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MS Patient Management : Optimizing Immunomodulatory Therapy for MS Patients

Based on a roundtable meeting held on December 15–16, 2001, in Miami Beach, Florida

Introduction

In the last 10 years, neurologists have seen the development of new agents to treat patients with multiple sclerosis (MS)—moving from an era limited to symptomatic therapy to an era of disease-modifying therapies that can affect the course of the disease. Many patients now benefit from the use of the immunomodulatory agents interferon beta-1a, interferon beta-1b, and glatiramer acetate to reduce relapse rates and magnetic resonance imaging (MRI) evidence of disease, and to slow the development of disability.¹⁻¹¹ United States, Canadian, and international guidelines for the use of disease-modifying agents in MS all emphasize the need to start treatment early in the disease course.¹²⁻¹⁴

Although many patients show good control of disease activity, others continue to experience frequent relapses, active disease on MRI scans, and progression of disability. The clinical utility of disease-modifying agents in MS was reviewed in January 2002.¹⁵ However, clinicians still lack criteria for defining optimal and suboptimal responses to therapy. The purpose of this paper is to provide some guidance on how to treat MS patients on a day-to-day basis and determine when their immunomodulatory therapy is working optimally and when it is not. Optimizing Immunomodulatory Therapy for MS Patients

In December 2001, ten neurologists with extensive experience in treating persons with MS—many of whom have participated in one or more of the pivotal clinical trials for immunomodulatory therapy—convened for a two-day roundtable discussion on optimizing immunomodulatory therapy for MS patients. The purpose of the meeting was to create some guidelines on how physicians can assess the status of patients on immunomodulatory therapy and decide when it may be necessary to reconsider therapeutic options.

Physicians, the group agreed, are trying to prevent attacks that disrupt quality of life and prevent the accumulation of disability that eventually may limit a patient's ability to function at work and at home. Participants would prefer to treat most patients having relapsing-remitting MS with immunomodulatory agents, but because of the circumstances under which they practice (eg, reimbursement and access-to-care issues in other countries), this is not possible for some.

During the course of the discussion, it became clear that many factors—including changes on neurologic examination, relapses, disability, magnetic resonance imaging (MRI) results, and side effects—must be considered when judging response to therapy.

Recommendations

Participants agreed on the need for regular clinical assessments of patients with MS—not just at the time of relapse—and that a quantitative neurologic examination should be performed at every visit. It was recommended that physicians see patients every three to six months for the

first two years after MS is diagnosed and treatment is initiated, and again, at the same frequency, if treatment changes. They also underscored the importance of documenting relapses and other changes. Some participants asserted that they want patients to call them about every relapse and change in disability; others thought it was sufficient that patients keep good records and report minor changes at their next visit. All participants agreed that medication change should be based on a comprehensive assessment, rather than focusing on one aspect of the disease.

Participants felt that an up-front contract with the patient is essential to help promote adherence to current therapy and to let patients know that there may be a time when it is reasonable to reconsider the choice of therapy.

Relapses

Relapse rate, severity, type, and speed and extent of recovery were all judged to be important factors in defining an acceptable versus a less-than-optimal response to treatment.

Participants agreed that the pretreatment baseline relapse rate should decrease when treatment is initiated. The panel suggested that a 50% to 75% reduction in the relapse rate would be a good indicator that the treatment is working. Evaluation should start six months after treatment is initiated. The question arose whether relapses mattered if recovery was complete. It was pointed out that although some attacks are strategic hits (ie, occurring in an “eloquent” brain area and more likely to produce symptoms and signs), most are probably the result of the random location of lesions. As one participant said, “If you put enough holes in the system, eventually a random attack will hit something important.”

There were a number of considerations for severity. One factor was the system affected: motor, sphincter, and cerebellar systems are particularly crucial, although even sensory attacks can adversely affect quality of life. Relapses affecting several systems are associated with poor prognosis.^{16,17} It was generally agreed that all relapses are significant, but some are more significant than others, and that any relapse necessitating treatment with steroids is significant.

Regarding recovery, the panel agreed that a relapse that did not respond to early steroid treatment is worrisome, particularly early in the disease process (in later stages, relapses may prove refractory to steroids¹⁸). Recovery that takes more than a few months or is incomplete should also raise suspicion that a patient is not responding optimally to a drug.

Table 1			
<i>Relapses</i>			
	Notable	Worrisome	Actionable
Frequency/ Severity	Single mild attack	Single moderate in year, beginning 6 months after start of therapy	> 1 moderate or 1 severe attack in year, beginning 6 months after start of therapy
Recovery	Rapid following prompt steroid treatment	Slow following prompt steroid treatment	Incomplete recovery

Progression

The Kurtzke Expanded Disability Status Scale (EDSS) is used by many of the participants to assess progression.¹⁹ Other measures mentioned by participants were the MS Functional Composite (MSFC)²⁰ and a well-documented clinical exam. Regardless of the method, all agreed that disability assessment must be quantifiable. Progression in disability would indicate that response to treatment is less than optimal.

MRI

The participants agreed that although a lot of MRI activity is not desirable, standards for interpreting MRI activity are still under development. MRI measures of disease activity include new gadolinium (Gd)-enhancing lesions and new or enlarging T2 hyperintense lesions. New or enlarging T1 hypointense lesions and atrophy should also be measured. It was recently reported that change in T2 lesion burden is an important predictor of disability progression in patients with secondary progressive MS.²¹

In the future, fully automated image analysis of MRI should be available, allowing physicians to send MRI scans to a central facility for analysis and receive a standardized report indicating the level of disease activity. Until that time, decisions must be based upon “eyeballing” the MRI scans.

Table 2			
<i>Progression</i>			
	Notable	Worrisome	Actionable
EDSS ≤ 3.5	< 2 point change	2 point change	> 2 point change
EDSS ≥ 4	< 1 point change	1 point change	> 1 point change
Clinically documented progression	No motor, minor sensory	Some motor, cognitive, or more pronounced sensory	Pronounced motor, cognitive, etc

Other Measures

Physicians should keep in mind a number of other factors in their overall assessment of patient functioning. These factors include cognition, fatigue, and depression, as well as social functioning and overall quality of life.

Cognition is important to quality of life. Cognitive deficits often affect a patient’s ability to work and are a common reason for loss of employment. There is some evidence that immunomodulatory agents affect cognition; therefore, a noticeable change in cognitive ability may be an indicator that the treatment is no longer optimal. Before making treatment changes based on cognitive decline, physicians should ensure that the decline is not due to depression. Independent confirmation from family members and objective testing is merited.

Although cognitive testing has value, universal baseline testing was not recommended. If there is clear evidence that cognition has declined over six months or a year, the physician might want to change the patient’s treatment. If the evidence is questionable, the physician may want to test, and then retest after six months. Although the participants agreed that fatigue is an extremely important factor in quality of life, there is no reliable measure for this symptom and little data showing that immunomodulatory agents affect it.

Depression can be part of MS, as well as a side effect of immunomodulatory agents. If depression is associated with or exacerbated by therapy, the therapeutic agent should be reconsidered.

The group agreed that the presence of neutralizing antibodies to interferons was probably not useful in determining optimal or less-than-optimal response to treatment, though there might be individual cases when results could help sway a clinical decision. The test is costly, takes four to six weeks to obtain results from a reference laboratory, and is not standardized for all interferon products. In addition, changes in neutralizing antibodies may be transitory. A panel

member pointed out that, in one of the clinical trials, patients who were positive for neutralizing antibodies had a better prognosis than those who were negative.²²

THE MODEL—AN INTEGRATED APPROACH TO MANAGEMENT

Participants created an analog model for day-to-day management of patients based upon the position of three gauges: one for relapse, one for progression, and one for MRI (Figure). Each gauge represents a continuum from no concern (0 [zero] on the dial) to a low level of concern (Notable), to a moderate level of concern (Worrisome), all the way to a high level of concern (Actionable). For a particular patient, if all three gauges read Notable, any two read Worrisome, or a single one reads Actionable, the neurologist may want to reconsider that patient's therapeutic options.

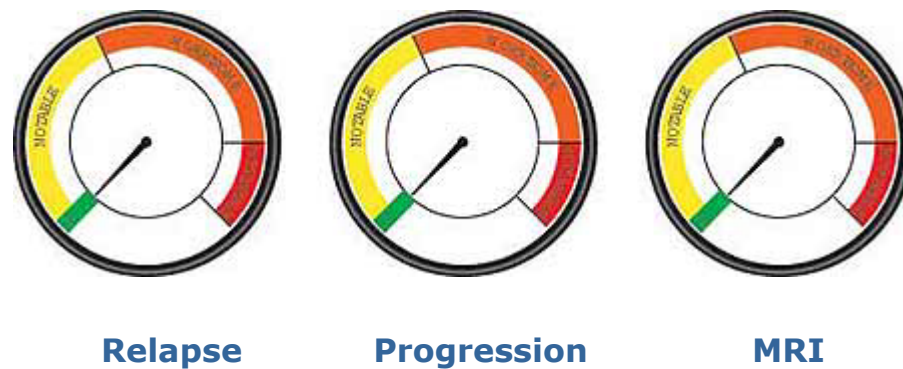


Figure. A visual representation of the analog model created to assess the effectiveness of therapeutic strategies. Each gauge represents a continuum from no concern (0 [zero]) all the way to a high level of concern (Actionable), and can be used to guide clinical decision-making.

Mini- or sub-gauges within each gauge can help determine a cumulative assessment as to how the patient is doing. Within the relapse gauge, for example, mini-gauges could measure frequency, severity, and lack of recovery. For progression, the mini-gauges might be EDSS, MSFC, or another tool. For MRI, the mini-gauges could measure Gd-enhancement, new or increasing T2 lesions, appearance or enlargement of T1 black holes, and atrophy (Tables 1, 2, and 3). Participants emphasized that overall assessment and weighting will vary from clinician to clinician, but the model is a useful framework for considering the issues.

Table 3			
<i>Progression</i>			
Change re previous MRI	Notable	Worrisome	Actionable
New Gd-enhancing lesions			
New T2 lesions			
Enlarging T2 (burden of disease)	Changes in 2 categories	Changes in 3 categories	Changes in > 3 categories
New T1 hypointense lesions			
Enlarging T1 hypointense lesions			
Increased atrophy			

Implicit in the model is the importance of performing regular and standardized examinations, and documenting relapses, progression, and MRI changes, if available. All agreed that the model is an excellent first step. Eventually the best option would be to go back and reanalyze clinical data from various trials to assign numbers to the scales, but until that can be done it is important to validate the model through clinical use. The participants thought the model should be disseminated to neurologists and, eventually, to patients as well.

Roundtable Participants:

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- **Linda Buchwald, MD**, Harvard Medical School, Cambridge, Mass
- **Patricia K. Coyle, MD**, SUNY at Stony Brook, NY
- **Mark Freedman, MD**, University of Ottawa, Ontario, Canada
- **Douglas Jeffery, MD**, Wake Forest University, Winston-Salem, NC
- **Clyde Markowitz, MD**, Hospital of the University of Pennsylvania, Philadelphia
- **Kottil Rammohan, MD**, Ohio State University, Columbus
- **Anthony Reder, MD**, University of Chicago, Ill
- **Mo Sharief, MD**, Guy's Hospital, London, United Kingdom
- **Jerry Wolinsky, MD**, University of Texas Health Science Center, Houston

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