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Treatment With Erythropoietin for Patients With Optic Neuritis

Long-term Follow-up

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Abstract

Background and Objective

Erythropoietin (EPO) is a candidate neuroprotective drug. We assessed its long-term safety and efficacy as an adjunct to methylprednisolone in patients with optic neuritis and focused on conversions to multiple sclerosis (MS).

Methods

The TONE trial randomized 108 patients with acute optic neuritis but without previously known MS to either 33,000 IU EPO or placebo in conjunction with 1,000 mg methylprednisolone daily for 3 days. After reaching the primary end point at 6 months, we conducted an open-label follow-up 2 years after randomization.

Results

The follow-up was attended by 83 of 103 initially analyzed patients (81%). There were no previously unreported adverse events. The adjusted treatment difference of peripapillary retinal nerve fiber layer atrophy in relation to the fellow eye at baseline was 1.27 μm (95% CI −6.45 to 8.98, $p = 0.74$). The adjusted treatment difference in low-contrast letter acuity was 2.87 on the 2.5% Sloan chart score (95% CI −7.92 to 13.65). Vision-related quality of life was similar in both treatment arms (National Eye Institute Visual Functioning Questionnaire median score [IQR]: 94.0 [88.0 to 96.9] in the EPO and 93.4 [89.5 to 97.4] in the placebo group). The rate of multiple sclerosis–free survival was 38% in the placebo and 53% in the EPO group (hazard ratio: 1.67, 95% CI 0.96 to 2.88, $p = 0.068$).

Discussion

In line with the results at 6 months, we found neither structural nor functional benefits in the visual system of patients with optic neuritis as a clinically isolated syndrome, 2 years after EPO administration. Although there were fewer early conversions to MS in the EPO group, the difference across the 2-year window was not statistically significant.

Classification of Evidence

This study provides Class II evidence that for patients with acute optic neuritis, EPO as an adjunct to methylprednisolone is well tolerated and does not improve long-term visual outcomes.

Trial Registration Information

The trial was preregistered before commencement at clinicaltrials.gov (NCT01962571).

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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TONE Study Group coinvestigators are listed in the appendix at the end of the article.

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Glossary

EDSS = Expanded Disability Status Scale; **EPO** = erythropoietin; **ETDRS** = early treatment of diabetic retinopathy; **NEI-VFQ** = National Eye Institute Visual Functioning Questionnaire; **OCT** = optical coherence tomography; **pRNFL** = peripapillary retinal nerve fiber layer; **VEP** = visually evoked potential.

Optic neuritis is the most common optic neuropathy in young adults and leads to retinal nerve fiber and ganglion cell layer thinning. It has a close relationship to multiple sclerosis (MS): It is the presenting symptom of MS in about 25% of patients, 70% of patients with MS will experience optic neuritis within the disease course,[1] and 50% of patients with optic neuritis develop MS within 15 years.[2] Visual recovery in optic neuritis is accelerated by high-dose methylprednisolone,[3] but no therapy has been established to improve long-term outcomes. Thus, as in MS, there remains an unmet need of clinical long-term neuroprotection.

The role of the visual system in treatment assessment of neuroinflammatory diseases has been recently reviewed.[4] One candidate neuroprotective agent gaining interest is the human cytokine erythropoietin (EPO). It crosses the blood-brain barrier[5,6] and confers anti-inflammatory, anti-apoptotic, and neuroprotective effects in preclinical models of autoimmune neuroinflammation.[7] Following ambiguous results from smaller clinical studies,[8-10] we conducted the TONE trial (treatment of optic neuritis with erythropoietin) to assess retinal ganglion cell neuroprotection.[11] The primary end point was set at 6 months as most atrophy occurs in the first 4 months, plateauing thereafter.[12] Because conversions to MS occur within years after optic neuritis,[2] we scheduled an additional long-term open-label assessment 2 years after treatment, the results of which are reported herein. The primary research question was to assess the safety and efficacy of erythropoietin in improving visual outcomes 2 years after acute optic neuritis.

Methods

The TONE study protocol,[13] baseline characteristics, and the 6-month results[11] have previously been described in detail. In brief summary, 108 patients within 10 days of onset of a first episode of acute optic neuritis and high-contrast visual acuity <3/6 in the affected eye were randomized to receive either placebo (saline solution) or 33,000 IU EPO as an adjunct to high-dose methylprednisolone daily for 3 consecutive days. Recruitment took place at 12 German academic tertiary referral centers between November 25, 2014, and October 9, 2017. Patients with previously known MS were not included, but conversion as a result of the subsequent neurologic workup did not lead to exclusion. Patients with positive serum tests for aquaporin-4 antibodies were excluded.

Outcomes and Procedures

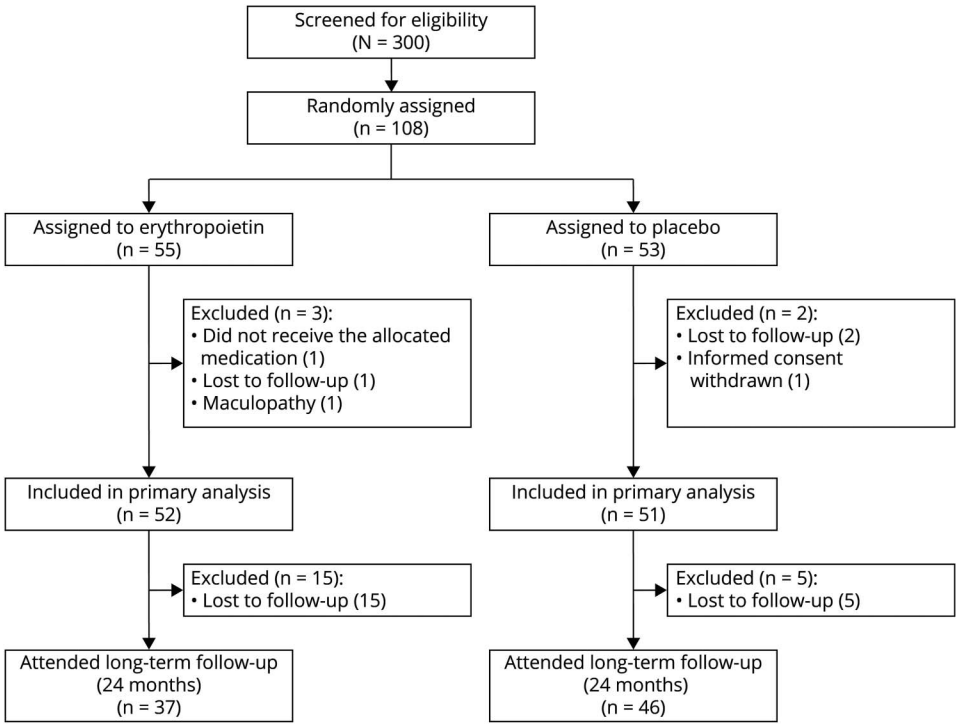
The first primary outcome was the atrophy of the peripapillary retinal nerve fiber layer (pRNFL), defined as the change in pRNFL thickness in relation to the fellow eye at baseline. It was measured using spectral domain optical coherence tomography (OCT) along a peripapillary circle 3.5 mm in diameter. The second primary outcome was low-contrast letter acuity, measured as the 2.5% Sloan Chart score.

Structural changes were assessed by spectral domain OCT imaging (Nsite Analytics, version 6.0, and Spectralis-OCT, Heidelberg Engineering, Heidelberg, Germany), with reporting in adherence to the APOSTEL 2.0 recommendations.[14] They included the peripapillary RNFL thickness in predefined nasal superior, superior, temporal superior, temporal inferior, inferior, and nasal inferior sectors and in the papillomacular bundle, each measured along circles of 3.5 mm, 4.1 mm, and 4.7 mm diameters. The central retina was assessed using the 1/3/6 mm early treatment of diabetic retinopathy (ETDRS) grid on volume scans derived from 61 B scans. Each of the 12 study centers served as an OCT operating site. All OCT scans were uploaded to the Bern Photographic Reading Center (Bern, Switzerland), which served as the single grader. Quality control according to the OSCAR IB[15] criteria led to exclusion of 28 central retinal scans and 4 circumpapillary scans. Retinal layer thicknesses were measured by manual segmentation. The functional secondary endpoints consisted of high-contrast visual acuity (measured by ETDRS charts) contrast sensitivity (Mars charts), and static automated perimetry of the central 60° visual field with recording of the mean defect, the square root of loss variance, false-positive and false-negative answers. Electrophysiologic secondary end points were the P100 amplitudes and peak times of visually evoked potentials (VEPs). Neurologic secondary end points were the Expanded Disability Status Scale (EDSS) and the time to conversion to MS according to the 2010 McDonald criteria.[16] Vision-related quality of life was assessed by the German version of the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ). The current report is of the open-label follow-up of the study cohort, performed 24 months after randomization.

Statistical Analysis

The analysis was conducted in the full analysis set of all randomized patients with optic neuritis who received at least 1 dose of study medication and had at least 1 postinterventional OCT measurement. The primary and secondary outcomes were assessed by linear regression models with the outcome after 24 months as the dependent variable and treatment assignment, baseline measurement of the fellow eye, and study site as independent variables. The rates of multiple sclerosis–free survival and optic neuritis relapse-free survival were estimated by assigned treatment with the Kaplan-Meier

Figure 1 Patient Flowchart



method and an unadjusted Cox proportional hazards model. Missing data from the 24-month follow-up were addressed by characterizing the populations who did and did not attend the follow-up.

Post Hoc Analyses

Postacute changes were defined as the difference in the 24 months and 6 months observations of the study outcomes. Adjusted treatment differences for such changes were calculated with linear regression models as described above.

Sample Size Calculation and Statistical Reporting

The sample size calculation for the TONE trial was based on the first primary end point at week 26 and has been described in detail.[11,13] The current report of long-term open-label outcomes is observational and adheres to the STROBE guidelines.[17] In the spirit of the American Statistical Association's statement on *p* values[18] and recent addendum,[19] we report outcomes as adjusted treatment differences with 95% CIs. *p* Values are included for the main study outcome and rate of MS-free survival to facilitate comparisons with the results at week 26.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the ethics committee of the University of Freiburg, Germany, and the institutional review boards of all participating sites. Written informed consent was obtained from all participating patients. The trial was preregistered before commencement at clinicaltrials.gov (NCT01962571).

Data Availability

Individual participant data of 2-year results, including data dictionaries, will be made available together with previous study data of the TONE trial to researchers with a methodologically sound proposal.

Results

Patient Characteristics and Compliance With Long-term Follow-up

The 2-year follow-up was completed by 37/52 patients in the EPO (71%) and 46/51 patients (90%) in the placebo arm (Figure 1). The baseline characteristics of these patients were akin to those of the initial study population (Table 1). Patients with long-term follow-up had a similar age distribution between treatment groups. The female:male ratio was approximately 4:1 in the EPO and 3:1 in the placebo arm. The median time from onset to treatment was equal in both groups. Optic disk swelling and pain on eye movements were slightly more common in the placebo than in the EPO arm, as was a new diagnosis of MS because of baseline diagnostics. The pRNFL of the affected eye was on average 9 μm thicker in the placebo than in the EPO group. Scores for low-contrast letter acuity were similar.

Patients who did not attend the 2-year visit were slightly younger than the general study population (median age: 28 vs 30 years) and had a similar sex distribution (69% vs 67% female). At 6 months, they had less pRNFL atrophy (median:

Table 1 Baseline Characteristics of the Entire TONE Trial and of Patients Who Went on to Attend the 24-Month Follow-up, by Treatment Group

	Baseline characteristics of the TONE trial		Baseline characteristics of patients who attended the long-term follow-up	
	EPO group (n = 52)	Placebo group (n = 51)	EPO group (n = 37)	Placebo group (n = 46)
Age[a]	30 (25–36)	30 (26–37)	30 (25–36)	30 (27–37)
Sex[b]				
Female	38 (73%)	33 (65%)	27 (73%)	29 (63%)
Male	14 (27%)	18 (35%)	10 (27%)	17 (37%)
Time from onset to treatment, days[a]	6 (5–8)	7 (5–8)	6 (4–7)	6 (4–7)
Pain on eye movements[b]	40 (77%)	44 (86%)	28 (76%)	41 (89%)
Optic disk swelling in the affected eye[b]	10 (19%)	13 (25%)	8 (22%)	13 (29%)
New diagnosis of multiple sclerosis[b]	7 (13%)	11 (22%)	2 (5%)	8 (17%)
pRNFL thickness (3.5 mm), μm[c]				
Affected eye	112.5 ± 26.2	116.8 ± 36.5	110.1 ± 20.2	119.0 ± 37.7
Fellow eye	101.3 ± 11.9	99.1 ± 12.0	101.7 ± 12.5	99.7 ± 12.4
LCLA, 2.5% Sloan chart score[a]				
Affected eye	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Fellow eye	68.0 (59.0–70.0)	66.0 (58.0–71.0)	68.0 (62.0–71.0)	66.5 (58.8–71)

Abbreviations: LCLA = low-contrast letter acuity; pRNFL = peripapillary retinal nerve fiber layer.
Data are [a]: median (IQR), [b]: n (%), or [c]: mean ± SD, as indicated by the superscript in the first column.

5.5 μm vs 11 μm) but similar low-contrast visual acuity compared with the general study population (median 56 on the 2.5% Sloan chart score in both groups). Dropouts who had received EPO had worse low-contrast letter acuity at month 6 compared with placebo recipients who dropped out (median 54 vs 61) but similar pRNFL atrophy (median 6 μm vs 5 μm). The median age of dropouts in the EPO group was higher than in the placebo group (28 years vs 22 years); the sex distribution of dropouts was similar between treatment arms (data not shown).

Safety

In patients with available long-term data, no previously unreported severe adverse events occurred.

Long-term Outcome

At 24 months, the amount of pRNFL atrophy was similar between treatment groups (adjusted treatment difference: 1.27 μm, 95% CI −6.45 to 8.98, $p = 0.74$), as was low-contrast letter acuity (adjusted treatment difference: 2.87 on the 2.5% Sloan chart score, 95% CI −7.92 to 13.65) (Figure 2). All secondary psychophysical and structural outcomes were similar between the treatment groups (Table 2, Figure 2). The rate of MS diagnosis-free survival is depicted in Figure 3. At 24 months, the rate was 0.38 in the placebo and 0.53 in the EPO group (hazard ratio: 1.67, 95% CI 0.96–2.88, $p = 0.068$). Of note, the 2 survival curves separated early within the first 3 months after optic neuritis and continued in parallel thereafter (Figure 3). Optic neuritis relapses occurred in 4 EPO and 3 placebo recipients. The optic neuritis relapse-free rate at 24 months was 0.9 in the EPO and 0.94 in the placebo group (hazard ratio: 0.69, 95% CI 0.15–3.08). Vision-related quality of life was similar in both trial arms (Table 2).

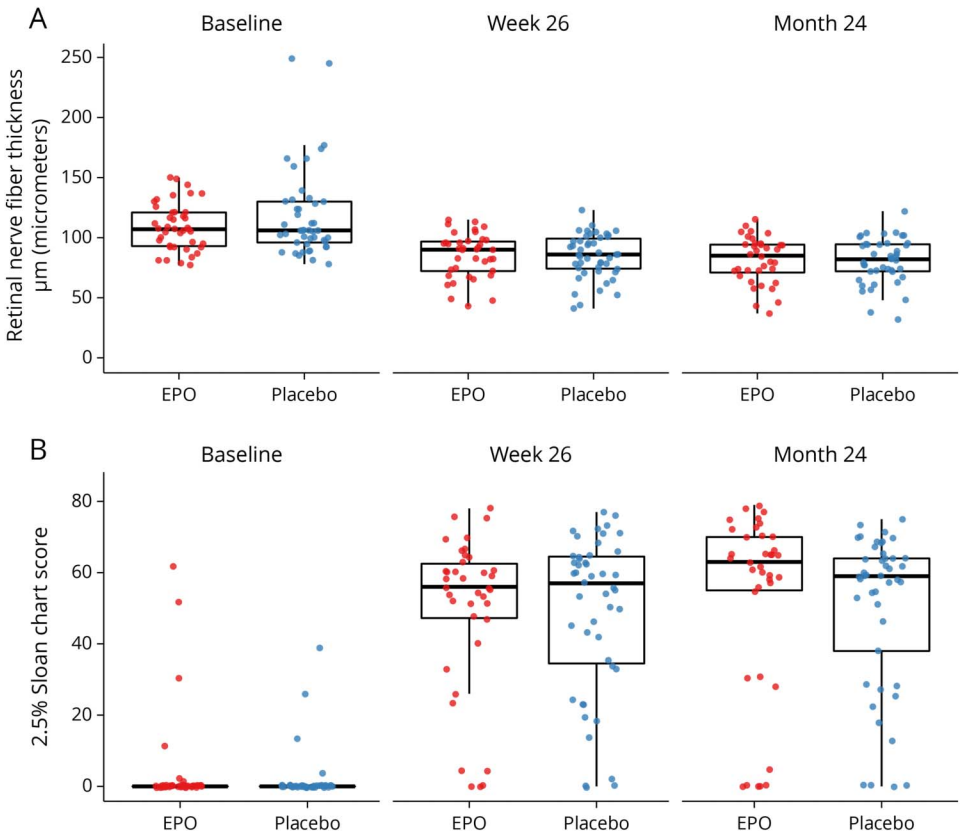
Postacute Changes

Compared with the 6-month observations, patients in both treatment arms had continued structural atrophy but functional improvement. Improved function was seen in both treatment arms in low-contrast letter acuity and VEP peak times, whereas VEP amplitudes, high-contrast visual acuity, and visual fields did not change. Continued but limited structural atrophy was observed for pRNFL thickness and macular volume in both treatment arms and combined ganglion cell and inner plexiform layer (GC/IPL) volume in placebo recipients. EPO recipients had a higher gain in low-contrast letter acuity (adjusted treatment difference: 7.02 on the 2.5% Sloan chart score, 95% CI 1.58–12.47) and less reduction of GC/IPL volume (adjusted treatment difference: 0.06, 95% CI 0.01–0.1) compared with patients in the placebo group (Table 3).

Discussion

High-dose erythropoietin did not result in long-term improvement in functional or structural outcomes in the visual

Figure 2 Visual Outcomes by Treatment Group



(A) Retinal nerve fiber layer thickness in the affected eye. (B) Low-contrast letter acuity in the affected eye. Data are shown for the baseline visit, the primary end point at 26 weeks, and the long-term follow-up at 24 months. Dots are individual data points; horizontal bars are medians, and boxes are interquartile ranges. Whiskers extend to the largest/smallest value no further than 1.5 * IQR from the hinge.

pathway of patients with acute optic neuritis. In the postacute phase, patients in both treatment arms showed continuous but mild improvement in low-contrast letter acuity and VEP peak times, whereas structural measures continued to deteriorate. This postacute structural-functional discrepancy has previously been observed[20] and is consistent with recent observations.[21,22] It is likely to result from a resolution of conduction block by mechanisms of repair and remyelination resulting in increased function, while the neuroaxonal loss does not recover but slowly continues. Compared with patients in the placebo group, EPO recipients presented better trajectories in 2.5% low-contrast letter acuity and, less pronounced, GC/IPL atrophy between 6 and 24 months, possibly due to the lower percentage of patients with MS in the EPO group. However, there was no long-term visual benefit of EPO therapy as outcomes at 24 months were equal between treatment arms.

A notable result at the 6-month end point of the TONE trial was a difference in MS-free survival favoring the EPO group ($p = 0.032$ for the 6-month interval[11]). We previously stated that this finding might be explained by baseline imbalances of previous (undiagnosed) MS or predisposing factors, an effect of EPO on subclinical lesions and gadolinium enhancement outside the visual system, or a combination thereof. With 2 years' follow-up, the difference between treatment groups did not increase further and lost statistical significance ($p = 0.068$, Figure 3). This observation would be in line with both baseline imbalances or with an effect of EPO, as any treatment effect would likely be limited in time and, once worn off, lead to a similar rate of MS conversion. The fact that similar observations were made in the Vision Protect study,[8] which included 40 patients with an intervention protocol similar to TONE, argues against baseline imbalances in TONE and for a true effect of EPO. In Vision Protect, standardized MRI was performed at baseline, week 4, week 8, and week 16. Here, subsequent conversions from clinically isolated syndrome to MS occurred more frequently in the placebo than in the EPO group, with a pronounced difference in early conversions.[23] A smaller trial reported randomized 10 patients with optic neuritis as a clinically isolated syndrome and at least 3 hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI to either 20′000 IE EPO/d or placebo as an adjunct to methylprednisolone pulse therapy for 5 days. One patient in the placebo group and no patients in the EPO group fulfilled the McDonald criteria for the diagnosis of MS within 1 year.[24] The same treatment protocol was used in a randomized study comprising 20 participants with a severe motor relapse of relapsing-remitting MS (RRMS), reported by Varzaneh and colleagues. Over a follow-up

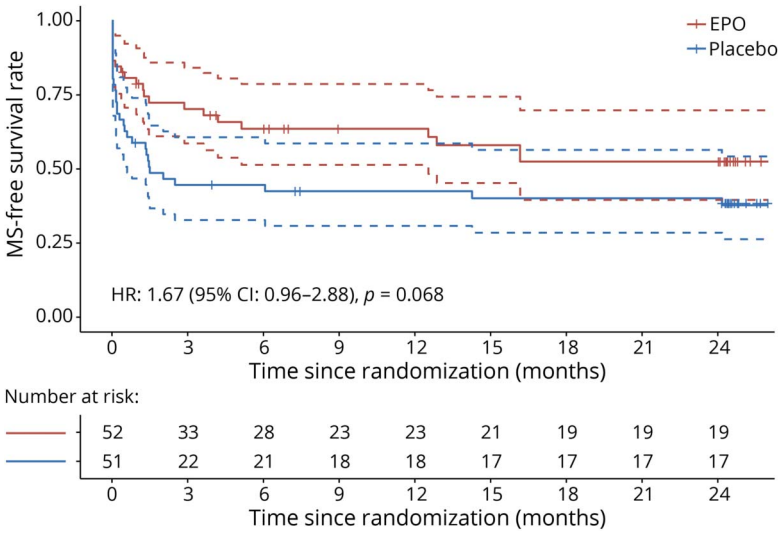
Table 2 Outcomes at Month 24, by Treatment Group

		EPO group		Placebo group		
	Eye	n	Mean ± SD	n	Mean ± SD	Adjusted treatment difference (95% CI)
pRNFL atrophy in the affected eye[a], µm		36	20.81 ± 17.19	41	19.02 ± 16.71	1.27 (−6.45 to 8.98)[b]
LCLA, 2.5% Sloan chart score	Affected eye	37	52.76 ± 26.00	45	50.13 ± 22.28	2.87 (−7.92 to 13.65)
	Unaffected eye	37	66.54 ± 14.27	45	66.22 ± 9.55	—
Contrast sensitivity, log	Affected eye	37	1.57 ± 0.29	45	1.54 ± 0.41	0.04 (−0.13 to 0.20)
	Unaffected eye	37	1.70 ± 0.16	45	1.72 ± 0.15	—
HCVA, letters ETDRS	Affected eye	37	86.38 ± 13.99	45	81.76 ± 21.61	3.95 (−3.85 to 11.74)
	Unaffected eye	37	92.43 ± 4.33	45	90.53 ± 6.60	—
pRNFL thickness, global, µm	Affected eye	36	81.5 ± 19.4	43	80.7 ± 18.9	−1.27 (−8.98 to 6.45)
	Unaffected eye	35	99.9 ± 12.4	43	97.4 ± 13.1	—
pRNFL thickness, temporal sector, µm	Affected eye	36	49.9 ± 17.2	43	50.9 ± 19.0	0.50 (−6.65 to 7.65)
	Unaffected eye	35	66.3 ± 12.4	43	69.3 ± 15.9	—
pRNFL thickness, papillomacular bundle, µm	Affected eye	36	37.8 ± 11.7	41	38.8 ± 13.2	−1.29 (−6.98 to 4.40)
	Unaffected eye	35	49.3 ± 8.4	42	50.2 ± 9.7	—
Macular volume, mm^3	Affected eye	35	8.20 ± 0.39	42	8.24 ± 0.39	−0.02 (−0.17 to 0.13)
	Unaffected eye	36	8.62 ± 0.31	44	8.65 ± 0.37	—
GCL volume, mm^3	Affected eye	35	0.88 ± 0.17	42	0.87 ± 0.14	0.01 (−0.06 to 0.08)
	Unaffected eye	36	1.07 ± 0.11	44	1.06 ± 0.11	—
GC/IPL volume, mm^3	Affected eye	35	1.66 ± 0.26	42	1.63 ± 0.23	0.01 (−0.1 to 0.13)
	Unaffected eye	36	1.96 ± 0.18	44	1.94 ± 0.18	—
Perimetric mean defect, dB	Affected eye	27	3.8 ± 5.0	37	4.0 ± 5.2	−0.03 (−2.68 to 2.62)
	Unaffected eye	27	1.8 ± 2.3	37	1.6 ± 1.7	—
VEP peak times, ms	Affected eye	35	116.9 ± 18.4	44	117.0 ± 21.7	1.73 (−7.36 to 10.83)
	Unaffected eye	36	107.2 ± 13.6	44	107.9 ± 14.1	—
VEP amplitude, µV	Affected eye	35	9.89 ± 5.88	43	9.76 ± 5.38	0.69 (−1.13 to 2.51)
	Unaffected eye	36	11.80 ± 5.99	44	11.47 ± 5.06	—
		n	Median (IQR)	n	Median (IQR)	
Vision-related QoL, NEI-VFQ overall score		36	94 (88.0–96.9)	44	93.4 (89.5–97.4)	—
EDSS score		37	0 (0–0)	46	0 (0–2)	−0.38 (−0.81 to 0.06)

Abbreviations: EDSS = Expanded Disability Status Scale; GC/IPL = ganglion cell and inner plexiform layer; GCL = ganglion cell layer; HCVA = high-contrast visual acuity; LCLA = low-contrast letter acuity; NEI-VFQ = National Eye Institute Visual Function Questionnaire; pRNFL = peripapillary retinal nerve fiber layer; QoL = quality of life; VEP = visually evoked potential.
Treatment estimates (EPO vs placebo) were calculated by linear regression models with the baseline measurement of the fellow eye and treatment site as covariates.
[a] Only the affected eye is reported as atrophy was defined in relation to the unaffected eye baseline value.
[b] $p = 0.744$.

of 3 months, the authors observed lower ambulatory index and EDSS values and fewer hyperintense lesions on T2-weighted MRI in EPO recipients compared with patients in the placebo group.[25] Most recently, a randomized controlled trial including 50 patients with progressive, primary, or secondary MS found no significant treatment effect of weekly then biweekly application of high-dose (48′000 IU) EPO on a composite outcome of hand dexterity, maximum gait distance, and cognition.[26] Taken together and considering the preclinical evidence, a limited case might be made for beneficial systemic effects of EPO in acute but not chronic activity of clinical or preclinical demyelinating disease.

Figure 3 Kaplan-Meier Plot of Multiple Sclerosis–Free Survival by Treatment Group



Diagnoses were made by the 2010 McDonald criteria. Vertical bars depict censored data. Dashed lines indicate the 95% CI of estimated MS-free survival. HR = hazard ratio.

The long-term data of this study are limited by possible biases introduced by losses to follow-up. The higher percentage of males, patients with MS, and optic disk swelling in placebo recipients may point toward more severe disease in this group. However, if so, such a bias would likely have exacerbated, not masked, any treatment differences. Data on MS conversions in the TONE trial should be interpreted cautiously due to baseline differences and lack of standardized MR imaging. Other limitations of this study have been previously discussed and include the unknown influence of previous subclinical disease activity and trans-synaptic retrograde degeneration and the possible inclusion of a small number of patients with anti–MOG-related optic neuritis.

Table 3 Postacute Changes in the Visual System, by Treatment Group (Post Hoc Analysis)

	EPO group		Placebo group		
Parameter	**Mean unadjusted postacute change (SD)**	**Percent change**	**Mean unadjusted postacute change (SD)**	**Percent change**	**Adjusted treatment difference (95% CI)**
LCLA, 2.5% Sloan chart score	7.17 (13.19)	14.5	1.71 (11.47)	3.5	7.02 (1.58 to 12.47)
Contrast sensitivity, log	0.03 (0.20)	1.8	0.00 (0.21)	0.3	0.02 (−0.07 to 0.11)
HCVA, score	2.09 (5.96)	2.4	−2.80 (13.13)	−3.3	4.43 (−0.24 to 9.1)
pRNFL thickness, global, μm	−2.21 (3.00)	−2.6	−4.05 (5.92)	−4.8	1.77 (−0.56 to 4.09)
pRNFL thickness, temporal sector, μm	−1.06 (2.47)	−2	−2.81 (8.21)	−5.2	1.42 (−1.54 to 4.39)
pRNFL thickness, papillomacular bundle, μm	−1.29 (2.41)	−3.3	−0.95 (5.08)	−2.4	−0.21 (−2.22 to 1.81)
Macular volume, mm^3	−0.05 (0.09)	−0.6	−0.11 (0.18)	−1.3	0.05 (−0.01 to 0.12)
GCL volume, mm^3	0.00 (0.04)	0.5	−0.03 (0.07)	−3.3	0.03 (0.01 to 0.06)
GC/IPL volume, mm^3	0.01 (0.07)	0.6	−0.05 (0.12)	−3.0	0.06 (0.01 to 0.1)
Perimetric mean defect, dB	0.39 (3.62)	16.1	0.32 (2.02)	8.6	0.21 (−1.06 to 1.47)
VEP peak time, ms	−4.06 (7.92)	−3.4	−1.83 (17.64)	−1.5	−1.85 (−9.06 to 5.36)
VEP amplitude, μV	0.55 (4.94)	5.7	0.99 (4.51)	11.2	−0.35 (−2.6 to 1.9)

Abbreviations: EDSS = Expanded Disability Status Scale; GC/IPL = ganglion cell and inner plexiform layer; GCL = ganglion cell layer; HCVA = high-contrast visual acuity; LCLA = low-contrast letter acuity; pRNFL = peripapillary retinal nerve fiber layer; VEP = visually evoked potential.
Postacute changes were defined as the differences in the 24- and 6-month observations of the study outcomes. Percent change refers to the 24- vs the 6-month observations. Treatment estimates were calculated by linear regression models with the baseline measurement of the fellow eye and treatment site as covariates.

In conclusion, the open-label follow-up of the TONE trial provides Class II evidence that high-dose erythropoietin as an adjunct to methylprednisolone does not improve long-term visual outcomes in acute optic neuritis. Its efficacy in systemic demyelinating disease remains unclear and warrants further investigation.

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Disclosure

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Appendix 1 Authors

Name	Location	Contribution
Sebastian Küchlin, MD	Freiburg, Germany	Data analysis, visualization, and interpretation, literature research, verified underlying data, and authored the first manuscript draft
Gabriele Ihorst, PhD	Freiburg, Germany	Trial statistician, data analysis, study design (sample size calculation), and revision and approval of the final manuscript draft
Birgit Grotejohann, PhD	Freiburg, Germany	Project manager and revision and approval of the final manuscript draft
Flemming Beisse, MD	Heidelberg, Germany	Leading contribution in patient recruitment and revision and approval of the final manuscript draft
Sven P. Heinrich, PhD	Freiburg, Germany	Study design, definition of protocols for VEP, high-contrast visual acuity, and contrast sensitivity testing, and revision and approval of the final manuscript draft
Philipp Albrecht	Düsseldorf, Germany	Study design, data interpretation, and revision and approval of the final manuscript draft
Judith Ungewiss, PhD	Aalen, Germany	Central reading of visual field data and revision and approval of the final manuscript draft
Michael Wörner, PhD	Aalen, Germany	Central reading of visual field data and revision and approval of the final manuscript draft
Martin J. Hug, PhD	Freiburg, Germany	Trial pharmacist and revision and approval of the final manuscript draft
Sebastian Wolf, MD	Bern, Switzerland	Central reading of OCT data and revision and approval of the final manuscript draft
Ricarda Diem, MD	Heidelberg, Germany	Study design, funding acquisition, co–principal investigator, leading contribution in patient recruitment, and revision and approval of the final manuscript draft
Wolf A Lagrèze, MD	Freiburg, Germany	Study design, funding acquisition, co–principal investigator, leading contribution in patient recruitment, coauthored the first manuscript draft, and revision and approval of the final manuscript draft

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
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Appendix 2 *(continued)*

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Treatment With Erythropoietin for Patients With Optic Neuritis: Long-term Follow-up

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