Emerging Methods for Evaluating the Effectiveness of Intramuscular Interferon Beta-1a for Relapsing-Remitting Multiple Sclerosis

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ABSTRACT

Newer outcome-based assessment methods have been developed that complement and improve upon the ability of historical clinical and magnetic resonance imaging (MRI) outcome measures to measure multiple sclerosis (MS) disease activity, patient functionality, treatment efficacy, and the risk of MS disease progression. These newer MS outcome assessments include instruments to evaluate cognitive function and patient quality of life; enhanced measures of disability, such as the Multiple Sclerosis Functional Composite instrument; and newer MRI measures of MS disease activity and neuronal changes, such as permanent T1 hypointensities and central nervous system atrophy. When utilized in conjunction with standard MS outcome measures, these newer MS outcomes provide a more comprehensive picture of disease status and course and hold promise as tools for use in the development and testing of future MS therapies. The well-established first-line MS therapy intramuscular interferon beta-1a, which has been evaluated using a broad range of assessment methods, was used as a reference MS disease-modifying therapy to provide specific examples of studies utilizing newer evaluation methods. Utilization of evolving disease and assessment measures for patients with MS should improve MS patient diagnosis, treatment decisions, and monitoring of therapy.


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Summary Points Presented in this Article

• Multiple sclerosis (MS) is a chronic, immune-mediated neurologic disease that is associated with progressive patient disability and diminished quality of life (QoL).
• Historical clinical outcomes, such as MS relapses, physical disability measures, and magnetic resonance imaging (MRI) endpoints, do not capture important elements of MS, such as the impact of MS and MS therapies on a patient’s perceived QoL.
• This article provides an overview of several key newer MS patient outcomes, including instruments used to assess MS patient cognition, QoL, composite disability measures, and emerging MRI clinical endpoints.
• Newer MS patient outcomes have the potential to improve MS patient care and the development and testing of future therapeutic intervention.

First-line disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) have consistently demonstrated positive effects on historical clinical outcomes such as MS relapses; magnetic resonance imaging (MRI) outcomes such as the number, location, and volume of brain and lesions; and in some studies, disability progression, as measured by the Expanded Disability Status Scale (EDSS). However, older measures do not capture the entire impact of the disease (e.g., cognition, upper limb function, etc.) on patient function and well-being.

Newer outcome measures are being developed with the purpose of capturing additional aspects of the disease and facilitating a more comprehensive assessment of MS disability, progression, and therapeutic efficacy. The primary purpose of this article is to provide the managed care audience with an overview of the most prominent newer MS measures. The potential benefits of these newer outcomes are illustrated using published clinical data on intramuscular interferon beta-1a (IM IFNβ-1a) as an extensively evaluated, representative first-line MS therapy.

Measures of Disability: Cognition and the MS Functional Composite

Cognitive Dysfunction: A Key Component of Disability

Maintenance of cognitive function is an important long-term consideration in MS and has been evaluated in a number of MS clinical trials as a secondary study endpoint. Given the substantial impact of cognitive deficits in MS, it is noteworthy that these deficits are not incorporated into the EDSS, which has been widely used for measuring disability in MS.1 Cognitive measures and their relationships with MS disease outcomes have been gaining increasing prominence in MS clinical research. Since complete clinical cognitive assessment is expensive and requires expert staff and specialized equipment, brief cognitive assessment instruments have been developed to assess cognition in the clinical setting with minimal impact on patients, staff, and resources. This section reviews the instruments that are currently used to assess cognitive function in patients with MS. For representative illustration, published IM IFNβ-1a clinical data are presented to show the impact of MS therapy on these outcomes.

Cognitive impairment occurs in roughly 50% of patients with MS,2 and cognitive deficits are frequently observed even in patients with early disease3 or mild physical disability,4 with reported incidences of 26% and 20% of MS patients, respectively. These cognitive deficits can negatively impact many aspects of a patient’s life, including employment, social and family relationships, and self-care.3,5-7

Based on a reported meta-analysis of 57 studies that enrolled a total of 3,891 participants,5 patients with RRMS are more likely than healthy control subjects to be impaired in general cognitive function (intellectual ability, verbal-intellectual...
Although methods for cognitive assessment in MS continue to evolve, first-line DMTs for MS such as IFNβ are generally reported to slow cognitive change in relapsing MS. Using data on the DMT IM IFNβ-1a as an example, a prospective analysis of the placebo-controlled phase 3 Multiple Sclerosis Collaborative Research Group (MSCRG) study also demonstrated the beneficial effects of IM IFNβ-1a on cognitive function in patients with clinically definite RRMS. In these analyses, IM IFNβ-1a (n=83) performed significantly better than placebo (n=83) at 2 years on both a composite endpoint of information processing and learning/recent memory measures (P=0.036) and a composite measure of visual-spatial abilities and executive functions (P=0.005). However, the latter result was nonsignificant following adjustment for baseline group differences (P=0.085). Longitudinal analyses showed that IM IFNβ-1a also significantly lengthened the time to sustained deterioration in patient PASAT scores (Figure 1), with fewer IM IFNβ-1a patients (19.5%) than placebo patients (36.6%) meeting criteria for sustained PASAT deterioration by the end of the treatment phase.

A separate study that assessed the effect of IM IFNβ-1a on long-term cognitive function is CHAMPIONS, a 10-year, open-label, long-term observational extension study of the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS), which examined the benefits...
of IM IFNβ-1a therapy in patients with clinically isolated syndrome (CIS). Analysis of PASAT scores obtained during study years 5-10 showed that more than 95% of the patients followed in CHAMPIONS 10 and treated with IM IFNβ-1a remained cognitively stable over this span. However, data from serial cognitive assessments must be interpreted with caution because of the potential for practice effects resulting from test repetition to influence results.
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The MSFC: An Enhanced Measure of Disability Progression Incorporating Cognitive Function
Among the alternate assessments of disability that have been developed to overcome the limitations of EDSS, the MS Functional Composite (MSFC) has been the most widely studied. The MSFC is a 20- to 30-minute quantitative instrument consisting of 3 timed tests of neurologic function, which are combined into a single score that is expressed along a continuous scale. The 3 parts of MSFC measure arm, leg, and cognitive function with the 9-Hole Peg Test (arm/hand dexterity), the Timed 25-Foot Walk (leg function), and the PASAT 3-second version (PASAT3; cognition), respectively. This instrument is reported to have excellent test-retest reliability and provides a focused and sensitive evaluation of disability in patients with MS. But, the MSFC also has certain limitations. Indeed, the PASAT in MSFC may lack sufficient sensitivity to detect mild cognitive changes in MS, and the SDMT, which is reported to show greater sensitivity to cognitive changes than PASAT, has been suggested as a replacement. However, MSFC also has the beneficial qualities of providing information on patient upper limb and ambulatory function and good sensitivity and reliability with minimal patient inconvenience. The ability of MSFC to predict future disability during treatment for RRMS was demonstrated in a reported 8-year follow-up of a phase 3 study of IM IFNβ-1a. In this study, the change in patient MSFC scores from baseline to year 2 correlated with the EDSS score and the severity of whole brain atrophy at follow-up. Significant correlations were also identified between MSFC scores during the clinical trial and patient-reported quality of life (QoL) at follow-up. This relationship between MSFC and disability has also been confirmed elsewhere.

Looking Beyond Disability: QoL as an Outcome Measure in the Treatment of Patients with MS
Patient QoL has received increasing recognition as a critical consideration in MS management. Patient QoL measures in MS and data on the impact of IM IFNβ-1a on patient QoL are reviewed below.

Patients with MS rank their QoL an average of 30% lower than individuals who do not have MS and score lower on QoL assessments than patients affected by other chronic diseases such as inflammatory bowel disease and rheumatoid arthritis. For example, patients with MS also score even lower on the Short Form Health Survey-36 (SF-36) physical functioning subscale (21 of a possible 100) than patients with Parkinson’s disease. However, another study found no difference between these 2 populations.

A number of studies in RRMS have demonstrated that measures of patient QoL negatively correlate with disability as assessed by EDSS or MSFC, although other studies have not found a correlation. QoL has been shown to correlate separately with relapses, brain lesions, brain atrophy, and changes in cognitive function (as assessed by PASAT), vision, and ambulation. In addition, QoL has been shown to correlate with employment status in MS. Continuing the use of IM IFNβ-1a as a widely evaluated, representative DMT, Table 1 provides an overview of studies that have investigated the effects of IM IFNβ-1a on QoL in RRMS. The majority of studies show a consistent trend of improved QoL with IFNβ-1a therapy, particularly in the physical domains of QoL ratings. Even in the studies that did not show an improvement with therapy, patient QoL was stable and did not worsen over time.

The ASSURANCE (ASSessment of Drug Utilization, EarLy TreAtmenT, and Clinical Outcome Es) study is particularly worth highlighting, given its long-term findings. ASSURANCE was a 15-year, single time point follow-up of patients who originally participated in the randomized, placebo-controlled phase 3 trial of IM IFNβ-1a in RRMS. The purpose of ASSURANCE was to evaluate the long-term tolerability of IM IFNβ-1a and effects on disability and QoL. After 15 years, patients on IM IFNβ-1a therapy versus those no longer taking IM IFNβ-1a had a better QoL based on SF-36 physical component summary (PCS) scores (39.3 vs. 31.0, P < 0.001) and were more likely to be living independently (P = 0.002) based on a visual analog scale (VAS) for independence with self-care. A subanalysis of data from ASSURANCE revealed that patients who demonstrate IFNβ-1a clinical efficacy early in their treatment course, as measured by disability progression or relapse status at 2 years after starting treatment, had significantly better QoL outcomes than those who continued to have MS disease activity at 2 years. Thus, in addition to the established clinical benefits of early initiation of therapy in MS, early evidence of clinical efficacy may help guide treatment decisions and enable patients to maximize their longer-term QoL outcomes as well.

Evolving MRI Methods for Improved Imaging in MS
Conventional MRI measures have proven useful for detecting subclinical lesion activity in patients with MS. Common measures evaluated in patients with MS include changes in T2-weighted lesions, which appear as bright spots on MRI, and gadolinium-enhancing (Gd+) lesions, which are detected using Gd contrast enhancement of brain MRI scans. Relapses are clearly an important measure, since they have an immediate impact on patients’ functional mobility and QoL and can be associated with significant residual deficits. However, changes on MRI can provide evidence of disease activity that may be of great benefit in patient monitoring, since inflammatory events occur more often than clinical events. For example, in a study of 222 patients with RRMS who were treated with IM IFNβ-1a, the combined presence of new active lesions on MRI and presence of relapses (odds ratio [OR] 4.4; 95% confidence interval [CI] 1.6-12.5), disability progression (OR 7.1; 95% CI = 1.6-33.9), or both factors (OR 6.5; 95% CI = 1.9-23.4) after 1 year were shown to have predictive value in identifying patients...
who went on to experience clinical disease activity in the second and third year of therapy. Composite MRI scores have also been shown to correlate more strongly with EDSS than do individual MRI measures and may prove to be important prognostic indicators in MS.

Improvements in MRI methodology and broader availability of instruments with more powerful 3-tesla magnets are increasing the accuracy of lesion detection and the ability to detect certain lesion types such as gray matter T2 lesions. One study used an optimized MRI protocol incorporating 3-tesla MRI endpoints and monthly brain imaging to document MRI lesion evolution and to compare the efficacy of IFNβ-1b and glatiramer acetate (GA) for treatment of relapsing MS. Results indicated that greater than 40% of enhancing lesions detected using the trial MRI protocol represented persistent enhancement. New contrast-enhancing brain lesions were rare, with only 77 out of 1,161 monthly scans (6.6%) showing new T2 lesions from baseline through month 24. Another study using ultra-high-field 7-tesla MRI imaging to evaluate MRI-detected white matter lesions in MS diagnosis found that periventricular white matter lesion appearance was more predictive of MS (OR 14, P < 0.001) than subcortical or periventricular lesion location (OR 4.5, P < 0.001, and OR 2.4, P < 0.009). With traditional standard MRI enhancement protocols that incorporate monthly MRI, the majority of lesions enhance for approximately 1 month. However, newer high-sensitivity contrast enhancement techniques can extend lesion enhancement to several months. To this end, in a direct comparison, 3-tesla imaging detected a higher lesion load than 1.5-tesla imaging. Comparison of older 1-tesla and 1.5-tesla images with newer, higher-resolution MRI images to gain insight into MS lesion evolution over time may prove challenging.

Despite the value of conventional MRI in characterizing discrete lesions in MS, it does not detect diffuse abnormalities in normal-appearing tissue. Also, mainstream MRI approaches capture both reversible and irreversible components of MS neuronal pathology. Researchers have investigated new imaging measures that are thought to be more closely related to the most disabling pathological features of MS, such as irreversible demyelination and neuroaxonal injury. Promising but less frequently used MRI tools to assess neuronal and axonal damage in MS include central nervous system (CNS) atrophy and T1 hypointensities ("black holes"). A summary of these measures is provided below, together with an overview of relevant studies conducted to date with IM IFNβ-1a as examples of DMT impact on these measures.

### CNS Atrophy

Unlike more conventional MRI endpoints such as T2 hyperintense and Gd+ lesions, CNS atrophy reflects the net impact of severe and potentially irreversible processes such as demyelination and axonal loss in both white matter (WM) and gray matter (GM). Brain atrophy is present even at the earliest stages of MS, and longitudinal structural imaging studies have provided robust evidence of progressive brain atrophy in patients with MS, especially in the frontotemporal cortices. Unsurprisingly, then, CNS atrophy has been shown to be linked to clinical aspects of MS, including patient disability progression and cognitive decline. Indeed, several studies have demonstrated that CNS atrophy is a stronger predictor of disability progression than conventional MRI endpoints.

Early studies assessing the impact of DMTs on whole-brain atrophy in MS used a measurement termed the brain parenchymal fraction (BPF), which is defined as the ratio of the brain parenchymal volume to the total brain volume. Computation of the BPF involves selection of the intensity threshold that best separates the brain parenchyma from the cerebrospinal fluid (CSF) surrounding the brain and in the ventricles and application of that threshold to pixel intensity maps of brain images. A post hoc analysis of BPF using MRI scans from the 2-year, phase 3 placebo-controlled MSCRG trial found that while the percentage change in BPF during the first year was similar in the IM IFNβ-1a and placebo groups, brain atrophy during the second year was significantly reduced (55% decrease) in the IM IFNβ-1a group compared with the placebo group. Over another 2 years of follow-up, the percentage change in BPF was 18% lower in the IFNβ-1a group than in the placebo group. Long-term follow-up of this MSCRG trial of IM IFNβ-1a found that BPF at entry into the trial, and its change over 2 years, was correlated with disability change over 8 years.

Subsequent studies of 2 or 3 years’ duration incorporating various study designs assessing the effects of IM IFNβ-1a alone or in combination have all demonstrated the ability of this DMT to reduce the progression of whole-brain atrophy or cortical-brain atrophy versus placebo or no treatment. In addition, a recent study of patients with RRMS evaluating the effects of daily GA, weekly IM IFNβ-1a, or subcutaneous IFNβ (IFNβ-1a or IFNβ-1b) use on brain volume loss over 5 years found that all DMTs significantly reduce the loss of brain volume in MS compared with no treatment. While it has been argued that early changes in brain volume, so-called pseudoatrophy, observed during the first year of treatment with anti-inflammatory treatments such as IFNβ, may be due to resolution of edema related to MS-associated inflammation; data on microglial activation in MS suggest that treatment-related inactivation and shrinkage of microglia may underlie the volume changes associated with pseudoatrophy.

Whole-brain, GM, and WM atrophy have all been associated with MS disability progression, but GM atrophy has emerged as the type of atrophy that is potentially most closely linked to functional decline in MS. GM involvement is detectable at the earliest stages of MS and may occur earlier than WM atrophy. Several studies have suggested that GM atrophy
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is more strongly correlated with disability than whole-brain or WM atrophy, particularly in early MS.\textsuperscript{59,61} In the Avonex-Steroid-Azathioprine (ASA) study, changes in GM volume over 5 years were significantly correlated with disability progression as assessed with EDSS.\textsuperscript{62} A separate 3-year, open-label, controlled, single-blind, post-marketing observational study in 54 patients with MS reported that IM IFNβ-1a therapy significantly slowed the progression of whole-brain atrophy compared with no therapy, predominantly through inhibition of the progression of GM atrophy.\textsuperscript{53} Similar findings with IFNβ-1a were seen in a recent study presented by Fisher et al. (2010)\textsuperscript{62} However, a recent report on GM atrophy in 105 patients presenting with CIS and 42 normal controls studied over 4 years found that except for cerebellar cortical volume, there were no differences in brain volume change between CIS and controls.\textsuperscript{63} When a subgroup analysis compared results for the 59 patients with CIS who converted to MS during the follow-up with results from the control group, statistically significant atrophy was identified in the precentral gyrus, superior frontal gyrus, thalamus, and putamen. Additional support for a relationship between GM atrophy, MS diagnosis, and MS disability progression may come from ongoing clinical trials and observational studies in MS.

T\textsubscript{1} Hypointensities (“Black Holes”)  
T\textsubscript{1} hypointense lesions (“black holes”) are focal areas of severe CNS tissue damage detected by MRI in patients with MS. Persistent T\textsubscript{1} hypointensities are thought to represent tissue loss, including axonal damage, and appear to be better predictors of disability progression than are T\textsubscript{2} or Gd+ lesions. For example, post hoc analysis of MRI data from the MSCRG study of IM IFNβ-1a for MS revealed that treatment with the DMT IM IFNβ-1a reduced T\textsubscript{1} hypointensity formation by 68% versus placebo.\textsuperscript{64} In this analysis, the median change from baseline over a 2-year interval in brain MRI T\textsubscript{1} lesion load was 40.0 cubic millimeters (mm\textsuperscript{3}; range, -2,424 to 4,042) for patients treated with IFNβ-1a (P=0.164) and 124.5 mm\textsuperscript{3} for placebo (P<0.001). Although the cohort treated with IM IFNβ-1a showed reduced accumulation of T\textsubscript{1} hypointense lesions over 2 years, this difference was not statistically significant (P=0.065). Due to the challenges of measuring the conversion of T\textsubscript{1} lesions to persistent “black holes” using repeated MRI, limited data are currently available demonstrating the relationship between baseline T\textsubscript{1} hypointensities and disability progression. In 1 randomized controlled trial of patients with RRMS receiving IM IFNβ-1a, T\textsubscript{1} hypointensities were found to be a strong predictor of disability progression (OR 6.8; P<0.001).\textsuperscript{65} Another small study of T\textsubscript{1} cortical hypointense lesions using 3-tesla MRI found that patients with lesions performed more poorly (P=0.020) than patients without lesions on the delayed recall component of the California Verbal Learning Test, demonstrating a weak correlation between specific T\textsubscript{1} lesions and cognitive decline.\textsuperscript{66} Additional confirmatory studies are needed to validate the utility of T\textsubscript{1} hypointensities in predicting future disability progression in patients with MS.

Other Emerging Imaging Measures  
Other imaging techniques have been investigated, including functional MRI (fMRI), an MRI procedure that measures brain activity by detecting associated changes in blood flow; MRI diffusion tensor imaging, which measures random motion of water molecules in tissue; MRI magnetization transfer imaging, which uses pulsed radio frequencies to improve image contrast; and optical coherence tomography, a non-MRI assessment that uses high resolution and cross-sectional images of the eye to measure the thickness of the retinal nerve fiber layer, which frequently atrophies in MS.\textsuperscript{67,68} However, further data from well-designed, prospective clinical trials are needed to confirm the validity of these techniques.

Conclusions  
Conventional clinical and MRI outcome measures are moderately predictive of a patient’s risk of MS disease progression. Other outcome assessments have been introduced to overcome these limitations, such as tools to evaluate cognitive function, enhanced measures of disability such as the MSFC, and expanded imaging parameters such as T\textsubscript{1} hypointense lesions and CNS atrophy. When utilized in conjunction with the standard assessment tools discussed in this article, these measures permit a much broader yet also more precise assessment of MS disease status and progression. Standardization, validation, and adoption of newer measures may provide a more comprehensive view of a patient’s disease than historical measures alone and can also help guide individual therapy choices to potentially reduce disease progression and future disability. It will be important to critically evaluate the implications of new disease measures relative to the clinical effectiveness and personal and economic costs associated with different DMTs as well as the costs of untreated disease.

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REFERENCES

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