Efficacy Outcomes in Patients Randomized to Fingolimod or Injectable Disease-Modifying Therapies in PREFER*MS*: Effect of Previous Treatment Cycles

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Introduction

- Fingolimod 0.5 mg is a once-daily, oral therapy for relapsing forms of multiple sclerosis (RMS),[1] approved for first-line use in many countries
 - New American Academy of Neurology guidelines suggest high-efficacy therapies such as fingolimod should be considered as a first-line therapy for patients with active disease[2]
- In clinical practice, fingolimod is often prescribed as a second-line therapy following one or more injectable disease-modifying therapies (iDMTs), such as glatiramer acetate, interferon β-1a or interferon β-1b
- PREFER*MS* was a 12-month, Phase 4, active-controlled, open-label, multicenter study that compared treatment retention and clinical outcomes with fingolimod and iDMTs in patients with RMS[2,3]
 - Just over half the patients in PREFER*MS* had been treated with one class of iDMT; the remainder were treatment-naïve
 - Patients were randomized to fingolimod 0.5 mg or an iDMT, and allowed a single switch to an alternative, on-study treatment
 - For those randomized to an iDMT, efficacy outcomes improved following switch to fingolimod[4,5]
- We examined the number of iDMTs received before initiating fingolimod on efficacy outcomes in patients with RMS

Objective

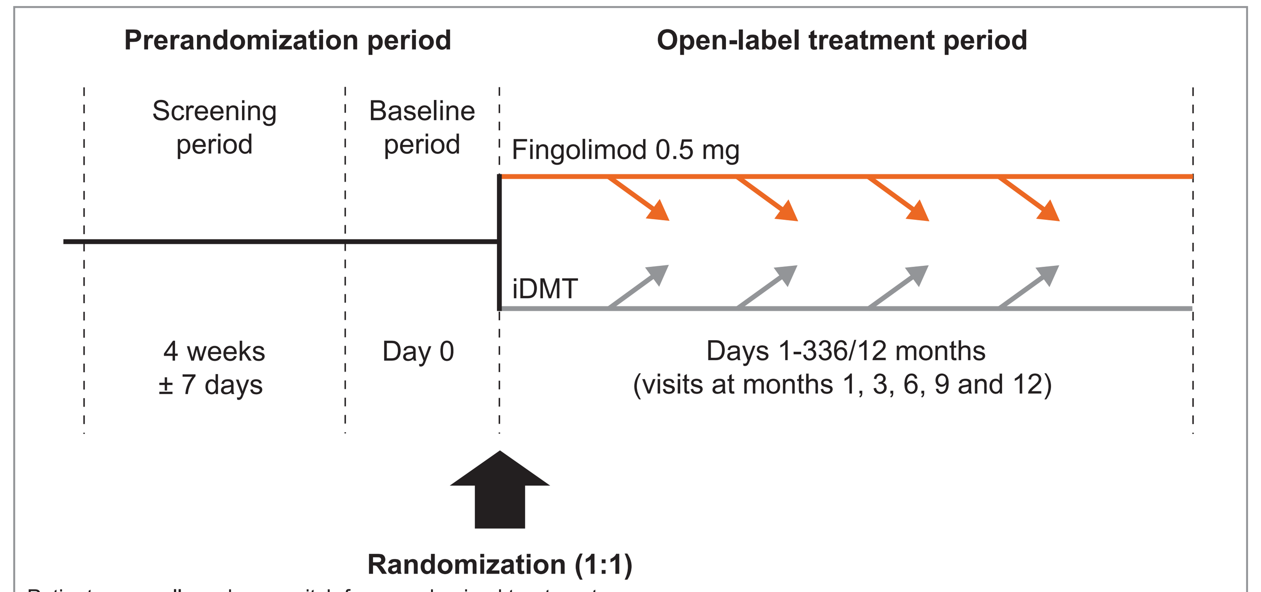
- Assess impact of number of previous cycles of iDMT (two, one or none) on response to fingolimod in PREFER*MS*

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 radiological outcomes, such as brain atrophy and lesion counts
- Enrolled patients were treatment-naïve or had previously received one class of iDMT (glatiramer acetate, interferon β-1a or interferon β-1b)
- Patients were randomized (1:1) to fingolimod 0.5 mg 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


Prerandomization period
Open-label treatment period
Screening period
Baseline period
Fingolimod 0.5 mg
iDMT
4 weeks ± 7 days
Day 0
Days 1-336/12 months (visits at months 1, 3, 6, 9 and 12)
Randomization (1:1)

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

- Three patient subgroups were analyzed post hoc according to iDMT treatment history:
 - **Group A (two iDMTs):** patients who had received one iDMT before PREFER*MS*, were randomized to a new iDMT and subsequently switched to fingolimod (n=155). Data for this subgroup are reported for two time points:
 - Last study visit before switching to fingolimod (ie pre-fingolimod, after two previous iDMTs)
 - End of study following the switch to fingolimod (ie post-fingolimod, after two previous iDMTs)
 - **Group B (one iDMT):** patients who had received one iDMT before PREFER*MS* and were randomized to fingolimod (ie after one previous iDMT cycle; n=233)
 - **Group C (no iDMT):** treatment-naïve patients who were randomized to fingolimod (ie no previous iDMT cycles; n=213)
 - Data from groups B and C were reported for last study visit at which patients received fingolimod
- Outcomes evaluated were:
 - exposure-adjusted percentage brain volume loss (BVL) from baseline
 - number of new gadolinium-enhancing (Gd+) lesions
 - change in overall Gd+ lesion count from baseline
- All outcomes are presented as means with 95% confidence intervals (CI)
- Effect of switching to fingolimod following two iDMT cycles was investigated in group A (two iDMTs) by assessing efficacy outcomes at the pre-fingolimod versus post-fingolimod time points, and compared with post-fingolimod outcomes in group B (one iDMT) and group C (no iDMT)
- Comparisons were for hypothesis generation only; PREFER*MS* was not powered to detect treatment effects in subgroups of patients

Results

- In total, 875 patients were randomized, and 861 (98.4%) were included in the full analysis set (fingolimod, n=433; iDMTs, n=428)
 - At baseline, 53.8% of patients (n=471) were treatment-naïve; 46.2% (n=404) had previously received one class of iDMT
 - Most patients randomized to an iDMT subsequently switched to fingolimod (58.5%); few patients receiving fingolimod switched to an iDMT (6.2%)
- Demographic and baseline characteristics were generally similar in the three groups (**Table 1**)
 - Compared with previously treated patients (groups A and B), treatment-naïve patients (group C):
 - were younger and more likely to be men
 - had been diagnosed with multiple sclerosis more recently
 - had fewer relapses in the 2 years before enrollment
 - had more Gd+ lesions (**Table 1**)
- In pre-fingolimod group A (previously received two iDMTs), mean (95% CI) BVL from baseline was –0.90% (–1.36, –0.44; **Figure 2**)

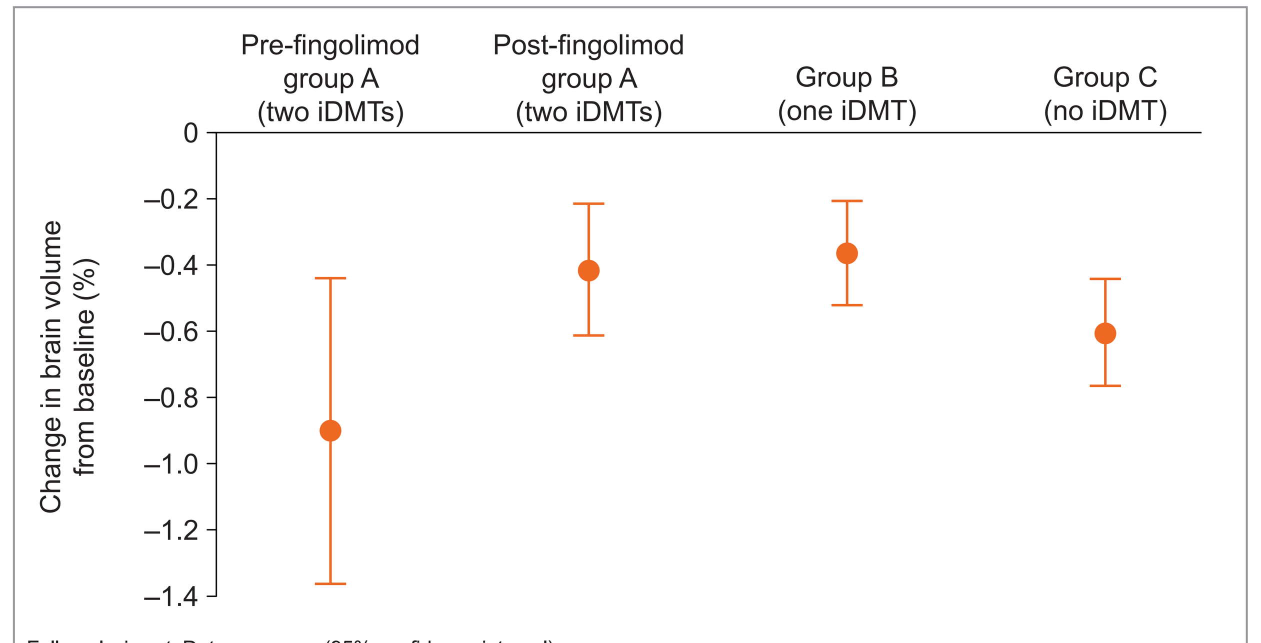
Table 1. PREFER*MS* patient demographic and baseline characteristics

Characteristic	Group A (two iDMTs, n=155)	Group B (one iDMT, n=223)	Group C (no iDMT, n=213)
Age, years	42.0 (10.4)	43.4 (10.8)	39.5 (10.6)
Sex, n (%)			
Male	39 (25.2)	57 (25.6)	68 (31.9)
Female	116 (74.8)	166 (74.4)	145 (68.1)
Race, n (%)			
Caucasian	131 (84.5)	188 (84.3)	167 (78.4)
Black	22 (14.2)	31 (13.9)	38 (17.8)
Asian	0	0	1 (0.5)
Native American	0	0	1 (0.5)
Pacific Islander	1 (0.6)	0	0
Other	1 (0.6)	4 (1.8)	6 (2.8)
Height, cm	167.2 (10.3)	167.8 (8.3)	169.1 (9.6)
Weight, kg	83.5 (21.2)	81.7 (19.9)	84.2 (20.3)
BMI, kg/m²	30.0 (7.9)	28.9 (6.4)	29.5 (7.0)
Duration of MS since diagnosis, years	n=155 6.0 (5.8)	n=222 7.0 (7.1)	n=212 1.7 (4.9)
Duration of MS since first symptoms, years	n=155 7.9 (6.8)	n=222 9.6 (8.9)	n=212 4.8 (6.6)
Number of relapses in the past year	n=155 0.7 (0.8)	n=222 0.7 (1.0)	n=208 0.5 (0.9)
Number of relapses in the past 2 years	n=155 1.1 (1.3)	n=222 1.2 (1.6)	n=208 0.6 (1.3)
Normalized brain volume, cm³	n=149 1501.5 (99.8)	n=221 1509.6 (83.8)	n=210 1533.8 (82.4)
Number of Gd+ lesions	n=150 0.6 (2.0)	n=220 0.6 (2.1)	n=209 1.6 (4.8)

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

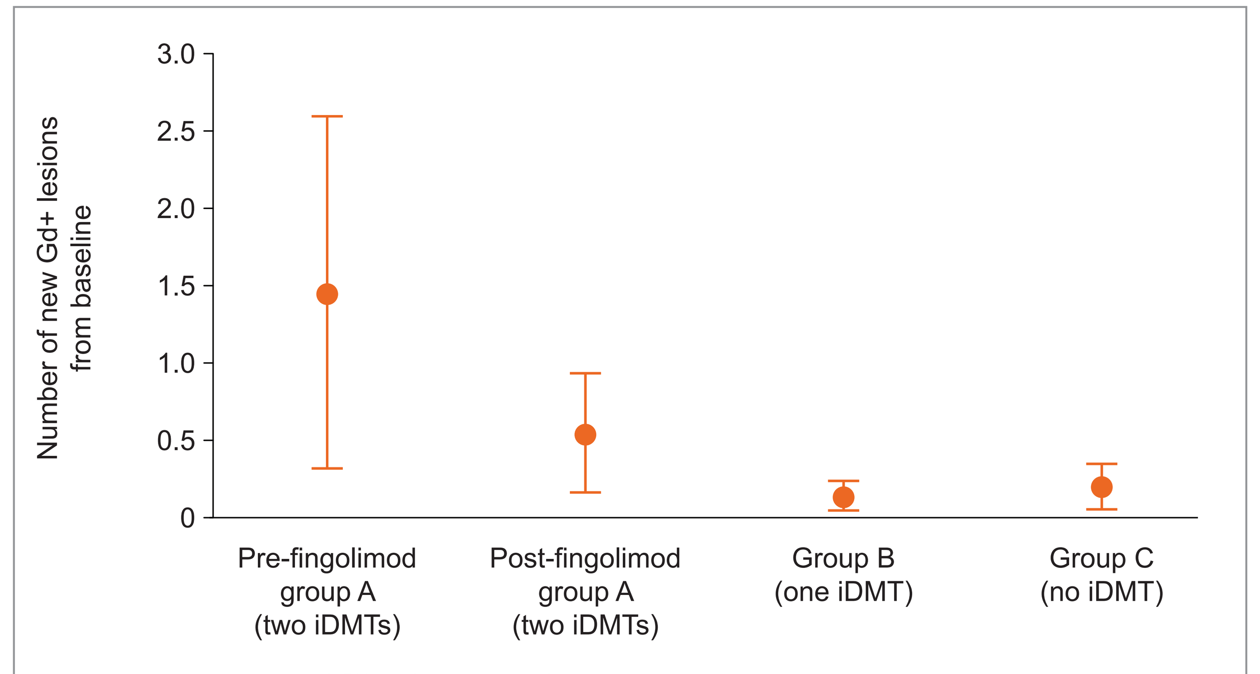
- Mean (95% CI) BVL from baseline was smaller in all groups after receiving fingolimod treatment (**Figure 2**)
 - Post-fingolimod group A (previously received two iDMTs): –0.42% (–0.62, –0.21)
 - Group B (previously received one iDMT): –0.37% (–0.52, –0.21)
 - Group C (previously received no iDMT): –0.61% (–0.77, –0.45)
- In pre-fingolimod group A (previously received two iDMTs), mean (95% CI) number of new Gd+ lesions was 1.46 (0.32, 2.61; **Figure 3**)
 - There were fewer new Gd+ lesions in all groups after receiving fingolimod treatment (**Figure 3**)
 - Post-fingolimod group A (previously received two iDMTs): 0.54 (0.15, 0.93)
 - Group B (previously received one iDMT): 0.13 (0.04, 0.22)
 - Group C (previously received no iDMT): 0.19 (0.05, 0.33)
- In pre-fingolimod group A (previously received two iDMTs), change in overall Gd+ lesion count showed no reduction from baseline: mean (95% CI) 0.04 (−1.24, 1.32; **Figure 4**)

Figure 2. Effect of iDMT cycles on BVL in PREFER*MS*


Change in brain volume from baseline (%)
0
–0.2
–0.4
–0.6
–0.8
–1.0
–1.2
–1.4
Pre-fingolimod group A (two iDMTs)
Post-fingolimod group A (two iDMTs)
Group B (one iDMT)
Group C (no iDMT)

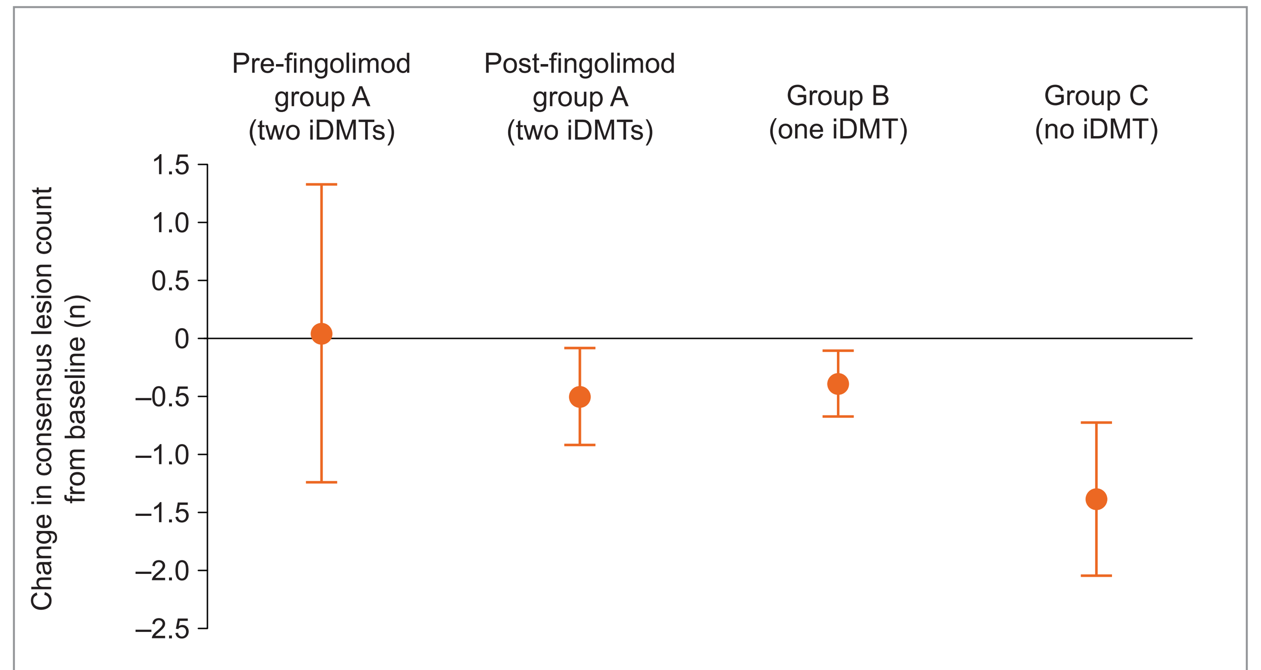
Full analysis set. Data are mean (95% confidence interval)
BVL, brain volume loss; iDMT, injectable disease-modifying therapy

Figure 3. Effect of iDMT cycles on new Gd+ lesions in PREFER*MS*


Number of new Gd+ lesions from baseline
3.0
2.5
2.0
1.5
1.0
0.5
0
Pre-fingolimod group A (two iDMTs)
Post-fingolimod group A (two iDMTs)
Group B (one iDMT)
Group C (no iDMT)

Full analysis set. Data are mean (95% confidence interval)
Gd+, gadolinium-enhancing; iDMT, injectable disease-modifying therapy

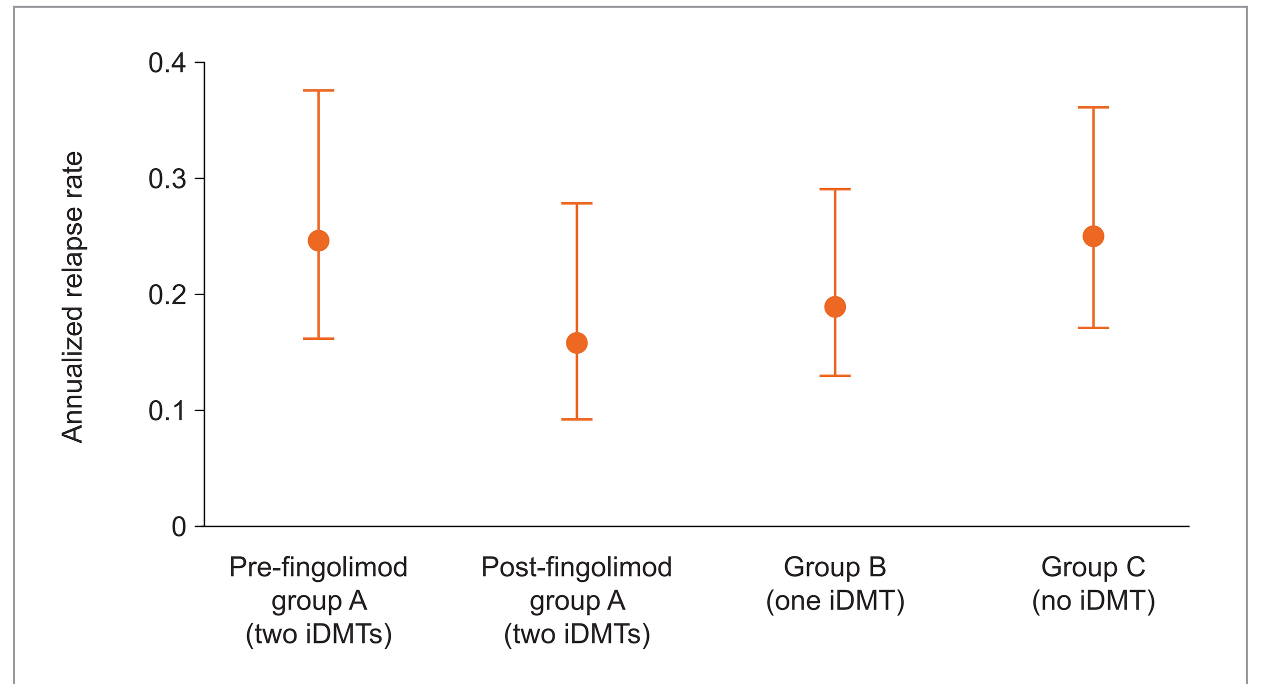
Figure 4. Effect of iDMT cycles on the overall change in Gd+ lesions in PREFER*MS*


Change in consensus lesion count from baseline (n)
1.5
1.0
0.5
0
–0.5
–1.0
–1.5
–2.0
–2.5
Pre-fingolimod group A (two iDMTs)
Post-fingolimod group A (two iDMTs)
Group B (one iDMT)
Group C (no iDMT)

Full analysis set. Data are mean (95% confidence interval)
Gd+, gadolinium-enhancing; iDMT, injectable disease-modifying therapy

- Overall Gd+ lesion count was lower in all groups after receiving fingolimod (**Figure 4**)
 - Post-fingolimod group A (previously received two iDMTs): –0.49 (−0.90, −0.08)
 - Group B (previously received one iDMT): –0.39 (−0.67, −0.10)
 - Group C (previously received no iDMT): –1.38 (−2.04, −0.72)
- In pre-fingolimod group A (previously received two iDMTs), mean (95% CI) annualized relapse rate (ARR) was 0.25 (0.16, 0.38; **Figure 5**)
 - ARR was similar in all groups after receiving fingolimod (**Figure 5**)
 - Post-fingolimod group A (previously received two iDMTs): 0.16 (0.09, 0.28)
 - Group B (previously received one iDMT cycle): 0.19 (0.13, 0.29)
 - Group C (previously received no iDMT): 0.25 (0.17, 0.36)

Figure 5. Effect of iDMT cycles on ARR in PREFER*MS*


Annualized relapse rate
0.4
0.3
0.2
0.1
0
Pre-fingolimod group A (two iDMTs)
Post-fingolimod group A (two iDMTs)
Group B (one iDMT)
Group C (no iDMT)

Full analysis set. Data are mean (95% confidence interval)
ARR, annualized relapse rate; iDMT, injectable disease-modifying therapy

Conclusions

- Outcomes were favorable in patients with two previous iDMTs, following fingolimod treatment
 - Similar data were obtained for patients with one or no previous iDMT
- These data suggest that benefits may be seen with fingolimod irrespective of number of previous iDMTs
- Understanding the impact of previous treatments could help inform treatment decision-making in early stages of MS

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