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eLITERATURE REVIEW
eMultipleSclerosis Review

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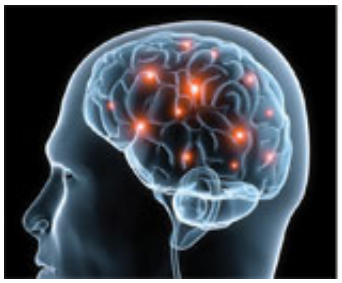



**eMultipleSclerosis Review VOLUME 1, ISSUE 5**

## *Incorporating MRI Results in Treatment Decision Making*



## In this Issue...

The expansion of therapeutic options, while a welcome change for both patients and clinicians, has created a more complicated process for making treatment decisions. Of particular note is the value of MRI findings—although long used to assist in the diagnosis and monitoring of multiple sclerosis, the evidence basis of their utility remains incomplete.

In this issue, we review recent publications describing:

- Correlations between brain volume loss and MRI
- Correlations between MRI findings and outcomes in early MS
- The use of MRI lesions as a surrogate marker for relapses
- The incorporation of MRI findings into NEDA (no evidence of disease activity) relative to long term clinical outcomes
- The comparative effects of oral DMTs on the probability of a patient achieving NEDA

## LEARNING OBJECTIVES

**After participating in this activity, the participant will demonstrate the ability to:**

- Describe the prognostic significance of MRI findings at the time of diagnosis.
- Explain the prognostic significance of MRI changes during the course of disease-modifying therapy
- Discuss the changing landscape of disease-modifying therapies and an approach to risk/benefit calculations.

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CME Info
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**Length of Activity**
1.0 hour Physicians

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October 29, 2015

**Expiration Date**
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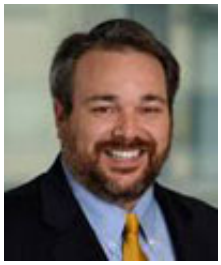

Commentary & Reviews
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**Program Directors' Disclosures**

***Guest Faculty Disclosure***

Dr. Greenberg has indicated that he has received grant support from Acorda Therapeutics, Biogen, Chugai Pharmaceutical Co., and MedImmune. He has served as a consultant for MedImmune, Novartis, and EMD Serano.

**Unlabeled/Unapproved uses**

Dr. Greenberg has indicated that his presentation will not reference unlabeled/unapproved uses of drugs or products.

## IN THIS ISSUE





## COMMENTARY

Relapsing remitting multiple sclerosis (RRMS) has had a dramatic increase in the number of FDA-approved disease-modifying therapies over the last 10 years. While the expansion of therapeutic options is a welcome change for both patients and clinicians, it has created a more complicated process for making treatment decisions. Patients and their health care providers first have to determine what defines success when a therapy is initiated. There is a lack of consensus about how relapses, disease progression, and MRI findings should be followed and the relative weight each should be given in adjusting treatment, with significant controversy about how clinicians and patients should incorporate the evolution

of asymptomatic changes on MRI into treatment decisions. The classification of patients as having 'no evidence of disease activity' (NEDA) is based on a lack of clinical relapses, disease progression (measured by the Expanded Disability Status Scale [EDSS]), new T2 hyperintense lesions, and post-contrast enhancement.

Several of the studies reviewed in this issue reported a statistically significant correlation between MRI changes and clinical changes. Dr. Sormani and colleagues noted a correlation between MRI changes and relapse rates, which is one way to validate the value of surveillance MRIs when following patients over time. Identifying breakthrough disease, even asymptomatic lesions, may have long-term importance to patients and might be an important part of care decisions. Data presented by Drs. Magzhi and Radue (in separate studies) validated the correlation between brain atrophy (total volume and gray matter) and progressive disability. Of interest, the studies identified variance between the type of atrophy and the clinical measures that were correlated, with some clinical measures correlating more strongly with atrophy (ie, the Symbol Digit Modality Test [SDMT]) than others (ie, Paced Auditory Serial Addition Test [PASAT]). These data are critical to deciphering the variance among published studies that report correlations between 'cognitive measures' and imaging findings. It is clear that specific anatomic changes will correlate with some clinical measures but not others and reminds us about the diversity of clinical measures used in MS research. As this research progresses, we will be able to track patient responses to therapy in a more nuanced way and predict the potential real-world implications for each patient.

MRI data are incredibly important as findings from clinical trials are interpreted. Two studies presented here examined the concept of NEDA (no evidence of disease activity) in RRMS patients. The first paper reported data from the CLIMB study, evaluating a cohort of patients systematically followed for seven years in a real-world clinical setting. NEDA was achieved if a patient had no relapses, no progression of disability, no new T2 lesions on MRI, and no evidence of new enhancing lesions. The study noted a relatively low rate of achieving NEDA at seven years, but found that more than half of patients had not progressed on the EDSS scale over the same period of time. Critical to the management of MS patients in this era of a multitude of therapeutic options is the ability to track patients early in their disease course to determine if they are having an ideal or suboptimal response to therapy. Predictive measures of outcomes are incredibly important for patients and clinicians to make informed decisions about treatment. Just as patients and clinicians would want an early warning about a treatment failure, they also would want to avoid changing therapy based on an unimportant marker. For example, if T2 lesion changes do not predict ultimate outcome, then the current definition of NEDA would have to be amended. Although each study reviewed provides significant insight, a comprehensive assessment of imaging and clinical outcomes is needed (in a large longitudinal study) to decipher the complex relationship between short-term clinical, short-term radiographic, and long-term clinical outcomes.

Also reviewed in this issue is a novel meta-analysis and modeling study that used published data from controlled clinical trials of the available oral RRMS therapies. The authors attempted to control for the differences between design, inclusion criteria and baseline characteristics of the studies to determine the relative ability of each oral therapy to induce NEDA in a study patient. Going further, they used mathematical modeling to estimate the relative impact of one therapy on a cohort enrolled in another trial. For example: what would happen to patients enrolled in a fingolimod trial if they took dimethyl fumarate instead? This study presented data that indicated fingolimod was the most potent of the oral agents for inducing NEDA. While the authors noted the limitations of their results and cautioned about overinterpretation, their approach highlights a novel method for deciphering clinical trial data in a landscape that lacks head-to-head studies.

In the end, clinicians and patients will continue to make treatment decisions with incomplete data and will have to employ rationale strategies for monitoring responses to therapy.

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# CORRELATING BRAIN VOLUME LOSS TO MRI

Radue EW, Barkhof F, Kappos L, et al. Correlation between brain volume loss and clinical and MRI outcomes in multiple sclerosis. *Neurology.* 2015; 84:784-793.

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MRI has long been used to assist in the diagnosis and monitoring multiple sclerosis (MS). However, controversy exists about the usefulness of this technology to predict clinically meaningful outcomes for patients. A variety of MRI techniques have been used in the past, including T2 lesions, T1 hypointense lesions, and gadolinium enhancing lesions. Currently, brain volume has been investigated as a potentially useful marker for longitudinal follow-up of patients with MS. Identifying a valid radiographic prognosticator for MS would be incredibly useful, given the challenging therapeutic decisions that patients routinely make.

The authors of this studied combined imaging and clinical data from three randomized, controlled, phase III trials of fingolimod to investigate the potential correlation of MRI findings to clinical outcomes. In this combined analysis, the baseline normalized brain volume was correlated with age, duration of MS, baseline T2 volume, and measures of disability (MS Functional Composite [MSFC] > Expanded Disability Status Scale [EDSS]). For patients with higher gadolinium enhancing lesion count, T2 lesion volume, T1-hypointense lesion volume or decreased normalized brain volume at baseline, there was a higher risk of brain volume loss while on study. Throughout the studies, the amount of brain volume loss correlated with new gadolinium enhancing lesions, new or enlarging T2 lesions, and clinical relapses. If longer intervals were considered (> 1 year), there was a correlation between volume loss and disability measures.

Although the data for this study were "repurposed" from three phase III clinical trials, the design of the study takes advantage of the large dataset available. The strengths of this study include the prospective data acquisition, the uniform imaging collection protocols, central reading facilities, standardized clinical data acquisition, and sample size. While it would be difficult to fund an independent longitudinal study of imaging in MS, the current study used the existing infrastructure and data collected in the context of phase III clinical trials. The findings indicate a strong correlation between brain volume and clinical functions, suggesting that brain volume could be used as a surrogate marker in clinical trials or used to inform clinicians monitoring patients on medication. A stabilization of brain volume loss over time would suggest a beneficial effect of medication. Furthermore, the correlations between baseline features and on-study brain volume loss suggest that certain findings at diagnosis would place a patient in a higher risk category for future disability. Given the increasing complexity of MS therapeutics, clinicians and patients would benefit from having validated prognostic markers of MS disability.

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# CORRELATION BETWEEN MRI FINDINGS AND OUTCOMES IN EARLY MS

Maghzi AH, Revirajan N, Julian LJ, et al. Magnetic resonance imaging correlates of clinical outcomes in early multiple sclerosis. *Mult Scler Relat Disord*. 2014 Nov;3(6):720-727.

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For decades, clinicians and researchers have attempted to create and validate a disability measure for multiple sclerosis. The longest and most widely used measure is the Expanded Disability Status Scale (EDSS), which has been adopted by the FDA as a measure of disability. While other outcome measures have been validated in large cohorts of patients with MS, (including the MS Functional Composite [MSFC)], none have yet to be designated by regulatory authorities as a valid disability outcome in registrational drug trials. Although quite good as a multimodal outcome measure in MS, the MSFC historically lacks a measure of visual function, and cognitive testing (ie, the Paced Auditory Serial Addition Test [PASAT]) has been criticized by some as being inferior to the Symbol Digit Modality Test (SDMT). Once a clinical measure is validated as reproducible and clinically



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meaningful, it can be quite useful in clinical trials and clinical care of patients. Furthermore, clinically validated outcome measures can be used as a gold standard of disability when developing surrogate markers of disease progression (eg, imaging outcomes) in prospective studies.

Dr. Maghzi and colleagues studied 43 patients over a three-year period with clinical and imaging measures to determine the correlations between imaging findings and clinical outcome measures. These patients were studied in the context of a randomized, double blind, placebo-controlled trial of riluzole as a potential add-on therapy to interferon beta 1a. Changes in brain volume between two time points were obtained from 3D-IRSPGR images. Brain volume metrics for each time point included normalized normal-appearing white matter volume (nNAWMV), normalized gray matter volume (nGMV), and normalized brain parenchymal volume (nBPV). The number of T2 and contrast-enhancing lesions were counted using simultaneous visualization of T2 and T1 pre- and post-enhancement images. Clinical measures included the EDSS, MSFC (timed 25 foot walk [T25FW], nine-hole peg test [9HPT], and PASAT), SDMT, and low contrast visual acuity. Patients were enrolled within one year of disease onset and followed for three years; 43 patients were enrolled, with 22 completing all 36 months of the study (38 completed 24 months of the study).

The study reported on the correlations between baseline MRI features and longitudinal changes as predictors of clinical worsening. Baseline nBPV, nGMV, and nNAWMV all predicted longitudinal changes in MSFC score. There were associations with T25FW, but not with PASAT or 9HPT. Baseline T2 lesion volume predicted changes in both PASAT (P = .004) and changes in SDMT ( P = .08). Notably, changes in brain volume were associated with longitudinal changes in cognition (as measured by the SDMT), with a 1% decrease in brain volume associated with a 1.14 decrease in SDMT (but not associated with PASAT). A 1% reduction in brain volume was also associated with a reduction in low contrast visual acuity.

This paper followed a small cohort of patients over a three-year period with standardized imaging and clinical protocols. The data confirmed that MRI measures can be correlated with clinical outcomes, but there is variability between imaging findings and their associated clinical measure. These findings offer insight into the need for prospective trials to increase the variety of different imaging and clinical measures to more decisively validate appropriate correlations.

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## MRI LESIONS AS A SURROGATE FOR RELAPSES

Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomized trials. *Lancet Neurology*. 2013; 12:669-76.

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Disease-modifying therapies have been studied in relapsing, remitting multiple sclerosis for over 25 years. Registrational drug trials in the US have been powered around the ability of a medication to reduce annualized relapse rates. Secondary endpoints have frequently centered around the ability of a medication to prevent disease associated progression of disability, as measured by a variety of MRI findings. To date, while regulatory agencies such as the FDA have not certified MRI measures as an appropriate surrogate marker to be used as a primary outcome in a registrational drug trial, clinicians and patients frequently use MRI surveillance to monitor for evidence of breakthrough disease. Patients frequently obtain annual MRIs for review by their neurologist, and conversations about changing disease-modifying therapy often occur when asymptomatic new demyelinating lesions are observed.

Drs. Sormani and Bruzzi published a meta-analysis of data from clinical trials to determine if there was a statistically significant correlation between the suppression of MRI disease activity and relapse rates. Furthermore, the study attempted to determine the sample sizes needed to design appropriately powered phase 3 drug studies using imaging as a primary endpoint. After screening 347 articles identified in a PubMed search, 31 studies were

identified as meeting inclusion criteria for the meta-analysis. Trials were included if they reported MRI data for T2 activity (new or enlarging T2 lesions). If T2 lesions were not included in the report, the study had to include data on the number of gadolinium-enhancing lesions and the use of monthly scan protocols. The authors computed a treatment effect on relapses and a treatment effect on MRIs by comparing the treated patients' annualized relapse rate and new MRI lesions to the same metrics for control patients within the trial. The total number of patients included in the 31 studies was 18,901.

The authors found a significant correlation between the treatment effect of disease-modifying therapies on relapses and on MRI changes. Although the authors had to account for differences in trial design, trial length and differences in when the trial occurred, even with these controls, they found a continued association between treatment effects on relapses and treatment effects on MRI changes. Based on these data, the investigators then explored the impact on trial sample size if MRI was used as a primary outcome. Compared to two-year trials that enroll 300-800 patients per comparator arm to identify 20%-30% reductions in annualized relapse rate, a trial using MRI lesions as a primary outcome would last six months and enroll 110-290 patients per arm (a reduction in sample patient size of >50%).

This study uses the size of a meta-analysis to investigate the correlation between MRI changes and relapses in patients with MS. While there are limitations to any meta-analysis, this study did find correlations between MRI changes and longitudinal clinical changes. Furthermore, the authors explored the potentially groundbreaking change in MS clinical trials that could occur if imaging data was used as a primary outcome. However, the authors do concede that more work is needed to ultimately trust MRI changes as a clinically significant marker of disease activity from a regulatory perspective.

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## NEDA (NO EVIDENCE OF DISEASE ACTIVITY) IN A LONGITUDINAL COHORT

Rotstein D, Healy B, Malik M, Chitnis T, Weiner H. Evaluation of No Evidence of Disease Activity in a 7-Year Longitudinal Multiple Sclerosis Cohort. *JAMA Neurology*. 2015; 72(2):152-158.

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Dr. Rotstein and colleagues use data from their longitudinal study of MS (CLIMB study) to explore the concept of no evidence of disease activity (NEDA) in a real-world clinical cohort of patients. In the introduction they explain that the concept of NEDA has been evolving as a potential goal of therapeutic interventions. Specifically, if a disease-modifying therapy could suppress all clinical and radiographic evidence of MS disease activity, it would lead to the best possible outcomes for patients. NEDA is defined as the absence of new or enlarging T2 or post-gadolinium enhancing lesions, no sustained progression as measured by the Expanded Disability Status Scale (EDSS), and an absence of clinical relapses. In the current study, the investigators examined data from 219 patients who had clinical examinations every six months and annual MRIs. They determined the impact of achieving NEDA on long-term disability. After seven years, only 17 patients fulfilled the full NEDA criteria.

Several features of the cohort were notable. First, 56.5% of patients had no evidence of disease progression at seven years; second, 24.2% of patients had no evidence of MRI disease activity at seven years; and third, 15.8% of patients had no evidence of MRI disease activity at year 7, but did have evidence of clinical disease activity. The authors discussed their findings in the context of previously reported data and noted that the combined NEDA measure allowed for "better early prediction of freedom from progression at long term follow up (7 years) than absence of relapses, disability progression, relapses and disability progression, or new MRI lesions alone." However, while the positive predictive value of NEDA was excellent for long-term disability, the authors noted that the negative predictive value was lacking. Patients were capable of having some evidence of disease activity but would go on to have little disability over time. The noteworthy finding

that came as a surprise to the authors was the number of patients who lost NEDA status based on clinical rather than MRI criteria. This finding was different from previous studies that found MRI changes to be the primary reason a patient would not meet NEDA criteria; however, those studies were shorter in follow-up duration. Finally, the authors noted that alternate MRI parameters (ie, brain atrophy) might have the best association with long-term disability and may have to be incorporated into future assessments of NEDA.

When treating patients with disease-modifying therapy, the goal of the intervention is to prevent new relapses and protect against long-term disability. Unfortunately, it is currently impossible to predict with any certainty which patients will respond to which disease modifying therapies. Establishing an early marker of response to therapy would be critically important to patients and clinicians. The authors of this study note that while achieving NEDA may be a key outcome measure, more research is needed to validate the best measures to include in this categorization of patients.

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## INDIRECT COMPARISONS OF ORAL THERAPIES TO ACHIEVE NEDA

Nixon R, Bergvall N, Tomic D, Sfikas N, Cutter G, Giovannoni G. No Evidence of Disease Activity: Indirect Comparisons of Oral Therapies for the Treatment of Relapsing Remitting Multiple Sclerosis. *Advances in Therapy*. 2014, 31:1134-1154.

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Disease modifying therapy choices have significantly expanded over the last 20 years, from injectable options to infusible and ultimately to oral therapies. Three oral disease-modifying therapies are currently approved by the FDA for patients with relapsing remitting multiple sclerosis. Each gained approval based on placebo controlled trials, but no controlled head-to-head trials comparing them have been conducted. Dr. Nixon and colleagues used published data about these three oral medications to calculate the ability of each therapy to achieve no evidence of disease activity (NEDA) status among the studied patient populations. NEDA is achieved if a patient has no clinical relapses, no disease progression (as measured by the Expanded Disability Status Scale [EDSS]), and no new T2 or post-gadolinium enhancing lesions on MRI.

Patient cohorts were pooled from the FREEDOMS and FREEDOMS II (fingolimod) trials, the DEFINE and CONFIRM trials (dimethyl fumurate [DMF]), and TEMSO trial (teriflunomide) and compared. At baseline the patients were clinically similar, except for prior disease-modifying therapy use and baseline MRI findings. Models were created to determine the relative risk (RR) of achieving NEDA compared to placebo for the oral agents, with higher relative risks (> 1.0) associated with a higher probability of a good outcome (ie, NEDA). Fingolimod, teriflunomide, and DMF were compared based on the RR of achieving NEDA.

The authors analyzed the data in multiple ways. The rates of NEDA were determined for each patient cohort as compared to placebo within each trial. Given the differences between trial designs and enrolled cohorts, the authors modelled the expected rates of NEDA if patient cohorts from one trial were treated with a different drug — for example, the authors noted the estimated RR of NEDA if patients enrolled in the FREEDOMS trials were enrolled in either the DMF or teriflunomide trials. All of the models identified fingolimod as the most likely oral agent to induce NEDA in a patient. The authors cautioned that the findings should be interpreted with caution, but in the absence of head-to-head trial data there are limited means of comparing these therapies.

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# KEY TAKEAWAYS

• MRI changes have been shown to provide prognostic value relative to long-term clinical outcomes in MS
• There is a relatively low rate of 'no evidence of disease activity' (NEDA) among a longitudinally followed cohort of MS patients, but has some prognostic value relative to future levels of disability.
• While there are no head-to-head trials of oral disease-modifying therapies in RRMS, existing data suggests there are different rates of NEDA among patients treated with different oral therapies.

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