Brain volume change by quartile and disability progression in multiple sclerosis: a 4-year analysis of the phase 3 FREEDOMS trial and its extension

INTRODUCTION

- Accelerated brain volume loss (BVL) occurs throughout the course of multiple sclerosis (MS) and is evident from the earliest stages.
- The estimated mean rate of BVL in patients with relapsing-remitting MS (RRMS) is in the range of 0.5–1.5% per year, which is considerably higher than the age-related rate of BVL in the general population (0.1–0.3% per year).
- Both local and diffuse damage in grey and white matter contribute to MS progression, and BVL is increasingly recognized as a measure that captures these pathologies.
- In MS, BVL correlates with and predicts future disability, in terms of both physical and cognitive decline.
- In the 2-year phase 3 FREEDOMS trial, fingolimod reduced BVL in patients with RRMS by approximately one-third compared with placebo.
- Patients who were randomized to placebo during FREEDOMS and subsequently switched to fingolimod at month 24 had the greatest risk of reaching EDSS scores ≥4.0 and ≥6.0.

METHODS

- **INTRODUCTION**
  - In FREEDOMS and its extension, the quartile of patients with the most brain volume loss at month 24 had the highest on-study risk of reaching milestone EDSS scores and the highest on-study rates of confirmed disability progression.
  - Patients were categorized by quartile at month 24, based on PBVC from baseline.

- **OBJECTIVES**
  - To investigate whether BVL at month 24 is associated with and is predictive of brain volume change in the long-term evolution of MS and the need to reduce brain volume loss as early as possible in the disease course.

- **METHODS**
  - **Study design and participants**
    - In FREEDOMS, patients with RRMS randomized to receive fingolimod 0.5 mg, fingolimod 1.25 mg or placebo for 24 months. Patients completing FREEDOMS and its extension were eligible to enter the extension on the same dose of fingolimod, and those taking placebo were randomized to receive fingolimod 0.5 mg or 1.25 mg. All patients receiving fingolimod 1.25 mg were subsequently switched to fingolimod 0.5 mg.
    - This analysis included all patients who were randomized and received at least one dose of study medication during both FREEDOMS and its extension.
  - **Analyses**
    - Percentage brain volume change (PBVC) from baseline to month 24 was estimated using 'structural image evaluation, using normalization of atrophy' (SIENA).
    - Patients were categorized by quartile at month 24, based on PBVC from baseline, and quartile 4 (Q4) was used as the reference category in subsequent analyses.
    - The annualized rate of BVL was determined by transforming PBVC using the formula:
      \[(PBVC/100 + 1)(365.25/days) – 1\] × 100, where days is the number of days between magnetic resonance imaging assessments at baseline and at month 24.
      (Figure 1)

RESULTS

- **Study population**
  - In total, 1,029 patients were included in the analysis; baseline characteristics by PBVC quartile are shown in Table 1.
  - At baseline, patients in Q1 had more relapses in the previous 2 years, greater levels of disability (higher mean EDSS score and lower mean MSFC z-score), more relapses in the previous 2 years, and more brain tissue damage (greater T1 hypointense lesion volume and T2 lesion volume).
  - ORs and p values were derived from a logistic regression of CDP on PBVC as covariate.

- **BVL and disability progression**
  - Patients with the most BVL at 24 months had the greatest risk of reaching EDSS score ≥4.0 and ≥6.0 during the study.
  - Higher rates of BVL at 24 months were associated with greater increases in EDSS scores and decreases in MSFC score during the study than were lower rates of BVL.

CONCLUSIONS

- In FREEDOMS and its extension, the quartile of patients with the most brain volume loss at month 24 had the highest on-study risk of reaching milestone EDSS scores and the highest on-study rates of confirmed disability progression.
- MS disability progression at baseline in FREEDOMS was predictive of brain volume stability up to month 24.
- These findings support the clinical relevance of brain volume changes in the long-term evolution of MS and the need to reduce brain volume loss as early as possible in the disease course.

Table 1. Baseline characteristics by PBVC quartile and association with brain volume stability

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Q1 (n=256)</th>
<th>Q2 (n=254)</th>
<th>Q3 (n=257)</th>
<th>Q4 (n=262)</th>
<th>OR for prediction of brain volume stability</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.1 (8.0)</td>
<td>37.1 (8.6)</td>
<td>36.6 (8.0)</td>
<td>36.6 (8.6)</td>
<td>0.99</td>
<td>0.171</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>191 (74.6)</td>
<td>186 (73.2)</td>
<td>176 (69.3)</td>
<td>180 (68.7)</td>
<td>1.34</td>
<td>0.137</td>
</tr>
<tr>
<td>Time from first symptom, years</td>
<td>7.6 (4.1)</td>
<td>8.3 (4.4)</td>
<td>8.1 (4.3)</td>
<td>7.7 (4.0)</td>
<td>0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of relapses in the previous 2 years</td>
<td>2.3 (1.1)</td>
<td>2.2 (1.0)</td>
<td>2.1 (1.0)</td>
<td>2.0 (1.1)</td>
<td>0.82</td>
<td>0.011</td>
</tr>
<tr>
<td>EDSS score</td>
<td>3.7 (1.1)</td>
<td>3.9 (1.0)</td>
<td>3.8 (1.2)</td>
<td>3.8 (1.2)</td>
<td>0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSFC score</td>
<td>0.02 (0.07)</td>
<td>0.00 (0.05)</td>
<td>0.13 (0.35)</td>
<td>0.16 (0.57)</td>
<td>2.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gd+ lesion count</td>
<td>3.1 (5.6)</td>
<td>3.3 (6.1)</td>
<td>3.3 (6.1)</td>
<td>3.3 (6.1)</td>
<td>0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1 hypointense lesion volume, mm³</td>
<td>11 266 (10 215)</td>
<td>5988 (6697)</td>
<td>4424 (5363)</td>
<td>3316 (4371)</td>
<td>0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T2 lesion volume, mm³</td>
<td>1484 (87.1)</td>
<td>1532 (87.0)</td>
<td>1527 (87.5)</td>
<td>1536 (87.1)</td>
<td>1.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normalized brain volume, %</td>
<td>3.1%</td>
<td>3.1%</td>
<td>3.1%</td>
<td>3.1%</td>
<td>0.68</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The annualized rate of brain volume change was estimated using SIENA, and the results are shown in Figure 2.

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References