Effect of Fingolimod on Brain Atrophy: MRI Data From Phase 3 Studies

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CONCLUSIONS
• Brain atrophy (as measured by PBVC) was reduced in fingolimod-treated patients compared with controls, regardless of baseline factors. The treatment effect was evident in patients with and without Gd-enhancing lesions at baseline.
• Baseline T2 lesion volume and presence of Gd-enhancing lesions significantly predicted PBVC over the course of the studies.
• On-study brain volume loss correlated with new T2 lesion formation and worsening disability.

Fingolimod is the only approved MS treatment that provided a consistent and significant treatment effect on PBVC across all three phase 3 studies compared with placebo or IFN-β1a.

INTRODUCTION
• Brain atrophy occurs as a measure of brain atrophy and assesses neurodegeneration and provides a means to evaluate neurodegeneration in clinical trials.
• In patients with MS, brain atrophy occurs at ~5–10 times the rate of that observed in healthy individuals (baseline–month 24).
• Brain atrophy corroborates with physical disability and cognitive dysfunction in people with MS, and is observed before the development of new T2 lesions.
• Brain atrophy may be a stronger predictor of disability than MRI-based lesions.
• In recent years, several studies have demonstrated associations between therapy and brain atrophy in patients with MS. The association between treatment and brain atrophy may be mediated by changes in lesion volume.

OBJECTIVE
• To evaluate the effect of fingolimod on brain atrophy in patients with relapsing-remitting MS in three randomized, placebo-controlled studies.

METHODS
• Study design: FREEDOMS and FREEDOMS II were double-blind, randomized, multicenter, placebo-controlled, in brain volume.
• Methods: PBVC was estimated using Statistical Parametric Mapping (SPM8) software and the Neuroimage (Vienna, Austria) SIENAX software.
• Baseline brain volume was estimated using a cross-sectional method (SEM).
• MRI scans were obtained at baseline and 12 months (FREEDOMS and FREEDOMS II) or at baseline and 12 months (TRANSFORMS).
• Analyses were conducted using multiple regression models with treatment as a factor and T2 volume and number of Gd-enhancing lesions at baseline as predictor variables.

RESULTS
• Significant Brain Atrophy Correlation With Disease Characteristics
• The study population included 543 participants in FREEDOMS I, 532 in FREEDOMS II, and 559 in TRANSFORMS.
• Brain atrophy correlated with age, MS duration, disability, and MRI lesion burden (Table 2).

DISCUSSIONS
• Baseline T2 lesion volume and number of Gd-enhancing lesions were significant independent predictors of PBVC across treatment groups.

TABLE 2. Correlation of Baseline Brain Tissue Volume With Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PBVC</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>-0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MS duration (y)</td>
<td>-0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDSS</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gd-enhancing lesion</td>
<td>-0.04</td>
<td>&lt;0.01</td>
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<tr>
<td>T2 lesion number</td>
<td>-0.03</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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