MULTIPLE SCLEROSIS
MONITOR and Commentary
Practical Analysis on Today's Findings in Multiple Sclerosis
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From the editor...


ROBERT P. LISAK, MD

Most of the studies discussed in this issue were designed to generate practical clinical messages. For instance, a controlled trial of mindfulness training impressed our commentator, Dr. Ruth Whitham of Oregon Health & Science University. Although she did not think the study was without flaws, she agreed that the data provide a reasonable basis for considering this approach to controlling depression and improving quality of life in patients with multiple sclerosis (MS) who are open to the idea. In a similar vein, in a review of a study claiming that sleep problems are largely the result of depression in MS patients, Dr. Bruce Cohen of the Feinberg School of Medicine in Chicago found a number of problems in study design and measurement tools. He agrees that depression and sleep problems are both significant clinical issues in MS, but was less impressed by the link claimed in this study.

In this issue, we also hear from Dr. Aaron Miller of the Mount Sinai School of Medicine in New York City about new data on the oral agent laquinimod, from Dr. Hans Lassman of the Medical University of Vienna on the failure of hematopoietic stem cell transplantation to reverse the inflammatory process of MS once it has begun, and from Dr. Samuel Ludwin of Queen's University in Kingston, Ontario about a complex study that looks at differences in demyelination and remyelination between primary and secondary MS.

In all cases, we have enlisted experts who can comment on papers in their area of interest. Their commentary is not the final word but a second opinion. We encourage readers to consult the original sources, but we hope our commentators allow a broader perspective on the issues involved. If you have comments or suggestions, 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.

Bruce Cohen has no conflict of interest regarding the article he reviewed, but reports that he receives funds from Teva Neuroscience to support an annual education conference and for speaking to neurology residents in the Chicago area.

Laura Balcer, Hans Lassman, Samuel Ludwin, Aaron Miller, and **Ruth Whitham** have no relevant conflicts to report.

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Neuroinflammation and demyelination in multiple sclerosis after allogeneic hematopoietic stem cell transplantation.

First Author and Institution:
Jian-Qiang Lu, MD, University of Calgary, Calgary, Alberta, Canada.

Citation:
Archives of Neurology. 2010;67:716-722.

Objective:
Evaluate the effect of allogeneic hematopoietic stem cell transplantation (allo-HSCT) on immune activity in the brains of patients with and without multiple sclerosis (MS).

Type of Study:
Postmortem histopathological examination.

Result:
Despite some changes in the proportion of T lymphocytes, there was no evidence that allo-HSCT halted the demyelinating or inflammatory process of MS.

Conclusion:
This treatment does not alter the processes that drive MS.

Autologous and allo-HSCT represent methods of essentially ablating immune function to permit regeneration of the host immune system in the hope of normalizing the immune response. In MS, the potential for benefit from HSCT remains controversial.

This report was based on the analysis of postmortem tissue from patients with and without MS who had received allo-HSCT for the treatment of malignancy. A variety of variables in regard to morphological appearance and immune activity, particularly quantification of inflammatory cells, were compared in these individuals as well as in five control individuals who neither had MS nor received allo-HSCT.

In the MS lesions, there were significantly higher numbers of $CD3^+$ T cells and $CD8^+$ cytotoxic T cells and significantly higher numbers of $CD68^+$ microglia/macrophages than in normal-appearing white matter. Similarly, all three of these leukocyte subsets were higher in the brains of those without MS who received allo-HSCT when compared to the controls. The demyelinating and inflammatory activity in the brains of patients with MS persisted at the time of death despite allo-HSCT.

Commentary:
Hans Lassmann, MD
Department for Neuroimmunology
Center for Brain Research
Medical University of Vienna
Vienna, Austria

The message from this study is that when inflammation of MS is established in the brain compartment, it does not appear that the process can be stopped by bone marrow stem cell transplantation. The inflammation and tissue injury can be reduced with autologous HSCT and probably with allo-HSCT, but some inflammatory and demyelinating activity remains because complete eradication of the inflammatory process is not achieved. For allo-HSCT, the authors also suggest that the graft-versus-host (GVH) reaction may promote inflammation in the central nervous system.

From these types of postmortem studies, we do not know the level of inflammation in the patient before the HSCT. This is a weakness, since it remains unresolved how much inflammation and active tissue injury has been reduced in comparison to the pretreatment situation. Overall, however, enthusiasm for HSCT for treatment of MS is limited because of the high risk of complications in relation to potential benefits. There appear to be other methods of reducing inflammation that pose less danger to the patient.

If allo-HSCT had been more effective, it might have provided important new insight into the pathogenesis of MS, but the goal to completely eradicate inflammation in the brains of patients with MS was not achieved by this procedure. M

Oral laquinimod in patients with relapsing-remitting multiple sclerosis: 36-week double-blind active extension of the multi-centre, randomized, double-blind, parallel-group placebo-controlled study.

First Author and Institution:
Giancarlo Comi, MD, University Vita Salute, San Raffaele, Italy.

Citation:
Multiple Sclerosis. 2010;16:1360-1366.

Objective:
Assess safety and efficacy of laquinimod over an extended time period.

Type of Study:
Open-label extension of a double-blind study.

Result:
On imaging, patients who remained on laquinimod or were switched to laquinimod from placebo after completing the double-blind study demonstrated low rates of disease activity.

Conclusion:
The persistent protection from disease progression provided by laquinimod, coupled with a favorable side effect profile, encourages on-going development of this drug.

Laquinimod, an oral therapy, has been associated with a variety of immunomodulating effects in experimental models of multiple sclerosis (MS). In the clinical trials conducted so far, laquinimod has been associated with a reduction in disease activity over periods of up to 36 weeks as measured with magnetic resonance imaging (MRI). These effects have led to an extensive clinical development program.

In this study, 257 patients who participated in a 36-week, placebo-controlled, double-blind trial were entered into an extension phase. In the original trial, patients had been randomized to 0.6 mg laquinimod, 0.3 mg laquinimod, or placebo. In the extension-phase, laquinimod subjects remained on their initially assigned dose, while the placebo subjects were crossed over to the active drug.

In those who remained on laquinimod, the suppression of MRI activity as measured by gadolinium-enhancing lesions was sustained for another 36 weeks of follow-up. In those initially randomized to placebo, the proportion free of gadolinium-enhancing lesions increased from 31% to 47% over the course of the extension. As in the double-blind phase, elevations in liver enzymes were the major safety concern, but discontinuation for liver enzyme elevations were uncommon, and the elevations were readily reversed upon discontinuation.

This study provides additional encouragement for further clinical development of laquinimod. Two 24-month, phase III trials (ALLEGRO and BRAVO) are in progress. [Editor's Note: Preliminary ALLEGRO results were released December 9, 2010, showing significant reductions in relapse rate and disability progression with laquinimod.] In addition, this open-label study will be further extended, but all patients will be stepped up to the 0.6-mg dose, because the results so far suggest that it is as well-tolerated as the lower dose but more efficacious.

Commentary:
Aaron E. Miller, MD
Medical Director
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It is always useful to have more and longer-term data regarding emerging therapies, including data generated from open-label studies, but it is difficult to draw meaningful conclusions about the future of laquinimod until we have results of a phase III multicenter study. Patients in this analysis were drawn from a study that required gadolinium-enhancing lesions at baseline. This entry criterion is a reasonable strategy to enrich the population with active disease in order to demonstrate a benefit with a disease-modifying therapy, but it makes the results difficult to generalize to a more typical population. Presumably, the phase III study will enroll a more representative sample.

One aspect of this study that raises concern was that the authors reported a large increase in gadolinium-enhancing lesions when the active therapy was stopped for a short washout period before the extension phase. This raises the possibility of a rebound phenomenon, but it was difficult to assess the risk from the data presented in this publication. However, laquinimod does appear to be active, and it has demonstrated a good tolerability profile so far. Although these results encourage a licensing study, the bottom line is that we need phase III results to judge the drug's clinical potential. M

Neither retinal nor brain atrophy can be shown in patients with isolated unilateral optic neuritis at the time of presentation.

First Author and Institution:
Klaus Kallenbach, MD, Glostrup Hospital and University of Copenhagen, Copenhagen, Denmark.

Citation:
Multiple Sclerosis. 2010; Epub ahead of print.

Objective:
Evaluate retinal and brain atrophy as early signs of multiple sclerosis (MS).

Type of Study:
Prospective, observational, cohort imaging study.

Result:
No significant differences could be detected between patients with clinically isolated syndrome (CIS) and healthy controls on either optical coherence tomography (OCT) or brain atrophy measures.

Conclusion:
This study suggests that the structural changes in the retina or the brain associated with MS do not occur early in the disease and therefore will not be useful for early MS detection.

Patients with CIS defined by optic neuritis may provide a unique opportunity to evaluate the pathophysiologic processes of MS at their earliest stages. Past studies in patients with CIS have produced discordant results regarding the onset of brain atrophy, which correlates with disability in patients with definite MS, and CIS features.

In this prospective, observational, cohort study, normalized brain volumes were calculated on the basis of magnetic resonance imaging (MRI) in 60 patients who had optic neuritis as an isolated clinical event within the previous 28 days and in 19 healthy volunteers. OCT was also performed in affected and unaffected eyes, and visual-evoked potentials (VEP) were correlated with the presence and severity of brain atrophy.

Relative to controls, neither generalized nor localized atrophy could be detected on either MRI or OCT in patients. This was true even when white matter lesions were employed to stratify patients according to their likelihood of progressing to definite MS. Although VEP latency did not correlate with OCT, there was a trend for decreased VEP amplitude in patients at high risk for MS on the basis of white matter lesions.

Although previous studies have found atrophy in patients with CIS, most were conducted months or years after the initial CIS event. The fact that this study, which evaluated patients within a few weeks of the event, did not show a difference suggests atrophy is a time-dependent process.

Commentary:
Laura J. Balcer, MD
Chief, Multiple Sclerosis Division
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

This and other imaging studies conducted at the first clinical signs of potential MS may reveal an opportunity for very early intervention. This is an issue that may become more important as we move toward neuroprotective agents that could reach clinical trials within the next 5 years. In patients with established MS, there is evidence that both demyelination and brain atrophy correlate with the risk of disability, but it is important to understand whether one of these processes drives the other and how these processes can be targeted to prevent or delay disability.

This study had several good design features, including the selection of an age-balanced control group and a focus on OCT as a tool to evaluate axonal changes in a target organ. The inability of the authors of this study, unlike previous investigators, to find differences between patients with CIS and controls in regard to brain volume and average retinal nerve fiber layer thickness may reflect the fact that these changes are not present at the time of the first CIS event, but more study is needed. One potential problem was that the relatively thin nerve fiber layers in their control group relative to previous healthy volunteers may have made differences more difficult to show.

This study addresses an important area of inquiry, but the complexity of the relationship between atrophy and axonal loss continues to be challenging. M

Demyelination versus remyelination in progressive multiple sclerosis.

First Author and Institution:
Stephan Bramow, MD, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark.

Citation:
Brain. 2010;133:2983-2998.

Objective:
Compare features of primary and secondary progressive multiple sclerosis (MS).

Type of Study:
Retrospective clinico-pathologic studies.

Result:
The greater vulnerability of remyelinated plaques to destruction by autoimmune processes in secondary-progressive MS (SPMS) relative to primary-progressive MS (PPMS) may explain clinical differences in these MS types.

Conclusion:
Better definition of the relative differences in the inflammatory immune processes in SPMS versus PPMS may guide strategies and goals for treatment for each disease subtype.

SPMS and PPMS have distinct clinical features, but neuropathological differences are less well understood. A better understanding of these differences may provide clues on how to target therapies more specifically for these disease processes.

In this study, the brains and spinal cords of 34 patients with SPMS and 13 patients with PPMS were evaluated with particular attention to levels of inflammation, plaque types, plaque number, and total plaque burden. The degrees of active demyelination and remyelination were also compared between the two groups.

In the brains of patients with SPMS, there was a greater plaque burden, more plaques with high-grade inflammation, and a greater degree of demyelination than in the brains of patients with PPMS. In contrast, there was more remyelination and remyelination capacity in the brains of patients with PPMS. There were no differences in plaque burden, active demyelination, or remyelination capacity in the spinal cords of either of the subject types, but there was more active demyelination of the remyelinated areas in the patients with SPMS.

The data suggest remyelination may be more effective in delaying the onset of symptoms in patients with PPMS relative to those with SPMS. Although the authors report that basic disease processes are similar in these two groups, they propose that the white matter of the brain is protected in the brains of patients with PPMS, and they may be spared from symptoms until the spinal cord is affected.

Commentary:
Samuel K. Ludwin, MD
Associate Dean of Research
Faculty of Health Sciences
Queen's University
Kingston, Ontario, Canada

This is a well-done and important article. It is also a very dense paper with far-reaching implications that are difficult to summarize in a few hundred words. One of the larger issues it addresses is the critical balance between demyelination and remyelination in understanding the pathogenesis of SPMS and PPMS. The study raises the question as to whether it is possible to distinguish inflammation-causing demyelination in MS from the inflammatory response that drives remyelination to stimulate repair. Most of our treatment strategies in MS involve anti-inflammatory effects, but this may also then interfere with the stimuli to remyelination.

This paper also provides evidence that remyelinated plaques are more vulnerable to subsequent demyelination. In SPMS, slowly expanding lesions appear to be more important to clinical progression than the development of new lesions, which may explain why the same symptoms tend to recur in new attacks.

While this study suggests that the basic pathophysiology is similar for SPMS and PPMS, the differences in how each progresses may depend on the anatomic differences between the brain and spinal cord. These might provide insight for understanding how inflammatory pathways both advance disease and serve as a source of defense. The greater differences observed in plaque burden in the brains versus the spinal cords of patients with SPMS and PPMS may also provide a platform on which to differentiate the inflammatory processes involved in demyelination and remyelination. This area of study may provide an important opportunity to isolate key pathological events that drive MS progression and to guide future therapy in these differing situations. M

MS quality of life, depression, and fatigue improve after mindfulness training: A randomized trial.

First Author and Institution:
Paul Grossman, MD, University Hospital Basel, Basel, Switzerland.

Citation:
Neurology. 2010;75:1141-1149.

Objective:
Evaluate mindfulness training for improving quality of life and reducing fatigue and depression in multiple sclerosis (MS).

Type of Study:
Randomized, controlled study.

Result:
When compared to usual care, mindfulness training was associated with significant reductions in reports of fatigue, depression, and anxiety while improving overall quality of life.

Conclusion:
A nonpharmacologic intervention that was well-accepted by patients improved quality of life and well-being and reduced common symptoms of fatigue and depression associated with MS and may be feasible for broad application.

In addition to characteristic physical disabilities, MS is commonly accompanied by a variety of nonphysical symptoms, including fatigue, depression, and anxiety, which diminish quality of life. Such symptoms are not well-addressed by disease-modifying therapies (DMTs), suggesting alternative treatments are needed to manage these associated problems.

In this study, 150 patients with relapsing-remitting or secondary-progressive MS were randomized to usual care or mindfulness training, which included a stress-reducing program offered in weekly 2.5-hour sessions over 8 weeks and a 7-hour session at week 6. Standardized tools measured depression, fatigue, health-related quality of life (HRQOL), and anxiety prior to the intervention, immediately after the intervention, and 6-months post-intervention.

When compared to usual care, there were significant advantages for mindfulness training immediately after treatment and 6 months post-treatment for all outcomes. In patient subgroups that had clinically relevant degrees of depression, fatigue, or anxiety prior to treatment, the effect size of mindfulness training was even greater than that observed for the total sample.

In addition to the objective improvements in the rating scales, patients expressed a high degree of satisfaction with mindfulness treatment. Good adherence to the program, including practicing the principles between training sessions, supports a high degree of acceptance. The authors believe that this approach is feasible for broader application.

Commentary:
Ruth Whitham, MD
Professor of Neurology
Oregon Health & Science University
Portland, Oregon

This was a carefully designed single-blind study with a comprehensive set of predefined outcomes and well-validated measures. Overall, the effect size of the mindfulness training on multiple outcome measures is compelling, and the evidence of benefit is reinforced by the greater effect size in those most impaired at baseline. However, the usual care group had only two clinic visits over the course of the study, and it is not clear what degree of benefit was derived from the mindfulness training itself relative to the reassurance that might be generated by weekly sessions of any kind. In addition, patients were self-referred, so they may have been more open to this type of mindfulness approach and more likely to benefit. The patient group, which had limited disability (Expanded Disability Status Scale score ≤6), also may not have been representative of an unselected MS population.

Still, this is an important study. It identifies a therapy for complaints common in patients with MS that can be provided at a reasonable cost without side effects. The results of the study suggest that mindfulness training improves mental outlook and quality of life, which are aspects of MS not necessarily improved by currently available DMTs. A study comparing mindfulness training to an active intervention of a different kind might be even more convincing, but on a practical level, this study does generate enough information that it is very reasonable to encourage a mindfulness training approach when patients are suitable and interested. M

Beyond fatigue: Assessing variables associated with sleep problems and use of sleep medications in multiple sclerosis.

First Author and Institution:
Alyssa M. Bamer, MPH, University of Washington, Seattle, Washington.

Citation:
Clinical Epidemiology. 2010;2:99-106.

Objective:
Identify variables that contribute to sleep disturbances in patients with multiple sclerosis (MS).

Type of Study:
Self-report survey of patients with MS.

Result:
Regression analysis suggests that sleep disturbances were most closely associated with depression followed by leg cramps, relatively young age, and pain. Fatigue plays a minor role.

Conclusion:
More attention is needed for strategies to treat the underlying causes of sleep disorders in MS, such as associated depression, rather than provide sleep medications.

Several studies have suggested that sleep disturbances are common in patients with MS. Some estimates place the prevalence at 50%. However, few studies have been performed to identify the causes of sleep disturbances, which might be useful both for the effort to identify the underlying problem and to offer appropriate therapy.

In an initial investigation, 7,806 persons enrolled with a regional MS society were invited by mail to enter a longitudinal study of health outcomes in MS. Of the 1,271 who completed the initial survey, a subgroup of 473 patients was included in this cross-sectional analysis. All completed the Medical Outcomes Study Sleep (MOSS) scale and other measures, including the modified Fatigue Impact Scale (MFIS) and a self-report version of the Expanded Disability Status Scale (EDSS).

On the basis of MOSS, 46.8% reported moderate or severe sleep disturbances. In a regression model, sleep problems were associated with depression, leg cramps, younger age, pain, female gender, fatigue, shorter duration of MS, and nocturia. EDSS score was not correlated with sleep disturbances. Of these factors, depression explained 33% of the variance and was, by far, the most dominant association in this analysis.

The authors conclude that the relationship between depression and sleep problems should be considered when treating either problem in the MS population. They speculate that agents such as tricyclic antidepressants may address both issues. More research is recommended to explore the treatment of sleep disorders in MS, including nonpharmaceutical treatment options.

Commentary:
Bruce Cohen, MD
Professor of Neurology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

The most important point to draw from this study is the reiteration that depression is a common complication of MS, producing a variety of problems including sleep disturbances. However, there are a number of important limitations to the self-report survey design of this study, which evaluated <10% of those initially contacted to participate in the longitudinal natural history study.

This study population, which had an average age of 52 years, a reported EDSS of >4.5 in 69%, and an average disease duration of 14 years, should not be considered broadly representative of an MS population. While the MOSS tool employed in this study is particularly sensitive for insomnia, it is less sensitive for daytime sleepiness and other types of sleep disturbances, which might have been better captured with the addition of a more sensitive measure of fatigue such as the Epworth scale (a relationship found in previous studies). Hence, the authors' conclusion that fatigue may play a minor role in sleep disturbance in MS may reflect acquisition bias in a subpopulation with significant disease duration and disability, and methodology that may be more sensitive to sleep disruption due to depression than to other factors.

Comprehensive studies that will provide additional information on causative factors and better management techniques, as the authors suggest, are important areas for future research in MS and should include broadly representative patient cohorts, a more detailed evaluation of sleep problems, and longitudinal designs. M

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