Treatment Retention and Satisfaction in Patients Randomized to Fingolimod or Injectable Disease-Modifying Therapies in PREFER*MS*: Effect of Previous Treatment

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Introduction

- Various first-line injectable disease-modifying therapies (iDMTs) are available for relapsing forms of multiple sclerosis (RMS), including glatiramer acetate, interferon β-1a and interferon β-1b
- Fingolimod 0.5 mg is a once-daily oral therapy for RMS,[1] and is approved as a first-line therapy in many countries, including the USA, Australia and Switzerland
  - However, in clinical practice fingolimod is often prescribed as a second-line therapy
- PREFER*MS* was a 12-month, Phase 4, randomized, active-controlled, open-label study that demonstrated that treatment retention and medication satisfaction were higher with fingolimod than with iDMTs in patients with RMS[2]
- At enrollment, approximately half the patients in PREFER*MS* were treatment-naïve and the remainder had been previously treated with one class of iDMT
  - This affords the opportunity to examine the impact of previous treatment status on treatment retention, medication satisfaction and adverse events (AEs) in patients prescribed oral fingolimod or iDMTs
  - Understanding the impact of previous treatment could help inform treatment decision-making in early disease stages

Objective

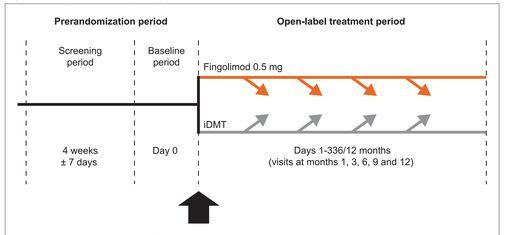
- Assess impact of previous treatment status (treatment-naïve or previously treated), in patients randomized to oral fingolimod or iDMTs in PREFER*MS*, on treatment retention, medication satisfaction and AEs

Methods

Study design

- PREFER*MS* was conducted at 117 sites in the USA (**Figure 1**)
- Primary endpoint was retention on randomized treatment over 12 months
  - Secondary endpoints included medication satisfaction (measured using the Medication Satisfaction Questionnaire [MSQ]), reasons for treatment discontinuation, and occurrence of AEs overall and AEs leading to study discontinuation
- Enrolled patients were either treatment-naïve or had previously received only one class of iDMT (glatiramer acetate, interferon β-1a or interferon β-1b)
- Patients were randomized (1:1) to fingolimod 0.5 mg/day or a preselected iDMT and observed quarterly over 12 months
  - Patients previously treated with an iDMT received an alternative iDMT class if randomized to iDMT
- One treatment switch was allowed for any reason after 3 months, although patients could switch earlier for efficacy or safety reasons

Figure 1. PREFER*MS* study design



Patients were allowed one switch from randomized treatment
Reason for switch ≤3 months: safety or efficacy
Reason for switch at 3-12 months: safety, efficacy, tolerability or convenience
iDMT, injectable disease-modifying therapy

Analyses

- Outcomes evaluated were:
  - Retention rates
    - Treatment satisfaction (defined as percentage of patients with an MSQ score ≥5 on the 7-point Likert scale [patient responses of "somewhat satisfied", "satisfied" or "very satisfied" combined])
  - Reasons for discontinuation of randomized treatment
  - AEs leading to study discontinuation
- Post hoc analyses were stratified according to treatment history (treatment-naïve or previously treated)
  - Analyses of retention and treatment satisfaction were conducted at end of randomized treatment in the full analysis set (FAS) using a Cochran–Mantel–Haenszel test adjusted for treatment
  - Rates of AEs leading to study discontinuation were reported for the safety set in the randomized treatment phase
- Analyses were for hypothesis generation because the study was not powered to detect treatment effects in subgroups of patients; p values are for comparison only
- No adjustment was made for multiple comparisons

Results

- 875 patients were randomized, and 861 (98.4%) were included in the FAS (fingolimod, n=433; iDMTs, n=428)
  - At baseline, 404 patients (46.2%) were treatment-naïve and 471 (53.8%) had been treated with one class of iDMT
- Demographic and baseline characteristics were generally similar in the overall population and subgroups (**Table 1**)
- Compared with patients previously treated, treatment-naïve patients had:
  - Multiple sclerosis diagnosed more recently
  - Fewer relapses in the 2 years before enrollment
  - More gadolinium-enhancing lesions (**Table 1**)

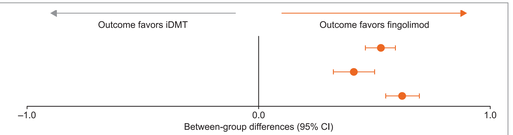
Table 1. PREFER*MS* patient demographic and baseline characteristics, grouped by treatment history

Characteristic	Overall (n=875)		Treatment-naïve (n=404)		Previously treated (n=471)	
	Fingolimod (n=436)	iDMT (n=439)	Fingolimod (n=213)	iDMT (n=191)	Fingolimod (n=223)	iDMT (n=248)
Age, years	41.5 (10.8)	41.9 (10.4)	39.5 (10.6)	40.1 (10.8)	43.4 (10.8)	43.2 (9.9)
Sex, n (%)						
Male	125 (28.7)	110 (25.1)	68 (31.9)	46 (24.1)	57 (25.6)	64 (25.8)
Female	311 (71.3)	329 (74.9)	145 (68.1)	145 (75.9)	166 (74.4)	184 (74.2)
Race, n (%)						
Caucasian	355 (81.4)	355 (80.9)	167 (78.4)	153 (80.1)	188 (84.3)	202 (81.5)
Black	69 (15.8)	72 (16.4)	38 (17.8)	34 (17.8)	31 (13.9)	38 (15.3)
Asian	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)	0	0
Native American	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)	0	0
Pacific Islander	0	2 (0.5)	0	0	0	2 (0.8)
Other	10 (2.3)	8 (1.8)	6 (2.8)	2 (1.0)	4 (1.8)	6 (2.4)
Height, cm	168.5 (9.0)	167.5 (10.1)	169.1 (9.6)	167.6 (9.7)	167.8 (8.3)	167.4 (10.4)
Weight, kg	82.9 (20.1)	83.6 (22.3)	84.2 (20.3)	83.3 (22.3)	81.7 (19.9)	83.8 (22.4)
BMI, kg/m²	29.2 (6.7)	29.8 (7.6)	29.5 (7.0)	29.6 (7.3)	28.9 (6.4)	29.9 (7.8)
Duration of MS since diagnosis, years	n=434 4.4 (6.7)	n=434 4.2 (5.9)	n=212 1.7 (4.9)	n=191 1.9 (4.8)	n=222 7.0 (7.1)	n=243 6.0 (6.1)
Duration of MS since first symptoms, years	n=434 7.3 (8.2)	n=434 7.2 (7.7)	n=212 4.8 (6.6)	n=191 5.6 (7.5)	n=222 9.8 (8.9)	n=243 8.5 (7.5)
Number of relapses in the past year	n=430 0.6 (1.0)	n=436 0.6 (0.9)	n=208 0.5 (0.9)	n=188 0.5 (1.0)	n=222 0.7 (1.0)	n=248 0.6 (0.9)
Number of relapses in the past 2 years	n=430 0.9 (1.5)	n=436 0.9 (1.4)	n=208 0.6 (1.3)	n=188 0.5 (1.2)	n=222 1.2 (1.6)	n=248 1.1 (1.5)
Normalized brain volume, cm³	n=431 1521.4 (83.9)	n=412 1511.2 (90.5)	n=210 1533.8 (82.4)	n=183 1528.1 (81.1)	n=221 1509.6 (83.8)	n=229 1497.7 (95.4)
Number of Gd+ lesions	n=429 1.1 (3.7)	n=414 0.9 (3.0)	n=209 1.6 (4.8)	n=182 1.3 (4.1)	n=220 0.6 (2.1)	n=232 0.5 (1.8)

Randomized set. Data are mean (SD) unless stated otherwise
BMI, body mass index; Gd+, gadolinium-enhancing; iDMT, injectable disease-modifying therapy; MS, multiple sclerosis; SD, standard deviation

Figure 2. Retention on randomized treatment, grouped by treatment history

Treatment history	Fingolimod, % retained (n/N)	iDMT, % retained (n/N)	Between-group difference, % (95% CI)	p value
Overall	81.3 (352/433)	29.2 (125/428)	52.1 (46.4-57.8)	<0.0001
Treatment-naïve	78.7 (166/211)	38.1 (72/189)	40.6 (31.7-49.4)	<0.0001
Previously treated	83.8 (186/222)	22.2 (53/239)	61.6 (54.5-68.8)	<0.0001



Full analysis set. Retention analyzed using a Cochran–Mantel–Haenszel test adjusted for treatment. Between-group differences assessed by normal approximation using continuity correction
CI, confidence interval; iDMT, injectable disease-modifying therapy

Table 2. Reasons for discontinuation of randomized treatment in PREFER*MS*, grouped by treatment history

Reason for discontinuing randomized treatment, n (%)	Overall (N=875)		Treatment-naïve (n=404)		Previously treated (n=471)	
	Fingolimod (n=436)	iDMT (n=439)	Fingolimod (n=213)	iDMT (n=191)	Fingolimod (n=223)	iDMT (n=248)
Overall[a]	27 (6.2)	257 (58.5)	16 (7.5)	101 (52.9)	11 (4.9)	156 (62.9)
Injection-site reaction[b]	0 (0.0)	61 (13.9)	0 (0.0)	25 (13.1)	0 (0.0)	36 (14.5)
Flu-like symptoms[b]	0 (0.0)	34 (7.7)	0 (0.0)	10 (5.2)	0 (0.0)	24 (9.7)
Inconvenient administration[b]	0 (0.0)	33 (7.5)	0 (0.0)	10 (5.2)	0 (0.0)	23 (9.3)
Frequency of injections[b]	0 (0.0)	29 (6.6)	0 (0.0)	10 (5.2)	0 (0.0)	19 (7.7)
Needle phobia[b]	0 (0.0)	13 (3.0)	0 (0.0)	5 (2.6)	0 (0.0)	8 (3.2)
Occurrence of relapse	5 (1.1)	14 (3.2)	2 (0.9)	8 (4.2)	3 (1.3)	6 (2.4)
Presence of disease activity on MRI	0 (0.0)	6 (1.4)	0 (0.0)	3 (1.6)	0 (0.0)	3 (1.2)
Depression	1 (0.2)	4 (0.9)	1 (0.5)	1 (0.5)	0 (0.0)	3 (1.2)
Hepatic side effects	7 (1.6)	3 (0.7)	6 (2.8)	2 (1.0)	1 (0.4)	1 (0.4)
Spasticity	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Lipoatrophy	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Macular edema	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other	13 (3.0)	58 (13.2)	6 (2.8)	26 (13.6)	7 (3.1)	32 (12.9)

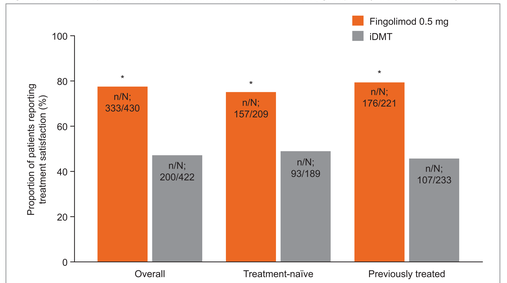
Randomized set. Data are n (%). Data shown are the primary reasons for discontinuation
[a]Two patients discontinuing their randomized iDMT opted to switch to an alternative iDMT; the remainder switched to fingolimod
[b]Injection-related reason for discontinuing randomized treatment
iDMT, injectable disease-modifying therapy; MRI, magnetic resonance imaging

Table 3. PREFER*MS* AEs causing study discontinuation, grouped by treatment history

AEs causing study discontinuation (>2% of patients in any group)	Overall (n=861)				Treatment-naïve (n=400)				Previously treated (n=461)			
	Fingolimod (n=433)		iDMT (n=428)		Fingolimod (n=211)		iDMT (n=189)		Fingolimod (n=222)		iDMT (n=239)	
System organ class; preferred term	n (%)	Rate (n/py)	n (%)	Rate (n/py)	n (%)	Rate (n/py)	n (%)	Rate (n/py)	n (%)	Rate (n/py)	n (%)	Rate (n/py)
Any AE	40 (9.2)	0.112	100 (23.4)	0.540	20 (9.5)	0.117	46 (24.3)	0.488	20 (9.0)	0.108	54 (22.6)	0.595
General and administration site	4 (0.9)	0.011	79 (18.5)	0.420	3 (1.4)	0.017	34 (18.0)	0.352	1 (0.5)	0.005	45 (18.8)	0.492
Injection-site reaction	0 (0.0)	0.000	26 (6.1)	0.131	0 (0.0)	0.000	14 (7.4)	0.138	0 (0.0)	0.000	12 (5.0)	0.124
Flu-like illness	1 (0.2)	0.003	19 (4.4)	0.096	1 (0.5)	0.006	8 (4.2)	0.079	0 (0.0)	0.000	11 (4.6)	0.114
Injection-site pain	0 (0.0)	0.000	18 (4.2)	0.091	0 (0.0)	0.000	7 (3.7)	0.069	0 (0.0)	0.000	11 (4.6)	0.114
Fatigue	0 (0.0)	0.000	9 (2.1)	0.045	0 (0.0)	0.000	4 (2.1)	0.039	0 (0.0)	0.000	5 (2.1)	0.051
Injection-site erythema	0 (0.0)	0.000	7 (1.6)	0.035	0 (0.0)	0.000	5 (2.6)	0.049	0 (0.0)	0.000	2 (0.8)	0.020
Musculoskeletal and connective tissue	2 (0.5)	0.006	8 (1.9)	0.040	1 (0.5)	0.006	2 (1.1)	0.019	1 (0.5)	0.005	6 (2.5)	0.062
Myalgia	1 (0.2)	0.003	6 (1.4)	0.030	0 (0.0)	0.000	1 (0.5)	0.010	1 (0.5)	0.005	5 (2.1)	0.051
Nervous system	6 (1.4)	0.017	11 (2.6)	0.055	3 (1.4)	0.017	6 (3.2)	0.059	3 (1.4)	0.016	5 (2.1)	0.051
Headache	2 (0.5)	0.006	8 (1.9)	0.040	2 (0.9)	0.012	3 (1.6)	0.029	0 (0.0)	0.000	5 (2.1)	0.051
Psychiatric	0 (0.0)	0.000	15 (3.5)	0.075	0 (0.0)	0.000	6 (3.2)	0.059	0 (0.0)	0.000	9 (3.8)	0.092
Anxiety	0 (0.0)	0.000	9 (2.1)	0.045	0 (0.0)	0.000	5 (2.6)	0.049	0 (0.0)	0.000	4 (1.7)	0.041

Safety set
AE, adverse event; iDMT, injectable disease-modifying therapy; py, patient-year

Figure 3. Patient-reported satisfaction with randomized treatment, grouped by treatment history



*p<0.0001
Full analysis set. Treatment satisfaction was defined as a score of ≥5 on the Medication Satisfaction Questionnaire
iDMT, injectable disease-modifying therapy

- Retention rates over 12 months were higher for fingolimod than for iDMTs (**Figure 2**)
  - Overall: fingolimod, 81.3% (n/N=352/433); iDMT, 29.2% (n/N=125/428); p<0.0001
  - Treatment-naïve: fingolimod, 78.7% (n/N=166/211); iDMT, 38.1% (n/N=72/189); p<0.0001
  - Previously treated: fingolimod, 83.8% (n/N=186/222); iDMT, 22.2% (n/N=53/239); p<0.0001
- Most patients (58.5%) randomized to an iDMT switched treatment; only 6.2% of patients on fingolimod switched to an iDMT (**Table 2**)
  - Most patients switching from an iDMT did so for injection-related reasons (**Table 2**)
  - Similar trends were observed irrespective of previous treatment status (**Table 2**)
- A trend favoring fingolimod was observed for treatment satisfaction, regardless of previous treatment status (**Figure 3**)
  - Overall: fingolimod, 77.4% (n/N=333/430); iDMT, 47.4% (n/N=200/422); p<0.0001
  - Treatment-naïve: fingolimod, 75.1% (n/N=157/209); iDMT, 49.2% (n/N=93/189); p<0.0001
  - Previously treated: fingolimod, 79.6% (n/N=176/221); iDMT, 45.9% (n/N=107/233); p<0.0001
- AE rates were lower with fingolimod than with iDMTs, regardless of previous treatment status
  - Overall: fingolimod, 4.008 per patient-year (n/N=394/433; exposure, 98.3 years); iDMT, 7.011 per patient-year (n/N=355/428; exposure, 50.7 years)
  - Treatment-naïve: fingolimod, 3.902 per patient-year (n/N=189/211; exposure, 48.4 years); iDMT, 7.606 per patient-year (n/N=167/189; exposure, 22.0 years)
  - Previously treated: fingolimod, 4.110 per patient-year (n/N=205/222; exposure, 49.9 years); iDMT, 6.555 per patient-year (n/N=188/239; exposure, 28.7 years)
- Rates of AEs leading to study discontinuation were lower for fingolimod than for iDMTs, regardless of previous treatment status (**Table 3**)
  - Overall: fingolimod, 9.2% (n/N=40/433); iDMT, 23.4% (n/N=100/428)
  - Treatment-naïve: fingolimod, 9.5% (n/N=20/211); iDMT, 24.3% (n/N=46/189)
  - Previously treated: fingolimod, 9.0% (n/N=20/222); iDMT, 22.6% (n/N=54/239)
- Rates of AEs leading to study discontinuation in patients grouped according to treatment history were generally consistent with the overall fingolimod and iDMT groups (**Table 3**)

Conclusions

- In PREFER*MS*, compared with iDMTs, fingolimod was associated with greater treatment retention and satisfaction rates and lower rates of AEs leading to drug discontinuation in both previously treated and treatment-naïve patients
- Benefits of initiating fingolimod were independent of previous treatment status

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