European Study on Intravenous Immunoglobulin in Multiple Sclerosis

Results of Magnetization Transfer Magnetic Resonance Imaging Analysis

Massimo Filippi, MD; Maria A. Rocca, MD; Elisabetta Pagani, PhD; Giuseppe Iannucci, MD; Maria Pia Sormani, PhD; Franz Fazekas, MD; Stefan Ropele, PhD; Otto R. Hommes, MD; Giancarlo Comi, MD

Background: Magnetization transfer magnetic resonance imaging (MT MRI) can provide in vivo markers reflecting the severity of multiple sclerosis–related brain damage occurring within and outside T2-visible lesions.

Objective: To investigate the effect of intravenous immunoglobulin (IVIG) treatment on the accumulation of brain damage in patients with secondary progressive multiple sclerosis (SPMS), measured using MT MRI.

Design, Patients, and Intervention: Seventy patients with SPMS participating in the European, multicenter, randomized, double-blind, placebo-controlled trial of IVIG in SPMS underwent brain T2-weighted and MT MRI at baseline and after 12 and 24 months. The MT MRI scans were post-processed and analyzed to obtain MT ratio values from T2-visible lesions and MT ratio histograms from the normal-appearing brain tissue (NABT).

Results: At baseline, a significant difference was found for NABT MT ratio histogram peak height \((P = .003)\) between treated patients and patients receiving placebo. No significant differences between treated patients and those receiving placebo were found for any of the considered MT MRI–derived metrics in terms of treatment \(\times\) time interaction. Nevertheless, over the 24-month period, the placebo patients experienced a 6.75% reduction of the NABT MT ratio histogram peak height, whereas treated patients experienced only a 0.92% reduction of the NABT MT ratio histogram peak height.

Conclusions: This study did not show any statistically significant effect of IVIG on MT MRI quantities. Nevertheless, the markedly different percentage change of the NABT MT ratio histogram peak height over time between patients receiving placebo and treated patients suggests a possible role of IVIG treatment in preventing the loss of “truly” normal brain tissue in SPMS patients.

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Several placebo-controlled clinical trials have shown a favorable effect of treatment with intravenous immunoglobulin (IVIG) in reducing the relapse frequency in patients with relapsing-remitting multiple sclerosis (MS).4 In some of these trials,2,4 IVIG treatment resulted in a significant suppression of blood-brain barrier abnormalities as measured with magnetic resonance imaging (MRI). On the contrary, the beneficial effect of IVIG on relapse rate and MRI-measured disease activity was not detected in the patients with secondary progressive (SP) MS enrolled in the European Study on IVIG treatment in MS (ESIMS), which was a multicentered, randomized, double-blind, placebo-controlled trial.4,6 Despite this, IVIG treatment was shown to reduce the accumulation of brain atrophy in these patients.7

There is increasing evidence that, especially in patients with SPMS, inflammation and neurodegeneration might be, at least partially, dissociated.8 There is also evidence that IVIG might enhance remyelination,9 and that blood-brain barrier disruption is not a necessary prerequisite for IVIG effectiveness.10 Magnetization transfer (MT) MRI provides quantitative metrics with some specificity to MS demyelination/remyelination11,12 and, as a consequence, has the potential to be a valuable adjunctive tool to monitor IVIG-treatment efficacy in SPMS.13,14 In this study, we investigated whether IVIG treatment is effective in reducing the accumulation of MT MRI–measured damage of T2-visible lesions and normal-appearing brain tissue (NABT) in a subcohort of patients with SPMS who participated in the ESIMS trial.
Table 1. Main Clinical, Conventional, and MT MRI Characteristics at Baseline of Placebo and Treated Patients Who Participated in the MT MRI Substudy of the ESIMS Trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo Group (n=36)</th>
<th>Treated Group (n=41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.9 (6.3)</td>
<td>42.3 (6.1)</td>
<td>.26</td>
</tr>
<tr>
<td>Disease duration, mo</td>
<td>13.8 (6.4)</td>
<td>14.2 (5.8)</td>
<td>.37</td>
</tr>
<tr>
<td>EDSS, median (range)</td>
<td>5.5 (3.0-6.5)</td>
<td>5.5 (3.0-6.5)</td>
<td>.37</td>
</tr>
<tr>
<td>Dual-echo lesion load, mL</td>
<td>20.2 (17.0)</td>
<td>17.8 (11.5)</td>
<td>.89</td>
</tr>
<tr>
<td>T1-hypointense lesion load, mL</td>
<td>3.54 (5.21)</td>
<td>3.03 (3.23)</td>
<td>.29</td>
</tr>
<tr>
<td>Enhancing-lesions lesion load, mL</td>
<td>0.22 (0.4)</td>
<td>0.25 (0.77)</td>
<td>.78</td>
</tr>
<tr>
<td>Average lesion MTR, %</td>
<td>35.4 (2.0)</td>
<td>34.2 (2.6)</td>
<td>.06</td>
</tr>
<tr>
<td>Average NABT MTR, %</td>
<td>36.1 (1.5)</td>
<td>35.5 (1.6)</td>
<td>.08</td>
</tr>
<tr>
<td>NABT MTR histogram peak height, %</td>
<td>81.0 (10.5)</td>
<td>73.7 (9.6)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, expanded disability status scale score; ESIMS, European Study on intravenous immunoglobulins treatment in multiple sclerosis; MRI, magnetic resonance imaging; MT, magnetization transfer; MTR, magnetization transfer ratio; NABT, normal-appearing brain tissue. *All data are presented as mean (SD) unless otherwise indicated.

METHODS

The full study, planned to have a 24-month duration, included 318 patients with SPMS. The trial design has been described elsewhere and comprised yearly T2- and T1-weighted brain MRI scans. Ninety-two SPMS patients from 10 participating centers entered the present study. Seventy-seven patients (36 in the placebo and 41 in the IVIG arm) were scanned with MT MRI at baseline. Seventy patients (34 in the placebo and 36 in the IVIG arm) had a complete MT MRI follow up (ie, 3 scans), whereas 9 had only 1 MT MRI scan, and 83 had 2 MT MRI scans. Data loss was the result of patient exit from the trial, missing MRI data, and rejection of poor-quality MRI scans.

Scanners at the 10 centers were all Siemens Magnetom Vision (Siemens Medical Solutions, Munich, Germany) operating at 1.5 T. The MRI protocol consisted of dual-echo (TR/TE = 2000-2500/60-120 milliseconds) and 2-dimensional (2D) gradient echo images (TR/TE = 600/12 milliseconds; $\alpha = 20^\circ$) with and without an MT saturation pulse (offset frequency = 1.5 kHz, gaussian envelope duration = 7.68 milliseconds, flip angle = 300$^\circ$). Twenty-eight (20 for gradient echo) contiguous, interleaved axial slices were acquired, with 5-mm thickness, 256×256 matrix, and 250×250-mm field of view, giving an in-plane spatial resolution of about 1×1 mm. The gradient echo slices had the same offset and orientation as the 20 central slices of the dual echo set.

After coregistration of the 2 gradient echo scans using a surface-matching technique based on mutual information, MT ratio images were derived pixel by pixel, as previously described. Extracerebral tissue was removed from MT ratio maps using a local thresholding segmentation technique and the resulting images were coregistered with the T2-weighted images. The final step consisted of automatic transfering of lesion outlines onto the MTR maps and calculation of average lesion MT ratio. Using the same coregistration technique, the resulting MT ratio maps from months 12 and 24 were registered with the baseline, to compensate for repositioning errors. To study the MT ratio of NABT, pixels lying inside lesion outlines were nulled out, and MT ratio histograms of the remaining NABT were produced as previously described. For each histogram, the relative peak height (the proportion of pixels at the most common MT ratio) and the average MT ratio were derived. Given the strong correlation between average histogram measures and the histogram peak location, the latter quantity was not considered for this study, to reduce the risk of type I errors.

Differences in conventional MRI metrics at baseline between patients who entered this MT MRI study and those who did not, as well as those between patients receiving placebo and treated patients in the MT MRI subcohort, were tested using a t test for unpaired data. Treatment effect on MT MRI-derived metrics was assessed using an analysis of variance model for repeated measures (using only patients with complete information) and a random effect model (using all available information). Both these analyses were corrected for center effect. Since the results obtained using these 2 analyses were similar, only the results derived from the patients with the complete MT MRI data set are presented. A significance of a treatment × time interaction term would indicate that the treatment is able to modify the MT MRI parameter variations over time, taking into account the differences between centers. All the correlations were evaluated using the Spearman rank correlation coefficient.

RESULTS

At baseline, the cohort of patients who entered this MT MRI study did not differ from the whole study population in terms of number of enhancing lesions and in terms of brain parenchymal fraction (data not shown), but they had a lower mean T2-lesion volume (19.6 mL vs 27.7 mL, $P = .003$). At baseline, average NABT MT ratio and average lesion MT ratio, as well as all the main clinical characteristics and metrics derived from conventional MRI, did not differ between treated patients and placebo patients. On the contrary, a significant difference was found for NABT MT ratio histogram peak ($P = .003$, Table 1).

No significant differences between treated patients and patients receiving placebo were found for any of the considered MT MRI–derived metrics in terms of treatment × time interaction. Nevertheless, during the 24-month period, the placebo group experienced a 6.75% reduction of the NABT MT ratio histogram peak height, whereas the treated group experienced a reduction of only 0.92% of the NABT MT ratio histogram peak height (this difference was mainly accumulated during the second year of the study and did not reach statistical significance) (Table 2). The estimated treatment effect size (average over time adjusted for center), expressed as a percentage difference between baseline and 24-month values, was 0.05% (95% confidence interval [CI], −1.95% to 0.81%) for average lesion MT ratio; 0.37% (95% CI, −0.68% to 1.42%) for average NABT MT ratio; and 2.78% (95% CI, −1.57% to 7.11%) for NABT MT ratio histogram peak.

In the entire MT patient group and over the entire study period, expanded disability status scale score (EDSS) changes were significantly correlated with average lesion MT ratio ($r = −0.30, P = .01$) and average NABT MT ratio ($r = −0.37, P = .002$). Changes of T2-lesion volumes and MT MRI metrics were not correlated ($r$ values were −0.01 for average lesion MT ratio, −0.04 for average NABT MT ratio, and −0.08 for NABT MT ratio histogram peak height).

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The ESIMS trial, the first large-scale study of IVIG treatment in patients with SPMS, failed to show any effect of IVIG treatment on the primary outcome measures (time to confirmed EDSS progression) and the secondary outcome measures (annual relapse rate, gadolinium-enhancing lesions, and T2-lesion volumes).\footnote{6,7} Given that patients enrolled in this trial were in an advanced phase of the disease, where “fixed” neurological deficits are likely to be present, our results agree with those of a previous trial\footnote{15} in inflammatory demyelinating optic neuritis, where IVIG administration was shown not to reverse persistent visual loss. Despite these disappointing results, a significant effect of IVIG on the rate of brain atrophy development was shown in the ESIMS trial.\footnote{6,7} This is important in light of several recent findings showing that inflammation and neurodegeneration are partially dissociated in MS,\footnote{16-18} and that there is evidence of substantial irreversible tissue damage occurring in the absence of, or with only modest clinical and MRI signs of, ongoing inflammation, especially in SPMS patients.\footnote{16-18} As a consequence, the main MRI analysis of the ESIMS trial suggests a potential treatment effect of IVIG on irreversible tissue damage of patients with SPMS (ie, on brain volume loss), which might occur independently of inflammatory demyelination. Against this background, we postulate that one of the most plausible mechanisms that might explain the effect of IVIG on brain atrophy development of these patients is the ability of this treatment to enhance remyelination.\footnote{1,4,9} To test this hypothesis we analyzed MT ratio changes in T2-visible lesions and in the NABT of a relatively large and representative subgroup of patients (about one fourth of those who contributed to the main analyses of this trial), from whom annual MT MRI scans were obtained.

Previous studies have shown that MT MRI is sensitive to MS changes over time, particularly in patients with SPMS, where other, more conventional MRI markers of disease activity are rather insensitive,\footnote{19,20} is reproducible,\footnote{21-23} is relatively cost-effective (high-quality MT ratio data can be obtained with scanning time of <10 minutes); and provides metrics that are correlated with changes of disability over time,\footnote{24} as shown by the present study. Most importantly, MT ratio provides accurate in vivo estimates of the amount of myelin present in lesions and NABT of patients with MS.\footnote{11} Despite all of this, perhaps because of the challenge of standardizing MT MRI across multiple centers and over time, MT ratio-derived metrics have been used as adjunctive outcome measures in only 1 other parallel-group, placebo-controlled, multicenter study, where MT MRI was obtained annually over a 3-year period in 47 patients with SPMS enrolled in the European trial of interferon (IFN) \(\beta\)-1b.\footnote{11} Interestingly, this study showed a dramatic effect of IFN \(\beta\)-1b of MRI-measured disease activity,\footnote{25} and showed no effect of the treatment in reducing the accumulation of irreversible brain damage, measured using either brain atrophy\footnote{26} or MT ratio.\footnote{13}

Although no statistically significant difference between the placebo group and the treated group was found in the present study for any of the investigated MT MRI quantities, an encouraging observation was that the percentage change of the NABT MT ratio histogram peak height over time was markedly reduced in the treated group. It is likely that statistical significance was not reached because of the relatively small number of patients included in this substudy, which was not powered for such an additional analysis. Since MT ratio histogram peak height is considered to be a measure of “truly” normal tissue present in the brains of MS patients,\footnote{22} this might suggest an efficacy of the experimental treatment in reducing the damage to the brain tissue, which is known to occur at a relatively rapid pace in patients with SPMS.\footnote{13,19} This effect might be exerted through the ability of IVIG in enhancing remyelination,\footnote{1,4,9} which might limit axonal loss and prevent the development of brain atrophy. However, an alternative explanation for the marked difference between patients receiving placebo and treated patients in terms of NABT MT ratio changes over time is also possible. At baseline, treated patients had a significantly lower NABT MT ratio histogram peak height than those receiving the placebo and, as a consequence, it could be argued that the probability to worsen was a priori lower in the former group. No treatment effect was observed on average lesion MTR, thus suggesting that IVIG ability to favor remyelination might be graded according to the severity and extent of demyelination.

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**Correspondence:** Massimo Filippi, MD, Neuroimaging Research Unit Department of Neuroscience, Scientific Institute and University Ospedale San Raffaele, Via Olgettina, 60, 20132 Milan, Italy (m.filippi@hsr.it).

**Author Contributions:** Study concept and design: Filippi, Fazekas, Ropele, and Hommes. Acquisition of data: Filippi, Fazekas, Ropele, and Hommes. Analysis and interpretation of data: Filippi, Assunta, Pagani, Iannucci, Sormani, Fazkas, Ropele, and Comi. Drafting of the manuscript: Filippi. Critical revision of the manuscript for important intellectual content: Filippi, Assunta, Pagani, Iannucci, Sormani, Fazekas, Ropele, Hommes, and Comi.

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**Table 2. Percentage Changes of MT MRI–Derived Quantities in Placebo and Treated Patients Who Participated in the MT MRI Substudy of the ESIMS Trial**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n = 34)</th>
<th>Treated Group (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Changes from baseline to month 24</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average lesion MTR</td>
<td>1.98 (5.2)</td>
<td>0.84 (6.7)</td>
</tr>
<tr>
<td>Average NABT MTR</td>
<td>0.16 (5.7)</td>
<td>0.26 (5.3)</td>
</tr>
<tr>
<td>NABT MTR histogram peak height</td>
<td>-8.75 (11.7)</td>
<td>-9.2 (11.7)</td>
</tr>
<tr>
<td><strong>Changes from baseline to month 12</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average lesion MTR</td>
<td>0.35 (4.3)</td>
<td>-0.52 (4.3)</td>
</tr>
<tr>
<td>Average NABT MTR</td>
<td>-0.48 (3.6)</td>
<td>0.46 (5.6)</td>
</tr>
<tr>
<td>NABT MTR histogram peak height</td>
<td>-2.08 (10.1)</td>
<td>-1.65 (9.6)</td>
</tr>
<tr>
<td><strong>Changes from month 12 to month 24</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average lesion MTR</td>
<td>1.66 (3.9)</td>
<td>1.44 (6.2)</td>
</tr>
<tr>
<td>Average NABT MTR</td>
<td>0.69 (3.4)</td>
<td>0.02 (6.6)</td>
</tr>
<tr>
<td>NABT MTR histogram peak height</td>
<td>-4.48 (10.8)</td>
<td>1.27 (12.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ESIMS, European Study on intravenous immunoglobulin treatment in multiple sclerosis; MRI, magnetic resonance imaging; MT, magnetization transfer; MTR, magnetization transfer ratio; NABT, normal-appearing brain tissue.

*Data are presented as mean (SD) percentages.

REFERENCES