MULTIPLE SCLEROSIS
MONITOR and Commentary
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COMMENTATORS

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From the editor...


ROBERT P. LISAK, MD

In this issue, like most issues of *Multiple Sclerosis Monitor and Commentary*, several articles are devoted to studies employing magnetic resonance imaging (MRI). Each incremental advance in MRI, whether it involves new technologies or better use of an existing technology, generates interest for its potential to better gauge multiple sclerosis (MS) activity. With the obvious limitations of direct access to the central nervous system, each improvement in non-invasive imaging provides one more tantalizing step toward a more precise correlation between pathology and clinical disease expression.

In this issue, Dr. Aaron Miller of the Mount Sinai School of Medicine in New York City critiques a Dutch study on MRI to predict MS in patients with clinically isolated syndrome, while Dr. Anne Cross of Washington University in St. Louis evaluates a study claiming that MRI activity at the initiation of therapy may predict treatment failure. Not least important, Dr. Bruce Trapp of the Cleveland Clinic discusses the merits of a study that compares MRI changes in primary-progressive versus secondary-progressive MS.

Not all articles concern MRI. For example, Dr. Hillel Panitch from the University of Vermont evaluates the implications of the substantial rates of non-compliance in patients taking injectable therapies. Indeed, we hope to address a spectrum of interests in each issue. As always, we encourage our readers to consult the original source when a topic has generated interest. Our brief redactions simply summarize the conclusions from a given set of research. Discussion sections of peer-reviewed journals often provide important context. However, even if readers choose to go the original source to learn more, we hope the commentaries provide an orientation for considering the findings. Comments and suggestions are welcome. Please feel free to reach me at *msmonitor@delmedgroup.com*.

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IN THIS ISSUE

MS MONITOR AND COMMENTARY

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Robert Lisak has served on an advisory board or panel for MediciNova, Inc. and Teva Neuroscience and has been a consultant to Bayer Healthcare, EMD Serono, Genentech, and Teva Neuroscience. He is also on Speakers' Bureaus for Bayer Healthcare and Teva Neuroscience. He has received grants/research support from Acorda Therapeutics, BioMS Medical Corporation, Ilex Medical Systems, Novartis, and Teva Neuroscience.

Anne Cross reports that she serves on Scientific Advisory Boards for Eli Lilly and BioMS. She has received speaker honoraria for non-industry-sponsored activities and serves on the Speakers' Bureaus for Bayer Healthcare, Biogen Idec, Genentech, Inc., and Teva Neuroscience; and receives research support from the NIH and the National MS Society. Dr. Cross is the Washington University site Primary Investigator for clinical trials sponsored by Acorda Therapeutics and Sanofi-Aventis.

Aaron Miller reports that he receives research support from Acorda Therapeutics, Genentech, Genzyme, Novartis, Sanofi-Aventis, and Teva Neuroscience. He is a consultant to Barofold, Bayhill Therapeutics, Biogen Idec, Daiichi Sankyo, EMD Serono, GlaxoSmithKline, Medicinova, Merck Serono, Novartis, Sanofi-Aventis, and Teva Neuroscience. He is on the Speakers' Bureaus for Biogen Idec, EMD Serono, Pfizer, Inc., and Teva Neuroscience.

Corey Ford, David Irani, Hillel Panitch, and Bruce Trapp have nothing to disclose.

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Factors that influence adherence with disease-modifying therapy in MS.

First Author and Institution:
Katherine Treadaway, LCSW, University of Texas Southwestern Medical Center, Dallas.

Citation:
Journal of Neurology. 2009;256:568-576.

Objective:
Identify factors that interfere with adherence to injectable therapies.

Type of Study:
Web-based surveys of patients with multiple sclerosis (MS).

Result:
Slightly less than 40% of subjects admitted to non-adherence. The most common reason for non-adherence was forgetting to take the medication.

Conclusion:
Non-adherence is common. The results suggest the need to provide patients with systems to prompt adherence.

The risk of inadequate adherence to a given therapy may be particularly high for injectable therapies that are administered for disease control rather than symptom relief. Seven hundred ninety-eight patients with MS taking one of the beta interferons or glatiramer acetate at 17 neurology clinics participated in three web-based surveys. The study definition of adherence was missing any injection within the previous 4 weeks.

In the three surveys, covering three consecutive 4-week periods, the rates of non-adherence were 39%, 37%, and 36%, respectively. About half of patients reported full adherence during all three time periods. The most common reason for non-adherence, accounting for 58% of episodes, was forgetting to take the drug. The second two most common reasons (22% and 16%, respectively) were "not feeling like taking the medication" and "tired of taking the medication." Pain at the injection site, injection-site reactions, and injection anxiety were reported less frequently.

Results of the study suggest that the two most important steps for improving adherence are (1) providing patients with strategies for reducing forgetfulness, and (2) better education of patients and family members about the importance of consistent adherence.

Commentary:

Hillel Panitch, MD
Director, Multiple Sclerosis Center
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University of Vermont College of Medicine
Burlington, Vermont

This is a potentially important study for emphasizing that non-adherence is a substantial problem in patients taking disease-modifying agents in MS. Although a relatively rigorous definition of non-adherence was employed, the rates were higher than I would have predicted. For an investigator-initiated study with limited funding, the study was well designed and well conducted, and the data deserve to be widely disseminated to neurologists and neuroscience nurses. However, the study might have been stronger with a more detailed analysis of the stated reasons for non-adherence. The most common reasons were forgetting to take the medication and "not feeling" like taking the medication, which are vague and not very helpful for understanding the problem or for developing interventions that might be useful to motivate or re-motivate patients to adhere to their drugs.

Although it is reasonable to presume that therapies do not work when they are not taken, it would also be useful to have data documenting the specific consequences for a specific degree of non-adherence, and the effects of strategies to improve adherence on clinical outcomes. However, such studies would be difficult and expensive to perform. This clinical problem deserves more attention, and patients with MS probably require more and better education about the reasons and need for adherence to injectable therapies. M

Incidence and factors associated with treatment failure in the CLIMB multiple sclerosis cohort study.

First Author and Institution:
Susan A. Gauthier, MD, Judith Jaffe Multiple Sclerosis Center, Weill Cornell Medical College, New York City.

Citation:
Journal of Neurological Sciences. 2009; Epub ahead of print.

Objective:
Determine rate of treatment failure and what factors predicted it in a relapsing-remitting multiple sclerosis (RRMS) and clinically isolated syndrome (CIS) cohort outside of a clinical trial.

Type of Study:
Longitudinal observational clinical investigation.

Result:
Baseline and subsequent magnetic resonance imaging (MRI) findings were possible predictors of treatment failure.

Conclusion:
Greater disease activity on MRI when initiating therapy, even with quiescent clinical disease, should prompt more aggressive therapy and close monitoring of the therapeutic response.

There are no validated treatment algorithms for switching MS therapies when response is inadequate. In this study, the goal was to identify factors associated with inadequate response and physician criteria for treatment failure.

This on-going, single-center study (the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital or CLIMB study) includes 134 patients with RRMS or CIS who are being followed prospectively on glatiramer acetate (GA) or one of the beta interferon (IFN) therapies. Baseline serial MRI and clinical assessments are being collected for all patients. Treatment failure is defined as a switch from the initial immunomodulatory therapy or the addition of a new immunomodulatory therapy due to breakthrough disease activity as assessed by the physician.

Within 3 years of follow-up, the probability of failing initial therapy was 30%. The best predictor of failure was number of new gadolinium-enhancing lesions at baseline (P=0.0001). High T2-weighted lesion volume was a less significant predictor (P=0.015). There was a failure rate of 25% in the 41% of patients taking GA, and a failure rate of 60% in the 44% of patients taking a standard-dose beta IFN (30 µg intramuscular IFN beta-1a or 22 µg subcutaneous [SC] IFN beta-1a). The failure rate in the 15% of patients on high-dose beta IFN (either 0.44 µg SC IFN beta-1a or 0.25 mg IFN beta-1b) was 14%.

Patients with greater disease activity on MRI at time of enrollment, particularly new gadolinium-enhancing lesions, may be candidates for closer follow-up and introduction of more aggressive therapy. On-going follow-up in this patient population may yield more guidance.

Commentary:

Anne H. Cross, MD
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This well-monitored patient cohort may provide important information about predictors of treatment failure and the consequences of switching therapies, but longer follow-up is needed, and there were limitations in the present report. For example, there was no mention of statistical correction for the multiple comparisons; such a correction would lessen some of the reported statistical differences. Nonetheless, the significance of the presence of increased numbers of gadolinium-enhancing lesions at baseline as a predictor of eventual treatment failure (as defined in this study) is likely to persist even with such a correction. With longer follow-up, we may learn whether a switch in therapy makes any difference in outcomes, which is a critical question that the investigators may be able to help answer with the CLIMB study. It was surprising that 30% failed initial therapy, but this may reflect the patient population at this clinic. A higher than expected proportion of patients that failed initial therapy were taking lower-dosed beta interferons, but the authors did not report what criteria were used for the selection of the initial immunomodulatory drug. An observational study employing a stringent protocol like CLIMB may help us learn more about treatment failure, but many questions remain unanswered. M

Progressive multifocal leukoencephalopathy and relapsing-remitting multiple sclerosis: A comparative study.

First Author and Institution:
Aaron Boster, MD, Department of Neurology, Wayne State University, Detroit, Michigan.

Citation:
Archives of Neurology. 2009;66:593-599.

Objective:
Identify features that distinguish progressive multifocal leukoencephalopathy (PML) from multiple sclerosis (MS).

Type of Study:
Retrospective medical record review.

Result:
Although few absolute clinical or imaging differences between PML and MS were found, significant relative differences may help distinguish the two disorders.

Conclusion:
Magnetic resonance imaging (MRI), particularly magnetization transfer ratio (MTR) studies, may provide an opportunity for early detection of PML in individuals with MS.

PML, an opportunistic infection of the central nervous system (CNS) that is caused by the JC virus and leads to irreversible demyelination, has occurred in a small number of MS patients treated with natalizumab. Symptoms of PML and MS are similar to one another, potentially delaying diagnosis of PML.

The goal of this study was to identify features that could rapidly distinguish PML from MS. Forty-five PML cases collected over an 18-year period at two urban teaching hospitals were evaluated retrospectively in comparison to 100 consecutive cases of patients with relapsing-remitting MS (RRMS) from a single MS center. Brain MRI scans were reviewed by four study investigators, including one neuroradiologist.

A monosymptomatic presentation was more common in patients with MS than PML (85% vs. 47%, $P<0.01$). Among those patients with monosymptomatic presentations, patients with RRMS more often developed syndromes involving the brainstem (18% vs. 2%, $P=0.007$), spinal cord (18% vs. 0%, $P<0.0001$), or optic nerves (33% vs. 0%, $P<0.0001$). Patients with PML more commonly had early hemiparesis (24% vs. 5%, $P=0.001$) or altered mental status (19% vs. 0%, $P<0.0001$). In the 35 PML cases with available MRI scans, patients were more likely to have large, confluent T2-weighted lesions (74% vs. 2%; $P<0.0001$) and deep gray matter lesions (31% vs. 7%; $P<0.001$) compared with patients with RRMS. The only MRI lesions seen in PML but not in RRMS were crescentic cerebellar lesions (23% vs. 0%; $P<0.001$).

Brain MTR was low in PML and MS lesions, but there was more normal-appearing brain tissue in PML than MS cases (44.15% vs. 41.04%, $P=0.002$), which suggests that PML may be a relatively more focal disorder than MS.

Commentary:

David N. Irani, MD
Associate Professor
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University of Michigan Health System
Ann Arbor, Michigan

The considerable overlap between PML and MS is an important clinical issue. Identifying characteristic MRI features of PML, in particular, could permit a more rapid diagnosis and have important implications for outcome. Although the most helpful study would be to compare MRI features in natalizumab-treated MS patients with or without PML, only 10 such PML cases have been reported worldwide. The alternative approach taken by these investigators was to compare clinical and MRI features in any patient with PML to those with RRMS. The fact that all but three PML cases occurred in individuals co-infected with human immunodeficiency virus (HIV), the most common predisposing factor for PML, is a potential limitation of the study. HIV directly infects the CNS and patients with advanced HIV infection also may have other opportunistic CNS processes concomitant with their PML, thus complicating interpretation of these results.

One of the most interesting aspects of this study is the application of MTR imaging in a subset of patients with PML and MS. Although the number of subjects in this part of the study was small, results suggest this emerging methodology may be useful for differentiating PML from MS. This finding deserves further study and makes this paper a solid addition to the literature in this field. M

MRI characteristics are predictive for CDMS in monofocal, but not in multifocal patients with a clinically isolated syndrome.

First Author and Institution:
Jessica M. Nielsen, MD, MS Center, Department of Neurology, VU Medical Centre, Amsterdam, The Netherlands.

Citation:
BMC Neurology. 2009;9:19.

Objective:
Evaluate role of magnetic resonance imaging (MRI) in predicting progression of clinically isolated syndrome (CIS) to clinically definite multiple sclerosis (CDMS).

Type of Study:
Substudy of prospective randomized treatment trial.

Result:
MRI activity (≥9 T2 lesions or at least one gadolinium-enhancing lesion) was useful for predicting CDMS in patients with monofocal symptoms but not in those with multifocal symptoms.

Conclusion:
In patients with CIS who have monofocal symptoms, disseminated disease on MRI increases the likelihood of progression to CDMS.

Accurate predictors of CDMS in patients with CIS offer the potential for early initiation of aggressive therapy. Although lesion activity on MRI has limited predictive value for CDMS after CIS, there is substantial interest in correlating disease activity on MRI with clinical symptoms to improve prognostic accuracy.

In this substudy of the BENEFIT trial, which was designed to compare interferon beta 1-b therapy to placebo in patients with CIS, the goal was to assess the value of classifying disseminated MRI lesions for predicting CDMS in patients with either a monofocal or a multifocal presentation (based on their clinical signs and symptoms). Although baseline parameters were evaluated in all 468 study patients, the prediction of CDMS was conducted only in the 176 placebo patients to avoid any influence of therapy on disease course.

When the whole study population was evaluated, 53% of the 468 participants had monofocal disease, and the remainder had multifocal disease. A similar proportion of the placebo group analyzed for risk of CDMS also had monofocal disease. Time to CDMS was similar in monofocal and multifocal cases. When patients with a monofocal presentation were differentiated by the dissemination of central nervous system (CNS) lesions on MRI, an MRI finding of dissemination predicted increased likelihood of CDMS at the end of follow-up. Specifically, those patients with nine or more T2 lesions or at least one gadolinium-enhancing lesion were at higher risk of CDMS than those with more confined MRI abnormalities. However, dissemination of lesions on MRI did not add predictive value for CDMS in CIS patients with multifocal symptoms.

These findings support a careful neurological assessment to identify monofocal symptoms in CIS patients because of this evidence that these patients have a greater likelihood of progressing to CDMS.

Commentary:

Aaron E. Miller, MD
Co-Director Multiple Sclerosis Care Center
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New York, New York

This study is a straightforward confirmation that MRI is capable of adding prognostic information in selected CIS patients. Basically, we would anticipate a greater number of MRI abnormalities to predict a greater likelihood of progressing to CDMS, so the results are not surprising. Presumably, the reason that MRI did not add much prognostic information in multifocal disease is that disseminated lesions in the CNS are already associated with a high probability of progressing to CDMS in these individuals, so there is little room for further discrimination.

In monofocal patients, these data reinforce the association between disseminated lesions on MRI for progression to CDMS and therefore may be useful to physicians when counseling patients. The baseline evaluations conducted in the context of the BENEFIT study provided an opportunity to look more closely at multifocal disease, but the real need is a definitive marker that will rule in or out the potential for progressing to CDMS. This study primarily adds more data about what has been previously presumed about relative risks. M

Greater loss of axons in primary progressive multiple sclerosis plaques compared to secondary progressive disease.

First Author and Institution:
Emma C. Tallantyre, MD, Department of Clinical Neurology, University of Nottingham, United Kingdom.

Citation:
Brain. 2009;132:1190-1199.

Objective:
Compare axonal damage between primary-progressive (PPMS) and secondary-progressive multiple sclerosis (SPMS).

Type of Study:
Autopsy study of PPMS, SPMS, and control tissue.

Result:
Patients with PPMS and SPMS had a similar degree of axonal loss. Demyelination was more extensive in both the white and gray matter of the cervical spinal cord of patients with SPMS, while axonal density was more reduced in the white matter of patients with PPMS.

Conclusion:
Patients with PPMS had a lower level of white matter demyelination but greater loss of axonal density in demyelinated areas than patients with SPMS, supporting the key role of axonal loss in defining extent of disability in both forms of MS.

Although the patterns of disease differ in PPMS and SPMS, the rates at which disability accumulate have been similar. It has been noted that white matter demyelination occurs in relatively low levels in PPMS, but the types of axonal damage and demyelination have not been well compared in the gray and white matter among patients with PPMS relative to patients with SPMS.

In this study, tissue from the cervical spinal cord was collected at autopsy from individuals who had confirmed PPMS or SPMS. Tissue sections were stained to allow the entire cord cross-section to be evaluated with a 40x magnification.

There were 17 PPMS and 30 SPMS samples available for analysis. Seven control, non-MS patients were evaluated using the same techniques. Most patients had advanced disability (Expanded Disability Status Scale score ≥8) at the time of death. There was a more extensive reduction in axonal density of demyelinated regions (compared to normal-appearing tissue) in the white matter of patients with PPMS relative to SPMS (33% vs. 16% reduction, respectively, $P<0.001$). However, SPMS cases showed more extensive demyelination. The total number of axons in the corticospinal tissue was low and similar in both groups.

Axonal loss appears to be the key pathophysiologic event in both PPMS and SPMS. The authors conclude that the findings are consistent with a lesion-centric mechanism that links axonal loss and disability.

Commentary:

Bruce D. Trapp, PhD
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This was a well-done study using appropriate methodology to help answer an important question: Is PPMS and SPMS the same disease or different diseases? Importantly, the authors demonstrate that axonal loss within areas of demyelination is greater in PPMS than SPMS, suggesting that the pathological pathways differ.

One limitation of this study is that the authors did not attempt to account for differences in atrophy. Although it is true that atrophy is difficult to quantify and evaluate as an independent variable in the setting of an autopsy study, the focus on axonal loss may limit the conclusions that can be drawn about the relative characteristics of neurologic deterioration in these two MS subtypes. Still, this is a reasonable first step toward better understanding the differences. Progress in imaging is making such differences easier to see and easier to quantify. With the disappointing activity of currently available drugs, including the anti-inflammatory drugs that have proven useful in relapsing-remitting MS, it is reasonable to hope that a better understanding of the pathologies of PPMS and SPMS may provide more information about how the disease progresses and what tissues are most important for symptom expression. The high levels of axonal loss despite relatively low levels of demyelination provide some basis to consider new targets for treatment. M

Demyelinating events in early multiple sclerosis have inherent severity and recovery.

First Author and Institution:
Ellen M. Mowry, MD, Multiple Sclerosis Center, University of California, San Francisco.

Citation:
Neurology. 2009;72:602-608.

Objective:
Identify factors associated with severity of relapses and poor recovery in multiple sclerosis (MS).

Type of Study:
Prospective evaluation of patients in single-center database.

Result:
Severe relapses and poor recovery predict subsequent severe relapses and incomplete recovery.

Conclusion:
Severe relapses and poor recovery appear to be self replicating. It is unclear whether more aggressive therapy for an initial severe relapse might reduce the severity of subsequent relapses.

There is limited information about the predictors of severe relapses and poor recovery, which are both risk factors for accelerated disability in MS. Although the unpredictability and heterogeneity of MS are well established, a better understanding of the clinical factors that predict relapse and recovery might lead to strategies to improve long-term outcome.

In this study, logistic regression analysis was used to determine predictors of event severity and recovery in 330 patients with MS or clinically isolated syndrome (CIS) who had been entered into a prospective database within 1 year of disease onset. Of the 330 patients followed for a mean of approximately 2 years, 152 had a second event, and 63 had a third event. The factors evaluated for their predictive value for event severity and degree of recovery included age, ethnicity, location, and disease-modifying therapy.

The greatest predictor of severity for a second or third event was the severity of the previous event. For instance, when those with a severe first event were compared to those with a mild first event, the likelihood of a severe second event was almost 5-6 times greater ($P<0.0001$). Likewise, poor recovery from a prior event predicted a more severe subsequent event and poor subsequent recovery.

Based on the similarity of the degree of severity when recurrences are compared to each other and to the initial episode, specific patterns may be inherent to the disease. The authors are now evaluating genetic polymorphisms that may predict severity and likelihood of recovery.

Commentary:

Corey C. Ford, MD, PhD
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The main conclusions of this study have been suspected, but evidence that poor recovery from an initial demyelinating event predicts poor recovery from subsequent events has not previously been studied prospectively. This information is clinically useful. It focuses attention on the prognostic importance of the clinical characteristics of an early relapse. Even though we do not know from this study whether the patients with more severe episodes and poor recovery will have a worse long-term outcome, it does show that they have a worse short-term outcome, and it raises the issue of considering more aggressive therapies in this population.

I was impressed by the effort to evaluate the relationship of the initial demyelinating event to subsequent events, but it has to be noted that only 63 patients of the initial 330 were still available for evaluation by the third event. This led to wide confidence intervals for conclusions drawn about the third event relative to the second event, but the premise of the study and conclusions remained well supported by the data.

The authors suggest that disease severity might be inherent and plan to look for genetic or biologic factors that control this tendency. If the effort is successful, such markers would be helpful in guiding therapy decisions, but the more urgent need is for controlled studies to determine whether altering treatment strategies in these patients can alter their long-term disease course. M

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MULTIPLE SCLEROSIS MONITOR and Commentary

Practical Analysis on Today's Findings in Multiple Sclerosis

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