

Effect of EPI-743 on the Clinical Course of the Mitochondrial Disease Leber Hereditary Optic Neuropathy

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Objective: To evaluate the safety and efficacy of a new therapeutic agent, EPI-743, in Leber hereditary optic neuropathy (LHON) using standard clinical, anatomic, and functional visual outcome measures.

Design: Open-label clinical trial.

Setting: University medical center.

Patients: Five patients with genetically confirmed LHON with acute loss of vision were consecutively enrolled and treated with the experimental therapeutic agent EPI-743 within 90 days of conversion.

Intervention: During the course of the study, 5 consecutive patients received EPI-743, by mouth, 3 times daily (100-400 mg per dose).

Main Outcome Measures: Treatment effect was assessed by serial measurements of anatomic and functional visual indices over 6 to 18 months, including Snellen visual acuity, retinal nerve fiber layer thickness

measured by optical coherence tomography, Humphrey visual fields (mean decibels and area with 1-log unit depression), and color vision. Treatment effect in this clinical proof of principle study was assessed by comparison of the prospective open-label treatment group with historical controls.

Results: Of 5 subjects treated with EPI-743, 4 demonstrated arrest of disease progression and reversal of visual loss. Two patients exhibited a total recovery of visual acuity. No drug-related adverse events were recorded.

Conclusions: In a small open-label trial, EPI-743 arrested disease progression and reversed vision loss in all but 1 of the 5 consecutively treated patients with LHON. Given the known natural history of acute and rapid progression of LHON resulting in chronic and persistent bilateral blindness, these data suggest that the previously described irreversible priming to retinal ganglion cell loss may be reversed.

Arch Neurol. 2012;69(3):331-338

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LEBER HEREDITARY OPTIC NEUROPATHY (LHON) is a mitochondrial disease that is caused by single-point mutations occurring in mitochondrial DNA (mtDNA). LHON predominantly affects young male patients and leads in most cases to persistent bilateral blindness.¹ There are no effective or approved treatments for LHON or other related mitochondrial optic neuropathies.² LHON is the most common mtDNA mitochondrial disease, with a prevalence of 1 in 50 000.³ There are 3 common pathogenic mtDNA mutations affecting nicotinamide adenine dinucleotide (NADH) dehydrogenase (ND) subunit genes at positions 11778/ND4, 3460/ND1, or 14484/ND6, leading to dysfunction of complex I of the mitochondrial respiratory chain.⁴ LHON, the first genetically defined inherited respiratory chain disorder, differs from other respiratory chain diseases by its tissue specificity.⁵ In contrast to most mito-

chondrial diseases that affect the brain, heart, muscle, and other vital organs, the clinical features of LHON are usually from compromise of the retinal ganglion cells.⁶ Typically, LHON presents with sudden unilateral, followed by bilateral, central visual loss and blindness. With the exception of the less common 14484/ND6 mutation, which may be associated with spontaneous partial and late (1-5 years) recovery, the resulting visual impairment is irreversible.⁷

Interestingly, most individuals carrying LHON point mutations do not manifest clinical blindness. Several theories and mechanisms have been advanced to explain how unaffected mutation carriers are triggered into acute clinical conversion, thus becoming affected. These include oxidative stress, reduced bioenergetic capacity, gender, and nuclear-modifying and environmental factors that predispose or prompt retinal ganglion cells to undergo apoptotic cell death.⁸

Given the attendant oxidative stress associated with mitochondrial disease in general, and specifically as a purported LHON trigger, the therapeutic benefit of a number of antioxidants has been explored. Recent data suggest that a coenzyme Q₁₀ analogue, idebenone, may have limited beneficial clinical effects.⁹⁻¹¹ Other antioxidants and cofactors including cyanocobalamin, folic acid, ascorbic acid, and coenzyme Q₁₀ have also been clinically evaluated without demonstrable benefit.^{2,12,13} Today, there is no effective treatment for LHON or any inherited mitochondrial optic neuropathy arising from either nuclear or mtDNA errors affecting the mitochondrial respiratory chain.¹⁴

Given the absence of an effective drug and the known clinical outcome of severe blindness in LHON, we gained US Food and Drug Administration (FDA) and internal review board approval to evaluate EPI-743 in patients with LHON who were actively losing vision, on an emergency treatment basis. EPI-743 is an experimental therapeutic agent that has been developed for life-threatening inherited respiratory chain diseases of the mitochondria. Herein, we describe 5 consecutive patients with LHON who were treated with EPI-743 in the active converting phase of their clinical course.

METHODS

STUDY PARTICIPANTS

Nine eyes of 5 consecutive and unrelated patients carrying either the 11778/ND4, 14484/ND6, or 3460/ND1 homoplasmic mutation were studied during and after the acute visual loss stage of the disease. All patients were followed up at the Doheny Eye Institute, Department of Ophthalmology, USC-Keck School of Medicine. Baseline measurements were performed prior to initiation of EPI-743 therapy and throughout the course of treatment. Inclusion criteria for this study included molecular characterization of LHON and active loss of vision from LHON. All subjects had an extensive neuro-ophthalmologic and psychophysical examination with particular attention to optic nerve assessments. All patients received EPI-743 orally, 3 times daily (100-400 mg per dose), in a solution of US Pharmacopeia sesame oil. Each patient had pharmacokinetic analyses to confirm plasma level of drug at peak plasma concentration (C_{max}) and minimum plasma concentration (C_{min}). All participants gave their informed consent according to the Declaration of Helsinki, and the study was approved by the internal review board of the USC-Keck School of Medicine.

INSTRUMENTATION AND PROCEDURES

All subjects underwent retinal nerve fiber layer (RNFL) thickness measurement by optical coherence tomography (OCT) (Stratus OCT, software version 4.0.1; Carl Zeiss Meditec Inc) using the RNFL thickness 3.4 acquisition protocol, as previously reported.¹⁵ For each eye, we studied the mean RNFL thickness (360° measure) and each quadrant separately, all automatically calculated by OCT using the existing software. Visual fields were obtained using the Humphrey 30-2 strategy with Stimulus III White (Carl Zeiss Meditec Inc). Measurements included mean deviation (MD) and total deviation relative to the Glaucoma Change Probability Analysis. Visual acuity assessments were performed using a Snellen chart at 6 m. The criteria used to determine significant change in visual acuity and

visual fields are 2 or more lines of improvement in Snellen acuity, 2 or more plates improving for color vision, and a 5-dB or more improvement in MD of visual field sensitivity.

PHARMACOKINETICS

The analysis of EPI-743 was performed using an Agilent 1100 high-performance liquid chromatography (HPLC) system (Agilent Technologies) connected to a Sciex API 5000 triple quadrupole LC-MS/MS (liquid chromatography–tandem mass spectrometry) (AB Sciex) with a Turbo V Ion Spray Source (AB Sciex). The HPLC system used a Zorbax Eclipse Plus Phenyl-Hexyl (1.8 μm), 2.1 × 50-mm analytical column (Agilent Technologies), with an aqueous phase of acetic acid, 1M ammonium acetate, and water (2/2/96, volume/volume/volume) and an organic phase of acetonitrile. This bioanalytical method was determined to be accurate and precise in the validated calibration range from 1.00 to 1000 ng/mL. Samples with a concentration higher than the upper limit of quantification were accurately quantified by diluting the samples up to a 20-fold dilution with blank matrix to achieve a concentration within the range of the calibration curve. All processed plasma samples of EPI-743 were exposed to air to fully oxidize EPI-743 to its quinone state before LC-MS/MS quantification. Deuterated EPI-743 (d₄-EPI-743) was used as an internal standard. All EPI-743 analyses were conducted in compliance with the US FDA Good Laboratory Practices (21 CFR part 58) using a validated method developed in accordance with the US FDA *Guidance for Industry: Bioanalytical Method Validation*.¹⁶ All samples were analyzed by MPI Research Inc.

STATISTICAL ANALYSIS

Mean values of RNFL thickness at different time points were compared by ordinary analysis of variance with the Dunnett posttest; Gaussian distribution was assessed using the Kolmogorov-Smirnov test. $P \leq .05$ was considered statistically significant. All statistical analyses were performed using GraphPad InStat version 3a for Macintosh (GraphPad Software).

RESULTS

CLINICAL COURSE

Of the 5 subjects, 4 demonstrated objective and clinically significant signs and symptoms of improvement independent of the specific genetic form of LHON and age (8-54 years). Only these 5 subjects were issued approvals by the USC-Keck School of Medicine institutional review board and the US FDA and were treated with EPI-743 for a minimum of 1 year. Subjectively, 4 of the 5 subjects, their care providers, or both, noted improvement in vision. Objective improvements were noted in frequent and serial measures of visual acuity, visual fields, color vision, and quality of life. Details of specific subjects are discussed in the following subsections (**Table**). No participants experienced a drug-related adverse event.

REPORT OF CASES

Patient 1

Patient 1 was a 24-year-old man who had been diagnosed with LHON 1 month earlier (11778/ND4 muta-

Table. Summary of Visual Acuity and Related Parameters Over Time and Treatment With EPI-743^a

Patient No.	mtDNA Mutation	EPI-743 Plasma C _{max} (by Mouth, 200 mg) ^b	Time of Treatment (as of June 15, 2011)	Treatment Status	Visual Acuity ^c		Visual Field (VF) ^d			Color Vision, No. of Ishihara Plates of 8		
					OD	OS	VF OD	MD OD, dB	VF OS	MD OS, dB	OD	OS
1	11778	816 ng/mL	557 d	Pre	20/400	20/200	15.0° × 20.0°	-11.63	10.0° × 10.0°	-5.46	2/8	8/8
				Post	20/40	20/25	7.5° × 7.5°	-1.70	5.0° × 5.0°	-1.34	8/8	8/8
2	11778	516 ng/mL	546 d	Pre	20/400	NA	15.0° × 5.0°	-9.62	NA	NA	2/8	NA
				Post	20/400	NA	10.0° × 7.5°	-8.65	NA	NA	3/8	NA
3	11778	178 ng/mL	399 d	Pre	CF 1 ft (0.3 m)	20/60	27.5° × 27.5°	-32.91	5.0° × 5.0°	-2.78	0/8	8/8
				Post	CF 6 ft (1.8 m)	CF 6 ft (1.8 m)	27.5° × 27.5°	-30.99	25.0° × 25.0°	-32.11	0/8	0/8
4	14484 (100-mg dose)	265 ng/mL	280 d	Pre	20/50	20/20	25.0° × 25.0°	-29.9	5.0° × 5.0°	-2.48	5/8	8/8
				Post	20/20	20/20	NL	-3.06	NL	-1.45	8/8	8/8
5	3460	268 ng/mL	204 d	Pre	CF 6 ft (1.8 m)	20/400	30.0° × 30.0°	-25.36	30.0° × 30.0°	-24.05	0/8	0/8
				Post	CF 1 ft (0.3 m)	CF 1 ft (0.3 m)	15.0° × 20.0°	-18.29	27.5° × 27.5°	-14.68	0/8	0/8

Abbreviations: CF, count fingers (at number of feet); I, inferior; LHON, Leber hereditary optic neuropathy; MD, mean deviation; mtDNA, mitochondrial DNA; NA, not applicable; NL, normal; OD, right eye; OS, left eye; Post, posttreatment; Pre, pretreatment.

^aPatient 1 showed improvements in all visual parameters in both eyes after treatment with EPI-743. See Figure 1 that demonstrated results longitudinally (rows 1 and 2 = visual acuities for right and left eyes; and rows 3 and 4 = visual fields for right and left eyes). This is a dramatic reversal in the natural history of 11778 mutation sustained for over 1 year. Patient 2 stabilized in her vision. She showed modest improvements in her visual field of her 1 testable eye, not in accordance with the natural history of 11778 mutation. Patient 3 continued to deteriorate in a trajectory consistent with the natural history of 11778 mutation. Patient 4 showed immediate and dramatic recovery, which was much too soon and much too complete to be the natural history of LHON, even for 14484 mutation. Patient 5 (mutation 3460) showed improvement in visual field in both eyes.

^bPeak plasma concentration (C_{max}) was obtained from a single oral 200-mg dose and sampled between 1 to 4 hours.

^cBest corrected.

^dVisual field is presented both as area lost (with criteria of each point being ≥2 SDs below normal and therefore <5% by chance) and MD (in decibels of sensitivity).

tion), but had demonstrated decreased visual acuity 7 months (OD) and 3 months (OS) earlier. There was no family history of the disease.

On examination, visual acuity was 20/400 (OD) and 20/200 (OS), color vision (measured as number of Ishihara plates of 8) was 2/8 (OD) and 8/8 (OS), and there was a 2+ afferent pupillary defect (APD) (OD). Fundus examination showed 2+ optic atrophy (OU [both eyes]), and OCT revealed nasal RNFL swelling (OU). Results of a 30-2 Humphrey visual field (HVF) test showed a large and dense central scotoma (OD) with an MD of -11.63 dB, and a less dense and smaller central scotoma (OS) with an MD of -5.46 dB (**Figure 1**). He was started on EPI-743 therapy, 100 mg 3 times daily, and then increased to 200 mg 3 times daily, after 2 weeks. At 2 weeks, color vision had improved to 5/8 (OD). At 2 months, visual acuity improved to 20/200 (OU). Color vision improved to 8/8 (OD). Results of an HVF test showed a decreased central scotoma (OD). At 3 months, the HVF results improved (OS), and at 5 months, the HVF results improved further (OD). At 7 months, visual acuity improved to 20/80 (OD) and 20/30 (OS) and HVF results showed further improvements (OU). At 1 year, visual acuity improved to 20/40 (OD) and 20/25 (OS) and HVF results showed further marked improvements with MDs of -1.70 (OD) and -1.34 (OS) (Table).

Patient 2

Patient 2 was a 52-year old self-referred woman who complained of loss of vision (OD) for 3 to 4 weeks. Her history revealed long-standing, very poor vision (OS) due to several retinal detachments. Therefore, in this report only changes in OD are presented. There was no family history consistent with LHON.

On examination, visual acuity was 20/40 (OD) and HM (hand motion) at 6 ft (1.8 m) (OS), color vision was 2/8 (OS) and 0/8 (OD), and there was an APD (OS). Fundus examination revealed RNFL swelling between optic disc and fovea (OD) (**Figure 2**). Results from a 30-2 HVF test showed generalized depression (OD). One month later, visual acuity had dropped to 20/400 (OD), and the HVF results showed a deeper central scotoma with an MD of -7.82 dB, which prompted LHON testing that revealed the 11778/ND4 mutation. She was then started on EPI-743 therapy at 100 mg 3 times daily, and then increased to 200 mg 3 times daily, after 2 weeks. At 1 and 2 months, visual acuity had increased to 20/300 but the HVF scotoma was larger. At 6 months, the visual acuity was 20/300, color vision was 0/8, and the HVF scotoma was denser and larger. At 7 months, although the visual acuity was 20/400, the HVF scotoma was smaller and less dense. At 12 months, the visual acuity had im-

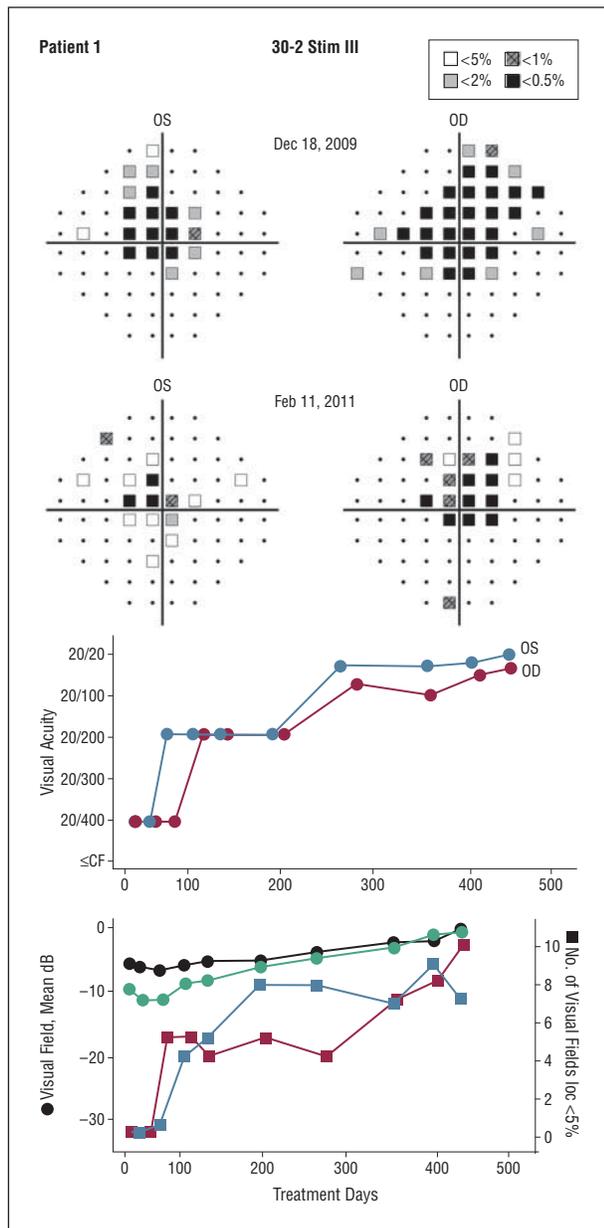


Figure 1. Longitudinal analysis of patient 1. Note, examples of central scotoma become smaller in both eyes and graphs depict improvements in visual acuities as well as both visual field parameters over time. "loc <= 5%" Indicates there is a greater than 95% chance that the sensitivity at that point is "truly" depressed. OD indicates right eye; OS, left eye; 30-2 Stim III, Humphrey 30-2 strategy with Stimulus III White (Carl Zeiss Meditec).

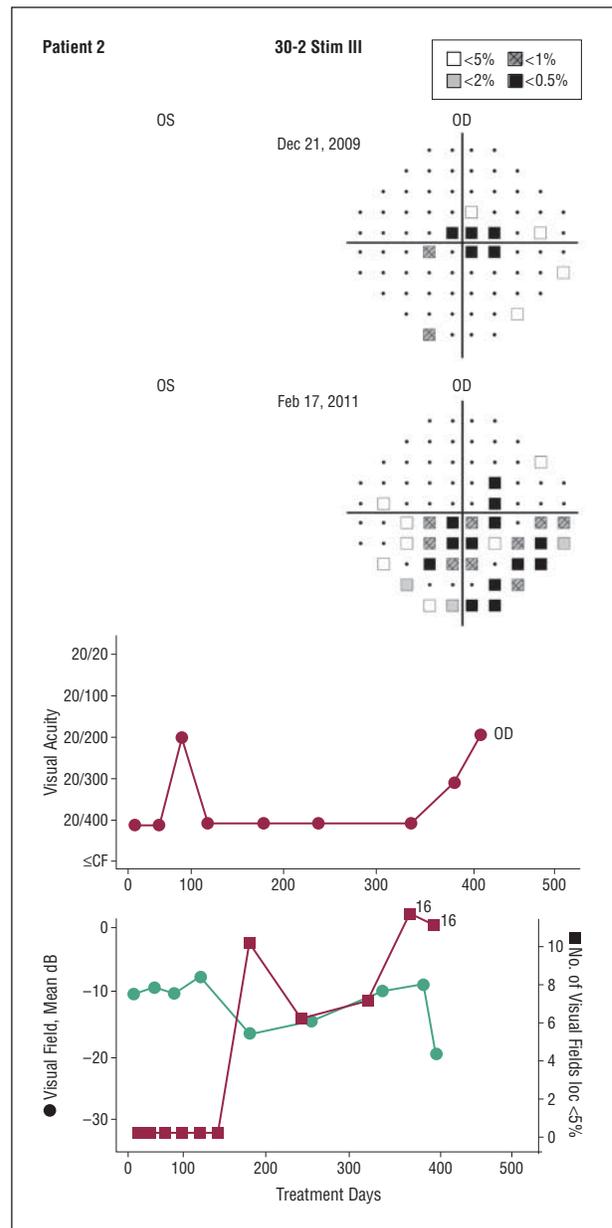


Figure 2. Longitudinal analysis of patient 2. The top shows the visual field in the right eye; the left eye was lost to retinal detachments decades earlier. The graphs depict improvement in visual acuity and visual field by the same criteria as Figure 1. "loc <= 5%" Indicates there is a greater than 95% chance that the sensitivity at that point is "truly" depressed. OD indicates right eye; OS, left eye; 30-2 Stim III, Humphrey 30-2 strategy with Stimulus III White (Carl Zeiss Meditec).

proved again to 20/200 and the HVF was stable. At 18 months HVF had improved (Table).

Patient 3

Patient 3 was a 17-year-old man in whom LHON (11778/ND4 mutation) was diagnosed 15 days after complaints of severe loss of vision (OD). There were other cases of LHON in his family. Visual acuity was CF (count fingers) at 18 in (45 cm) (OD) and 20/20 (OS), color vision was 0/8 (OD) and 8/8 (OS), and there was no APD. Fundus examination and OCT revealed RNFL swelling in superior and inferior areas (OD) (**Figure 3** and Table). His left eye showed

areas of peripapillary swelling with telangiectatic vessels, and OCT revealed moderate inferior RNFL swelling (OS). The 30-2 HVF results showed a large and dense central scotoma (OD) with an MD of -21.12 dB, and a normal OS with an MD of -2.53. Two months later, there was loss of vision (OS), measured as 20/60, with HVF results showing a central scotoma with an MD of -5.79 (OD now had a denser and larger central scotoma). He was placed on EPI-743 therapy, 100 mg for 2 weeks and then increased to 200 mg 3 times daily. Over the next 2 months, visual acuity worsened and stabilized to CF at 2 ft (0.6 m) (OD) and CF at 4 ft (1.2 m) (OS). At this point, pharmacokinetic

analysis showed his drug levels to be lower than expected, possibly due to bile acid deficiencies and absorption issues, and his EPI-743 dose was increased to 300 mg 3 times daily. This persisted at 3 months, so the EPI-743 dosage was again increased to 400 mg 3 times daily. At 5 months, the HVF scotoma was still denser and bigger (OS). But at 7 and 8 months, the visual acuity improved to CF at 6 ft (1.8 m) (OD) and had stabilized (OS), and there was also some improvement in visual field (OU) (Stimulus V; Carl Zeiss Meditec). At 12 months, visual acuity was stable and visual field had improvement (OU) (Stimulus V) (Table).

Patient 4

Patient 4 was an 8-year-old boy who presented with a history of vision loss (OD) for 1 month. His family history was positive for LHON (14484/ND6 mutation). His brother had lost vision without recovery at a similar age, and a maternal uncle and great uncle were also blind by LHON. On day 1, visual acuity was 20/50 (OD) and 20/20 (OS), color vision was 5/8 (OD) and 8/8 (OS), and there was a 1+ APD (OD). Results from fundus examination and OCT were normal (OU). The 30-2 HVF results showed a dense central scotoma measuring $30^\circ \times 30^\circ$ (OD) with an MD of -29.90 and also a very small central scotoma (OS) with an MD of -2.48 (Figure 4). He was started on EPI-743 therapy, 100 mg 3 times daily. At 1 month, visual acuity had improved to 20/20 (OD) and color vision had improved to 8/8 (OD). Remarkably, the HVF had improved, with a very mild and small central scotoma (OD), and was now normal (OS). At 2, 3, 4, and 6 months, his examination results remained normal (OU) (Figure 4 and Table).

Patient 5

Patient 5 was a 22-year-old man who had been diagnosed with LHON elsewhere a month earlier (3460/ND1 mutation), after noting decreased visual acuity for 3 months and 1 month (OD and OS, respectively). His family history was positive for LHON in 2 maternal uncles. On examination at presentation, visual acuity was CF at 6 ft (1.8 m) (OD) and 20/400 (OS), color vision was 0/8 (OU), and there was a 1+ APD (OD). Fundus examination revealed 1+ optic atrophy (OU), and OCT revealed temporal and inferior loss of RNFL fibers (OD) and temporal RNFL loss (OS). Results from 30-2 HVF showed a large and dense central scotoma (OU) with an MD of -25.36 (OD) and -24.05 (OS) (Figure 5). He was started on EPI-743 therapy, 100 mg 3 times daily, and then increased to 200 mg 3 times daily, after 2 weeks. At 2 months, visual acuity decreased to HM at 6 ft (1.8 m) (OD) and CF at 3 ft (0.9 m) (OS). At 3 months, visual acuity decreased even more to HM at 2 ft (0.6 m) (OD) and HM at 3 ft (0.9 m) (OS), OCT revealed diffuse loss of RNFL fibers. The HVF test was only possible with Stimulus V. At 4 months, visual acuity had improved to CF at 1 ft (0.3 m) (OU) and HVF had improved, with a superior island of vision with an MD of -17.01 (OD), and some fenestrations and an MD of -20.13 (OS). At 6 months, HVF improved additionally (OS) with an MD

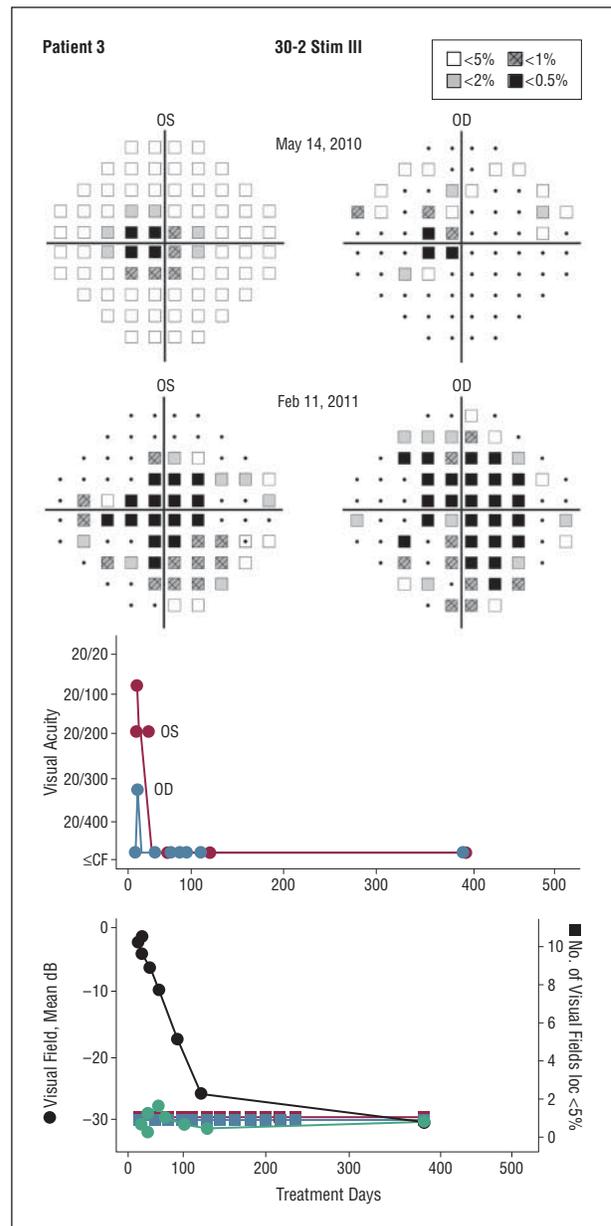


Figure 3. Longitudinal analysis of patient 3. The top shows a comparison of visual fields. Note that central scotomas increased in size for both eyes. The graphs depict worsening of visual acuities and visual field by the same criteria as Figure 1. "loc <5%" Indicates there is a greater than 95% chance that the sensitivity at that point is "truly" depressed. OD indicates right eye; OS, left eye; 30-2 Stim III, Humphrey 30-2 strategy with Stimulus III White (Carl Zeiss Meditec).

of -14.68 and a smaller scotoma more nasal-inferior (Figure 5 and Table).

COMMENT

EPI-743 significantly changed the well-established natural history of progression of LHON in 4 of 5 consecutive subjects treated, as assessed by serial measures of visual acuity, visual field, color vision, and OCT metrics. The magnitude of the treatment response was clinically meaningful in all 4 responders. Patients 1 and 4 demonstrated improvements in all parameters, while patients

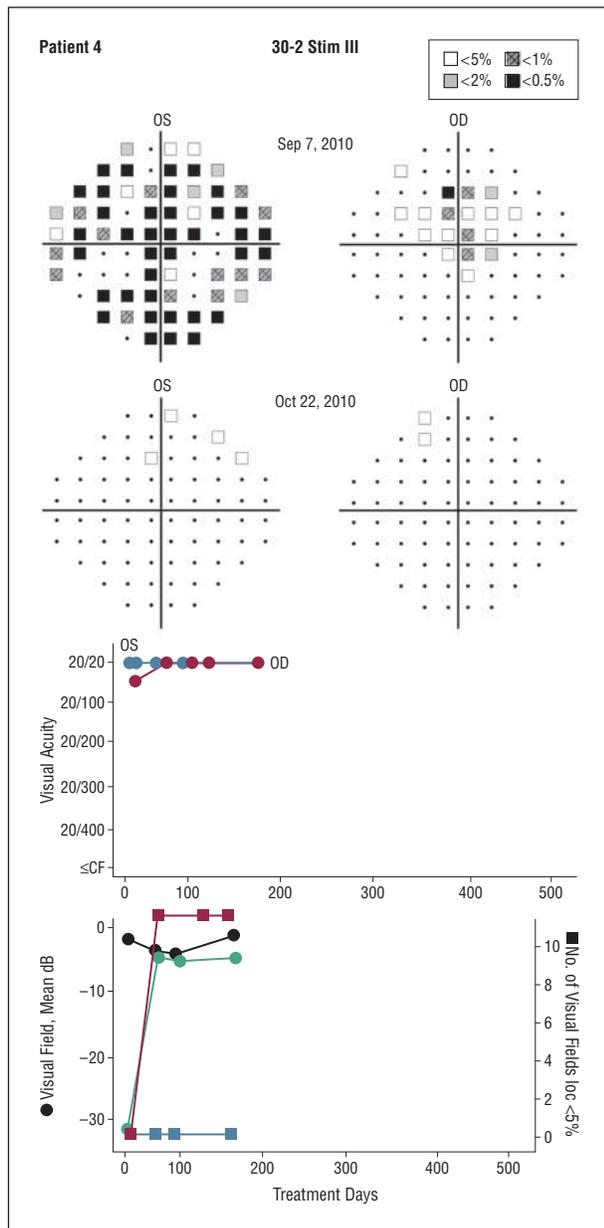


Figure 4. Longitudinal analysis of patient 4. The top shows a comparison of visual fields, with large (left) and small (right) scotomas completely resolving. The graphs depict improvements of visual acuities and visual fields by the same criteria as Figure 1. "loc $\leq 5\%$ " Indicates there is a greater than 95% chance that the sensitivity at that point is "truly" depressed. OD indicates right eye; OS, left eye; 30-2 Stim III, Humphrey 30-2 strategy with Stimulus III White (Carl Zeiss Meditec).

2 and 5 exhibited improvements in visual field and minor improvements in visual acuity. Interestingly, patient 3 may have exhibited an early arrest of disease, followed by relapse correlated with lack of drug absorption. Hence, while classified as a nonresponder, the lack of initial response was associated with low plasma drug levels.

These results are particularly promising in that EPI-743 is the first experimental therapeutic agent clinically proven to reverse visual loss in the face of retinal ganglion degeneration. Given the objective anatomic and functional metrics used in the studies, a placebo re-

sponse appears unlikely. While spontaneous recovery has been reported in patients with the 14484/ND6 mutation, recovery is typically partial and occurs after at least 1 year. In patient 4, recovery was complete and occurred in less than 4 weeks. This finding suggests that a therapeutic window may exist to rescue injured retinal ganglion cells that have been previously considered lost. If true, EPI-743 would represent a novel therapeutic agent for the treatment of mitochondrial disease and neuronal cell injury.

EPI-743 is a member of a new class of drugs being developed termed *digital biochemical information transfer and sensing* compounds (D-BITS).¹⁷ EPI-743 is a stable orally bioavailable small molecule, which readily crosses into the central nervous system. While its precise biochemical mechanism of action is still under investigation, EPI-743 works through regulation of metabolic control and closely coupled programmed cell death. In addition, EPI-743 has been shown to replenish reduced glutathione pools, critical to cellular antioxidant defense systems.^{18,19} This open-label study showed treatment benefit using established and recently developed metrics of visual structure and function. The mechanism of neuronal injury in LHON may be similar to that observed with other inherited mitochondrial diseases including Leigh syndrome, Friedreich ataxia, and subgroups of neurodegenerative diseases such as Alzheimer and Parkinson diseases, and the vision-based metrics of the present study may apply as new assessment tools for these diseases as well.²⁰⁻²³

The present study has limitations consistent with rare, heterogeneous, and acute diseases. The number of subjects in the study was small and it was longitudinally subject controlled. None of the patients engaged in excessive drinking or smoking. Patient follow-up was of a variable duration, and 1 of the subjects carried the LHON mutation for which a high rate of spontaneous recovery has been reported.^{24,25} Notwithstanding these limitations, 80% of the subjects exhibited a favorable clinical response. This is a marked departure from the natural history of progression of this disease based on many objective visual metrics that are not prone to placebo response. This natural history has been described by Riorda-Eva et al,²⁶ by Sprujit et al,²⁵ and, most recently, by Carelli et al¹¹ in patients. In particular, for the presently described 14484/ND6 case, recovery with EPI-743 treatment began only 4 weeks after visual loss and treatment. In addition, this recovery was complete and without optic atrophy, which invariably occurs as part of LHON.

Given these encouraging preliminary findings, we are undertaking an international multicenter study to validate results of this pilot study in a prospective controlled trial. EPI-743 may represent a novel and safe class of therapeutics that can provide hope for treatment of an otherwise devastating and untreatable disease that leads to blindness in young adults.

CONCLUSIONS

In this initial small prospective clinical trial, EPI-743 demonstrated disease arrest and reversal in 80% of treated patients with LHON. Given the well-established natural his-

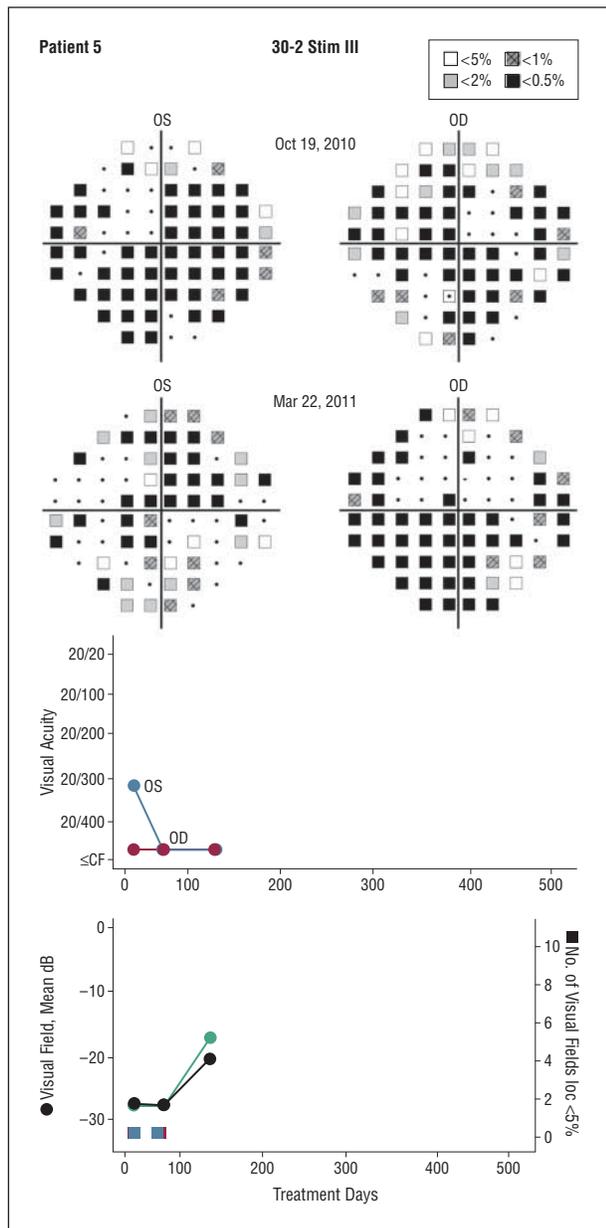


Figure 5. Longitudinal analysis of patient 5. The top shows stabilization of visual acuities and improvement of visual fields by the same criteria as Figure 1. "loc <5%" Indicates there is a greater than 95% chance that the sensitivity at that point is "truly" depressed. OD indicates right eye; OS, left eye; 30-2 Stim III, Humphrey 30-2 strategy with Stimulus III White (Carl Zeiss Meditec).

tory of irreversible vision loss in patients with LHON, EPI-743 may represent the first effective treatment for LHON. Furthermore, the observation of restoration of vision also suggests that there may be a reversible component to retinal ganglion cells previously thought to have undergone cell death. We are in the process of initiating a multicenter randomized controlled study to confirm these initial observations. If positive, EPI-743 may represent a new class of drugs for the treatment of mitochondria optic neuropathy and other diseases with mitochondria pathophysiologic conditions.

This is the first report on the evaluation of EPI-743 for the treatment of a mitochondria optic neuropathy,

LHON. Idebenone, a quinone and antioxidant, probably has minimal but real efficacy. EPI-743 is a third-generation quinone and has been reported to possess in vitro activity approximately 1000 times greater than idebenone. In this initial open-label study, we have presented data that suggest that EPI-743 may also be clinically more effective.

Accepted for Publication: October 28, 2011.

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Author Contributions: Dr Sadun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Sadun, Chicani, Thoolen, Shrader, Kubis, Carelli, and Miller. *Acquisition of data:* Sadun, Chicani, Ross-Cisneros, Kubis, and Carelli. *Analysis and interpretation of data:* Sadun, Chicani, Barboni, Carelli, and Miller. *Drafting of the manuscript:* Sadun, Chicani, Kubis, and Carelli. *Critical revision of the manuscript for important intellectual content:* Sadun, Chicani, Ross-Cisneros, Barboni, Thoolen, Shrader, and Carelli. *Obtained funding:* Sadun, Chicani, Carelli, and Miller. *Administrative, technical, and material support:* Sadun, Chicani, Ross-Cisneros, Thoolen, Shrader, and Miller. *Study supervision:* Sadun, Barboni, and Kubis.

Financial Disclosure: Dr Sadun reports receiving unrestricted research funds from Edison Pharmaceuticals Inc. Dr Chicani and Mr Ross Cisneros report that they receive partial salary support from Edison Pharmaceuticals Inc. Dr Carelli reports that he is a consultant for Edison Pharmaceuticals Inc. Drs Shrader, Thoolen, and Miller are employees of Edison Pharmaceuticals Inc.

Role of the Sponsor: The sponsor of the study had a role in the development of the emergency treatment protocol, and writing background information related to EPI-743 and inherited mitochondrial disease clinical trials, but not in final study design, data collection, data analysis, or data interpretation. The corresponding author, Dr Sadun, had full access to all study data and had final responsibility for the decision to submit this paper for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

Additional Contributions: Shellee Rockwell and Richard Cornwell provided clinical care to our patients.

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