New Treatments for Optic Neuritis

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Abstract

Optic neuritis is used as a general term for any acute optic neuropathy caused by inflammation, and in a more specific sense, to refer to the optic neuritis that occurs in patients with multiple sclerosis. The latter disease, often called demyelinating optic neuritis, occurs most often in women, is usually retrobulbar, is accompanied by pain with eye movements, and generally recovers spontaneously. For patients with no prior history of neurologic disease, the 10-year risk of a second demyelinating event after an initial attack of optic neuritis is 38%. This risk is greater in patients who have demyelinating plaques present on brain magnetic resonance imaging. The Optic Neuritis Treatment Trial showed no benefit of corticosteroid therapy on visual acuity, measured six months after an attack of optic neuritis. However, at one month there was more rapid improvement in acuity in patients treated with intravenous steroids. Long-term treatment with interferon, an immunosuppressive agent, has been shown to reduce the rate of demyelinating events and plaque accumulation measured by magnetic resonance imaging. A new drug, natalizumab, has also been shown to reduce the formation of new demyelinating plaques in patients with multiple sclerosis. Unfortunately, treatment with both interferon and natalizumab has resulted in progressive multifocal leukoencephalopathy, a rare and fatal opportunistic viral infection of the brain, in 3/5000 patients. Despite this tragic setback, the advent of new drug therapies has brightened the prognosis for patients with multiple sclerosis.

Key Words: Steroids, interferon, demyelinating plaque, magnetic resonance imaging, multiple sclerosis, CHAMPS, ONTT, natalizumab

The diagnosis of demyelinating optic neuritis has become relatively simple for the ophthalmologist, thanks to better knowledge of the natural history of this condition and the advent of magnetic resonance imaging. The Optic Neuritis Treatment Trial, funded by the United States National Eye Institute in 1988, provided a clear epidemiologic profile. The study enrolled a cohort of 457 patients, aged 18-46, with a first attack of optic neuritis occurring within the prior eight days. Most patients were female (77%), reported ocular pain (92%), and had a normal fundus (65%). Their acuity ranged from 20/20 (10%) to no light perception (3%), with a majority seeing better than 20/200 (64%). Although a cecocentral visual scotoma has been associated with optic neuritis, a wide variety of field defects was reported among patients in the Optic Neuritis Treatment Trial. This means that the pattern of visual field loss is often not helpful in the diagnosis of optic neuritis (Figure 1).

For typical cases, the only ancillary test recommended routinely is magnetic resonance imaging. In the Optic Neuritis Treatment Trial, 90% of patients had demyelinating lesions consistent with an underlying diagnosis of multiple sclerosis. Laboratory tests were not generally helpful. In 15 patients the antinuclear antibody titer was positive at a titer of 1:320, but subsequent evaluation in most subjects failed to support the diagnosis of rheumatologic disease. No patient had op-
tic neuritis from syphilis. A chest roentgenogram did not suggest an alternative diagnosis in any patient. The Optic Neuritis Study Group concluded that if the patient's history and findings conform to the classical picture of demyelinating optic neuritis, no laboratory evaluation is required. Obviously, this recommendation is valid only if the physician has made a diligent effort to identify alternative etiologies. For example, Bartonella tigers are mandatory in a patient with disc edema and fresh scratches from a newly adopted kitten, even without a macular star.

Optic neuritis and anterior ischemic optic neuropathy are occasionally confused, because they have overlapping clinical profiles. The disc edema produced by optic neuritis and anterior ischemic optic neuropathy can be indistinguishable. In both conditions, a second attack in the other eye is common. Finally, in both conditions, magnetic resonance imaging often shows multiple, small, white matter lesions on T2-weighted images. The demyelinating plaques of multiple sclerosis can resemble the lesions of subcortical arteriosclerotic encephalopathy, which are associated with anterior ischemic optic neuropathy and vascular disease. It is vital to differentiate accurately between optic neuritis and anterior ischemic optic neuropathy because the evaluation and management of patients with these two diseases is completely different. Features suggesting anterior ischemic optic neuropathy are lack of pain, poor visual recovery, older age, optic disc hemorrhage, and sectorial optic disc edema.

GLUCOCORTICOID TREATMENT: A MARGINAL BENEFIT

For decades, physicians argued about the value of glucocorticoids in the treatment of optic neuritis. Neurologists usually prescribed a short course of oral prednisone, whereas ophthalmologists generally offered nothing. The Optic Neuritis Treatment Trial was commissioned to resolve the longstanding controversy surrounding steroids and optic neuritis. Enrolled patients were randomized to receive either: 1) placebo, 2) oral prednisone (1 mg/kg for 14 days) or 3) three days of intravenous methylprednisolone (250 mg four times per day) followed by 11 days of oral prednisone (1 mg/kg). There were about 150 patients in each arm of the trial. Patients in the placebo group and the oral steroid group were unaware of their treatment assignments, but naturally, it was impossible to mask those who received intravenous steroid infusion. Personnel measuring visual function usually did not know what treatment the patient had undergone.

Disappointingly, the Optic Neuritis Treatment Trial showed only a minor benefit of steroid treatment. The main outcome measures were visual field thresholds, contrast sensitivity, and visual acuity at six months after treatment. On Humphrey perimeter the patients who received intravenous methylprednisolone, followed by oral steroids, had a mean deviation of only -1.81 dB compared with a value of -2.18 dB in the placebo group. This trivial difference was marginally significant (p=0.054). Contrast sensitivity showed only a single line improvement on the Pelli-Robson chart (p=0.026). For visual acuity, no improvement was detected: 60.9% of patients treated with intravenous steroids recovered to a normal level of acuity, compared with 58.7% in the control group (p=0.66) (Figure 2). Because visual acuity is the most important functional parameter, most clinicians concluded that intravenous steroids are of little value for the treatment of optic neuritis. Oral prednisone alone also proved ineffective in the study.

In retrospect, the Optic Neuritis Treatment Trial had little chance of showing any long-term benefit from steroid therapy, because the prognosis for recovery after a first attack of optic neuritis is so good even without treatment. At one year, 71/100 placebo-treated patients

enjoyed a visual acuity of 20/20, and 95/100 had restored to at least 20/40. It would be hard to show a treatment benefit for any medication, given such a favorable outcome with placebo alone. These data underscore a basic management principle for optic neuritis: spontaneous recovery should occur. If one makes a diagnosis of optic neuritis in a patient and recovery fails, the original diagnosis should be reconsidered.

Although intravenous steroids do not affect the ultimate outcome in optic neuritis, they hasten visual recovery. The average patient treated with intravenous steroids reached a level of acuity at four weeks that was not attained by patients treated with placebo until seven weeks. This may be important in a patient with bilateral optic neuritis, who is incapacitated by visual loss. Within a matter of days, the infusion of intravenous methylprednisolone produces relief of pain induced by eye movements. This observation suggests that glucocorticoids reduce inflammation in the nerve, resulting in a more rapid recovery of function. My policy is to recommend intravenous steroids to all patients with an acuity worse than 20/200. These patients have the poorest prognosis for visual recovery. If their visual acuity remains depressed, they are apt to report not having received intravenous steroids. However, the dews do not indicate any difference in visual outcome, even for patients with a starting acuity worse than 20/200."

In the Optic Neuritis Treatment Trial, patients treated with oral prednisone (without three days of intravenous methylprednisolone) had a 27% rate of recurrent optic neuritis compared with a 15% rate among placebo-treated patients over a 6-24 month follow-up period. Ten years later, this discrepancy has persisted, with recurrence among 44% of patients in the oral prednisone treatment group compared with 31% in the placebo group. This surprising result has no biological explanation, but it has led to the following edict: do not treat optic neuritis with oral steroids alone.

This policy has made it more expensive and inconvenient to treat patients with steroids, because parental administration is required. Usually it is possible to arrange intravenous therapy in an outpatient clinic or at home, but some patients must be admitted to the hospital.

**STEROIDS AND THE PREVENTION OF MULTIPLE SCLEROSIS**

Over a two year follow-up period, it was reported that treatment with intravenous methylprednisolone reduced the risk of subsequent development of multiple sclerosis. This conclusion of the Optic Neuritis Treatment Trial pertained only to patients who had two or more demyelinating plaques on their magnetic resonance scan at entry. It was based on follow-up data in only a small number of patients. There was a fresh neurological event, tantamount to a diagnosis of multiple sclerosis, in 14/39 placebo-treated patients but only 6/37 methylprednisolone-treated patients. It was venture-some, from such limited data, to report that treatment with methylprednisolone can forestall the development of multiple sclerosis.

Data gathered after 10 years of follow up have failed to support the idea that steroid treatment can prevent multiple sclerosis. Of the original 457 patients in the Optic Neuritis Treatment Trial, 388 had no history of multiple sclerosis. Among this subgroup, the risk of developing multiple sclerosis (defined as a new neurological deficit occurring more than a month after the initial attack of optic neuritis) was 38% after 10 years. This risk did not vary according to whether the patient's original treatment was intravenous steroids, oral prednisone, or placebo (p=.49). As one might expect, the risk of multiple sclerosis was correlated with the presence of demyelinating lesions on the brain magnetic resonance image obtained at study entry. The rate of development of multiple sclerosis was 56% among the 160

![Diagram showing Normal Visual Acuity](image-url)
TREATMENT OF OPTIC NEURITIS WITH INTERFERON

It is logical to treat multiple sclerosis by suppression of the immune response, because it is probably an autoimmune disease. An early study used a combination of adrenocorticotropic hormone and cyclophosphamide to treat multiple sclerosis. Encouraging results were reported but the drug regimen was poorly tolerated by patients because of alopecia and neutropenia. The modern era of immunosuppression for multiple sclerosis was inaugurated with the publication of a double-blinded, prospective study of interferon beta-1b. The study enrolled 372 patients with multiple sclerosis to receive either a placebo, low-dose interferon beta-1b, or high-dose interferon beta-1b. The study used self-administered injections every other day. At two years, the annual exacerbation rate for patients who received the placebo was 1.27%, whereas for patients treated with high-dose interferon beta-1b it was only 0.84% (p < 0.0001). An analysis of magnetic resonance scans showed a reduction in the number of new lesions per year, from 3.2 in the placebo group to 1.2 in the high-dose interferon beta-1b group (p = 0.05). Subsequent studies have confirmed that interferon beta-1b can reduce the rate of recurrent attacks, slow the progression of disability, and reduce the development of new plaques on MRI.

Interferon has complex effects on immune function. Exactly how it reduces the development of multiple sclerosis is unknown. It interferes with the replication of T lymphocytes, reduces the production of tumor necrosis factor, blocks antigen presentation, modifies cytokine production to favor helper T cells, increases the secretion of interleukin-10, and impairs immune cell passage across the blood-brain barrier.

Interferon beta-1b is made in E. coli and differs from human interferon beta because it lacks glycosylation and has a single amino acid substitution. The use of Chinese hamster ovary cells has permitted the production of interferon beta-1a, a drug identical to human interferon beta. A double-blinded, placebo-controlled study of 301 patients showed that interferon beta-1a reduced the proportion of patients progressing in their level of disability from 35% in the placebo group to 22% in the interferon group over a period of 104 weeks. Interferon beta-1a also reduced the number and volume of new lesions on magnetic resonance studies.

In multiple sclerosis practice, most patients with relapsing-remitting multiple sclerosis are treated with either interferon beta-1b or interferon beta-1a. Interferon beta-1b (Rebif®) is injected subcutaneously, 250 mcg every other day, whereas interferon beta-1a (Avonex®) is injected intramuscularly, 30 mcg once per week. A formulation of interferon beta-1a (Reblif®) is also available for subcutaneous injection, 44 mcg three times per week. Interferon treatment may be well tolerated, although about 50% of patients experience fever and chills as a side effect. An alternative to interferon is glatiramer (Copaxone®), a random synthetic polypeptide containing glutamic acid, lysine, alanine, and tyrosine. It reduces the rate of relapses in multiple sclerosis and the accumulation of new demyelinating plaques on magnetic resonance images.

The CHAMPS study

To address the role of interferon therapy in patients with a first demyelinating attack, Biogen (manufacturer of Avonex®) funded the CHAMPS study. This clinical trial was conducted to control High-Risk Subjects, Avonex Multiple Sclerosis Prevention Study. The study was conducted at 50 centers from April 1996 to March 2000. Eligible patients were aged 18-50 and had a first, isolated, demyelinating event consisting of either optic neuritis (50%), transverse myelitis (22%), or a brainstem/cerebellar syndrome (28%). To qualify volunteers also had to have two or more silent magnetic resonance lesions of diameter ≥ 3 mm. All patients received a course of intravenous methylprednisolone followed by oral steroids according to the protocol of the Optic Neuritis Treatment Trial. After steroid treatment, one group was randomized to weekly intramuscular injections of 30 mcg interferon beta-1a, whereas the other group received injections of a placebo. Follow-up magnetic resonance images and neurological exams were obtained every six months. The endpoint was the development of clinically definite multiple sclerosis.
multiple sclerosis, defined by a new neurological abnormality lasting more than 48 hours.

At three years, 50% of the placebo group had suffered a second event to confirm the diagnosis of multiple sclerosis, whereas only 35% of the interferon beta-1a group had experienced a second event (Figure 3). Magnetic resonance images showed objective evidence of an effect on the evolution of new brain lesions. There were a mean of 2.1 new lesions in the interferon beta-1a group and 5.0 in the placebo group (p < 0.001). Only one patient receiving interferon beta-1a dropped out of the study due to side effects.

The results of this study have been confirmed by another trial of interferon beta-1a, sponsored by the Swiss manufacturer of this drug (Conu et al., 2001). Again, fewer treated patients developed a second demyelinating event and the accumulation of new plaques on magnetic resonance scans was retarded.

A NEW APPROACH: T-CELL INTEGRIN BLOCKADE WITH NATALIZUMAB (Tysabri®)

The penetration of the blood-brain barrier by activated leukocytes is a critical link in the chain of events responsible for the development of demyelinating plaques. In experimental autoimmune encephalomyelitis, a rodent model of multiple sclerosis, natalizumab impedes the entry of white cells into the brain. The drug binds to the glycoprotein alpha4 beta1 integrin on the surface membrane of monocytes and lymphocytes. With blockade of the integrin molecule, the migration of these cells across the endothelium of cerebral vessels is prevented. This offers a new strategy to treat multiple sclerosis. A major advantage is that immunodeficiency does not occur; in fact, intravascular levels of circulating white cells actually increase slightly during treatment.

The first major, double-masked, study of natalizumab enrolled 213 patients with multiple sclerosis and a minimum of three lesions on magnetic resonance imaging. There were three treatment arms: placebo, low-dose natalizumab (3 mg/kg), and high-dose natalizumab (6 mg/kg). The drug was infused intravenously once every 28 days for six months. Patients underwent monthly magnetic resonance imaging to quantify the number of new, gadolinium-enhancing lesions acquired during the treatment period. The mean number of new lesions/patient was 9.6 in the placebo group, 0.7 in the low-dose group, and 1.1 in the high-dose group (Figure 4). The difference between the placebo group and the natalizumab groups was significant. There were also fewer patients with objective relapses among the treated groups. Natalizumab was well tolerated, al-

![Figure 3](image3.png)  
**Figure 3.** Interferon beta-1a retards the development of clinically definite multiple sclerosis. The proportion of patients with clinically definite multiple sclerosis is graphed as a function of months after an initial demyelinating attack. At three years, the risk of conversion to define multiple sclerosis is about 50% for the placebo group and 35% for the interferon beta-1a group. Data from: Jacobs LD et al. Intramuscular interferon beta-1a therapy initiated during a first de-myelinating event in multiple sclerosis. N Engl J Med 2000;343:989-904.

![Figure 4](image4.png)  
**Figure 4.** Natalizumab prevents new demyelinating plaques in patients with multiple sclerosis. There is a significant reduction in the cumulative mean total of new lesions enhancing with gadolinium detected on monthly surveillance magnetic resonance scans with either high dose or low dose natalizumab. (Data from: Miller DS et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003;348:15-23.)
though one patient had an anaphylactoid reaction with urticaria and bronchospasm which required treatment with antihistamines and corticosteroids.

A single infusion of natalizumab after an acute re-lapse of multiple sclerosis has also been shown to de-crease the volume of gadolinium-enhancing lesions, both over week and three weeks after treatment. However, function assessed with the Kurtzke Expanded Disability Status Scale showed no benefit. This outcome mea-sure, commonly employed in studies of multiple scle-rosis, uses a scale of 0-10 to assess the degree of functional impairment. It is not surprising that a decrease in the number of brain lesions imaged by magnetic resonance correlates poorly with improvement in neurological func-tion. Not infrequently, patients with a relatively benign neurological examination are found to have a large num-ber of occult demyelinating plaques. Most plaques pro-duce no obvious symptoms, unless they are located in primary motor or sensory pathways. No one doubts, however, that a greater number of plaques eventually increases the risk of developing a disability.

About 5,000 patients have been treated with monthly infusion of natalizumab over the past two years. Un-fortunately, two patients have died from progressive multi-focal leukoencephalopathy and another patient has be-come seriously ill with the disease. In February 2005 the manufacturers of natalizumab suspended sale of the medi-cation because of these unfortunate cases. It is uncertain whether the drug will be re-introduced for the treatment of multiple sclerosis. Regulatory agencies, doctors, and patients may decide that the risk of contracting progressive multifocal leukoencephalopathy is too great.

There are several lessons to be gleaned from this diffi-cult experience with natalizumab. First, the risk of infec-tion by opportunistic organisms may not be detected by pilot studies of a new immunosuppressive drug. Until the drug is released for general use, and taken by thousands of patients, rare complications will not surface. Second, the risk of complications may be compounded by taking mul-tiple immunosuppressive drugs. It is noteworthy that the patients who developed progressive multifocal leuko-en-cephalopathy were being treated with interferon beta-1a and natalizumab. Perhaps either drug alone is safe, but taken together they pose an unacceptable risk.

CONCLUSIONS

Optic neuritis is only one of the protean manifes-tations of multiple sclerosis. The development of new treatments for multiple sclerosis has altered profoundly the management of optic neuritis for the ophthalmolo-gist. The studies reviewed in this article, if correct, indi-cate that patients presenting with a first attack of opt-ic neuritis should be treated with interferon, provided that magnetic resonance imaging shows two or more typical demyelinating plaques. Therefore, it is essential to obtain a magnetic resonance scan in every patient with optic neuritis. The goal is to identify plaques, which can be present but asymptomatic. If detected, the op-tion of immunomodulatory therapy should be discussed with the patient. It is also advisable to refer the patients to a neurologist for further management and follow-up.

If the screening magnetic resonance scan is nega-tive, no action is necessary, although the option of intravenous steroids should be discussed, and offered if visual function is seriously affected. If visual loss is mild, there is no need to administer steroids. Unless immunomodulatory treatment is planned because plaques were discovered on brain imaging. In this set-ting, steroid treatment is commonly given, although optional. One could argue, given the limited value of steroid therapy, that one should simply commence treatment with interferon or natalizumab (if sale is re-sumed).

If magnetic resonance imaging is negative in a pa-tient with a first attack of optic neuritis, it might be worthwhile to schedule follow-up scans, to monitor for future development of demyelinating plaques. If asympto-matic plaques develop in the ensuing months and years, treatment with immunomodulatory agents could retard the development of clinical manifestations of multiple sclerosis. It is unknown whether interferon treatment in a patient with a single attack of optic neu-ritis and no plaques is beneficial. Treatment of such patients does not conform to current treatment guide-lines, but might be considered.

It is important to obtain a magnetic resonance scan in every patient with optic neuritis, or else the diagnosis of multiple sclerosis could be overlooked. If a brain scan is negative, but the patient has motor and sensory findings, one should consider magnetic resonance im-a ging of the spinal cord. The long era of therapeutic nihilism for multiple sclerosis is over. The issue of mul-tiple sclerosis should be broached directly in patients when they present with optic neuritis. The findings on magnetic resonance imaging, the history of demyelinat-ing events, the neurological examination, and the patient’s wishes help one to decide whether immunomodulatory therapy should be commenced.
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