Early treatment of multiple sclerosis to prevent neurologic damage

ABSTRACT

Multiple sclerosis (MS) involves ongoing accumulating CNS damage. Precisely which environmental factors trigger onset and progression of the disease are not known. However, clinical trials indicate benefits from early use of disease-modifying therapies (DMTs). All the completed clinically isolated syndrome trials (CHAMPS, ETOMS, BENEFIT, PRECISE) reported significant suppression of subsequent relapse and MRI lesion formation from use of DMT at the first relapse. This article reviews data on early treatment. Such an approach requires the ability to recognize clinically isolated syndrome features that indicate a diagnosis of MS. NEUROLOGY 2008;71 (Suppl 3):S3–S7

Even in its early stages, multiple sclerosis (MS) involves neurologic damage at the time of relapse, some of which may be irreversible. Clinical abnormalities do not necessarily correlate with lesions detected by MRI. Microscopic neurologic damage may occur even before detection of lesions with conventional MRI.

One or more environmental factors not yet identified somehow lead to an immunologic attack on the CNS. Initially, this attack may be directed against a single antigen, but subsequent damage results in epitope spread and ultimately involvement of multiple antigen targets.

Typically, MS evolves over time from a relapsing-remitting course to a continuously progressive one where disability steadily increases. Early in the disease course, when the CNS lesion load is low, the brain may be able to compensate for neurologic damage. Because the lesion load increases and there is less CNS reserve, each new lesion may be more likely to affect functional status.

Disease-modifying therapies (DMTs) have demonstrated significant effectiveness in treating MS by reducing clinical relapses, slowing disease disability and progression, minimizing MRI lesion activity, and improving quality of life measures. MS focal inflammatory lesions that are associated with the relapsing phase of the disease predominate early and are particularly amenable to suppression by the DMTs. The DMTs involve four distinct classes of agents that are relatively well tolerated: low- and high-dose interferon-β (IFNβ), glatiramer acetate, natalizumab, and mitoxantrone.

Given that MS involves ongoing accumulating damage, minimizing damage with an early diagnosis and potentially early treatment would seem important. There remain unanswered questions with regard to whether there is a critical “window of opportunity,” and whether early treatment is more effective than later treatment. Awareness of the diagnostic and prognostic features of the clinically isolated syndromes (CIS) will aid subsequent therapeutic decisions.

CIS AND THE ROLE OF MRI CIS is the clinical presentation of relapsing-remitting MS (RRMS). Because a definite diagnosis of MS requires proof of dissemination in time and space to meet formal diagnostic criteria, patients must have further clinical attacks or new MRI lesions. Follow-up is not only appropriate but also essential. The initial evaluation of CIS needs to rule out other disorders that can be mistaken for MS. Careful characterization can identify those patients who have high probability of MS. Patients to be evaluated should be between 15 and 50 years of age. Common CISs suggestive of MS include unilateral optic neuritis, incomplete trans...
verse myelitis, internuclear ophthalmoplegia, trigeminal neuralgia, and paroxysmal attacks. Many disorders can produce an abnormal MRI, but certain lesions (number, size, shape, location, orientation, and enhancement) may suggest MS, or alternatively, a non-MS diagnosis. Appropriate early treatment is contingent upon making an accurate initial assessment.

Earlier diagnostic algorithms such as the Poser criteria did not incorporate MRI. The International Panel McDonald criteria were the first to use MRI to document dissemination in time and space. In the 2005 revised McDonald criteria, dissemination in space requires the patient meets three of four criteria: at least one gadolinium-enhancing lesion or \( \geq 9 \) T2 hyperintense lesions; at least one infratentorial lesion; at least one juxtacortical lesion; or \( \geq 3 \) periventricular lesions. An enhancing spinal cord lesion meets two of these criteria (infratentorial lesion and enhancing lesion), whereas all spinal lesions can be counted to reach the threshold of nine required lesions. Abnormal CSF (positive oligoclonal bands or elevated IgG index) allows two T2 lesions to meet the criteria. Swanton et al. have subsequently recommended simplified McDonald criteria for CIS patients, which improved sensitivity without loss of specificity. In this system (table 1), dissemination in space is met when there are T2 lesions in at least two of the four regions specified by the McDonald criteria. Dissemination in time is demonstrated with one or more new T2 lesions on a follow-up MRI 3 months after the initial event. The presenting event must be a well-characterized syndrome consistent with MS. These simplified criteria are 90% specific for MS, and correctly predicted 30 of 39 CIS patients (76% sensitivity) who went on to a second clinical attack during a median follow-up time of 39 months.

Recent clinical trials evaluating therapy for CIS have shown differences in when MS can be diagnosed based on clinical vs MRI-based criteria. All of the clinical trials which include the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS), Early Treatment of Multiple Sclerosis (ETOMS), Betaseron in Newly Emerging MS For Initial Treatment (BENEFIT), and Presenting With A Clinically Isolating Syndrome (PRECISE) enrolled CIS patients with two or more clinically silent lesions on brain MRI. During the 2- to 3-year follow-up period in these studies, 45% to 50% of patients had a second attack (i.e., met clinical criteria for MS). In the ETOMS trial, patients with nine or more T2 lesions, or a contrast-positive lesion, had a sixfold greater risk of conversion to clinically definite MS (CDMS) than patients who lacked these features on their baseline MRI. Having \( \geq 9 \) T2 lesions conferred greater risk of CDMS (odds ratio, 3.6; \( p = 0.01 \)) compared with the presence of a contrast-enhancing lesion alone (odds ratio, 1.5; \( p = 0.09 \)). In BENEFIT, patients were also assessed using the 2001 International Panel McDonald criteria. By 2 years, 85% of patients qualified for a definite diagnosis of MS using the McDonald criteria. Similarly, other studies have reported that most CIS patients (56% to 88%) who have an abnormal MRI will have further clinical attacks in the next few years, whereas the risk for a second attack is much less (8% to 22%) when the initial MRI is normal (table 2).

### Table 1: Simplified CDMS criteria

<table>
<thead>
<tr>
<th>simplified CDMS Criteria (^{(Swanton et al.18)})</th>
<th>International Panel McDonald Criteria (^{(20,21)})</th>
<th>simplified CDMS Criteria (^{(Swanton et al.18)})</th>
<th>International Panel McDonald Criteria (^{(20,21)})</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>95</td>
<td>79</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
<td>71</td>
<td>78</td>
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</tr>
<tr>
<td>Accuracy</td>
<td>81</td>
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**DMTS FOR CIS** In the CHAMPS, ETOMS, and BENEFIT trials, patients with abnormal brain MRI were randomized to IFN\(\beta\) or placebo to determine whether treatment would delay a second attack and MRI lesion activity.

The cumulative probability of experiencing a second attack was estimated in CHAMPS patients with a monofocal demyelinating event treated once weekly with 30 \( \mu g \) IFN\(\beta\)-1a IM or placebo over 3 years. Patients in the IFN\(\beta\)-1a group were found to be 15% less likely to have a subsequent event compared with placebo (50% vs 35%; \( p = 0.002 \)). In the 2-year ETOMS trial, patients who were treated once weekly with 22 \( \mu g \) IFN\(\beta\)-1a subcutaneous (SC) were also less likely to have a subsequent clinical attack vs placebo (34% vs 45%; \( p = 0.046 \)). Treatment effects on MRI brain lesion burden in the CHAMPS and ETOMS studies are shown in figure 1. ETOMS used a low dose, one-sixth of the approved IFN\(\beta\)-1a SC dose for patients with active RRMS. This dose of 22 \( \mu g \) once weekly had an effect in patients with CIS but not in patients with RRMS, reinforcing the concept that patients are more responsive to treatment early in the disease course. IFN\(\beta\)-1a SC is currently being reevaluated in
another 2-year CIS study (REFLEX). Patients enrolled in this ongoing trial are currently being treated once or thrice weekly, with 44 μg IFN-β-1a SC or placebo. All data for the primary outcome measure is expected to be collected by the end of 2008.

In the BENEFIT study, CIS patients were randomized to treatment, with 250 μg IFN-β-1b every other day for 2 years or placebo. Those who had a second attack were offered enrollment into a follow-up study where blinding to the initial randomization was maintained, but all patients received IFN-β-1b open-label. After 2 years, 44% of patients in the placebo group had a second attack, compared with 26% treated with IFN-β-1b (p < 0.0001; figure 2). After 3 years of follow-up, with all patients being treated, 34% of patients in the immediate treatment group had developed further attacks, compared with 48% in the delayed treatment group (p = 0.001). A recent Cochrane Review analyzed the 3 IFN trials in 1,160 patients with a first demyelinating event. The analysis confirmed efficacy in preventing conversion to CDMS over 2 years of follow-up. The meta-analysis found no significant differences in serious adverse events between IFNβ vs placebo.

The PRECISE trial randomized unifocal CIS patients with abnormal brain MRI to glatiramer acetate 20 mg/day or placebo. CIS patients who received glatiramer acetate were less likely to develop CDMS (25% vs 43%; p < 0.0001). They showed a 61% decrease in new T2 lesions and a 60% decrease in new contrast lesions compared with placebo.

Clearly, tracking patients over the long term is an important feature of early treatment research to delineate possible delays to progression or disability. Of note, there are extension studies of some of the trials reviewed here. The Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance (CHAMPIONS) study is a 5-year extension of CHAMPS, and a 2006 publication confirmed the benefits of early treatment measured by both MRI and relapses, but not Extended Disability Status Scale. CHAMPIONS will continue its follow-up for 10 years. Also, although the initial 3-year BENEFIT follow-up trial was completed that evaluated the effect of early vs delayed IFNβ on disability (mentioned above), another BENEFIT long-term follow-up study was undertaken and data collection was completed in May 2008. There is also an ongoing 5-year extension to the PRECISE study evaluating the effect of early vs delayed treatment with glatiramer acetate.

CIS = clinically isolated syndromes; ON = optic neuritis.

### Table 2 CIS prognosis

<table>
<thead>
<tr>
<th>CIS type</th>
<th>n</th>
<th>Years</th>
<th>Normal MRI (%)</th>
<th>Abnormal MRI (%)</th>
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<tbody>
<tr>
<td>ON</td>
<td>183</td>
<td>5</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Mixed</td>
<td>136</td>
<td>6.5</td>
<td>8</td>
<td>63</td>
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<tr>
<td>Mixed</td>
<td>42</td>
<td>8</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>ON</td>
<td>388</td>
<td>10</td>
<td>22</td>
<td>56</td>
</tr>
<tr>
<td>Mixed</td>
<td>71</td>
<td>14</td>
<td>19</td>
<td>88</td>
</tr>
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CIS = clinically isolated syndromes; ON = optic neuritis.

### Figure 1
Low-dose IFNβ-1a (IM and SC) reduced conversion to CDMS and MRI lesion burden vs placebo in CHAMPS and ETOMS studies

### Figure 2
Immediate IFNβ-1b treatment—delayed conversion to CDMS by 46% at 3 years and reduced risk of sustained disability by 40% vs delayed treatment in BENEFIT study
CONCLUSION MS represents a significant burden to patients, families, providers, and to the entire healthcare system. This disease is now known to involve ongoing, often insidious, accumulating damage. Early DMT therapy is a logical strategy to combat disease when focal inflammatory processes dominate the pathology. All the phase 3 CIS trials have demonstrated benefits for immediate use of DMTs to decrease clinical and MRI disease activity. Future studies are needed to determine more precisely the best approach to CIS, including how to follow response to therapy, how much disease activity is acceptable, and whether early therapy can prevent as well as delay transition to progressive MS.

REFERENCES

33. Clerico M, Faggiano F, Palace J, et al. Recombinant interferon β or glatiramer acetate for delaying conversion of the


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