Treatment Effect on Brain Atrophy Correlates with Treatment Effect on Disability in Multiple Sclerosis

Maria Pia Sormani, PhD,1 Douglas L. Arnold, MD,2 and Nicola De Stefano, MD3

Objective: To evaluate the extent to which treatment effect on brain atrophy is able to mediate, at the trial level, the treatment effect on disability progression in relapsing–remitting multiple sclerosis (RRMS).

Methods: We collected all published randomized clinical trials in RRMS lasting at least 2 years and including as endpoints disability progression (defined as 6 or 3 months confirmed 1-point increase on the Expanded Disability Status Scale), active magnetic resonance imaging (MRI) lesions (defined as new/enlarging T2 lesions), and brain atrophy (defined as change in brain volume between month 24 and month 6–12). Treatment effects were expressed as relative reductions. A linear regression, weighted for trial size and duration, was used to assess the relationship between the treatment effects on MRI markers and on disability progression.

Results: Thirteen trials including >13,500 RRMS patients were included in the meta-analysis. Treatment effects on disability progression were correlated with treatment effects both on brain atrophy ($R^2 = 0.48$, $p = 0.001$) and on active MRI lesions ($R^2 = 0.61$, $p < 0.001$). When the effects on both MRI endpoints were included in a multivariate model, the correlation was higher ($R^2 = 0.75$, $p < 0.001$), and both variables were retained as independently related to the treatment effect on disability progression.

Interpretation: In RRMS, the treatment effect on brain atrophy is correlated with the effect on disability progression over 2 years. This effect is independent of the effect of active MRI lesions on disability; the 2 MRI measures predict the treatment effect on disability more closely when used in combination.

The role of focal white matter lesions on magnetic resonance imaging (MRI) as a surrogate endpoint for clinical relapses in relapsing–remitting (RR) multiple sclerosis (MS) clinical studies has been extensively studied both at the trial1,2 and at the individual patient3–5 level. The most recent findings indicate that in RRMS patients the effect of treatments on active T2 lesions predicts an effect on clinical relapses that can be quantitatively and precisely estimated2 by means of a regression equation. In addition, a significant although weaker relationship has been found between the treatment effect on active MRI lesions and that on short-term disability progression.6

Based on the results of these previous studies, the relationship between the effect of therapies on active MRI lesions and on clinical endpoints is well established for the anti-inflammatory effect of treatments in the RR phase of MS. However, neurodegeneration also occurs, beginning at the earliest stages of MS, and is responsible at least in part for the accumulation of irreversible disability.7 Thus, the treatment effect on disability also should take into account the neurodegenerative component of the disease, which should be reflected by MRI markers related to neuroprotection or repair.

Measurements of percentage brain volume changes and brain parenchymal fraction (BPF) over time are among the best-studied methods for quantifying neurodegeneration in MS.7,8 Atrophy measures have been shown to correlate with neurological and neuropsychological disability9,10 and to be feasible in large-scale multicenter studies.11 However, the ability of the treatment effect on brain atrophy to predict an effect on disability

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.24018

Received May 28, 2013, and in revised form Jul 23, 2013. Accepted for publication Aug 24, 2013.

Address correspondence to Dr Sormani, Department of Health Sciences (DISSAL), Via Pastore 1, Genova, Italy.
E-mail address: mariapia.sormani@unige.it

From the 1Biostatistics Unit, Department of Health Sciences, University of Genoa, Genoa, Italy; 2McConnell Brain Imaging Centre, Montreal Neurological Institute and Hospital, Montreal, Canada; 3Department of Medicine, Surgery, and Neuroscience, University of Siena, Siena, Italy.

© 2014 American Neurological Association
accumulation has not been assessed. Against this background, we performed a meta-analysis, which includes all the randomized trials that evaluated both the effects of disease-modifying drugs (DMDs) on brain atrophy and disability progression in RRMS, to assess the relationship between the size of the treatment effect on brain atrophy and the treatment effect on disability progression.

**Subjects and Methods**

**Search Strategy and Selection Criteria**

We searched electronic databases (Ovid MEDLINE [1950–December 2012], PubMed [1965–December 2012]), to identify trials fulfilling the following inclusion criteria: randomized, controlled trials in RRMS, assessing the efficacy of DMDs of any class, lasting at least 24 months, and reporting data on the number of MRI lesions, on brain atrophy, and on disability progression over the follow-up period. Only trials in which brain atrophy was assessed using the SIENA\(^1\)\(^2\) or the BPF\(^3\) methods were included, because these are the most used methods in MS clinical research studies.

We used search terms for the disease name (“multiple sclerosis,” “demyelinating disease”) and disease phenotype (“relapsing,” “relapsing-remitting”), and MeSH terms used for indexing articles for MEDLINE/PubMed (“Multiple Sclerosis” [MeSH] AND “Clinical Trials as Topic” [MeSH] AND “relapsing-remitting”). No language restriction was used. Abstracts were independently screened by 2 reviewers, and full papers were examined if relevant information could not be ascertained from the abstracts. To find any additional trials, reference lists of included studies and systematic reviews were evaluated. When data useful for this analysis were not reported in the published trial reports, we contacted the owners of the data, and included the trial if they consented to include additional unpublished material.

**Data Extraction**

Data extraction was done independently by 2 reviewers, and the accuracy of extraction was validated by consensus. Trials satisfying the inclusion criteria were considered for the analysis if they had data on brain volume changes between month 6 or month 12 from treatment start and the end of follow-up (to correct for any possible pseudo-atrophy effect),\(^5\) contained MRI data on active T2 lesions (defined as new or “new or enlarging”), and reported data on disability progression defined as an increase in the Expanded Disability Status Scale (EDSS) of 1 point (0.5 if baseline EDSS \(\geq\) 6) confirmed at month 6 (or at month 3 as a second option).

For each trial, data were collected on year of publication; number of randomized patients; number of patients with complete data on brain atrophy, MRI lesions, and disability progression; DMDs used; number of MRI lesions per treatment arm; brain volume change per treatment arm; probability of disability progression; follow-up duration; and technique used to measure brain atrophy.

**Endpoints**

The actuarial probability of progression per treatment arm was extracted from each trial as the clinical endpoint for the analysis. The ratio between the probability of progression at the end of follow-up in the experimental and the control arm was used as the estimate of the treatment effect on disability progression (DIS effect). The brain volume change between month 6 or month 12 and the end of follow-up was extracted from each trial. The ratio between the mean or the median brain volume change in the experimental and the control arm was used as the estimate of the treatment effect (ATROPHY effect) on brain atrophy progression. The cumulative number of active T2 lesions counted over the follow-up period was extracted from each trial. The ratio between the average number of MRI lesions per patient in the experimental and the control arm was used as the treatment effect on MRI lesions (LESION effect).

**Statistical Methods**

The treatment effects on MRI lesions, brain atrophy, and disability progression were extracted when reported or estimated using the available data, if possible. For trials with multiple arms, a contrast with the control arm was studied for each arm. For superiority trials with active control arms, the experimental arm was chosen a priori as the 1 for which superiority had to be assessed. Each contrast was given a weight decided a priori before data inspection and analysis, accounting for trial size and duration and for the nonindependence of contrasts within the same trial, according to previously described procedures.\(^5\)\(^2\)

To study the relationship between the treatment effect on disability progression and the treatment effect on brain atrophy and MRI lesions, a weighted regression analysis was run, using the weighting system described above, with DIS effect as the dependent variable and ATROPHY and LESION effects as the independent variables. Because the analysis based on log-transformed values gave very similar results, only the analysis on the untransformed ratios is reported. The coefficient of determination (\(R^2\)) was used to assess the goodness of fit for each model. Sensitivity analyses were conducted to test the stability of the fitted models; the stability of results was evaluated using an unweighted regression, a log-transform of the variables representing treatment effects, and quantification of the effect of treatment on disability progression as an absolute difference rather than a relative ratio. When proportions are small (which is the case for proportions of patients with a disability progression over a time frame of 2 years), a ratio can overestimate the effect of a treatment. Finally, a weighted multivariate model (meta-regression) was run to test whether ATROPHY and LESION effects were independent predictors of the treatment effect on disability progression. The coefficients generated by the meta-regression model were used to calculate a linear combination of ATROPHY and LESION effects to be correlated with DIS effect.

**Results**

**Trials Included in the Analysis**

The research on PubMed retrieved 415 articles. Reasons for exclusions were the following: trials studying
symptomatic and reparative therapies, disease phase other than RR, missing data on brain atrophy or on MRI lesions or on disability progression, open label extensions of previous randomized studies, volume change reported from treatment start only, technique to measure brain atrophy not specified or different than SIENA\textsuperscript{12} and BPF\textsuperscript{13,15} and permission denied to include data not yet published in peer-reviewed papers. A final set of 13 trials (8 placebo-controlled, 5 active-controlled with either interferon or glatiramer acetate) were included in the meta-analysis, for a total of 34 arms, 21 contrasts, and 13,500 patients. The trials utilized in the analysis are reported in Table 1.\textsuperscript{13–25} Six trials had 2 arms, 6 trials had 3 arms, and 1 trial had 4 arms. Follow-up duration was 24 months for all the included trials.

**Relationship between Treatment Effect on Brain Atrophy and Treatment Effect on Disability Progression**

The weights and the values entered in the regression models are reported in Table 1. The primary analysis, regressing the DIS effect on the ATROPHY effect using the complete set of data, revealed a significant association between the 2 effects; the adjusted $R^2$ value of the weighted regression line was 0.48 ($p = 0.001$), indicating that 48% of the variance in DIS effect between trials is explained by the variance in ATROPHY effect. This value of the coefficient of determination corresponds to a correlation coefficient of $r = 0.69$. The regression line is reported in the Figure 1A.

**Relationship between Treatment Effect on MRI Lesions and Treatment Effect on Disability Progression**

The analysis evaluating the relationship between the LESION effect and the DIS effect on the complete set of data revealed a highly significant association between the 2 effects; the adjusted $R^2$ value of the weighted regression line was 0.61 ($p < 0.001$; corresponding to a correlation coefficient $r = 0.78$). This observation suggests that the 60% of the variance in DIS effect between trials is explained by the variance in LESION effect. The regression line is reported in the Figure 1B.

**Relationship between a Combined Effect on MRI Lesions and Brain Atrophy and on Disability Progression**

Treatment effects on brain atrophy and treatment effects on MRI lesions, when evaluated using the same weighted regression analysis, were weakly correlated ($R^2 = 0.20$, $p = 0.04$). When the effect of treatments on MRI lesions and brain atrophy were both put in a multivariate weighted regression to predict the effect on disability progression, both variables were retained as independently related to the treatment effect on disability progression (brain atrophy, $p = 0.005$; MRI lesions, $p < 0.001$). The coefficient of determination was higher ($R^2 = 0.75$, $p < 0.001$) than that found by using the 2 predictors alone, with a global correlation coefficient of $r = 0.88$. This suggests that about 75% of the variance in treatment effects on disability progression observed across trials of different drugs can be explained by the combined effect of the treatments on MRI lesions and brain atrophy. The regression line is reported in the Figure 1C.

**Sensitivity Analysis**

To test the stability of the fitted model, a sensitivity analysis was performed; the slopes and the $R^2$ values of the fitted models are reported in Table 2. The regression was run eliminating a trial at a time (see Table 1), and the $R^2$ value was re-estimated for each instance. The values of $R^2$ for the relationship between brain atrophy and disability ranged from 0.28 ($p = 0.016$) when eliminating the REGARD trial\textsuperscript{16} to 0.61 ($p < 0.001$) when eliminating the BEYOND trial.\textsuperscript{17} The values of $R^2$ for the relationship between active MRI lesions and disability ranged from 0.42 ($p < 0.001$) when eliminating the BEYOND trial\textsuperscript{17} to 0.71 ($p < 0.001$) when eliminating the MS-CARE 1 trial.\textsuperscript{23} The combined model was more stable, with $R^2$ values ranging from 0.60 to 0.76. The $R^2$ value was stable using a regression on log-transformed variables, an unweighted regression, or absolute differences rather than relative ratios to quantify the treatment effect on disability. Finally, no significant difference of slope in the regression lines was found when grouping trials classified according to the different atrophy measurement method (ie, BPF vs SIENA).

**Discussion**

The present meta-analysis of randomized trials evaluating a broad range of DMDs showed that, in patients with RRMS, the size of the treatment effect on brain atrophy is closely correlated with the size of treatment effect on 2-year disability progression. In addition, similar to what was observed in a previous meta-analysis,\textsuperscript{6} the treatment effect on active MRI lesions also was closely correlated with the effect on disability progression. Data showed that the effects on brain atrophy explain 48% of the variance in treatment effect on disability, and the effects on active MRI lesions explain 60% of this variance, suggesting a potential role of both magnetic resonance measures in mediating part of treatment effects detected on clinical disability in MS.

Interestingly, in our study, when the 2 MRI measures were put into a multivariate meta-regression model,
<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
<th>N</th>
<th>Weight</th>
<th>MRI Outcome</th>
<th>Brain Volume Measure</th>
<th>DIS</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>MSCRG</td>
<td>Placebo</td>
<td>IFNβ-1a 6 μg</td>
<td>301</td>
<td>233</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.67</td>
<td>0.64</td>
</tr>
<tr>
<td>2006</td>
<td>AFFIRM</td>
<td>Placebo</td>
<td>Natalizumab 300 mg</td>
<td>942</td>
<td>1,532</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.17</td>
<td>0.46</td>
</tr>
<tr>
<td>2006</td>
<td>SENTINEL</td>
<td>Placebo</td>
<td>IFNβ-1a 50 + Natalizumab 300 mg</td>
<td>1,171</td>
<td>1,421</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.17</td>
<td>0.77</td>
</tr>
<tr>
<td>2008</td>
<td>REGARD</td>
<td>Placebo</td>
<td>IFNβ-1a 44</td>
<td>764</td>
<td>1,077</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.67</td>
<td>0.50</td>
</tr>
<tr>
<td>2009</td>
<td>SENTINEL</td>
<td>IFNb-1a 250</td>
<td>IFNβ-1a 90 + Natalizumab</td>
<td>1,347</td>
<td>1,585</td>
<td>New T2</td>
<td>SIENA</td>
<td>0.72</td>
<td>1.29</td>
</tr>
<tr>
<td>2009</td>
<td>BEYOND</td>
<td>IFNb-1a 500</td>
<td>IFNβ-1a 90 + Natalizumab</td>
<td>1,345</td>
<td>1,588</td>
<td>New T2</td>
<td>SIENA</td>
<td>0.72</td>
<td>0.90</td>
</tr>
<tr>
<td>2009</td>
<td>BEYOND</td>
<td>Placebo</td>
<td>Natalizumab 300 mg</td>
<td>1,171</td>
<td>1,421</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.56</td>
<td>0.82</td>
</tr>
<tr>
<td>2009</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>IFNβ-1a 44</td>
<td>845</td>
<td>902</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.67</td>
<td>0.77</td>
</tr>
<tr>
<td>2010</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>Natalizumab 300 mg</td>
<td>847</td>
<td>897</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.67</td>
<td>0.77</td>
</tr>
<tr>
<td>2010</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>Natalizumab 500 mg</td>
<td>893</td>
<td>979</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.67</td>
<td>0.77</td>
</tr>
<tr>
<td>2010</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>Natalizumab 14 mg</td>
<td>728</td>
<td>766</td>
<td>Active T2</td>
<td>BPF</td>
<td>0.67</td>
<td>0.77</td>
</tr>
<tr>
<td>2011</td>
<td>TEMSO</td>
<td>Placebo</td>
<td>Cladribine 3.5 mg</td>
<td>687</td>
<td>921</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.27</td>
<td>0.81</td>
</tr>
<tr>
<td>2011</td>
<td>TEMSO</td>
<td>Placebo</td>
<td>Cladribine 5.25 mg</td>
<td>928</td>
<td>976</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.23</td>
<td>0.81</td>
</tr>
<tr>
<td>2011</td>
<td>TEMSO</td>
<td>Placebo</td>
<td>Cladribine 7 mg</td>
<td>721</td>
<td>766</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.23</td>
<td>0.81</td>
</tr>
<tr>
<td>2011</td>
<td>TEMSO</td>
<td>Placebo</td>
<td>Cladribine 14 mg</td>
<td>684</td>
<td>921</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.23</td>
<td>0.81</td>
</tr>
<tr>
<td>2011</td>
<td>TEMSO</td>
<td>Placebo</td>
<td>Cladribine 21 mg</td>
<td>721</td>
<td>766</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.23</td>
<td>0.81</td>
</tr>
<tr>
<td>2012</td>
<td>CLARITY</td>
<td>Placebo</td>
<td>FTY 1.25 mg</td>
<td>870</td>
<td>921</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>CLARITY</td>
<td>Placebo</td>
<td>FTY 1.25 mg</td>
<td>870</td>
<td>921</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>CLARITY</td>
<td>Placebo</td>
<td>FTY 1.25 mg</td>
<td>870</td>
<td>921</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>TEMSO</td>
<td>Placebo</td>
<td>BG-12 240 mg 3× daily</td>
<td>818</td>
<td>876</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>CONFIRM</td>
<td>Placebo</td>
<td>BG-12 240 mg 3× daily</td>
<td>870</td>
<td>921</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>CONFIRM</td>
<td>Placebo</td>
<td>BG-12 240 mg 3× daily</td>
<td>870</td>
<td>921</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>MSCARE-I</td>
<td>Placebo</td>
<td>IFNβ-1a 44</td>
<td>713</td>
<td>821</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>MSCARE-I</td>
<td>IFNβ-1a 500</td>
<td>IFNβ-1a 90 + Natalizumab</td>
<td>708</td>
<td>763</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>MSCARE-I</td>
<td>IFNβ-1a 500</td>
<td>IFNβ-1a 90 + Natalizumab</td>
<td>708</td>
<td>763</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>MSCARE-I</td>
<td>IFNβ-1a 500</td>
<td>IFNβ-1a 90 + Natalizumab</td>
<td>708</td>
<td>763</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>FTY 1.25 mg</td>
<td>1,187</td>
<td>1,421</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>FTY 1.25 mg</td>
<td>1,187</td>
<td>1,421</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>FTY 1.25 mg</td>
<td>1,187</td>
<td>1,421</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>2012</td>
<td>FREEDOMS</td>
<td>Placebo</td>
<td>FTY 1.25 mg</td>
<td>1,187</td>
<td>1,421</td>
<td>Active T2</td>
<td>SIENA</td>
<td>0.26</td>
<td>0.55</td>
</tr>
</tbody>
</table>

BPF = brain parenchymal fraction; CUAL = combined unique active lesions; FTY = FTY720 (fingolimod); GA = glatiramer acetate; INF = interferon; SIENA = Structural Image Evaluation of Normalized Atrophy.
the effect of treatments on both active MRI lesions and brain atrophy provided a much better explanation of the observed treatment effects on disability progression than did the single MRI measures alone; 75% of the variance in the treatment effect on disability could be explained by the combined effect of treatment on the 2 MRI measures. Because the correlation between the treatment effects on the 2 MRI markers was weak \((R^2 = 0.20)\), the data strongly suggest that both MRI markers independently contribute to treatment effect on disability in RRMS patients. This suggests that in RRMS patients a treatment effect on brain atrophy, a putative marker of neuroprotection, adds to the treatment effect on inflammation-related outcome measures, such as active MRI lesions, in explaining the overall reduction of disability progression induced by that treatment.

MRI-derived measures of global brain atrophy lack pathological specificity, as they may be related to changes in myelin, axon, or glial content, as well as physiological fluctuations due to factors such as changes in water content. However, despite uncertainties regarding histopathological specificity, a substantial body of evidence supports the use of whole brain atrophy, at least after the initial 6 to 12 months following initiation of anti-inflammatory therapy, as a valid marker of tissue injury or loss and, as such, 1 of the most reliable imaging outcome measures of neuroprotection. Data reported here support this notion, suggesting a role for brain atrophy measures as potential mediators of the effect of treatments on irreversible clinical disability in MS.

Some caution is indicated when interpreting meta-analytic studies such as the present one. The observed correlations are at the “trial level.” This represents a form of “ecological” correlation, that is, a correlation between 2 variables that are group means, in contrast to a correlation between 2 variables that describe individuals. The detection of such group-level correlation does not allow the assessment of a causal relationship, but rather suggests that the treatment effects on the evaluated outcomes are concomitant effects. Analysis based on individual patients using the Prentice criteria, a set of 4 operational rules to validate surrogate endpoints, are needed to infer “causal” relationships and to clarify to what extent treatment effects on brain atrophy and MRI lesions mediate effects on disability progression. An additional important limitation is that in all the included studies the treatment effects on MRI markers and disability progression were observed over the same time period (2 years) after randomization. As a consequence, the present study does not provide direct evidence supporting the hypothesis that the early effects of a treatment on MRI markers can predict long-term effects on preventing or postponing the progression of disability. Conversely, the predictive effects of reduced brain atrophy on disability might well be more evident when evaluated over a longer period of time, as the confound of physiological fluctuations in...
brain volume have a limited dynamic range that may be on the order of the atrophy expected in MS over 1 year, but not over long intervals. Finally, as specified in Subjects and Methods, the analysis is limited to trials in the RR phase of the disease. The possibility of extending the analyses to trials in the progressive phase of MS is limited by the low number of trials that have collected the data needed for such assessment. In general, however, a similar analysis would be even more interesting in the progressive phases of MS, where the neurodegenerative aspect of the disease is paramount and a larger impact of brain atrophy as a mediator of clinical progression should be expected.

Notwithstanding the limitations discussed above, this study provides evidence that treatment effects on brain atrophy add to those on focal lesions to explain the slowing of disability progression observed after initiating treatment with DMDs. These observations are clinically relevant and have practical implications for MS clinical trial design, including the possibility of using reduced sample sizes (about 100 patients per arm for a treatment effect causing a 50% reduction of MRI lesions18 and atrophy,11 as compared to about 103 more for trials based on disability outcomes14,18).

Future studies are needed to support this preliminary report by including more data from new upcoming MS clinical trials that include brain atrophy as a main outcome measure, and that benefit from the improved brain atrophy measurement methodologies that are now available. In addition, individual patient-based analysis of clinical trial data would allow for a better understanding of the validity of brain atrophy as a surrogate marker for disability progression, alone or in combination with inflammatory markers.

**TABLE 2. Sensitivity Analysis: Coefficients of Determination ($R^2$) Values according to Different Subgroups of Trials and Different Methods of Analysis**

<table>
<thead>
<tr>
<th>Technique</th>
<th>$R^2$ Atrophy ($p$)</th>
<th>$R^2$ Lesions ($p$)</th>
<th>$R^2$ Atrophy + Lesions ($p$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIENA, 7 trials$^d$</td>
<td>0.51 (0.001)</td>
<td>0.66 (0.001)</td>
<td>0.76 (0.001)</td>
</tr>
<tr>
<td>BPF, 6 trials$^d$</td>
<td>0.37 (0.14)</td>
<td>0.50 (0.001)</td>
<td>0.69 (0.001)</td>
</tr>
</tbody>
</table>

BPF = brain parenchymal fraction; SIENA = Structural Image Evaluation of Normalized Atrophy.

$^a$The analysis was run excluding each trial at a time, to test the dependence of the regression equation on single trials.

$^b$A log transform was applied to the treatment effect estimates (relative risk).

$^c$The treatment effect estimate on disability progression was included as an absolute difference (proportion of patients with a disability progression in the experimental arm − proportion of patients with a disability progression in the control arm).

$^d$Test for difference in slopes (interaction): $p = 0.24$. 

---

brain volume have a limited dynamic range that may be on the order of the atrophy expected in MS over 1 year, but not over long intervals. Finally, as specified in Subjects and Methods, the analysis is limited to trials in the RR phase of the disease. The possibility of extending the analyses to trials in the progressive phase of MS is limited by the low number of trials that have collected the data needed for such assessment. In general, however, a similar analysis would be even more interesting in the progressive phases of MS, where the neurodegenerative aspect of the disease is paramount and a larger impact of brain atrophy as a mediator of clinical progression should be expected.

Notwithstanding the limitations discussed above, this study provides evidence that treatment effects on brain atrophy add to those on focal lesions to explain the slowing of disability progression observed after initiating treatment with DMDs. These observations are clinically relevant and have practical implications for MS clinical trial design, including the possibility of using reduced sample sizes (about 100 patients per arm for a treatment effect causing a 50% reduction of MRI lesions and atrophy, as compared to about 10^3 more for trials based on disability outcomes).

Future studies are needed to support this preliminary report by including more data from new upcoming MS clinical trials that include brain atrophy as a main outcome measure, and that benefit from the improved brain atrophy measurement methodologies that are now available. In addition, individual patient-based analysis of clinical trial data would allow for a better understanding of the validity of brain atrophy as a surrogate marker for disability progression, alone or in combination with inflammatory markers.
Potential Conflicts of Interest


References