Depression, Fatigue, and Clinical Improvements After Switch to Fingolimod

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CONCLUSIONS

- In patients with relapsing MS who were candidates for therapy change, higher proportions reported themselves to be not depressed 3 months after switching to fingolimod 0.5 mg vs SoC DMT, with sustained benefit at 6 months (LOCF).
- There was a numeric difference favoring fingolimod 0.5 mg vs SoC DMT for improvement in fatigue at months 3 and 6 (LOCF).
- In addition, higher proportions of patients switching to fingolimod 0.5 mg vs SoC DMT were rated by their clinician as very much/much/minimally improved at months 3 and 6 (LOCF).
- These data demonstrate that the benefits of therapy switch from SoC DMT to fingolimod are perceived by both patients and physicians.

INTRODUCTION

- Fatigue and depression are common in patients with multiple sclerosis (MS) and play a major role in quality of life. However, the effects of MS immunotherapy on fatigue and depression can not well understood.
- Some data suggest that interferon (IFN) and glatiramer acetate (GA) may trigger or aggravate depression in some patients, whereas other data show little effect of IFN on depression.2,3
- Improvements or mental effects on fatigue have generally been reported with these immunotherapies.1

- Patients randomized 3:1 to fingolimod or SoC DMT for 6 months with no washout period.
- The phase 4 study to Evaluate Patient Outcomes, Safety, and Tolerability of Fingolimod (DX18) sought to assess Peds and physician assessments of a change in therapy to fingolimod 0.5 mg daily and standard of care disease-modifying therapy (SoC DMT) patients with relapsing forms of MS candidates to change or maintain MS treatment.

- This paper: analyses categorical data for the secondary Peds, depression, and fatigue, and physician assessed clinical improvement.

METHODS

- DX18 was a 6-month, randomized, open-label, multicenter study conducted in the United States and Canada.
- Patients randomized 3:1 to fingolimod or SoC DMT for 6 months with a washout period.
- The protocol and interim analysis were reviewed and approved by an institutional review board or independent ethics committee at each study center, and each patient provided written informed consent.

RESULTS

- 1303 patients were randomized, 780 (75.0%) to fingolimod 0.5 mg and 263 (25.0%) to SoC DMT; demographics and clinical characteristics are shown in Table 1.

- Patients
  - 148 patients were 18-45 years of age with relapsing forms of MS (RELIANCE-B) enrolled in an expanded Disability Status Scale (EDSS) score of ≤3.5.
  - Patients were required to be relapse-free to receive oral treatment for at least 6 months prior to study entry, to have ≤1 relapse in the 12 months prior to study entry (EDSS ≤3.5 within 6 months prior to study entry), and not have been exposed to other SOTCs (SC) within 12 months prior to study entry.

Patient-Reported Outcomes

- The Beck Depression Inventory (BDI)-II6 and Fatigue Severity Scale (FSS)7 were administered at the screening visit and months 3 and 6.
- The phase 2 study analysis revealed categorical data in secondary Peds and physician-assessed Clinical Global Improvement of Fingolimod (CGI-I).

By month 6, proportions of patients were very much/much/minimally improved at the 3-month mark (45.4% vs 14.0%, P < 0.001).

- Patient-Reported Outcome

  - At months 3 and 6 (LOCF), there was a trend toward lower proportions of patients with scores indicative of clinical depression significantly lower with fingolimod vs SoC DMT (0.5 mg once daily), with trend for better outcomes in fatigue.

  - For these data, see Figure 1. At baseline, proportions of patients with scores of moderate severity of fatigue (FSS) were all equivalent in the fingolimod (58.5%) and SoC DMT (56.8%) groups (P = 0.660).

  - Improvements in CGI-I (LOCF) were also seen from trend level lower between patients with scores of baseline depression or fatigue with fingolimod vs SoC DMT, 9 months (82.6% vs 68.4%, P < 0.001; months 9, 12, and 18, P < 0.001).

- Physician Improvement of Disease

  - For these data, see Figure 3. The proportions of patients with scores of very much/much/minimally improved were significantly higher with fingolimod at SoC DMT at months 3-6 (46.4% vs 36.5%), P < 0.001 and months 9-12 (47.9% vs 13.5%, P < 0.001).

- Figure 1. Proportions of patients with BDI-II scores of moderate/very much severity of depression* at baseline, month 3, and month 6 (full-analysis set, LOCF).

- Figure 2. Proportions of patients with FSS scores of moderate/very much severity of fatigue* at baseline, month 3, and month 6 (full-analysis set, LOCF).

- Figure 3. Proportions of patients with CGI-I scores of very much/much/minimally improved at baseline, months 3 and 6 (full-analysis set, LOCF).

Table 1. Patient demographics and clinical characteristics (randomized set)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fingolimod 0.5 mg (n=789)</th>
<th>SoC DMT (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD) (years)</td>
<td>38.5 (10.7)</td>
<td>38.6 (11.2)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>629 (79.6)</td>
<td>229 (87.3)</td>
</tr>
<tr>
<td>Women, %</td>
<td>76.1</td>
<td>79.1</td>
</tr>
<tr>
<td>Race (n=619)</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>612 (84.7)</td>
<td>211 (80.2)</td>
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<tr>
<td>Black or African American</td>
<td>21 (3.0)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>51 (7.2)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>24 (3.4)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (2.4)</td>
<td>12 (4.6)</td>
</tr>
<tr>
<td>Prior MS treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>144 (18.4)</td>
<td>33 (12.6)</td>
</tr>
<tr>
<td>No</td>
<td>645 (81.6)</td>
<td>230 (87.4)</td>
</tr>
<tr>
<td>EDSS score at screening (range, median)</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>Previous MS treatment, % (n=778)</td>
<td>28 (5.8)</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>Baseline EDSS score, mean (SD)</td>
<td>1.8 (1.2)</td>
<td>1.7 (1.1)</td>
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<tr>
<td>CGI-I scores, mean (SD)</td>
<td>2.8 (1.0)</td>
<td>2.4 (1.0)</td>
</tr>
<tr>
<td>Previous MS treatment, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (2.5)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>No</td>
<td>632 (83.7)</td>
<td>260 (99.2)</td>
</tr>
<tr>
<td>Prior MS treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (1.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>No</td>
<td>659 (88.7)</td>
<td>262 (99.6)</td>
</tr>
<tr>
<td>Number of relapses, mean (SD)</td>
<td>0.7 (0.9)</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>601 (76.1)</td>
<td>208 (79.1)</td>
</tr>
<tr>
<td>Women, %</td>
<td>76.1</td>
<td>79.1</td>
</tr>
<tr>
<td>Past 2 years</td>
<td>1.4 (2.0)</td>
<td>1.4 (1.9)</td>
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<td>Past 5 years</td>
<td>2.9 (4.0)</td>
<td>2.8 (4.0)</td>
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<tr>
<td>White</td>
<td>642 (15.8)</td>
<td>46 (17.5)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>14 (6.9)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>30 (14.5)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>22 (10.9)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (6.4)</td>
<td>7 (2.7)</td>
</tr>
</tbody>
</table>

Table 1. Patient demographics and clinical characteristics (randomized set)

- Number of relapses, mean (SD) 0.7 (0.9) vs 0.8 (1.0), P = 0.052.
- However, at months 3 and 6 (LOCF), the proportions of patients with scores indicative of clinical depression were significantly lower with fingolimod vs SoC DMT (0.5 mg once daily), with trend for better outcomes in fatigue.

Patient-Reported Outcomes

- For these data, see Figure 1. At baseline, proportions of patients with scores of moderate severity of fatigue (FSS) were all equivalent in the fingolimod (58.5%) and SoC DMT (56.8%) groups (P = 0.660).

- Improvements in CGI-I (LOCF) were also seen from trend level lower between patients with scores of baseline depression or fatigue with fingolimod vs SoC DMT, 9 months (82.6% vs 68.4%, P < 0.001; months 9, 12, and 18, P < 0.001).

- Physician Improvement of Disease

- For these data, see Figure 3. The proportions of patients with scores of very much/much/minimally improved were significantly higher with fingolimod at SoC DMT at months 3-6 (46.4% vs 36.5%), P < 0.001 and months 9-12 (47.9% vs 13.5%, P < 0.001).