Depression, Fatigue, and Clinical Improvements After Switch to Fingolimod

DX18

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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, but the effects of MS immunotherapy on fatigue and depression are not well understood.[1]
- Some data suggest that interferon β (IFNβ), but not glatiramer acetate (GA), may trigger or aggravate depression in some patients,[1] whereas other data show little effect of IFNβ on depression.[2]
- Improvements or neutral effects on fatigue have generally been reported with these immunotherapies.[1-3]
- Patient-reported outcomes (PROs) can provide insight into patient perspectives on treatment efficacy.[4]
- Fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, was the first oral therapy approved in the United States and more than 60 other countries for treatment of relapsing MS.[a]
- The phase 4 study to Evaluate Patient Outcomes, Safety, and Tolerability of Fingolimod (EPOC; NCT01216072) sought to assess PROs and physician assessments of a change in therapy to fingolimod 0.5 mg once daily vs standard-of-care (SoC) disease-modifying therapy (DMT) in patients with relapsing forms of MS who are candidates for change in DMT.
  - This post hoc analysis evaluated categorical data for the secondary PROs, depression and fatigue, and physician-assessed clinical improvement.

METHODS

Study Design

- EPOC was a 6-month, randomized, open-label, multicenter study conducted in the United States and Canada.
- Patients were randomized 3:1 to fingolimod or SoC DMT for 6 months with no washout period.
- The protocol and informed consent form were reviewed and approved by an institutional review board or independent ethics committee at each study center, and each patient provided written informed consent.

Patients

- Eligible patients were 18–65 years of age with relapsing forms of MS (2005 revised McDonald criteria[5]) and an Expanded Disability Status Scale (EDSS) score of 0–5.5.
- Patients were required to be fingolimod-naive, to have received continual treatment for ≥6 months with a single SoC DMT (IFNβ-1b subcutaneous [SC] 0.25 mg every other day, IFNβ-1a intramuscular 30 µg once weekly, IFNβ-1a SC 22 or 44 µg 3 times weekly, or GA SC 20 mg once daily), and to be candidates for therapy change.
- Key exclusion criteria were significant cardiac history; macular edema; active infection; treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies ≤6 months before screening; live or live-attenuated vaccines ≤1 month before screening; treatment with cladribine, cyclophosphamide, or mitoxantrone at any time; and current treatment with class Ia or class III antiarrhythmic drugs.

Assessments

- This post hoc analysis reports categorical data on secondary PROs and physician-assessed Clinical Global Impression of Improvement (CGI-I).

Patient-Reported Outcomes

- The Beck Depression Inventory (BDI)-II[6] and Fatigue Severity Scale (FSS)[7] were administered at the screening visit and months 3 and 6.

Physician-Rated Assessment

- At months 3 and 6, investigators completed the CGI-I, a global evaluation of patient clinical change over time.

Statistical Analysis

- This post hoc analysis evaluated categorical data at months 3 and 6 (last observation carried forward [LOCF]); categories were defined by clinically relevant thresholds.[6,8,9]
- Differences in categorical proportions between groups were statistically analyzed using the Cochran-Mantel-Haenszel test with no adjustment for multiple comparisons.

RESULTS

Patients

- 1053 patients were randomized, 790 (75.0%) to fingolimod 0.5 mg and 263 (25.0%) to SoC DMT; demographics and clinical characteristics are shown in **Table 1**.

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

Characteristic	Fingolimod 0.5 mg (n=790)	SoC DMT (n=263)
Age, y, mean (SD)	46.0 (9.8)	45.1 (9.8)
Women, n (%)	601 (76.1)	208 (79.1)
Race, n (%)		
White	642 (81.3)	211 (80.2)
Black	113 (14.3)	43 (16.3)
Native American	4 (0.5)	1 (0.4)
Asian	3 (0.4)	0
Other	28 (3.5)	8 (3.0)
Duration of MS symptoms, y, mean (SD)	12.1 (8.4)	11.7 (8.4)
Number of relapses, mean (SD)		
Past year	0.8 (1.2)	0.8 (1.3)
Past 2 years	1.4 (2.0)	1.4 (1.9)
EDSS score, mean (SD)	2.4 (1.3)	2.4 (1.3)
Previous MS treatments, n (%)		
Glatiramer acetate	263 (33.3)	92 (35.0)
IFNβ-1a IM	205 (25.9)	60 (22.8)
IFNβ-1a SC	196 (24.8)	65 (24.7)
IFNβ-1b SC	125 (15.8)	46 (17.5)
Other	1 (0.1)	0

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; IFN=interferon; IM=intramuscular; MS=multiple sclerosis; SC=subcutaneous; SoC=standard of care.

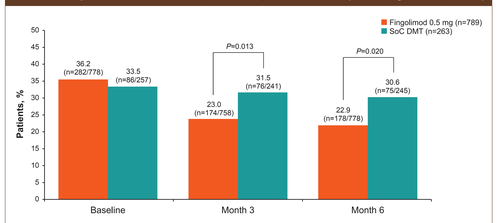
Patient-Reported Outcomes

- Results for BDI-II are shown in **Figure 1**. At baseline, similar proportions of patients in the fingolimod 0.5-mg (36.2%) and SoC DMT (33.5%) groups had scores indicative of clinical depression (score ≥14; *P*=0.515).
- However, at months 3 and 6 (LOCF) of treatment, the proportions of patients with scores indicative of clinical depression were significantly lower with fingolimod vs SoC DMT (month 3, 23.0% vs 31.5%, *P*=0.013; month 6, 22.9% vs 30.6%, *P*=0.020).
- Results for the FSS are shown in **Figure 2**. At baseline, proportions of patients with scores of borderline fatigue or fatigue (score ≥4) were equivalent in the fingolimod (66.5%) and SoC DMT (66.4%) groups (*P*=0.866).
- At months 3 and 6 (LOCF), there was a trend toward lower proportions of patients with scores of borderline fatigue or fatigue with fingolimod vs SoC DMT (month 3, 60.6% vs 66.8%, *P*=0.066; month 6, 59.9% vs 67.3%, *P*=0.052).

Physician Impression of Improvement

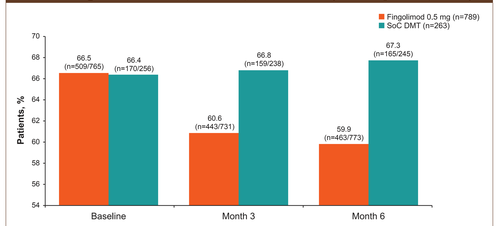
- Results for CGI-I are shown in **Figure 3**. The proportions of patients with scores of very much, much, and minimally improved were significantly higher with fingolimod vs SoC DMT at month 3 (45.4% vs 14.0%, P<0.001) and month 6 (LOCF; 49.9% vs 13.5%, P<0.001).

Figure 1. Proportions of patients with BDI-II scores indicative of clinical depression* at baseline, month 3, and month 6 (full-analysis set, LOCF)



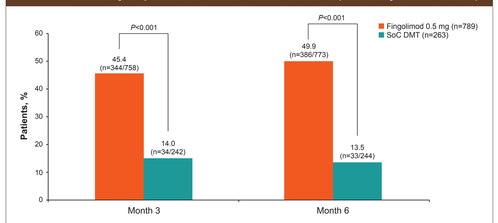
BDI-II=Beck Depression Inventory-II; DMT=disease-modifying therapy; LOCF=last observation carried forward; SoC=standard-of-care.
**Scores ≥14.*

Figure 2. Proportions of patients with FSS scores of borderline fatigue or fatigue* at baseline, month 3, and month 6 (full-analysis set, LOCF)



DMT=disease-modifying therapy; FSS=Fatigue Severity Scale; LOCF=last observation carried forward; SoC=standard-of-care.
**Score ≥4.*

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



CGI-I=Clinical Global Impression of Improvement; DMT=disease-modifying therapy; LOCF=last observation carried forward; SoC=standard-of-care.

[a]*The approved indication may vary from country to country. In the United States, it is approved for the treatment of patients with relapsing forms of MS. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS.*

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