Four-year Expanded Disability Status Scale outcomes in patients treated with fingolimod in the phase 3 and extension trial program

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CONCLUSIONS

- In the combined phase 3 and extension trials of patients with MS treated with fingolimod for up to 4 years, the vast majority remained ambulatory without the need for walking assistance.
- Approximately two-thirds of patients remaining on fingolimod treatment had better EDSS scores after 2, 3, and 4 years of treatment within this group 16-18% had improved scores.
- Younger patients and those with more recent onset disease were more likely to demonstrate EDSS improvement or stability while treated with fingolimod.
- Patients with EDSS scores 3 or higher at the start of fingolimod treatment had better odds of improving or remaining stable, perhaps reflecting better treatment response or more reliable EDSS score determination in this range compared to EDSS scores between 0 and 1.5.
- Absence of a control group and selective drop-outs may bias these results.
- Additional analysis of factors associated with long-term EDSS status could help clinicians better understand and optimize long-term treatment with fingolimod.

INTRODUCTION

- Multiple sclerosis (MS) is a chronic neurological disease characterized by considerable variability in disability progression. Expanded Disability Status Scale (EDSS) score is the standard measure of disability in MS. There are considerable variations in disability progression among patients and among systems and allows neurologists to assign scores. EDSS scores 1.0–5.5 refer to patients who are fully ambulatory, and EDSS scores 5.5–6.5 define impairment to ambulation. Assessment of long-term disability is important for characterizing the benefit-risk profile of disease-modifying MS therapies.
- Once-daily oral fingolimod 0.5 mg (FTY720; Galapagos, New York, NY, USA) is approved for the treatment of relapsing MS.
- Fingolimod 0.5 mg demonstrated efficacy on measures of MS disease activity including disability progression, relapses, MRI activity and brain volume loss in the FREEDOMS and TRANSFORMS extension studies.2-4
- Here we explore longitudinal EDSS outcomes in the pooled cohort of patients treated with fingolimod in the phase 3 and extension trials.

OBJECTIVE

- To evaluate EDSS score over time in fingolimod-treated patients in the phase 3 FREEDOMS and FREEDOMS II trials and their extensions.

METHODS

- The analysis cohort consisted of patients initiating treatment with fingolimod in the 24-month FREEDOMS and FREEDOMS II studies, 12-month TRANSFORMS study or their respective extension studies.
- EDSS data for the extension after the first dose of fingolimod were pooled for the analysis.
- Kaplan-Meier estimates of proportions reaching EDSS scores 4 or 6 were calculated from start of fingolimod treatment for the 0.5 mg and combined 0.5 mg and 1.25 mg cohorts.
- Proportions with EDSS scores 2–2.5 or 3–3.5 were calculated from start of fingolimod treatment.
- Logistic regression analyses were conducted in the larger combined-dose group to explore factors associated with stable EDSS score or improved EDSS score after 48 months as dependent variables. Fixed independent variables in the models included age, and EDSS scores at the start of fingolimod treatment (categorized as 0–1.5, 1.5–2.5, 2.5–3.5, 3–4.5, 4–5.5 and ≥5.5).
- The following single variables were then evaluated, each in a separate logistic regression model that also included the fixed variables: disease duration prior to study entry, number of relapses in the 2 years prior to study entry, prior disease-modifying treatment before start of study, T2 lesion volume at start of fingolimod treatment, number of gadolinium-enhancing T1 lesions at start of fingolimod treatment, and normalized brain volume at start of study.

RESULTS

- The pooled fingolimod 0.5 mg/fingolimod dose (n=104/228) cohorts had mean and median (25%, 75% percentiles) treatment exposures of 905/982 and 967/956 (95% CI 894/992, 924/1252) days. Numbers of patients by time point are shown in Table 1.
- Kaplan-Meier estimates of the proportions of patients reaching EDSS scores 2.5 or ≥7 indicate 90% of fingolimod-treated patients remained ambulatory without assistance after 2 years (Figure 2).
- Figure 3 shows the proportions of fingolimod-treated patients with stable or improved EDSS scores after the start of fingolimod treatment.
- Baseline (at the start of the fingolimod treatment) factors associated with stable EDSS score at 48 months
- Fingolimod-treated patients with higher age (OR: 1.09, p<0.0001), longer disease duration (OR: 1.21, p<0.0001) at baseline were less likely to have a stable EDSS score after 4 years (Figure 4). An overall analysis was significant (p<0.0001) with Fingolimod patients exhibiting a greater trend toward stability; however, differences between individual studies were not significant.
- Baseline (at the start of the fingolimod treatment) factors associated with improved EDSS score at 48 months
- Patients with EDSS scores ≥2 at the start of fingolimod treatment had higher odds of improving compared to the reference group with EDSS score 1.5–2.5 (OR: 1.8, p<0.0001). EDSS scores 3–3.5 (OR: 5.5, p<0.0001), EDSS scores ≥4 (OR: 4.0, p<0.0001) (Figure 4).

Figure 3. Proportions of fingolimod-treated patients with stable or improved EDSS scores from the start of fingolimod treatment to months 24, 36 and 48

Table 1. Duration of exposure to fingolimod by dose

<table>
<thead>
<tr>
<th>Exposure (days)</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
<th>Range (n=316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–120 (n=208)</td>
<td>920 (465.5)</td>
<td>967 (1,782)</td>
<td>118–21,247</td>
</tr>
<tr>
<td>121–240 (n=54)</td>
<td>882 (480.1)</td>
<td>918 (1,782)</td>
<td>64–22,070</td>
</tr>
<tr>
<td>241–360 (n=54)</td>
<td>1036 (87.4)</td>
<td>1087 (662)</td>
<td>82–26,629</td>
</tr>
<tr>
<td>361–480 (n=108)</td>
<td>724 (44.1)</td>
<td>1350 (41.1)</td>
<td>60–36,281</td>
</tr>
<tr>
<td>481–600 (n=118)</td>
<td>193 (18.8)</td>
<td>360 (11.1)</td>
<td>60–36,281</td>
</tr>
</tbody>
</table>

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REFERENCES


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