Categorical change in T2 lesion volume and clinical outcomes in the phase 3 FREEDOMS and extension study, evaluating fingolimod in patients with relapsing–remitting multiple sclerosis

INTRODUCTION

• Baseline change in multiple sclerosis (MS) is generally assessed using magnetic resonance imaging (MRI) measurements of T2 lesion volume (T2LV).
  - In T2LV, approximately 15–25% of patients at baseline showed an increase in the number of lesions.
  - Cross-sectional and longitudinal studies suggest an association between the burden of focal lesions, as assessed by baseline T2LV, and estimates of disability progression.
• Once-daily fingolimod 0.5 mg (FTY720; Gilenya®, Novartis Pharma AG) is a sphingosine 1-phosphate receptor (S1P) modulator approved for the treatment of relapsing MS (RRMS).
• Approximately 14,000 patients have been treated with fingolimod in both the clinical trial and post-market settings; total patient exposure now exceeds 195,000 patient-years.
• Compared with placebo in 24-month studies, patients treated with FINGOLIMOD and FREEDOMS trials, fingolimod treatment had beneficial effects on disability endpoints, including 3- and 6-month confirmed disability progression (CDP). Expanded Disability Status Scale (EDSS) scores and MS Functional Composite (MSFC) z-scores.

CONCLUSIONS

• In the FREEDOMS trial in patients with RRMS, change in T2 lesion volume at 2 years was related to disability at both 2 years and 4 years.
• Compared with patients with stable or decreased T2 lesion volume, patients with increased T2 lesion volume appeared to be at risk of long-term disease progression, based on worsening disability scores and increased rates of confirmed disability progression.
• Fewer patients receiving fingolimod than placebo had 2-year disability increases, demonstrating the ability of fingolimod to slow the accumulation of focal MRI disease, which in turn may be associated with a reduction in long-term disease progression.

OBJECTIVE

To investigate disability outcomes at months 24 and 48 in the FREEDOMS study and its extension in relation to categorical changes in T2LV from baseline to month 24.

METHODS

• FREEDOMS was a 24-month, double-blind, randomized, multicenter, placebo-controlled, parallel group study comparing the effect of fingolimod 0.5 mg and 1.25 mg doses with that of placebo. In the study extension, patients continued on the fingolimod or placebo treatment that they had been randomly assigned to at baseline. The final responsibility for the content lies with the authors.

RESULTS

• Change in T2LV at month 24 was available for 1057 of the 1172 patients randomized in FREEDOMS (the FAS), which included 372 of the 425 patients randomized to fingolimod 0.5 mg and 342 of the 418 patients randomized to placebo.

• A summary of baseline characteristics by T2LV category is presented in Table 1 — Baseline characteristics were mostly similar across the treatment groups and T2LV categories.

• Compared with patients in other T2LV categories, those whose T2LV had decreased at month 24 had generally had MS for a longer period, and those whose T2LV had increased at month 24 had enrolled with greater levels of disability (higher EDSS scores).

• At month 24, 62.2% of patients in the fingolimod 0.5 mg group showed stable or decreased T2LV (67.5% and 17.7%, respectively) compared with 56.1% of patients in the placebo group (table 1: data collected from 24-month analysis groups).

• A similar trend was evident when considering 3- and 6-month CDP in the FAS. Proportionally more patients experienced disability progression in the increased T2LV category than in the other categories, and this association was seen both at month 24 and at month 48.

• The changes from baseline to month 48 in mean MSFC z-scores (Figure 3) also suggested an ongoing association between disability progression and changes in T2LV observed at month 24.

• Among patients treated with fingolimod 0.5 mg, the slight improvements in mean MSFC and mean MSFC scores in the increased and stable T2LV groups suggest that presenting increase in T2LV presents accrual of disability.

• Mean changes in EDSS scores from baseline to month 24 are presented in Figure 2. In all analysis groups, worsening disability (increasing EDSS score) was greatest among the group of patients with increased T2LV, the greatest increase in mean EDSS score being in the placebo group.

• Finally, all analysis groups, worsening disability based on decreases in MSFC z-scores was generally greater among those patients with increased T2LV (Figure 2).

• A similar trend was evident when considering 3- and 6-month CDP in the FAS. Proportionally more patients experienced disability progression in the increased T2LV category than in the other categories, and this association was seen both at month 24 and at month 48.

• Table 1: Baseline characteristics analyzed in FAS. Data analysis compared the fingolimod 0.5 mg and 1.25 mg dose groups with the placebo group.

• Number of patients with MRI data available./Number of patients with change in T2LV data available; % total number of patients.

• Abbreviations: FAS, full analysis set; MSFC, Multiple Sclerosis Functional Composite; T2LV, T2 lesion volume.

DISCLOSURES

• This study was funded by Novartis Pharmaceuticals Corporation | Poster presented at the 2015 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) | May 27–30, 2015 | Indianapolis, Indiana, USA.