Improved processing speed on fingolimod therapy: oral Symbol Digit Modalities Test response in PREFER*MS*

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Introduction

- Cognitive impairment is common in patients with relapsing forms of multiple sclerosis (RMS) and can be assessed using a variety of instruments, including the Symbol Digit Modalities Test (SDMT).[1,2]
- Oral and written versions of the SDMT are available; however, because motor deficits may confound responses to the written version,[3] the oral version is recommended in RMS.[4]
- PREFER*MS* was the first large, randomized, prospective study to compare treatment retention in patients with RMS treated with fingolimod 0.5 mg/day or an injectable disease-modifying therapy (iDMT).[5]
- Changes in cognition in PREFER*MS* were assessed using oral and written response versions of the SDMT; analyses of results of the oral SDMT are reported here.

Objective

- To understand the magnitude of changes in cognitive function in patients with RMS treated with fingolimod or iDMTs, using the oral SDMT.

Methods

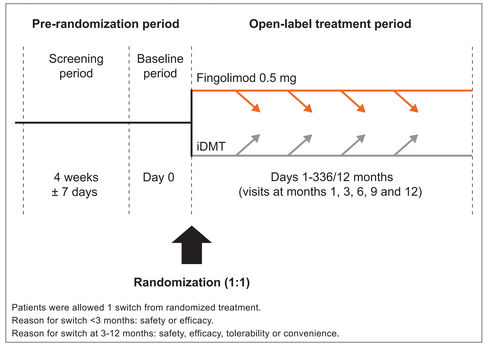
Study design

- PREFER*MS* was a 12-month, phase 4, open-label, active-controlled, randomized, multicenter study conducted at 117 sites across the United States.
- Enrolled patients were treatment naïve or had previously received only 1 class of iDMT (interferon β or glatiramer acetate).
- Patients were randomized (1:1) to fingolimod or to a pre-selected iDMT (glatiramer acetate was given if patients had previously received an interferon β, or vice versa) and followed up quarterly for 12 months.
- A single on-study treatment switch was allowed at any time after 3 months, or earlier for efficacy or safety reasons only (**Figure 1**).
- The primary endpoint, patient retention over 12 months, was the proportion of patients completing the study on randomized treatment.

Analyses

- Mean change in oral SDMT score was calculated from baseline to end of randomized treatment (EoRT), and from baseline to end of study (EoS).
  - At EoRT, patients had received only randomized treatment.
  - At EoS, some patients had received only randomized treatment, and some had received both randomized treatment and a treatment switch.
- The proportions of patients experiencing clinically meaningful improvements in oral SDMT scores of ≥3 or ≥4 points were also determined at EoRT and at EoS.
- PREFER*MS* was only powered to detect between-group differences in the primary endpoint.
- No adjustments for multiple comparisons were made.

Figure 1. PREFER*MS* study design



Patients were allowed 1 switch from randomized treatment.
Reason for switch <3 months: safety or efficacy.
Reason for switch at 3-12 months: safety, efficacy, tolerability or convenience.

Results

- 875 patients were randomized (fingolimod, n=436; iDMT, n=439); in the oral SDMT subgroup (n=146), demographics and baseline characteristics were similar in the 2 treatment groups (**Table 1**).
- Responses to the oral SDMT were provided by 76 patients receiving fingolimod and 70 receiving iDMTs.
- In the oral SDMT subgroup, treatment retention rates were significantly higher in patients randomized to fingolimod (90.0%) than in those randomized to an iDMT (32.8%; p<0.0001).
- Most common reasons for discontinuation were injection-site reaction in patients receiving iDMTs and hepatic side effects in those receiving fingolimod (**Table 2**).

Oral SDMT scores

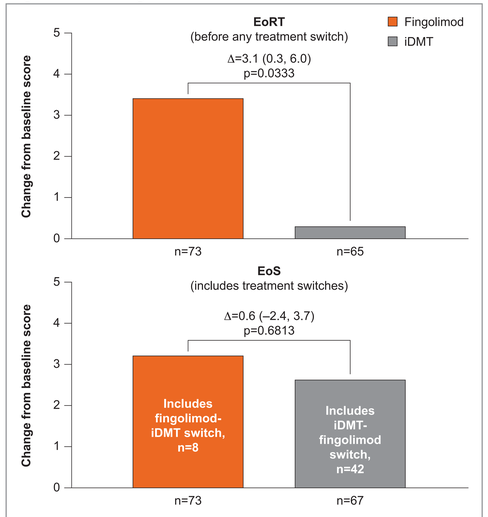
- At EoRT, oral SDMT scores had improved from baseline in both groups, but mean improvement was significantly greater with fingolimod than with iDMTs (3.4 vs 0.3, p=0.0333; **Figure 2**).
  - By EoS, when many patients had switched from iDMTs to fingolimod, improvements in mean oral SDMT scores had become similar in both groups (**Figure 2**).
- At EoRT, numerically greater proportions of patients receiving fingolimod experienced clinically meaningful improvements in oral SDMT scores of ≥3 and ≥4 points from baseline compared with those receiving iDMTs (**Figure 3**).
  - By EoS, when many patients had switched from iDMTs to fingolimod, the proportions of patients experiencing clinically meaningful improvements in oral SDMT score were similar in the 2 treatment groups (**Figure 3**).

Table 1. PREFER*MS* patient demographics and baseline characteristics in the oral SDMT sugroup

Demographics and baseline characteristics[a]	Fingolimod (n=76)	iDMT (n=70)	p-value
Age, years	42.5 (9.58)	42.0 (10.45)	0.7684
Sex, n (%) Male Female	 19 (25.0) 57 (75.0)	 14 (20.0) 56 (80.0)	0.4705
Race, n (%) Caucasian Black Other	 66 (86.8) 9 (11.8) 1 (1.3)	 59 (84.3) 11 (15.7) 0	0.5097
Height, cm	167.4 (8.98)	166.4 (9.53)	0.5340
Weight, kg	80.2 (20.07)	81.7 (21.50)	0.6683
Body mass index, kg/m²	28.53 (6.58)	29.47 (7.35)	0.4152
Duration of MS since diagnosis, years	n=76 2.97 (5.17)	n=70 2.81 (4.04)	0.8336
Duration of MS since first symptoms, years	n=76 6.77 (7.68)	n=70 5.79 (6.14)	0.3963
Number of relapses in the past year	n=75 0.6 (0.96)	n=70 0.5 (0.76)	0.4772
Number of relapses in the past 2 years	n=75 0.9 (1.35)	n=70 0.7 (0.90)	0.4288
Expanded Disability Status Scale score	n=76 2.65 (1.65)	n=70 2.89 (1.35)	ND
T2 lesion volume, cm³	n=75 6.92 (9.67)	n=69 7.65 (10.35)	ND
Normalized brain volume, cm³	n=75 1510.1 (81.76)	n=69 1501.6 (93.41)	ND
Number of gadolinium-enhancing lesions	n=74 0.46 (1.38)	n=69 0.52 (2.14)	ND

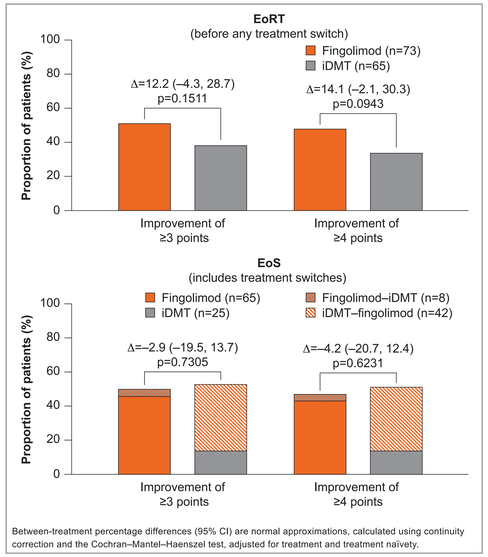
[a]Data shown are mean (SD) unless stated otherwise.
Treatment group comparisons were made using the Cochran–Mantel–Haenszel test for categorical variables and a 2-sample *t*-test for continuous variables.
MS, multiple sclerosis; ND, not determined.

Figure 2. Mean change from baseline in oral SDMT scores at EoRT and EoS



Treatment comparisons are between-group difference in mean change in score from baseline (95% CI), calculated using rank analysis of covariance, adjusted for treatment, treatment naïvety, corresponding baseline values and age.

Figure 3. Proportion of patients with clinically meaningful improvements from baseline in oral SDMT scores at EoRT and EoS



Between-treatment percentage differences (95% CI) are normal approximations, calculated using continuity correction and the Cochran–Mantel–Haenszel test, adjusted for treatment and treatment naïvety.

Table 2. Primary reasons for discontinuing randomized treatment

Reason	Fingolimod (n=70)	iDMT (n=64)
Injection-site reaction	–	9 (14.1)
Frequency of injections	–	6 (9.4)
Inconvenient administration	–	6 (9.4)
Relapse	–	2 (3.1)
Needle phobia	–	2 (3.1)
Presence of disease activity on MRI	–	–
Influenza-like symptoms	–	4 (6.3)
Lipoatrophy	–	–
Depression	1 (1.4)	–
Hepatic side effects	2 (2.9)	1 (1.6)
Spasticity	–	–
Infection	–	–
Macular edema	–	–
Bradycardia	–	–
Presence of neutralizing antibodies	–	–
Other	3 (4.3)	13 (20.3)

Data are *n* (%).
MRI, magnetic resonance imaging.

Conclusions

- In PREFER*MS*, some patients in both treatment groups experienced clinically meaningful improvements in oral SDMT score.
- The data suggest an overall trend towards greater improvements in cognition with fingolimod than with iDMTs.

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Acknowledgments

Editorial support was provided by Oxford PharmaGenesis, Oxford, UK and funded by Novartis Pharmaceuticals Corporation.

Disclosures

Ralph H.B. Benedict: Acorda Therapeutics, Biogen, EMD Serono, Genentech-Roche, Mallinckrodt, the National Multiple Sclerosis Society, Novartis Pharmaceuticals Corporation and Sanofi Genzyme. **Douglas L. Arnold:** Acorda Therapeutics, Biogen, Hoffman-La Roche, MedImmune, Mitsubishi, NeuroRx Research, Novartis Pharmaceuticals Corporation, Receptos and Sanofi-Aventis. **Bruce A.C. Cree:** AbbVie, Biogen, EMD Serono, MedImmune, Novartis Pharmaceuticals Corporation, Sanofi Genzyme, Shire and Teva Neuroscience. **Xiangyi Meng, Lesley Schofield, Fernanda Boulos** and **Nadia Tenenbaum:** Novartis Pharmaceuticals Corporation (employees).

Poster presented at the 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC), May 24-27, New Orleans, LA, United States.

This study was sponsored by Novartis Pharmaceuticals Corporation, United States.

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