Early Intervention in Multiple Sclerosis CME/CE

Douglas R. Jeffery, MD, PhD

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This activity is intended for neurologists; primary care practitioners, including physicians, nurse practitioners and physician assistants; pharmacists; specialists in multiple sclerosis (MS); and other healthcare professionals who care for patients with MS.

Goal
The goal of this activity is to provide a comprehensive review on advances in the pathophysiology of MS for early intervention and differentiation in therapies.

Learning Objectives
Upon completion of this activity, participants will be able to:
1. Describe the potential clinical benefits of the early recognition of and intervention for MS
2. Identify and contrast efficacy profiles of immunomodulatory therapies for patients with a clinically isolated syndrome
3. Evaluate new data in neuroimaging related to diagnosis and therapeutic monitoring of patients with MS

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting the central nervous system. Nearly 400,000 Americans have MS, and it is the leading cause of disability in young adults in the United States.[1,2] The first treatment for MS was approved by the US Food and Drug Administration 17 years ago to reduce the frequency and severity of relapses. In the following years, several other agents were approved for the treatment of relapsing forms of MS. These included intramuscular and subcutaneous formulations of interferon beta-1a (IFN beta-1a), glatiramer acetate (GLAT), and IFN beta-1b. In the first decade of this century, 2 additional agents were approved for worsening MS and were targeted for patients with an inadequate therapeutic response to the IFNs and GLAT and for those patients with active disease who are unable to tolerate standard therapies. These include mitoxantrone and natalizumab. The knowledge gained in the years since the approval of these agents has revolutionized the treatment of MS. A mere 20 years ago, the diagnosis of MS was devastating. In the present day, MS is regarded as a treatable disease with a variable prognosis. Among the other insights realized in the past 2 decades is that, like many other diseases, early diagnosis and treatment is essential to limiting and preventing long-term disability.

An understanding of the natural history of MS and an understanding of the pathology and the role of inflammatory disease activity is critical to understanding the importance of early diagnosis and treatment of MS. The natural history of relapse and disability progression confused clinicians for many years. It has only been in recent years that a better understanding of disease dynamics and the role of lesion location and the degree of tissue destruction has allowed us to piece together a basic understanding of the disease dynamics. Even now, there are many more aspects of the disease of which we have little knowledge or understanding. As a result of a better understanding of the natural history of MS and because of clinical trials in patients with early disease, the importance of early treatment in MS has now become clear and constitutes the accepted standard of practice, especially in those patients with active inflammatory disease.

The Diagnosis of MS: The Role of MRI

The most basic principle of MS diagnosis is the establishment of lesion dissemination in time and space in the absence of a more likely explanation. This principle has constituted the basis for every diagnostic criterion ever used in MS and is the basis of the revised McDonald criteria.[2] This set of diagnostic criteria is summarized in the Table. This was the first diagnostic criteria to use MRI lesions to satisfy the criteria of lesion dissemination in time and space and it allowed for an earlier diagnosis of MS. The criteria are highly specific but slightly less sensitive than more recently formulated criteria.[3]

Table. Poser and McDonald Diagnostic Criteria for Multiple Sclerosis[2,4,5]

Poser Criteria	McDonald Criteria	
	Clinical Presentation	**Additional Data Needed**
Clinically definite MS • 2 attacks and clinical evidence of 2 separate lesions • 2 attacks, clinical evidence of one and paraclinical evidence of another separate lesion	• 2 or more attacks (relapses) • 2 or more objective clinical lesions	• None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
Laboratory-supported definite MS • 2 attacks, either clinical or paraclinical evidence of 1 lesion, and CSF OB/IgG • 1 attack, clinical evidence of 2 separate lesions and CSF OB/IgG • 1 attack, clinical evidence of 1 and paraclinical evidence of another separate lesion, and CSF OB/IgG	• 2 or more attacks • 1 objective clinical lesion	Dissemination in space, demonstrated by: • MRI or • A positive CSF and 2 or more MRI lesions consistent with MS or further clinical attack involving different site

CSF = cerebrospinal fluid; IgG = immunoglobulin G; OB = oligoclonal bands; MRI = magnetic resonance imaging; MS = multiple sclerosis

According to the McDonald criteria,[2,4,5] lesion dissemination in space may be accomplished at the time of a clinically isolated syndrome (CIS) if the MRI shows 1 asymptomatic gadolinium enhancing lesion or at least 9 T2 lesions, 3 of which are periventricular, 1 subcortical, and 1 infratentorial. These are the Barkhof-Tintore criteria for dissemination in space and are based on a study in which patients who satisfied this criterion had an 85% probability of a second attack within 2 years of follow-up.[6,7] The criterion of lesion dissemination in time is satisfied when a new T2-weighted lesion or a new gadolinium-enhancing lesion is present on an MRI scan done at least 1 month after the onset of a CIS. One problem with these criteria is that they lack sensitivity even though their specificity is quite good. In the 14-year follow-up of the Queens Square CIS cohort, 88% of patients with at least 1 MRI lesion had a second attack within 14 years and another 10% had new MRI lesions.[8] Many of these patients would not have satisfied McDonald criteria for a considerable period of time despite that biologically they had MS from the start.

As a result of issues such as this, newer and simpler criteria for lesion dissemination in space at the time of CIS have been investigated.[3,9] One study examined the predictive value of 1 or more asymptomatic locations in at least 2 of 4 locations strongly suggestive of MS (juxtacortical, periventricular, infratentorial, spinal cord). In this study,[3] these criteria proved to be as specific as and more sensitive than the McDonald criteria for predicting conversion to definite MS as defined by a second clinical attack. An earlier review suggested that dissemination in space by MRI could be defined using the presence of 3 or more asymptomatic MRI lesions.[10] This criterion also results in improved sensitivity, but specificity is lower than that achieved using the McDonald criteria.[9]

One recent study evaluated the use of a single MRI with gadolinium-enhancing lesions as a criterion for dissemination in time.[9] Because the presence of active gadolinium-enhancing lesions and inactive T2 lesions suggests the presence of both new and old lesions, the presence of gadolinium would be a marker for lesion dissemination in time. In this study, a gadolinium-enhancing lesion observed in conjunction with asymptomatic T2 lesions suggestive of MS predicted conversion to definite MS with high specificity but lower sensitivity.

Whereas any formal diagnostic criteria must include criteria to prove lesion dissemination in time and space, the most consistent and compelling data suggest that in patients with a CIS and asymptomatic MRI lesions suggestive of MS, the rate of conversion to definite MS is nearly 100%. This suggests that this group of patients already has MS even though they do not yet satisfy diagnostic criteria.

The Natural History of MS: Clinical Course of Relapsing Disease

Approximately 80% of patients present with a CIS that takes the form of optic neuritis, partial transverse myelitis, or a syndrome localizable to infratentorial structures. Many actually have coexistent constitutional symptoms such as fatigue and memory difficulty. As noted, the rate of conversion to clinically definite MS (CDMS) is very high for those patients with asymptomatic T2 lesions suggestive of MS.[8] For patients with CIS and a normal cranial MRI, the risk for conversion to MS is considerably lower but still reaches 40% at 10-year follow-up.[11] Of those patients, approximately 17% will have a second clinical attack and new MRI lesions suggestive of MS will develop in 23%.[11]

Overall, 85% of patients present with relapsing forms of MS and 15% present with primary progressive forms. In the entire cohort of the MS population, disability accumulation tends to be slow.[12,13] The median time to an expanded disability status score (EDSS) of 6 (requiring unilateral assistance for ambulation) is 14.97 years. In other words, it takes approximately 15 years for the average patient to require a cane for ambulatory assistance.[12,13] Some will progress much faster and others far slower. In long-term follow-up studies, the majority of patients initially classified as having benign MS eventually worsen. Patients with disease duration of 10 years with little or no disability (EDSS < 3.0) have been defined as having benign MS. In cross-sectional studies, as much as 20% of relapsing remitting MS (RRMS) has been defined as benign.[12,13]

Hawkins and colleagues[14] followed a group of patients with benign disease at 10 years. Follow-up 10 years later revealed that only 25% of those initially classified as benign still had mild disability. Most had progressed and disability had become more advanced. At 20 years of follow-up, very few of those initially classified as benign still had little disability. These studies demonstrate that patients with MS are always at risk for progression at any time after disease onset. Other studies have demonstrated that as many as 50% of those with low-grade disability or benign disease have significant neuropsychologic deficits. In summary, benign MS does occur but it is uncommon, and patients with MS are always at risk for progression.

In the early stages, disease disability progression often occurs in the context of relapse.[15] Approximately 50% of patients have residual disability after an MS relapse. In a study that evaluated the placebo groups of several combined clinical trials, Lublin and Reingold[16] found that approximately 30% of placebo-treated patients had residual disability of at least 1 EDSS point for at least 90 days, and 41% had at least a one-half point increase on the EDSS that was maintained for at least 90 days.

Over time, patients with RRMS will transition to a secondary progressive (SP) form in which disability accumulates gradually with or without continued periods of relapse. After 15 years, nearly 60% of patients have reached the SP stage, and after 26 years, 89% have SPMS.[13] In SPMS, the accumulation of disability tends to be more rapid. The median time to EDSS 6 varies between 2-1/4 and 4-1/2 years.[13] The benefit of treatment for SPMS is less than that seen in the RR phase. In the population of patients with SPMS who continue to have relapses, there does appear to be evidence of treatment benefit in the form of decreased relapse rates and fewer new MRI lesions. An effect on disability progression in SPMS is debatable. However, evidence from long-term follow-up studies indicate that patients treated with IFN or GLAT have a lower rate of conversion to SPMS compared with historical cohorts and when compared with populations in the same study who did not stay on therapy.[17-19]

Life expectancy is also decreased in patients with MS. Mortality generally occurs 5 to 10 years earlier than that of the general population, and in patients with more advanced disability, the mortality rate may be 8 times greater than the general population. This is related, in part, to less mobility and an increased susceptibility to infection with advanced disease.

The Natural History of MS: MRI Studies

Although the clinical course of MS is variable, most patients progress, and the rate at which they progress is highly variable in both rate and extent. It has often been said that the clinical course of MS represents the "tip of the iceberg." The wealth of information provided by MRI studies that have examined both natural history and the effects of immunomodulatory agents has revolutionized our understanding of MS and its treatment. The pathologic event most frequently observed on MRI is the appearance of gadolinium-enhancing lesions. The histopathologic correlation of gadolinium enhancement in MS is breakdown of the blood brain barrier, edema, infiltration of macrophages and lymphocytes into the tissue, myelin destruction, and axonal transaction.[20,21] Within an active lesion are roughly 11,000 transected axons per cubic millimeter.[20] Most lesions in the periventricular white matter are asymptomatic and have no associated motor or sensory symptoms. This is not true for tumefactive lesions, which are large, highly destructive, and interfere with the conduction of action potentials.

When an enhancing lesion develops in an eloquent location such as the optic nerve, brain stem, or spinal cord, it is associated with symptoms. This is the biologic underpinning of a relapse. In patients with untreated RRMS, gadolinium-enhancing lesions occur quite frequently. Studies using monthly MRI report the development of 20 enhancing lesions each year in the average patient.[22] There are roughly 5 to 10 enhancing lesions for every clinical relapse. Of interest is that the median duration of an enhancing lesion is only 12 days, and two thirds have resolved after a month.[23] In the absence of treatment, there is extensive ongoing inflammatory disease activity and associated injury to neural issue.

Studies evaluating brain volume have demonstrated that inflammation, as measured by gadolinium enhancement, is followed by reductions in brain volume (atrophy).[24] Brain atrophy is one of the best predictors of disability progression; it is evident at the time of CIS in patients in whom MS later develops. Studies of brain atrophy in patients with RR disease reveal that the rate of atrophy may be higher earlier in the disease. On histopathology, every lesion is associated with some degree of permanent damage to the nervous system. It makes good theoretical sense that the suppression of new active lesions would lead to better long-term outcomes.

Many but not all new enhancing lesions leave a residual T2-weighted abnormality.[25] In actuality, only 19% of enhancing lesions are associated with residual T2-weighted lesions, but on histopathology, all enhancements leave some degree of residual injury to the tissue. Over time, T2 lesion load accumulates and it does so at a rate of about 5% to 7% per year. T2 lesion load at the time of CIS is predictive of subsequent disability progression many years later.[8] Each new T2-weighted lesion began with an inflammatory lesion. Approximately 30% of new enhancing lesions evolve into chronic T1 hypointense lesions known as "black holes."[26] Black holes are associated with greater progression of disability in both RRMS and SPMS and reflect a disease process in which there is a greater tendency to cause more severe injury to neural tissue with each inflammatory event.[27]

After a variable period of time, the damage caused by inflammatory disease activity accumulates, and this injury becomes clinically manifest. This can occur very early in the disease process when a destructive lesion strikes an eloquent location, or it can become apparent much later. Early on, reparative mechanisms may function more effectively and patients may be able to compensate for some degree of injury. In the later stages, the compensatory mechanisms may be overcome so that every inflammatory injury becomes clinically manifest in the form of worsening cognition or disability progression.

The Effects of Immunomodulatory Therapy

All of the immunomodulatory agents (IMAs) reduce the rate of clinical relapse.[28-32] IFN beta-1b was also shown to reduce the severity of relapse.[28] Relapse rates have been reduced by 18% with intramuscular IFN beta-1a,[31] by 32% with subcutaneous IFN beta-1a,[30] by 33% with IFN beta-1b,[29] and by 29% with GLAT.[32] Although the effects of the IMAs on clinical relapse have been relatively mild, the effect on MRI metrics has been more impressive. In various studies, the IMAs decreased enhancing lesion frequency by between 35% and 91% and reduced the frequency of new T2 lesions.[33-35] In addition, in clinical trials in patients with established RRMS, all of these agents reduced the accumulation of T2-weighted lesion burden. Of note, patients enrolled in the earlier clinical trials had disease duration and disease activity that was far greater than that observed in later trials. Clinical trials examining the effects of IMAs in early disease have demonstrated much more robust effects.

CHAMPS

Four clinical trials have examined the effects of IMAs in patients with CIS. The purpose of these trials was to determine whether the rate of conversion to CDMS was lower in IMA-treated patients with CIS and MRI lesions suggestive of MS. The first trial was the Controlled High risk subjects Avonex® MS Prevention Study (CHAMPS).[36] This trial enrolled 383 patients with CIS and 2 clinically silent lesions detected by MRI. Patients were randomly assigned to receive placebo or intramuscular IFN beta-1a 30 µg/week for 3 years or until conversion to CDMS. For patients receiving intramuscular IFN beta-1a, the risk for conversion to CDMS was 44% lower than that for patients who received placebo ($P = .002$). The probability of converting to CDMS during the study was 35% in the treatment group and 50% in the placebo group ($P = .002$).[36] The risk for conversion to CDMS was 42% lower for treated patients presenting with optic neuritis, 60% lower for those patients with infratentorial syndromes, and 70% lower for those presenting with a spinal cord syndrome. In addition, for patients at high risk for progression as defined by having 9 or more T2-weighted lesions and at least 1 enhancement on their baseline MRI, the risk for CDMS was reduced 66%. Of note, the effect on MRI metrics in this early population was far more robust than that observed in patients with established RRMS. A long-term follow-up study of the patients enrolled in this trial suggests that the benefits of early treatment are evident at 10-year follow-up.[37]

At the end of the trial, all patients were started on treatment with intramuscular IFN beta-1a and follow-up was carried out at 5 and 10 years.[37,38] At both the 5- and 10-year follow-up, those patients assigned to early treatment had relapse rates roughly half those of patients who began therapy at the time of conversion to CDMS or at the end of the trial (0.17 vs 0.32). In addition, the risk for conversion to CDMS was still reduced 40% at 10 years, and 79% of patients still had an EDSS less than 3.[37] The benefits of early treatment are clearly evident in this study.

ETOMS

The Early Treatment of MS (ETOMS) trial was a similar trial in patients with CIS. This trial evaluated effects of early treatment with subcutaneous IFN beta-1a 22 µg once weekly on disease progression in patients with CIS and an MRI scan highly suggestive of MS.[39] During the 2-year study period, the risk for conversion to CDMS was 34% in the subcutaneous IFN beta-1a group compared with 45% in the placebo group ($P = .047$). The time to a second relapse was delayed by 317 days in the treatment group compared with the placebo group ($P = .023$). Of interest is that patients who had a multifocal presentation had a twofold higher rate of conversion to CDMS compared with those with a monofocal presentation. There was no effect on disability progression, and no long-term follow-up was carried out. Of note, the dose of IFN beta-1a used in this trial was far lower than the standard approved doses used in clinical practice. Despite that, clinical effects were still evident. Further, as in the CHAMPS trial, the effect of this dose of IFN beta on MRI metrics was far more robust than what would be expected in a population of patients with untreated RRMS. The burden of disease on T2-weighted MRI scans increased by 10% over 2 years in the placebo group, whereas in the treated group, the lesion burden was reduced by 12%. Again, this is a far greater effect than would be expected in patients with established RRMS.

BENEFIT

Two more recent clinical trials have examined the effects of GLAT and IFN beta-1b in patients with CIS and MRI scans highly suggestive of MS. The BEtaseron in Newly Emerging MS For Initial Treatment (BENEFIT) study[40] examined the effects of IFN beta-1b in patients with CIS and at least 2 MRI lesions suggestive of MS. Patients had either monofocal or multifocal presentations and were randomly assigned to placebo or IFN beta-1b for 2 years or until a second attack occurred to confirm the diagnosis of CDMS.[40] Patients who had a second clinical attack were switched to active treatment at the time of relapse, and all patients were converted to active treatment with IFN beta-1b at the end of the 2-year trial. Of note, this trial was also powered to detect effects on disability progression, and there was a planned 5-year follow-up.

As expected, the risk for conversion to CDMS was significantly reduced in the group assigned to active treatment. The hazard ratio for conversion to CDMS decreased 50% in the early treatment group. In all, 45% of the placebo group underwent conversion to CDMS compared with only 28% of the treated group ($P < .0001$). Of note is that this trial also measured the conversion rate to McDonald criteria MS. Not surprisingly, within 2 years, 85% of the placebo group had either a new attack or a new MRI lesion

confirming MS. This is consistent with earlier results suggesting that patients with CIS and an abnormal MRI have a very high rate of conversion to definite MS. The time to conversion to CDMS was delayed 363 days in the group assigned to early treatment. The rate of conversion to McDonald criteria-positive MS was reduced 46% ($P < .00001$). The risk for disability progression was reduced by 40% ($P = .0218$).

Follow-up at 3 and 5 years revealed that the benefits of early treatment were retained.[41,42] At 3 years the risk for conversion to CDMS was still reduced by 41% and at 5 years it remained 37% lower than that of the initial placebo group, even though all patients had received treatment after 2 years. Conversion to McDonald criteria MS was reduced by 46% at year 3 and 45% at year 5. New lesion formation was markedly reduced throughout the 5 years of follow-up, and disability progression was still decreased by 24% but this did not reach statistical significance.[42]

The results of this trial provide additional support for the benefits of early treatment and suggest that these advantages are retained for years after the start of therapy. Given the natural history of the disease and the extensive damage caused by inflammatory disease activity it is not surprising that earlier treatment with agents that suppress inflammation is more effective.

PRECISE

The PRECISE trial was similar to the other trials and evaluated the effects of GLAT in patients presenting with CIS and an abnormal MRI with at least 2 asymptomatic lesions on MRI. This 3-year trial enrolled 481 patients who were randomly assigned to receive placebo or GLAT.[43] Patients experiencing a second clinical event were switched to active treatment, and all patients were moved to active treatment at the end of the 3-year trial. Patients in the GLAT arm had a 45% reduction in the risk for CDMS, and the time to CDMS was delayed 386 days ($P = .0005$). New T2 lesions were reduced by 56%, and gadolinium-enhancing lesions were reduced by 62%. The number of new T1 hypointense lesions decreased 80%. These results clearly demonstrate that GLAT is effective in lowering the risk for conversion to CDMS. Moreover, the effects observed on MRI are far more robust than those observed in early clinical trials.

Clinical trials in patients who experience the earliest clinical events associated with MS convincingly demonstrate a benefit of early treatment. Despite different patient populations and different IMAs used at differing doses, all of the trials were overwhelmingly positive. Each trial showed a reduction in the risk for CDMS, and each agent was associated with a beneficial effect on MRI metrics. Not all of the trials were powered to detect an effect on disability progression, but the BENEFIT trial clearly demonstrated a reduction in the progression of disability. Long-term follow-up of patients in the CHAMPS trial and in the BENEFIT trial suggested that the advantages of early treatment persisted for 5 to 10 years. A more definitive demonstration of the benefits of early treatment is evident in long-term follow-up studies in patients enrolled in the earliest clinical trials. Again, this body of literature demonstrates that patients with RRMS who were treated earlier fared better than those for whom treatment was delayed.

The Long-Term Follow-up Cohorts

Several long-term follow-up studies have provided evidence that strongly supports the need for early treatment in MS. Each of these is an open-label long-term study in which patients who were enrolled in pivotal clinical trials were ascertained at points in time long after the original trial. All of the long-term follow-up studies suffer from biases that cannot be avoided in this type of evaluation. That being said, they are all informative and provide evidence suggesting that patients treated earlier in the course of their disease have far better long-term outcomes. The IFN beta-1b clinical trial began in 1988 and concluded in 1993.[28] Sixteen years after the trial ended, in 2005, the investigators located 328 of the original 372 (88.2%) patients in the trial.[18] Of those patients, 35 were deceased and 293 were still alive; 253 of those agreed to participate in a cross-sectional study to evaluate clinical outcomes, MRI metrics, cognition, quality of life, and resource utilization. Of the patients initially randomly assigned to placebo, 20 had died compared with 6 in the group randomly assigned to receive IFN beta-1b. Although the causes of death are unknown, clearly there were many more deaths in the group originally assigned to placebo.

For clinical outcomes, the groups were divided into those who were continuously treated with IFN beta-1b during the 16-year follow-up and those who were not continuously treated with IFN beta-1b or other IMAs. The time to EDSS 6 was 8.4 years in the group not on continuous treatment and 13.1 years in the group on continuous treatment, a delay of 4.7 years ($P = .016$). The conversion to SPMS was also reduced in the group receiving continuous treatment. The time to conversion to SPMS was 11.4 years in the group that did not receive continuous treatment and 17.9 years in the group that did receive continuous treatment. This constitutes a delay of 6.6 years ($P = .003$). These results provide compelling support for the benefit of early and continuous therapy. Of note, those who respond to therapy are far more likely to stay on therapy. Poor responders are likely to have a greater frequency of relapse and disability progression and are more likely to stop therapy, which creates a bias in the data set.

The Prevention of Relapses and Disability by IFN beta-1a Subcutaneous in Multiple Sclerosis (PRISMS) study enrolled 560 patients with RRMS who were randomly assigned to receive placebo, IFN beta-1a 22 µg 3 times weekly or 44 µg 3 times weekly.[44,45] At the end of the trial, the placebo group was randomly assigned to active treatment with 22 µg 3 times weekly or 44 µg 3 times weekly. As expected, disability progression was greatest in the group that was initially assigned to placebo and then treated with the lower dose. The group initially assigned to placebo and then treated with 44 µg 3 times weekly had disability progression comparable to that seen in the group receiving the low dose over the 4-year period. The group initially assigned to the high dose had the least disability progression, again suggesting that patients treated earlier had better 4-year outcomes.

A long-term follow-up evaluation of the original PRISMS population evaluated the available group in cross-section 8 years after the trial began[17]; 68% of the patients were available for evaluation. Of note, relapse rates remain lowest in the group initially assigned to receive IFN-beta-1a 44 µg 3 times weekly. This is consistent with results of the 10-year follow-up of patients from the CHAMPS study who were treated with intramuscular IFN beta-1a.[37] Lesion burden on T2-weighted MRI was also best in the group initially assigned to receive IFN beta-1a 44 µg 3 times weekly, and the rate of conversion to SPMS was reduced compared with natural history cohorts. Once again, these results suggest that patients treated early fare better at long-term follow-up.

One of the most informative long-term follow-up cohorts is the population of patients enrolled in the pivotal trial that led to the approval of GLAT.[44] Patients were randomly assigned to receive placebo or GLAT and continued in the double-blind trial for 3 years. At the conclusion of the trial, all patients were offered open-label treatment with GLAT and have been followed prospectively ever since. At the 6-year timepoint, patients initially assigned to the placebo group were more likely to have worsened by 1 EDSS point, but relapse rate did not differ.[45] Those initially randomly assigned to receive GLAT were also less likely to have gadolinium-enhancing lesions. At 10-year follow-up, patients who remained on GLAT were more likely to be stable or improved compared with those who stopped therapy (55% vs 28%).[45]

Taken together, the results of the long-term follow-up consistently support a benefit of early intervention in patients with MS. In the CHAMPS 10-year follow-up, relapse rates remained lower in the early treatment group even at the 10-year follow-up. This effect was also evident in the PRISMS long-term follow-up. In the BENEFIT 5-year follow-up, the risk for conversion to CDMS was still reduced by 37%.

Summary and Conclusions

The clinical course of MS is variable, but in the long-term, untreated patients accumulate disability in the process of relapse and with secondary progression. Early in the course of disease, the process is one in which inflammatory disease activity leads to demyelination and axonal loss. Bouts of inflammatory disease activity are followed by tissue loss and an increasing burden of disease on T2-weighted MRI scans. Eventually, in the secondary progressive phase, the inflammatory process subsides and a degenerative process becomes dominant.

Theoretically, early treatment should significantly limit inflammatory disease activity and modify the process of tissue injury. This has been largely substantiated in 4 clinical trials evaluating the effects of IMAs in patients with CIS. The benefits demonstrated in these trials revealed effects that were more robust than those observed in populations of patients with established RR disease. Further, the benefits conferred by early treatment persisted at 5 and even 10 years of follow-up. Finally, the results long-term follow-up studies of patients enrolled in early clinical trials demonstrated that early and consistent therapy was associated with better outcomes many years later. As a result of this body of knowledge, early treatment has now become the accepted standard of care in those with MS.

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Summary and Conclusions

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple Sclerosis. N Engl J Med. 2000;343:938-952.
2. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50:121-127.
3. Swanton JK, Fernando K, Dalton CM, et al Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry. 2006;77:830-833.
4. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58:840-846.
5. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol. 1983;13:227-231.
6. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain. 1997;120(Pt 11):2059-2069.
7. Tintore M, Rovira A, Rio J, et al. New diagnostic criteria for multiple sclerosis: application in first demyelinating episode. Neurology. 2003;60:27-30.
8. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med. 2002;346:158-164.
9. Rovira A, Swanton J, Tintoré M, et al. A single, early magnetic resonance imaging study in the diagnosis of multiple sclerosis. Arch Neurol. 2009;66:587-592.
10. Frohman EM, Goodin DS, Calabresi PA, et al. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003;61:602-611.
11. O'Riordan JI, Thompson AJ, Kingsley DP, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain. 1998;121:495-503.
12. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain. 1989;112(Pt 6):1419-1428.
13. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain. 1989;112(Pt 1):133-146.
14. Hawkins SA, McDonnell GV. Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors. J Neurol Neurosurg Psychiatry. 1999;67:148-152.
15. Lublin FD. Clinical features and diagnosis of multiple sclerosis. Neurol Clin. 2005;23:1-15.
16. Lublin FD, Reingold SC. Placebo-controlled clinical trials in multiple sclerosis: ethical considerations. National Multiple Sclerosis Society (USA) Task Force on Placebo-Controlled Clinical Trials in MS. Ann Neurol. 2001;49:677-681.
17. Cohen BA, Rivera VM. PRISMS: the story of a pivotal clinical trial series in multiple sclerosis. Curr Med Res Opin. 2010;26:827-838.
18. Ebers GC, Reder AT, Traboulsee A, et al. Long-term follow-up of the original interferon-beta1b trial in multiple sclerosis: design and lessons from a 16-year observational study. Clin Ther. 2009;31:1724-1736.
19. Karussis D, Teitelbaum D, Sicsic C, et al. Long-term treatment of multiple sclerosis with glatiramer acetate: natural history of the subtypes of anti-glatiramer acetate antibodies and their correlation with clinical efficacy. J Neuroimmunol. 2010;220:125-130.
20. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998;338:278-285.
21. Nesbit GM, Forbes GS, Scheithauer BW, Okazaki H, Rodriguez M. Multiple sclerosis: histopathologic and MR and/or CT correlation in 37 cases at biopsy and three cases at autopsy. Radiology. 1991;180:467-474.
22. Thompson AJ, Miller D, Youl B, et al. Serial gadolinium-enhanced MRI in relapsing/remitting multiple sclerosis of varying disease duration. Neurology. 1992;42:60-63.
23. Cotton F, Weiner HL, Jolesz FA, Guttmann CR. MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. Neurology. 2003;60:640-646.
24. Richert ND, Howard T, Frank JA, et al. Relationship between inflammatory lesions and cerebral atrophy in multiple sclerosis. Neurology. 2006;66:551-556.
25. Lee MA, Smith S, Palace J, Matthews PM. Defining multiple sclerosis disease activity using MRI T2-weighted difference imaging. Brain. 1998;121(Pt 11):2095-2102.
26. Filippi M, Rovaris M, Rice GP, et al. The effect of cladribine on T(1) 'black hole' changes in progressive MS. J Neurol Sci. 2000;176:42-44.
27. McFarland HF.Correlation between MR and clinical findings of disease activity in multiple sclerosis. AJNR Am J Neuroradiol. 1999;20:1777-1778.
28. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993;43:655-661.
29. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology. 1995;45:1277-1285.
30. Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet. 1998;352:1498-1504.

31. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39:285-294.
32. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45:1268-1276.
33. Stone LA, Frank JA, Albert PS, et al. The effect of interferon-beta on blood-brain barrier disruptions demonstrated by contrast-enhanced magnetic resonance imaging in relapsing-remitting multiple sclerosis. Ann Neurol. 1995;37:611-619.
34. Stone LA, Frank JA, Albert PS, et al. Characterization of MRI response to treatment with interferon beta-1b: contrast-enhancing MRI lesion frequency as a primary outcome measure. Neurology. 1997;49:862-869.
35. Johnson KP, Brooks BR, Cohen JA, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Neurology. 1998;50:701-708.
36. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med. 2000;343:898-904.
37. Bermel R, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick R. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study. Mult Scler. 2010;16:588-596.
38. Kinkel RP, Kollman C, O'Connor P, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology. 2006;66:678-684.
39. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet. 2001;357:1576-1582.
40. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and Mc Donald MS in patients with clinically isolated syndromes. Neurology. 2006;67:1242-1249.
41. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet. 2007;370:389-397.
42. Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. Lancet Neurol. 2009;8:987-997.
43. Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1503-1511.
44. PRISMS. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998;352:1498-1504.
45. PRISMS. PRISMS-4: long-term efficacy of interferon-beta-1a in relapsing MS. Neurology. 2001;56:1628-1636.

Suggested Reading

- Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol. 2004;55:458-468.
- Brex PA, Miszkiel KA, O'Riordan JI, et al. Assessing the risk of early multiple sclerosis in patients with clinically isolated syndromes: the role of a follow up MRI. J Neurol Neurosurg Psychiatry. 2001;70:390-393.
- Dalton CM, Brex PA, Jenkins R, et al. Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2002;73:141-147.
- Dalton CM, Brex PA, Miszkiel KA, et al. Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. Ann Neurol. 2002;52:47-53.
- Ewing C, Bernard CC. Insights into the aetiology and pathogenesis of multiple sclerosis. Immunol Cell Biol. 1998;76:47-54.
- Ford CC, Johnson KP, Lisak RP, Panitch HS, Shifronis G, Wolinsky JS. A prospective open-label study of glatiramer acetate: over a decade of continuous use in multiple sclerosis patients. Mult Scler. 2006;12:309-320.
- Jacobs L, Kinkel PR, Kinkel WR. Silent brain lesions in patients with isolated idiopathic optic neuritis. A clinical and nuclear magnetic resonance imaging study. Arch Neurol. 1986;43:452-455.
- Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol. 1996;39:285-294.
- Jeffery DR. Early intervention with immunomodulatory agents in the treatment of multiple sclerosis. J Neurol Sci. 2002;197:1-8.
- Lublin FD. History of modern multiple sclerosis therapy. J Neurol. 2005;252:3-9.
- Masjuan J, Alvarez-Cermeno JC, Garcia-Barragan N, et al. Clinically isolated syndromes: a new oligoclonal band test accurately predicts conversion to MS. Neurology. 2006;66:576-578.
- Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part 2: non-conventional MRI, recovery processes, and management. Lancet Neurol. 2005;4:341-348.
- Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. Lancet Neurol. 2005;4:281-288.
- Ormerod IE, Miller DH, McDonald WI, et al. The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions. A quantitative study. Brain. 1987;110:1579-1616.
- Panitch H, Goodin D, Francis G, et al. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. J Neurol Sci. 2005;239:67-74.
- Polman C, Kappos L, Freedman M, et al. Baseline characteristics and patient adherence in the BENEFIT study. J Neurol. 2005;252:169. Abstract P487.

- Polman C, Kappos L, White R, et al. Neutralizing antibodies during treatment of secondary progressive MS with interferon beta-1b. Neurology. 2003;60:37-43.
- Pozzilli C, Prosperini L, Sbardella E, Paolillo A. Interferon after 10 years in patients with multiple sclerosis. Neurol Sci. 2006;27:s369-s372.
- Rice GP, Paszner B, Oger J, Lesaux J, Paty D, Ebers G. The evolution of neutralizing antibodies in multiple sclerosis patients treated with interferon beta-1b. Neurology. 1999;52:1277-1279.
- Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Neurology. 1997;49:358-363.
- SPECTRIMS. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: clinical results. Neurology. 2001;56:1496-1504.
- Thrower BW. Clinically isolated syndromes: predicting and delaying multiple sclerosis. Neurology. 2007;68:S12-15.

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