Measuring the impact of therapeutic intervention

Thinking beyond traditional outcomes

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GLOSSARY

DMT = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **HRQoL** = health-related quality of life; **MS** = multiple sclerosis; **MSFC** = Multiple Sclerosis Functional Composite.

In 1981, 113 years after Jean Martin Charcot's initial description of multiple sclerosis (MS), an international workshop considered the challenges facing investigators in developing effective therapies for MS.[1] Many of the neurologists at the workshop felt that the hurdles were too great and that efforts to develop effective therapies would require a fundamental understanding of the etiology of the disease. Prominent among the hurdles were the variability of the disease—both between and within patients—and difficulties measuring the disease. In hindsight, the 1981 workshop was a watershed event. Since then, in only 29 years, there has been remarkable progress in measuring and treating MS. Patients are now diagnosed earlier and with greater accuracy with the advent of MRI and its inclusion in diagnostic criteria.[2] In addition, there has been a lively debate on the best approach to measuring the disease. Are traditional measures optimal? Does a treatment effect on relapses translate into a meaningful long-term therapeutic response for the patient? Does the Kurtzke Expanded Disability Status Scale (EDSS) optimally measure MS-related disability? Does a therapeutic effect on the EDSS during the relapsing-remitting stage of MS mean there will be a reduction in irreversible disability? Is the EDSS optimal for developing therapies for the progressive stages of MS? Are there more precise and responsive measures of disability that could supplant the EDSS, such as the Multiple Sclerosis Functional Composite (MSFC)? What about patient-reported outcomes that more meaningfully reflect the impact of the disease on the patient? Answers will emerge as nontraditional measures are included in clinical studies. What about measures of neuropsychological function, fatigue, and measures of bowel, bladder, and sexual function? What is the economic effect of treatment? Can the effects of therapy on MRI lesions and brain volumes be translated into clinical efficacy, potentially providing an imaging surrogate for clinically meaningful outcomes? Some of these novel measures are making their way into clinical studies, potentially supplementing the traditional measures of relapse and EDSS.

The MS disease process is active by MRI criteria in many patients without obvious clinical symptoms, suggesting that "disease activity and progression" can be dissociated from "clinical disability progression." How does one properly evaluate clinical efficacy during the early stage of MS, when the disease is active by MRI criteria but with minimal or no sign of clinical disease progression? Can any particular measurement tool be usefully applied to all stages of MS and to all patients in a clinical study? Certain aspects of MS, such as neuropsychological functioning or fatigue, do not lend themselves to simple or precise measures. Therefore, despite the progress, challenges and controversies remain, and measurement of treatment efficacy is still heavily dependent on relapses and the EDSS. Acceptance of other outcome measures, including cognitive function, visual function, health-related quality of life (HRQoL), the MSFC, brain atrophy, and other nontraditional outcomes is gradual, and there is no consensus on the best measure or group of measures.

Against this background, the idea for a collection of articles reviewing the effects of disease-modifying therapies (DMTs) on nontraditional measures of disease activity in MS was conceived. Publishing these articles together in a supplement should help the reader better appreciate the breadth of outcome measures and how these measures may be used in a complementary way to more comprehensively characterize the efficacy profile of a DMT.

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In the first article, Havrdova and colleagues draw on comparisons with treatment for patients with rheumatoid arthritis and the impact of biologic therapies in discussing the concept of "freedom from disease activity" as a treatment goal in MS. Disease activity in MS can be measured according to clinical and radiologic outcomes that are routinely used in clinical studies. Potentially, freedom from disease activity (analogous to disease remission in rheumatoid arthritis) could be determined without additional outcome measures. The combined clinical and radiologic criteria described by Havrdova and colleagues were applied to the placebo-controlled Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study of natalizumab and easily could be applied to other MS therapeutic trials. As more effective therapies are developed, it is anticipated that greater proportions of patients will achieve freedom from disease activity in future clinical studies. An important research question to be answered is whether freedom from disease activity, as defined by Havrdova, will lead to long-term clinical stability.

The MSFC is a multidimensional instrument that was designed to combine quantitative measures of the major clinical dimensions of MS into a single reproducible and responsive measure of disability. It is made up of 3 components that measure arm and hand dexterity, walking speed, and cognition. The MSFC overcomes some of the limitations of other measures of disability such as the EDSS, but it is not without disadvantages. Although it has not yet achieved the status of a primary outcome measure in MS clinical studies, the MSFC has been widely used and data are accumulating rapidly. Polman and Rudick discuss the MSFC as a measure of disability in MS and review its use as an efficacy outcome in previous studies of DMTs.

Impaired visual function is a common symptom of MS that can have marked effects on quality of life. Balcer and Frohman review the visual deficits that can occur in patients with MS and the available methods of assessment. Low-contrast letter acuity testing is a readily available method for quantitative and standardized testing of visual function. Compared with high-contrast letter acuity testing, low-contrast acuity testing is more sensitive to changes in visual function in patients with MS. Moreover, low-contrast letter acuity has demonstrated significant correlation with measures of disability (EDSS and MSFC), MRI results, and retinal nerve fiber thickness. Treatment effects on low-contrast letter acuity in patients with MS have been demonstrated in the phase 3 studies of natalizumab, but use of this test as a clinical study outcome is otherwise in its early stages. It has been suggested that low-contrast letter acuity testing may be a useful addition to the MSFC, and this is currently being evaluated.

Although increasing attention is being given to the patient's experience of MS, the number of phase 3 clinical studies that have included patient-reported outcomes or HRQoL measures as prespecified secondary or tertiary outcomes is relatively small. Considering the profound negative effects that MS can have on HRQoL, there is a major knowledge deficit with respect to how current MS treatments affect HRQoL. Miller and colleagues provide a summary of the status of HRQoL research in MS and an overview of the generic and MS-specific instruments that are most frequently used in MS clinical studies. Their review of published clinical studies clearly illustrates the general lack of class I evidence demonstrating HRQoL benefits for most of the available DMTs. As with the MSFC and low-contrast visual acuity testing, it is anticipated that HRQoL evaluation will become more frequently included in phase 3 pivotal study protocols as the value of these measures within the neurology community is more widely perceived.

This supplement brings together a collection of review articles that examine nontraditional measures of disease activity in MS and how they are affected by currently available DMTs. The reader should expect to see reports on nontraditional measures increase as clinical trials incorporate new, potentially valuable measures of the multiple dimensions of MS.

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DISCLOSURE

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REFERENCES

1. Multiple sclerosis. Proceedings of the International Conference on Therapeutic Trials in Multiple Sclerosis; Grand Island, NY, April 23–24, 1982. Arch Neurol 1983;40:663–710.
2. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840–846.