DISEASE-MODIFYING agents approved for treatment of patients with multiple sclerosis (MS) are glatiramer acetate, interferon beta-1b and -1a, and mitoxantrone hydrochloride. Natalizumab was Food and Drug Administration approved in November 2004, but the manufacturers suspended marketing and clinical trials in 2005 because of safety concerns. Interferon beta-1a is approved for individuals with clinically isolated syndromes (CISs) who are at relatively high risk to “convert to MS.”1-3 Opinions vary about whom and when to treat. On one hand, the Medical Advisory Board of the National Multiple Sclerosis Society consensus statement (updated in February 2005) recommends initiation of a disease-modifying agent “as soon as possible following definite diagnosis of MS with a relapsing course, and in selected patients with first attack who are at high risk for MS (CIS).”4-5 Alternatively, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines suggest “it is appropriate to consider” treatment with approved therapies in these patients.1

We do not believe that all patients with MS or CIS should begin indefinite treatment at the time of diagnosis. Until it is clear that the patient has continuing disease activity clinically and/or radiologically, in which case the need for treatment is clear to the physician and to the patient, it is advisable to observe a period of no treatment while monitoring for inflammatory disease activity. The final decision about whether and when to initiate treatment should be shared by the patient and physician after an unbiased review of the relevant information with the patient.

Our current approach is predicated on the following: (1) MS often has a favorable natural history; (2) disease-modifying drugs are only partially effective in the short-term and prevention of disability in the long-term is unproven; (3) with prolonged treatment, it is hard to distinguish whether a favorable outcome reflects a favorable natural history or successful treatment in an individual patient, especially if treatment is started without a period of observation; (4) expense, adverse effects, and neutralizing antibodies are a concern and patients may be reluctant to commit to long-term parenteral medications, especially within the first few months following diagnosis; and (5) prospective clinical and magnetic resonance imaging (MRI) monitoring may allow identification of patients who need treatment.

Because disease-modifying agents do not benefit patients with primary progressive MS (approximately 10% of all patients with MS) and their benefit in secondary progressive MS (approximately 30% of all patients with MS) remains questionable,2,11 this discussion is limited to patients with a diagnosis of relapsing-remitting MS and CIS.

Patients with MS often do well without any treatment.12-17 A recent Olmsted County, Minnesota, study found that patients with minimal or no disability (Expanded Disability Status Scale [EDSS] score ≤2) at more than 10 years from onset have a 90% chance of remaining fully ambulatory (EDSS score ≤3.0) 10 years later.23,30,69 This group accounted for 17% of all patients with MS or 33.3% (28/94) of patients with relapsing-remitting MS in that population-based cohort. Kurtzke et al20 reported similar findings. Extrapolating these data to all patients with “destined to be benign” MS in the United States would result in approximately 35 870 individuals (17% of 211 000 patients with MS in the United States) unnecessarily receiving a potentially lifelong medication.13,21

Currently available approved treatments offer a mild to moderate short-term benefit in individuals with active recent disease who are most likely to respond. However, long-term efficacy is unproven.3,22-25 One needs to treat 5.6 patients with interferon beta-1b, 6.3 with interferon beta-1a, and 14.3 with glatiramer acetate to generate 1 person free of relapse for 2 years.25-28 Reduction in relapse rate is more evident in the first year and then declines.23,24 Number needed to treat (NNT) estimates for natalizumab are more favorable; early results suggest that the NNT to render 1 patient relapse free after 2 years of therapy is 2 to 2.4. However, serious safety concerns have led to voluntary cessation of natalizumab production.

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Extrapolating the results of short-term studies can be difficult. The Mayo Clinic sulfasalazine study demonstrated that short-term clinical measures of efficacy do not predict an important sustained effect (after 3.7 years) on clinical disability. Jacobs et al\textsuperscript{29} showed that interferon beta-1a substantially slowed the progression of disability in patients with MS and that after 2 years of treatment, 34.9% of placebo-treated patients had sustained worsening in disability vs 21.9% of interferon-treated patients. However, the efficacy of interferon was substantially reduced in the second year of treatment and the difference in proportions of patients worse at 2 years (sustained progression in 28 of 56 placebo-treated patients vs 18 of 55 interferon-treated patients, \(P > 0.05\)) was not significant. In addition, follow-up was limited; only 57% of enrolled patients were followed up for 24 months or more. Additionally, the NNT for 2 years to prevent 1 patient having a sustained progression of disability (defined as deterioration of \(\geq 1\) EDSS score point persisting \(\geq 6\) months) on the EDSS is 8.3 (33.3% probability for placebo group vs 21.1% for interferon-treated patients).\textsuperscript{29,30} Furthermore, the significance of “progression” of disability in a short-term clinical trial of relapsing-remitting MS is uncertain, in particular whether it is associated with development of secondary progressive MS, the major route to permanent long-term disability in MS. Liu and Blumhardt\textsuperscript{31} found that 40 of 84 patients in the placebo cohort with at least 2 years of follow-up originally exhibiting deteriorating disability subsequently improved. Thus, 47% of patients in the placebo group considered treatment failures were in fact transient treatment failures, likely a relapse-related phenomenon, a finding also supported by others.\textsuperscript{32}

A favorable effect of disease-modifying agents on MRI measurements (T2, gadolinium-enhancing lesion load, and brain atrophy) is cited as evidence in favor of early treatment. Although Brex et al\textsuperscript{33} showed that EDSS score at 14 years correlated with change in lesion volume on MRI at 5 years (\(r = -6.1, 0.8\) (53%) of 15 patients with 4 to 10 lesions at CIS presentation had an EDSS score of 3 or lower 14 years later. It seems intuitive that attack and/or enhancement suppression might reduce disability, but MRI gadolinium-enhancing lesions predict relapses, not disability.\textsuperscript{34,35} Filippi et al\textsuperscript{36} noted a 30% reduction in the rate of global brain atrophy over 2 years in interferon-treated compared with placebo-treated patients after the first clinical attack suggestive of MS. However, other studies have not shown this effect. Brain atrophy measures are confounded by changes in brain water and inflammation, regional differences in distribution, and lack of compelling evidence of a correlation between atrophy and disability.\textsuperscript{39} Magnetic resonance imaging measurement is a surrogate of therapeutic efficacy and not a therapeutic goal. Surrogate endpoints must be validated with long-term studies before they can be accepted as biomarkers of treatment effect on clinical outcome.\textsuperscript{40}

The CHAMPS and ETOMS studies demonstrated that treatment with interferon beta-1a reduces the likelihood of conversion to clinically definite MS within 2 years of a CIS.\textsuperscript{4,5} However, there is no evidence that delaying the second attack by 6 months has any long-term effect on disability. Based on CHAMPS, the NNT to prevent 1 person from developing clinically definite MS at 3 years was 7. Additionally, more than half of placebo-treated patients in both studies did not have a second attack during the 2- to 3-year follow-up, and those who did convert to clinically definite MS usually did so during the first year, suggesting that a brief period of observation could adequately identify the group in most need of treatment. The incomplete benefit from early interferon treatment is shown by the finding that approximately 50% of interferon beta-1a-treated patients still demonstrated clinical or MRI evidence of active disease during the initial 18 months of treatment in the CHAMPS trial.\textsuperscript{41}

The need for injection, high cost, and adverse effects further reduces the attractiveness of disease-modifying drugs to patients. In a study of 300 survey responses from patients in the NARCOMS Registry, 71% taking interferon beta-1b discontinued therapy and only 43% changed to another drug (40% taking interferon beta-1a discontinued therapy and 28% changed drugs; 21% of those taking glatiramer acetate discontinued and 8% changed).\textsuperscript{42} Two thirds of those discontinuing therapy were advised to do so by their physicians. The most common reasons that respondents discontinued treatment were lack of obvious benefit (15%), increase of MS (21%), and flu-like symptoms (14%).\textsuperscript{43} In the 2000 Olmsted County study, 44% of patients receiving these therapies stopped their initial treatment and half did not start another.\textsuperscript{12}

Neutralizing antibodies occur with variable frequencies (from 5% with interferon beta-1a intramuscular injection to 35% receiving interferon beta-1b) in patients treated with interferons and are associated with a reduction in therapeutic efficacy (relapse-rate reduction).\textsuperscript{43-45} Interpretation of these data are difficult because of assay reliability, antibody disappearance over time, and small patient numbers.\textsuperscript{46}

We acknowledge that “absence of evidence” does not constitute “evidence of absence” (at least some protection from long-term disability by disease-modifying agents). However, pronouncements and guidelines based on unproven surrogates that are weakly correlated with disability and for which long-term predictive value is unknown are not helpful. Until long-term benefit is proven, it seems most appropriate to limit treatment with these drugs to patients with the most to gain (ie, presence of clinical and/or radiological markers of continuing, active inflammation).

We avoid treating those with a greater chance of benign course (ie, those with a low EDSS score at 5 years and/or a low attack rate and little accumulation of MRI lesions early in the disease course), a low chance of benefit (ie, patients with established progressive disease without clinical or radiological markers of ongoing inflammatory disease), and those with an indeterminate prognosis (eg, CIS or early relapsing-remitting MS with infrequent mild attacks and a favorable prognostic profile).\textsuperscript{46-50} Until properly designed studies demonstrate unequivocal and long-term benefits on disability progression, we support observation and monitoring for patients with CIS and relapsing-remitting MS with recent diagnosis and without indicators of an aggressive course. Some
well-informed and motivated patients request early treatment with a disease-modifying agent, and their wishes should be respected within the “shared decision-making” model.

One (unproven) monitoring approach might be to perform annual neurological evaluations and MRI of the head (with gadolinium) at least for neurological evaluations and MRI of the head (with gadolinium) at least for the first few years after diagnosis. Testable guidelines for initiation of treatment and monitoring clinical and MRI response in clinical practice are needed. Well-designed observational studies will be required to answer the question of whether early or delayed application of currently approved therapies delays the development of disability in patients with relapsing MS to a clinically meaningful extent.

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Most Patients With Multiple Sclerosis or a Clinically Isolated Demyelinating Syndrome Should Be Treated at the Time of Diagnosis

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HE QUESTION “HOW early should multiple sclerosis (MS) be treated?” implies that we can accurately pinpoint the onset of the disease. At the time of the first clinically isolated demyelinating syndrome (CIS), many patients describe antecedent symptoms that suggest an earlier disease onset. Further, the occurrence of occult disease prior to the onset of clinical symptoms is corroborated by the observation that up to 80% of individuals with a CIS who go on to have confirmed MS (clinically definite MS [CDMS]) already had radiographic evidence of MS at the time of initial examination.1-8 Unfortunately, the true onset of MS cannot be determined in most patients, suggesting that “early” treatment is, for most, not early at all.

Multiple sclerosis is a lifelong illness that causes significant and progressive disability in a majority of affected individuals. Its nature and the severity of its progression are wildly variable and unpredictable. None of today’s MS medicines is reparative or restorative, leaving prevention as the primary focus of treatment. Thus, the question of when to begin preventive therapy in a variably acting illness represents a formidable challenge. Our objective is to underscore the evidence to support early (and even earliest) treatment for most patients with MS or CIS.

OUTCOME PREDICTIONS FOR INDIVIDUAL PATIENTS

Unfortunately, we lack a validated means to precisely differentiate between individuals who are destined for a milder vs a more ominous disease course. Nevertheless, natural history studies demonstrate that 20 to 25 years after diagnosis nearly 90% of patients with MS will have substantial disability.9,10 These same studies show that individuals who have more frequent early attacks are more likely to eventually develop compromising physical limitations. Despite the clear merits of natural history studies in MS, they are generally limited by their application of disability measurement instruments (eg, the Expanded Disability Status Scale11 [EDSS]) that have since been shown to lack sufficient association with some of the most important collateral manifestations of MS, such as activities of daily living, quality of life, loss of gainful employment, hopelessness, and cognitive and intellectual deterioration.

MAGNETIC RESONANCE IMAGING METHODS CONFIRM OCCULT AND DISSEMINATED CENTRAL NERVOUS SYSTEM DAMAGE IN EARLY MS

It is increasingly recognized that neuronal cell injury and axonal loss (characterized by a loss of N-acetylaspartate) precede the process of brain atrophy in patients with relapsing-remitting MS (RRMS).12 Patients with early-stage RRMS, even those with minimal disability, have evidence of both gray and white matter changes in tissue architecture.13,14 Strikingly, brain atrophy occurs at similar rates in both RRMS and secondary progressive MS (SPMS),13 whereas treatment with interferon beta exerts a favorable effect on slowing brain atrophy in patients with RRMS but not in those with SPMS.15,16 Studies that have carefully and systematically analyzed axonal damage with sophisticated magnetic resonance imaging (MRI) measures suggest that central compensatory mechanisms may mask such damage until a critical injury threshold has been exceeded.17 Further, while cognitive dysfunction occurs early in MS, progressive atrophy and other MRI measures prospectively predict worsening intellectual decline.18,20 Several MRI studies have convincingly shown that irreversible tissue