ABSTRACT

Recently a group of community and academic neurologists gathered to discuss current topics of interest in multiple sclerosis (MS). The goal of the meeting was to provide an up-to-date review of the literature and to gather consensus opinions regarding key aspects of each of these topics. This article is the product of one of these sessions that focused on the initial clinical event suggestive of demyelinating disease: the so-called clinically isolated syndrome (CIS). One of the key questions addressed in this monograph is how to stratify risk in the patient with CIS. How useful are brain magnetic resonance imaging (MRI), cerebrospinal fluid analysis, evoked potential tests, and serological assays in determining which patients with CIS will go on to have subsequent attacks and who is at highest risk for neurologic disability? Do recent advances in our understanding of cognitive changes and ultrastructural changes revealed by non-conventional MRI in patients with CIS indicate that more widespread injury to the central nervous system has already occurred at the time of the initial presenting event? Lastly, how useful are disease-modifying therapies in preventing further attacks, reducing the accumulation of new lesions apparent on brain MRI, and, most importantly of all, preventing neurologic disability? Does our understanding of MS pathophysiology help support early treatment in MS and CIS? (Adv Stud Med. 2008;8(8):257-265)

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) and is the most common cause of neurologic disability in young adults. The initial clinical presentation suggestive of relapsing MS is termed the "clinically isolated syndrome" (CIS). CIS is a neurologic episode caused by inflammation in 1 or more sites within the CNS and lasting at least 24 hours. Diagnosing MS as early as possible is important because the use of disease-modifying therapies (DMTs) early in the course of the disease may significantly slow disease progression.

Diagnostic Criteria for MS

Before the use of magnetic resonance imaging (MRI), diagnostic criteria for MS relied exclusively on clinical features. Clinically definite MS was defined by 2 or more relapses, separated by at least 1 month, or a slow, stepwise progressive disease for at least 6 months with documented neurologic signs in more than 1 area of the CNS, thereby defining dissemination of the disease in both space and time.
MRI EVALUATION OF MS

Community neurologists recognize the importance of the baseline MRI in CIS. In fact, in an informal survey of community neurologists (N = 43), all agreed that baseline MRIs are necessary during the evaluation of a patient with a CIS. Ninety-eight percent of neurologists suggested that baseline MRI data are very important in counseling patients with CIS about the need to start treatment with DMTs early in the course of disease. Only 2% considered baseline MRIs “somewhat important.” Also, when it came to counseling patients with CIS on the risk of subsequent attacks, 91% of respondents (N = 44) considered baseline MRI information very important, whereas 9% considered this information somewhat important (Think Tank ARS Data).

Indeed, MRI has revolutionized the diagnosis and management of MS. Although characteristic abnormalities are found in 95% of patients with MS, the diagnosis of MS is complicated by the fact that no single clinical feature or diagnostic test is sufficient for the definitive diagnosis of MS and there are several diseases that can mimic MS. Two studies performed early in the history of the clinical use of MRI demonstrated the relationship between CNS lesions on MRI and MS. A study of patients with isolated optic neuritis (ON) revealed a pattern of clinically silent lesions on MRI that were similar in appearance, extent, and location to lesions seen in patients with MS. Another study found that brain stem or spinal cord lesions identified by MRI in patients presenting with their first clinical relapse heralded further attacks consistent with MS.

An international panel of MS experts was convened in 2001 to apply an evidence-based approach for developing diagnostic criteria for MS that incorporated findings on brain MRI. To establish a diagnosis of MS, there must be evidence of at least 2 lesions that meet specific diagnostic requirements, disseminated anatomically in space and in time over at least a 30-day period. Certain MRI findings are highly suggestive of MS (Table 1) even before a patient demonstrates dissemination in time.

The International Panel on the Diagnosis of MS reconvened several years later to update the criteria in order to incorporate new evidence and revise several concepts. They decided that the evidence for dissemination of lesions in time might be more important than that of space. MRI criteria now specified that any new T2 lesion occurring at any point beyond 30 days of the initial clinical event may be used to reach the diagnostic criteria of “dissemination in time.” The radiographic appearance of an MS spinal cord lesion was specified—a lesion must be at least 3 mm in size but less than 2 vertebral segments in length, while occupying only a part of the spinal cord in cross section.

Recently, the revised criteria were used to evaluate patients with CIS who were classified as “multifocal” on the basis of clinical evaluation and MRI. These patients were more likely to fulfill MRI criteria for dissemination in space to reach a diagnosis of clinically definitive MS (CDMS) when compared with patients who had a monofocal CIS presentation. Another study compared the original International Panel Criteria with the modified version and concluded that for patients with CIS, the revised criteria were more accurate (86% vs 73%) and sensitive (77% vs 46%) in predicting the development of CDMS.

DIFFERENTIAL DIAGNOSIS

The International Panel Criteria emphasize the importance of a differential diagnosis and assert that its use reduces the risk of an incorrect diagnosis because the criteria are based on the specificity of MS-like lesions, which are less likely to occur in conditions that mimic MS. However, several neurologic conditions can mimic the initial clinical presentations of MS, potentially making diagnosis in this setting more challenging (Table 2).

The possibility of an alternative diagnosis should be considered when patients are younger than 15 years, or alternatively, older than 60 years. Other fac-

Table 1. MRI Criteria for Brain Abnormality

<table>
<thead>
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<th>Criteria for Brain Abnormality</th>
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<tr>
<td>A diagnosis of MS is made if 3 of the 4 following criteria are met:</td>
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<tr>
<td>1. One Gd-enhancing lesion or 9 T2-hyperintense lesions if there is no Gd-enhancing lesion</td>
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<tr>
<td>2. At least 1 infratentorial lesion</td>
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<tr>
<td>3. At least 1 juxtacortical lesion</td>
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<tr>
<td>4. At least 3 periventricular lesions</td>
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Note: One spinal cord lesion may be substituted for 1 brain lesion. Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis. Data from McDonald et al; Barkhof et al; and Tintore et al.
torso that point away from a diagnosis of MS are symptoms that locate exclusively to the posterior fossa, craniocervical junction, or spinal cord. Also, although approximately 10% of cases of MS are progressive from onset (primary progressive MS), immediate progression is often a sign that points away from a definitive diagnosis of MS. Furthermore, if patients have not experienced visual, sensory, or bladder symptoms, an alternative diagnosis should be considered. And, finally, atypical or normal laboratory findings, on MRI, cerebrospinal fluid (CSF), and evoked potentials (EPs), may suggest that the patient does not have MS.

WHICH PATIENTS WITH CIS ARE AT GREATEST RISK FOR A SECOND ATTACK?

The baseline MRI is the most powerful prognostic tool clinically available. In general, at the time of CIS, patients with brain MRI scans revealing either T2 or gadolinium diethylenetriamine-pentaacetic (Gd-DTPA)-enhancing lesions are at greater risk for having a second clinical attack diagnostic of MS. Patients can be separated into low-, medium-, and high-risk groups for experiencing a second attack depending on the number of brain MRI lesions present at the time of CIS presentation. In contrast, a normal baseline MRI scan is a strong prognostic factor against the development of further attacks, although this is not always the case.

Several clinical trials provided a framework for identifying prognosticating factors for the conversion from CIS to CDMS. The treatment trials had similarities and differences; note that the patients were of approximately the same age range and all presented with a CIS (Table 2).

The ONTT (Optic Neuritis Treatment Trial) concluded that the 10-year risk of developing MS after an episode of ON was significantly higher if even a single lesion was seen on MRI. However, increased numbers of MRI lesions were not shown to significantly increase the risk of further attacks. In the ONTT, a lower risk of MS was noted in patients with acute ON associated with male gender, optic disk swelling, no lesions on MRI, as well as features atypical for ON, such as no light perception vision, absence of pain, and ophthalmoscopic findings of severe optic disk edema, retinal exudates, or hemorrhages. These last features likely indicate that the ON in said patients was not a result of MS, but of another ophthalmologic condition.

The CHAMPS (Controlled High Risk Subjects Avonex MS Prevention) study group analyzed 190 patients with CIS in the placebo arm with abnormal baseline brain MRIs consistent with demyelination to evaluate the predictive value of existing MS diagnostic criteria. The primary end point was the occurrence of a second clinical attack by 18 months. Two secondary MRI end points were also used: CDMS/MRI1 (either CDMS or >1 new or enlarging T2 lesion over 18 months) and CDMS/MRI2 (either CDMS or ≥1 new or enlarging T2 lesions over 18 months).

At 18 months, 27% of all subjects had developed CDMS, and 52% of patients who had 2 or more Gd-enhancing lesions at baseline had developed CDMS, compared with only 24% of patients with fewer than 2 Gd-enhancing lesions. The presence of enhancing lesions on the baseline scan was the single best predictor of which patients ended up developing CDMS during the study period. With respect to secondary end points, results were again most pronounced in

<table>
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<th>Table 2. Conditions That May Be Confused with MS</th>
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<tr>
<td><strong>Vascular:</strong> vascularitis causing multifocal areas of cerebral ischemia or infarction, spinal dural arteriovenous malformations causing progressive paraparesis</td>
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<tr>
<td><strong>Infectious:</strong> Lyme disease, syphilis and HTLV-1, and Bartonella henselae</td>
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<td><strong>Tumors:</strong> paraneoplastic disorders causing cerebellar ataxia and limbic encephalitis</td>
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<td><strong>Autoimmune:</strong> collagen vascular diseases, such as systemic lupus erythematosus, antiphospholipid antibody syndrome, and Sjögren’s syndrome</td>
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<td><strong>Metabolic:</strong> adult-onset leukodystrophies, such as adrenomyeloneuropathy</td>
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<td><strong>Idiopathic:</strong> demyelinating diseases that can be monophasic, including acute disseminated encephalomyelitis, neuromyelitis optica, and acute transverse myelitis</td>
</tr>
<tr>
<td><strong>Nutritional:</strong> vitamin B12 deficiency</td>
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<td><strong>Sarcoidosis</strong></td>
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HTLV-1 = human T-cell lymphotropic virus.
patients who had 2 or more Gd-enhancing lesions at baseline. By 18 months, 92% of these patients had reached the CDMS/MRI1 end point, and 96% had reached the CDMS/MRI2 end point.

Among patients with 4 or more large T2 lesions, 87% developed the CDMS/MRI1 outcome and 97% developed the CDMS/MRI2 outcome. Likewise, among patients with 2 or more juxtacortical lesions, 82% reached the CDMS/MRI1 outcome, and 94% reached the CDMS/MRI2 outcome.

PRESENTATION EFFECTS PROGNOSIS

A cohort study of over 2000 patients in France classified patients with MS based on initial symptoms. Isolated ON was the initial presentation in

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**Table 3. Comparison of Patient Cohorts Across 3 Trials on Patients with Early MS/CIS**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>ONTT</th>
<th>CHAMPS Study</th>
<th>ETOMS</th>
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<tbody>
<tr>
<td>Age range, yr</td>
<td>18–46</td>
<td>18–50</td>
<td>18–40</td>
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<tr>
<td>Diagnosis</td>
<td>Acute unilateral optic neuritis with visual symptoms of ≤8 days</td>
<td>First isolated, well-defined neurologic event, such as unilateral optic neuritis, incomplete transverse myelitis, or brain stem or cerebellar syndrome, confirmed by examination</td>
<td>Clinical syndrome indicating unifocal or multifocal involvement of the CNS with neurologic episode suggesting MS in the previous 3 months</td>
</tr>
<tr>
<td>Imaging</td>
<td>–</td>
<td>Presence of ≥2 clinically silent lesions of the brain of at least 3-mm diameter on MRI (with at least 1 lesion periventricular or ovoid)</td>
<td>“Positive” MRI: presence of at least 4 white-matter lesions on T2-weighted scan or 3 lesions if at least 1 was infratentorial or enhancing after Gd-DTPA injection</td>
</tr>
<tr>
<td>Steroids</td>
<td>–</td>
<td>Onset no more than 14 days prior to IV steroid therapy started</td>
<td>Steroid treatment for “moderate” or “severe” exacerbations—EDSS of ≥3 in 1 functional system or score of 2 in 3 functional systems</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>–</td>
<td>Prior neurologic or visual event lasting &gt;48 hours</td>
<td>Prior immunosuppressive or immunomodulatory treatment, participation in any experimental procedure during the year prior to the study, other serious intercurrent systemic or psychiatric illness, pregnancy, or unwillingness to use reliable methods of contraception during the study</td>
</tr>
<tr>
<td>Treatment protocol</td>
<td>Randomized to receive either: a) a single course of IV methylprednisolone followed by oral prednisone or b) oral prednisone alone or c) oral placebo</td>
<td>All patients received 1 g of methylprednisolone/day IV × 3 days, followed by 1 mg/kg of prednisone by body weight/day orally × 11 days and 4-day period of tapering from 20 mg, 10 mg, 0 mg, and 10 mg. Then randomized to: a) 30 µg IFNβ-1a weekly IM injection or b) placebo weekly IM injection</td>
<td>Randomized to receive either: a) 22 µg IFNβ-1a or b) placebo injection once weekly for 2 years</td>
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</table>

CHAMPS = Controlled High Risk Avonex MS Prevention; CIS = clinically isolated syndrome; CNS = central nervous system; EDSS = Expanded Disability Status Scale; ETOMS = Early Treatment of MS Study; Gd-DTPA = gadolinium diethylenetriamine-pentaacetic; IFN = interferon; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; ONTT = Optic Neuritis Treatment Trial.

Data from Comi et al; Jacobs et al; and Beck et al.
18% of patients, whereas 9% presented with brain stem dysfunction; 52% presented with isolated corticospinal tract dysfunction, and 21% presented with a combination of symptoms. Disability progression as measured by the Disability Status Scale (DSS) was correlated with the initial presenting symptoms. The DSS score ranges from 0, indicating no neurologic abnormality, to 10, meaning death from MS. Three benchmark scores used were: 4, limited walking but without an aid; 6, walking with a cane; and 7, essentially wheelchair bound. Patients who initially presented with isolated ON had the longest time from onset of symptoms to reach a DSS of 4, at 14.1 years, whereas patients with initial brain stem dysfunction reached the same status at a median of 10.5 years, and those with corticospinal tract dysfunction showed the most rapid deterioration with a DSS of 4 reached at a median of 6 years.

Another study conducted on patients with CIS (presenting with ON, brain stem/cerebellar syndrome, spinal cord syndrome, hemimotor or hemisensory syndrome, or who were multisymptomatic) assessed the relationship between MRI lesions and transition to CDMS. This study found that 2 or more infratentorial lesions were the best predictors of long-term disability in this cohort. Gd-enhancing and hypointense T1-weighted lesions did not have a prognostic value in these patients.

A study from Queens Square in the United Kingdom concluded that patients who presented with CIS, who then subsequently had increased lesion volume on MRI, had corresponding increased degrees of long-term disability from MS. A 14-year controlled, longitudinal study of 57 subjects (28 with CDMS and 29 controls) study found that early, rather than later, focal lesion accumulation predicts development of brain atrophy and correlates with long-term disability.

**Paraclinical Measures in CIS and MS**

In addition to MRI data, CSF analysis and EP testing are paraclinical indicators used to confirm the diagnosis of MS. These studies are particularly helpful in clarifying the diagnosis when MRI findings are nonspecific or unusual.

In direct contrast to the certainty about the role of MRI data, surveyed neurologists (N = 46) were less certain about whether abnormal EP test results are helpful in predicting a second demyelinating event. Data showed that 43.5% of respondents found abnormal EPs predictive, 20% did not, and 37% said that they were unsure about the predictive potential of abnormal EP results. CSF analysis was favored by the majority of surveyed neurologists (N = 46) when they were asked if they consider the presence of oligoclonal bands in the CNS of patients with ON predictive of MS. Although 15% were unsure about the predictive value of oligoclonal bands in patients with ON, 78% responded that their presence does have predictive value, and only 6.5% suggested that there was absolutely no predictive value.

Evoked potential testing evaluates the function of afferent or efferent CNS pathways using computer averaging to measure CNS electrical potentials evoked by repetitive stimulation of selected peripheral or optic nerves. Fifty percent to 70% of patients with MS have abnormal results when evaluated. It is important to note, however, that with regards to patients with CIS, one study showed no statistically significant differences on visual EP, brain stem auditory EP, and somatosensory EP testing between patients who did or did not convert to CDMS.

Cerebrospinal fluid analysis can enhance the diagnostic process by providing additional insight into the inflammatory and immunologic disturbances that may represent MS. The most common CSF abnormalities found in patients with MS include mononuclear cell leukocytosis and an increased level of intrathecally synthesized immunoglobulin (Ig) G in the form of oligoclonal bands. The utility of checking for CSF abnormalities in helping to establish a clinical diagnosis of MS was supported by a study following 86 patients with ON for a median of nearly 13 years. At onset of ON, CSF pleocytosis and oligoclonal IgG were measured. Abnormal CSF, along with a younger age at onset and early recurrence of ON, correlated with the development of CDMS. Another study found an even stronger correlation between abnormal IgG levels in the CSF relative to abnormal MRI in predicting the conversion of patients from CIS to CDMS. Indeed, intrathecal synthesis of oligoclonal bands correlates closely with MS. Although the intrathecal synthesis of oligoclonal bands was detectable in only 68% of patients with possible onset symptoms of MS, it was detected in 96% of patients with CDMS. The predictive value of abnormal CSF was also observed in an observational cohort that followed patients for up to 30 years after an initial attack.
of ON. The risk for a second clinical attack diagnostic of MS increased significantly when oligoclonal IgG bands or a mononuclear pleocytosis were present in the CSF at onset of ON. A new version of CSF analysis—intrathecal synthesis of oligoclonal IgG band (OCGB)—was shown to have greater sensitivity and specificity compared with older CSF analytical methodologies. The sensitivity for OCGBs in the diagnosis of MS was 96.2% and the specificity was 92.5%. OCGB increases the positive predictive power of MRI. In one study, a group of 52 patients underwent OCGB assessment and was followed for up to 6 years. Ninety-seven percent of OCGB-positive patients with CIS and 15.8% of OCGB-negative patients experienced a second clinical attack. Detection of OCGB in the CSF yielded a sensitivity of 91.4% and specificity of 94.1% for a second clinical attack. Combining OCGB testing and MRI during CIS was very sensitive and moderately specific with regard to predicting a second attack within 6 years. These sensitivity and specificities clearly rival results seen with MRI and prove that CSF studies continue to be an important instrument for diagnosing MS.

**Biomarkers in CIS**

The utility of biomarkers for predicting disease progression following CIS is intriguing. One study found that the presence of IgM antibodies directed at myelin basic protein and myelin oligodendroglial protein at the time of CIS were predictive of a second clinical attack diagnostic of MS. Unfortunately, the utility of this technique is uncertain. A subsequent study from a large clinical trial was unable to replicate this observation, whereas a smaller study also found predictive value of these antomyelin autoantibodies. These studies used different techniques and to some extent different patient populations. Thus serologic study of antomyelin antibodies may one day become clinically useful.

In the case of neuromyelitis optica (NMO), a CNS demyelinating disease characterized by severe attacks of ON and longitudinally extensive transverse myelitis, a recently developed biomarker can be very useful clinically in distinguishing NMO from typical MS. This biomarker is an autoantibody directed against aquaporin 4, a water channel ubiquitously expressed throughout the CNS that regulates flow of water across biologic membranes, such as those found in capillaries and the podocytes of astroglial cells. The presence of this NMO-IgG antibody in patients who suffer from the first attack of longitudinally extensive myelitis is highly predictive of further attacks.

**Is There More to CIS Than the Isolated Lesion? Cognitive and Ultrastructural Changes in CIS and Early MS**

A group of patients with “clinically isolated lesions” (ie, a single neurologic deficit) was given a series of neuropsychiatric tests that identified cognitive impairments in the absence of other manifestations of brain pathology, such as physical impairments. The main neurocognitive deficit was that of attention deficit, which was related to the duration of neurologic symptoms and the overall extent of brain pathology as seen on MRI.

A more recent study revealed a close relationship between cortical atrophy and cognitive impairment in patients with relapsing-remitting MS. Similar findings were found in a study of patients in the early phase of relapsing-remitting MS, which determined that cognitive impairments noted on neuropsychologic testing were related to loss of brain parenchymal volume more than the extent of brain lesions. This atrophy of brain tissue may be related to early axonal loss, supporting the arguments for early use of DMTs in MS.

The limitations of conventional MRI were identified in a study by Filippi et al, which revealed that normal-appearing brain tissue (NABT) in fact has changes associated with cognitive deficits in patients with MS. The ultrastructural and functional changes in NABT can be revealed by magnetization transfer histogram analysis.

**Treatment of CIS and Early MS**

Axonal transection occurs extensively in actively demyelinating lesions, and therefore irreversible neurologic injury is presumed to begin to occur early in the MS disease process. In an autopsy series of 11 patients with MS, axonal transection was much more abundant in active than in chronic lesions. Some have argued that early intervention with anti-inflammatory MS treatments is justified because axonal transection is irreversible and most abundant in areas of active inflammation. Most treating clinicians agree with this approach. Of surveyed community neurologists (N = 40), 72.5%
cite axonal injury as the cause of disability, compared with 22.5% who feel that demyelination is the pathologic culprit, and 5% who blame oligodendroglial apoptosis (Think Tank ARS Data). It is proposed that by reducing the inflammatory response in the brains of patients with CIS and MS, the long-term consequences of this disease may be prevented.

The interferon (IFN) drugs exert an anti-inflammatory effect, which can have a positive impact on patients with MS during the early stages of the disease. Several randomized controlled clinical trials demonstrated improved outcomes for patients with CIS who start therapy with DMTs early in the course of disease.

The ETOMS (Early Treatment of MS) study was designed to study the effect of 22 µg subcutaneous IFNβ-1a on the occurrence of relapses in patients who have presented with CIS and are at high risk for second attacks based on the presence of brain MRI lesions. In this 2-year, double-blind, randomized, placebo-controlled trial, 154 of 309 patients were randomized to treatment with once-weekly subcutaneous IFNβ-1a 22 µg. Two hundred and seventy-eight of the patients completed the study. The primary outcome measure was conversion to CDMS, as defined by a second neurologic exacerbation. Brain MRI was performed at 12 and 24 months. The ETOMS study found several benefits of early treatment with IFNβ-1a including: (1) a reduction in conversion to CDMS from CIS; (2) the time to conversion to CDMS by 30% of the cohort was delayed by a factor of more than 2 when compared to the placebo group; (3) a lower annual relapse rate in patients with MS; and (4) fewer new T2-weighted MRI lesions and overall lesion burden on MRI. It should be noted that despite these differences, the vast majority of patients in both groups had evidence of MRI conversion based on the appearance of at least 1 new lesion that was at least 10 mm in diameter or 3 new lesions that were less than 10 mm in diameter, indicating that the underlying pathologic process continued.

The CHAMPS study group also validated the benefits of initiating treatment with IFNβ-1a at the time of a first demyelinating event in patients with brain lesions on MRI suspicious for CDMS. In addition to the resultant lower rate in the development of CDMS, patients on IFN had fewer new or enlarging lesions, fewer Gd-DTPA–enhancing lesions, and a relative reduction in the volume of brain lesions on MRI compared to the patients in the control group. Over a 3-year period, the rate of development of CDMS from CIS was reduced by 42%.

A follow-up study, coined CHAMPIONS (Controlled High Risk Avonex MS Prevention Study in Ongoing Neurologic Surveillance), noted that the development of CDMS continued to remain reduced in patients with CIS 5 years after first event. A statistically significant benefit was seen among patients who started early IFN treatment (within 1 month of the first clinical demyelinating event) compared to those who started treatment at a median of 2.5 years after the first neurologic event.

The BENEFIT (Betaferon in Newly Emerging MS for Initial Treatment) trial was designed to study the efficacy, safety, and tolerability of IFNβ-1b (250 µg subcutaneous) administered every other day in high-risk patients who had presented with CIS suggestive of MS and had at least 2 clinically silent T2 lesions. A total of 437 patients between the ages of 18 and 45 were enrolled in this 2-year double-blind, placebo-controlled, randomized, parallel-group trial.

In the IFNβ-1b–treated group, the risk for a second clinical attack was reduced by 50% (hazard ratio with 95% confidence interval [CI], 0.5; 0.36–0.7, P < .0001) and for developing MS based on the International Panel Criteria by 46% (hazard ratio with 95% CI, 0.54; 0.43–0.67, P < .00001). The probability of reaching MS, according to the International Panel Criteria, was 51% for placebo-treated patients and 28% for IFNβ-1b–treated patients. Within 2 years, these probabilities adjusted upward to 85% and 69%, respectively (P < .0001). IFNβ-1b also prevented the development of new inflammatory T2 lesions and decreased the volume of existing hyperintense T2 lesions, suggesting regression of inflammation.

Even more importantly, a 40% reduction in disability was demonstrated in those subjects who were treated with IFNβ-1b from disease onset compared to those who either did not receive treatment with IFNβ-1b or who had a second clinical or radiographic event and received subsequent treatment for conversion to MS. This important observation showed for the first time that early treatment in CIS with IFN was associated with a reduction in neurologic disability and clearly justifies treatment from disease onset.

Similar results have recently been reported in a study of treatment with glatiramer acetate (GA) in patients with CIS. In the PRECISE Study, 481 patients with CIS were randomized to treatment with GA or placebo. After 3 years of treatment, the GA-treated patients showed significant decreases in T2,
When community neurologists (N = 42) were asked what they thought about treatment with IFNβ after the first demyelinating event, 86% responded that treatment prolongs the time to a second attack, slows progression to confirmed disability, and reduces the burden of disease in T2 MRI. The remaining 14% of respondents felt that it accomplished some, but not all, of these things. Not one respondent suggested that early IFNβ treatment was not helpful in modifying disease progression or manifestation of early disease (Think Tank ARS Data).

CONCLUSIONS

Available clinical evidence showed that the risk of further attacks in patients with CIS and a positive baseline MRI increases over time to as high as 89%, compared with only an 11% risk in patients with a normal baseline MRI. Many indicators suggest that what happens early in the course of the disease influences outcomes over the long term. Arguments for not initiating early therapy are based on the idea that not all patients progress to CDMS; however, baseline MRI criteria can provide prognostic insight to support treatment decisions. The vast majority of community neurologists believe that baseline MRI data in patients with CIS are critical for counseling patients about short- and longer-term outcomes, as well as the decision to initiate therapy with DMTs (Think Tank ARS Data). This widespread consensus is underscored by strong evidence that shows that treatment with IFNβ or GA reduces the risk of further attacks, lowers MRI disease burden, and slows progression of neurologic disability.

REFERENCES