Acute optic neuritis
Unmet clinical needs and model for new therapies

ABSTRACT

Idiopathic demyelinating optic neuritis (ON) most commonly presents as acute unilateral vision loss and eye pain and is frequently associated with multiple sclerosis. Although emphasis is often placed on the good recovery of high-contrast visual acuity, persistent deficits are frequently observed in other aspects of vision, including contrast sensitivity, visual field testing, color vision, motion perception, and vision-related quality of life. Persistent and profound structural and functional changes are often revealed by imaging and electrophysiologic techniques, including optical coherence tomography, visual-evoked potentials, and nonconventional MRI. These abnormalities can impair patients’ abilities to perform daily activities (e.g., driving, working) so they have important implications for patients’ quality of life. In this article, we review the sequelae from ON, including clinical, structural, and functional changes and their interrelationships. The unmet needs in each of these areas are considered and the progress made toward meeting those needs is examined. Finally, we provide an overview of past and present investigational approaches for disease modification in ON. Neurology, Neuroimmunol Neuroinflamm 2015;2:e135; doi: 10.1212/NXI.0000000000000135

GLOSSARY

| Term                    | Definition                                                                 |
|-------------------------|-----------------------------------------------------------------------------|
| Axial diffusivity       | The direction of water diffusion along the optic fiber tract                 |
| Diffusion tensor imaging | A technique that measures water diffusion in multiple directions             |
| Fractional anisotropy   | A measure of the degree of anisotropy in diffusion tensor imaging            |
| Ganglion cell layer     | The layer of nerve cells in the retina and optic nerve                       |
| Inner plexiform layer   | The innermost layer of the retina and optic nerve                            |
| Multifocal VEP          | A visual-evoked potential stimulus that evokes responses from multiple areas |
| Multiple sclerosis      | A chronic inflammatory disease of the central nervous system                 |
| Magnetization transfer  | A technique that measures the magnetic properties of tissue                 |
| National Eye Institute  | An organization that funds and conducts research in眼科和视觉科学           |
| Visual Functioning      | A measure of vision-related quality of life                                 |
| Optic Neuritis Treatment Trial | A clinical trial that examined the effects of corticosteroid treatment  |

Although idiopathic demyelinating optic neuritis (ON) broadly describes the vision loss associated with any inflammation of the CNS white matter tract referred to as the optic nerve, the term is most commonly associated with the unilateral visual loss that occurs in multiple sclerosis (MS). Atypical ON may be associated with neuromyelitis optica, infections, or systemic etiologies, but this article will focus predominantly on the typical demyelinating ON syndrome associated with MS. Typical ON is characterized by a loss of vision that develops over days and is associated with dyschromatopsia, visual field loss, and pain that is often exacerbated by eye movements. Usually there are no retinal exudates or severe disc swelling and vision is better than no light perception.

Significant knowledge about the clinical course of ON derives from the Optic Neuritis Treatment Trial (ONTT). First published in 1992, the ONTT established that high-dose IV corticosteroid treatment slightly accelerated the rate of recovery but had no effect on long-term visual

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outcomes. Visual fields and contrast sensitivity were the primary measures of efficacy and showed a slight advantage of high-dose IV corticosteroids over placebo at 6 months. Nevertheless, vision for most patients in all treatment groups at 6 months was characterized as “normal” based on high-contrast visual acuity, a secondary outcome measured using Snellen charts, which was 20/50 or better for >90% of patients regardless of treatment assignment. This created the impression that most patients make an excellent recovery following acute ON. However, a follow-up study 5–8 years later found abnormalities in affected eyes vs fellow eyes for the primary endpoints of contrast sensitivity (58% vs 17%) and visual field (33% vs 12%), as well as the secondary endpoints of high-contrast visual acuity (39% vs 16%) and color vision (37% vs 18%). Furthermore, as described in the sections that follow, advances in imaging and electrophysiologic techniques over the past 2 decades have revealed that persistent structural and functional damage is detectable following episodes of acute ON and that the associated visual deficits may have considerable impact on quality of life (QOL) measures. Given the development of therapies with the potential to prevent neuroaxonal loss and facilitate remyelination following acute ON, it is time to reassess the extent of spontaneous recovery in ON and the approaches to determining outcomes so that unmet needs may be identified and addressed.

In this article, we review the evidence for persistent functional and structural abnormalities in ON and their impact on visual function and vision-related QOL. We also provide an overview of investigational approaches to treat the underlying pathology in ON.

**CLINICAL COURSE AND ASSESSMENT OF VISUAL FUNCTION** Typical ON develops over a 7- to 10-day period and begins to resolve within 2–3 weeks. Initial rapid improvement in visual function within the first month begins to slow in an asymptotic fashion over succeeding months, and improvements have been observed up to 2 years later. Numerous studies have found evidence of persistent retinal thinning, optic nerve atrophy, and reduced amplitude and increased latency of visual-evoked potentials (VEPs), consistent with chronic demyelination and neuroaxonal loss as sequelae of acute ON (see next sections). The extent of latency recovery appears to be more complete in younger patients vs older patients, females vs males, and patients with less severe attacks vs more severe attacks. Moreover, recovery of different aspects of visual function may proceed at different rates, with different sensitivities among tests, and to a different extent (figure 1). Recovery of different aspects of visual function may also involve distinct mechanisms, as patients who achieve partial recovery of static visual functions (e.g., high- and low-contrast visual acuity) after 1 month may recover those functions completely, whereas dynamic visual function (motion perception) appears to recover at a slower constant rate irrespective of the severity of the initial deficit.

Although patients with ON frequently regain visual acuity to a large extent as measured by full-contrast letter charts (e.g., Snellen charts), low-contrast acuity/sensitivity reveals permanent deficits and is a better predictor of impairment for daily activities that require vision, such as reading, facial recognition, and driving. Persistent deficits in low-contrast letter acuity characteristic of ON are better measured using Sloan charts (Sloan low-contrast letter acuity [SCLA]) that include versions with 2.5% and 1.25% contrast levels to better stratify deficits. The pattern of visual field defects may help distinguish ON from other neuropathies. In ON, a central scotoma is common and Humphrey central visual field perimetry frequently shows diffuse loss, whereas peripheral, altitudinal, or other defects may occasionally be evident on formal perimetry. Color vision is commonly affected in ON, but there is no consistent pattern of dyschromatopsia. More complex visual functions, such as motion perception, are also frequently affected by ON. Binocular summation (improved vision with binocular viewing) has also been shown to be reduced, and in some instances patients demonstrate binocular inhibition (worse vision with binocular viewing), perhaps reflecting concomitant disease activity in postgeniculate pathways in some patients. Thus, evaluation of visual function after ON requires multiple tests to ensure comprehensive assessment of the potential deficits.

**APPROACHES TO ASSESSMENT OF ON** Optical coherence tomography. Assessment of structural changes in the course of ON has been revolutionized over the past 2 decades by advances in optical coherence tomography (OCT), a technique that uses interferometry of reflected light to obtain images of the retinal layers (figure 2). Most OCT studies of patients with ON have used time-domain OCT (TD-OCT), which provides cross-sectional images from different tissue levels. Since the peripapillary
The retinal nerve fiber layer (RNFL) is composed of unmyelinated optic nerve axons, RNFL thinning detected by OCT is directly interpretable as neuroaxonal degeneration. More modern systems using spectral-domain OCT (SD-OCT) provide considerably improved resolution and speed and can be used to generate 3-dimensional images for measurements of thickness of neuronal layers.

Acute ON often results in inflammatory swelling of the RNFL of the affected eye. The inflammatory swelling generally resolves within 3 months\(^1\) and is accompanied by a period of RNFL thinning that continues for up to 7–12 months but is most prominent in the first 6 months after acute ON onset.\(^5\)\(^,\)\(^15\)

The initial period of swelling prevents examination of the timing of axonal loss in the RNFL with TD-OCT. In contrast, the thickness of the retinal ganglion cell layer (RGCL) appears to be less affected by edema.\(^16\)\(^,\)\(^17\) so the more detailed resolution with SD-OCT may allow for a better assessment of the timing of thinning in reference to acute ON. Recent studies suggest that thinning of the RGCL starts within several weeks after an episode of ON and may precede RNFL thinning.\(^16\)\(^,\)\(^17\)

Ultimately, RNFL thinning in affected eyes correlates with visual acuity, low-contrast letter acuity, visual field, color vision, and VEPs (see also below),\(^18\)\(^,\)\(^19\) thereby supporting its functional relevance, and RNFL thickness \(<\)75 µm has been shown to predict reduced visual field function.\(^2\)\(^,\)\(^20\)

Although it is not yet clear whether preventing RNFL thickness from crossing that threshold can reduce the extent of associated visual deficits, it is worth noting that it is also near the lower limit of RNFL thickness, when virtually all retinal ganglion cell (RGC) axons have been lost (20–40 µm).\(^21\)

Thinning of the RNFL following an episode of ON is thought to result from axonal loss subsequent to axonal injury during the inflammatory demyelinating lesion of the affected optic nerve. However, it is noteworthy that detectable RNFL thinning and associated visual deficits are also observed in unaffected eyes of patients with MS in the absence of history of ON.\(^15\)

One possibility is that some “mild” attacks are not reported or do not result in deficits that are

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**Figure 1** Evolution of visual function after acute optic neuritis

Figure shows the measurement of high-contrast visual acuity (VA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts (A), the 2.5% and 1.25% low-contrast VA using Sloan charts (B, C), and color vision using the Hardy-Rand-Rittler (HRR) pseudoisochromatic plates (D) in a cohort of 37 patients with acute optic neuritis (AON) and visual assessment at baseline (presentation) and months 2, 4, and 6 after onset (data from Gabrilo, I et al. 2015\(^16\)). Each colored line is data from an individual patient, the solid black line represents the mean from all patients, and the dashed black line shows the normal values for healthy individuals for binocular testing (ETDRS = 70; 2.5% low-contrast VA = 43; 1.25% low-contrast VA = 34; HRR = 36). Reprinted with permission from Elena H. Martinez-Lapiscina.
immediately evident to patients. Thus, in nonacute ON eyes there is a component of RNFL thinning that may be attributable to other causes, such as subclinical optic nerve inflammation, neurodegeneration within normal-appearing white matter, or transsynaptic degeneration associated with lesions elsewhere in the visual pathway.22–24 The increased resolution of SD-OCT and the use of segmentation algorithms have allowed a more detailed analysis of the effects of ON and MS on retinal structure25 (figure 2). These studies found that RNFL thinning associated with MS with or without ON is not confined to the peripapillary region but also affects the macula. In addition, a similar pattern
of thinning is observed for the ganglion cell layer/inner plexiform layers (GCL + IPL) in the peripapillary region and macula. A recent study in patients with ON found that decreases of $4.5 \text{ mm} GCL + \text{IPL}$ thickness after 1 month predicted low-contrast visual acuity dysfunction at 6 months, whereas decreases of $7 \text{ mm}$ predicted visual field and color vision deficits. In another study in patients with MS with or without a history of ON, thinning of GCL + IPL was most closely associated with visual function and vision-specific QOL. Results of these studies suggest that degeneration associated with ON and MS is widespread in the RGCL.

Together, these studies provide compelling evidence for structural damage from acute ON, and they also provide a powerful demonstration of the potential for SD-OCT as a tool to assess neurodegenerative changes in acute ON. However, both TD-OCT and
SD-OCT appear to be less sensitive than VEPs for assessing the clinical and subclinical effects of ON.\textsuperscript{27,28} so interpretation of OCT may require complementary assessments using functional techniques. Furthermore, improvements are needed to standardize and reduce test-retest variability in SD-OCT systems.\textsuperscript{29} Given the rapid evolution of the technology, the technical expertise required, and differences between commercially available instruments,\textsuperscript{30} it is also important that criteria be established to ensure quality control for OCT as a validated outcome measure, a process that is under way.\textsuperscript{31}

**VEPs.** Standard VEPs elicited by visual stimuli and measured in the occipital cortex can be used to detect functional changes in the visual pathway, including the optic nerve.\textsuperscript{32} In multifocal VEPs (mfVEPs), visual stimuli are provided independently to localized regions of a wider visual field (48°) and responses to the stimuli are measured individually,\textsuperscript{33} allowing for a more detailed analysis of visual function covering a much larger area of the visual pathway than standard VEPs (figure 3).

The severity of an attack of ON and the extent of inflammation are correlated with an acute reduction in the amplitude of VEPs.\textsuperscript{34} Reduction in VEP amplitude is thought to reflect functional impairment of axonal conduction either transiently (e.g., due to acute inflammation or demyelination) or persistently (due to axonal loss). Within 3–4 months after the acute episode, the amplitude generally shows some recovery, reflecting resolution of edema, and the waveform of the VEP is well-preserved, but the latency is significantly increased. This residual latency delay is thought to result from demyelination of surviving axons, which interferes with saltatory conduction of the action potential along the optic nerve lesion. Some investigators have reported subsequent improvement in latency for up to 2 years,\textsuperscript{6} whereas others have reported no further recovery after 4 months.\textsuperscript{8} Prolongation of latency is most evident in the central visual field, perhaps indicating that the central (macular) region of the optic nerve is more susceptible to demyelination or resistant to remyelination.\textsuperscript{32} The central region of the optic nerve contains the greatest density of parvocellular fibers that convey static information (e.g., form and color), but VEP latency in patients with ON correlates more strongly with dynamic functions (e.g., motion detection) than with static functions. This may suggest more specific effects on magnocellular fibers or greater vulnerability of fibers required for accurate signal timing.\textsuperscript{8}

Effects of ON on VEPs have also been shown to reflect structural changes in the RNFL. In a study of 21 patients following a first episode of unilateral ON, VEP latency prolongations and amplitude reductions of affected eyes at baseline and 3 months after onset were associated with RNFL thinning,\textsuperscript{39} suggesting a relationship between the initial structural loss and residual functional impairment. In a separate study of 25 patients with ON with incomplete recovery after 1 year, similar relationships between VEP latency/amplitude and RNFL thinning were still evident,\textsuperscript{18} further supporting the clinical relevance of this technique.

mfVEPs have been used in a growing number of small studies to examine the pathology of ON in greater detail.\textsuperscript{35–38} mfVEPs detect functional changes associated with onset and evolution of acute ON and may be particularly useful to assess treatment outcomes in clinical trials as it appears to be more reproducible than standard VEPs.\textsuperscript{39} One study of 25 patients with ON between 6 and 12 months after onset found an apparent discrepancy between structural and functional measures in these patients.\textsuperscript{35} As RNFL thinning progressed in the affected eyes over this time period, the mfVEP amplitude partially recovered, suggesting that functional recovery may be due in part to remyelination and/or neuronal plasticity.

Functional data provided by VEPs and mfVEPs make an ideal counterpart to structural retinal assessments using OCT. However, as with OCT, criteria need to be established to ensure reproducibility and validity of VEP results. Furthermore, larger-scale studies are needed to confirm the results of current smaller studies.

**MRI.** Nonconventional MRI techniques offer novel tools to examine the structure of CNS tissues in detail. For example, magnetization transfer (MT) imaging exploits the difference in resonance in free protons and protons associated with macromolecules (e.g., myelin), the ratio of which may provide a measure of myelin content.\textsuperscript{40} Diffusion tensor imaging (DTI) can be used to measure asymmetric radial diffusivity (RD), axial diffusivity (AD), or fractional anisotropy (FA) of water as a gauge of tissue in major nerve tracts (e.g., optic nerve and optic radiations).\textsuperscript{41}

A small number of studies have provided support for use of these techniques to assess pathologic changes in ON. For example, in an MT study in 11 patients with ON, MT ratios of affected optic nerves closely followed the course of the disease: they were significantly higher at baseline (within 8 days of onset) but were reduced at months 3 and 6.\textsuperscript{42} In a separate study in 37 patients with ON, MT ratios of affected optic nerves were not found to be different from those of unaffected nerves until 3 months after onset.\textsuperscript{51} In that study, ON-associated alterations in MT ratios at 3 months correlated with high-
low-contrast visual deficits and with VEP latency at 6 months as well as with RNFL thinning at 12 months.

In a study of DTI performed within 30 days of onset and after 1 year in 12 patients with ON, FA of affected optic nerves (which is also considered a potential measure of myelination) was the only parameter correlated with vision at onset but did not correlate with the extent of recovery of visual acuity or contrast sensitivity at 1 or 3 months.44 The AD (considered a measure of axonal integrity) was the only parameter that was correlated with worse contrast sensitivity at 1 and 3 months. This was confirmed in a follow-up study in 25 patients, in which a lower baseline AD was also found to be correlated with the extent of RNFL thinning and with VEP amplitude and latency.45 These were small studies and should be interpreted with caution as eye motion makes imaging of the optic nerve by MT ratio and DTI challenging, but they do not seem to support a model in which the extent of neurodegeneration is determined solely by chronic demyelination. Rather, they suggest that the initial neuroaxonal effects of the acute inflammatory injury may be more important.

Although these “nonconventional” MRI techniques hold promise as a tool to investigate underlying processes and assess recovery in ON, there are substantial challenges to widespread use. For example, the acquisition times are frequently longer than is practical for routine human studies, and imaging is complicated by motion artifacts caused by moving the eye or head.46 In addition, there is no consensus on sequences and protocols for their application in ON. These factors have limited widespread adoption of these approaches and have likely contributed to the inconsistencies in findings. Thus, further technological improvements and standardization of techniques for imaging of ON lesions will be required before they can be considered as reliable measures of outcomes in clinical trials.

**QOL** Visual deficits in patients with ON are likely to have a marked impact on daily activities and QOL. Patients frequently rate vision among the most important physical functions affected by MS.47 However, vision is poorly or insufficiently represented on standard objective measures of physical function, such as the Expanded Disability Status Scale, and functional assessment instruments, such as the Multiple Sclerosis Functional Composite (MSFC). Addition of SLCLA charts to the MSFC has been reported to better capture MS-related disability.48 One patient-reported outcome instrument, the 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), has become a commonly used measurement of vision-specific health-related QOL. When administered to patients from the ONTT 5–8 years after the episode of acute ON, scores on the NEI-VFQ-25 were lower than for an older disease-free cohort.3 In patients with MS, correlations with NEI-VFQ-25 scores have been demonstrated for low-contrast visual acuity,49 binocular summation,12 motion perception,50 and loss of RGCs25 (figure 4). Moreover, a 10-item supplement has been developed to better capture aspects more relevant to neuroophthalmology, such as double vision and difficulties with viewing motion.51 A follow-up study has also reported its ability to distinguish patients with MS with a history of ON.52

**TREATMENTS** An important unmet need with respect to ON is the availability of effective treatments to prevent or reverse long-term visual dysfunction. Given the narrow window of time during which most recovery occurs, it seems reasonable to suggest that an effective treatment be initiated as soon as possible after ON onset, with the aim of promoting RGC survival and either extending the window for remyelination or accelerating the rate and extent to which it occurs. Data emerging from OCT studies suggest that RGC loss may begin within weeks of the event, thereby narrowing the time to initiate neuroprotective therapy.

Despite the lack of long-term benefits of high-dose corticosteroids, patients with acute ON are frequently
provided these drugs as symptomatic treatment to speed resolution of acute inflammation. Patients are often assessed by MRI to determine their risk for MS, but it is not clear that disease-modifying therapies for relapsing forms of MS are effective to prevent neurodegeneration when ON occurs while receiving these treatments. For example, interferon β was not found to prevent RNFL thinning in patients with ON.

Natalizumab has been shown to reduce loss of vision and improve VEPs in patients with relapsing-remitting MS, but there are no data to indicate treatment benefits specifically in patients with ON. A phase II study of fingolimod in acute demyelinating ON is complete, although it is not provided these drugs as symptomatic treatment to speed resolution of acute inflammation. Patients are often assessed by MRI to determine their risk for MS, but it is not clear that disease-modifying therapies for relapsing forms of MS are effective to prevent neurodegeneration when ON occurs while receiving these treatments. For example, interferon β was not found to prevent RNFL thinning in patients with ON.

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Table Phase II and III studies in typical optic neuritis

| Start/end datesa | Treatment | Time from event to study initiation | Primary endpoint | Status| Primary efficacy results | Study numbera |
|------------------|-----------|------------------------------------|------------------|------|--------------------------|---------------|
| July 1995-December 1997 | Immunoglobulin 0.4 g/kg IV QD for 3 d, then 3 infusions/mo for 3 mo vs placebo | ≥6 mo | High-contrast visual acuity (100% ETDRS charts) | Completed | No significant effect | NCT00000171 |
| August 2006-July 2011 | Erythropoietin 33,000 units IV for 3 d vs placebo | ≤10 d | RNFL thickness at 4, 8, and 16 wks | Completed | Significantly less RNFL thinning at 16 wk | NCT00355095 |
| September 2006-March 2011 | Simvastatin 80 mg QD PO vs placebo | <4 wk | Contrast sensitivity at 3 mo | Completed | No significant effect | NCT00261326 |
| March 2008-January 2011 | Atacicept 150 mg SC weekly vs placebo | Not specified | RNFL thickness up to 48 wks | Terminated | None available | NCT00624468 |
| February 2009-February 2011 | Glatiramer acetate 20 mg SC QD vs placebo | Not specified | RNFL thickness at 6 mo | Completed | None available | NCT00856635 |
| February 2010-January 2013 | Minocycline 100 mg BID vs no treatment | ≤30 d | RNFL thickness every 3 mo for 9 mo | Terminated | None available | NCT01073813 |
| May 2010-March 2013 | Visual reconstitution therapy vs saccadic eye movement training | 60-80 d or <12 mo | Visual field at 6 mo | Completed | None available | NCT01274702 |
| May 2011-December 2013 | Dalfampridine 10 mg BID vs placebo | ≥12 mo | Contrast sensitivity (5% ETDRS charts) | Completed | None available | NCT01337986 |
| July 2011-December 2012 | Vitamin D 50,000 units/wk vs vitamin withheld | Not applicable (prevention study) | RNFL thickness at 10-32 d after optic neuritis | Unknown | None available | NCT01465893 |
| November 2011-August 2014 | Phenytoin 15 mg/kg/d for 3 d, then 4 mg/kg/d for 13 wks vs placebo | ≤14 d | RNFL thickness at 6 mo | Completed | Significantly less RNFL thinning at 6 mo | NCT01451593 |
| March 2012-September 2014 | Oral prednisone 1,250 mg vs methylprednisolone 1,000 mg IV for 3 d each | ≤14 d | VEP latency | Unknown | None available | NCT01524250 |
| December 2012-October 2014 | BIBO33 (anti-LINGO-1) 100 mg/kg IV every 4 wks vs placebo | ≤28 d | VEP latency | Completed | None available | NCT01721161 |
| February 2013-February 2015 | Amiloride 10 mg QD vs placebo for 5 mo | ≤28 d | RNFL thickness at 6 mo, 12 mo | Recruiting | None available | NCT01802489 |
| July 2013-June 2016 | Fingolimod 0.5 mg QD vs interferon β-1b | ≤30 d | VEP latency | Recruiting | None available | NCT01647880 |
| August 2013-May 2014 | Fingolimod 0.5 mg QD vs placebo | Not specified | RNFL thickness at 18 wks | Completed | None available | NCT01757691 |
| October 2013-January 2016 | MD1003 100 mg TID vs placebo | Not specified | High-contrast visual acuity (100% ETDRS charts) | Recruiting | None available | NCT02220244 |
| March 2014-April 2016 | Amiloride hydrochlorothiazide 100 mg/d vs placebo | ≤10 d | RNFL thickness at 24 wks | Recruiting | None available | NCT01879527 |
| November 2014-December 2018 | Erythropoietin 33,000 units IV for 3 d vs placebo | ≤10 d | RNFL thickness at 6 mo | Recruiting | None available | NCT01962571 |

Abbreviations: ETDRS = Early Treatment Diabetic Retinopathy Study; RNFL = retinal nerve fiber layer; SC = subcutaneous; VEP = visual-evoked potential.

a From ClinicalTrials.gov, except where indicated otherwise.

b The Optic Neuritis Treatment Trial, included a 15-year follow-up period.

c Based on published result.

d Reported at American Academy of Neurology 2015 Annual Meeting, April 18-25, Washington, DC.
clear that enrollment goals were met. Another phase II/III study is under way but study results are not yet available (table).

Based on promising results from animal studies and small clinical studies, IV immunoglobulin was investigated in patients with one or more episodes of typical ON and irreversible loss of visual acuity but was terminated early due to negative results\(^56\) (table). Since that time, various investigational therapies have shown promise in early preclinical and clinical studies, and a number of phase II and III studies have been completed or are under way. For example, in a placebo-controlled study of IV erythropoietin for 3 days as an add-on to methylprednisolone in patients with a first episode of ON within the previous 10 days, those treated with erythropoietin demonstrated reduced RNFL thinning, less decrease in optic nerve diameter, and shorter VEP latency.\(^57\) Although the mechanism by which erythropoietin may exert these effects is poorly understood, it may involve the neuroprotective effects of this hormone during acute inflammation. In another placebo-controlled study in patients with symptom duration of <4 weeks and reduced contrast sensitivity, simvastatin (a hypercholesterolemia medication) narrowly missed significance on the primary efficacy outcome (contrast sensitivity), but improvements were noted for VEP latency and amplitude.\(^58\) However, imbalances in randomization and technical issues may have contributed to the observed effects.\(^59\) A study in ON testing possible neuroprotective effects of phenytoin, an anticonvulsant, has recently completed, and another study testing effects of amiloride hydrochlorothiazide, a diuretic, is currently underway. Nevertheless, it is an open question whether a neuroprotective agent can do more than delay degeneration of axons if they remain chronically demyelinated. Finally, BIIB033, a fully-human antibody to LINGO-1, an inhibitor of myelination and neuroaxonal growth, has shown promise in preclinical and early clinical testing,\(^60\) and a phase II study in ON was recently completed.

**CONCLUSIONS** It is now clear that recovery from ON is frequently incomplete, which adversely affects the QOL of patients. In addition, there remain considerable gaps with respect to understanding, assessing, and treating this disease to prevent long-term deficits. Nevertheless, ongoing work holds promise for all of these areas. The application of newer technologies continues to provide new insight into the underlying disease processes and increased appreciation of the injury that occurs following ON. The development of these new tools may increase the ability to detect meaningful changes in vision with therapeutic intervention and study results suggest that timing is critical. Development of guidelines to ensure consistency in their application should also improve interpretation of findings and thereby improve the quality of assessments. Finally, several therapies have shown promise in preclinical and early clinical testing. Therefore, there is reason to be optimistic that strategies may soon be identified to improve the prognosis for patients with ON. Given the relationship between ON and MS, it seems likely that any such developments for ON may have substantial implications for understanding, assessing, and treating MS as well.

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All authors participated in the conception of the article, interpretation of the data, and revision of the manuscript, and they approved the final version. Biogen provided funding for writing and editorial support in the development of this paper, and they reviewed and provided feedback on the paper to the authors. The authors had full editorial control of the paper and provided their final approval of all content.

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