THE OPTIC NERVE: “TIP OF THE ICEBERG” OF DEMYELINATION

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LEARNING OBJECTIVES
1. The attendee will be able to understand the close connection between damage to the optic nerve and the brain and spinal cord in multiple sclerosis (MS) and neuromyelitis optica (NMO).
2. The attendee will be able to distinguish optic neuropathy in NMO and MS.
3. The attendee will be able to explain the evolving role of optic nerve assessment in the study of MS.

CME QUESTIONS
1. Which of the following statements about optic nerve involvement in MS is FALSE:
   a. Optic atrophy only occurs in patients who have suffered symptomatic optic neuritis.
   b. Following a bout of optic neuritis, the affected eye usually loses about 20% of its baseline retinal nerve fiber layer thickness.
   c. Visual dysfunction may also result from damage to the optic chiasm, tract and radiations.
   d. Mechanisms of damage include both demyelination and axonal loss.
   e. Upon initial presentation with unilateral optic neuritis, the fellow eye may show asymptomatic loss on perimetry or other tests in almost half of cases.

2. Which of the following statements about optic neuropathy associated with NMO is FALSE:
   a. A history of optic neuritis is required for the diagnosis of NMO by current criteria.
   b. NMO may present as recurrent optic neuritis years before a disease-defining attack of myelitis.
   c. Attacks of optic neuritis tend to be worse at onset in NMO than in MS, are more often bilaterally symptomatic and recover less completely.
   d. NMO produces a pathognomonic pattern of change on OCT that fully distinguishes it from MS.
   e. A positive aquaporin-4 (NMO-IgG) antibody helps to predict conversion to definite NMO in patients who present with optic neuritis.

3. Retinal nerve fiber layer thickness as measured with OCT correlates with which of the following in MS:
   a. Visual function
   b. Overall neurological disability as measured by EDSS
   c. Brain atrophy
   d. Macular volume
   e. All of the above

KEYWORDS
1. Optic Neuritis
2. Multiple Sclerosis
3. Neuromyelitis Optica
4. Optical Coherence Tomography
5. Optic Atrophy

INTRODUCTION
Multiple sclerosis (MS) and neuromyelitis optica (NMO) are distinct immune-mediated inflammatory conditions that characteristically attack the optic nerve, brain and spinal cord. Associated optic nerve demyelination and axonal loss lead to a range of visual complaints and disabilities that may be the presenting symptoms of these disorders. Physiological and anatomical measures, including visual evoked potentials, optical coherence tomography and magnetic resonance imaging, quantify optic nerve involvement and often identify subclinical damage. Such tests of structural and functional loss within the optic nerve correlate with similar tests of the brain and spinal cord in MS. The optic nerve and its fibers of origin thus offer a readily measureable perspective on the rest of the central nervous system, much as the tip of an iceberg reflects its larger, invisible portion.

IDIOPATHIC INFLAMMATORY DEMYELINATING DISEASES - “THE ICEBERG”
MS is estimated to affect up to 400,000 Americans, with a prevalence of approximately 0.15%. It damages the brain, spinal cord and optic nerves to variable degrees in each patient, such that disability is an unpredictable mix of dysfunction of all three structures. No single cause of MS has been identified, although several established risk factors give clues to its pathogenesis. Evidence of a genetic
The classic, or monophasic, form of NMO presents with acute erythematosus or Sjogren's syndrome. Familial cases are rare. Of autoimmunity, including coexistent systemic lupus and there is no recurrence. More commonly, however, NMO presents with attacks of unilateral or bilateral optic neuropathy, P-cell axons may be involved. The optic nerve head, loss of the retinal fiber layer and disappearance of RGC bodies attest to retrograde degeneration that occurs after MS-related damage within the myelinated, retrolaminar portion of the nerve. RGC axons include two principal populations, each with distinct physiological properties. The much more numerous parvocellular or "P" cells have smaller, slower-conducting axons and carry color-opponent information to laminae 3-6 of the lateral geniculate nucleus (LGN). The signals carried in P-cell axons are well suited to the ventral or "what" stream of visual processing that is concerned with object identification. Magnocellular or "M" cells have larger, quicker-conducting axons that carry transient, low-contrast information to laminae 1-2 of the LGN. Their characteristics are best suited to visual motion and spatial signals (the dorsal or "where" processing stream). Although there is functional loss of both types of visual information in patients with chronic optic neuropathy, P-cell axons may be more vulnerable to damage in MS.

Visual disability in MS may range from subclinical to profound and may result from involvement anywhere from retina to brain. Although damage to the optic nerve is most readily recognized, as in acute optic neuritis, RGC axons may also be lost with lesions in the optic chiasm or tract. MS-associated retinal inflammatory activity, especially
prominent around venules, could also directly damage RGCs and account for loss of neurons in the inner nuclear layer. Retrogeniculate lesions may involve the optic radiations or the white matter tracts that connect higher-level visual areas. Cerebral cortical plaques, an increasing focus of study in MS, might also affect visual processing.

Intimately familiar to all neuro-ophtalmologists, optic neuritis is one of the most common forms of MS relapse. It occurs sometime in the course of about half of all patients with MS and is the presenting condition in about 20%. Optic neuritis typically presents as painful visual loss, with symptoms evolving over a few days. Pain may precede visual loss; it is worse with eye movement and may be associated with ocular tenderness and photosensitivity. Although many smaller studies have contributed to our understanding of optic nerve disease in MS, the Optic Neuritis Treatment Trial (ONTT) has provided irreplaceable data on the natural history and steroid treatment response of this condition. The ONTT enrolled over 450 patients with the clinical syndrome of acute optic neuritis, only 6% of whom had been diagnosed with MS, and randomized them to receive intravenous followed by oral steroids, oral steroids alone or placebo. The patient cohort was followed for visual outcome and the development of MS. The final results were reported at a mean of 15 years from initiation and represented data from about 65% of the original group. Entry data reflected typical MS demographics, with 3:1 female predominance and mean age of 32.

Eye pain was reported in 92% and optic disc edema was seen in 35% of affected eyes. Median visual acuity was 20/80, with 36% of eyes measured at 20/200 or worse. Significant deficits of color vision and contrast sensitivity were typical. Visual fields usually revealed central or generalized loss. Visual outcomes, initially reported at the six-month mark, were similarly good in most patients regardless of therapy; 75% had acuity of 20/20 or better, although many of these still had abnormalities of contrast sensitivity (46%), color vision (26%) or visual fields (20%). Some patients perceived visual difficulty even when all tests were normal. After 15 years of follow-up, 72% of the originally affected eyes had acuity of 20/20 or better and only 8% had acuity of 20/40 or worse, even though many patients had converted to definite MS or suffered recurrent optic neuritis. Although the ONTT excluded patients with bilateral visual symptoms, mildly abnormal function was quite common in fellow eyes: visual acuity was subnormal in 14%, contrast sensitivity in 15%, color vision in 22% and visual fields in 48%. In most patients, fellow eye abnormalities improved in parallel with those in the symptomatic eye, suggesting that they reflected true bilateral involvement rather than serial test artifact.

Perhaps equally important to its visual outcome data were the ONTT results regarding conversion to definite MS among the 94% of enrollees without a pre-existing diagnosis. The overall conversion rate by clinical (Poser) criteria, which required a second symptomatic episode of neurological dysfunction outside of the optic nerves, was 50%. This risk was strongly influenced by MRI appearance at study entry. For patients with one or more MRI lesions potentially consistent with MS at entry, the conversion rate to definite MS was 72% by 15 years. In contrast, those with normal initial MRI scans had a conversion rate of only 25%, and only one such patient suffered an MS-defining second event after ten years. Of those with normal MRI, male gender or initial optic disc swelling in the affected eye carried lower risk than female gender or an initially normal disc. Importantly, no patient with a normal neurological history, examination and MRI converted to MS if they presented without eye pain or with disc or peripapillary hemorrhage, macular exudates, severe optic disc swelling or no light perception vision. One might take this observation to suggest that these patients had another form of optic neuropathy such as neuretinitis or ischemia, rather than demyelination. Such patients could be reassured that their risk of developing MS is quite low. For patients with an abnormal baseline MRI, the number of T2 lesions alone does not appear to be a helpful predictor of MS conversion. However, the location of lesions in the periventricular region and the presence of gadolinium enhancement increase risk. Conventional CSF analysis has not proven to add significant prognostic information to MRI regarding conversion from isolated optic neuritis to clinically definite MS.

Current diagnostic criteria for NMO require that patients have suffered at least one bout of each of optic neuritis and myelitis at some time in their illness. In the relapsing form of NMO, about half of patients present with isolated optic nerve disease before any signs or symptoms of myelopathy. In patients presenting with optic neuritis alone, the lag to a disease-defining attack of myelitis averages over a year. Many patients suffer several bouts of optic neuritis in either eye before this occurs. Recurrent visual loss may also precede brain or spinal symptoms in MS. Of those MS patients in whom optic neuritis is the initial presentation, about 25% have further attacks in the same or fellow eye before other clinical manifestations. In a series of 72 patients with recurrent optic neuritis, 8 (11%) converted to NMO, 20 (28%) converted to MS and 44 (61%) did not develop signs of either condition over a mean follow-up of about 9 years.

Optic neuritis associated with NMO is similar to MS in that it is typically painful, not associated with disk edema and improves over weeks to months. NMO differs from MS chiefly in that attacks tend to be worse both at their peak and after recovery. In a French cohort, for example, 45% of patients with relapsing NMO demonstrated baseline acuity of 20/200 or worse in one (32%) or both (13%) eyes after about 10 years of disease; almost half of patients developed this severe deficit after their first bout of optic neuritis. Simultaneous symptomatic bilateral optic neuritis is about as common as unilateral optic neuritis in the monophasic form of NMO, but occurs in only about 20% of patients with relapsing NMO. Some authors
have pointed to other clinical findings that might help to distinguish patients bound to develop NMO from those who are prone to MS. Vascular findings, including retinal arteriolar narrowing, are more common in NMO than in MS. Visual field analysis shows localized defects more frequently when optic neuritis is associated with NMO than with MS, but there is considerable overlap since both conditions cause predominantly central loss. 

While brain MRI is the best measure of MS risk in a patient presenting with optic neuritis, serological testing for the ‘NMO-IgG’ antibody to aquaporin-4 is the best predictor of conversion to NMO. In patients presenting with a single attack of optic neuritis and no neurological history, the prevalence of aquaporin-4 antibody positivity has been reported in the range of 3-5%. Antibody positivity prevalence typically rises into the 10-20% range in groups with recurrent optic neuritis. Two recent series studied aquaporin-4 antibodies in patients presenting with optic neuritis, mostly recurrent and many bilateral. A subsequent attack of myelitis consistent with NMO occurred in 10/20 (50%) of those with positive antibodies, but only 1/82 (1%) of those with a negative test during follow-up averaging over two years. These findings raise the question of which optic neuritis patients to screen for the antibody. In support of widespread screening is the observation that attacks of NMO are particularly disabling. Relapse rates are about twice those of MS and disability thresholds are reached much faster. Thus, effective early treatment would be most valuable in NMO. Against widespread screening is the relative infrequency of NMO in patients presenting with uncomplicated optic neuritis, the cost of the test and uncertainty regarding the best course of therapy in antibody-positive, at-risk individuals. Since immune suppression is the consensus therapy for NMO, potential long-term side effects are more serious than for first-line MS treatment with interferons or glatiramer. Most would recommend antibody testing in patients at higher risk for NMO, including those with bilateral visual symptoms, recurrent optic neuritis, poor visual outcome after a single attack or concurrent autoimmune disease, assuming that they lack typical changes of MS on MRI. Since about 40% of patients with clinically-defined NMO do not demonstrate significant titers of aquaporin-4 antibodies, one should maintain a high index of suspicion and consider long-term immune suppression in patients with recurrent, severe bouts of unexplained optic neuropathy. Kidd et al. defined a group of patients with no associated brain or spinal cord disease who they designated chronic relapsing inflammatory optic neuropathy (CRION). Features that might be consistent with NMO-associated optic neuritis in these patients included severe, painful, recurrent visual loss and predominance in young women. Symptoms usually involved both eyes within one month of onset and were associated with swollen optic disks. In contrast to NMO, patients with CRION appeared exquisitely sensitive to steroids, improving rapidly when they were introduced and relapsing within weeks when they were tapered. A subsequent report showed positive aquaporin-4 antibodies in only 1/19 CRION patients (5%).

Treatment of acute unilateral optic neuritis with high-dose intravenous (IV) steroids followed by an oral prednisone taper was shown to improve vision within the first month, but not at intervals of six months or longer, in the ONTT. Lower-dose oral steroids alone were of no benefit. Variants of the ONTT protocol, using for example high-dose IV steroids without an oral taper or very high-dose oral steroids alone, are frequently used by clinicians but have not been thoroughly studied. Two randomized trials of intravenous immunoglobulin failed to show benefit in patients with persistent visual loss from optic neuritis, while other non-randomized studies have suggested improvement in atypical patients with stable, severe visual loss more than three months after onset. No studies similar to the ONTT have been done in NMO-associated optic neuritis and it is unlikely that any study of that magnitude ever will. In the absence of randomized trial data, most authors suggest using high-dose IV steroids initially, followed by plasma exchange for those who do not improve rapidly. Some have suggested starting both treatments simultaneously, at least for severe NMO relapses.

Many MS patients with no history of acute or subacute visual loss demonstrate abnormal optic nerve structure and function. In some cases, these changes might reflect subclinical bouts of optic neuritis that did not cause enough pain or visual loss to become noticeable to the patient. In other cases, optic nerve integrity might be compromised by a slowly progressive process akin to brain atrophy, a characteristic finding that is not closely correlated with ongoing inflammatory disease in MS. Asymptomatic tissue loss has long been recognized clinically as visible generalized or segmental atrophy of the optic nerve head and peripapillary retinal nerve fiber layer (RNFL). Optical coherence tomography (OCT) demonstrates RNFL loss in PPMS patients who have never suffered optic neuritis or any other form of acute neurological attack. Visual evoked potentials (VEP) show latency prolongation consistent with demyelination in 30-35% of never-symptomatic eyes in MS patients.

Increasing Interest in Measuring the Optic Nerve—“The Surge”

As the most easily tested part of the central nervous system, the optic nerve offers an excellent vantage point from which to investigate important pathophysiological and therapeutic principles of demyelinating disease. There are three general methods for quantifying the integrity of the optic nerve: psychophysical, physiological and anatomical. Psychophysical tests determine an individual’s visual sensory performance. They require full cooperation for maximum validity and may be subject to learning effects and other artifact. Such measures include visual acuity under high and low contrast conditions, contrast sensitivity threshold, color perception, perimetry and critical flicker
fusion frequency. Other subjective assessments that correlate with optic nerve function include pendulum testing for the Puflich phenomenon and the flight of colors test. Physiological measurements objectively assess the function of the visual system without requiring responses from subjects other than attentive fixation. These include pupillometry, pattern electroretinography (PERG) and conventional and multifocal visual evoked potentials (VEP). Finally, anatomical measurement assesses structural integrity and includes optical coherence tomography (OCT), scanning laser polarimetry (SLP), confocal scanning laser ophthalmoscopy (CSLO) and magnetic resonance imaging (MRI). OCT, SLP and CSLO use laser technology to scan the retina or optic nerve head, taking advantage of the transparency of these tissues to provide data on tissue depth and density. Conventional MRI can provide direct evidence of optic nerve swelling or atrophy through measurement of cross-sectional area and can show changes in tissue composition. Advanced imaging techniques like magnetization transfer ratio (MTR) and diffusion-tensor imaging (DTI) can help to distinguish axonal loss from demyelination.

High-contrast visual acuity is usually evaluated with black letters on a white background. It is a time-tested, nearly-universal screening tool, but is a relatively insensitive measure of optic neuropathy. Visual fields (assessed with Humphrey perimetry), color vision (tested with the Farnsworth-Munsell 100 Hue test) and contrast sensitivity (measured with Pelli-Robson charts) all proved to be more sensitive to residual optic neuropathy in the ONTT.\(^5\) However, these latter all require special equipment. Perimetry and color testing may be time-consuming and difficult, especially for patients with poor vision. Balcer and colleagues have thoroughly examined the value of low-contrast visual acuity as a rapid, sensitive screen of optic neuropathy in MS patients.\(^5\) They have most often employed Sloan charts with gray letters at 1.25% and 2.5% contrast over a white background and have shown them to be more sensitive than high-contrast black letters. Deficits of low-contrast acuity correlate with OCT measurement of RNFL loss, with MS-associated MRI changes and with scores reflecting general neurological disability like the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC).

Conventional VEP testing has remained popular as an objective physiological screen for optic neuropathy. It uses an alternating checkboard stimulus that is displayed within the central 30 degrees of visual field. Multifocal testing (mfVEP) allows selective stimulation of a designated visual field area. In either type of VEP, summed electroencephalographic potentials are recorded from the occipital scalp to assess response latency and amplitude. Of these, latency is the more reliably measured; prolongation is thought to reflect demyelination, while amplitude reductions may chiefly signal axonal loss. The time course of VEP abnormalities mirrors that of visual dysfunction in optic neuritis, being most apparent at onset and improving over several months thereafter.\(^6\) Residual VEP changes are common, even in those who have regained normal visual acuity. Selective VEP testing with color\(^5\) or low-contrast\(^6\) stimuli may be more sensitive than conventional black and white stimuli. In two recent studies comparing VEP to OCT, sensitivity for eyes with previous optic neuritis was 81% for conventional VEP latency\(^6\) and 89% for mfVEP latency or amplitude.\(^6\) Both studies demonstrated lower sensitivities of about 60% for OCT, using proprietary cutoffs for overall RNFL thickness. This difference might in part reflect the notion that VEP abnormalities reflect both demyelination and axonal loss, while OCT reflects axonal loss alone. Also, the use of mean RNFL thickness as the only OCT measure reduces the potential for identifying localized defects. As measures of physiology and anatomy respectively, VEP and OCT are complementary rather than competitive.\(^6\)

PERG uses a patterned stimulus that is similar or identical to conventional VEP, recording potentials from the cornea or periocular skin surface. PERG responses most closely reflect RGC function and commonly show abnormalities of latency and amplitude after optic neuritis. These correlate with RNFL and macular volume loss on OCT.\(^6,6\) Abnormalities of the pupillary light reflex are commonplace in optic nerve disease; the presence of a relative afferent pupillary defect was an inclusion criterion for the ONTT. Quantitative pupillometry can assess the motor responses of each pupil upon stimulation of one or both eyes. Abnormalities correlate with OCT measures like RNFL thickness and macular volume and with psychophysical parameters like low-contrast acuity in MS.\(^66\)

Perhaps the most exciting development in optic nerve assessment over the last decade has been the ability to image the structures of the posterior pole accurately and non-invasively. OCT, SLP and CSLO can all assess the peripapillary RNFL, estimating tissue thickness as a reflection of axonal swelling or loss. All of these methods have shown RNFL thinning in post-optic neuritis eyes.\(^6,67\) OCT has been studied more extensively than SLP or CSLO. Of the three techniques, OCT changes most closely correlate both demyelination and axonal loss, while OCT reflects axonal loss alone. Of these, latency is the more reliably measured; prolongation is thought to reflect demyelination, while amplitude reductions may chiefly signal axonal loss. The time course of VEP abnormalities mirrors that of visual dysfunction in optic neuritis, being most apparent at onset and improving over several months thereafter.\(^6\) Residual VEP changes are common, even in those who have regained normal visual acuity. Selective VEP testing with color\(^5\) or low-contrast\(^6\) stimuli may be more sensitive than conventional black and white stimuli. In two recent studies comparing VEP to OCT, sensitivity for eyes with previous optic neuritis was 81% for conventional VEP latency\(^6\) and 89% for mfVEP latency or amplitude.\(^6\) Both studies demonstrated lower sensitivities of about 60% for OCT, using proprietary cutoffs for overall RNFL thickness. This difference might in part reflect the notion that VEP abnormalities reflect both demyelination and axonal loss, while OCT reflects axonal loss alone. Also, the use of mean RNFL thickness as the only OCT measure reduces the potential for identifying localized defects. As measures of physiology and anatomy respectively, VEP and OCT are complementary rather than competitive.\(^6\)

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One of the most interesting OCT findings in MS is the decidedly non-linear relationship between steady-state mean RNFL thickness and visual sensory parameters like perimetric mean deviation and high-contrast acuity\(^7\) (Figure 1). The slope of this relationship is nearly flat between normal RNFL values of about 100μm and a breakpoint of 70-75μm. Below this threshold, sensory performance falls off dramatically with relatively small decrements in RNFL thickness. The flat portion of the curve implies that there is a certain amount of axonal ‘reserve’. It also explains why patients generally recover well after their first bout of optic neuritis, since most end up with mean RNFL values above 75μm.\(^7\) Mean RNFL thickness seldom falls below 40μm, even in eyes with no light perception.\(^7\) Thus, one has a total range of about 60μm of RNFL thickness to lose between normal and absolute axonal loss and one must lose about half of this amount to manifest measureable visual impairment.

![Figure 1: Relationship between mean RNFL thickness and mean deviation measured with Humphrey perimetry in the affected eyes of 54 patients with MS, at least three months after optic neuritis. (Reprinted with permission from: Costello F, Coupland S, Hodge W, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. Ann Neurol 2006;59:963-9.)](image)

In addition to the rapid thinning of the RNFL that occurs after optic neuritis, there is evidence of gradual axonal dropout in MS as measured by OCT. A large longitudinal study estimated loss of RNFL in MS eyes at 2μm/year, independent of optic neuritis.\(^7\) This value is an order of magnitude greater than normal age-related RNFL loss, which has been estimated to be only 0.2μm/year. Similarly, brain atrophy is accelerated in MS patients compared to normal subjects, even early in the disease. RNFL thickness in MS correlates with low-contrast acuity and contrast sensitivity, color vision, visible optic atrophy, MRI parameters like T2 lesion burden and brain atrophy, and general neurological disability as measured by EDSS and MSFC.\(^7\) Reductions in macular volume correlate well with those of peripapillary RNFL thickness in MS eyes with or without an optic neuritis history, suggesting retrograde degeneration of macular ganglion cells and their axons.\(^8\) Macular volume loss is much smaller in proportion to normal baseline values than is RNFL thinning, comprising about 30% of the latter. This observation fits with the relative contributions of the retinal nerve fiber and ganglion cell layers to overall macular thickness. VEP, mVEP and PERG results have all been shown to correlate with RNFL thickness; amplitudes offer a somewhat tighter relationship than latencies, perhaps since they are a more direct reflection of axonal loss.\(^9\)\(^4\)\(^6\)\(^5\)\(^8\)\(^5\)

Compared to MS, patients with NMO-associated optic neuritis show much more severe RNFL loss on OCT, with average thickness reductions of about 40μm versus about 20μm in MS.\(^9\)\(^\)\(^1\)\(^\)\(^8\)\(^8\) The pattern of loss is also somewhat different in NMO; RNFL thinning is more evenly distributed around the circumference of the peripapillary region, while it often selectively involves the temporal quadrant in MS. There is, however, enough overlap that OCT changes cannot be considered pathognomonic for either condition. As in MS, RNFL thickness has been correlated with high- and low-contrast visual acuity, contrast sensitivity, visual fields, and overall disability (EDSS score) in NMO.

MRI allows measurement of the size and signal characteristics of the retrobulbar optic nerve. Conventional and advanced techniques demonstrate a variety of changes in MS-associated optic neuropathy.\(^7\) Technical challenges include the small size, mobility and tortuousness of the nerve and the competing signal qualities of the surrounding CSF, fat and bone. Studies of cross-sectional area in optic neuritis show an initial increase consistent with swelling, followed by gradual atrophy.\(^8\) After a year or more, optic nerve area may be reduced by 10-30% compared to its unaffected fellow.\(^8\)\(^9\) Correlations between optic nerve area on MRI, RNFL thickness on OCT, visual acuity, visual fields and VEP amplitude suggest that atrophy chiefly reflects axonal loss.\(^9\) Magnetization transfer ratio (MTR) indirectly measures tissue membrane integrity and is reduced in cerebral MS plaques compared to normal white matter; this may reflect both demyelination and axonal loss. Not surprisingly, MTR falls after optic neuritis, taking about 8 months to reach its nadir.\(^9\)\(^2\)\(^9\) In a healthy optic nerve, water molecules diffuse predominantly along axonal fibers and thus parallel to its long axis. Diffusion tensor imaging (DTI) measures the movement of water through tissues; excessive diffusion that is not parallel to the predominant fiber tracts of a white matter structure is thought to indicate axonal disruption. Abnormalities of optic nerve DTI do occur and tend to parallel visual outcome.\(^9\)\(^3\)\(^4\) In a small study that employed a wide variety of psychophysical and anatomical measures, Frohman and colleagues\(^9\) found that RNFL thickness measured with OCT and optic nerve size on MRI correlated better with visual function than DTI or MTR measures.
CME ANSWERS

1. A
2. D
3. E

ABBREVIATIONS


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LEARNING OBJECTIVES

1. The attendee will be able to recognize the clinical, laboratory, and neuroimaging characteristics of neuromyelitis optica (NMO) and contrast them from characteristics of multiple sclerosis (MS).

2. The attendee will be able to describe the association of the autoantibody NMO-IgG (anti-aquaporin-4) with NMO.

3. The attendee will be able to describe the treatment options for acute relapses and relapse prevention in NMO.

CME QUESTIONS

1. Brain MRI lesions in neuromyelitis optica:
   a. Usually mimic those of typical multiple sclerosis.
   b. Often occur in regions of known high aquaporin-4 density.
   c. Decrease in number during the disease course.
   d. Do not enhance after gadolinium administration.

2. Pathological assessment of neuromyelitis optica lesions reveals:
   a. Deposition of immunoglobulin and complement around blood vessels.
   b. Thinning of penetrating spinal blood vessels.
   c. Predominant T-cell infiltrates.
   d. Multifocal infarctions and vasculitis.

3. Which of the following therapies is not recommended for neuromyelitis optica:
   a. Azathioprine
   b. Mycophenolate mofetil
   c. Rituximab
   d. Interferon beta

KEYWORDS

1. Neuromyelitis Optica
2. Optic Neuritis
3. Transverse Myelitis
4. Aquaporin-4

NEUROMYELITIS OPTICA: BACKGROUND

The last decade has witnessed rapid developments in the clinical understanding and scientific foundation of neuromyelitis optica (NMO). The landmark events were the late 19th century report by Devic and Gault describing the association of severe acute transverse myelitis and optic neuritis and the late 20th century discovery that the syndrome was associated with a specific autoantibody, NMO-IgG, that targets the water channel aquaporin-4 (AQP4). Between these events, there were numerous case series suggesting that the disorder usually followed a relapsing course (rather than being monophasic) and pathological studies, which were limited to technology of the time, revealed inflammatory demyelinating lesions of the optic nerve and spinal cord with sparing of the brain. There was ongoing debate about the relationship between NMO and multiple sclerosis (MS), the prototypic and relatively common (one per thousand population) but whether NMO was distinct or simply a subset of MS was not resolvable with the available science.

Within the last twenty years, new case series emerged and incorporated modern neuroimaging and laboratory studies, especially cerebrospinal fluid analysis, to demonstrate that NMO was associated with certain diagnostic test results that were atypical for MS. These included findings such as a normal brain magnetic resonance imaging (MRI) scan, unusually long spinal cord lesions associated with acute myelitis attacks ("longitudinally extensive transverse myelitis [LETM]), and an unusual cerebrospinal fluid pleocytosis, often with a differential containing neutrophils rather than the lymphocytes more typical for MS. These reports began to consolidate the concept that NMO was a clinical entity distinguishable from MS on objective grounds, something that was affirmed, and subsequently validated by numerous groups worldwide, by the discovery of the specific autoantibody NMO-IgG. Revised NMO
diagnostic criteria (Table 1) using a combination of clinical, neuroimaging, and NMO-IgG criteria have also been validated.\(^1\) The next step has been to utilize the strong specificity of NMO-IgG to demonstrate that the clinical and neuroimaging features of NMO are actually much broader than just optic neuritis and myelitis; these are collectively referred to as “NMO spectrum disorders” (Table 2).\(^1\)

**Table 1. Diagnostic Criteria for Neuromyelitis Optica**

**Required criteria:**
- Transverse myelitis
- Optic neuritis

**Supportive criteria (at least two of the following three elements):**
1. MRI brain nondiagnostic for MS
2. MRI spinal cord lesion extending over ≥3 vertebral segments
3. NMO-IgG seropositivity

**Table 2. NMO Spectrum Disorders**

- Neuromyelitis optica
  - Limited forms of NMO
    - “Idiopathic” single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord MRI lesion)
    - Optic neuritis, recurrent or simultaneous bilateral
  - Asian optic-spinal MS
  - Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
  - Optic neuritis or myelitis associated with NMO-typical brain lesions (hypothalamic, corpus callosal, periventricular, brain stem)

NMO-IgG testing has allowed early diagnosis of these disorders even after a single event of optic neuritis or LETM.

**EPIDEMIOLOGY**

 Neuromyelitis optica is a rare disorder but few studies provide population-based incidence and prevalence estimates. A population-based study in the French West Indies and Martinique found NMO prevalence of 2.5 per 100,000 and annualized incidence of 0.1 per 100,000 individuals in a retrospective cross-sectional record review; all NMO cases were of Afro-Caribbean background.\(^6\) A population-based Cuban study reported a prevalence of 0.52 per 100,000 individuals with an average annual incidence rate of 0.53 per million and the rates were similar in self-reported racial groups defined as white, black, mixed, or non-white.\(^5\) These estimates are similar to non-population-based assessments in Mexico (prevalence 1.3 per 100,000 individuals of Mestizo ancestry), the United Kingdom (prevalence 0.44 per 100,000 and annual incidence 0.05 per 100,000; cases were Caucasian), and south Florida (0.99 per 100,000; cases included Caucasians and Hispanics).\(^6,7\) In Italian tertiary MS clinics, 0.5% of 780 patients had NMO.\(^8\)

There may be an overrepresentation of NMO as a proportion of all CNS demyelinating disease cases in patients of non-Caucasian ancestry, such as African-Americans, Hispanics, and Asians. Moreover, at least some cases of Asian “optic-spinal MS”, which represents a sizeable proportion of CNS demyelinating disease in Japan, are in fact NMO. However, more population-based data are needed to better establish this because of the relatively similar prevalence and incidence rates noted in various populations worldwide. However, there are groups, notably black Africans and North American aboriginal peoples, in whom typical MS is extremely rare and most if not all cases of CNS demyelinating disease are consistent with NMO. Genetics of NMO may be complex; familial cases exist but are uncommon.\(^9\)

Virtually all reports of NMO worldwide describe female predominance with female: male ratios ranging from 2:1 to 10:1.\(^1,10\) Up to 90% of patients with relapsing NMO are female. Its incidence rate peaks at approximately age 40 but it can occur at any age.

**CLINICAL CHARACTERISTICS**

The cornerstone clinical syndromes of NMO are optic neuritis and acute transverse myelitis. Occasionally, these events will occur simultaneously but usually they evolve months to years apart. The concept of “NMO spectrum disorders” recognizes that other syndromes involving the cerebrum and neuroendocrine systems occur in patients who are seropositive for NMO-IgG and who may or may not also have experienced optic neuritis and myelitis (Table 2).\(^1\)

Optic neuritis may occur as a unilateral event or as simultaneous or sequential bilateral events. The optic chiasm may be affected and optic nerve lesions tend to be extensive, as detected by orbital MRI with gadolinium. Although visual loss tends to be more severe in NMO, clinical symptoms cannot otherwise differentiate optic neuritis events in MS from NMO. Retinal vascular abnormalities in NMO have been reported, including attenuation of the peripapillary vasculature and focal arteriolar narrowing.\(^11\) Ocular coherence tomography has also demonstrated a greater reduction in the thickness of the retinal nerve fiber layer in NMO than MS as well as asymptomatic nerve fiber layer thinning in NMO-IgG seropositive patients with recurrent transverse myelitis.

Spinal cord attacks in NMO are usually, but not exclusively, clinically severe and accompanied by a MRI lesion that extends over 3 or more vertebral segments; this pattern is termed “longitudinally extensive transverse myelitis” (LETM). Paraparesis or quadriplepsis, spinal cord sensory syndromes, sphincter dysfunction occur with spinal cord events. L’hermitte’s symptom (paresthesias along the spine
or limbs precipitated by neck flexion) and paroxysmal tonic spasms (repetitive, stereotypic, painful muscle spasms) occur in about 40% of patients.

Extension of a myelitis attack into the brain stem, or individual brain stem lesions, can cause nausea, vomiting, and hiccoughs, probably due to involvement of the area postrema and medial and lateral portions of the nucleus tractus solitarius.13 These symptoms affect up to 40% of patients in some series and in pediatric patients seropositive for NMO-IgG, up to 45% have vomiting and encephalopathy.13 Brain stem lesions may also cause neurogenic respiratory failure. Other unusual clinical syndromes now linked to NMO or NMO-IgG seropositivity include endocrinopathies (which may be either autoimmune or owing to hypothalamic dysfunction), encephalopathy, and the posterior reversible encephalopathy syndrome (PRES).14,15

LABORATORY STUDIES
Cerebrospinal fluid cell counts during active NMO relapses vary but can be very high (50 to 1000 x 10⁶ WBC/L) and sometimes reveal a neutrophil-predominant differential) and high protein level (100 to 500 mg/dL).2 In typical MS, the CSF may show a mild lymphocytic pleocytosis (fewer than 25 x 10⁶ WBC/L). Unique CSF oligoclonal bands, which are detected in ~85% of MS cases, are found in only 20-30% of NMO cases.

About half of NMO patients harbor one or more serum autoantibodies, such as antinuclear antibody and extractable nuclear antigen and about one-third have one or more systemic autoimmune diseases, typically thyroid disease. Coexisting myasthenia gravis also occurs more often than expected.22 Patients who meet formal diagnostic criteria for connective tissue diseases such as systemic lupus erythematosus or Sjogren syndrome and also have the clinical NMO syndrome should be tested for NMO-IgG. Those who are seropositive for NMO-Ig most likely have coexisting autoimmune diseases rather than “lupus myelitis” or a Sjogren’s-related myelopathy/myelitis.

NMO-IgG AND AQUAPORIN-4
The original serological test, NMO-IgG, was based on an indirect immunofluorescence technique using mouse cerebellum tissue.23 It was found to be 73% sensitive and 91% specific for distinguishing NMO from optic-spinal presentations of MS. Soon after, the antibody target was discovered to be the water channel aquaporin-4. This and other assay techniques, including detection of aquaporin-4 antibodies using cell based assays, radioimmunoprecipitation assays (RIPA), fluoroimmunoprecipitation assays (FIPA), and enzyme-linked immunosorbent assays (ELISA) have since consistently replicated the original results with reported specificities between 85-100%. Sensitivity rates are somewhat lower and less consistent, ranging from 47-91%, which may reflect actual assay differences, variability in the clinical gold standard definition, control group characteristics, treatment status and other factors. Cell-based assays may characte...
have the best diagnostic accuracy but studies are ongoing to optimize assay technique.\textsuperscript{24,25} Occasionally, retesting initially seronegative NMO-IgG patients will yield a positive result and rare cases in which NMO-IgG was detected in CSF but not serum have been reported.\textsuperscript{26} Therefore, when diagnostic suspicion is high but there remains uncertainty, retesting serum or testing CSF is reasonable.

Some evidence suggests that antibody levels rise prior to clinical relapses, are reduced with immunosuppressive therapy, and that attack severity may be related to the degree of complement activation initiated by antibody.\textsuperscript{16,27,28} However, it remains to be determined if antibody titers or other similar data can be used to inform therapeutic decisions.

Aquaporin-4 is the most common of the aquaporin family of water transport proteins in the CNS.\textsuperscript{29,30} It regulates bidirectional water flux between blood and brain or CSF. It is expressed on astrocyte foot processes and the abluminal surface of blood vessels and is not found on neurons, oligodendroglia, or choroid epithelium cells. Normally, aquaporin-4 is expressed at high levels in the brain stem, hypothalamus, and periventricular regions. It is also expressed highly in perivascular, periependymal, and subpial regions as well as areas such as the area postrema (likely accounting for episodic nausea/vomiting events), and the supraoptic nucleus. There is an association between these high-density regions and patterns of MRI lesions in some NMO patients.

**PATHOLOGY AND PATHOGENESIS OF NMO**

Focal NMO lesions in the optic nerve and spinal cord reveal inflammation and demyelination. In the cord, both gray and white matter is typically involved, sometimes with necrosis and cavitiation. Unlike MS lesions, eosinophils and neutrophils are common in the inflammatory infiltrates of active NMO lesions and penetrating spinal vessels may be thickened and hyalinized.

Immunoglobulin and complement are deposited in a vasculocentric “rim” and “rosette” pattern in active NMO lesions.\textsuperscript{31} Postmortem studies confirm that brain lesions visualized on MRI in NMO patients have the same immunohistochemical characteristics as spinal cord lesions and that these are distinct from both MS and acute disseminated encephalomyelitis.

Aquaporin-4 immunoreactivity is strikingly depleted in NMO lesions regardless of the stage of demyelinating activity or extent of tissue necrosis.\textsuperscript{32} This contrasts from active demyelinating MS lesions, in which aquaporin-4 expression is increased. Furthermore, a novel NMO lesion type, encountered in the spinal cord and medullary tegmentum and extending into the area postrema, shows loss of aquaporin-4 with inflammation and edema, but neither demyelination nor necrosis.

Mounting evidence supports the potential for NMO-IgG as the primary cause of NMO.\textsuperscript{33} The association of NMO with other serum autoantibodies and systemic autoimmune diseases, together with the beneficial treatment effects seen with plasma exchange, implicate humoral immune pathways. Lesional immunoglobulin and complement deposition also suggests a primary antibody-mediated or initiated mechanism. Also, areas of aquaporin-4 loss coincide with sites of vasculocentric immune complex deposition, suggesting that a complement-activating, aquaporin-4-specific autoantibody is the primary initiator of the NMO lesion. In vitro experiments support these findings; they have demonstrated that NMO-IgG modulates expression of aquaporin-4 on the astrocyte surface. Moreover, in the presence of complement, NMO-IgG initiates cell membrane injury, cell death, disruption of the blood-brain barrier, and enhances granulocyte recruitment.\textsuperscript{33,34} Paranodal aquaporin-4 disruption may result in demyelination with loss of astrocyte endfoot integrity and failure of osmotic regulation, among other mechanisms. Finally, NMO-IgG modulates the glutamate transporter EAAT2 and reduces glutamate reuptake.\textsuperscript{35} Therefore, the cumulative evidence supports the likelihood that NMO-IgG directly causes tissue injury through complement-initiated inflammatory mechanisms and excitotoxic pathways.

There are numerous ongoing efforts to establish an animal model of NMO. Three of these have exposed Lewis rats to aquaporin-4 antibodies after induction with experimental allergic encephalomyelitis (EAE), a T-cell mediated CNS inflammatory disease, and each model resulted in NMO-like pathology.\textsuperscript{36-38} Fourth model, which did not utilize EAE induction, showed that intracerebral injection of NMO-IgG and human complement produces pathological lesions in mice very much like that seen in human NMO.\textsuperscript{39} These exciting advances promise to further elucidate the pathogenic mechanisms underlying the disease though passive transfer models and models of relapsing disease have not yet been reported.

**TREATMENT**

1. **ACUTE ATTACKS**

Acute clinical relapses are treated with intravenous corticosteroids such as methylprednisolone (1000 mg daily for five consecutive days). For severe relapses that worsen or fail to respond promptly despite corticosteroid therapy, evidence from a randomized, controlled trial supports use of rescue plasma exchange.\textsuperscript{40} The standard course involves treatment on alternate days for a total of seven exchanges. Subsequent observational experience also supports use of plasma exchange for treatment-refractory myelitis and optic neuritis attacks in NMO.\textsuperscript{41}
2. RELAPSE PREVENTION

Prophylactic immunotherapy is indicated for patients who have established relapsing disease or who have experienced a first-ever clinical event (such as LETM) and are seropositive for NMO-IgG. In NMO spectrum disorders, disability is related entirely to the residual effects of attacks because secondary progressive disease is very uncommon. Anecdotal experience and case series indicate that standard MS immunomodulatory therapies (e.g., interferon-beta, glatiramer acetate) are likely ineffective for NMO; in fact, interferons may aggravate the disease. Instead, either general immunosuppression or B cell depletion regimens seem to improve the natural history of the disease by reducing attack frequency. Oral azathioprine (target daily dose 2.5-3 mg/kg) may be employed by starting therapy along with an oral prednisone “bridge” of 0.5-1 mg/kg/d. The goal is to establish azathioprine monotherapy by beginning a gradual prednisone dose reduction when azathioprine exerts its full effect, typically within 4-6 months. Oral mycophenolate mofetil, typically 1000 mg twice daily, is sometimes used in place of azathioprine. The chimeric anti-CD20 monoclonal protein rituximab is now commonly used because it quickly and selectively depletes B cells. Two reports demonstrated favorable post-rituximab clinical courses after rituximab therapy. Repeated infusions are required every 6-12 months to maintain B cell depletion. Other immunosuppressive approaches include cyclophosphamide, mitoxantrone, or intravenous immune globulin.

Patients with established relapsing NMO require long-term immunosuppression. There are no data regarding if and when it is reasonable to discontinue therapy in patients who have been clinically stable for several years. Five years of relapse-free immunosuppression has been recommended for NMO-IgG seropositive patients with a single clinical event such as a LETM attack who are at high risk for relapse, with the rationale that the risk of adverse effects of therapy (e.g. malignancy) begin to emerge beyond that time frame.

Advances in the understanding of the sequential mechanisms that result in NMO lesions are expected to identify many new and specific targets for long-term immunotherapy in NMO.

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CME ANSWERS

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2. a
3. d

REFERENCES


LEARNING OBJECTIVES

1. The attendee will be able to describe the latest guidelines for establishing a diagnosis of multiple sclerosis in a child.

2. The attendee will be able to describe what features in children with optic neuritis place them at higher risk for developing future multiple sclerosis.

3. The attendee will be able to explain a potential Pediatric Optic Neuritis Treatment Trial.

CME QUESTIONS

Please indicate whether the following statements are true or false with regard to MS in children:

1. Altered mental status is a criterion for the diagnosis of MS in childhood.

2. White matter lesions on MRI at presentation are predictive of risk of conversion to MS in children with optic neuritis.

3. The risk of conversion to MS after optic neuritis in a child depends on the unilaterality or bilaterality of the optic neuritis.

KEYWORDS

1. Pediatric Optic Neuritis
2. Multiple Sclerosis
3. Pediatric Optic Neuritis Treatment Trial

INTRODUCTION

Optic neuritis is an inflammatory disorder of the optic nerve. Associated with a variety of autoimmune disorders, optic neuritis is most commonly considered a demyelinating disease, and it is often the initial manifestation of multiple sclerosis (MS). The relationship between optic neuritis and multiple sclerosis has been more thoroughly investigated in adults than in children. Clinically, optic neuritis in the pediatric age group is diagnosed by the same criteria used in adults, including sudden or subacute visual loss, central or cecocentral visual field defect, impairment of color vision, afferent pupillary defect, and ocular pain on eye movements. The purpose of this review is to discuss the risk factors for MS in children after optic neuritis.

DIAGNOSIS OF MULTIPLE SCLEROSIS IN CHILDREN

The diagnosis of MS in children is made by demonstration of at least two episodes of CNS demyelination separated in time in space (Krupp et al. 2007).

Dissemination in space can be satisfied by either:


2. Positive MRI by the McDonald (2001) criteria: 3 of 4 of
   i) nine or more white matter lesions or one gadolinium enhancing lesion,
   ii) three or more periventricular lesions,
   iii) one juxtacortical lesion, or
   iv) an infratentorial lesion.

3. Combination of abnormal CSF (oligoclonal bands or an elevated IgG index) and two lesions on MRI, of which one must be in the brain.

Dissemination in time can be demonstrated by either:


2. A new T2 or contrast-enhancing lesion which develops at least 3 months after the initial clinical event.

The events must not satisfy the diagnosis of ADEM (see below), which is a demyelinating or inflammatory event, and includes white or gray matter lesions on MRI, which is i) polysymptomatic and ii) includes encephalopathy (i.e. behavioral or mental status change). Multiple events of this type would be more appropriately termed recurrent or multiphasic ADEM (Krupp et al., 2007).

Neuromyelitis optica (NMO) must be excluded, but it is unclear in children whether the absence of NMO-IgG antibodies excludes the diagnosis.
**ACUTE DISSEMINATED ENCEPHALOMYELITIS VS. MULTIPLE SCLEROSIS**

Post-infectious neurologic disease is not uncommon in children. For example, acute cerebellar syndrome follows varicella infections, sensorineural hearing loss follows mumps infections, and Sydenham’s chorea is associated with streptococcal infections (Dale et al. 2000). Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease that typically follows an illness or vaccination. As opposed to MS, ADEM is typically a monophasic illness that does not require long-term treatment. ADEM is more common in children than adults (Dale et al. 2000). Although patients with ADEM can present with fulminate neurologic signs and symptoms, most patients have an excellent recovery.

The International Pediatric MS Study Group has defined ADEM by its clinical and radiographic features: encephalopathy, multifocal neurologic signs, and large, predominantly white matter, lesions on brain MRI, without alternative explanations (Kelly 2006). When relapses after ADEM occur, such cases are difficult to distinguish from MS. The Study Group has defined ADEM as a single episode lasting up to 3 months. New symptoms may appear during this timeframe. Children who have a second episode involving the same clinical and radiographic areas are diagnosed with recurrent ADEM. If different areas are affected, the child has multiphasic ADEM.

**CONVERSION RATE TO MULTIPLE SCLEROSIS AFTER PEDIATRIC OPTIC NEURITIS**

According to the ONTT, after acute unilateral optic neuritis, adults have a 50% chance of developing MS within 15 years (Optic Neuritis Study Group 2008).

In contrast, the conversion rate to MS in children is unclear, perhaps due to the variability in study methodologies in published reports, and because prospective data is lacking. One pediatric study reported a low conversion rate to MS (4%); however, the mean follow-up was 13 months (range 1-41 months) (Lana-Peixoto et al. 2001). Another study calculated the risk of developing MS after childhood optic neuritis using Kaplan-Meyer methods (Lucchinetti et al. 1997). The risk of MS was estimated to be 13% at 10 years, 19% by 20 years, 22% by 30 years, and 26% by 40 years. A different study reported a two-year risk of 36% (Wilejto et al. 2006).

A fourth study reported 16% of their patients with optic neuritis had MS; however, the purpose of that study was to define the presentation and visual prognosis in children, and children with a prior history of demyelinating disease were not excluded (Brady 1999). In our retrospective study (Bonhomme et al. 2009), eighteen patients were followed for more than 24 months, and 3 of the 18 (17%) developed MS.

The results of these and other studies are summarized in Table 1.

**WHITE MATTER LESIONS ON MRI ARE PREDICTIVE OF RISK OF MS IN CHILDREN**

As established by the Optic Neuritis Treatment Trial, an abnormal baseline brain MRI with white matter lesions is a strong predictor of MS after isolated optic neuritis in adults. Fifteen years after a bout of optic neuritis, 72% of adults with one or more brain MRI lesions at presentation developed MS, in contrast with a 25% conversion rate in those with no lesions (Optic Neuritis Study Group 2008). In children, an abnormal MRI at presentation is likely also predictive.

Mikaeloff et al. (2004) studied 296 patients after a first demyelinating event. Patients were ultimately diagnosed with MS using Poser’s criteria, ADEM (defined as polysymptomatic onset with mental status change, and poorly limited lesions on MRI with thalamus or basal ganglia involvement), or a single focal episode. Similar to the optic neuritis data, there were age differences between the patients with MS (12 years, SD 3.4) and ADEM (7.1, SD 4.3). Twenty-two percent of the patients presented with optic neuritis. Of the patients with optic neuritis at presentation, 86.6% were ultimately diagnosed with MS, whereas as 9% had monophasic ADEM. At the conclusion of the study, 53% of patients met diagnostic criteria for MS. The authors conclude that age of onset greater than 10 years, presence of an optic nerve lesion, and the presence of well-defined periventricular and/or subcortical lesions on MRI were associated with conversion to MS.

In the Wilejto et al. (2006) study, none of the patients with a normal brain MRI at presentation developed MS (although 1 developed NMO). All of the patients who presented with optic neuritis as the first manifestation of MS had at least 1 lesion on their initial MRI of the brain. Four patients with MRI lesions in the brain at presentation did not develop subsequent clinical attacks or further radiographic evidence of MS. Of this subgroup, 2 patients initially met McDonald’s criteria for dissemination in space, and the other 2 patients had multiple lesions (one with 6 lesions and one unavailable to the investigators for further review). None of these patients developed new lesions on subsequent MRI scans. Patients with ADEM were included in this study.

In our study (Bonhomme et al. 2009) we reviewed the medical records of children (<18 years) presenting with optic neuritis between 1993 and 2004 at the Children’s Hospital of Philadelphia. Children with a history of demyelinating disease or prior optic neuritis were excluded. Symptoms, ophtalmologic findings, MRI findings, and clinical outcomes were recorded. We identified 29 consecutive children with idiopathic optic neuritis. Eleven patients (38%) had white matter T2/FLAIR lesions in the brain (not including the optic nerves). Eighteen patients were followed for more than 24 months, and, as stated above, 3 of the 18 (17%) developed MS. All three patients...
had an abnormal brain MRI scan at their initial presentation of optic neuritis. None of the patients with a normal brain MRI scan at presentation developed MS over an average follow-up of 88.5 months. Patients with one or more white matter lesions on MRI were more likely to develop MS (3/7 vs. 0/11, p=0.04, Fisher’s exact test). We concluded that children with brain MRI abnormalities at the time of the diagnosis of optic neuritis have an increased risk of MS.

The results of these and other studies are summarized in Table 1. Larger collaborative prospective studies are needed to define better the prognosis for childhood optic neuritis.

**BILATERAL VS. UNILATERAL OPTIC NEURITIS, OR AGE, AS RISK FACTORS**

Compared to adults, bilateral ON is more common in children and is often simultaneous. It has been suggested that unilateral ON carries a greater risk for the development of multiple sclerosis (MS) in children compared to bilateral ON, but age may be a confounder.

We therefore performed a meta-analysis of published series to determine if age is a risk factor for unilateral vs. bilateral simultaneous optic neuritis and establish the risk of multiple sclerosis in children after unilateral vs. bilateral optic neuritis (Waldman et al. 2009). A MEDLINE search (1950 to May, 2010) was performed to identify published studies containing individual patient data of children (<18 years) with ON. References were scanned to identify additional pediatric studies. Patient age at onset of ON, laterality (unilateral vs. bilateral simultaneous ON), presence of brain MRI abnormalities outside the visual system (if available), and outcome (the development of MS) were recorded. Logistic regression was used to determine the risk of MS after unilateral vs. bilateral ON, adjusting for age and MRI abnormalities. Sixteen studies met the inclusion criteria, and 227 patients were analyzed. After unilateral ON as a first demyelinating event compared to bilateral ON, children were perhaps more likely to develop MS (OR 2.0, p=0.07). However, unilateral ON occurred more frequently in older children (OR 1.26, p<0.0001). After adjusting for age, the risk of MS after unilateral vs. bilateral ON was not significant (OR=1.67, p=0.2). For every 1 year increase in age, the risk of MS increases by 32% (p=0.006). After adjusting for age, the risk of MS significantly increases in children with abnormal brain MRI scans at presentation (OR 3.0, p<0.001). Thus, the relation between unilateral vs. bilateral ON and the development of MS is dependent upon age. Unilateral ON is more common in older children; this population may be at greater risk for MS, especially in those children with brain MRI abnormalities at presentation.

**RECURRENT OPTIC NEURITIS**

In our study of pediatric optic neuritis (Bonhomme et al. 2009), nine patients (31%) had relapses of optic neuritis during the study period and 5 had more than one relapse. The pattern and location of the recurrent episodes showed no specific pattern. For example, 3 patients who initially presented with bilateral optic neuritis had subsequent unilateral relapses. In contrast, the remaining 6 patients presented with unilateral optic neuritis, half of whom ultimately met criteria for bilateral sequential optic neuritis and the other half for recurrent optic neuritis. Of the nine patients with recurrent optic neuritis, two patients developed MS. The relative risk of developing MS among patients with optic neuritis recurrence was 4.0 (p=0.25).

It is unclear whether this would be confirmed in larger cohorts. Patients with bilateral simultaneous or sequential optic neuritis did not have a greater risk of MS compared to patients presenting with unilateral disease (p=0.53).

**A POSSIBLE PEDIATRIC OPTIC NEURITIS TREATMENT TRIAL**

In order to resolve the controversy concerning the benefit of corticosteroids for pediatric optic neuritis and to establish appropriate treatment guidelines, a multi-center Pediatric Optic Neuritis Treatment Trial (PONTT) is needed.

In such a trial, patients can be randomly assigned to one of three treatment groups, consisting of two corticosteroid groups and a placebo group:

1. IV methylprednisolone group: 1,000 mg/day or 30 mg/kg/day (depending upon the child’s weight) for 3 days, followed by a 15 day prednisone taper (starting at 1 mg/kg).
2. Oral methylprednisolone group: 1,136 mg/day or 34 mg/kg/day (depending upon the child’s weight) for 3 days, followed by 15 day prednisone taper (starting at 1 mg/kg).
3. Oral placebo: inert substance given using the same schedule as the oral placebo group.

Primary end points will be related to visual function and OCT measurements, but secondary outcome measures will be related to conversion to multiple sclerosis.

**CONCLUSION**

Prospective studies in adults such as the ONTT have provided important, useful data regarding the prognosis of optic neuritis with regards to conversion to MS. There are now several good retrospective studies in pediatric optic neuritis and the risk of MS, particularly those studying the role of an abnormal MRI at presentation. We are sorely in need of a prospective, multi-center study in children to supply data comparable to the adult ONTT for the pediatric age group.
<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>F:M (ratio)</th>
<th>Age (years)</th>
<th>Mean f/u (years)</th>
<th>Bilateral BS or BSeq</th>
<th>Unilateral (CIS)</th>
<th>Recurrent ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkin 1984</td>
<td>19</td>
<td>13:6 (2.2:1)</td>
<td>5.5-12 (8.0)</td>
<td>18 (0.5-30)</td>
<td>All*</td>
<td>N/A</td>
<td>N/A</td>
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<td>Mean = Median = Mode</td>
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<td></td>
<td></td>
<td>&lt;6: 1</td>
<td>6-10: 15</td>
<td>&gt;=11: 3</td>
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<tr>
<td>Riikonen 1988</td>
<td>21</td>
<td>16:5 (3.2:1)</td>
<td>4-14 (9.9)</td>
<td>6.7 (0.8-13)</td>
<td>13 (62%) BS vs Bseq@</td>
<td>8 (38%)</td>
<td>9</td>
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<td></td>
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<td></td>
<td></td>
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<td>(all pts w/ MS developed a 2nd attack of ON within 1 year)</td>
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<td>BS vs Bseq 3 sequentially over periods of 1-5 months</td>
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<tr>
<td>Kriss 1988</td>
<td>39</td>
<td>29:10 (2.9:1)</td>
<td>3-15 (8.6)</td>
<td>8.8 (0.25-29)</td>
<td>29 (74%) 25 BS 4 Bseq</td>
<td>10 (26%)</td>
<td>4 (10%)</td>
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<td>(2 w/ b/l)</td>
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<td>(1/4 developed MS)</td>
</tr>
<tr>
<td>Brady 1999</td>
<td>25</td>
<td>13:12 (1.1:1)</td>
<td>1.75-18 (9.4)</td>
<td>0.92 (0.04-4.7)</td>
<td>14^^^ (56%) 6/7 under 6 years, 85% (8/18 over 7 years, 44%) B/L Simul: 11/14 B/L Recurrent: 3/14</td>
<td>11 (44%) (1/7 &lt;6 yrs, 15%) (10/18 &gt;7 yrs, 56%)</td>
<td>B/L Recurrent 3^^^</td>
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<tr>
<td>Lana-Peixoto 2001 BRAZIL</td>
<td>27</td>
<td>12:15 (1:1.25)</td>
<td>3-16 (10.9)?</td>
<td>10 (37%) 8 BS 2 Bseq16%</td>
<td>17 (63%)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

* This is a follow-up study for patients with bilateral optic neuritis only.
^ Patient was originally classified at probable MS in 1959; upon further review, diagnosed with ADEM
° Defined bilateral as involvement of both eyes within one month or less between attacks
# excluded possible MS
+ Other diagnoses: Encephalitis (parotitis), ALL, encephalomyeloradiculitis after autoimmune reaction to sulphafurazole, post-vaccinal reaction, Leigh's disease
^^ Other diagnoses: Encephalomyelitis (5), Meningitis (1), Pyramidal involvement (3)
<table>
<thead>
<tr>
<th>Family History of MS/ON</th>
<th>Lesion on MRI excluding orbits at time of ON</th>
<th>LP Abnormalities at time of ON</th>
<th>ADEM</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1^</td>
<td>1 (5%) Female, EP/L MS</td>
</tr>
<tr>
<td>3 (14%) (3 of 9 pts w/ MS had a family history of MS)</td>
<td>57% Performed in 14/21 Abnormal: 8/14 (57%) 2 w/ mono-symptomatic ON 5 w/ MS 1 w/ encephalomyeloradiculitis</td>
<td>57-92% Performed in 12/21 --Abnl WBC in 12 (57%) WBC 6-76 (mean 14 cells/mm³) --OCB 2/4 at onset of ON**** --IgG 11/12 (92%) at onset --Viral Ab 2/4</td>
<td>5/9 (56%) children w/ MS had a URI or vaccine prior to ON 5 w/ s/s of disseminated dz at 1st attack, 2 prior to 1st attack</td>
<td>9 (43%) CDMS# 9/16 (56%) Subgroups 8/9 Female (7/8 with unilateral 2/13 with bilateral) 1/9 w/ Devic 7 (34%) possible MS 5 w/ other diagnoses*</td>
</tr>
<tr>
<td>0 pts w/ possible MS had a fm hx</td>
<td>47.6% Performed in 21/39 (10 abnl) --3 w/ modest WBC and protein --5 w/ WBC --2 w/ protein</td>
<td>46% w/ febrile prodome 9 (23%) other s/s during or within 6 weeks of onset of ON^^ Of these, 1/9 developed MS</td>
<td>6 (15%) Subgroups 2 w/ CDMS 4 probable MS (3 w/ b/l simult 3 w/ seq or unilateral) 5/30 without neuro s/s developed MS</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>13/23 (56.7%) Performed in 23/25 Brain Abnl: 12 SC Abnl: 1 B/L ON: 11 Uni ON: 2</td>
<td>9/21 (43%) Performed in 21/25 Abnl 9/21 ↓ prot 7/9 OCB none</td>
<td>8 patients w/ documented viral prodome B/L: 4 Unil: 4</td>
<td>4 (16%)## B/L 3</td>
</tr>
<tr>
<td>N/A</td>
<td>16.7% Performed in 6/27 Abnl: 1 (16.7%)</td>
<td>0% Performed in 12/27 All WNL</td>
<td>1 (4%) --Male, Unilateral</td>
<td></td>
</tr>
</tbody>
</table>

---

**^** Defined bilateral simult as both eyes affected within 1 month of each other, and bilateral recurrent disease as 1 or both eyes affected more than once

**##** It is unclear whether these patients were known to have MS at the time of diagnosis. Conclusions about the risk of developing MS after ON cannot be drawn from this study.

* Weeky associated with developing MS (hazard ratio 2.99, p 0.071, 95% CI 0.91-9.86)

** Recent infection within 2 weeks before onset of ON decreased risk of developing MS (hazard ratio 0.24, p 0.060, 95% CI 0.05-1.06)

*** All 13 patients had abnormal brain MRI

**** Performed by agarose electrophoresis
<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>F:M (ratio)</th>
<th>Age (years)</th>
<th>Mean f/u (years)</th>
<th>Bilateral BS or BSeq</th>
<th>Unilateral (CIS)</th>
<th>Recurrent ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales 2000</td>
<td>15</td>
<td>9:6 (1.5:1)</td>
<td>4-15 (9.8)</td>
<td>1.5 years (17.5 months)</td>
<td>10 (67%) (BS)</td>
<td>5 (33%)</td>
<td>4</td>
</tr>
<tr>
<td>Lucchinetti 1997</td>
<td>94</td>
<td>58:36 (1.6:1)</td>
<td>2-16 (Median: 11)</td>
<td>22 (2.7-43.2)</td>
<td>54 (57%)</td>
<td>40 BS 14 Bseq</td>
<td>37 (39%)</td>
</tr>
<tr>
<td>Wijelto 2006</td>
<td>36</td>
<td>21:15 (1.6:1)</td>
<td>2.2-17.8 (12.2)</td>
<td>2.4 years (0.3-8.3)</td>
<td>42% (13/36=36%????)</td>
<td>58% (64%)</td>
<td>??</td>
</tr>
</tbody>
</table>

* This is a follow-up study for patients with bilateral optic neuritis only.
^ Patient was originally classified at probable MS in 1959; upon further review, diagnosed with ADEM
© Defined bilateral as involvement of both eyes within one month or less between attacks
@ Excluded possible MS
+ Other diagnoses: Encephalitis (parotitis), ALL, encephalomyeloradiculitis after autoimmune reaction to sulphafurazole, post-vaccinal reaction, Leigh's disease
^^ Other diagnoses: Encephalomyelitis (5), Meningitis (1), Pyramidal involvement (3)
<table>
<thead>
<tr>
<th>Family History of MS/ON</th>
<th>Lesion on MRI excluding orbits at time of ON</th>
<th>LP Abnormalities at time of ON</th>
<th>ADEM</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (20%)</td>
<td>3/9</td>
<td>7/9 Mild pleocytosis 2 w/ +Lyme</td>
<td>10/15 w/ antecedent viral illness within 2 weeks of visual sx</td>
<td>4 (26%)</td>
</tr>
<tr>
<td>Not statistically significant. Details not reported.</td>
<td>N/A</td>
<td>47% Performed in 51/94 24 (47%) abnl Subgroup Pleocytosis 19/21 (90%) Inc protein** 11/45 (24%) IgG 5/20 OCB 0/6</td>
<td>43 (46%) w/ neurologic signs and symptoms Subgroup 10 w/ myelitis 9 w/ seizures 9 w/ encephalopathy 8 w/ meningismus Infection**</td>
<td>15 (19%) Subgroups 8 Female, 7 Male 13/15 (87%) CDMS 4/13 w/ Devic Dz 12/15 w/ bilateral (5/12 BS, 7/12 Bseq) Devic subgroup 3/4 BS 1/4 Bseq 2/15 Unilateral 1/15 Recurrent ON 2/15 (13%) LSDM</td>
</tr>
<tr>
<td>6 (16.7%)</td>
<td>54% brain abnl (17/35=49%)?? 11 McDonald + 4 &gt;/=2 lesions 2 only 1 lesion</td>
<td>43 (62%)</td>
<td>13 (36)** 1 Devic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>54% brain abnl (17/35=49%)?? 11 McDonald + 4 &gt;/=2 lesions 2 only 1 lesion</td>
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<td>54% brain abnl (17/35=49%)?? 11 McDonald + 4 &gt;/=2 lesions 2 only 1 lesion</td>
</tr>
<tr>
<td></td>
<td>21/21 WBC&gt;6 2/12 also had inc protein</td>
<td>3/18 OCB****</td>
<td>1 diplopia 9 other neuro sx 10 viral prodome 2 immunization 11 Abnl exam Subgroups Without MS --3/22 =abnl exam --12/22=prodrome With MS --9/13 =abnl exam --7/13 prodrome NMO --0/1 abnl exam --0/1 prodome</td>
<td></td>
</tr>
</tbody>
</table>

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* Weakly associated with developing MS (hazard ratio 2.99, p 0.071, 95% CI 0.91-9.86)

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*** All 13 patients had abnormal brain MRI

**** Performed by agarose electrophoresis
## ADDITIONAL STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>F:M (ratio)</th>
<th>Age (years)</th>
<th>Mean f/u (years)</th>
<th>Bilateral BS or BSeq</th>
<th>Unilateral (CIS)</th>
<th>Recurrent ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikaeloff 2004</td>
<td>296</td>
<td>169:127 (1.3:1)</td>
<td>0.7-16 (9.9)</td>
<td>2.9 (0.5-14.9) Med 1.9</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MS: 2-16</td>
<td>Mean 12</td>
<td>Med 13.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADEM: 0.7-16</td>
<td>Mean 7.1</td>
<td>Med 6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Focal: 0.7-16</td>
<td>Mean 8.8</td>
<td>Med 9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>67 (22%) had ON (type unspecified)</td>
<td>By final dx: MS 58 (87%)</td>
<td>ADEM 6 (9%)</td>
<td>Focal 3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Dale 2000</td>
<td>48</td>
<td>22:26 (0.85:1)</td>
<td>3-15 (8)</td>
<td>9</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADEM (28)</td>
<td>Mean 7.3</td>
<td>Med 5.5 Mode 3.5</td>
<td>ADEM 5^</td>
<td>ADEM 0^</td>
<td>ADEM 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MDEM (7)</td>
<td>Mean 8</td>
<td>Med 7 Mode 4</td>
<td>MDEM 3^</td>
<td>MDEM 0^</td>
<td>MDEM 2 w/ B/L recurrent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS (13)</td>
<td>Mean 9.4</td>
<td>Med 11 Mode 10.3</td>
<td>MS 1^</td>
<td>MS 3^</td>
<td>MS 5 (including UON and BON dz)</td>
</tr>
</tbody>
</table>

* MRI was performed in all patients, but stratified by type of lesion (suggestive of MS, suggestive of ADEM, subtentorial, thalamus, BG, ON, etc). MRI was suggestive of MS if there were well-limited multiple lesions with periventricular and/or subcortical locations.

^ In the ADEM group, 5 patients had bilateral optic neuritis as part of their initial presentation. In the MDEM group, 3 patients had bilateral optic neuritis as part of their initial presentation. One patient in the MDEM group had unilateral optic neuritis during a relapse but did not have visual symptoms at initial presentation. In the MS group, 4 patients presented with ON (3 unilateral, 1 bilateral); however, 9 of the 13 patients had optic neuritis (including bilateral, unilateral, and recurrent) at some point during their disease.
<table>
<thead>
<tr>
<th>Family History of MS/ON</th>
<th>Lesion on MRI excluding orbits at time of ON</th>
<th>LP Abnormalities at time of ON</th>
<th>ADEM</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (5%)</td>
<td>N/A*</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI suggestive of MS*: 96</td>
<td></td>
<td>85/296 (29%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final dx of MS: 96</td>
<td></td>
<td></td>
<td>168/296 (57%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48 (100%)</td>
<td>ADEM/MDEM 32 available for review</td>
<td>31</td>
<td>13 (27%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>91% had subcortical or deep white matter lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>44% had PV lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS 12 available for review</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>92% had subcortical or deep white matter lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>92% had PV lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADEM/MDEM: 26 had a preceding illness in month before presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS: 5 had a preceding illness in month before presentation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CME ANSWERS

1. False
2. True
3. False

REFERENCES


LEARNING OBJECTIVES

1. The attendee will be able to understand the evidence underlying the use of disease modifying therapies in the treatment of MS.

2. The attendee will be able to understand the challenges and limitations of cross-trial comparisons related to MS therapies.

3. The attendee will be able to create awareness of results of head-to-head clinical trials in MS.

4. The attendee will be able to understand putative mechanisms of action for existing/approved drugs in MS.

5. The attendee will be able to discuss symptomatic therapies in MS.

CME QUESTIONS

1. Which of the following statements is TRUE?
   a. Natalizumab has demonstrated efficacy as a 2nd line monotherapy in patients who fail treatment with interferon.
   b. Over 2 years high dose high frequency interferons are associated with similar efficacy to Glatiramer Acetate.
   c. All interferons are molecularly identical.
   d. All interferons have identical clinical efficacy in head-to-head trials.

2. Which of the following is a standard primary outcome in Phase III MS clinical trials?
   a. New Gadolinium enhancing lesions on MRI
   b. Long term Sustained Disability Progression by EDSS
   c. Annualized Relapse Rate
   d. Brain atrophy measured via brain parenchymal fraction (BPF) on MRI
   e. Circulating levels of MOG specific lymphocytes

3. Which of the following is true about PML associated with Tysabri treatment?
   a. PML is associated with concurrent use of interferon.
   b. PML is associated with prior use of immune suppressants and/or steroids.
   c. PML occurs at a rate of 1/1000 regardless of length of use.
   d. PML after Tysabri is usually fatal.
   e. PML risk can be stratified based on CSF measurements of JC virus.

4. Which of the following about Gilenya (Fingolimod) is FALSE?
   a. Fingolimod results in reduced levels of circulating lymphocytes.
   b. Fingolimod is associated with macular edema.
   c. Fingolimod initiation requires assessment by an Endocrinologist.
   d. Fingolimod may modify host response to live vaccines.
   e. Fingolimod is the first approved oral therapy.

KEYWORDS

1. Multiple Sclerosis
2. Optic Neuritis
3. Clinically Isolated Syndrome
4. Medical Treatment
5. Clinical Trials

DISEASE MODIFYING THERAPY

The first disease modifying therapy for the treatment of MS was approved in 1993. In the 17 years since 7 additional medicines have been approved. More than 250,000 patients worldwide are currently treated.
Basic issues in clinical trial design

End point selection - The primary clinical endpoint in most MS clinical trials has been annualized relapse rate reduction. It has been debated whether an effect on relapse rate should be the primary outcome of interest as relapses are distressing but their impact on disability may be self-limited. Additional, primary and major secondary endpoints have been percentage of patients with sustained disability progression (1st), new contrast enhancing lesions on MRI (2nd), new T2 lesions on MRI (2nd), and disability progression on EDSS (2nd).

Population selection – There have been marked reductions in observed relapse rates over last 10-20 years in MS clinical trials evidencing a shifting MS demographic for patients available for clinical trials. This has made demonstrating efficacy more challenging, although most drugs appear to perform significantly better when used at the earliest phases of disease. Therapies are far less efficacious for the treatment of progressive disease.

There are three major trends-

1. Temporal/secular changes in underlying MS demographics (earlier disease identified, less severe disease treated, increasing proportion of female patients)
2. Changes in MS population available for trial (less severe disease) as other approved therapies are available
3. Changes in trial sites/countries – the relative efficacy and safety of different agents in different populations is unknown. Examples: African-Americans may not evidence same clinical response to IFN, non-Caucasian patients may suffer side effects like hair-loss that are less common in other populations

In addition given the availability of proven therapies there is increasing pressure to perform active comparator trials as opposed to placebo-controlled trials.

Disease Modifying Therapies:

Traditional 1st line agents:
Interferon B1a (IM) [Avonex], InterferonB1b (SC) [Betaseron/Extavia], Interferon B1a (SC) [Rebif] and Glatiramer (SC) [Copaxone].
All these agents are currently injectable. 4/5 are subcutaneous injections.

Take home: High dose/high frequency interferons and glatiramer have superior efficacy over 2 years at cost of increased frequency of injections and higher rates of neutralizing antibodies (for interferon-B1a (SC), interferon-B1b (SC) and extavia).
Choice of a “1st line” agent should be influenced by co-morbidities (depression, liver disease), frequency of injections, issues related to tolerability and relative importance of MR outcome.

Although approved as a “1st line” medication fingolimod’s use in this setting is controversial as there is far more limited safety data to justify its use prior to a trial with a well-established 1st line agent.

Interferon B-
Almost all human cells express receptors for type I interferons (interferon alpha and interferon beta). Interferons show a variety of immunological, anti-tumor, and antiviral effects. The original basis for assessing interferons as DMT for MS was their presumed antiviral effect. This is almost certainly not the basis for their clinical efficacy. IFN induces a variety of modifications in the immune response including attenuation of T cell migration and activation. In general IFN should be viewed as an anti-inflammatory cytokine but it must be remembered that it also enhances certain components of the immune response.

Major side effects of interferon therapy are uncommon. There is no long-term cancer risk, cardiovascular risk, risk of opportunistic infection or mortality risk. However, adverse events including the development of liver toxicity, worsening of underlying depression and injection site reactions (very infrequently necrotizing and serious) occur.

These medications can be poorly tolerated and as many as 15-50% of patients may discontinue because of tolerability issues (injection site reactions, constitutional symptoms in the minute, hours (Glatiramer) and day (Interferon-B1a (SC), Interferon-B1b (SC), Interferon-B1a (IM weekly)) following injection. Most drug companies have patient programs intended to enhance patient compliance.

Betaseron (SC) - Interferon Beta 1B subcutaneous administration.
This was the first agent approved for treatment in MS. The Betaseron (interferon-B1b) trial demonstrated that, compared to treatment with placebo, treatment with 28 million international units (MIU) per week of IFNb subcutaneously reduced the clinical attack rate, the MRI attack rate, and the volume of white matter disease seen on MRI. This trial also showed a reduction in confirmed one-point progression rate on the extended disability status scale (EDSS), however, this change was not statistically significant. Treatment with 8 MIU/wk of interferon-B1b (SC) was also better than placebo on several outcome measures but was, in general, not as beneficial as the higher dose.

A subsequent trial [BENEFIT] in patients with high risk clinically isolated syndrome (a first demyelinating attack and at least two lesions on brain MRI) showed a 50% reduction in progression to MS (2nd exacerbation) over 2 years. Direct head-to-head clinical trials indicate the short term (2 year) superiority of high dose/high frequency interferons when compared to interferon-B1a (IM weekly) (INCOMIN). Interferon-B1b (SC) is more immunogenic than the other interferons. It is unclear if this difference relates
to structural differences between interferon-B1b (SC) and interferon B1a formulations or the dose and frequency of administration.

Interferon-B1a (IM weekly)- The results of the interferon-B1a (IM weekly) trial published in 1996 were similar to the earlier interferon-B1b (SC) trial. After two years, compared to placebo, treatment with 6 MIU/wk of interferon-B1a (IM weekly) intramuscularly produced a reduction in the clinical attack rate, the MRI attack rate, and the confirmed one-point EDSS progression rate. The total volume of white matter disease seen on MRI was also reduced in the treated group but this was not statistically significant.

Interferon-B1a (SC)- The PRISSMs trial in 1998 (N=533) demonstrated ~30% reduction in relapse rate over two years and lead to approval in two doses (higher dose with modestly greater efficacy). This trial also showed an effect on accumulation of new T2 and contrast enhancing lesions on brain MRI. A subsequent trial evaluating Interferon-B1a (SC) in CIS showed a 27% reduction in relapse rate and a significant delay in the occurrence of an MS defining relapse. Interferon-B1a (SC) is given 3x weekly and is associated with neutralizing antibodies at a rate between that of interferon-B1a (IM weekly) (low) and interferon-B1b (SC) (high).

Extavia- This is identical to Betaseron (distinction is strictly one of distribution and branding).

Glatiramer –
Mimicking the ligand for T-Cell receptor binding can theoretically result in a modification of the immune response by stimulating clonal anergy. This therapeutic approach has been investigated using oral myelin and altered peptide ligand, with the only agent showing clinical efficacy being copolymer (glatiramer acetate or Copaxone). Clinical trials show efficacy similar for glatiramer to interferons (30% reduction in relapse rate in pivotal trial, 41% reduction in conversion to MS over 2 years in CIS trial PRECISE). Head-to-head clinical trials indicate a similar clinical efficacy to high dose high frequency interferon, although data shows less effect on MRI metrics of disease activity. Uncontrolled, unblinded clinical data suggests that patients who fail interferon therapy have a similar response rate to glatiramer as other new starts. The original pivotal trial for glatiramer had suggested that clinical response by glatiramer may be delayed by up to 6 months and effect on disability progression was less robust. However, the head-to-head trials discussed below reveal that these were not the case.

BEYOND- Randomized assessor blinded clinical trial comparing interferon-B1b (SC) to glatiramer (N= 2244) with two interferon-B1b (SC) arms (usual dose and double dose).

REGARD- Randomized assessor blinded clinical trial comparing interferon-B1a (SC) to Glatiramer 96 weeks duration (N= 764). In both trials, glatiramer demonstrated better efficacy but worse tolerability than anticipated.

Outcomes- Clinical relapse rates were nearly identical between both arms (in both trials). However, in REGARD interferon showed 40% lower rate of new gad-enhancing lesions as well as better MR “response” on a few other measures. Patients in Glatiramer arm had higher total number of prior relapses and were more likely to have required steroids in the prior year.

NEWER BIOLOGIC AGENTS

Natalizumab (Tysabri)
There are two pivotal trials establishing the efficacy of natalizumab in treating RRMS. AFFIRM found a 68% risk reduction in relapse rate in natalizumab treated patients compared to placebo and ~50% reduction in risk of disability progression over 2 years. Approximately 6% of patients on natalizumab develop persistent neutralizing antibodies to the treatment which attenuates its efficacy.

Natalizumab was initially approved in late 2004 for the treatment of MS before the completion of the two clinical trials. However, in early 2005 following the development of progressive multifocal leukoencephalopathy in 2 patients from the AFFIRM study (and 1 additional patient in a concurrent Crohn's disease clinical trial), Natalizumab was pulled from the market. It was reintroduced in 2006 with a clinical program (TOUCH) meant to monitor the occurrence of new PML cases and establish a “risk map” for following patients on treatment. Since then more than 75,500 patients have been treated with the drug (55,100 ongoing) worldwide with 55,100 still on treatment. Seventy-five patients have developed PML (33 in the US and 38 in the EU) and 20% of those patients have died as a consequence of the infection (November 2010).

PML does not occur (only 1 reported case at 11 months) in patients treated for less than 12 months. PML risk increases dramatically in patients treated for > 24 months. (rate of PML 0-1 years 1/50,000, 1-2 years 0.4/1000, 2+ years 2/1000). The new JC virus serum antibody test shows great promise at risk stratification for patients considering treatment with natalizumab. Of the 20 cases of PML with available serum from before the clinical development of the infection, all 20 were sero-positive for JC virus at “baseline”. Using this test to assess PML risk is partially dependent on baseline rate of JC virus antibody seropositivity in the population in question (different between Biogen and NIH) and the accuracy (positive predictive value and negative predictive value) of the test. All observers agree that the rate of JC virus exposure increases with age. Some models for the development of PML in immunocompromised individuals have suggested that post-seroconversion mutations are required for passage into the CNS and/or development of PML. This is because the pathogenic virus is actually believed to be much less efficient at transmission and may suggest that sero-negativity is associated with a more prolonged protection to the development of PML.
In summary seropositivity may be associated with PML rates of 1:250 in patients treated for 2 years whereas seronegativity may pose of risk of less than 1: 10,000 (risk primarily attributable to false negative cases).

Recent evidence indicates that in some patients immune reconstitution may occur with drug cessation. Many patients return to pre-treatment initiation rate of disease activity but in some cases dramatic increases in attack rate and the detection of new gad enhancing lesions has been reported. (West, Khan)

**Fingolimod (FTY-720)**

FTY-720 (Gilenya) is an oral S1P1 inhibitor initially developed for the treatment of organ rejection after transplantation. It leads to sequestration of lymphocytes in lymphoid organs and thereby prevents their egress into the periphery. It also is believed to have a relatively selective impact on naïve central memory T cells with less impact on effector cell populations. Subsequently it was tested in MS. Three Phase III double blinded placebo controlled trials have established the efficacy of Fingolimod in MS: FREEDOMS I, FREEDOMS II (ongoing) and TRANSFORMS. Freedoms I showed a 55% reduction in relapse rate on Fingolimod and 27% reduction in likelihood of progression in disability compared to placebo and the higher dose it was associated with less tolerability. TRANSFORMS showed relatively greater efficacy of Fingolimod when compared to interferon-B1a (IM weekly) over 1 year. The trials included two patients with fatal herpes virus infections (1 disseminated zoster in a previously Varicella naïve patient and the other with HSV encephalitis). In addition there were approximately 16 cases of macular edema and 8 cases of skin cancer (basal cell and melanoma) as well as episodes of symptomatic bradycardia and elevations in systolic blood pressure on therapy. Patients also had a higher rate of upper respiratory infections on therapy. The impact on memory T cells does raise concerns about development of infections against which the patient may have been previously immune.

**Cladribine** is an adenosine deaminase inhibitor that functions as a potent immunosuppressive agent that is relatively selective for lymphocytes compared to other cell types. It has been used successfully to treat a variety of lymphoid malignancies but it is especially effective in the treatment of hairy-cell leukemia in both IV and SC formulations. The Scripps Clinic, in two small studies, reported fairly modest benefits to treatment in patients with either SPMS or RRMS.

More recently the CLARITY trial (N=1184) showed that an oral formulation of the medication (in two doses) has 55-58% reduction in relapses compared to placebo and 33% reduction over 96 weeks in the likelihood of having sustained disability progression.

Safety and upcoming consideration for approval: The formulations used for leukemia are associated with an elevated risk of solid organ tumors and dose related leukopenic fevers. In addition, lymphoid malignancies, opportunistic infections including zoster reactivation and peripheral neuropathy have been observed. Cladribine reduces levels of circulating lymphocytes. Patients in the Clarity trial had an increased rate of solid organ tumors compared to placebo as well as lymphocytopenia ~20-30% of the time and Herpes Zoster in 8 cases. Concerns about the safety of this agent persist. EMEA has rejected the manufacturer’s application for drug approval in Europe.

**Mitoxantrone** Mitoxantrone (Novantrone) is an immunosuppressive agent reported to be of value in the treatment of MS. This agent has been studied in both RRMS and SPMS at doses of 12 mg/m2 and 5 mg/m2 administered by IV infusion every 3 months for 2 years. The pivotal trial for Novantrone demonstrates that, compared to placebo, treatment with high dose mitoxantrone resulted in a significant reduction in the clinical attack rate, as well as marginally significant reductions in MRI attack rate, the one-point EDSS progression, and the total lesion load on MRI. The FDA has subsequently approved this agent for use in MS. In general, mitoxantrone was well tolerated, although, because of concerns regarding potential cardiac toxicity, the recommended total lifetime dose of mitoxantrone (Novantrone) is limited such that continuous treatment with quarterly 12 mg/m2 mitoxantrone (Novantrone) beyond 2-3 years is not possible. Serious side effects include cardiotoxicity and Leukemia. Given these risks use of this agent for secondary progressive MS has declined. However, the use of other broad class immune suppressants early in the course of secondary progressive MS is common at many MS centers. The agent selected varies by site.

**Disease Modifying Treatment Summary:**

- **Interferons:**
  - Interferon β1a - (Betaseron) given as SQ injection every other day
    - reduces number of relapses by ~35% (1.27 → 0.84/year)
    - stabilizes MR lesion load
    - modest reduction in long term disability
    - side effects include flu-like symptoms, injection site reactions, anemia, elevated liver enzymes, leukopenia and depression
    - blood work recommended every 3 months (CBC, LFTs)
  - 1/3 patients develop neutralizing antibodies
  - Interferon β1b (Avonex) – given as IM injection once weekly
    - reduction in relapse rate, symptom progression and stabilization of MR lesion load
    - side effects the same except much less injection site problems and no reported liver toxicity
• lower incidence of neutralizing antibodies (originally thought to be 24%, more recent data suggests a rate closer to 5%)
• Interferon β₁₄ (Rebif) - given as SQ injection three times a week
  • higher dose than Interferon-B1a (IM weekly)
  • neutralizing antibodies 1/8- 1/5)
  • similar benefit and side effect profile when compared to Betaseron
• All the interferons may be used in secondary progressive MS, but probably are only useful in those patients who are continuing to have relapses though they have entered progressive phase.
• Clinical significance of neutralizing antibodies is controversial.
• Glatiramer Acetate (Copaxone) - given as SQ injection every day. It is a racemic mixture of multiple polypeptides (initial design based on the composition of myelin basic protein – the largest constituent of CNS myelin).
  • Similar reduction in exacerbation rate and new MRI lesions as compared to interferons
  • Side effects include injection site reactions and chest pain/dyspnea/anxiety with injections
  • No lab monitoring necessary
• Natalizumab Monthly IV infusion
  • Blocks lymphocyte egress into the central nervous system
  • Clinical trials suggest but do not prove greater efficacy when compared to traditional first line agents
  • Typically better tolerated than IFN or GA
  • Risk of PML serious limited toxicity but also potentially associated with liver toxicity and melanoma
  • Frequently used as second line or rescue agent but role in this regard uninvestigated
• Fingolimod/Gilenya
  • S1P1 inhibitor with widely expressed receptor
  • Clinical trials show good efficacy
  • Concerning safety signals for infection, melanoma and increases in blood pressure
  • Risk of macular and pulmonary edema
  • Required monitoring includes ophthalmologic exams and cardiac monitoring
• Mitoxantrone (Novantrone)
  • An anthracenedione – intercalates into DNA producing strand breaks and interstrand crosslinks, interferes with RNA synthesis, and inhibits topoisomerase II (DNA repair).
  • FDA-approved for use in SPMS, PRMS and severe/worsening RRMS
  • May slow long term progression
  • Reasonably high risk of cardiotoxicity (i.e. cardiomyopathy, CHF) and secondary malignancy (leukemia), >40% of women experience amenorrhea which may be permanent.
  • Given once monthly IV
• May be used in treatment non-responders or progressive patients (rarely used at UCSF MS center)
• Frequently replaced with other broad class immune suppressants given toxicities
• Oral Cladribine
  • Not yet approved by FDA, rejected by EMEA

Cross-trial comparisons are potentially misleading about the relative efficacy of the approved agents because of differences in the underlying populations enrolled. Head-to-head trial data is limited but does indicate differences in efficacy, safety and side effects of the agents available for treatment.
### Head to Head Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs compared</th>
<th>Method</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGARD 2008</td>
<td>Interferon-B1a (SC) vs Glatiramer</td>
<td>Assessor blinded N=764</td>
<td>No difference on clinical outcomes</td>
<td>1) No significant difference in time to first relapse&lt;br&gt;2) Favored Rebif on number of new lesions on MRI Patients on Rebif had decreased number of Gad-enhancing lesions&lt;br&gt;3) Patients in the Glatiramer arm had significantly less relapses in the year preceding the trial, and had significantly increased lesions load at baseline.</td>
</tr>
<tr>
<td>BEYOND 2008</td>
<td>High dose Interferon-B1b (SC) vs regular dose Interferon-B1b (SC) vs Glatiramer</td>
<td>Assessor blinded N=2244 2 years Primary outcome relapse rate and secondary outcome of percentage with disability progression and new T1 black holes</td>
<td>No difference on clinical outcomes Suggestion of better MR outcome with IFN</td>
<td>1) No significant difference in time to first relapse&lt;br&gt;2) No difference between doses of Betaseron</td>
</tr>
<tr>
<td>EVIDENCE 2007</td>
<td>Interferon-B1a (SC) vs Interferon-B1a (IM weekly)</td>
<td>Assessor Blinded N= 677 Average follow-up 64 weeks (1-2 years) with crossover after trial</td>
<td>Interferon-B1a (SC) superior over 1-2 years</td>
<td>1) Rebif had an increased time to relapse&lt;br&gt;2) Rebif showed decreased number of MRI lesions&lt;br&gt;3) Rebif had increased neutralizing antibodies&lt;br&gt;4) No significant difference in adverse events&lt;br&gt;5) Patients converting to high dose IFN in crossover period had 50% reduction in ARR (could be biased by regression to mean)</td>
</tr>
<tr>
<td>INCOMIN 2006</td>
<td>Interferon-B1b (SC) vs Interferon-B1a (IM weekly)</td>
<td>Randomized N=188 Primary outcomes were (1) the proportion of patients free from relapses and (2) free from new T2 lesions on MRI</td>
<td>Interferon-B1b (SC) Superior</td>
<td>1) Betaseron had decreased MRI lesions&lt;br&gt;2) Betaseron had increased time to relapse&lt;br&gt;3) Betaseron group had delay in confirmed disease progression&lt;br&gt;3) Betaseron group had increased neutralizing antibodies</td>
</tr>
<tr>
<td>EUROPEAN HIGH DOSE INTERFERON 2006</td>
<td>Interferon-B1b (SC) (European high-dose interferon β₁b) vs Interferon-B1a (SC) vs Interferon-B1a (IM weekly)</td>
<td>Not blinded 2 years follow/up N=90</td>
<td>Interferon-B1a (SC) and Interferon-B1b (SC) superior</td>
<td>1) Betaferon was similar to Rebif and both were superior to Avonex in decrease of EDSS at 2 years&lt;br&gt;2) Betaferon was similar to Rebif and both were superior to Avonex in decreasing relapse rate&lt;br&gt;3) Study was not truly blinded, only involved 90 patients</td>
</tr>
</tbody>
</table>
### Trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs compared</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SENTINEL 2006</td>
<td>Interferon-B1a (IM weekly) vs Natalizumab +Interferon-B1a (IM weekly)</td>
<td>Blinded Enrolled patients who had breakthrough disease on Avonex alone N=1171 Annualized relapse rate 2+ years</td>
<td>Add on Natalizumab reduced disease activity in interferon failures</td>
<td>1) Addition of Natalizumab led to 54% reduction in relapse rate and 24% reduction in chance of developing sustained progression in disability 2) Identified first two cases of PML</td>
</tr>
<tr>
<td>TRANSFORMS 2010</td>
<td>Fingolimod vs Interferon-B1a (IM weekly)</td>
<td>Blinded N=1153 Annualized relapse rate, progression in disability and brain atrophy 1 year</td>
<td>Fingolimod Superior</td>
<td>1) FTY-720 was associated with 40-50% reduction in relapse rate compared to weekly IM IFN 2) Similar results seen on MR outcome 3) Two subjects in FTY-720 arm died from herpes virus infections 4) Unclear why trial design was in comparison to agent with least demonstrated efficacy</td>
</tr>
<tr>
<td>SURPASS Ongoing</td>
<td>Natalizumab switch vs continued 1st line DMT</td>
<td>2 years</td>
<td>Unknown</td>
<td>Pending</td>
</tr>
</tbody>
</table>

### SYMPTOMATIC MANAGEMENT

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
<th>Non-medicinal Rx Approaches</th>
<th>Medications</th>
</tr>
</thead>
</table>
| Fatigue                          | ~90% of MS patients | • Energy conservation strategies  
• Cooling measures  
• Elimination of contributing factors, including some medications or poor dietary habits | • Modafinil, amantadine methylphenidate (addictive potential), dextromethorphan, and pemoline (CAUTION black box warning for hepatic failure)  
• Low dose naltrexone |
| Walking impairment                | ~20-40% of patients | • Physical therapy  
• Monitored exercise  
• Assistive devices | • Dalfampridine (4AP) is approved with modest demonstrated efficacy at very high cost |
| Bladder dysfunction               | >90% of MS patients | • Monitor for UTI  
• Adequate and appropriate fluid intake  
• Avoidance of stimulant such as caffeine and aspartame  
• Intermittent self catheterization | • Oxybutin, hyoscyamine, tolterodine, flavoxate, desmopressin, trospium, solifenacin |
<p>| Sensory visual impairment (glare and low contrast deficits) | ~50-80% of patients | • Colored lenses | • ? Dalfampridine |
| Nystagmus (especially acquired pendular nystagmus) | ~10% of MS patients | • None | • Neurontin, memantine, low dose benzodiazepines |</p>
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
<th>Non-medicinal Rx Approaches</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>~30-70% of patients</td>
<td>• Physical Therapy</td>
<td>• Neurontin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exercise</td>
<td>• Sativex (UK and Canada)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Opioids</td>
</tr>
<tr>
<td>Depression</td>
<td>~50% of MS patients, Suicide risk 7.5x normal population</td>
<td>• Regular screening</td>
<td>• Antidepressant medications such as fluoxetine, paroxetine HCL, sertraline, citalopram, venlafaxine, duloxetine, bupropion, mirtazapine</td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>Constipation present in ~30% of MS patients</td>
<td>• Dietary and fluid modification</td>
<td>• Psyllium hydrophilic, methylcellulose, mucilloid lactulose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exercise</td>
<td>• Docusate, lactulose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Establish a bowel routine</td>
<td>• Suppositories, stimulants, enemas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Amitiza</td>
</tr>
<tr>
<td>Pseudobulbar affect</td>
<td>~5%</td>
<td>• None</td>
<td>• Quinidine/dextromethorphan</td>
</tr>
<tr>
<td>Spasticity</td>
<td>&gt;30% have moderate to severe spasticity</td>
<td>• Stretching and rehabilitation</td>
<td>• Baclofen, tizanidine, gabapentin, clonazepam, diazepam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Eliminating noxious stimuli</td>
<td>• Botox injections for spasticity</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td>• Patterning, immobilization, weighting</td>
<td>• Clonazepam, propanolol, gabapentin, isoniazid</td>
</tr>
<tr>
<td>Sexual Dysfunction</td>
<td></td>
<td>• Thalamic electrostimulation, thalamotomy</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>~30-60% of patients</td>
<td>• Neuropsychological evaluation</td>
<td>• Donepezil HCL</td>
</tr>
<tr>
<td>Paroxysmal Tonic Spasms</td>
<td></td>
<td>• Frequently accompany transverse myelitis and are very painful</td>
<td>• Tegretol (start at 100mg PO BID) can titrate up to 400 BID, if still having spasms ADD tizanidine and titrate to effect</td>
</tr>
</tbody>
</table>

Drugs in bold are approved for this indication. All meds listed above are otherwise off-label use.

**CME ANSWERS:**
1. B
2. C
3. B
4. C
REFERENCES


LEARNING OBJECTIVES

1. The attendee will be able to list novel therapies on the horizon for treatment of relapsing forms of MS.

2. The attendee will be able to elaborate immunologic strategies for the treatment of MS.

3. The attendee will be able to discuss the novel concept of chronic cerebrospinal venous insufficiency in MS.

CME QUESTIONS

1. Novel targets for immunomodulatory therapy in MS include all of the following except:
   a. B lymphocytes
   b. Pyrimidine synthesis
   c. Natural killer cells
   d. Astrocytes

2. Chronic cerebrospinal venous insufficiency is associated with:
   a. Elevated intracranial pressure
   b. Venous sinus thrombosis
   c. Extracranial venous sinus stenosis
   d. Pulmonary hypertension

3. A unique complication associated with alemtuzumab therapy is:
   a. antibody-mediated autoimmunity
   b. macular edema
   c. cardiac conduction block
   d. malignancy

KEYWORDS

1. Multiple Sclerosis
2. Immunotherapy
3. Stem Cells
4. Venous Insufficiency
5. Monoclonal Antibody

Multiple sclerosis (MS) is a complex immunopathologic disorder of the central nervous system (CNS). For the past several years, there have been six agents approved by regulatory agencies to treat relapsing forms of multiple sclerosis (MS): interferon beta-1b, intramuscular interferon beta-1a, subcutaneous interferon beta-1a, glatiramer acetate, natalizumab, and mitoxantrone. Phase III registration trials and post marketing experience have delineated the efficacy, tolerability, and relative safety of these agents. The recent approval of oral fingolimod to the MS therapeutic roster has added a novel agent to our current therapeutic options, but many additional compounds, antibodies, cell therapies, and treatment interventions remain on the horizon.

As a result of animal research, clinical translational studies, and past therapeutic successes, emerging MS therapies are primarily focused on limiting CNS inflammation. Mechanistic approaches include immunomodulation, inhibition of immune cell migration, immunodepletion, and immune cell transplantation. Recently, an alternative theory of MS pathophysiology has been raised: chronic cerebrospinal venous insufficiency (CCVSI). The result has prompted a several studies designed to examine the role of transluminal angioplasty and venous sinus stenting in MS therapy. In this review, we will examine the current list of emerging MS therapies in later phase development and inventory the ongoing clinical trials designed to evaluate their efficacy.

IMMUNOMODULATION

Four immunomodulatory MS therapies in late phase clinical development are teriflunomide, laquinomod, dimethyl fumarate, and daclizumab. While the overall design of these therapies is to modify immune system function in the absence of cell depletion, the modes of action, clinical and MRI data are quite distinct.

*Teriflunomide*

Teriflunomide is an oral, redox silent coenzyme Q antagonist of dihydroorotate dehydrogenase that blocks de novo pyrimidine synthesis.³ Teriflunomide is an active metabolite of leflunomide (Arava), an immunomodulatory and anti-inflammatory prodrug used worldwide for the treatment of rheumatoid arthritis. Teriflunomide reduces T cell and B cell proliferation² and may inhibit tyrosine kinase activation and calcium mobilization.
In an initial Phase II clinical trial, the effects of teriflunomide (7 mg/day or 14 mg/day) on MRI and disease activity were compared to placebo in 179 relapsing-remitting (RRMS) and secondary progressive (SPMS) multiple sclerosis patients. The number of combined unique active lesions, T1 Gad+ lesions, new or enlarging T2 lesions, T2 lesion burden, and proportion of subjects with increased disability were monitored over a 36-week treatment period. Both doses of teriflunomide showed a significant reduction in the median number of combined unique active lesions (0.5 placebo vs. 0.2 teriflunomide 7 mg/day [p < 0.03 vs. placebo] vs. 0.3 teriflunomide 14 mg/day [p < 0.01 vs. placebo]). Teriflunomide-treated subjects had reduced mean T1 Gad+ lesions and reduced mean new or enlarging T2 lesions. Subjects receiving the higher dosage demonstrated reduced median change T2 lesion burden and a reduced proportion of subjects with disability increase. The results of a recently completed Phase III study (TEMSO) were presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting (O’Connor. [2010, October 15]). A placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis: clinical efficacy and safety outcomes. Platform session conducted at the ECTRIMS conference. Abstract retrieved from http://www.congres.ch/ectrims2010.html). Teriflunomide (7 mg or 14 mg/day) was compared to placebo in 1088 RRMS subjects over a 108-week duration. Both doses of teriflunomide showed a significant reduction in the primary outcome measure: annualized relapse rate (Placebo: 0.539 vs. teriflunomide 7 mg: 0.370 [– 31.2%, p=0.0002] vs. teriflunomide 14 mg: 0.369 [– 31.5%, p=0.0005]. The risk for disability progression (sustained for 12 weeks) was significantly reduced only in subjects receiving 14 mg/day of teriflunomide (29.8% [p=0.0279]) but not 7 mg/day (23.7% [p=0.0835]). However, the number of T1 Gad+ lesions (7 mg: 0.570 [– 57.2%, p<0.001]; 14 mg: 0.261 [– 80.4%, p<0.001]), the mean reduction in T2 burden of disease (7 mg: 39.4% [p=0.0317]; 14 mg: 67.4% [p=0.0003]), and the proportion of subjects free of T1 Gad+ lesions (7 mg: 51.4% [p<0.001]; 14 mg: 64.1% [p<0.001]) were significantly reduced in both treatment arms.

Teriflunomide was well tolerated in the Phase II and III trials. There was no difference in the frequency of adverse events (AEs) and severe adverse events (SAEs) in teriflunomide-treated and placebo subjects. The most common reported AEs in teriflunomide-treated subjects were nasopharyngitis, alopecia, nausea, alanine aminotransferase increase, paresthesia, back pain, limb pain, diarrhea, and arthralgias. In the Phase II trial 19 subjects (placebo, n=7; teriflunomide 7 mg/day, n=5; teriflunomide 14 mg/day, n=7) suffered SAEs that included elevated liver enzymes, hepatic dysfunction, neutropenia, rhabdomyolysis, and trigeminal neuralgia. In the TEMSO trial, no difference was observed in the incidence of serious transaminase elevations in treated and untreated subjects. There were no serious infections reported. Eleven pregnancies were reported in the TEMSO trial. There were 4 spontaneous abortions (1 - placebo, 3 - 14 mg/day), 6 induced abortions (5 – 7 mg/day, 1 – 14 mg/day), and 1 healthy baby was delivered in the 14 mg/day treatment group.

A Phase III trial investigating the efficacy of teriflunomide in subjects with high-risk clinically isolated syndromes (CIS) is currently underway. This double blind placebo-controlled trial will enroll 1200 subjects for a 24-month duration. Trial endpoints include relapse rate, expanded disability status scale (EDSS), MRI (T1/T2/black holes, brain volume), and multiple sclerosis functional composite (MSFC).

Laquinomod
Laquinomod is an orally administered quinoline-3-carboxamide derivative that is structurally related to roquinimex (linoamide). Although the direct mechanism of action has yet to be illuminated, possibilities include modulation of Th1/Th2 cytokine axis; increased production of interleukin-4 (IL-4), IL-10 and transforming growth factor b (TGF-β); reduction of MHC-class II gene transcription factors; stimulation of neurotrophin-3 (NT-3), neurotrophin-4 (NT-4) and brain derived neurotrophic factor (BDNF) secretion, promotion of CD8+ T cell and B cell apoptosis; and suppression of the metabolic activity of CD14+ monocyte and natural killer (NK) cells.

In an initial phase Ib clinical trials (LAQ5062), four doses of laquinomod (0.3 mg/day and 0.6 mg/day) were compared to placebo in 283 RMS subjects over a 36-week duration. Only the 0.6 mg/day dosage was effective in meeting the primary outcome measure and demonstrated a 40% reduction (p = 0.0048) in the cumulative number of T1 Gad+ lesions. The same dosage showed a 33% reduction in annualized relapse rate (p = 0.09). In a 36-week extension of the original phase Ib trial (LAQ5063), subjects were either continued on their original laquinomod dosage or switch from placebo to 0.3 mg or 0.6 mg of laquinomod. Subjects maintained on 0.6 mg/day of laquinomod continued to have a significant reduction in the mean number of T1 Gad+ lesions, and subjects switched from placebo to laquinomod showed a significant reduction in T1 Gad+ lesions. Due to the results of the Phase II trials, only the 0.6 mg/day dosage of laquinomod was brought forward into Phase III testing.

There were no differences in the frequency of AEs and SAEs in laquinomod- and placebo-treated subjects in the LAQ5062 and LAQ5063 trials. No opportunistic illnesses were reported in laquinomod-treated subjects, and there were no instances of AEs that characterized linomide: myocardial ischemia, infarction, pleuritis, or pericarditis. SAEs reported in laquinomod-treated subjects included Budd-Chiari syndrome in a Factor V Leiden positive subject, menometrorrhagia associated with myofibroma, liver transaminase elevation, and exacerbation of glaucoma.
Two Phase III trials investigating the efficacy of laquinomod for the treatment of subjects with RRMS are currently underway. The ALLEGRO trial will enroll 1000 subjects for a 24-month placebo-controlled, double masked trial to evaluate oral laquinomod 0.6 mg/day in the treatment of relapsing MS. Trial endpoints include relapse rate, MRI (T1/T2/black holes, brain volume), and MSFC. The BRAVO trial is a 24-month, three-armed trial that includes both placebo and active comparator (β-interferon 1α 30 µg IM). 1200 subjects will be enrolled in a 1:1:1 ratio, and the trial endpoints are identical to the ALLEGRO study.

**Dimethyl Fumarate**

Dimethyl fumarate (BG00012) is an oral fumaric acid ester with a long history of use in treatment of psoriasis. BG00012 is administered 2-3 days daily. The primary metabolite is monomethyl fumarate which has multiple immunomodulatory effects through the activation of nuclear factor E2-related factor-2 transcriptional pathway. BG00012 induces apoptosis of activated T cells and stimulates a Th1 to Th2 cytokine shift. In the murine model of neuroinflammation, experimental autoimmune encephalomyelitis (EAE), dimethyl fumarate demonstrated both anti-inflammatory and neuroprotective properties, elevating IL-10 and producing antioxidant effects.

A Phase II clinical trial compared several dosages of BG00012 to placebo in RRMS subjects. The trial enrolled 257 subjects for a 24-week treatment phase and a 24-week extension. The primary outcome was the total number of T1 Gad+ lesions at 12, 16, 20, and 24 weeks. Secondary outcomes included new or enlarging T2 lesions, T1 black holes, and annualized relapse rate. BG00012 at 240 mg TID was the only dose to achieve the primary outcome measures. This dosage showed a 69% reduction (p < 0.0001) in the total number of T1 Gad+ lesions, a 48% reduction (p = .006) in new or enlarging T2 lesions, and a 53% reduction (p = .01) in T1 black holes. A 32% reduction in annualized relapse rate was not significant.

In the Phase II trial, BG00012 was well tolerated. The incidence of infection was not significantly different in BG00012-treated subjects when compared to placebo. The most common AEs were gastrointestinal problems (10% diarrhea; 11% abdominal pain; 14% nausea), flushing, headache, fatigue. The frequency of AEs decreased significantly following the first month of treatment. SAEs were similar between BG00012-treated and placebo subjects and most were MS relapse-related.

Two Phase III trials investigating the efficacy of BG00012 in RRMS are currently underway. The DEFINE trial will enroll 1011 subjects for a 24-month placebo-controlled, double masked trial to evaluate oral BG00012 (240 mg BID or TID) in the treatment of relapsing MS. The primary endpoint of the trial will be the proportion of relapsing patients. The CONFIRM trial is a 24-month, three-armed trial that includes an active comparator (glatiramer acetate 20 mg SQ daily). Subjects will be enrolled in a 1:1:1 ratio, and the primary endpoint will be annualized relapse rate.

**Daclizumab**

Daclizumab is a humanized IgG1 monoclonal antibody (mAb) against the interleukin-2 (IL-2) receptor (IL-2R) α chain (CD25). The antibody is currently delivered subcutaneously SQ every other week; however, initial successful single center pilot trials on RRMS and SPMS subjects delivered the medication intravenously. The mAb blocks binding of IL-2 to the high-affinity IL-2R inhibiting IL-2R-mediated T cell and B cell activation and down-modulating IL-2R on activated T cells. Daclizumab expands a subpopulation of CD56 bright (CD56b) NK cells that can lyse activated autologous T cells and augment NK cell function. The expansion of CD56b NK cells is inversely proportional to T1 Gad+ lesion load in daclizumab-treated subjects suggesting that this mechanism plays an important role in the immunomodulatory action of the mAb.

A recent placebo-controlled Phase II trial, daclizumab (1 mg/kg SQ every 2 weeks alternating with placebo or 2 mg/kg SQ q 2 weeks) was evaluated in 230 RRMS subjects failing β-interferon. Enrolled subjects required either stable β-interferon therapy for 6 months with 1 clinical relapse or stable β-interferon therapy for 1 year with one or more T1 Gad+ lesions. The treatment phase lasted 24 weeks and was followed by a 48-week washout phase. The 2 mg/kg dose of daclizumab demonstrated a 72% reduction (p < 0.004) in the primary outcome measure: mean number of T1 Gad+ lesions. A significant reduction was also observed on new or enlarging T2 lesions (68%, [p = .007]); however, there was no significant effect on the volume of T1 black hole or T2 lesions nor the annualized relapse rate. The MRI activity returned to baseline quickly during washout period. Interestingly, consistent with one of the presumed mechanisms of action, CD56b NK cells were 8-9x higher in daclizumab-treated subjects.

There was no difference in frequency of AEs and SAEs between daclizumab-treated and placebo subjects. The most common AEs were gastrointestinal disorders, fatigue, cutaneous reactions, and infections; no novel autoimmune disorders were observed. Two malignancies were reported: breast cancer and pseudomyxoma peritonei. SAEs were elevated in daclizumab-treated versus placebo subjects (13% versus 5%). Most were infections (5% daclizumab vs. 1% placebo).

There are two ongoing clinical trials investigating the efficacy of daclizumab in RRMS. Both trials use daclizumab high-yield process (DAC HYP), a new high concentration, liquid formulation of the mAb developed to reduce the frequency of subcutaneous delivery. The SELECT trial is a Phase IIb trial that will enroll 600 RRMS subjects for a 48-week placebo-controlled, double masked trial to evaluate the relative efficacy of two dosages of DAC HYP (150 mg or 300 mg SQ monthly). The primary endpoint of the
trials will be the reduction in the annualized relapse rate. The secondary endpoint will be the reduction in new or enlarged T1 Gad+ lesions. The DECIDE trial is a two-armed trial (96-144 week duration) that compares DAC HYP (150 mg SQ monthly) to an active comparator (β-interferon 1a 30 µg IM weekly). The primary outcome measure is relapse rate; secondary endpoints include reduction in disability progression, MRI outcomes, improvement in quality-of-life indices.

CELL MIGRATION
There are two FDA-approved medications for the treatment of relapsing MS that primarily affect immune cell migration: natalizumab and oral fingolimod. Natalizumab is a humanized anti-very late antigen 4 (VLA4) mAb that inhibits activated leukocyte migration across the blood-brain barrier. Oral VLA-4 inhibitors have been developed but currently there are no active Phase II or Phase II clinical trials in progress. This is likely due to significant concerns for the risk of progressive multifocal leukoencephalopathy (PML) in treated subjects. Once risk-modification strategies are developed for PML in natalizumab-treated patients, new oral inhibitors may emerge into the developmental pipeline. Oral fingolimod is a S1P receptor agonist that prevents lymphocyte egress from secondary lymphoid organs. There is a novel S1P receptor agonist with enhanced S1P_3 selectivity (ONO-4641) that is currently in Phase II clinical testing (DreaMS). Three dosages of ONO-4641 (0.05, 0.1 or 0.15 mg daily) are being evaluated in a 26-week, placebo-controlled trial with 1:1:1:1 enrollment. The primary endpoint is the total number of T1 Gad+ lesions. Multiple pharmaceutical companies are currently developing a variety of S1P receptor agonists with varying subtype selectivities. The ultimate objective is to maintain or improve clinical efficacy while limiting significant adverse events such as first-dose bradycarrhythmias.

IMMUNODEPLETION
Immunodepleting strategies have a long history in the treatment of MS. Older non-selective agents such as cyclophosphamide and azathioprine have been used off-label under varying clinical circumstances for years, and in October 2000, mitoxantrone was approved for the treatment of patients with secondary progressive, progressive relapsing or worsening relapsing-remitting multiple sclerosis. Two novel immunodepleting strategies have reached Phase III clinical testing in MS. Both are centered on the use of mAb technology but their targets, efficacy and adverse events are distinct.

Alemtuzumab
Alemtuzumab is a humanized mAb directed against CD52 antigen. CD52 is a cell surface glycoprotein of unknown function that is present on >95% of T cells, B cells (not plasma cells), monocytes, and eosinophils. Following intravenous infusion, there is targeted depletion of CD52-expressing cells within 2 days with a rapid destruction of B cells, T cells, monocytes by complement-dependent (CDC) and antibody-dependent cell-mediated (ADCC) cytotoxicity. The result is a prolonged lymphopenia and reduced CNS inflammation. T cells recover over 16 months, whereas B cells recover over 3 to 6 months.

The clinical efficacy of alemtuzumab was originally investigated in small single center pilot trials using SPMS subjects. While there were significant reductions in relapse rate and MRI activity, there was no significant reduction in disability progression. Focus was then diverted to the treatment of earlier relapsing disease, and a Phase II clinical trial was conducted comparing two doses of intravenous alemtuzumab (12 mg/day or 24 mg/day for 5 d at month 0 and 3 d at month 12 and 24) to an active comparator β-interferon 1a 44 μg SQ tiw. 334 RRMS patients were enrolled in the 36-month protocol; however, dosing of alemtuzumab was halted during the trial when a fatality occurred in the alemtuzumab arm due to the complications of idiopathic thrombocytopenic purpura (ITP). As a result, only some subjects received alemtuzumab at 24 months. Despite the abrupt interruption in alemtuzumab administration, clinical and MRI data demonstrated strong efficacy in the alemtuzumab-treated subjects. Both doses of alemtuzumab showed 72% reduction (p < 0.001) in annualized relapse rate and 71% reduction (p < 0.001) in 6-month sustained disability progression versus high frequency β-interferon 1a. Secondary outcomes were equally impressive with a 55% reduction (p = 0.005) in mean T2 lesion load and reduced brain atrophy (change T1-weighted brain volume: -0.2 vs. 0.9 [p = 0.02]).

Several safety concerns, however, were identified in alemtuzumab-treated subjects. There were an increased number of infections associated with alemtuzumab treatment (66% alemtuzumab vs. 47% β-interferon 1a) and sporadic alemtuzumab-induced infusion reactions. Of particularly novel concern was the significantly increased incidence of antibody-mediated autoimmunity in alemtuzumab-treated subjects. Conditions observed included Grave’s disease (23%), ITP (2.7%), and Goodpastures Syndrome (1%). The frequency of SAEs was not different among the treatment groups. The frequency of serious infusion reactions was 1.4%.

As noted previously, there was a fatal hemorrhage secondary to ITP that halted the 24-month infusion in most subjects. Malignancies included non–EBV-associated Burkitt’s lymphoma, breast cancer, and cervical cancer in situ.

There are two ongoing Phase III clinical trials investigating the efficacy of alemtuzumab in RRMS (CARE-MS I and CARE-MS II). In CARE-MS I, alemtuzumab (2 annual cycles of 12 mg/day for 5 days) is being compared to β-interferon 1a 44 μg SQ tiw in a 24-month, double-masked trial enrolling 525 RRMS patients with 2:1 enrollment favoring alemtuzumab. The primary endpoints are reduction in the annualized relapse rate and time to sustained disability progression. In
CARE-MS II, 1200 RRMS patients, relapsing on glatiramer acetate or β-interferon 1a, are being enrolled 2:2:1 in a 24-month trial to compare two doses of alemtuzumab (12 mg/day or 24 mg/day) to β-interferon 1a 44 mg SQ tiw. The primary endpoints are reduction in the annualized relapse rate and time to sustained disability progression.

**Rituximab/Ocrelizumab**

Rituximab and ocrelizumab are mAbs against the CD20 antigen. Rituximab is a chimeric murine-human mAb; whereas, ocrelizumab is a humanized mAb. Due to their engineering, there are slight differences in the effector function of the mAbs on CD20-bearing cells. Ocrelizumab has 3-4x lower CDC activity and 2-5x greater ADCC activity than rituximab. CD20 is a cell surface protein on pre-B cells, naïve B cells, memory B cells than is absent on plasmablasts and mature plasma cells. The intravenous infusion of rituximab or ocrelizumab causes a rapid and targeted depletion of CD20-expressing naïve and memory B cells resulting in the loss of B cell antigen presentation, a potential reduction in B cell proinflammatory mediators, and a potential redistribution of proinflammatory and regulatory B cell populations.21-23 The mAbs are reinfused at 24-week intervals when the B cell population begins to reconstitute.

Phase II clinical trials were recently completed for rituximab and ocrelizumab. 104 RRMS subjects were evaluated in a 48-week placebo controlled trial using a single treatment with rituximab at study onset (1000 mg IV on days 1 and 15).21 In the rituximab-treated population, there was a 91% reduction (p < 0.001) in total T1 Gad+ lesions at weeks 12, 16, 20, and 24 and a 50% reduction (p = 0.04) in the proportion of relapsing patients. The results of a Phase II ocrelizumab trial were recently presented at the 2010 ECTRIMS meeting (Kappos. [2010, October 15]. Efficacy and safety of ocrelizumab in patients with relapsing–remitting multiple sclerosis: results of a phase II randomized placebo-controlled multicentre trial. Platform session conducted at the ECTRIMS conference. Abstract retrieved from http://www.congrex.ch/ectrims2010.html). The Phase II study enrolled 220 RRMS subjects for a 24-week placebo controlled study investigating two doses of ocrelizumab (600 or 2000 mg IV on days 1 and 15) and an active comparator (β- interferon 1a 30 mg IM weekly). Both doses of ocrelizumab showed significant effects on the total number of T1 Gad+ lesions at weeks 12, 16, 20 and 24 versus placebo: 600 mg (90% reduction [p < 0.001]) and 2000 mg (96% reduction [p < 0.001]). Similarly, both doses significantly reduced the annualized relapse rate versus placebo: 600 mg (80% reduction [p < 0.001]) and 2000 mg (73% reduction [p < 0.001]). Both ocrelizumab groups were superior to β-interferon 1a for the primary endpoint. There was no clear dose separation on the efficacy endpoints. Future Phase III investigations with anti-CD20 therapy will be limited to ocrelizumab.

There was no significant difference in the frequency of SAEs between rituximab- or ocrelizumab-treated, placebo, and β-interferon 1a subjects in the respective Phase II trials. Infusion-related adverse events were significantly higher in the first 24 hours following anti-CD20 treatment: rituximab (78.3% versus 40% placebo)21 and ocrelizumab placebo (34.5% and 43.6% for 600 mg and 2000 mg doses versus 9.3% placebo). Infusion reactions were predominantly mild to moderate and decreased to rates comparable to placebo with the second infusion. There were an equal frequency of infections in the treatment groups, and no opportunistic infections were observed. There was a single death in an ocrelizumab-treated subject due to acute onset thrombotic microangiopathy. The death occurred following a bee sting and may have been secondary to systemic inflammatory response syndrome.

**CELL THERAPIES**

Advancement in our understanding of adult stem cell biology has led to significant progress in the field of cell therapy in MS. Autologous hematopoietic stem cell transplantation (AHsCT) and mesenchymal stem cell transplantation (MSC) offer two alternative approaches to cell-based immunotherapy in MS. The use of AHsCT has already been shown to be a powerful, high-risk therapy for some forms of MS, while the study of MSC in MS is just initiating a Phase I investigation.

**Autologous Hematopoietic Stem Cell Transplantation (AHsCT)**

AHsCT is a common treatment strategy proposed for severe autoimmune disorders. The therapeutic mechanism centers on intense immunosuppression with destruction of autoreactive cells followed by immune reconstitution resulting in qualitative changes in the reconstituted immune repertoire.22, 23 Although the renewed immune repertoire is established with naive CD4+ T cells of recent thymic origin, self-reactive T cells may persist after transplantation.

The AHsCT procedure is accomplished through several distinct steps. First, peripheral blood stem cells (PBSCs) are mobilized from marrow stores. Following mobilization, PBSCs are collected by leukopheresis and cryopreserved. Prior to grafting, the collected PBSCs are conditioned for subsequent transplantation through positive (CD34+ stem cells) and negative (T cell) selection. Before receiving the graft, the recipient is conditioned through a high, medium or low intensity protocol. High intensity protocols include total body irradiation or busulphan-containing chemotherapy. Medium intensity protocols include BEAM chemotherapy (BCNU, Carmustine, etoposide, Cytosine-arabinoside, melphalan), Carmustine, or cyclophosphamide. Low intensity protocols generally involve cyclophosphamide or fludarabine treatment. The conditioned PBSCs are subsequently reinfused with antithymocyte globulin (ATG) and re-engraftment occurs.
Initial Phase I/II studies\textsuperscript{24, 25} of AHSCRT in MS showed limited therapeutic success. This was likely due to the enrollment of multiple disease forms and the use of diverse treatment protocols. Overall, the progression-free survival favored the AHSCRT treatment groups with 60-70% of the treated subjects remaining stable at 3 years and 50-60% at 6-8 years. Subsequent studies have focused on early, aggressive forms of disease. AHSCRT was examined in 50 subjects with either early RRMS (EDSS 1.5) or late SPMS (EDSS 8.0) disease.\textsuperscript{26} EDSS improved at least 0.5 points in 62% of patients, particularly in those who were treated early in their disease course. Overall, progression-free survival was 72% at 6 years. The Canadian MS BMT Study evaluated 17 aggressive MS patients with AHSCRT using a high-intensity conditioning regimen.\textsuperscript{27} Of the subjects, 75% showed progression-free survival at 3 years, and there were no relapses or new MRI lesions nearly 5 years following treatment. A Phase I/II Low Intensity AHSCRT Trial was recently completed.\textsuperscript{28} 21 RRMS patients with mild disability and short disease duration were subjected to a low-intensity conditioning regimen of cyclophosphamide 200 mg/kg followed by alemtuzumab or ATG. Of the subjects, 81% showed a 1-point EDSS improvement at years and 62% of the subjects were disease free at 3 years. AHSCRT has also proven to be successful in individual case studies of MS subjects with rapidly evolving, “malignant” disease.\textsuperscript{29, 30} In these cases, AHSCRT was able to halt disease progression and reverse disability in individuals that were refractory to conventional treatments.

One of the major drawbacks of AHSCRT is the high rate of mortality, approximately ~5.3-6% across trials. Most of the mortality was secondary to myelotoxic or infectious sequelae of the procedure. AHSCRT with low intensity conditioning may significantly lower the frequency of these issues but may not sufficiently clear autoreactive clones from the repertoire.

There are two ongoing studies of AHSCRT in MS. The Halt-MS study is a multicenter US trial involving BEAM conditioning, ATG and CD34+ cell selection in RRMS or relapsing-progressive MS subjects. A second study involves the use of stem cell therapy for patients with MS failing interferon. The Phase II ASTIMS (Autologous Stem cell Transplantation International Multiple Sclerosis) study comparing AHSCRT and mitoxantrone was recently stopped for the insufficient accrual of patients.

\textbf{Mesenchymal Stem Cell Transplantation}  

MSCT involves the transfer of autologous multipotential stromal precursors (MSCs) isolated from bone marrow. Similar cells with the phenotype of MSCs may be present in the perivascular region.\textsuperscript{31, 32} Recent studies have demonstrated that MSCs have regulatory effects of the innate and adaptive immune systems\textsuperscript{33} and may have the ability to differentiate into unrelated germ lineages including neural cells.\textsuperscript{34, 35} The immunomodulatory effects of MSCs include the inhibition of T cell proliferation in-vitro.\textsuperscript{36, 37} the inhibition of B cell proliferation and differentiation in vitro,\textsuperscript{38-40} the production of immunosuppressive factors such as indoleamine 2,3 dioxygenase and nitric oxide,\textsuperscript{41} and the impairment of dendritic cell maturation.\textsuperscript{42, 43} Injection of MSCs have been shown to ameliorate murine EAE.\textsuperscript{44} An international, multicenter Phase I trial is currently underway.

\textbf{CIRCULATORY THERAPY}  

A recent publication has reported a significant incidence of chronic cerebrospinal venous insufficiency (CCSVI) in individuals with MS.\textsuperscript{45} CCSVI is defined as chronic impaired venous drainage from the central nervous system and is operationally diagnosed by the observation of at least 2 of 5 patterns of anomalous CNS venous drainage by ultrasound: (1) reflux in the internal jugular (IJV) and vertebral veins (VV); (2) reflux in the deep cerebral veins; (3) high-resolution B-mode evidence of IJV stenosis; (4) flow not detectable by Doppler in the IJV and/or the VV; or (5) reversed postural control of the main cerebral venous outflow pathways. In the initial study of 65 MS patients and 235 controls, there was 100% sensitivity, 100% specificity, 100% positive predictive value, and 100% negative predictive value.\textsuperscript{46} CCSVI was not observed in neurologic disease controls including Parkinson’s, amyotrophic lateral sclerosis, cerebrovascular disease, myasthenia gravis, and multifocal motor neuropathy. Selective catheterization demonstrated stenosis of the azygous veins (AV) in 86% of patients and the IJV in 91% of patients. It is hypothesized that CCSVI causes venous reflux leading to iron buildup in the brain and subsequent CNS injury.\textsuperscript{47}

As a result of these clinical observations, an 18-month observational single center trial was performed on 65 MS subjects using transluminal angioplasty study.\textsuperscript{47} During the trial, subjects remained on their disease-modifying therapy. 35 of 65 treated subjects improved in some clinical outcomes. 47% of the treated subjects had restenosis. The study design, however, was flawed by the small sample size, lack of controls, lack of standard MRI protocols, and unblinded neurologic evaluations. Nevertheless, the favorable results have prompted several centers to provide off-label treatment of MS subjects at significant cost.

Is there truly a strong association between CCSVI and MS? And, if so, is the association due to correlation or causation? Ultrasound is a rather poor modality for ultrasound between CCSVI and MS.\textsuperscript{48} There were 235 controls, there was 100% sensitivity, 100% specificity, 100% positive predictive value, and 100% negative predictive value.\textsuperscript{49} CCSVI was not observed in neurologic disease controls including Parkinson’s, amyotrophic lateral sclerosis, cerebrovascular disease, myasthenia gravis, and multifocal motor neuropathy. Selective catheterization demonstrated stenosis of the azygous veins (AV) in 86% of patients and the IJV in 91% of patients. It is hypothesized that CCSVI causes venous reflux leading to iron buildup in the brain and subsequent CNS injury.\textsuperscript{46}
other neurodegenerative disorders, an association between CCSVI and MS will need to address several key questions to establish a causal link. Examples include:

- How does mechanism explain female bias towards disease in MS?
- How does mechanism explain HLA-DR bias? Other genetic links?
- What is the link with geography, vitamin D, EBV?
- Why is MS pathology not observed after radical neck procedures or venous sinus thrombosis or stenosis?

SUMMARY
The future of MS therapeutics remains bright. Endeavors are being made along multiple fronts to address inflammatory injury, and new theories are being proposed to challenge current paradigms. Over the next decade, MS patients and their caregivers will have a large number of therapies to choose from for the treatment of relapsing disease. Anticipated benefits include multiple routes of administration (subcutaneous, intravenous, oral), improved tolerability, and greater efficacy. The use of new therapies, however, will be accompanied by long-term safety concerns such as those observed with natalizumab. The balance of efficacy, safety, and tolerability data will ultimately determine the adoption of new medications into the MS treatment algorithm.

CME ANSWERS
1. D
2. C
3. A

REFERENCES


LEARNING OBJECTIVES
1. The attendee will be able to describe the features of the radiologically isolated syndrome and its implications for the development of multiple sclerosis (MS).
2. The attendee will be able to explain the risks and benefits of treating patients with the clinically isolated syndrome.
3. The attendee will be able to discuss the entity of benign MS.
4. The attendee will be able to discuss the options for switching therapies in patients with active MS.

CME QUESTIONS
1. In a period of less than 5 years, approximately what percentage of patients with a radiologically isolated syndrome consistent with MS develop a clinically isolated syndrome or clinically definite MS?
   A) 10%
   B) 15%
   C) 20%
   D) 30%
   E) 50%
2. The risk of developing MS with a clinically isolated syndrome such as optic neuritis and an MRI scan showing multiple high signal abnormalities over a 15 year period is:
   A) 10 to 20%
   B) 30 to 40%
   C) 50 to 60%
   D) 70 to 90%
   E) 100%
3. True or False. The MRI scan has no predictive value in the clinical course of MS.

INTRODUCTION
When to start or switch MS therapy is a hotly debated topic. In this talk, we will examine the issues surrounding the initiation of therapy for those patients with the clinically isolated syndrome, the radiologically isolated syndrome and benign MS. Since none of our therapies are curative, many patients continue to have disease activity. There are no large randomized prospective studies that guide the switching of therapy for MS patients. Nonetheless, there are clinical and MRI criteria that predict recurrent demyelinating disease and these outcome measures may be used until better studies can be performed.

STARTING THERAPY: THE CLINICALLY ISOLATED SYNDROME AND EARLY MS
The majority of patients with multiple sclerosis (MS) present with a relapsing course. Nearly all of these patients manifest with a clinically isolated syndrome, a term used to describe patients with their first demyelinating neurological event. The three most common clinically isolated syndromes associated with MS include optic neuritis, brainstem disorders and spinal cord syndromes. Patients with the clinically isolated syndrome may be classified as being high risk vs. low risk for the development of MS by virtue of their baseline brain MRI scan. Two long term natural history studies have defined the risk to be about 20 to 25% for those with a normal brain MRI at baseline while those that harbor typical demyelinating lesions may have a risk of clinically definite MS (CDMS) in the 70 to 90% range over a fifteen year observation period (1, 2).

Some have argued that optic neuritis presentations have a better prognosis regarding the conversion to MS. This only appears to be true for those patients with a normal baseline brain MRI. In a series of 320 clinically isolated patients, baseline MRI was normal in 49.2% patients with...
optic neuritis as compared to 24% in patients presenting with brainstem and spinal cord syndromes\textsuperscript{10}. However, when patients with abnormal baseline brain MRI’s were considered, there were no differences for clinical or MRI conversion to MS. Although optic neuritis patients have less conversion to MS overall, this is not the case when they have an abnormal baseline brain MRI. In this situation the conversion to MS is similar to those with brainstem and spinal cord presentations.

Several phase 3 clinical trials have examined the benefits of therapy in the clinically isolated syndrome patient. All the platform drugs including intramuscular interferon beta 1a, subcutaneous interferon beta 1a, subcutaneous interferon beta 1b and glatiramer acetate have been shown to be beneficial in this population of patients in delaying the onset of CDMS\textsuperscript{4-7}.

The main criticism of these studies is that they have been short term and none of them have shown a sustained disability benefit. Furthermore, the drugs are highly expensive costing tens of thousands of dollars per year and injections are required. Furthermore, side effects which are largely manageable can be limiting. Patients taking the interferons frequently experience flu-like side effects which can improve over time, but a small minority of patients continue to suffer from chills, fever, fatigue and muscle aches around the time of their injection. Patients on glatiramer acetate do not have flu-like side effects, but they may experience frequent injection site reactions, lipoatrophy and a self limited panic attack condition characterized chest pain, palpitations and anxiety.

Those wanting to defer treatment feel that a certain percentage of patients will have benign MS\textsuperscript{8}. Unfortunately, such a designation can only be made in retrospect. In a recent study of “benign MS” patients, half of them experienced worsening disability over the next decade\textsuperscript{10}. Disability accumulates in MS patients over a prolonged period of time. The longer you follow patients, the greater percentage of them that develop disability. One of the biggest problems is defining benign MS. MRI, cognitive dysfunction and OCT studies would suggest that these patients have ongoing disease not detected by their Kurtzke score. Cognitive impairment can occur early in MS and the frequency of involvement has varied from 20 to 60% over the past decade\textsuperscript{10,15}. In one series of clinically isolated syndrome patients, nearly 60% of patients had evidence of cognitive dysfunction\textsuperscript{10}. Our definition of benign MS is limited to the tools that we currently use. As our examination and imaging techniques improve, we recognize a very tiny minority of patients have truly benign MS. We are only beginning to learn now that MS is a more continuous disease and that lesions that are silent today may be extremely important a decade or two later to the individual patient.

Nonetheless, evidence has accumulated from multiple spheres to show the benefits of therapy for the high risk clinically isolated syndrome patient. I favor an aggressive approach to the treatment of the high risk patient based on the following pieces of a data. Both fatigue and cognitive dysfunction can occur without obvious change on conventional imaging. Recent advances in neuro-imaging have demonstrated that a significant amount of the disease burden in MS actually lies in the gray matter. This gray matter burden may better correlate with disability progression, fatigue and cognitive dysfunction\textsuperscript{12,13}.

In reality, there is a significant amount of MS disease burden that starts subclinically, manifesting as gadolinium enhancement and new T2 lesions. Initially, there was reassurance that a patient could have significant amount of disease burden and look good clinically. Unfortunately, there can be a significant time lag between what we see on neuro-imaging and what happens to the patient clinically. In a study by Rudick et al., they found that the accumulation of lesion burden on brain MRI in the first two years of the disease predicted brain atrophy and physical disability 13 years later\textsuperscript{14}. We now recognize that axonal degeneration may be at its height in the earliest phases of the disease and its presence correlates well with disability\textsuperscript{15,16}.

Perhaps, the most compelling reason to consider early treatment is the fact that the vast majority of patients in the high risk category of disease have a new MRI lesion within 2 years fulfilling the McDonald criteria for MS\textsuperscript{17}. In the CHAMPS study, 82 % of the patients had a new T2 MRI lesion within 18 months of onset while 85% of patients in the BENEFIT trial had a new lesion within 3 years\textsuperscript{18-20}.

In the CHAMPIONS study, a post hoc analysis of the immediately treated vs. the delayed treated group of patients initially enrolled in the CHAMPS study showed that the delayed treated group (beginning therapy on average 30 months from initial enrollment in the trial), there was still a 40% difference in conversion to CDMS favoring the immediately treated group\textsuperscript{20}. This difference was still evident at 10 years and the delayed treated group also had twice the relapse rate. Although there was not a disability difference found between the delayed and immediately treated groups, it must be remembered that patients in the placebo arm who had conversion to CDMS were offered therapy at that time. Therefore, meaningful disability data was not obtained in the CHAMPS or CHAMPIONS studies. Nonetheless, the disability in both groups was quite low at 10 years. Only 9% of patients had an EDSS score greater than 4.0, much less than expected from natural history studies (unpublished data from the CHAMPIONS study).

Further impetus to treat the CIS patient comes from natural history studies that demonstrate that the relapse rate in the first 2 years is strongly predictive of subsequent disability\textsuperscript{21,22}.
In the pivotal trial of intramuscular interferon beta 1-a, patients initially randomized to drug had significantly less progression to an EDSS score of 4.0, eight years later when compared to those initially in the placebo arm. This is similar to the findings observed in the pivotal trial of subcutaneous interferon beta 1a. These long term observations from the pivotal interferon trials suggest that there is an irreversible penalty for delaying the onset of therapy.

THE RADIOLOGICALLY ISOLATED SYNDROME (RIS)

The increasing use of magnetic resonance imaging (MRI) of the brain to evaluate a wide variety of neurological complaints has lead to the discovery of patients who are in the preclinical stages of MS. These patients may show lesions that are disseminated in space and fulfill the Barkof criteria (3 out of the following 4): 1) 9 T2 lesions or gadolinium enhanced lesion 2) 3 periventricular lesions, 3) an infratentorial lesion including spinal lesions and a 4) juxtacortical lesion. In attempt to balance sensitivity and specificity for the diagnosis of MS, neuro-imaging criteria for the diagnosis of MS have evolved over the last decade. In 2005, the McDonald criteria allowed for the diagnosis of MS by establishing imaging criteria for lesions that are disseminated in space and time. Dissemination in space (DIS) was achieved by fulfilling the Barkof described above and dissemination in time (DIT) was fulfilled by showing either a new gadolinium lesion 3 months after the initial clinical event or a new T2 lesion compared to a baseline scan obtained at least one month after the clinical event (Table 1).

The McDonald criteria require at least one clinical event. More recently, studies have defined of group of patients who have been scanned and found to have radiological findings suggesting a demyelinating process without a clinical event. These patients are classified as having a radiologically isolated syndrome. In 2009, Okada et al. reported 44 patients from UCSF. Among 30 patients followed clinically, 10 patients (33%) developed a clinically isolated syndrome with a median observation period of 5.4 years. In addition, 59% of patients (24/41) developed a new radiological lesion confirming dissemination in time over a median follow-up period of 2.7 years. Of note, 12% of the patients in this cohort were treated with immunomodulatory therapy before the onset of a clinical event. Detecting spinal cord demyelination in these patients may be the most predictive factor for the subsequent development of clinical demyelinating disease.

Table 1. Summary of MRI and Clinical Outcomes of Radiologically Isolated Syndrome Reports

<table>
<thead>
<tr>
<th>Authors, years of publication, country of survey</th>
<th>MRI-based DIT (median time until DIT, range)</th>
<th>Clinical DIT (median time until DIT, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okuda et al., (2009) USA</td>
<td>24/41 (59%)</td>
<td>10/30 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>2.7 years (0.1-26.0)</td>
<td>5.4 years (1.1-9.8)</td>
</tr>
<tr>
<td>Lebrun et al. (2009) France</td>
<td>64/70 (91%)</td>
<td>23/70 (32.9%)</td>
</tr>
<tr>
<td></td>
<td>3-30 months</td>
<td>2.3 years (0.8-5.0)</td>
</tr>
<tr>
<td>Silva et al. (2009) Turkey and USA</td>
<td>N/A</td>
<td>8/22 (36.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.4 years (2.6-111.0)</td>
</tr>
<tr>
<td>Summary</td>
<td>88/111 (79.3%)</td>
<td>41/136 (30.1%)</td>
</tr>
</tbody>
</table>

* Table modified from Sellner, et al.: J Neurol, published online May 26, 2010.
Lebrun et al. published a French series of RIS patients; 23 out 70 (33%) of these patients developed a first demyelinating event after a mean of 2.7 years and 64/70 (91%) had a new MRI lesion. 12/23 (52%) of patients developing CIS were treated with immunomodulatory therapy and 10% of patients received therapy with just the radiological findings. These two studies suggest that asymptomatic MS is not an infrequent finding in patients undergoing brain MRI for other conditions such as head trauma and migraine headaches. Spinal cord lesions have not been well studied in patients with the radiologically isolated syndrome. In general, spinal cord MRI’s have been helpful in establishing DIS and not DIT.

There are no guidelines regarding the management of these patients. I recommend serial imaging on an every 6 month basis for one year and then yearly thereafter. I favor doing a spinal tap on these patients to look for oligoclonal banding and to firm up the notion that these T2 lesions have an inflammatory etiology. If the patient has a clinical event, I will offer them immunomodulatory therapy. I will also strongly consider immunomodulatory therapy for the patient who has a new MRI lesion and positive oligoclonal banding.

BENIGN MS

As briefly discussed above, the definition of benign MS has been long debated. Initially, the term was used to describe a patient who was socially and occupationally unimpaired even though they may not be symptom free. The most common definition of benign MS has been an EDSS score of 3.0 or less for a period of at least 10 years after disease onset. Wide variations in the estimates of benign MS partly reflect the various definitions used to define the entity, but most estimates have put the number in the 5 to 25% range. Most studies suggest a more aggressive course when the age of disease onset is >40 years, there is a progressive course, pyramidal or cerebellar dysfunction at onset, short interval between relapses and high EDSS score at onset and five years later. In one 10 year study, a cutoff of an EDSS of ≤2.0 yielded 14.5% benign patients while increasing the score to ≤3.0 gave a frequency of 26.3%. Other studies have shown that even when using a definition of benign MS as an EDSS of ≤2.0 at 10 years of disease onset that one-third to one half of these patients can convert to a non-benign course over the next 10 years.

There is no reliable clinical, demographic, genetic or imaging marker that can predict a benign course. In fact, MRI studies have shown that patients with benign MS and progressive and secondary progressive MS do not have major differences in their amount of disease burden. Most authorities have suggested that this apparent conundrum may be explained by more axonal loss in the secondary progressive disease. In support of the concept that axonal loss plays a critical role in disease course, patients with benign MS (EDSS <2.0 for 15 years) have low rates off brain atrophy over 2 years when compared to patients with early MS (less than 5 years in duration). By largely relying on EDSS scores, our current scales to determine benign MS lack vital information about their vision and cognitive performance. In a recent study of 62 patients with benign MS, Rovaris et al. found that 12 patients had cognitive impairment and MRI findings similar to those patients with secondary progressive MS. Portaccio et al. have also shown that cognitive changes in patients thought to have benign MS predict subsequent disease progression. Non motor symptoms such as depression, fatigue, and pain are also poorly captured by the EDSS. In fact, studies have shown that such non-motor symptoms may play a prominent role in the life of a MS patient irrespective of their disability scores and duration of disease. In one study, depressive symptoms were highly correlated with unemployment in MS and this finding ran independent of their EDSS score. In practice, it is very difficult not to offer immunomodulatory therapy to the patient presenting with a high risk clinically isolated syndrome. The important point to be made here is that the diagnosis of benign MS can only be made in retrospect and it may take decades to be confident about this prognosis. The wide variety of definitions and the incomplete assessment of neurological dysfunction (limited visual, cognitive and fatigue information in the EDSS scores) only add to the confusion regarding the existence of truly benign MS.

SWITCHING THERAPIES

Any statement about switching therapies has to be tempered by the fact that there are no large prospective studies that demonstrate any benefit to switching therapy. Furthermore, there is no consensus as to what constitutes treatment failure. Two prospective studies have a slight benefit of interferon beta subcutaneously (Betaseron and Rebif) over interferon beta intramuscularly (Avonex), but these are limited by their short duration of observation (less than 2 years) and the fact that persistently high neutralizing antibodies tend to have their negative effect years after treatment initiation. Although these studies did not examine the issue of switching therapies, they have provided the rationale for authorities to recommend switching from IM interferon (low dose) to a subcutaneous version (high dose) in patients deemed to be treatment failures.

Most of the earlier retrospective studies confirm no benefit of switching from one platform therapy (interferon beta or glatiramer acetate) to another. The Quality Assessment in MS therapy (QUASIMS) study examined the charts of 4754 patients on interferon beta and found that the products had similar effectiveness in terms of relapse reduction and disability progression and there was no benefit to switching amongst the interferon products. The benefits of therapy were superior when the interferons were used as initial therapy compared to their use as a follow-up therapy.
Recent head to head studies have shown no significant treatment differences between interferon beta and glatiramer acetate. In the BECOME trial, no differences were found in clinical and imaging findings at 24 months when comparing interferon beta 1b (Betaseron) to glatiramer acetate. Likewise, in the REGARD trial, no significant differences were observed between glatiramer acetate and interferon beta 1a (Rebif) in terms of relapse rate. Unfortunately, the REGARD trial was underpowered because the relapse rate in both groups was lower than expected \(^{(39-41)}\).

More recently, there are several retrospective studies that suggest switching from a platform drug may be highly effective \(^{(42-44)}\). Some have argued that the large QUASIMS study did not stratify patients in terms of treatment failure vs. other reasons for switching therapy. In one large retrospective study that examined patients based on treatment failure, there was a benefit in going from one interferon therapy to another \(^{(42)}\). These findings included patients that had neutralizing antibodies on high dose interferon beta and switched to IM once a week regimen.

In a study from Argentina, 112 patients with relapsing remitting MS were switched from one platform therapy to another \(^{(45)}\). The majority of patients switched because of inadequate response (60% of interferon beta patients and 75% of glatiramer acetate patients). All switches were deemed to be associated with a better outcome. Outcome was considered better when going from an interferon beta to glatiramer acetate or an immunosuppressant and less robust when switching from glatiramer acetate to interferon beta or from intramuscular interferon beta (low dose) to subcutaneous interferon beta. However, the number of patients in this study was small, particularly in the group switching from glatiramer acetate to interferon beta. These observational studies have suggested a benefit to switching therapy. Switching patient therapy based on one’s judgment of treatment failure is reasonable until randomized controlled trials comparing the platform drugs are completed. The CombiRx study which a large randomized controlled trial is comparing intramuscular interferon beta to glatiramer acetate. There is an arm that will also receive both products together. Enrollment of this study was completed in the spring 2009. This 3 year study should report results within the next 2 years.

The decision to switch from one platform drug has to be discussed with the patient. Some patients are willing to switch to natalizumab when failing either glatiramer acetate or interferon beta while others are not. In this case, patients are often willing to switch to another platform drug (glatiramer acetate or interferon beta). Most authorities would consider treatment failure when the patient has had 2 or more relapses per year which is above average for the untreated patient \(^{(43)}\) (Table 2). In earlier clinical trials, the placebo patients were averaging 1 relapse per year since seems to a reasonable number of relapses to declare treatment failure. Disability progression of 1.0 sustained for 6 months is another reasonable criterion to consider changing therapy. In a 8 year retrospective analysis of patients in the original phase 3 double blind placebo control trial of intramuscular interferon beta 1-a, worsening of 1 point on EDSS scale lasting 6 months was the most powerful predictor of disability 8 years after randomization \(^{(46)}\).

### Table 2. A Set of Criteria for Treatment Failure

1. More than 2 relapses in one year
2. Disability progression of 1.0 sustained for 6 months
3. Worsening cognitive or visual dysfunction
4. Neuroimaging: 1 gadolinium enhancing lesion or 3 or more new T2 lesions on a yearly MRI scan

MRI criteria to switch therapy may include gadolinium enhancement and 3 or more new T2 lesions in a yearly scan. There have been many studies that have examined the predictive effects of yearly MRI scans and subsequent disability. These studies have used a variety of conventional measures of disease activity including T2 lesion load, T1 lesion load, gadolinium enhancement or a combination of these measures.

The study of Prosperini et al. was a single-centre, prospective study designed to examine the predictive value of clinical and MRI characteristics in identifying RRMS patients with sustained disability progression during interferon beta treatment \(^{(47)}\). Data were collected from 394 patients with a mean follow-up of 4.8 years. All patients received treatment with an interferon beta preparation for ≥1 year. Poor clinical response was defined as the occurrence of sustained disability progression of ≥1.0 EDSS point during a follow-up period of nearly 5 years. Approximately 30% of patients met the “poor responders” criterion. According to this study, developing new T2-hyperintense lesions after one year of interferon beta treatment was associated with increased risk of poor outcome. In fact, the number of new lesions was predictive of increased risk of a poor outcome. 1 new lesion conferred a risk ratio of 9.6 (95% CI 3.9–23.7, P<0.001), 2 new lesions a risk ratio of 21.2 (95% CI 8.8–51.1, P<0.001), ≥3 new lesions a risk ratio of 29.8 (95% CI 12.5–70.8, P<0.001). In a mean follow-up period of 4.8 years, only 4.6 % of patients who had no new T2 lesions on a second MRI progressed by 1 point on the EDSS scale, compared to 70% of patients who had new lesions on their follow-up MRI.

Rio et al. performed a prospective, longitudinal study of 152 patients with RRMS treated with interferon beta \(^{(48)}\). The primary objective of the study was to evaluate whether brain MRI performed at the start of interferon beta treatment, and after 12 months, could identify patients with a disability increase during the first 2 years of therapy. An increase in disability was defined as an increase of ≥1.0
EDSS point confirmed and sustained during the first 2 years of therapy with interferon beta. Twenty-four patients (16%) developed a confirmed disability progression during the first 24 months of therapy and were considered non-responders. Considering baseline measures of clinical and MRI, only the presence of >2 active lesions (new or enlarging T2-weighted lesions plus Gd+ T1 weighted lesions in the MRI performed at 1 year) was related to an increase in disability after 2 years of therapy (OR 8.3, CI: 3.1–21.9, P<0.0001).

Natalizumab is a monoclonal antibody approved for the treatment of relapsing-remitting MS. Again, there is limited evidence that to show that natalizumab is effective in preventing disability progression in patients experiencing continued disease activity on platform therapy. In the pivotal AFFIRM trial, both disability progression and relapse frequency was significantly reduced compared to placebo. In a more rigorous definition of a disease free state, 37% of patients of patients receiving natalizumab were without radiological progression (no gadolinium or new T2 lesions) or clinical activity (no relapses or disability progression) compared to 7% the placebo arm [49]. In SENTINEL trial, the Avonex only arm had a 10% disease free state.

There have been several retrospective studies that have demonstrated natalizumab to be effective in patients who have failed platform therapies [50, 51]. In a retrospective study of 45 patients experiencing 1 relapse on interferon beta or glatiramer acetate, switching to Natalizumab, 29% had a sustained improvement in their EDSS scores over 44 weeks of treatment. In addition, 62% had no clinical or radiological progression. If the annual relapse rate was greater than 2 on the platform therapies, then 42% had sustained EDSS improvement [50].

The emergence of oral therapies will further complicate the decisions regarding switching therapies. Cladribine and fingolimod are the leading candidates to be the first oral therapies for the treatment of MS. Fingolimod has been recently approved for the treatment of relapsing remitting MS. In a study of fingolimod vs. interferon beta IM once weekly, fingolimod at a dose of 0.5mg was associated with a reduction of relapse frequency by over 50% when compared to the IM interferon regimen [52]. Decisions will have to be weighed regarding the unknown long term side effects of these new oral agents versus their favourable route of administration and therapeutic effect. A host of new oral therapies are expected to hit the market in the several years and a balance of therapeutic effect versus side effects will likely determine the frequency of use in the treatment of MS.

CME ANSWERS
1. D
2. D
3. False: The MRI scan has considerable value in predicting the subsequent course of MS. Multiple studies have shown that the appearance of gadolinium enhancement predicts future attacks and the accumulation of T2 lesions in the first two years of therapy may predict subsequent disability and brain atrophy.

REFERENCES


SHOULD WE EVER CONSIDER STOPPING DISEASE-MODIFYING TREATMENT FOR MS?

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LEARNING OBJECTIVES

1. The attendee will be able to recognize limitations in the predictive value of a diagnosis of “benign MS”.
2. The attendee will be able to question ongoing use of DMTs in patients with primary progressive MS or secondary progressive MS without relapses.
3. The attendee will be able to balance the risk of the future development of MS after CIS with the risk of unnecessary treatment with DMTs.

CME QUESTIONS

1. Which of the following statements is true?
   A) < 10% of MS patients meet criteria for “benign MS”.
   B) < 30% of patients with “benign MS” at 10 years will eventually develop significant disability.
   C) There is no single standard definition of “benign MS”
   D) Cognitive impairment is rare (< 10% of patients) in patients with “benign MS”.

2. Which of the following statements is true?
   A) DMTs have been proven effective for PPMS.
   B) DMTs have been proven effective for SPMS without relapses.
   C) DMTs have been proven effective for both PPMS and SPMS without relapses.
   D) DMTs have not been proven effective for PPMS or SPMS without relapses.

3. A patient with no previous medical history is newly diagnosed with CIS. What is the patient’s approximate risk of subsequently developing MS within the next 10 to 20 years?
   A) 20%
   B) 50%
   C) 80%
   D) The risk can not be determined without a brain MRI.

KEYWORDS

1. Multiple Sclerosis
2. Disease Modifying Therapy
3. Optic Neuritis

INTRODUCTION

The era of multiple sclerosis (MS) disease-modifying treatments (DMTs) is less than two decades old, but as the number and usage of DMTs has increased, MS survival has measurably increased and the development of disability has been delayed over time. Based on data from 1994, the annual cost of MS in the US was estimated to exceed $6.8 billion, a significant proportion of which was medication expenditures. A subsequent analysis using data from 2004 found that prescription drugs accounted for 2/3 of all MS-related direct medical costs and that, compared to the 1994 data, MS treatment costs had increased by 35% (from $9,515 to $12,879 per patient). Despite their significant (and increasing) costs, treatment with DMTs has been encouraged for nearly all patients diagnosed with MS. Early treatment with DMTs is encouraged as data has accumulated demonstrating that delays in treatment result in significantly worse outcomes.

According to the National Multiple Sclerosis Society’s Disease Management Consensus Statement, “Initiation of treatment ... should be considered as soon as possible following a definite diagnosis of MS,” and “Therapy is to be continued indefinitely, except for the following circumstances: there is clear lack of benefit; there are intolerable side effects; better therapy becomes available.”

Issues of DMT tolerability and side-effects notwithstanding, the general approach to MS treatment often seems to be, “treat early; treat everyone.” But, given that the financial costs of treatment to individual patients and to the health care system as a whole are considerable, are there any clinical settings in which a physician might consider stopping MS therapy?

“BENIGN MS”

It has been recognized that some patients with MS develop little disability over time. There are many different definitions of so-called “benign MS”, most of which require
that patients remain at EDSS \( \leq 2.0 \) or EDSS \( \leq 3.0 \) after 10 or 15 years.\(^5\)\(^7\) Depending on the criteria used, 17% to 30% of MS patients can be categorized as having “benign MS” – minimal disability despite a decade or more of MS.\(^6\)

**EDSS**

The Kurtzke Expanded Disability Status Scale (EDSS) is a commonly used approach to quantifying MS related neurologic impairment.\(^8\)

Eight “Functional Systems” (Pyramidal, Cerebellar, Brain Stem, Sensory, Bowel & Bladder, Visual, Cerebral, and Other) are rated and combined to generate a single EDSS score ranging from 0 (normal) to 10.0 (death due to MS) in half point increments.

EDSS scores below 4.0 generally indicate minimal disability. EDSS scores from 4.5 to 5.5 are given to fully ambulatory patients with moderate disability, with higher scores given as the distance a patient can walk without assistance decreases. Higher EDSS scores imply a need for support from a cane or brace (EDSS = 6.0) or the use of a wheelchair (EDSS = 7.0). Bed-bound patients receive EDSS scores from 8.5 to 9.5.

Although the EDSS has been used in almost every major MS clinical trial, it has been criticized by some for its emphasis on motor function and a lack of sensitivity to fluctuations in MS disability.\(^9\)

By the time “benign MS” is diagnosed a patient may have been on DMTs for years, in which case it may be difficult to determine if the mild clinical course is a result of immunomodulation or due to a benign form of the disease. Sometimes, a patient may be newly diagnosed with MS after many years of mild symptoms or with a decade or more separating the first two clinical episodes. In these cases, is it appropriate to consider stopping (or perhaps not starting) DMTs?

Although in some studies, 52% to 68% of patients designated as having “benign MS” remain so at 20 years, clearly a significant number of patients with benign MS go on to accumulate disability despite having had a mild initial clinical course.\(^6\)\(^10\) In one longitudinal study of 436 MS patients, only 7 of 47 (15%) patients identified as having “benign MS” in 1985 remained so when re-evaluated in 2006, suggesting that a benign course at 10 years was only poorly predictive of a good outcome at 25 years.\(^7\)

Furthermore, it has recently been recognized that the EDSS alone, with its bias toward motor disability, may not fully capture MS-related impairment. Rovaris et al studied patients with “benign MS” and found that 19% of patients were found to have significant cognitive impairment. These patients also had abnormal mean diffusivity and fractional anisotropy on diffusion tensor imaging.\(^11\) Amato et al reported that 45% of patients with “benign MS” that they studied had cognitive impairment, with roughly half of their patients reporting significant depression and fatigue.\(^12\) Portaccio et al reported that 29% of patients with “benign MS” were no longer “benign” after a mean follow-up of 5 years, with early evidence of cognitive dysfunction and T1-weighted lesion load, but not initial EDSS, being significant predictive factors.\(^13\)

**PROGRESSIVE MS**

All FDA-approved DMTs have an indication for the treatment of relapsing remitting MS, having demonstrated a modest reduction in relapse rate when compared against a placebo. Not all MS patients have relapses however. Some MS patients develop gradually worsening disability over time. These patients are categorized as having a progressive form of MS.

**Subtypes of MS**

Most MS patients are initially classified as having relapsing remitting MS (RRMS), characterized by discrete episodes of neurologic dysfunction separated by periods of clinical stability.

Some patients who have a relapsing-remitting course initially may subsequently develop a gradually worsening course, referred to as secondary progressive MS (SPMS). During the transition from RRMS to SPMS, patients may have both relapses and gradual progression. SPMS without relapses may occur later and is typically associated with greater disability.

A small number of MS patients (10% to 15%) present with gradual worsening only, without relapses, and are categorized as having primary progressive MS (PPMS).\(^5\)

Studies have consistently demonstrated that first-line DMTs (beta interferons and glatiramer) are ineffective in both PPMS or SPMS without relapses.\(^14\)\(^15\) In the US, there are no FDA-approved treatments for these MS subtypes. The Association of British Neurologists guidelines for treatment of MS in the UK go further, stating that DMTs should be stopped in patients with secondary progressive MS with an inability to walk without assistance (EDSS \( \geq 6.0 \)) that persists for 6 months.\(^20\)

Despite the evidence, DMTs are commonly prescribed even when they are no longer clinically effective.\(^21\) In a 2009 survey by Lonergan et al, 26 international MS experts were asked about their approach to stopping treatment in PPMS or SPMS without relapses. Two reported that they never stop treatment and only 15 made any effort to stop treatment in secondary progressive MS. Most did not insist on stopping if the patient resisted, reluctant to harm the doctor-patient relationship. One neurologist from the US advised, “if it ain’t broke, don’t fix it”.\(^21\)

Ineffective treatment of the 7,000 MS patients in Ireland was estimated to cost between 1.36 million to 3.57 million per year.\(^21\) The cost of ineffective treatment for the estimated 250,000 to 350,000 people with MS in the US is unknown.
NOT MS ... YET?

Optic neuritis is a common cause of monocular vision loss in young patients. Though it may occur in isolation (a so-called “clinically isolated syndrome” or CIS), it may also be the first of multiple demyelinating episodes that characterize MS. Many patients with CIS, but not all, go on to develop MS. The risk for future development of MS is particularly great when the initial brain MRI is abnormal.12-27

Clinically Isolated Syndrome

A “clinically isolated syndrome” (CIS) is a single event suggestive of an inflammatory demyelinating event involving the central nervous system. Typical presentations of CIS include optic neuritis, transverse myelitis, or a brainstem syndrome. CIS is by definition a single event, distinguishing it from multiple sclerosis, which requires multiple episodes or “dissemination in time” for diagnosis.

CIS may be followed by a second clinical event in the future, at which time a diagnosis of clinically definite MS (CDMS) could be made. Recently revised clinical criteria (McDonald criteria) also allow MS to be diagnosed if subsequent changes on MRI (new lesions or gadolinium enhancement) are found.28

Multiple studies have examined this relationship between CIS and MS over time. Depending on the study (with follow-up ranging from 7 to 20 years), the risk of developing clinically definite MS following CIS varies from 42% to 63%—roughly 50/50 odds.24-27 A recent analysis of one of the study cohorts revealed that an additional 10% to 15% of CIS patients may develop MRI changes suggestive of MS without any clinical exacerbations.29

Brain MRI appears to be very useful in predicting which patients with CIS will go on to develop MS. CIS patients whose initial brain MRI scans are normal have a relatively low risk of going on to develop MS, ranging from 8% to 25%, depending on the study and the length of follow-up. In CIS patients with an abnormal brain MRI, the risk of developing MS increases to 60% to 82%. Though this risk is significant, and much greater than the risk of MS in patients with a normal brain MRI, it should be noted that 18% to 40% of the “high-risk” patients in these studies did not go on to develop clinically definite MS after CIS even after extended follow-up.

Multiple studies have demonstrated improved outcomes in patients with a clinically isolated syndrome and an abnormal brain MRI who have been treated with DMTs.30-33 As a result, the FDA has approved the use of DMTs in patients with a clinically isolated syndrome (CIS) and a brain MRI suggestive of MS. Because these CIS treatment studies have demonstrated that patients who were randomized to placebo have measurably worse outcomes, many clinicians advocate placing all CIS patients at high-risk for developing MS on DMTs as soon as the brain MRI is found to be abnormal.

Though it appears clear that the majority of patients with CIS and an abnormal brain MRI will benefit from early treatment with DMTs, if all high-risk CIS patients are placed on DMTs immediately, the possibility arises that a significant minority of CIS patients may be receiving DMTs unnecessarily. Once treatment with a DMT has begun in this situation, there may be no way to determine if the patient is receiving any benefit, particularly if the patient develops no subsequent exacerbations.

SUMMARY

Since the advent of DMTs, it appears to be clear that patients with relapsing remitting MS benefit from early and ongoing treatment to prevent relapses and to slow disability progression. Several areas, however, remain controversial:

1. There is enough uncertainty about whether or not there is truly such a thing as “benign” MS to argue for continued treatment with DMTs even when there is relatively little evidence of progression on EDSS.

2. DMTs lack efficacy in the setting of primary progressive MS and secondary progressive MS without relapses. The general reluctance to stop DMTs in these clinical settings may be based more on physician and patient attitudes than on evidence and may be significant drain on health care resources.

3. Although most patients with CIS who are at high risk to develop MS benefit from early treatment with DMTs, a significant minority of patients may be being treated unnecessarily if all patients with CIS are treated immediately.

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*Percentage of patients meeting McDonald criteria for MS.
CME ANSWERS

1. C
2. D
3. B

REFERENCES