The strategies for monitoring and assessing therapies for multiple sclerosis (MS) are numerous and include clinical measures, which tend to be insensitive, and neuroimaging measures, which offer a more proximate view of MS pathology but which can dissociate from clinical outcomes. Various methods of evaluating disease progression and therapeutic response are discussed, including the number of magnetic resonance imaging lesions, gadolinium enhancement, brain atrophy, disability scales, and quality-of-life measures. (Adv Stud Med. 2006;6(7D):S701-S706)

The main tools for measuring therapeutic efficacy in multiple sclerosis (MS) include relapse rates and disability scales, which tend to be insensitive, and neuroimaging markers, which are sensitive to MS pathology but which can dissociate from clinical manifestations. Quality-of-life measures and patient feedback help us to complete the picture.

In terms of neuroimaging, clinicians and researchers traditionally gauge MS disease activity based on the presence of focal inflammatory gadolinium-enhancing white matter lesions. It is evident from serial magnetic resonance imaging (MRI) studies that focal inflammation of the brain in MS is many times more active than is evidenced by relapses.

The Role of Immunomodulatory Therapy in Focal Inflammation: Evidence from Magnetic Resonance Imaging

It is now well established that immunomodulatory therapies reduce focal inflammation, as evidenced by MRI data from multiple studies. High-dose, high-frequency interferon therapies reduce contrast-enhancing lesion frequency by approximately 70%.1,2 Low-frequency interferon administration and glatiramer acetate (Copaxone, Teva Neuroscience, Kansas City, Mo) reduce contrast-enhancing lesion frequency approximately 30%.3,4

Treatment with any one of the 4 main immunomodulatory therapies reduces relapses by approximately 30%, demonstrating that the effects on gadolinium enhancement can be dissociated from the effects on relapse frequency. That is, immunomodulatory treatment with high-dose/high-frequency interferons has a much greater effect on MRI scans than it does on relapse rates. This dissociation is not seen for...
Copaxone and likely reflects different mechanisms of action of these agents.

**The Role of Relapses on Disease Progression and Therapeutic Decisions**

What is the impact of early relapses on disease progression and, more importantly, on therapeutic decisions? In 1989, Weinshenker et al attempted to determine the predictive value of the early clinical course of MS in terms of later disease progression and long-term disability. The 3 parameters assessed in this study were the attack rate, the interval between the first and second attack, and the rate at which disability developed early in the disease. The authors followed the Expanded Disability Status Scale (EDSS) in 1099 patients with MS over 12 years and tracked the attainment of EDSS step 6 over time. Weinshenker et al demonstrated that if a patient had more frequent early relapses (eg, 5 relapses in the first 2 years), the patient was more likely to achieve a significant level of disability more quickly than patients who did not have numerous early relapses (increased the odds of progression by 40%). The authors concluded that “despite extensive interindividual variation in the rate at which disability developed, the early course of MS may be useful in determining the relative risk of rapid progression.”

More recent data from Confavreux et al extend these earlier findings. Eighteen hundred forty-four patients with MS were followed for a mean of 10 years. EDSS scores were utilized as a measure of disease severity and progression of disability, and Kaplan-Meier analyses were conducted to determine the influence of relapses on the time to the onset of irreversible disability. The authors found that time from the assignment of an EDSS score of 4 to a score of 6 were independent of relapses. The investigators concluded that relapses do not significantly influence the progression of irreversible disability, once progression has started to develop. In other words, the group with relapses and the group without prior history of relapses fall on essentially the same curve.

How can we integrate these 2 different data sets? The explanation may be that there are different rates of progression—some more rapid than others—at the beginning of the disease. However, once patients reach the progressive phase of MS, they all seem to have the same rate of disability progression such that it takes approximately 5 to 7 years to advance from EDSS step 3 to step 6 regardless of the time period that elapsed between progression from step 0 to step 3.

**The Changing Pathology of Multiple Sclerosis**

One possible explanation for the natural history of MS is that different mechanisms of pathological evolution take over with the passage of time. Early on in the disease process, conventional, “adaptive” inflammation may occur, with infiltration of cells from outside the central nervous system. Later on, there appears to be a different kind of inflammation behind the blood-brain barrier, which is not apparent on an MRI scan. This latter type of inflammation may be related to target-determined changes in immune cells and microglial activation. Another possible source of the dissociation of progression and focal white matter inflammation may be the accumulation of cortical gray matter lesions that likely develop as the disease evolves, but are not evident on MRI. These lesions affect the outer, subpial surface of the cortex and are not associated with opening of the blood-brain barrier or with the appearance of new visible white matter lesions that are usually considered markers of focal inflammatory pathology in MS. Later in the disease, there is evidence of diffuse inflammation throughout the brain and the meninges. These changes in the nature of the inflammation in MS are possible reasons why immunomodulatory therapies are not able to slow the gradual progression of MS once it moves into this phase.

Therefore, treatment of MS must focus on an attempt to slow the early progression of the disease because there is no proven way of slowing the progressive phase.

**The Role of Neuroimaging in Predicting Disease Evolution**

Magnetic resonance imaging can be valuable in directing treatment decisions in patients with new-onset MS or with clinically isolated syndromes suggestive of MS. Gadolinium enhancement on brain MRI detects disturbances of the blood-brain barrier with high sensitivity, and this is thought to be an early event in the development of inflammatory MS lesions. Data from the CHAMPS (Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study) study...
showed that certain baseline MRI characteristics can predict the development of clinically definite multiple sclerosis (CDMS) in patients with a first demyelinating event. Among patients with 2 or more gadolinium-enhancing lesions, 52% developed CDMS by 18 months compared to 24% of patients with less than 2 lesions. For those patients meeting the Barkhof criteria (a 4-parameter dichotomized MRI model, including gadolinium enhancement, juxtacortical, infratentorial, and periventricular lesions), 32% of patients developed CDMS compared to 16% of those not meeting these criteria.8 Thus, for patients with positive MRI findings at the time of their initial neurologic event, gadolinium-enhancing lesions and the Barkhof criteria are predictors for development of CDMS over a short interval. The more lesions present, the greater the probability of converting to CDMS.9

In another study, Brex et al evaluated whether early MRI events are predictive of disability on the EDSS scale.10 They showed that patients with more than 10 T2 lesions at initial presentation are at significantly greater risk of developing disability than patients with less than 10 lesions. Specifically, after 14 years, 60% of patients with more than 10 lesions had attained step 6 on the EDSS scale versus less than 20% of patients with fewer than 10 lesions (Figure 1).10

There is also some evidence that the presence of gadolinium-enhancing lesions in patients with clinically isolated syndromes is predictive of brain atrophy rates, although there is a lag in the development of atrophy (by approximately 18 months). This finding suggests that focal inflammation is important for the ultimate development of atrophy.11

THE VALUE OF IMAGING IN DETERMINING THE CLINICAL COURSE AND TREATMENT IN LATER DISEASE

We have already demonstrated that neuroimaging early in the course of disease may be important in predicting a patient’s clinical future. The question then arises as to whether neuroimaging may be helpful in making diagnostic and therapeutic decisions later in disease progression (ie, for patients with established relapsing-remitting MS [RRMS] or secondary progressive MS [SPMS]). A meta-analysis, by Kappos et al, of longitudinal MRI studies of patients at these later stages of disease demonstrated that gadolinium-enhancing lesions were only weakly predictive of relapses and progression of disability by EDSS criteria (after 1 year [odds ratio = 1.34; \( P = .082 \]) and 2 years [odds ratio = 1.65; \( P = .049 \)]) among a total of 307 patients (237 with RRMS and 70 with SPMS).12 The increase in relapse risk associated with gadolinium enhancement was on the order of only 13% per additional 5 lesions, and neither the initial scan nor monthly scans over 6 months were predictive of change in the EDSS in the subsequent 12 months or 24 months.12

Nonconventional neuroimaging techniques that are not currently utilized by practicing clinicians may be better predictors of disease progression for patients with established RRMS or SPMS. Santos et al demonstrated that magnetization transfer (MT) imaging could detect focal abnormalities in normally appearing occipital white matter (NAWM) before the appearance of lesions on conventional MRI.13 Significant differences were found in baseline MT values in NAWM (\( P = .005 \)) between clinically stable patients with MS and those who worsened over the course of 5 years of follow-up. In addition, a strong correlation was found between the 5-year EDSS changes and baseline MT values (\( P < .001 \)). Baseline MT correctly predicted clinical evolution in 15 of 18 patients.13

The diminished importance of conventional MRI techniques in monitoring patients with SPMS was underlined by the interferon beta-1b (Betaseron,
Berlex, Montville, NJ) trial in North America, which failed to demonstrate any clinical correlation between the suppression of gadolinium-enhancing lesions and progression of disability. Whereas Betaseron effectively suppressed 64% to 76% of lesions compared to the group receiving placebo, there was virtually no effect on the EDSS. This phenomenon may be due to the fact that the progressive component of the disease may be effectively independent of concurrent focal white matter inflammatory pathology, thus focal white matter lesions become less important over time in terms of monitoring disease activity.

The Consortium of MS Centers MRI task force advises clinicians not to use routine MRI to assess response to therapy. Instead, MRI should be performed after diagnosis for certain specific reasons, such as an unexpected clinical worsening, suspicion of an alternative diagnosis, or prior to the initiation or modification of treatment. Evidence for a predictive value of focal inflammatory lesions in patients with established MS was provided by analysis of the MRI data for interferon beta-1a therapy (Avonex, Biogen Idec, Cambridge, Mass)-treated patients with MS. The authors determined that patients in the responder group (with \( \leq 1 \) new gadolinium-enhancing lesion) did not experience a change in their EDSS scores during 2 years of follow-up. However, nonresponders (with \( \geq 2 \) lesions) did have a significant probability of developing disability. Results were similar with respect to T2 lesions.

As for predicting relapses by MRI findings, there is a limited amount of data available looking at the relationship of lesion frequency to clinical evolution. From the PRISMS (Prevention of Relapses and Disability by Interferon Subcutaneously in Multiple Sclerosis) data, there appears to be a threshold (approximately 2–3 new T2 lesions) at the 2-year mark that tends to be associated with a more benign or a more aggressive clinical evolution.

There may be other potentially useful neuroimaging data for assessment of MS progression, including evaluation of brain atrophy.

**THE ROLE OF BRAIN ATROPHY IN MONITORING MS PROGRESSION**

Although not commonly utilized as a criterion for MS diagnosis or prognosis, evaluation of brain atrophy may be another potentially useful neuroimaging technique for assessment of MS progression. Fisher et al studied patients with RRMS over 8 years, specifically evaluating whole brain atrophy, in an attempt to determine if it is related to subsequent disability status, and to identify MRI indicators of atrophy progression. The authors found a positive correlation between brain atrophy and disability (as measured by EDSS scale). They also noted that the atrophy rate in the 2 years prior to the start of this study was the most significant MRI predictor of subsequent disability. Specifically, patients from the original Avonex trial who over the first 2 years had zero atrophy (or a low rate of brain atrophy) had a 15% risk of attaining an EDSS score of 6 or greater over the next 8 years. In contrast, the risk was 60% in patients with an initially accelerated rate of brain atrophy (Figure 2).

**OTHER MEASURES FOR ASSESSING DISEASE PROGRESSION: DISABILITY SCALES AND QUALITY-OF-LIFE MEASURES**

The traditional disability scale in MS is the EDSS, measured on a 20-point ordinal scale (Figure 3). The main advantage to the EDSS is that it is well known and well established. However, there is no standardization for progression between steps (eg, from step 0 to step 1 indicates the development of subtle numbness,
whereas from step 5 to step 6 means having to use a cane to walk). Furthermore, the EDSS is a poor measure of upper limb and cognitive function, and has poor reproducibility due to a high rate of inter-rater, and even intra-rater, variability.

To address these issues, other scales have been developed, including the MS Functional Composite Scale. This scale includes a timed walk to evaluate lower extremity function, a 9-hole peg test to measure upper extremity function, and the Paced Auditory Serial Addition Test, a test of cognitive function. However, the latter 2 elements of this tool evaluate impairment rather than disability, and the regulatory authorities have been reluctant to accept the EDSS as a disability measure.

Another method of determining disease progression is to evaluate quality of life and patient expectations, although there are few data on the validity of specific instruments to do this. The most widely used quality-of-life measure is the Short Form 36. This tool is not specific for any disease state and has statistical limitations, including floor and ceiling effects, limited responsiveness, and underestimation of mental health issues. To improve this, Hobart et al developed the MS Impact Scale, which was developed using psychometric techniques and has been validated, although there has been little experience with its use as of yet. 20

**CONCLUSIONS**

There are numerous and varied strategies for monitoring MS disease progression and the effectiveness of treatment regimens. Neuroimaging plays a key role, although traditional measures (gadolinium enhancement and number of T2 white matter lesions) do not tell the entire story. Scientists need to develop techniques for investigating “invisible” pathology, such as gray matter lesions, and to determine the role of brain atrophy. Likewise, treatment decisions cannot solely be based on MRI data or on evidence of relapses. Clinicians and researchers also must fine-tune instruments for determining disability and for understanding how MS impacts quality of life—all with the ultimate goal of minimizing disease progression and maximizing function.

**REFERENCES**