International Consensus Statement on the Clinical and Therapeutic Management of Leber's Hereditary Optic Neuropathy

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Abstract: Leber hereditary optic neuropathy (LHON) is currently estimated as the most frequent mitochondrial disease (1 in 27,000–45,000). Its molecular pathogenesis and natural history is now fairly well understood. LHON also is the first mitochondrial disease for which a treatment has been approved (idebenone–Raxone, Santhera Pharmaceuticals) by

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Before initiation of this Consensus conference, scientific leaders and all members of the jury were required to complete conflict of interest statements. None of the experts had disqualifying conflicts of interest. With reference to authors of this paper: V. Carelli has a consultancy agreement and is the PI of clinical trials sponsored by GenSight Biologics and Santhera Pharmaceuticals, and has received travel reimbursements and speaker honoraria from Santhera Pharmaceuticals; M. Carbonelli is an investigator in clinical trials sponsored by Gensight Biologics and Santhera Pharmaceuticals; T. Klopstock has received research grants, travel reimbursements, speaker and consultancy honoraria from Santhera Pharmaceuticals and GenSight Biologics; W. Lagrèze has a consultancy agreement with Santhera Pharmaceuticals and has received speaker honoraria from Santhera Pharmaceuticals; C. La Morgia has received travel reimbursements and speaker honoraria from Santhera Pharmaceuticals and is an investigator in clinical trials sponsored by Gensight Biologics and Santhera Pharmaceuticals; N. J. Newman has a consultancy agreement with GenSight Biologics and Santhera Pharmaceuticals and is the PI of clinical trials sponsored by Gensight Biologics; C. Orssaud has a consultancy agreement with Santhera Pharmaceuticals; A. Sadun has a consultancy agreement and is the PI of clinical trials sponsored by Gensight Biologics and Stealth Peptides; J. van Everdingen has no disclosures; C. Vignal-Clermont has a consultancy agreement and is the PI of clinical trials sponsored by Gensight Biologics; M. Votruba is an investigator in clinical trials sponsored by Santhera Pharmaceuticals; P. Yu-Wai-Man has a consultancy agreement with GenSight Biologics and is the PI of clinical trials sponsored by Gensight Biologics and Santhera Pharmaceuticals; P. Barboni has a consultancy agreement with Santhera Pharmaceuticals, has received travel reimbursements and speaker honoraria from Santhera Pharmaceuticals, and is an investigator in clinical trials sponsored by GenSight Biologics. The remaining authors report no conflicts of interest.

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the European Medicine Agency, under exceptional circumstances because of the rarity and severity of the disease. However, what remains unclear includes the optimal target population, timing, dose, and frequency of administration of idebenone in LHON due to lack of accepted definitions, criteria, and general guidelines for the clinical management of LHON. To address these issues, a consensus conference with a panel of experts from Europe and North America was held in Milan, Italy, in 2016. The intent was to provide expert consensus statements for the clinical and therapeutic management of LHON based on the currently available evidence. We report the conclusions of this conference, providing the guidelines for clinical and therapeutic management of LHON.

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Leber hereditary optic neuropathy (LHON) is a paradigm for mitochondrial diseases in many regards. It was the first disease to be associated with mitochondrial DNA (mtDNA) point mutations (1) and is, therefore, maternally inherited. These mutations affect complex I subunit genes. LHON is the most frequent mitochondrial disorder with a prevalence ranging from 1 in 27,000 in North East England (2) to 1 in 45,000 in a meta-analysis of reports in the European population (3).

LHON is a blinding disorder, usually affecting young men and leading to selective degeneration of retinal ganglion cells (RGCs) and optic atrophy within a year of disease onset. The subset of macular RGCs, providing axons for the papillomacular bundle and serving central vision, is affected first and preferentially, resulting in a loss of visual acuity, dyschromatopsia, large central scotomas, and temporal pallor of the optic disc (4,5). Recent optical coherence tomography (OCT) and histopathology studies have substantiated the occurrence of a precise pattern in retinal nerve fiber layer (RNFL) loss, disease progression, and natural history (6,7). In particular, loss of macular RGCs precedes the clinical disease onset; by approximately 4 months, maximal loss has occurred (8).

In unaffected carriers of the LHON mutation, there may be recognizable changes on fundus examination and OCT measurements including vascular abnormalities (microangiopathy and telangiectatic vessels), hyperemia of the optic disc, and RNFL swelling (pseudoedema) that is detected by OCT as increased thickness of the RNFL in the inferior and temporal quadrants (9,10). Conversion to the symptomatic stage is characterized by a loss of macular RGCs on OCT (preclinical changes), but with visual acuity and fields still being normal (8). A central scotoma subsequently develops and central visual acuity starts to deteriorate rapidly, at which stage the patient usually seeks medical attention. The evolution in the first weeks/months is described as acute/subacute, depending on how rapidly the loss of central vision evolves (11). Within 4 to 6 months, visual acuity stabilizes, but clinical metrics such as visual fields and OCT measurements may still evolve, usually plateauing at 1 year after onset. At this point, the so-called acute phase ends with a transition into the chronic stage of the disease. Despite the fact that most patients remain stable for the rest of their lives with profoundly impaired vision, a subgroup may experience some degree of spontaneous visual recovery depending on the mutation subtype and the age at onset (12).

LHON primarily is a clinical diagnosis. The features common to all mitochondrial optic neuropathies consist of central or cecocentral scotomas, impaired color vision, and ultimately optic nerve head pallor, especially temporally. In this context, particularly in a young adult, a subacute onset and a maternal family history of visual loss can be very useful in determining the diagnosis. A definitive diagnosis of LHON is rapidly obtained by the molecular identification of one of the 3 common mtDNA mutations (m.11778G>A/MT-ND4, m.3460G>A/MT-ND1, m.14484T>C/MT-ND6), accounting for about 90% of cases. If this primary screen is negative and there is a high index of clinical suspicion supported by a maternal mode of inheritance in a patient with a family history, sequencing the entire mtDNA is advisable to identify other, but rare, mtDNA mutations (13).

Currently, there is no proven therapy for LHON despite many purported treatments being tested (14,15). However, in June 2015, the European Medicine Agency (EMA) approved idebenone (Raxone, Santhera Pharmaceuticals, Liestal, Switzerland) under exceptional circumstances because of the rarity and severity of LHON. EMA recognized a sufficient amount of clinical evidence for safety and partial efficacy in a subgroup of treated patients (16–20). The approved product label states that idebenone is indicated for the treatment of visual impairment in adolescents and adult patients with LHON at a dose of 900 mg per day in 3 divided doses. However, there remains some controversy on the optimal target population, timing, dose, and frequency of administration of idebenone in LHON patients, compounded by the lack of accepted definitions, criteria, and general guidelines for the clinical management of this mitochondrial disorder.

To address these issues, a consensus conference with a panel of experts from Europe and North America was held in Milan, Italy. The conference aimed at providing expert consensus statements for the clinical and therapeutic management of LHON based on the currently available evidence.

METHODS

In March 2016, there was an inaugural congress, "Update on Optic Nerve Degeneration—a European network: first international meeting", held in Milan, Italy, under the patronage of the San Raffaele Scientific Institute, a tertiary reference health care center in Northern Italy. There were approximately 200 attendees, and this provided the opportunity for gathering most of the world experts in

mitochondrial optic neuropathies. A satellite meeting "Consensus Conference" focused on the "Clinical and Therapeutic management of LHON".

The expert panel dealing specifically with LHON consisted of 16 investigators in the field from Europe and North America who were chosen on the basis of their international recognition as experts in mitochondrial optic neuropathies and, in particular, in LHON. The final consensus jury included 13 experts, neurologists, and ophthalmologists, who accepted to participate and were able to attend in person. Three additional experts (A.K., C.V.-C., and M.V.) did not attend the consensus conference, but contributed substantially to different phases of the process. All participants were clinicians and investigators who had extensive experience in clinical and genetic management and research, as well as treatment of optic neuropathies and LHON. Three scientific participants (V.C., P.B., and C.L.M.) were appointed to lead the consensus process serving as the scientific committee. They also participated in the voting sessions because of the limited number of LHON experts and their widely recognized expertise in the field. The consensus process was conducted in line with the last updated methodological indications of the Italian Institute of Health (21). It was developed in 4 stages:

1. Creation of clinically relevant questions on LHON and definition of preliminary statements on the basis of a nonsystematic literature review
2. Integration of the feedback from the components of the jury
3. Consensus meeting with discussion and voting on refined statements on the basis of participants' clinical experience and available evidence
4. Analysis and publication of the final consensus statements.

The scientific committee identified a number of clinically relevant questions about LHON suitable for consensus discussion and formulated a series of statements addressing each question according to their experience and clinical evidence. All relevant scientific literature, as identified by scientific leaders and 2 methodological experts, were reviewed in advance to identify questions and draft preliminary statements relating to each question. To this end, a literature search was undertaken and was last updated on March 15, 2016. The data pack included studies relevant for the questionnaire topics, as identified by a MEDLINE search using "Leber's Hereditary Optic Neuropathy" or "Leber Hereditary Optic Neuropathy" or "LHON" as query, with no restrictions on publication date, but only studies published in English were considered. Studies were selected for inclusion if they were 1) randomized, double-blind, placebo-controlled, or uncontrolled trials; 2) observational studies including prospective or retrospective cohort studies, case–control or cross sectional studies; 3) case series; 4) case reports; 5) systematic reviews and meta-analyses; 6) expert opinion–based pieces; and 7) guidelines. Six hundred seventy-three articles were identified and made available to all participants, representing the basis for the proposed statements.

Before the meeting, all members of the jury received the questions and the statements elaborated by scientific leaders, for their assessment and possible changes. All changes and suggestions were considered by the 3 scientific leaders, and the statements were consolidated in a version that served as the basis for discussion at the consensus meeting. Four main aspects of LHON were selected: (I) staging; (II) diagnosis and prognosis; (III) therapeutic management; (IV) screening family members. A total of 20 questions were generated.

The meeting at San Raffaele Scientific Institute in Milan lasted 7 hours during which the scientific leaders presented each of the questions/statements. Each statement was debated, reformulated when it was considered incorrectly posed or misleading, and then voted through a 4-point Likert-type scale handled by an electronic voting system ("1—completely disagree", "2—partially disagree", "3—partially agree", "4—completely agree"). The total maximum possible score for any given statement was 52 (in the case, all 13 voters completely agreed to the proposed statement allocating a score of 13×4). The "consensus" threshold was set at $\geq$60% of the total possible score, whereas the "strong consensus" threshold was set at $\geq$75%. Each participant (including scientific leaders) was equally weighted in scoring the statements. If one of these 2 thresholds was met, the statement was considered approved. If a consensus was not reached (i.e., a score of $<$60%), the statement was considered not approved.

The results that were originally tabulated at the consensus meeting were submitted in Microsoft PowerPoint form to all members of jury, for their final approval. The manuscript reporting the outcomes of the consensus conference was drafted by the scientific leaders and circulated to all members of the jury for final editorial additions and approvals.

RESULTS

The results of the consensus process, with all questions and related statements, are summarized in Table 1. A strong consensus was reached for 16/20 statements, and there was a lack of consensus for 3 statements. The jury decided that there was no scientific basis for voting on 1 statement (Table 1, statement 14).

(I) Staging

Rationale

Historically, LHON has been categorized into 3 distinct clinical groups: asymptomatic mutation carriers, patients with acute LHON (with disease duration of 1 year or less), and those with chronic LHON (with disease duration of

TABLE 1. Consensus questions and statements regarding the diagnosis and management of LHON

Question/ Statement	Final Formulation of the Question	Final Formulation of the Statement	Number of Voters	Maximum Score	Total Score	% of Maximum Score	Final Outcome
1	How would you describe the different clinical stages of LHON?	**Clinical stages of LHON can be defined according to time from onset and clinical investigations** (see text for details)	12*	48	46	95.8	**Strong consensus**
2	Are there any clinical characteristics, algorithms or investigations to reach a fast diagnosis of LHON?	**Diagnosis of LHON can be usually made based on patient and family clinical history as well as baseline investigations including a formal neuro-ophthalmological examination and mtDNA genetic testing**	12*	48	47	97.9	**Strong consensus**
3	Typically, how long does it take from symptom onset to confirmation of diagnosis?	**It can take months to reach a confirmed diagnosis**	12*	48	48	100	**Strong consensus**
4	What are the main differential diagnoses?	**Other optic neuropathies especially optic neuritis (neuromyelitis optica), toxic, metabolic and compressive optic neuropathies, maculopathies, nonorganic visual loss (not a diagnosis of exclusion)** (see text for further details)	13	52	49	94.2	**Strong consensus**
5	How would you assess a patient's prognosis? Does this impact on your management?	**In LHON, positive prognostic factors are younger age and type of mutation (14484/ ND6). However, prognostic factors do not affect management**	13	52	51	98.1	**Strong consensus**
6	Before initiating any treatment, what baseline assessments do you usually perform?	**The following examinations should be performed before starting any treatment: Visual acuity; Visual fields; OCT**	13	52	50	96.2	**Strong consensus**
7	In subacute/dynamic (<6 mo, 6–12 mo) patients, at which stage of disease would you ideally start 900 mg/d treatment?	**Idebenone should be started as soon as possible at 900 mg/d in patients with disease less than 1 yr**	13	52	48	92.3	**Strong consensus**
8	In chronic cases, do you consider treatment?	**There is not enough evidence to recommend treatment in chronic patients between 1 and 5 yr (after the 2nd eye onset), and no evidence to recommend treatment in chronic patients older than 5 yr (after the 2nd eye onset)**	13	52	42	80.8	**Strong consensus**

(Continued)

Question/ Statement	Final Formulation of the Question	Final Formulation of the Statement	Number of Voters	Maximum Score	Total Score	% of Maximum Score	Final Outcome
9	What is your suggested frequency of follow-up, would it differ by stage?	**The ideal frequency of follow-up is as follows: Approximately every 3 mo for subacute and dynamic cases, approximately every 6 mo for the 2nd yr, once a year thereafter**	13	52	51	98.1	**Strong consensus**
10	How would you define as a clinically relevant response (recovery of vision) to treatment?	**Response should be defined according to the following: Improvement of 2 lines of BCVA on Snellen charts (or from off-chart to on-chart), visual fields (mean deviation)**	13	52	46	88.5	**Strong consensus**
11	How long would you treat at 900 mg/d to assess response?	**In subacute/dynamic patients, treatment at 900 mg/d should be continued for at least 1 yr to assess response**	13	52	48	92.3	**Strong consensus**
12	Once you have confirmed a favorable clinically relevant outcome, for how long after plateau would you continue treatment?	**1 yr**	13	52	42	80.8	**Strong consensus**
13	If you treat a chronic patient, for how long would you continue treatment?	1 yr	8†	32	28†	53.8	Lack of consensus
14	For chronic patients, once you have confirmed a favorable clinically relevant outcome, for how long after plateau would you continue treatment?	1 yr	13	52	Not voted because of lack of consensus on statement 13		
15	What assessments do you perform to evaluate response during maintenance phase?	**The following examinations should be performed to assess response during maintenance phase: visual acuity, visual fields**	13	52	50	96.2	**Strong consensus**
16	Do you consider a maintenance dose also for nonresponders?	In nonresponders, the maintenance dose can be 300 mg/d	13	52	17	32.7	Lack of consensus
17	Is it necessary to perform genetic screening for LHON mutations in all maternally related family members?	**No**	13	60	43	71.6	**Strong consensus**
18	Should all maternally related relatives be clinically screened?	Yes	13	52	19	36.5	Lack of consensus
19	Would you consider treating them?	**Currently, treatment is not recommended for relatives of a LHON patient, but lifestyle counseling is recommended**	13	52	52	100	**Strong consensus**

(Continued)

Question/ Statement	Final Formulation of the Question	Final Formulation of the Statement	Number of Voters	Maximum Score	Total Score	% of Maximum Score	Final Outcome
20	Are you aware of any algorithm or predictive risk factors that could be used to assess the risk of becoming symptomatic?	**Currently, there is no clinical prognostic factor that can be used**	13	52	47	90.4	**Strong consensus**

Bolding indicates the final formulation of the statements and the final outcomes that reached a strong consensus.
*One expert did not vote on the first 3 statements because of logistical issues.
†Only 8 voters, the other participants did not vote.
BCVA, best-corrected visual acuity; LHON, Leber hereditary optic neuropathy.

more than 1 year) (9,11). More recently, the assessment by OCT of the different stages of LHON (10,22), in conjunction with the natural history (6,8) and established visual parameters, such as best-corrected visual acuity (BCVA) and visual fields, has provided new insights that have led to the subclassification of the acute stage into "subacute" and "dynamic" stages (Table 1, statement 1). Other phenotypic groups have been proposed, namely, childhood- and late-onset LHON (23,24), and the contribution of anatomic (25), environmental (26–30), and hormonal factors (31) have emerged as potential disease modifiers.

Question 1: How would you describe the different clinical stages of LHON?

Clinical stages of LHON can be defined as follows, according to time from onset and clinical investigations:

0. Asymptomatic (mutation carriers)
1. Subacute (<6 months from onset)
2. Dynamic (6–12 months)
3. Chronic (>12 months)

The following clinical variants also can be considered:

1. Slowly progressive, defined according to patients' characteristics independently from time since disease onset
2. Childhood disease, that is, onset in a patient younger than 12 years
3. Late onset, that is, onset in a patient older than 45 years

The jury emphasized that for the clinical diagnosis, the following clinical investigations were important: visual acuity, color vision, fundus examination, visual field perimetry, and OCT imaging. The participants also noted that for childhood disease, the optic nerve head size was important. For late-onset LHON cases, the participants also felt that it was important to consider toxic exposure (smoking, drinking, and environmental factors) and hormonal factors (estrogens).

For the statement, there was strong consensus.

(II) Diagnosis and Prognosis

Rationale

The diagnosis of LHON has been greatly improved by the availability of genetic testing (32). However, LHON remains a clinical diagnosis with recognizable clinical features and disease evolution (4,5), which is corroborated by the maternal inheritance of the disease, (33) when there is a family history, leading to Statement 2 (Table 1).

Question 2: Are there any clinical characteristics, algorithms, or investigations to reach a rapid diagnosis of LHON?

Diagnosis of LHON can usually be made based on patient and family clinical history as well as baseline investigations including neuro-ophthalmological examination and mtDNA genetic testing.

There was a strong consensus.

Rationale

Despite the greatly improved recognition of LHON, there can still be considerable diagnostic delay, that is, compounded by variability in the initial findings and misinterpretation of the clinical picture, in particular with optic neuritis (34,35) or toxic optic neuropathy (36). A differential diagnosis remains an important point to consider, as noted in statements 3 and 4 (Table 1).

Question 3: Typically, how long does it take from symptom onset to confirmation of diagnosis?

"It can take months to reach a confirmed diagnosis."

There was a strong consensus.

Question 4: What are the main differential diagnoses?

1. Other optic neuropathies especially optic neuritis (neuromyelitis optica), toxic, metabolic, and compressive optic neuropathies
2. Maculopathies
3. Nonorganic visual loss

If further extraocular features are present, consider LHON "Plus", including LHON/MS-like variant. Consider performing appropriate investigations including brain MRI and laboratory studies.

There was strong consensus.

Rationale

Multiple reports on large LHON cohorts from different countries have defined some prognostic factors, which may impact the clinical course (23,25,37–39) and possibly the management of the disease, leading to statement 5 (Table 1).

Question 5: How would you assess a patient's prognosis? Does this impact your management?

In LHON, positive prognostic factors are as follows:

1. Younger age
2. Type of mutation (14484/ND6)

However, prognostic factors do not affect management. There was a strong consensus.

(III) Therapeutic Management

Rationale

The standard clinical evaluation of LHON patients includes visual acuity and visual fields. OCT studies have proved to be a valuable tool in evaluating the clinical course of the disease (6,8,10,22). These considerations led to statement 6 (Table 1).

Question 6: Before initiating any treatment, what baseline assessments do you usually perform?

The following examinations should be performed before starting any treatment:

1. Visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] charts)
2. Automated visual field test
3. OCT (optic nerve head and RNFL analysis, and macular ganglion cell analysis)

There was a strong consensus.

Rationale

Idebenone has been used as treatment of patients with LHON since 1992 (40–43). A number of publications have recently evaluated the therapeutic benefit of idebenone in LHON, including a placebo-controlled randomized clinical trial of 85 patients treated for 24 weeks with a dosage of 900 mg/day (16,19,20) and a large retrospective case series of 44 patients treated with variable doses of idebenone over a mean treatment duration of 41 months compared with 59 untreated patients (17). Based on the available literature and the personal experience of the experts, statements 7–16 were formulated to critically evaluate a number of issues, including inclusion criteria for treatment, dosage, and duration of treatment, as well as follow-up evaluations for assessing a clinically relevant response to treatment.

Question 7: In subacute/dynamic (<6 months, 6–12 months) patients, at which stage of disease would you ideally start 900 mg/day treatment?

"Idebenone should be started as soon as possible at 900 mg/day in patients with disease less than 1 year."

There was a strong consensus with 1 participant in partial disagreement.

Question 8: In chronic cases, do you consider treatment?

There is not enough evidence to recommend treatment in chronic patients between 1 and 5 years (after the second eye onset), and no evidence to recommend treatment in chronic patients >5 years (after the second eye onset).

There was a strong consensus, but 2 participants disagreed.

Question 9: What is your suggested frequency of follow-up, would it differ by stage?

The ideal frequency of follow-up is as follows:

1. Approximately every 3 months for subacute and dynamic cases
2. Approximately every 6 months for the second year
3. Once a year thereafter

There was a strong consensus.

Question 10: How would you define a clinically relevant response (recovery of vision) to treatment?

Response should be defined according to:

1. Improvement of 2 lines of BCVA on ETDRS charts (or from off-chart to on-chart)
2. Automated visual field test (mean deviation)

There was strong consensus with 1 participant in partial disagreement.

Question 11: How long would you treat at 900 mg/day to assess response?
"In subacute/dynamic patients, treatment at 900 mg/day should be continued for at least 1 year to assess the start of therapeutic response or until a plateau in terms of improvement is reached."

There was strong consensus.

Question 12: Once you have confirmed a favorable clinically relevant outcome, for how long after plateau would you continue treatment?
"One year."

There was strong consensus, but 2 participants partially disagreed and 1 participant disagreed.

Question 13: If you treat a chronic patient, for how long you would continue treatment?
"One year."

Consensus was not reached. Five participants did not vote.

Question 14: For chronic patients, once you have confirmed a favorable clinically relevant outcome, for how long after plateau would you continue treatment?
"One year."

Not voted because of lack of consensus on statement 13.

Question 15: What assessments do you perform to evaluate response during maintenance phase?
The following examinations should be performed to assess response during maintenance phase:

1. Best-corrected visual acuity
2. Automated visual field test

There was strong consensus.

Question 16: Do you consider a maintenance dose also for nonresponders?
"In nonresponders, the maintenance dose can be 300 mg/day."

There was strong disagreement, with 1 participant in agreement.

(IV) Screening of Family Members

Rationale
The provision of genetic testing (32) of the proband's maternal lineage poses a number of ethical and economical issues, which led to statement 17 (Table 1).

Question 17: Is it necessary to perform genetic screening for LHON mutation in all maternally related family members?
"No."

There was a strong consensus.

Rationale
Similarly, the clinical evaluation and prophylactic treatment of unaffected LHON mutation carriers is a particularly relevant issue (9,10,25–27,29,39,44–47). This point has been developed in statements 18 and 19 (Table 1).

Question 18: Should all maternally related relatives be clinically screened?
Yes.

Eleven participants disagreed that all maternally related relatives should be screened. There was strong disagreement with 2 participants in agreement.

Question 19: Would you consider treating them?
"Currently, treatment is not recommended for relatives of a LHON patient, but lifestyle counseling is recommended."

There was a strong consensus.

Rationale
There are a few proposed risk factors for disease conversion (25,27,29,39,48). However, a systematic validation of these factors translated into a scoring system predicting disease risk is still pending. This issue led to the final statement 20 (Table 1).

Question 20: Are you aware of any algorithm or predictive risk factors that could be used to assess the risk of becoming symptomatic?
Currently, there is no clinical prognostic factor that can be used.

There was strong consensus, with 1 participant in disagreement.

The jury unanimously endorsed the final version of all questions and statements (Table 1).

DISCUSSION

There was strong consensus for 16 statements, whereas for 3 statements, there was a lack of consensus (13, 16, and 18). For statements 8, 12, and 20, there was specific disagreement from 2, 1, and 1 participants, respectively. Specifically, for statement 8, the 2 participants believed that there was sufficient evidence to justify the use of idebenone for chronic cases. For statement 12, 1 participant believed that idebenone treatment could be continued for more than 1 year after plateau in patients who had shown a treatment response. For statement 20, 1 participant disagreed that there is no reliable predictive risk factor to assess the risk of disease conversion in a LHON carrier.

There was strong disagreement for statements 16 and 18. Eleven of 13 participants fully disagreed that idebenone should be continued with a maintenance dose in nonresponder patients. Also, 11 of 13 participants fully disagreed that it was necessary to clinically screen all maternal relatives including asymptomatic carriers.

Statements 1 to 6 and 9 pertained to the diagnosis and work-up of patients who presented with LHON for which there was strong consensus. The group debated the historical staging (9,11) of the disease and introduced

a new distinction. Based on the currently available published evidence (6,8), the first year of the disease can be subdivided into subacute (less than 6 months) and dynamic (6–12 months) phases, based on both functional and structural changes. Visual acuity decreases throughout the subacute phase and then stabilizes at about 6 months. Thinning of the macular RGC layer measured by OCT is largely completed in 4–6 months, highlighting the severe cell loss of the cells originating the papillomacular bundle (8,49). RNFL thickness evaluated by OCT is characterized in the first 6 months by swelling, followed by progressive quadrant specific thinning (6). Thus, the dynamic stage, 6–12 months after onset, is characterized by still ongoing changes in RNFL as opposed to a substantial stability of RGC loss in the macula (8). Visual field defects may progress in this dynamic stage (50). Although the ideal therapeutic window for LHON remains unknown, it is possible that there is a greater potential for visual recovery in the subacute phase compared with the dynamic phase.

Statements 7, 8, and 10–16 pertained to the use of idebenone in LHON. The group reached consensus that idebenone was indicated in subacute and dynamic patients at 900 mg/day dosage (16), starting the treatment as soon as possible (17). There was also consensus about the continuation of the treatment in responders based on the established outcome measures of BCVA and visual fields, and the criteria for defining a clinically relevant response (17). The group strongly disagreed with the use of idebenone as a maintenance dose in nonresponders who have received treatment for 1 year. Concerning patients in the chronic stage (>1 year), it was determined that there was not enough evidence to support treatment for those patients with disease duration of 1–5 years, and no evidence for treatment after 5 years of disease. As a consequence, there was no consensus on statement 13 and the jury unanimously agreed not to vote on statement 14. The group based its judgment strictly on the existing data on clinical administration of idebenone in patients, as derived from the published literature (14–20,40–43) and the unpublished information publicly available at the EMA website, including the European public assessment report ([EPAR]; ema.europa.eu/Find medicine/Human medicines/EPARs) and the summary of the opinion of the Committee for Orphan Medicinal Products for Raxone (ema.europa.eu/Find medicine/Human medicines/Rare disease designation). Preclinical research also was considered (51–55), as was the fact that the effectiveness and mechanisms of action of idebenone are still a subject of debate.

Statements 17–20 pertained to the proband's maternally related relatives and specifically unaffected carriers. The group agreed that the unaffected mutation carriers did not require routine genetic or clinical testing. However, as best practice with any genetic disease, genetic counseling is offered to the patient who has the right to refuse any wider family involvement. Furthermore, the group reached a strong consensus that treatment is not recommended for asymptomatic carriers, and that there is currently no prognostic measure to predict disease conversion.

CONCLUSIONS AND RELEVANCE FOR CLINICAL PRACTICE

The diagnosis of LHON should be based on a careful history, evaluation of key structural and functional visual parameters, and on a molecular confirmation of a pathogenic mtDNA mutation. The management of LHON includes genetic counseling, informing the patient about potentially preventable lifestyle risk factors and, for subacute and dynamic cases, the use of idebenone at the currently approved dose. Idebenone should be discontinued in nonresponder patients and is currently not recommended in patients in the chronic stages of the disease. These guidelines and recommendations are based on a consensus developed on the current state of the literature. Further investigations and clinical trials are needed to lead to better disease-modifying treatments and to improve the management of patients with LHON.

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