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

E. M. Frohman, MD; E. Havrdova, MD; F. Lublin, MD; F. Barkhof, MD; A. Achiron, MD; M. K. Sharief, MD; O. Stuve, MD, PhD; M. K. Rache, MD; L. Steinman, MD; H. Weiner, MD; M. Olek, DO; R. Zivadinov, MD, PhD; J. Corboy, MD; C. Rainé, PhD, DSc; G. Cutter, PhD; J. Richert, MD; M. Filippini, MD

The 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),15 whereas treatment with interferon beta exerts a favorable effect on slowing brain atrophy in patients with RRMS but not in those with SPMS.16,17 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.18 Further, while cognitive dysfunction occurs early in MS, progressive atrophy and other MRI measures prospectively predict worsening intellectual decline.19,20 Several MRI studies have convincingly shown that irreversible tissue damage is already present at the time of diagnosis.21-23

Author Affiliations are listed at the end of this article.

Evidence suggests that the extent and rate of tissue loss and/or damage are milder in patients with CIS than in those with RRMS. Dalton et al.26,27 prospectively followed up 55 patients with CIS for 3 years and found that after the first year, patients who evolved to CDMS according to the McDonald criteria28 developed significantly more ventricular enlargement than did those without disease evolution. After 3 years, 53% of the patients had evolved to MS, and at this time, increased ventricular volume and gray matter atrophy were found in patients with MS compared with those who did not evolve. Similar findings have been documented when brain atrophy was measured in a trial of patients at the earliest clinical stage of MS.29 Average lesion and brain MTR values have been found to be lower (consistent with brain tissue disorganization) in patients with RRMS than in those with CIS, whereas no difference has been found in cross-sectional studies between patients with RRMS and those with SPMS.21,30

Notwithstanding the more favorable radiographic profile of CIS vs RRMS and SPMS, during a 1-year follow-up study of those with CIS, both average lesion MTR and normal-appearing brain tissue MTR worsened significantly.31 More recently, MTR and diffusion abnormalities were demonstrated in the gray matter of patients with RRMS, whereas no similar abnormalities were detected in patients with CIS at initial examination.23,32-36 A recent 18-month follow-up study with serial (every 3 months) diffusion MRI revealed that gray matter damage increases with time in patients with RRMS.37 Metabolite abnormalities, including a decrease of N-acetylaspartate, choline, and glutamate concentrations, have also been shown in the cortical gray matter of patients with early RRMS but not in patients with CIS.38,39 Recent studies of patients with CIS revealed no abnormality in cervical cord MTR, which is clearly damaged in established MS.40,41

The presence and extent of MRI abnormalities in patients with CIS suggestive of MS do predict subsequent disease activity. In a 3-year follow-up study of patients with CIS, Dalton et al.44 tested the ability of the new International Panel criteria to predict conversion to CDMS and found a sensitivity, specificity, and accuracy of 83%. These results were confirmed by Tintore et al.45 In the placebo arm of a trial involving patients in the earliest clinical stage of MS, the International Panel criteria for dissemination in space effectively predicted subsequent evolution to CDMS.46 When a new T2 lesion was allowed as evidence for dissemination in time, 1 study showed that 82% of patients with CIS who fulfilled the new MRI criteria for MS after 3 months had developed CDMS after 3 years; another study found that 80% of patients with CIS who fulfilled the same criteria after 1 year developed CDMS after 3 years.45,47

The presence of asymptomatic T2 lesions on brain MRI at initial examination increases the likelihood that MS will develop in the subsequent 5 to 14 years.44-48 The study with the longest follow-up showed that after a mean of 14.1 years CDMS developed in 88% (98% exhibiting multiphasic disease by either clinical or radiographic progression) of patients with CIS with abnormal MRI results at initial examination and in only 19% (44% exhibiting multiphasic disease by either clinical or radiographic progression) of those with normal MRI results.49 These data have been recently confirmed by Minneboo et al.50

The number (and volume) of T2 lesions on baseline MRIs from patients with CIS increases the likelihood of developing “fixed” disability.50,51 In the study by Brex et al.,49 none of the patients with CIS with normal MRI results at baseline reached an EDSS score of 3. Minneboo et al. also showed that the likelihood of reaching an EDSS score of 3 was best predicted by the presence of at least 2 infratentorial lesions, suggesting that the distribution of lesions may also be an important prognostic factor.50 A similar stratification has shown that advancement to a more substantial level of disability (EDSS score >6) is significantly more likely in those with the greatest radiographic burden of disease at baseline (>10 lesions).49

### RANDOMIZED CONTROLLED TRIALS SUPPORT “EARLIEST” TREATMENT

With the advent of immunomodulating drugs that have distinct benefits on the relapse rate, disability scores, and radiographic measures of tissue injury, our perception of what can be done to treat MS has shifted significantly.51-57 When mimicking conditions are excluded at the time of a CIS, the majority of those with multiple MRI lesions within the brain and spinal cord go on to exhibit a multiphasic course consistent with MS. As such, 2 large studies, ETOMS and CHAMPS, confirmed the clinical and radiographic benefits of beta interferon la (interferon beta-1a) treatment when initiated at the time of CIS.58,59 Similarly, intravenous immunoglobulin treatment was recently shown to reduce the rate of conversion to MS and diminish accumulation of several MRI abnormalities during a 1-year period after CIS.60 In addition, these well-designed class I studies have shown a reduced requirement for corticosteroid therapy and hospitalization following exacerbations, signifying an important mitigating effect of these therapies on attack severity. Such treatment also reduces the accumulation of brain atrophy by about 30% in 2 years.59
Multiple sclerosis is a lifelong disease with an unpredictable disease course. There has been great debate concerning the role of MS exacerbations in disability progression. Nevertheless, it is likely that many (if not most) patients do not fully recover from their attacks. While exacerbations can result in loss of function, their frequency and level of severity can be substantially mitigated by disease-modifying therapy. Alternately, these same therapies do not significantly alter the subsequent and almost uniformly stereotyped secondary progressive phase of the disease.

Treatment intervention during the earliest phase of MS constitutes an important preemptive strategy. Hypothetically, untreated patients may be more predisposed to an expansion in the repertoire of autoaggressive immune responses (ie, epitope or determinant spreading). While the initial immunological attack in an individual patient may be directed against a specific or restricted set of antigenic protein epitopes, subsequent attacks (either clinically documented or occult events) may spread to involve other epitopes. While epitope spreading may be an effective mechanism of clearing infectious agents, it has also been implicated in systemic and organ-specific autoimmune diseases.

HYPOTHESIS: THE TISSUE INJURY PENUMBRA IN MS IS MODIFIABLE BY EARLY TREATMENT

Histopathologic analysis of the early (acute) MS lesion and the expanding plaque of RRMS lends currency to the view that therapeutic intervention should commence soon after or at the time of diagnosis. In contrast to conditions in the established lesion, several features of fresh lesions are probably reversible, some of which are known harbingers of later permanent damage. Samples from a typical acute MS lesion, detected by MRI as an area of white matter manifesting as a tumeform mass in an individual with a CIS, reveal a highly edematous parenchyma heavily infiltrated by perivascular collections of small lymphocytes, patterns indicative of a breach in the blood-brain barrier. Widespread loss of myelin and axonal damage occur alongside macrophages laden with recognizable myelin debris. Astrocytes are characteristically hypertrophic, but glial scarring has not yet occurred. Despite the presence of demyelination, there may be considerable sparing (sometimes hyperplasia) of oligodendrocytes and some remyelination. Thus, if one compares this image with that of the chronic lesion with its intense glial scarring, significant depletion of axons, and almost total lack of remyelination, the acute lesion offers considerable hope for reversal and/or repair. It truly constitutes the inflammatory penumbra.

From the treatment standpoint, anti-inflammatory therapy may reduce the edema, which in turn might ablate the negative effects (particularly on axons) of extracellular compounds like reactive oxygen species, free radicals, glutamate, cytokines, and acid hydrolases, products of the infiltrating cells and macrophages. The down-regulation of these molecules can only bode well for myelin repair, some of which is usually in evidence in the acute lesion. The reduction of edema and its associated molecular cascade might also lead to the arrest and/or reversal of the ongoing injury to axons, rendering them available for remyelination. Importantly, the cumulative effect of the reversal of these events would likely impede the development of an astroglial scar, a known hazard in central nervous system repair. The existence of potentially remyelinating oligodendrocytes and oligodendrocyte progenitors in acute MS (which appear not to persist into chronic stages) provides further support for early intervention. Previous works on the animal model, experimental allergic encephalomyelitis (EAE), indicate that acute-phase treatment is more effective than later treatment, with remyelination occurring after the ablation of the inflammatory response. Thus, it is important to argue in favor of early treatment in the prevention of lasting damage to the blood-brain barrier in MS. Obviously, the later one intervenes, the greater the scarring around blood vessels and the increased likelihood of persistent cellular traffic. Since a defective blood-brain barrier is a key component of the lesion substrate in MS, any strategy capable of curbing this anomaly early on would be predicted to have beneficial effects on subsequent repair.

THE PRICE OF WITHHOLDING DISEASE-MODIFYING THERAPY

It is patently clear from class I, phase III controlled drug trials that individuals with RRMS who received placebo exhibited more severe disease activity than those receiving active therapy. In essence, placebo-treated patients experience accelerated and more profound disability accumulation with time. It has been suggested that particular MS phenotypes, such as optic neuritis, may carry a lower-risk profile of long-term disability. While this may be true in some patients, it appears that the MRI in such patients is more predictive of a more vs less ominous disease trajectory.

A retrospective population-based cohort study has suggested that the majority of 161 patients with MS remained stable or progressed minimally during a 10-year period. However, this ascertainment was principally based on EDSS measures of disability and did not systematically assess quality of life, cognitive dysfunction, symptomatic complaints, loss of employment, or the effect of 10 years of the disease on activities of daily living. Recognition of the frequent and manifold effects of MS on every aspect of a patient’s life has made the isolated use of the EDSS an obsolete approach in characterizing the true burden of disability in MS. Such a study cannot, and should not, justify not treating any individual patient at the time of diagnosis.

Ultimately, by the time untreated patients are “bad” enough to justify receiving therapy, they may no longer be optimal responders. We acknowledge that MS disease-modifying therapy is expensive. However, disability progression, loss of gainful employment, and intellectual deterioration are substantially more expensive. The available drugs provide tangible benefits to patients. They are well tolerated and do not appear to have any
Multiple sclerosis therapeutics has finally progressed to the point that a substantial component of disease activity is preventable, or at least modifiable. In contradistinction, while restoration occurs naturally in a few individuals, we cannot restore most patients with today’s treatments. Should every patient with a diagnosis of early MS or CIS be treated with disease-modifying agents? No, not every patient with MS or CIS should be treated. However, the incontrovertible evidence that disease-modifying therapy can significantly reduce the clinical and radiographic features of MS provides compelling justification to carefully consider offering therapy to “almost every” patient with MS.

Arguments in favor of early treatment of MS include:

1. The majority of patients with MS will go on to develop significant disability over time, and it is not possible to easily predict which patients will have a “benign” course until well after the time when some untreated patients will have developed significant disability.

2. Pathological and radiological studies clearly show irreversible axonal injury early in the course of the illness. In addition, even patients who may appear to be doing well clinically, with few clinically apparent relapses, may well be accumulating new lesions and progressive tissue damage and atrophy on brain MRI, which ultimately are associated with physical and cognitive disability.

3. The Food and Drug Administration–approved medicines to treat MS work best early in the course of the illness, even at the time of a CIS, and work poorly, if at all, later in the progressive phase of the illness.

4. The Food and Drug Administration–approved medicines decrease the number and severity of relapses, the number and size of new lesions, and the progression of disability. More relapses do translate into more disability, at least early in the illness.

5. Delay in therapy has been associated with a persistent, larger burden of disease on MRI and in the number of patients with progression of disability.

Accepted for Publication: December 27, 2005

Author Affiliations: Departments of Neurology and Ophthalmology (Drs Frohman, Stuve, and Racke), University of Texas Southwestern Medical Center at Dallas (Dr Frohman); Department of Neurology, Charles University, Prague, Czech Republic (Dr Havrdova); Department of Neurology, Mount Sinai School of Medicine, New York, NY (Dr Lublin); Department of Radiology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands (Dr Barkhof); Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel (Dr Achiorn); Department of Neurology, Guy’s Hospital, London, England (Dr Sharief); Department of Neurology, Stanford University, Stanford, Calif (Dr Steinman); Department of Neurology, Brigham and Women’s Hospital, Harvard University, Boston, Mass (Dr Weiner); Department of Neurology, University of California, Irvine (Dr Olek); Buffalo Neuroimaging Analysis Center, The Jacobs Neurological Institute, Department of Neurology, University of Buffalo, Buffalo, NY (Dr Zivadinov); Department of Neurology, University of Colorado, Denver (Dr Corboy); Department of Pathology, Albert Einstein College of Medicine, Bronx, NY (Dr Raine); Department of Biostatistics, University of Alabama, Tuscaloosa (Dr Cutter); Research and Clinical Programs, National Multiple Sclerosis Society, New York (Dr Richert); Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy (Dr Filippi).

Correspondence: E. M. Frohman, MD, PhD, Department of Neurology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, Texas 75325 (elliot.frohman@utsouthwestern.edu).


REFERENCES


Early Multiple Sclerosis

To Treat or Not to Treat?

E. S. Roach, MD

The truth is rarely pure and never simple.
Oscar Wilde

We are fortunate to now have several effective treatments for multiple sclerosis (MS), and it seems intuitive that such a serious neurological disorder should be treated. Glatiramer acetate, interferon beta-1b and -1a, and mitoxantrone hydrochloride have demonstrated efficacy for relapsing-remitting MS. None of these agents is effective in every individual, and like all medications, these drugs can have adverse effects. While indefinite treatment is no doubt a better option than progressive neurological deterioration, do we know that MS is so uniformly bad that every single individual who has it must be treated immediately and indefinitely? More to the point, do we have the luxury of deferring therapy in select individuals long enough to determine which patients, if any, could reasonably avoid long-term medication?

Clearly, some individuals with MS should begin immediate treatment and remain receiving treatment. Before we had effective treatment for MS, it was estimated that as many as a third of patients with MS never became disabled from their disease. Although many of these individuals doubt had more extensive disease than was then appreciated, there could still be a subgroup of patients with MS with an indolent course who could safely avoid a lifetime of treatment without paying a huge price in avoidable neurological disability. Even if such individuals exist, we are left with the practical problem of how to accurately identify them before treatment is started.

One approach, as proposed by Pittock and colleagues, is to defer treatment until the patient’s course is better established, possibly allowing those with less aggressive disease to avoid years of unnecessary treatment. But as Frohman and colleagues counter, most people with newly diagnosed MS do progress, and we must consider that treatment could be less effective if started later in the course of the illness. An even more intriguing question, not raised by either side, is whether an individual who begins treatment but does exceptionally well could ever safely discontinue treatment.

The issue of whether to treat a chronic neurological disorder is certainly not unique to MS. Several years ago, for example, children who had even 1 nonfebrile seizure were generally placed on daily medication for an extended period, and individuals with epilepsy in addition to a chronic neurological handicap were typically treated with antiepileptic medication for life. Armed with better natural history data (showing that only about a third of the otherwise normal patients who have a single seizure go on to have recurrent seizures), the recent trend has been to defer treatment at least until another seizure occurs. The medication risk coupled with the evidence that many patients can safely avoid treatment has made us reconsider the notion of treating every patient after the first seizure. Likewise, we now have enough information about the natural history of epilepsy to make it feasible to stop treatment in some individuals after a long seizure-free interval. Of course, many people with epilepsy must continue taking medication indefinitely, and some of those who try to stop must resume treatment after the seizures recur.

What has allowed us to alter our treatment approach for seizures is the accumulation of specific information that not everyone needs aggressive treatment and that others can safely halt therapy. Without such evidence for individuals with MS, it will be difficult to know for sure whether it is ever safe to defer treatment. While it would be wonderful if we could avoid treating some patients with MS, until we can distinguish these individuals from the others, it is probably better to offer treatment to all patients except in the setting of a clinical trial.

Accepted for Publication: December 27, 2005.
Correspondence: E. S. Roach, MD, Department of Neurology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157; phone (336) 716-1619; fax (336) 716-9489 (sroach@wfubmc.edu).

REFERENCES


We invite you to suggest controversies and 3 names of potential authors to write about either side of the issue. Do not feel that you need to exclude yourself. Please communicate with E. S. Roach, MD, Department of Neurology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157; phone (336) 716-1619; fax (336) 716-9489 (sroach@wfubmc.edu).