The Optic Neuritis Treatment Trial

A Definitive Answer and Profound Impact With Unexpected Results

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The Optic Neuritis Treatment Trial (ONTT) has had a highly significant impact on the practices of ophthalmology and neurology. The impact can be attributed to its systematic collection and analysis of enormous amounts of data, adherence to sound clinical trial methodology, as well as important unanticipated findings.

For lack of a more precise definition, optic neuritis is an acute, noninfectious inflammatory optic neuropathy that predominantly affects young people. By the end of the 19th century, the clinical profile of this disorder and its relationship to multiple sclerosis (MS) were well characterized. In the subsequent 100 years, numerous reports identifying erroneous etiologies and seemingly successful treatments were published; however, we still lacked the complete clinical profile and an understanding of its natural history. The value of treating optic neuritis with corticosteroids, a treatment first available in the 1950s, remained controversial. Although several investigators had reported that corticosteroid treatment did not alter the final visual outcome, neurologists and ophthalmologists tended to treat optic neuritis patients with oral prednisone, especially if, as is often the case, the patients had severe loss of vision. In a 1988 prospective study, Rizzo and Lessell established that patients who appeared to have idiopathic optic neuritis have a very high risk of developing clinical MS. The ONTT was conceived to define precisely the clinical profile of patients with optic neuritis, to determine the value of corticosteroid treatment, and to determine the risk of developing MS. With regard to the impact of treatment on vision, it should be noted that unlike many other clinical trials, there was little at stake because it had long been recognized that the vast majority of patients with optic neuritis would enjoy visual improvement even without treatment. On the other hand, the trial’s impeccably obtained data have standardized our approach to the diagnosis, treatment, and subsequent follow-up in patients with optic neuritis. Four of the trial’s major findings—the prevalence of fellow eye abnormalities, types of visual field defects, adverse effects of oral corticosteroid treatment, and delay in onset of MS in patients treated with intravenous corticosteroids—were all unanticipated. Though still controversial, each of these findings has altered our approach to patients with this disorder, provoked much debate, and spawned important subsequent investigations.

ONTT RESULTS

The findings of the ONTT, reported in more than 50 publications during the past 20 years, have numerous implications. Although the debate continues over the use of intravenous steroids in the management of acute optic neuritis to modify short-term risk of MS in patients with high-risk magnetic resonance imaging (MRI) results, there are other important evidence-based conclusions that make the ONTT legacy indisputable. As a result of the ONTT:

- Oral steroids (in standard 1 mg/kg doses) are not used to treat isolated optic neuritis.
- The risk of subsequent MS development can now be reliably estimated and MRI is firmly established as the single most important predictor of risk of developing MS.
- A low-risk profile (normal MRI results in men with poor vision, severe disc swelling, and no pain) for subsequent MS development was identified.
- There is an enormous body of data (vision deficits, MRI findings, spinal fluid analysis, neurologic disability, and vision-related quality of life issues) characterizing the clinical profile of optic neuritis obtained from analysis of carefully characterized and studied patients.
- Computerized threshold perimetry and its analysis were rigorously tested and used to characterize optic nerve dysfunction.
- Radiologic and laboratory testing of patients with optic neuritis to secure a diagnosis was shown to be unnecessary.
- Intravenous corticosteroid treatment was shown to be safe and to be associated with minimal adverse effects in this patient group.
- Novel electronic methods of data sharing and remote monitoring of clinical trials were established.
- More evidence-based information concerning the relationship of optic neuritis and MS is available for patients and physicians to discuss.
- Fellow eye abnormalities and the possibility of simultaneous bilateral or occult demyelinating disease involving the prechiasmatic and retrochiasmatic pathways were confirmed.
- Contrast sensitivity and vision testing in general became commonplace and important outcome measures in many MS treatment trials.
- Neurologic disability in patients who developed MS after optic neuritis was determined to be mild.
• An important subset of patients more apt to have permanent visual impairment with more severe initial vision loss was identified as a target group for future clinical trials, perhaps using neuroprotective drugs, myelin restoring compounds, or both.

STUDY DESIGN

The ONTT studied patients first within 8 days of symptom onset with unilateral vision loss in an eye that had not had optic neuritis.7 The study group of 448 eligible patients included those with a history of MS (13% definite or probable MS). The study population was 85% white, perhaps making some of its findings less applicable to populations that may have lower disease prevalence (Asian individuals) or different clinical profiles (African American individuals).9 Otherwise, the ONTT population analysis has stood up to rigorous scrutiny and comparison with other clinical data sets. Allowing for differences in study design and patient inclusion criteria, the patients enrolled in ONTT were comparable with those enrolled in other large studies of patients with non-symptomatic demyelinating events.10,11

GOALS

The primary goal was to determine whether oral or intravenous steroids altered the visual outcome in patients with acute optic neuritis. It would seem that ONTT definitively answered the question. Steroids, if given intravenously, accelerated the recovery of vision, but after 1 month there was no significant difference in visual acuity, visual fields, color vision, or contrast sensitivity. Similar findings have been reported in other studies specifically looking prospectively at the treatment of optic neuritis.12-15 Each of these studies was smaller and slightly different from ONTT but had similar conclusions. For instance, Kapoor et al12 also demonstrated no long-term benefit of intravenous corticosteroids, and Sellebjerg et al demonstrated an accelerated rate of recovery in patients treated with a high dose of oral steroids, but there was once again no long-term benefit. A Japanese prospective study showed faster recovery of visual acuity among patients receiving intravenous corticosteroids but no long-term effect on visual outcome. Other early studies, by Rawson et al16,17 demonstrated accelerated recovery in patients treated with intravenous corticotropin but no long-term difference compared with placebo, a finding that was also reported by Bowden et al.18 Although debate has continued since ONTT reported its findings and other literature reviews and meta-analysis have been performed,10,21 most continue to agree that there is no role for oral steroids in the acute management of optic neuritis. Oral steroids in standard doses had no effect on the rapidity of recovery and were associated with a higher recurrence rate, making them contraindicated in patients with acute optic neuritis,22 a recommendation that has been widely adopted.23,24 However, no other study has confirmed the increased recurrence rate of optic neuritis in patients treated with oral corticosteroids. The ONTT data did not answer why increased rates of optic neuritis recurrence (a presumed indicator of demyelinating disease activity) were not associated with increased rates of MS development. This result has been questioned and may have been influenced by reanalysis bias introduced when the authors focused their attention on this unexpected tertiary outcome, which the trial was not designed to study.25-27

Nevertheless, although the use of oral steroids has declined, many surveyed ophthalmologists and neurologists still think that steroids aid visual recovery.24 The ONTT did not explain the significance of a slight benefit of intravenous treatment seen in patients with more severe vision loss.6,28 Recognizing that this group is more likely to have permanent vision loss, further studying this subgroup with corticosteroid and/or other therapies seems warranted.29

The ONTT protocol called for 4 divided doses of 250 mg of methylprednisolone sodium succinate daily, a practice that interestingly has been largely abandoned for the untested and unproven, but admittedly more convenient, alternative of an outpatient, single daily dose of 1 g of methylprednisolone sodium succinate for 3 days. Steroid treatment was shown to be safe with minimal adverse effects, which, when more severe (in 2 patients), resolved quickly on discontinuing the medication.30 Patients in the intravenous group were aware of their treatment (open label) and therefore could have informed examiners of their treatment status, introducing examiner bias. The investigators did not include a treatment arm of patients receiving high-dose oral steroids, which may have proved to be similarly effective.13 Theories concerning the differences in results of intravenous vs oral steroids are predicated on the concept that high trough levels of steroids in intravenously treated patients have a different effect on the autoimmune process.31 Similar levels might be achieved with high-dose oral steroids.

CLINICAL PROFILE OF OPTIC NEURITIS

Secondarily, the ONTT investigators sought to characterize critically the clinical profile of patients with optic neuritis, acutely and during recovery. These issues were addressed in the Longitudinal Optic Neuritis Study. Through their definition of the clinical profile of study patients, these researchers achieved nearly perfect diagnostic accuracy, with only 2 known misdiagnoses of a pituitary adenoma and ophthalmic artery aneurysm.7 Other diagnostic tests, including blood work (anti-nuclear antibody and fluorescent treponemal antibody absorption), chest radiography, and lumbar puncture, were not found to be helpful in identifying alternative causes for optic neuropathy in the study patients and have largely been abandoned in typical cases as a result of ONTT. Studies of the visual dysfunction in optic neuritis identified the previously underappreciated importance of contrast sensitivity as a marker of optic nerve dysfunction in optic neuritis.32 The study demonstrated a nonspecific pattern of color vision loss.33 Surprisingly, a high prevalence of diffuse and nerve fiber bundle defects on visual fields (and a low prevalence of isolated central scotoma) was found.34 This finding was particularly unsettling because without exception individual clinician’s experiences and previous articles noted that most patients had central scotoma.35 This discrepancy may not be surprising given the nature of automated perimetry testing of the central 30° of visual field.36 Before
the study, most studies and experiences were based on Goldmann or tangent screen perimetry. These methods highlighted central field loss within 20° to 30° of fixation. Thus, the diffuse loss on quantitative threshold perimetry of the central 30° may be tantamount to the central scotoma of Goldmann and tangent screen perimetry. Fang et al further clarified this by demonstrating a component of diffuse loss of more than the 30° field, even in patients with more focal (arcuate) defects. In addition, while more than 97% of patients had some type of central vision loss, only 70% had peripheral defects. These visual field studies confirmed that it is unlikely that a specific group of nerve fiber bundles are vulnerable in optic neuritis patients and confirmed that automated perimetry alone cannot be used to reliably distinguish optic neuritis from other acute optic neuropathies. Standardized techniques for performing and analyzing quantitative perimetry were demonstrated and the ONTT paved the way for seemingly effective and nearly exclusive use of automated perimetry in neuro-ophthalmic vision loss. The finding of fellow eye abnormalities (at least 1 of 4 of the tested parameters was abnormal in 67% of patients, including 48% of visual fields) was not previously appreciated. These deficits changed or improved over time, suggesting a bilateral, simultaneous disease rather than preexisting deficits or testing artifacts. Despite these clinical findings, there was no report of acute optic nerve MRI lesions occurring with this same frequency in the asymptomatic eyes. Previously not appreciated in optic neuritis was the finding in a number of patients of visual field defects that suggested chiasmal or retrochiasmal visual field loss.

The time course of optic neuritis was characterized, confirming that many patients had abrupt onset of seemingly static vision loss while others progressed throughout days. Nearly all patients began to recover at least 1 line of vision by 3 weeks. If recovery does not begin, then an alternative diagnosis should be sought. Despite relatively rapid and seemingly complete recovery (median acuity at 6 months was 20/16, and 87% of patients had acuities of 20/25 or better at 5-years’ follow-up), patients often reported significant persistent complaints. Patients’ responses to the National Eye Institute Visual Function Questionnaire were shown to correlate with these persistent visual symptoms. Again, contrast sensitivity testing results were the most consistently abnormal in these patients. This finding laid the ground work for vision assessment and contrast sensitivity to become prominently featured in many MS treatment trials as a treatment end point. Patients in ONTT who subsequently went on to develop MS (many were treated with disease-modifying therapies) were found to have only mild neurologic disability.

**RELATIONSHIP BETWEEN OPTIC NEURITIS AND MS**

Finally, the ONTT investigators sought, as a clearly stated secondary objective, to investigate the relationship between optic neuritis and MS, though they did not design the trial to test whether corticosteroid treatment influenced this relationship. They demonstrated, even as many as 15 years after the initial optic neuritis attack, that the initial MRI result, if abnormal with white matter abnormalities, was the single most important predictor of the future risk of MS. During the last decade, ONTT and many other studies have demonstrated that MRI abnormalities are seen in patients before they go on to develop clinical symptoms of MS. In ONTT, 25% of patients with no MRI lesions still developed MS, 50% of patients with 1 or more lesions developed MS within 5 years, and 72% of patients with 1 or more lesions developed MS within 15 years. These percentages were remarkably similar to those previously reported by Rizzo and Lessell.

The most controversial and unanticipated outcome of ONTT was the finding that in patients with abnormal MRI results, intravenous steroids had a significant protective effect: 16% of intravenously treated patients and 30% of patients treated orally or with placebo developed MS at 2 years. The authors rigorously reviewed the data with respect to this finding and subjected these results to extensive external review before publication. This finding, which is of uncertain pathophysiologic significance, was not a study question by design but has a profound impact on clinical practice. This protective effect disappeared by the third year, with the intravenously treated patients catching up to patients treated orally and with placebo. Silberberg expressed concerns that intravenously treated patients were not blinded to their treatment, that there was the potential for misinterpretation because of retrospective analysis of data obtained for other reasons, and that sample sizes were small (19 patients developed MS in the oral and placebo groups vs 10 in the intravenous group). Goodin has questioned the significance of this finding because of the reanalysis bias that was likely introduced when baseline characteristics of patients were reanalyzed (with some patients excluded) to conclude that the intravenous corticosteroids influenced the rate of MS development. This finding was not found to be significant when the data were initially analyzed. Ultimately, this finding remains controversial and has not been subsequently tested in a clinical trial designed to specifically answer this question.

Physicians now believe they can predict, delay, and possibly alter the risk of MS in optic neuritis patients with abnormal MRI results by using intravenous steroids and/or immunomodulatory therapy. Again, both ophthalmologists and neurologists were initially slow to recommend MRI. Moreover, when they did order the study, they felt it would help secure the right diagnosis rather than gauge the MS prognosis. Regional and national differences related to MRI availability and access to the use of disease-modifying drugs in MS made widespread implementation of ONTT findings impractical in certain areas. Ultimately, some have rejected the notion of intravenous steroid use “because of the lack of long term benefit and because of the potential side effects of corticosteroids.” Other, less powerful predictors of MS development included previous optic neuritis, family history of MS, nonspecific neurologic symptoms, white race, and family history of MS. Significant negative predictors of MS development were male sex, severe disc swelling and hemorrhages, no pain, and poor vision. These are sufficiently atypical features, making it possible that the initial clinical diagnosis of ordinary optic neuritis was inaccurate and an alternative optic neuropathy was present.
LEGACY

At last, the debate over altering the long-term visual prognosis in patients with optic neuritis by using corticosteroids has ended and the relationship between optic neuritis and MS has been further defined. The ONTT has had significant impact on the practice of ophthalmology by establishing guidelines for examination and evaluation of patients with optic neuritis, firmly establishing MRI as the procedure of choice for determining relative risk and possible therapy for MS prevention, providing the substrate for evidence-based discussions between physicians and their patients concerning treatment and prognosis, and highlighting the possible importance of treatment and further clinical trial investigation on the clinical course of early MS. The stage is set for further investigation.

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REFERENCES