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

For the first issue of *Multiple Sclerosis Monitor and Commentary* in 2010, we have included an eclectic and provocative mix of studies in areas of clinical practice and basic research. Many of these studies have generated more questions than answers, according to our panel of experts. For example, a seemingly straightforward correlation between breastfeeding and protection against multiple sclerosis (MS) relapse made by one group of investigators is flatly rejected by Dr. Rhonda Voskuhl from UCLA, who lists multiple variables overlooked by these authors. In addition, a survey that purports to reconfirm the north-south gradient for MS risk is taken to task for numerous methodological problems by Dr. John Kurtzke, who has led several prevalence studies at the Veterans Affairs Medical Center in Washington, DC.

A study of one of the persistent controversies in MS—the potential importance of neutralizing antibodies in subverting the effects of interferons—is assessed by Dr. Joel Oger of the University of British Columbia. In his critique, he sheds light on both the strengths and the limitations of the approach that was taken. From the very practical issue of measuring disability, Dr. Susan Bennett of the University at Buffalo provides some insight about objectively measuring physical activity and walking mobility in her discussion of a negative study regarding the use of accelerometers.

We also have commentary from Dr. John Kamholz, an expert from my own center, evaluating the potential of a new biomarker for MS that is now in the early stages of development, while Dr. Suhayl Dhib-Jalbut of the Robert Wood Johnson Medical School in New Jersey evaluates some progress toward understanding the exact role of a disease-modifying therapy in modifying T-cell regulation to prevent MS relapse.

In this issue, as in every issue, we have matched recently published articles with investigators who have expertise in that specific field. Our commentaries are intended as an additional and often as an alternative viewpoint. We hope the articles and the commentaries we have selected are intriguing, provoking, and provide yet another avenue to absorb new information. 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.

Suhayl Dhib-Jalbut is a consultant to and has received research grants from Bayer Healthcare, Biogen-Idec, EMD Serono, and Teva Neuroscience.

Joel Oger discloses that neutralizing antibodies as well as acetylcholine receptor antibodies are measured in his neuroimmunology lab at UBC as a medical service paid for by the Canadian Healthcare system. Dr. Oger receives professional fees for this. Dr. Oger has received grants from Bayer/Schering/Berlex, Biogen Idec, EMD Serono, and Teva Neuroscience for setting up these assays. Dr. Oger is a consultant for Bayer Healthcare and BioMS, and has received speakers' fees from Bayer Healthcare, Cinnagen, EMD Serono, and Teva Neuroscience. Dr. Oger is also an investigator on a number of clinical trials involving multiple sclerosis and myasthenia gravis.

Susan Bennett, John Kamholz, John Kurtzke, and Rhonda Voskuhl have nothing to disclose.

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Accelerometry in persons with multiple sclerosis: measurement of physical activity or walking mobility?

First Author and Institution:
Madeline Weikert, BS, Department of Kinesiology, University of Illinois, Urbana.

Citation:
Journal of Neurological Sciences. 2010;290: 6-11.

Objective:
Evaluate the ability of an accelerometer motion sensor to measure both physical activity and walking in patients with multiple sclerosis (MS).

Type of Study:
Prospective analysis.

Result:
While self-report instruments appear to measure either physical activity or walking mobility in patients with MS, the accelerometer measures both.

Conclusion:
An accelerometer appears to be less useful than separate self-report tools for independent assessment of walking mobility and physical activity in patients with MS.

It can be clinically useful to evaluate the degree of deficit in ambulation and movement associated with progressive MS. Several strategies, particularly self-administered questionnaires, are now employed, but motion sensors have the potential to provide more objective data.

The authors enrolled 269 patients with relapsing-remitting MS (RRMS). Patients wore an accelerometer for 7 days. Physical activity was also measured with a variety of self-report measures, such as the International Physical Activity Questionnaire (IPAQ) and the Godin Leisure-Time Exercise Questionnaire (GLTEQ), while ambulation was measured with the Multiple Sclerosis Walking Scale-12 (MSWS-12) and the Patient Determined Disease Steps (PDDS) scale.

The self-report measures of physical activity and ambulation were both well-correlated to each other and the accelerometer data correlated with combined scores of all self-report measures, but did not appear to discriminate between physical activity and walking ability.

Commentary:
Susan E. Bennett, PT, DPT, EdD
Clinical Associate Professor
Department of Rehabilitation Science
University at Buffalo
Buffalo, New York

Unlike previous studies that suffered from a low sample size, this well-conducted study confirms that the motion detected by accelerometers is not a useful tool for evaluating the clinical limitations of ambulation for our patients. While an objective tool is attractive, we need to collect data that will provide relevant information about how the patient is performing in daily life. Accelerometers, by measuring both physical activity and mobility together, do not yield the type of information that enables us to identify the needs of our patients and intervene appropriately.

The authors did compare the accelerometer to useful and appropriate tools for evaluating ambulation, such as the MSWS-12. However, the IPAQ probably was not an appropriate comparator. Tools such as the IPAQ that focus on exercise and other forms of vigorous activity are simply not relevant to most individuals with MS who have more modest activity levels. Until accelerometers can be designed to discriminate between types of movement, the data generated by these instruments have limited clinical utility. If a motion is recorded every time the patient coughs or changes position in a chair, we cannot determine meaningful changes in status when measured over time. It is possible that an accelerometer could generate useful information if recordings were correlated with a patient diary of activity (time study analysis). Still, at this point, the current tools we have—including measures of ambulatory function—are reasonably accurate and reproducible. M

Effect of anti-IFNβ antibodies on MRI lesions of MS patients in the BECOME study.

First Author and Institution:
Andrew R. Pachner, MD, University of Medicine and Dentistry of New Jersey, Newark.

Citation:
Neurology. 2009;73:1485-1492.

Objective:
Evaluate the effect of neutralizing antibodies (NAbs) on bioactivity of interferon-beta (IFNβ) therapy.

Type of Study:
Unplanned retrospective evaluation of previously performed double-blind study.

Result:
A high level of NAbs that resulted in reduced bioactivity also correlated with reduced therapeutic efficacy as measured with magnetic resonance imaging (MRI).

Conclusion:
The association between high levels of NAbs and reduced therapeutic activity suggests that NAb screening in patients on IFNβ may be useful for monitoring therapy.

The presence of NAbs to IFNβ reduces bioactivity as measured by several different parameters, but there has been persistent controversy about whether the reduction in bioactivity precludes clinical benefit.

In an effort to consider the effect of NAbs on the clinical efficacy of IFNβ, MRI scans collected during the course of the BECOME (Betaseron Copaxone in Multiple Sclerosis with triple-dose gadolinium and 3-Tesla MRI Endpoints) study were retrospectively evaluated. Change in the MRIs was evaluated in the context of the presence of NAbs titers.

Of the 30 patients evaluated, 27 developed binding antibodies (BAbs) and 16 developed NAbs. Both proportions are consistent with previous studies. A NAbs level greater than 100 U was always associated with loss of bioactivity. The presence of BAbs at any level was not. Among those with preserved bioactivity, the enhancing lesion-to-scan ratio was reduced by 65%. In those with NAbs leading to loss of bioactivity, the ratio declined only by 31%.

These findings indicate that high titers of NAbs reduce the therapeutic efficacy of IFNβ in patients with MS. The authors suggest that it may be appropriate to screen for NAbs with the intention of treating these antibodies or considering an alternative therapy.

Commentary:
Joel Oger, MD
Professor of Neurology
University of British Columbia
Vancouver, Canada

This is a well-done study that is likely to be controversial. The question of the importance of NAbs has created two opposing groups. For those who believe NAbs are important, these data will be compelling. For those who are not yet convinced, this study will be challenged for being retrospective and not randomized on the appropriate endpoint resulting in a sufficient power to answer the question. However, the assays employed in this study were appropriate and very relevant to the question, and the conduct of the study was good.

These findings indicate that high titers of NAbs reduce the therapeutic efficacy of IFNß in patients with MS.

Although I have some criticisms about how the paper was organized, I do believe that it contributes to a now substantial body of data that NAbs are an issue for IFNß drugs and should be measured. This is not the conclusive, randomized, and prospective study that is needed to generate evidence-based data, but the conclusions drawn by the authors are warranted by the data with which they were provided.

There has not been a strong concern about NAbs in North America, unlike Europe, but the fact that this was published in a good journal on this side of the Atlantic indicates that the evaluation of reviewers may be changing. This study provides strong evidence that loss of bioactivity correlates with a loss of clinical effect, but definitive evidence will have to be generated by a study where randomization will be done on NAb positivity (or bioavailability result). It will probably require 18 months of follow-up for a study of 200 patients randomized to continuing therapy or discontinuing therapy after the development of NAbs. It is unclear why such a study has not been done, but these data encourage such a prospective study. M

Methylation patterns of cell-free plasma DNA in relapsing-remitting multiple sclerosis.

First Author and Institution:
Thomas Liggett, MD, Rush University Medical Center, Chicago, Illinois.

Citation:
Journal of the Neurological Sciences. 2010;290:16-20.

Lin up tops of columns to rule

Objective:
Evaluate cell-free plasma DNA (cfpDNA) methylation patterns as a potential biomarker for disease activity in multiple sclerosis (MS).

Type of Study:
Prospective analysis in two patient cohorts and healthy controls.

Result:
Significant differences in cfpDNA methylation patterns appeared to correlate with disease activity, suggesting this may be a discriminator for diagnosis and prognosis.

Conclusion:
Evaluating cfpDNA is relatively uncomplicated, requiring equipment that is widely available, making this an attractive new biomarker if subsequent studies support these initial findings.

The diagnosis of MS continues to be made on multiple criteria, such as clinical signs and symptoms and presentation on magnetic resonance imaging. A specific and characteristic biomarker has long been desired for speeding the time to diagnosis and for gauging disease activity, particularly as it pertains to likelihood of progression of disability. So far, no component of inflammation, such as cytokine upregulation, has proven specific to MS. The authors of this study pursued a novel approach based on cfpDNA methylation.

In this study, the concentration of cfpDNA was determined with a standard fluorometric assay in 30 patients with relapsing-remitting MS (RRMS) without any clinical symptoms for at least 3 months, defined for the purpose of this study as RRMS in remission (RRMS-r), 29 RRMS patients experiencing an exacerbation (RRMS-e), and 30 healthy controls. In the cfpDNA, methylation patterns in 56 gene promoters were evaluated with a microarray-based assay.

In patients relative to healthy controls, the cfpDNA concentration was 4- to 8-fold greater and the methylation patterns were sufficiently different to distinguish both RRMS-r and RRMS-e patients from healthy controls with a nearly 80% sensitivity (79.2% and 75.9% for RRMS-r and RRMS-e, respectively) and a greater than 90% specificity (93.9% and 91.5%, respectively). When RRMS-r and RRMS-e subjects were compared, differentially methylated gene promoters also indicated that these two states could be differentiated with around 70% sensitivity and specificity.

These preliminary results are considered encouraging and a basis for pursuing cpfDNA assays as a potential biomarker for RRMS diagnosis and prognostication. Larger studies with a wider assortment of methylation promoters are planned.

Commentary:

John Kamholz, MD, PhD
Professor of Neurology and Molecular Medicine and Genetics
Wayne State University School of Medicine
Detroit, Michigan

This is a novel idea for developing a clinically viable biomarker for RRMS, and might be very useful for identifying and following patients with RRMS. However, this work is at a relatively early stage, and many questions still need to be answered. For example, the authors should examine patients with other inflammatory diseases, such as rheumatoid arthritis or lupus, to confirm that the patterns they have identified are specific to MS rather than common to all inflammatory processes. Such studies will be crucial as this work moves forward. In addition, it will be important to determine if disease-modifying therapies can alter the methylation patterns already identified. Furthermore, the investigators should evaluate patients with clinically isolated syndromes to see if cfpDNA is predictive of MS, as well as patients with primary-progressive and secondary-progressive MS.

The assay described in this work appears to be relatively easy to perform, and can be done on peripheral blood, so it is likely to be widely adopted if it does eventually prove viable.

Although the data in this report are intriguing, there remains a long way to go to confirm that cfpDNA is a reproducible biomarker than can distinguish RRMS from other clinical processes or predict disease course. M

Glatiramer acetate improves regulatory T-cell function by expansion of naïve CD4+ CD25+ FOXP3+ CD31+ T-cells in patients with multiple sclerosis.

First Author and Institution:
Juergen Haas, MD, Department of Neurology, University of Heidelberg, Germany.

Citation:
Journal of Neuroimmunology. 2009;216:113-117.

Objective:
Evaluate the effect of glatiramer acetate (GA) on regulatory T(Treg) cell function.

Type of Study:
Prospective analysis.

Result:
GA increased the number of Treg cells and reversed the degree of functional defect in these cells associated with multiple sclerosis (MS) over follow-up of up to 6 months.

Conclusion:
A shift of impaired Treg cells to a more naïve phenotype with prolonged GA treatment suggests that at least some of the benefit of this disease-modifying therapy (DMT) is achieved through this mechanism.

Many Treg cells, including CD4+, CD25+, and FOXP3+, are functionally impaired in patients with relapsing-remitting multiple sclerosis (RRMS). A normalization of Treg function is of increasing interest as DMTs such as GA and the interferons appear to correct this defect in RRMS.

In this study, the function of Treg cells was evaluated in 15 patients with RRMS treated for 6 months with GA. Changes in the quantity and function of several Treg cell subsets were compared to baseline and to cells evaluated from 16 untreated healthy controls.

Although Treg cells were suppressed at baseline relative to controls, the frequencies of naïve Treg cells rose to levels that were greater than those of controls at both 3 and 6 months. Moreover, there was a progressive improvement in the functionality of Treg cells that correlated with the proliferation of naïve and recent thymic emigrant (RTE) Treg cell subsets.

Overall, the study associated GA with a shift of Treg and conventional CD4+ cells to a more naïve and presumably more functional phenotype. The higher prevalence of Treg cells observed on GA treatment in this study may represent one of the mechanisms that accounts for the association between GA and protection from relapses in RRMS.

Commentary:
Suhayl Dhib-Jalbut, MD
Professor and Chairman of Neurology
Robert Wood Johnson Medical School
University of Medicine and Dentistry of New Jersey
New Brunswick, New Jersey

Several groups, including ours, have associated DMTs, including both GA and the interferons, with restoration of Treg function, but the demonstration of an increase in the newly generated naïve RTE cells is new.

This study had several strengths, including the comparison of Treg function to healthy controls and the assessment of the function of the cells as well as their number over the course of 6 months. However, a longer follow-up would have been useful to demonstrate that the increase in Treg cells is sustained over time. The fact that 13 of the 15 patients showed a response also raises questions, because the clinical response to the DMTs is more on the order of 50% to 60%. Perhaps the observed increase in Treg cells may not necessarily be indicative of a clinically relevant effect, or alternatively, the threshold for a response of 10% increase over baseline was too low. Of course, it would also be useful to correlate this change in Treg cells with a clinical response as measured by magnetic resonance imaging, relapse rate, or clinical progression.

Similar findings were reported with the interferons, which is interesting because these agents appear to have overlapping pathways and convergent effects at the level of Treg function. It will be interesting to determine if the restoration of Treg function by DMTs at 3-6 months is predictive of the course of MS over 2 or more years of follow-up. M

Interferon-γ-producing T cells, pregnancy, and postpartum relapses of multiple sclerosis.

First Author and Institution:
Annette Langer-Gould, MD, Stanford University, Stanford, California.

Citation:
Archives of Neurology. 2010;67:51-57.

Objective:
Evaluate whether T-cell subset fluctuations predict multiple sclerosis (MS) relapses in pregnancy.

Type of Study:
Prospective, case-controlled comparison.

Result:
Changes in CD+ cell numbers, particularly falling numbers of CD4+ interferon-γ producing cells, appear to influence the risk of relapses during and after pregnancy.

Conclusion:
An association between a decline in interferon-γ-producing CD4+ cells and an increase in risk of MS relapse suggests a potential tool for monitoring relapse risk in pregnant or postpartum women.

Like many other inflammatory diseases, MS often enters a period of relative quiescence during pregnancy followed by a return of activity during the postpartum period. It is possible that markers of inflammatory activity, such as changes in populations of T-cell subsets, would be helpful for explaining this activity.

In this prospective study, peripheral blood mononuclear cells (PBMCs) were collected during each trimester of pregnancy in 26 women with MS and 24 healthy age-matched controls. PBMCs were further collected at 2, 4, 6, 9, and 12 months postpartum. Structured interviews were employed to gather information about pregnancy course and outcome and about postpartum variables with potential relevance to immune function, such as breastfeeding and menstruation.

Of the 26 women with MS, 15 had relapses within the first year after pregnancy. Of the T-cell subsets evaluated, change in interferon-γ-producing cell counts best correlated with risk of relapse. These cells rose or remained stable in non-relapsing women and control subjects, but declined in women with relapses. Lactational amenorrhea was associated with protection against relapse and a rise in interferon-γ-producing cells.

The authors conclude that change in interferon-γ-producing T cells during and after pregnancy may have an important role in mediating risk of relapse. They suggest steps to increase interferon-γ-producing T cells during the peripartum period might reduce relapse risk.

Commentary:
Rhonda R. Voskuhl, MD
Director
UCLA Multiple Sclerosis Program
Los Angeles, California

The most significant problem with this study is the small number of patients relative to the large number of confounders. The major confounders include the prepregnancy disease activity, and the influence of disease-modifying therapies (DMTs), which were taken by some but not all of the patients.

It has been previously shown that the prepregnancy relapse rate is the best predictor of the postpartum relapse rate. Thus, it is important that the baseline characteristics show that indeed the women with more relapses prior to pregnancy were those that were more often on DMTs prior to pregnancy, and had more relapses postpartum. The patients with more active disease were also the ones who were less likely to breastfeed. This does not support the notion that breastfeeding prevents postpartum relapses. Rather it suggests a selection bias whereby those with less active disease prior to pregnancy are those who choose to breastfeed.

The authors associate a decline in interferon-γ-producing T cells with relapse, thereby suggesting a protective role for these cells in prevention of postpartum relapse. However, the role of these cells is inconsistent since these same cells are higher at baseline in patients with MS compared to healthy controls. Further, these cells decline during the third trimester of pregnancy in MS, a time of well-characterized disease protection. These data would suggest that these cells are deleterious, not protective. The authors also failed to provide data to support their conclusion that lactational amenorrhea may provide protection against relapses by increasing interferon-γ-producing cell production.

Given the small population studied, and the above concerns, the paper should not influence clinical practice. M

The prevalence of multiple sclerosis in 3 US communities.

First Author and Institution:
Curtis W. Noonan, PhD, Centers for Disease Control and Prevention, Atlanta, Georgia.

Citation:
Preventing Chronic Disease. 2010;7:1-8.

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Objective:
Estimate the prevalence of multiple sclerosis (MS) in three geographically distinct areas of the United States.

Type of Study:
Medical record review.

Result:
A strong geographic gradient was observed, with an increasing prevalence of MS moving south to north, which is consistent with previous prevalence studies. Prevalence was also higher in women than men.

Conclusion:
These results may establish baseline prevalence rates in order to evaluate trends over time and for the purpose of looking for disease clusters within specific communities.

Prevalence rates for MS range substantially by geographical area internationally and within the United States. In the United States, prevalence reports have ranged from below 60 per 100,000 to more than 175 per 100,000 (in Olmstead County, Minnesota).

In this study, medical records were obtained from the private offices of neurologists as well as tertiary medical centers in three distinct geographic areas of the United States: Texas, Missouri, and Ohio. The authors noted that these locations were initially studied because of concern about case clusters related to environmental exposures, such as chemicals emitted by an oil refinery.

The MS prevalence rates per 100,000 climbed incrementally from 47.2 in the southern location to 86.3 in the central location and 109.5 in the northern location. The authors noted that ultraviolet (UV) light exposure decreased incrementally for these three locations when moving from south to north. In all three areas, prevalence rates were higher in women than in men, in Caucasians relative to African-Americans or Hispanic Caucasians, and in patients aged 49 to 55 relative to other age ranges.

The results are consistent with previous studies showing geographic variances in MS rates. Although the authors identify several limitations to this study, they suggest that the results may provide a baseline for future prevalence studies or for evaluating case clusters.

Commentary:
John Kurtzke, MD
Neuroepidemiology Section, Neurology Service
Veterans Affairs Medical Center
Washington, DC

Many investigators in the United States and elsewhere have demonstrated a north-south geographic gradient in the risk of MS. This study does not expand on that information. Rather, the methodology of this study has several problems. While the authors performed these prevalence studies in communities that they originally evaluated for case clusters, it would have made more sense to avoid such atypical areas if the goal were a representative survey. I do not see how this analysis serves to support (or negate) their previously reported cluster findings. In addition, there was only an 8° latitude difference from the southern- to the northern-most area, diluting the opportunity to show a latitude gradient or to evaluate correlates of latitude such as UV light exposure or vitamin D levels.

Although latitude gradients are well established, they remain of interest because of evidence that differences may be decreasing. In our studies comparing veterans from World War II to veterans from the Vietnam and subsequent wars, the north-south differences were much less marked in the data produced more recently than that produced earlier. This is in line with the recent decrease or even disappearance of geographic gradients previously observed in Sweden and Norway. What I think we need now for geographic studies of MS in the United States is a nation-wide prevalence survey like those conducted in northern Europe, but this is an expensive undertaking in time, people, and money, and so far has not won funding from public or private sources. M

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MULTIPLE SCLEROSIS MONITOR and Commentary

Practical Analysis on Today's Findings in Multiple Sclerosis

IN THIS ISSUE