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## EDITORIAL

# Simple MRI Metrics Contribute to Optimal Care of the Patient with Multiple Sclerosis

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**M**R imaging has been a critical element in multiple sclerosis care because it has been the basis, along with clinical measures, for testing treatment efficacy. MR imaging serves as a pri-

mary outcome measure in phase II and a secondary outcome measure in phase III clinical trials in MS.<sup>1</sup> There are now 10 approved MS disease-modifying drugs, all showing measurable impact in population studies on inflammatory disease as indicated by new T2 hyperintense and/or gadolinium-enhancing lesions on MR imaging. MR imaging initially impacted the field as an important component of diagnostic criteria,<sup>2</sup> in part because MR imaging is much more sensitive to early MS than are clinical features. For similar reasons, clinicians have embraced the practice of monitoring subclinical MR imaging activity for treatment decisions, though formal criteria for an actionable response to MR imaging activity in an individual patient have been limited (On-line Table 1). MR imaging monitoring is also critical for detecting complications of therapy—for example, infection (progressive multifocal leukoencephalopathy) or inflammation (immune reconstitution inflammatory syndrome).<sup>3</sup>

Several recent initiatives by the MS community have addressed the concept of individualized, more tailored, and sometimes more aggressive early treatment. Treatment escalation has only recently become feasible with the introduction of new, potentially stronger MS treatments based on differing mechanisms and molecular targets.<sup>4</sup> As a result, MR imaging activity will be increasingly used in clinical practice to determine whether patients are responding to treatment or may benefit from a change in treatment or escalation to higher-risk therapy (On-line Table 1). For example, the Canadian MS Working Group guidelines were updated in 2013,<sup>5</sup> on the basis of combinations of relapse, disability, and MR imaging scores, for recommendations classified as low, medium, or high concern. The Rio score, developed in Barcelona, was modified recently on the basis of a validation study to include only MR imaging activity and relapse indicators.<sup>6</sup> Enhancing lesions, followed by relapses and new T2 lesions during the initial 2 years, were the best predictors of disability 15 years later in treated (distinct from placebo) patients in the interferon (IFN)  $\beta$ -1a trial,<sup>7</sup> suggesting that persistent inflammatory disease activity in patients on IFN reflected nonresponse to therapy. An analysis by Dobson et al<sup>8</sup> from 11 studies with IFN- $\beta$  treatment found that those who develop new MR imaging lesions on IFN- $\beta$  within 2 years of starting therapy are at significantly higher risk of future relapses and/or disability worsening and that these patients can be identified after just 6–12 months of treatment.

The simple MR imaging measures of focal T2 hyperintense and enhancing lesions seem to contribute strongly to relapse and disability outcomes and contribute significantly to brain atrophy, a surrogate of disability. This association is highlighted in a recent meta-analysis by Sormani et al,<sup>9</sup> based on >13,500 patients with relapsing MS in 13 clinical trials. The correlation coefficients ( $R^2$ ) with downstream disability for new/enlarging T2 lesions and brain atrophy were 0.61 and 0.48, respectively, with both measures retained in a final model with a combined  $R^2$  of 0.75, strongly supporting the use of these MR imaging outcomes as clinical surrogate measures when applied in an appropriate clinical-/treatment-specific context.<sup>9</sup>

It is likely that in the future, advanced quantitative and functional measures by MR imaging will assume far greater impor-

 Indicates article with supplemental on-line tables.

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tance in measuring aspects of neurodegeneration, de- and remyelination, and particularly in progressive stages of MS, including in individual patients. However, the currently recognized success of the existing MS therapies is thought to be predominantly based on the impact on the early inflammatory stages of disease, with a variable and lesser, perhaps only secondary, impact on neurodegeneration. Standardized brain volume (atrophy) measures are predictive of disability and, when applied serially, can be used to assess atrophy patterns, including in individual patients,<sup>10</sup> but these are not widely available or currently thought to be practical in clinical practice unless and until MR imaging manufacturers or other third parties support these measures.

There is an emerging consensus in the MS field that successful treatment results in no evident inflammatory disease activity (NEIDA), defined as the absence of new relapses or new MR imaging lesions. This was discussed at a recent international consensus workshop sponsored by the Cleveland Clinic (Las Vegas; December 12–14, 2013). Standardized MR imaging lesion reporting was identified by survey as a critical element for future implementation and testing of NEIDA. There have been prior initiatives to improve MS clinical care through standardized requests, MR imaging acquisition, and interpretation templates, including by the Consortium of MS Centers.<sup>11</sup> More recent revisions recognize the improved hardware, including the potential shift to a 3D acquisition technique (see www.ms-care.org). MR imaging technology evolves rapidly, field strength is ever-increasing, and acquisition and processing techniques will continue to impact lesion counts, which will necessarily evolve as well. Nevertheless, well-planned 2D and 3D acquisition techniques and attention to detail in manual or computerized registration will provide a basis for accurate serial analyses.

While there is almost certain to be disagreement as to the optimal cut-point for lesion counts to support treatment for MS, standardized, high-quality MR imaging acquisition combined with reports that provide the essential elements for MS diagnosis or therapeutic decision-making (On-line Tables 2 and 3) can, no doubt, improve outcomes for patients with MS.

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