVA (Figure 1). In this study, the CRR from nadir was evaluated at both the eye level and at the patient level based on individual BCVA data, and the analysis was performed for patients who were aged 15 years or older at vision-loss onset.

Idebenone studies containing aggregate data were also considered for inclusion. Studies from our systematic literature review and the review of available unpublished reports on LHON were eligible if they included patients with *MT-ND4* LHON treated with idebenone, regardless of the age of the patient at the time of vision loss, and if they presented aggregate data on our visual outcomes of interest. For the meta-analysis of CRR from nadir and final BCVA, 6 and 2 studies were eligible, respectively (Figure 1).

A total of 7 and 3 studies were selected for the meta-analyses of CRR from nadir and final BCVA, regardless of whether the outcomes of interest were available in aggregate or individual form.

Table 2 shows the idebenone studies excluded and the reasons for their non-eligibility.

2.2.4. Studies of lenadogene nolparvovec-treated patients

All 4 phase 3 studies with lenadogene nolparvovec were included: RESCUE,[36] REVERSE,[59] RESTORE[2] (long-term follow-up study of RESCUE and REVERSE) and REFLECT.[37] For the ongoing REFLECT study, the results were analyzed at a data cutoff on February 20, 2024. Three separate datasets were used for each visual outcome of interest: RESCUE/RESTORE, REVERSE/RESTORE and REFLECT (Figure 1).

2.3. Statistical analyses

For the studies providing individual patient data, a CRR rate and a mean final BCVA with its associated standard error were calculated for each study. For the studies from the systematic review of the literature and the review from available unpublished reports on LHON, CRR, and final BCVA were directly extracted from the manuscripts/reports as aggregate data.

For the final BCVA, the "generic inverse variance method" procedure was used. In this procedure, final BCVA mean estimates and their standard errors are considered. The weight given to each study is the inverse of the square of its standard error. This choice of weight minimizes the imprecision (uncertainty) of the pooled effect estimate.

For the CRR, the Freeman-Tukey transformation[16] was used to calculate the weighted summary CRR proportion under the fixed and random effects model.[14]

Estimates were calculated using fixed and random effects models. The random effects model will tend to give a more conservative estimate and was chosen as the preferred model.

The results of each selected study, with 95 % confidence interval (CI) and the overall effect with 95 % CI, are presented as forest plots. The marker size varies in size according to the weights assigned to the different studies. The pooled effects are represented using a diamond. The location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate.

MedCalc version 22.023 was used for the analyses, and the tables and figures.

Patient characteristics were summarized using available descriptive statistics: mean age at onset of vision loss, percentage of male individuals, percentage of Asian individuals, and mean time from vision loss to last observation.

2.3.1. Tests for heterogeneity

Two different statistics, Cochran's Q and I^2, were performed to assess the agreement or disagreement among the studies. Q-associated p-values <0.10 were considered significant and percentages of I^2 >50 % show substantial heterogeneity, with the level of heterogeneity increasing with the value of I^2.

2.3.2. Tests for publication bias

To detect potential publication bias, the Egger's test and Begg's rank tests were used. For both tests, p-values <0.05 indicate a publication bias.

3. Results

3.1. Meta-analysis of CRR from nadir

Results of the meta-analysis of CRR from nadir were compared

Table 1
Characteristics of included studies.

Author/year or study name	Design	N patients	N eyes	Subgroup	Outcome of interest	Mean time from vision loss to lenadogene nolparvovec injection / idebenone initiation / baseline (NH) (months)	Mean time from vision loss to outcome (months)
Newman 1991[34]	Prospective	40	76	Natural history	BCVA	NR	4.0
Nakamura 1993[32]	Prospective	9	18	Natural history	BCVA	NR	314.7
Hotta 1995[21]	Retrospective	32	60	Natural history	BCVA	NR	6.6
Sadun 2004[46]	Prospective	14	28	Natural history	BCVA	NR	233.1
Qu 2007[41]	Retrospective	7	14	Natural history	BCVA	NR	229.7
Qu 2009[42]	Retrospective	12	24	Natural history	BCVA	NR	109.0
Zhou 2010[62]	Retrospective	15	30	Natural history	BCVA	NR	88.0
RHODOS 2011[25]	Prospective	18	36	Natural history (placebo arm)	CRR from nadir	23.7	29.7
		35	70	Idebenone	CRR from nadir	22.8	28.8
Carelli 2011[5]	Retrospective	41	82	Natural history	CRR from nadir	NR	≥ 60.0
		30	60	Idebenone	CRR from nadir	6.2	≥ 60.0
Romero 2014[45]	Prospective	15	30	Natural history	BCVA	NR	122.4
Lam 2014[17,27]	Prospective	36	72	Natural history[a]	CRR from nadir BCVA	85.5	112.3
Yang 2016[54]	Prospective	5	10	Natural history	BCVA	36.0	48.0
Stephenson 2022[49]	Retrospective	26	52	Natural history	BCVA	3.0	77.4
CRS−1[48]	Retrospective	55	110	Natural history[b]	CRR from nadir	3.6	14.9
		29	58	Idebenone[c]	CRR from nadir	6.0	19.2
CRS−1+CRS−2 NH[57]	Retrospective	-	47	Natural history[d]	BCVA	4.8	29.2
REALITY 2022[60]	Retrospective	8	16	Natural history	CRR from nadir BCVA	6.2	29.4
		15	30	Idebenone	CRR from nadir BCVA	7.1	40.1
Catarino 2020[8]	Prospective	54	-	Idebenone	CRR from nadir	4.3	29.2
Ishikawa 2021[22]	Prospective	51	102	Idebenone	BCVA	76.8	87.8
Van Everdingen 2022[15]	Retrospective	38	-	Idebenone	CRR from nadir	5.5	26.7
LEROS Module 4A[12]	Prospective	55	96	Idebenone[e]	CRR from nadir	7.4	31.4
		36	72		BCVA		
RESCUE/RESTORE[2,36]	Prospective	39	78	Lenadogene nolparvovec[f]	CRR from nadir BCVA	4.0	50.7
REVERSE/ RESTORE[2,59]	Prospective	37	74	Lenadogene nolparvovec[f]	CRR from nadir BCVA	9.5	60.6
REFLECT[37]	Prospective	98	196	Lenadogene nolparvovec[g]	CRR from nadir BCVA	7.4	56.3
				Natural history pool	**CRR from nadir**	**27.7**	**42.4**
					BCVA	**11.7**	**50.9**
				Idebenone pool	**CRR from nadir**	**8.9**	**28.6**
					BCVA	**29.4**	**49.9**
				Lenadogene nolparvovec pool	**CRR from nadir**	**7.1**	**56.0**
					BCVA	**7.1**	**56.0**

BCVA = best-corrected visual acuity; CRR = clinically relevant recovery; NH = natural history; NR = not reported.

[a] The Lam 2014 study included 15 patients treated with idebenone among the 44 *MT-ND4* LHON patients. No information is available on the treatment received by the 36 *MT-ND4* LHON patients ≥ 15 years included in the meta-analysis making it impossible to exclude some patients from the natural history pool and include them in the idebenone pool.

[b] CRS-1 NH: Only the natural history patients were considered; the subpopulation treated with idebenone was excluded.

[c] CRS-1 idebenone: A subpopulation of the CSR-1 study was treated with idebenone.

[d] CRS-1 and CRS-2 NH: The subacute/dynamic population was considered (source: LEROS 2024 publication). No information on CRR from nadir was available in the LEROS publication. Time from vision loss to outcome was only available for all LHON patients regardless of causative mutation (no information in the *MT-ND4* LHON population).

[e] LEROS: The subacute/dynamic population was considered (Source: Module 4 A – German reimbursement file). No information on CRR from nadir was available in the LEROS publication.

[f] RESTORE is the long-term extension study of RESCUE and REVERSE; date of database lock for the completed RESTORE study: 4-Jul-2022.

[g] REFLECT: Ongoing study; data cut-off: 20-Feb-2024.

among patients with the natural course of the disease, patients treated with idebenone, and patients treated with lenadogene nolparvovec gene therapy. The 3 subgroups of patients showed a comparable mean age at the time of onset of vision loss, around 30 years, and a similar percentage of males (ranging from 78 % to 80 %) (Table 3 and Table 4). Asian participants were included in idebenone and lenadogene nolparvovec studies. Natural history patients and patients treated with lenadogene nolparvovec had longer mean follow-up (42 and 56 months, respectively) than patients who received idebenone (29 months) (Table 3 and Table 4).

Five natural history studies (316 eyes), 5 idebenone studies (313 eyes) and all 4 lenadogene nolparvovec studies (348 eyes) were eligible for the meta-analysis of CRR from nadir at the eye level. CRR from nadir [95 % CI] occurred in 17 % [7 %; 30 %] of natural history eyes, 31 % [24 %; 40 %] of idebenone-treated eyes and 59 % [54 %; 64 %] of lenadogene nolparvovec-treated eyes (Table 3). Forest plots of proportions of eyes that reached CRR from nadir across studies are shown in Figure 2.

For the meta-analysis at the patient level, the same natural history studies (158 patients) and lenadogene nolparvovec studies (174

Table 2
Excluded studies.

Author/year or study name	Reason for exclusion
Natural history studies	
Stone 1992[50]	CRR from nadir not available; final BCVA only available in recovered patients
Oostra 1994[39]	CRR from nadir not available; time from vision loss not available
Riordan-Eva 1995[43]	CRR from nadir and final BCVA not available
Nikoskelainen 1996[38]	CRR from nadir and final BCVA not available
Mashima 2017[29]	CRR from nadir and final BCVA not available
Yuan 2018[55]	CRR from nadir and final BCVA not available
Moon 2020[31]	Different definition of CRR; final BCVA not available
Cherninkova 2023[11]	CRR from nadir and final BCVA not available
Samuel Kim 2024[47]	CRR from nadir and final BCVA not available
Idebenone studies	
PAROS	*MT-ND4* LHON patients' data not specified
Mashima 2000[30]	CRR from nadir and final BCVA not available
Mashima 2017[29]	CRR from nadir and final BCVA not available
Pemp 2019[40]	*MT-ND4* LHON patients' data not specified
Borreli 2022[3]	*MT-ND4* LHON patients' data not specified
Stephenson 2022[49]	CRR from nadir not available; final BCVA not specified for *MT-ND4* LHON patients

BCVA = best-corrected visual acuity; CRR = clinically relevant recovery.

patients) were considered. Concerning the idebenone studies, 2 additional studies were identified through the systematic review of published literature (Catarino[8] and van Everdingen[15]), giving a total of 7 studies selected (256 patients). In ascending order, overall CRR from nadir [95 % CI] at the patient level, *i.e.*, response in one or both eyes, was estimated at 22 % [10 %; 39 %], 42 % [36 %; 48 %] and 69 % [62 %; 75 %] in patients with the natural course of LHON, those treated with idebenone and those treated with lenadogene nolparvovec, respectively (Table 4 and Figure 3).

Among the 5 natural history studies selected, high level of heterogeneity was reported for both analyses at eye level (I^2= 87 %; P<0.0001) (Figure 2A) and patient level (I^2= 79 %; P=0.0007) (Figure 3A). Concerning idebenone studies, heterogeneity was moderate for CRR at the eye level (5 studies; I^2= 59 %; P= 0.0430) (Figure 2B), while there was no heterogeneity at the patient level (7 studies; I^2= 0 %; P= 0.7359) (Figure 3B). No heterogeneity was found across the lenadogene nolparvovec studies (4 studies; I^2=0 %; P=0.7398 at eye level and I^2=0 %; P=0.5942 at patient level) (Figures. 2C and 3C). No publication biases were observed for the natural history and the idebenone studies.

3.2. Meta-analysis of final BCVA

For the analyses of final BCVA, a total of 13 studies were selected for the natural history subgroup (243 patients and 477 eyes), 3 studies for the idebenone subgroup (102 patients; 203 eyes), and 4 studies for the lenadogene nolparvovec subgroup (174 patients; 348 eyes) (Figure 1).

Overall, patient characteristics were similar among the 3 subgroups in terms of mean age at onset of vision loss (ranging from 29 to 34 years), proportion of male patients (80 %), and mean time from vision loss to last observation (around 50–56 months). The percentage of Asian

Table 3
Meta-analysis for CRR from nadir at eye level.

	Natural history studies*	Idebenone studies**	Lenadogene nolparvovec studies
Number of studies	5	5	4
Patient characteristics			
Number of patients / eyes	191 / 382	257 / 514	174 / 348
Mean age at vision loss (years)	29.8	31.4	33.5
Male (%)	78.1 %	79.4 %	79.9 %
Asian (%)	0.0 %	0.5 %	8.6 %
Mean time from vision loss to baseline (months)	27.7	10.4	7.1
Mean time from vision loss to last observation (months)	42.4	28.8	56.0
Efficacy outcome			
Number of eyes	316	313	348
CRR from nadir at eye level [95 % CI]	17 % [7 %; 30 %]	31 % [24 %; 40 %]	59 % [54 %; 64 %]

CI = confidence interval; CRR = clinically relevant recovery.
* The baseline demographics and follow-up time were available for *MT-ND4* LHON patients in 3 studies, and for LHON patients regardless of causative mutation for CRS-1 NH and RHODOS placebo arm. CRS-1 NH, RHODOS placebo arm and Carelli 2011 included patients < 15 years old.
** The baseline demographics and follow-up time were available for *MT-ND4* LHON patients in 2 studies and for LHON patients regardless of causative mutation for CRS-1 idebenone, LEROS and RHODOS idebenone arm. All studies except REALITY included patients < 15 years old.

Table 4
Meta-analysis for CRR from nadir at patient level.

	Natural history studies*	Idebenone studies**	Lenadogene nolparvovec studies
Number of studies	5	7	4
Patient characteristics			
Number of patients / eyes	191 / 382	349 / 698	174 / 348
Mean age at vision loss (years)	29.8	32.1	33.5
Male (%)	78.1 %	79.9 %	79.9 %
Asian (%)	0.0 %	0.4 %	8.6 %
Mean time from vision loss to baseline (months)	27.7	8.9	7.1
Mean time from vision loss to last observation (months)	42.4	28.6	56.0
Efficacy outcome			
Number of patients	158	256	174
CRR from nadir at patient level [95 % CI]	22 % [10 %; 39 %]	42 % [36 %; 48 %]	69 % [62 %; 75 %]

CI = confidence interval; CRR = clinically relevant recovery.
* The baseline demographics and follow-up time were available for *MT-ND4* LHON patients in 3 studies, and for LHON patients regardless of causative mutation for CRS-1 NH and RHODOS placebo arm. CRS-1 NH, RHODOS placebo arm and Carelli 2011 included patients < 15 years old.
** The baseline demographics and follow-up time were available for *MT-ND4* LHON patients in 4 studies and for LHON patients regardless of causative mutation for CRS-1 idebenone, LEROS and RHODOS idebenone arm. All studies except REALITY included patients < 15 years old.

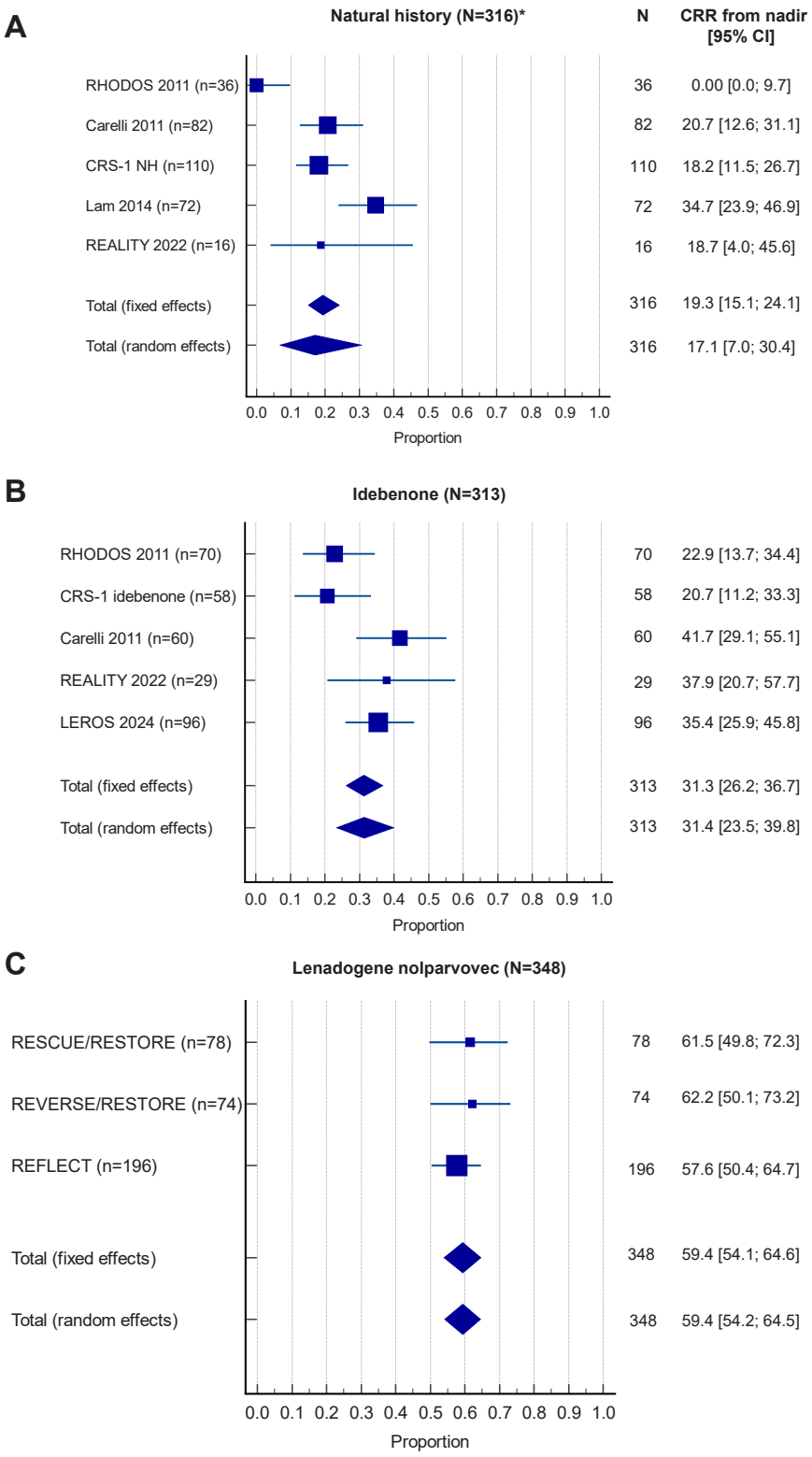

Fig. 2. Forest plots of CRR from nadir across natural history studies (A), idebenone studies (B) and lenadogene nolparvovec studies (C) at eye level. CI = confidence interval; CRR = clinically relevant recovery; N = number of eyes. Results of fixed effects and random effects models for each subgroup of eyes are presented with their 95 % CI (proportions). *CRR from Lam 2014 included some patients treated with idebenone (n=15/44 patients; of the 44 patients, 36 aged ≥ 15 years at disease onset were included in the meta-analysis). Idebenone-treated patients could not be excluded from the natural history subgroup and included in the idebenone subgroup as the publication from Lam and coworkers did not provide individual patient data.[17]

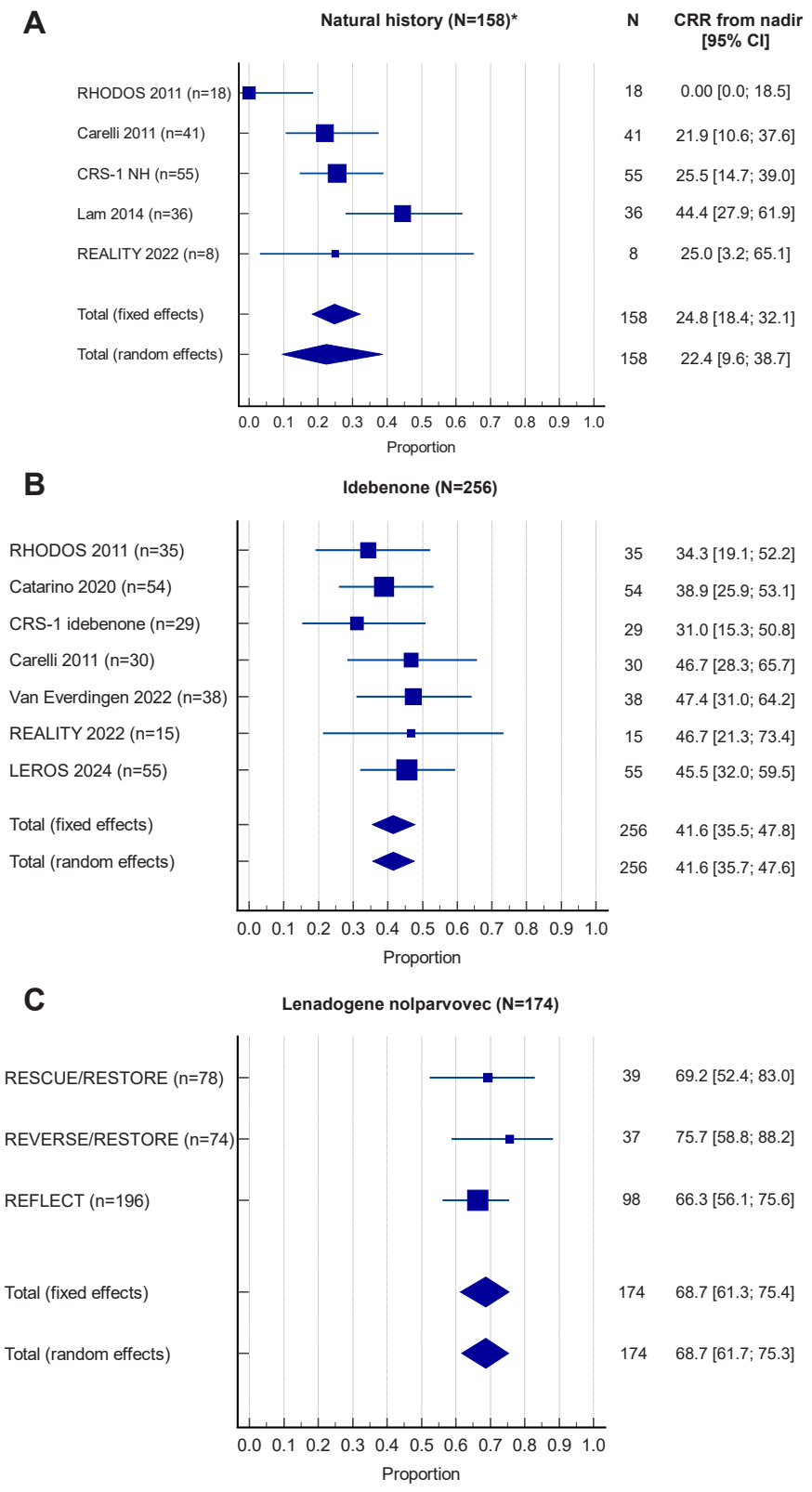

Fig. 3. Forest plots of CRR from nadir across natural history studies (A), idebenone studies (B) and lenadogene nolparvovec studies (C) at patient level. CI = confidence interval; CRR = clinically relevant recovery; N = number of patients. Results of fixed effects and random effects models for each subgroup of patients are presented with their 95 % CI (proportions). *CRR from Lam 2014 included some patients treated with idebenone (n=15/44 patients; of the 44 patients, 36 aged ≥ 15 years at disease onset were included in the meta-analysis). Idebenone-treated patients could not be excluded from the natural history subgroup and included in the idebenone subgroup as the publication from Lam and coworkers did not provide individual patient data.[17]

patients varied among the 3 subgroups, from 8.6 % in patients treated with gene therapy to 35.4 % in natural history patients (Table 5).

With the random effects model, mean estimates of final BCVA [95 % CI] reached, from the worst to the best values, 1.63 [1.50; 1.77] LogMAR for natural history patients, 1.38 [1.18; 1.58] LogMAR for patients treated with idebenone and 1.36 [1.29; 1.42] LogMAR for patients treated with gene therapy (Table 5). Figure 4 shows forest plots of final BCVA across studies.

A high level of heterogeneity was observed among the BCVA data of natural history studies (I^2= 86 %; P<0.0001), with the worst value reported by Sadun and coworkers[46] (2.09 LogMAR) and the best by Zhou and coworkers[62] (1.29 LogMAR). High heterogeneity was also observed among the 3 studies selected for meta-analysis in patients treated with idebenone (I^2= 83 %; P=0.0024), showing conflicting results between the LEROS study[12] and the 2 other studies (Ishikawa and coworkers[22] and REALITY[60]), with patients in the LEROS study achieving better visual outcomes. Conversely, the level of heterogeneity was low for lenadogene nolparvovec studies (I^2= 15 %; P=0.3079). There was no publication bias for natural history and idebenone studies.

4. Discussion

This meta-analysis is the largest comprehensive review of the available data on the natural history of patients with vision loss from the m.11778G>A *MT-ND4* LHON mutation and those treated with idebenone, as well as all the available results on the efficacy of lenadogene nolparvovec gene therapy. The *MT-ND4* LHON population included in each subgroup of interest was representative of the typical demographics of the disease as reported in a century and a half of literature,[33] with a majority (≥78 %) of men aged around 30 years at the time of onset of vision loss.

We observed that the estimated proportion of eyes achieving CRR from nadir was 3 times higher in lenadogene nolparvovec-treated patients than in natural history patients (59 % *vs* 17 %), with no overlap in the CI of the estimates. The magnitude of the greater effect of gene therapy compared with natural history was similar at the patient level (69 % *vs* 22 %). In our meta-analysis, the CRR rate of natural history patients using a unified definition of recovery[4] (22 %) was higher than the spontaneous recovery rates reported in the literature using various definitions of recovery (14 % in the meta-analysis of Newman and coworkers[33] and 18 % in the study of Yuan and coworkers[55]), suggesting that the actual rate of spontaneous recovery in *MT-ND4* LHON was not underestimated in our study. High heterogeneity was observed among the CRR from nadir extracted from the natural history studies, ranging from 0 % to 35 % at the eye level and from 0 % to 44 % at the patient level. The lowest proportion of natural history eyes or patients with CRR from nadir was reported in the prospective, double-masked, placebo-controlled, randomized RHODOS study, in which patients who received placebo had, on average, vision loss of 24 months at the time of enrollment and were followed over a 6-month period.[25] This particularly short follow-up in a chronic population probably explains the absence of CRR in these patients. Heterogeneity of methods and timing of visual acuity assessments are likely the most relevant reasons for the differences in recovery rates among all the natural history studies, as CRR is a BCVA-related parameter. Nevertheless, the magnitude of difference in CRR from nadir between lenadogene nolparvovec-treated patients and natural history patients makes a substantial attribution of this observation to residual biases associated with cross-study comparisons unlikely. Additionally, this large difference in CRR supports the conclusion that the visual response in patients treated with gene therapy is not driven by spontaneous recovery.

Eyes of patients who were injected with lenadogene nolparvovec also showed a better recovery rate than eyes of patients who were treated with idebenone (59 % *vs* 31 %). This superior effect of gene therapy was further supported by the absence of overlap in CI between the 2 treatment estimates. Consistent results were also observed with CRR at the patient level, with a superior effect of lenadogene nolparvovec as compared to idebenone (69 % *vs* 42 %). This is the first time that a comparison has been made between the visual outcomes of patients treated with the only drug approved for LHON treatment and those treated with an alternative therapeutic strategy. Moderate heterogeneity was observed among the idebenone studies selected for the meta-analysis at the eye level, with a CRR from nadir ranging from 21 % in CRS-1 idebenone[48] to 42 % in Carelli and coworkers,[5] probably resulting from differences in the use of idebenone therapy. In the retrospective study conducted by Carelli and coworkers, idebenone dosage varied between 270 and 675 mg per day and mean (standard deviation [SD]) duration of treatment was 49 (30) months for patients who showed visual recovery.[5] For patients treated with idebenone in Chiesi's CRS-1 case record survey, the mean dose used was 520 mg/day, and the mean duration of therapy was 12 months.[48] In the RHODOS study, patients were all administered a dosage of 900 mg/day for 6 months.[25] In LEROS, idebenone was administered at 900 mg/day and the mean duration of treatment in the safety population was 19 months,[12,57] while in REALITY, doses were unknown, but the mean (SD) cumulative duration of idebenone treatment was 70 (25) months[60]. Regarding the timing of therapy initiation, while all patients from the study of Carelli and coworkers, the retained LEROS subgroup and most patients from REALITY and CRS-1 idebenone received idebenone within 1 year after disease onset (*i.e.*, during the subacute/dynamic phase of the disease), patients from RHODOS could have been treated anytime within 5 years after the onset of LHON, meaning that some patients were treated during the chronic phase of the disease.[5,25,48,57,60] All these differences in treatment protocols were likely to have influenced the CRR outcomes of

Table 5
Meta-analysis for final BCVA.

	Natural history studies*	Idebenone studies**	Lenadogene nolparvovec studies
Number of studies	13	3	4
Patients' characteristics			
Number of patients / eyes	598 / 1175	181 / 362	174 / 348
Mean age at vision loss (years)	28.9	31.8	33.5
Male (%)	80.2 %	80.1 %	79.9 %
Asian (%)	35.4 %	32.0 %	8.6 %
Mean time from vision loss to baseline (months)	11.7	29.4	7.1
Mean time from vision loss to last observation (months)	50.9	49.9	56.0
Efficacy outcome			
Number of patients / eyes	243 / 477	102 / 203	174 / 348
Final BCVA [95 % CI] (LogMAR)	1.63 [1.50; 1.77]	1.38 [1.18; 1.58]	1.36 [1.29; 1.42]

BCVA = best-corrected visual acuity; CI = confidence interval; LogMAR = logarithm of the minimum angle of resolution.

* The baseline demographics and follow-up time were available for *MT-ND4* LHON patients in 11 studies and for LHON patients regardless of causative mutation for CRS-1 + CRS-2 NH and Stephenson 2022. CRS-1 + CRS-2 NH and Stephenson 2022 included patients < 15 years old.

** The baseline demographics and follow-up time were available for *MT-ND4* LHON patients in REALITY, and for LHON patients regardless of causative mutation for LEROS and Ishikawa 2021. LEROS and Ishikawa 2021 included patients < 15 years old.

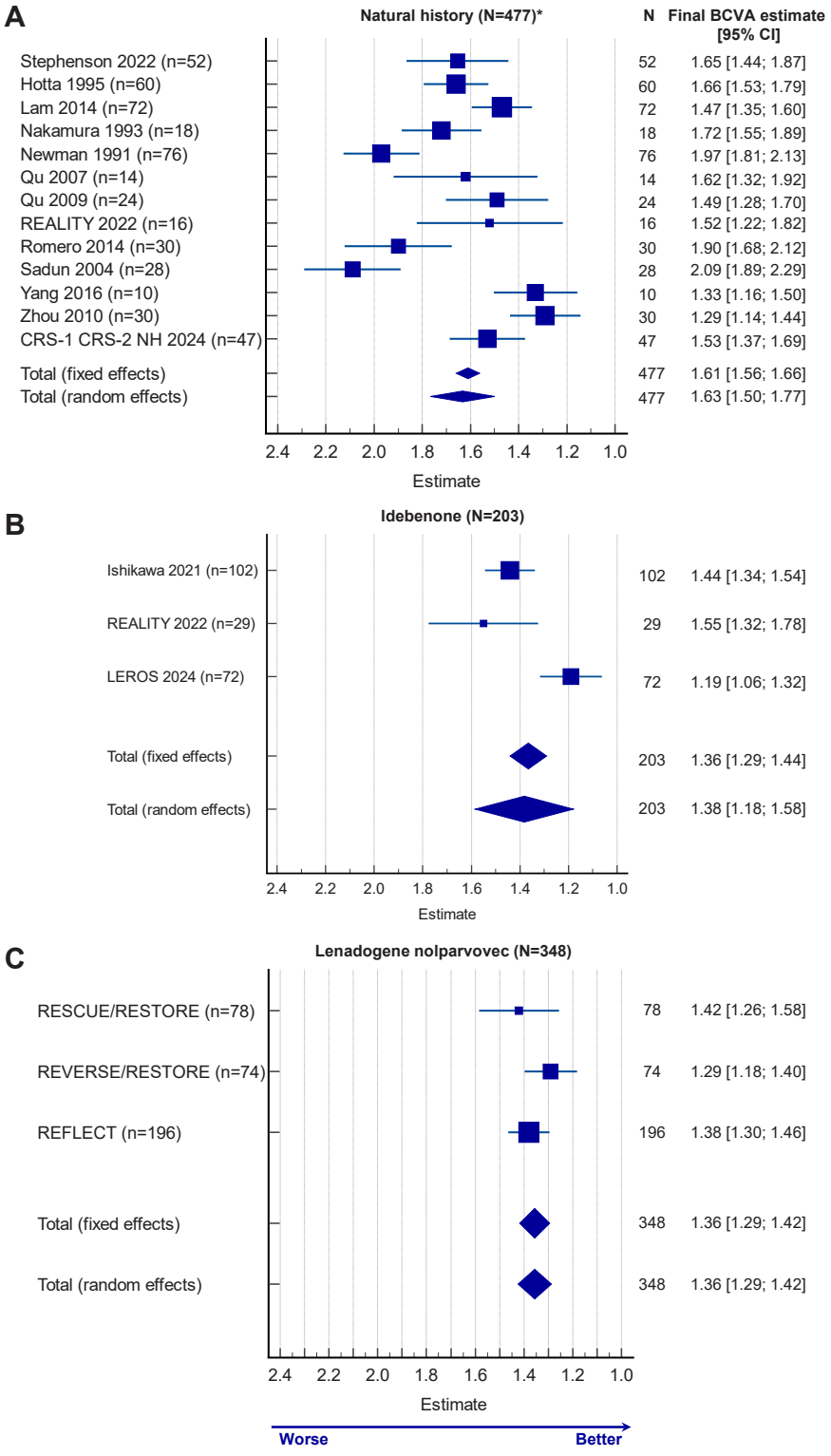

Fig. 4. Forest plots of final BCVA across natural history studies (A), idebenone studies (B) and lenadogene nolparvovec studies (C). BCVA = best-corrected visual acuity; CI = confidence interval; N = number of eyes. Results of fixed effects and random effects models for each subgroup of patients are presented with their 95 % CI (LogMAR values). *Final BCVA from Lam 2014 and Stephenson 2022 included some patients treated with idebenone (n=15/44 and 20/36 patients, respectively; of the 44 patients from Lam 2014, 36 aged ≥ 15 years at disease onset were included in the meta-analysis; of the 36 patients from Stephenson 2022, 26 were included in the meta-analysis).[17,49]

eyes treated with idebenone, as were the timing and methods of BCVA assessments. Indeed, although it has been reported that early initiation of idebenone treatment is the most predictive factor of visual recovery in patients with *MT-ND4* LHON,[5] more recent data suggest that visual outcomes might be better in *MT-ND4* patients treated with idebenone in later (dynamic/chronic) stages as compared to the subacute stage.[44] Importantly, the CRR from nadir at patient level was consistent across idebenone studies and no heterogeneity was observed, supporting the

meaningful difference observed in patient responder rates between idebenone and lenadogene nolparvovec, both providing homogeneous results for this endpoint.

Overall, eyes treated with lenadogene nolparvovec achieved a better final BCVA (*i.e.*, lowest logMAR value) as compared to natural history eyes (1.36 *vs* 1.63 LogMAR), with no overlap in the 95 % CI. The mean value of final BCVA of natural history patients from our meta-analysis (1.63 LogMAR) is in line with the final values reported in the literature of natural history studies, ranging between 1.5 and 2.0 LogMAR across studies in *MT-ND4* LHON patients.[23,43,46,55,60] The best final BCVAs were reported in the studies by Zhou and coworkers[62] and Yang and coworkers,[54] both of which exclusively included Asian patients. Indeed, more favorable visual outcomes and more frequent spontaneous recovery have been previously noted in LHON studies with Asian populations.[13,21,29] A similar superior effect of lenadogene nolparvovec over the natural course of *MT-ND4* LHON was reported in our previous indirect comparison between the 348 eyes treated with lenadogene nolparvovec and 408 untreated eyes from 11 natural history studies (1.23 [0.44] *vs* 1.59 [0.44] LogMAR), with a difference at 48 months after vision loss of −0.35 LogMAR in favor of eyes injected with gene therapy.[7] In our meta-analysis, the mean follow-up time after treatment was 48.9 months (*i.e.*, 4.1 years) for the lenadogene nolparvovec subgroup, suggesting that the superior effect of gene therapy is persistent over time when compared to the natural evolution of the disease

Treatment with lenadogene nolparvovec resulted in a similar mean final BCVA compared to idebenone (1.36 *vs* 1.38 LogMAR) in *MT-ND4* LHON patients. Data on final BCVA after idebenone therapy in *MT-ND4* LHON patients were sparse, with only 3 studies providing the necessary information. The main reason for non-inclusion of studies from the literature search or review of available unpublished LHON studies was the inclusion of patients with causative mutations other than the m.11778G>A *MT-ND4* LHON mutation, sometimes only providing the final BCVA for their entire LHON population. Cochran's Q and I^2 tests revealed high inconsistency among the 3 included idebenone studies, highlighting that the mean final BCVA is mainly driven by the LEROS results.

Although 2 other research groups have also developed an AAV2-*ND4* gene therapy program for *MT-ND4* LHON treatment with published clinical trials results,[18,26,52,53,56] we did not include their efficacy data in our meta-analyses because of some differences in the products used, their study designs, the characteristics of included patients, and their assessment of visual outcomes. The Bascom Palmer Eye Institute of Miami (US) conducted a phase 1 study with their AAV2-P1ND4v2 gene therapy, including 11 *MT-ND4* LHON patients with chronic bilateral visual loss (>12 months), 9 patients with acute bilateral visual loss (<12 months) and 8 patients with unilateral visual loss. In each group, patients received a unilateral intravitreal injection of gene therapy at 1 of 4 doses (from $5.0x10^8$ to $1.0x10^{10}$ vg/eye), with approximately 3 patients per dose group.[18,26] Improvement in visual acuity, considered as a gain of at least 0.3 LogMAR (15 ETDRS letters) from baseline, and final BCVA values were assessed; however, due to the design of the study with numerous subgroups according to the phase of LHON and dose of gene therapy, the low number of patients in each subgroup precludes any meaningful interpretation of the efficacy results and inclusion in this meta-analysis. The second research team, from the University of Science and Technology of Huazhong (China), conducted an open-label study in which 9 patients (age range: 9–46 years) with *MT-ND4* LHON and vision loss ranging from greater than 1 year to 17 years (4 patients 10 years old or younger) were injected with a unilateral intravitreal injection of rAAV2-*ND4* ($5x10^9$ vg/eye for patients younger than 12 years old or $1x10^{10}$ vg/eye for patients older than 12 years old). The primary endpoint of the study was significant recovery in visual acuity, defined as a gain of at least 0.3 LogMAR (15 ETDRS letters) in BCVA from baseline.[52] The small sample size of this study population, however, coupled with the substantial inclusion of children aged 10 years or less, whose prognosis is known to be more favorable than that of adult patients,[28,33,38,43] and the wide range of vision loss durations among their patients preclude the inclusion of these data in the gene therapy subgroup of this meta-analysis.

A strength of this meta-analysis is the choice of standardized and relevant endpoints for assessing the efficacy of treatments; the use of a unified and clinically relevant definition of recovery endorsed by an international panel of clinical experts in LHON[4] enabled a meaningful comparison across studies. Furthermore, in the literature of natural history studies, it has been reported that the visual acuity of *MT-ND4* LHON patients stabilizes within 2 years after disease onset,[55] making long-term final BCVA beyond 2 years after onset a suitable efficacy endpoint. Lastly, the results of this meta-analysis were based on a comprehensive analysis of all available natural history studies and idebenone studies that reported CRR from nadir or final BCVA data, either in aggregate or individually.

There are of course limitations in these analyses. The timing of lenadogene nolparvovec injection or idebenone initiation from vision loss was not always aligned. In the lenadogene nolparvovec studies, *MT-ND4* LHON patients were treated during the subacute/dynamic phase of the disease, *i.e.*, within 1 year after vision loss. Regarding the timing of idebenone initiation, while all patients in the study of Carelli and coworkers, the study of Catarino and coworkers, and the retained LEROS subgroup, and most patients in REALITY, CRS-1 idebenone and the study of van Everdingen and coworkers received idebenone within 1 year after disease onset, patients in RHODOS were treated within 5 years after the onset of LHON, *i.e.*, during the chronic phase of the disease;[5,8,15,25,48,57,60] however, restricting the analyses to only the subacute/dynamic study populations was not feasible for 2 reasons: (1) the information specifically on the subacute/dynamic patients was not always provided, such as in the RHODOS study; and (2) such restriction would have substantially impacted the comprehensiveness of the data and final sample sizes of the idebenone subgroup meta-analysis. Another limitation is the timing of the outcomes which varied across the 3 subgroup populations; however, most patients across subgroups had a follow-up duration beyond 2 years after vision loss, making the comparison relevant for long-term outcomes of the 3 populations. Additionally, the varied idebenone exposures across idebenone patients regarding dosage as well as length of treatment (from 6 months to 70 months) could have influenced the results. Nevertheless, the overall exposure for the 2 outcomes of interest was likely long enough to observe idebenone efficacy. An additional limitation is the high heterogeneity observed among the natural history studies. For final BCVA, the reported data from the natural history subgroup spanned a 30-year period (from 1991 to 2024), likely introducing a bias in standardized measurements of visual acuity. In addition, the design of most of the natural history studies was retrospective; however, a random effects model was appropriately performed to lower the sources of heterogeneity. Additionally, 3 bias factors could have led to an overestimation of the visual outcomes of natural history patients and idebenone-treated patients. First, some natural history studies[17,49] (2/13 for BCVA and 1/5 for CRR from nadir) included patients who were treated with idebenone and there were no aggregate data available for untreated patients only. Second, some studies selected from the review of the literature or available unpublished LHON reports included natural history and idebenone-treated *MT-ND4* LHON patients aged younger than 15 years, while the population treated with lenadogene nolparvovec consisted exclusively of patients aged 15 years or older. As young age at onset is associated with more favorable visual outcomes and more frequent spontaneous recovery,[28,33,38,43] this would have led to an overestimation of good visual outcomes among natural history patients and idebenone-treated patients. Lastly, all off-chart BCVA values were converted into LogMAR +1.8 in most idebenone studies, while a less favorable conversion ranging from LogMAR +2 to +4.5 was applied to lenadogene nolparvovec studies. Importantly, even assuming an overestimation of the data for the natural history and idebenone conditions, a greater effect of lenadogene nolparvovec was consistently

demonstrated compared with the natural history subgroup and higher responder rates were observed compared with the idebenone subgroup, suggesting that the effect of gene therapy could be even greater if these sources of bias were corrected. Finally, as *MT-ND4* LHON patients of Asian ethnicity appear to be more likely to have favorable visual outcomes than patients of other origins,[13,21,29] a difference in the proportion of Asian patients among the 3 subgroups may have biased the effect of the treatment studied. Notably, a high proportion of Asian patients was included in the natural history and idebenone subgroups of the meta-analysis of final BCVA.

5. Conclusions

This is the first report of 3 meta-analyses of visual outcomes conducted in *MT-ND4* LHON patients enabling an indirect comparison between the natural course of the disease, treatment with idebenone and treatment with lenadogene nolparvovec gene therapy. A gradient of efficacy in visual outcomes, more marked for CRR than for final BCVA, was observed, with lenadogene nolparvovec intravitreal gene therapy superior to idebenone treatment, and both superior to the natural history of the disease. These results support the need for continuous development and improvement of these therapies, which open avenues for improvement of vision in this population of substantially visually impaired individuals. Prospective clinical trials with a nontreated patient randomized control population and standardized visual outcome measures and follow-up could be performed to confirm this assessment of therapies.

6. Method of literature search

Literature search was performed using MEDLINE (via PubMed). For natural history studies, the natural history pool having been constituted on the basis of a previous systematic literature review performed in May 2020[7,35], the published literature review for this meta-analysis was extended to May 2024, using the search terms ‘Leber hereditary optic neuropathy’, ‘LHON’, ‘ND4’, ‘G11778A’, ‘natural history’, ‘registry’, ‘pedigree’, ‘visual acuity’, and ‘nadir’. For idebenone studies, the review of the published literature was performed using the search key words ‘idebenone’ OR ‘raxone’ combined with ‘LHON’ OR ‘Leber’ until May 2024. The searches were limited to English-language publications.

Studies were excluded if they were reviews, case reports, abstracts, or if they did not contain data on at least 5 patients with confirmed m.11778G>A *ND4* mutation. Studies using a definition of recovery/response to treatment different from CRR or not providing specific data for the m.11778G>A patients were not considered for these meta-analyses.

Disclosures

NJN is a consultant for GenSight Biologics, Chiesi, Neurophth, Stoke, and Neurophoenix, and receives research support from GenSight Biologics.

VB is a consultant for GenSight Biologics and Neurophoenix.

PYWM is a consultant for GenSight Biologics, Chiesi, Neurophth, and Stoke.

VC is a consultant for GenSight Biologics, Chiesi, Stoke, and Pretzel.

CVC is a consultant for GenSight Biologics, Chiesi and Neurophoenix.

FM is the CEO of eXYSTAT and is consultant for AbbVie, Arcagy, ARTIC, Biocodex, Bioprojet, Carely, CEVA, Cureety, Eurofins, Geneuro, GenSight Biologics, IFM, Imcheck, Mapreg, Orphelia, Ose immunotherapeutics, Pfizer, PTC and Takeda.

MT is an employee of GenSight Biologics.

JAS is a consultant/contractor for Avista Therapeutics and Tenpoint; has financial interests (stock/stock options) in GenSight Biologics, Sparing Vision, Prophesee, Chronolife, Tilak Healthcare, VegaVect, Inc., Avista, Tenpoint, SharpEye, Celanese and Netramind; is owner/co-owner/founder/co-founder for Gensight Biologics, Sparing Vision, Avista, Tenpoint, Prophesee, Chronolife, Tilak Healthcare, SharpEye, Celanese, Vegavect and Netramind; participates in scientific advisory board for Gilbert Foundation, Foundation Fighting Blindness, Institute of Ophthalmology Basel and Senses Institute Lausanne; is an observer at Gensight Biologics, SparingVision, Avista and Vegavect; is President of Fondation Voir et Entendre (Paris) and StreetLab (Paris); has patent for allotopic expression, rod-derived cone viability factor and related patents; is a recipient for patent royalties and GenSight Biologics.

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Montestruc reports a relationship with Orphelia Pharma Sas that includes: consulting or advisory. Montestruc reports a relationship with OSE Immunotherapeutics that includes: consulting or advisory. Montestruc reports a relationship with Pfizer Inc that includes: consulting or advisory. Montestruc reports a relationship with PTC that includes: consulting or advisory. Montestruc reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory. Taiel reports a relationship with GenSight Biologics SA that includes: employment. Sahel reports a relationship with Avista Therapeutics that includes: consulting or advisory. Sahel reports a relationship with Tenpoint that includes: consulting or advisory. Sahel reports a relationship with GenSight Biologics SA that includes: equity or stocks. Sahel reports a relationship with Sparing Vision that includes: equity or stocks. Sahel reports a relationship with Prophesee that includes: equity or stocks. Sahel reports a relationship with Chronolife SAS that includes: equity or stocks. Sahel reports a relationship with Tilak Healthcare that includes: equity or stocks. Sahel reports a relationship with VegaVect Inc. that includes: equity or stocks. Sahel reports a relationship with Avista that includes: equity or stocks. Sahel reports a relationship with Tenpoint that includes: equity or stocks. Sahel reports a relationship with SharpEye that includes: equity or stocks. Sahel reports a relationship with Celanese that includes: equity or stocks. Sahel reports a relationship with Netramind that includes: equity or stocks. Sahel has patent Allotopic expression licensed to 'not applicable'. Sahel has patent Rod-derived Cone Viability factor licensed to INSERM and CNRS. Sahel is owner/co-owner/founder/co-founder of GenSight Biologics, Sparing Vision, Avista, Tenpoint, Prophesee, Chronolife, Tilak Healthcare, SharpEye, Celanese, Vegavect, Netramind. Sahel participates in scientific advisory board for Gilbert Foundation, Foundation Fighting Blindness, Institute of Ophthalmology Basel and Senses Institute Lausanne. Sahel is an observer at Gensight Biologics, SparingVision, Avista and Vegavect. Sahel is President of Fondation Voir et Entendre (Paris) and StreetLab (Paris). Sahel is a recipient for patent royalties and GenSight Biologics.

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