Comparison of blood lymphocyte counts and reported rates of infection in patients treated with fingolimod and iDMTs in PREFER*MS*

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Introduction

- Fingolimod 0.5 mg/day is indicated in patients with relapsing forms of multiple sclerosis (RMS).[1]
- Fingolimod is a sphingosine 1-phosphate receptor (S1PR) modulator that downregulates S1PR on lymphocytes, causing their redistribution to secondary lymphoid tissues.[1,2]
- The reduction in absolute lymphocyte counts (ALCs) seen with fingolimod is therefore due to their retention in the lymph nodes, rather than their depletion.[1,2]
- PREFER*MS* was the first large, randomized, prospective study to compare treatment retention in patients with RMS treated with fingolimod or with an injectable disease-modifying therapy (iDMT).[3]
- Here, we present data from PREFER*MS* to relate ALCs to reported infection rates.

Objective

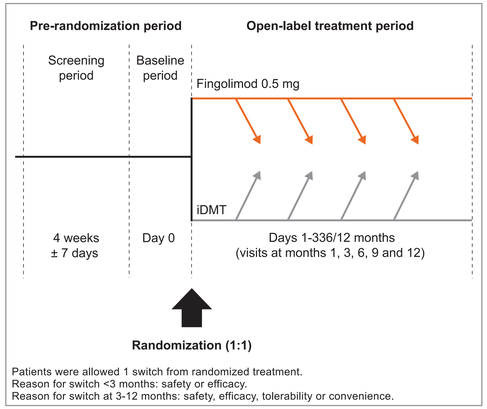
- To examine whether changes in ALCs are associated with changes in infection rates in individuals receiving fingolimod or iDMTs in PREFER*MS*.

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 and followed up quarterly for 12 months.
- A single on-study treatment switch was allowed after 3 months, or earlier for efficacy or safety reasons (**Figure 1**).

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.

- Changes in ALC of ≥10% from baseline to end of study were reported, along with instances of very low ALC (<0.2 × 10^9/L).
- A much greater proportion of patients switched to fingolimod from iDMT than switched to iDMT from fingolimod during the study, causing a substantial difference in exposure to randomized treatment in the two groups.
- Therefore, infection-related adverse events (AEs) in patients receiving randomized treatment were reported as n/patient-year to adjust for this difference in exposure.

Results

- 875 patients were randomized to treatment (fingolimod, n=436; iDMT, n=439; **Table 1**); 861 were included in the safety set (fingolimod, n=433; iDMT, n=428).

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

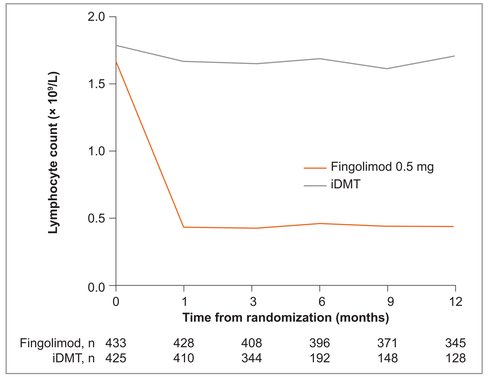
Demographics and baseline characteristics[a]	Fingolimod (n=436)	iDMT (n=439)	p-value
Age, years	41.5 (10.84)	41.9 (10.39)	0.6310
Sex, n (%)			
Male	125 (28.7)	110 (25.1)	0.2282
Female	311 (71.3)	329 (74.9)	
Race, n (%)			
Caucasian	355 (81.4)	355 (80.9)	
African American	69 (15.8)	72 (16.4)	
Asian	1 (0.2)	1 (0.2)	0.6553
Native American	1 (0.2)	1 (0.2)	
Pacific Islander	0 (0.0)	2 (0.5)	
Other	10 (2.3)	8 (1.8)	
Height, cm	168.5 (8.99)	167.5 (10.06)	0.1388
Weight, kg	82.94 (20.1)	83.56 (22.3)	0.6651
BMI, kg/m²	29.19 (6.70)	29.76 (7.55)	0.2335
Duration of MS since diagnosis, years	n=434 4.42 (6.67)	n=434 4.21 (5.94)	0.6314
Duration of MS since first symptoms, years	n=434 7.29 (8.21)	n=434 7.21 (7.66)	0.8871
Number of relapses in the past year	n=430 0.6 (0.95)	n=436 0.6 (0.94)	0.6041
Number of relapses in the past 2 years	n=430 0.9 (1.51)	n=436 0.9 (1.41)	0.9502
EDSS score	n=433 2.36 (1.56)	n=427 2.44 (1.51)	–
T2 lesion volume, cm³	n=431 7.65 (11.60)	n=415 7.44 (10.17)	–
Normalized brain volume, cm³	n=431 1521.42 (83.9)	n=412 1511.19 (90.5)	–
Number of gadolinium-enhancing lesions	n=429 1.08 (3.75)	n=414 0.85 (3.03)	–

[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.
BMI, body mass index; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale.

Lymphocyte counts

- In the fingolimod group, mean ALC decreased by approximately 73% from baseline after 1 month and remained stable thereafter (**Figure 2**); only a small fluctuation in mean ALC was observed in the iDMT group.
- 97.2% of patients (n=417) randomized to fingolimod had ALCs below normal, and 22.6% (n=97) had very low ALCs at ≥1 study visit while on randomized treatment (**Figure 3**).
- 91.6% of patients (n=384) randomized to iDMTs had normal ALCs (**Figure 3**).

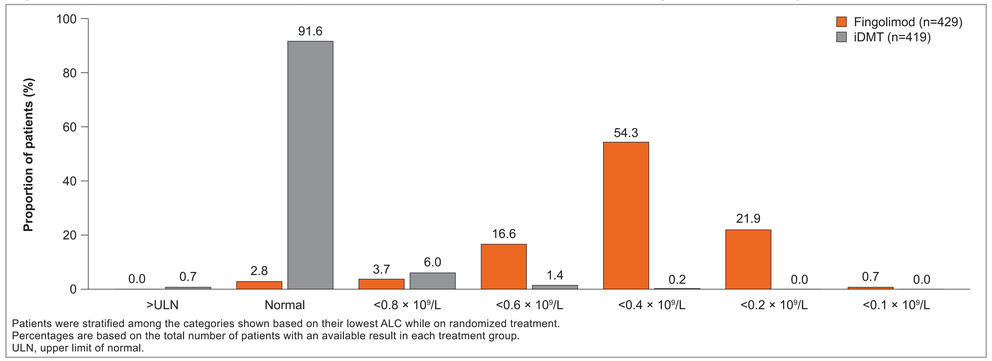
Figure 2. Change from baseline in mean ALC throughout the PREFER*MS* study



Infection-related AEs

- Mean duration of exposure to randomized treatment was 301 days for fingolimod and 163 days for iDMTs.
- Overall exposure-adjusted infection rates were similar in both treatment groups (0.586 vs 0.592/patient-year; **Table 2**).
  - Rates of the selected infection-related AEs were similar in the 2 groups, or lower in the fingolimod group than in the iDMT group.
  - No cases of opportunistic infections were reported.
- The overall rate at which patients experienced serious infection-related AEs in the fingolimod group was low (0.019/patient-year).

Figure 3. Proportions of patients with reduced, normal and elevated ALCs on randomized treatment during the PREFER*MS* study



Patients were stratified among the categories shown based on their lowest ALC while on randomized treatment.
Percentages are based on the total number of patients with an available result in each treatment group.
ULN, upper limit of normal.

Table 2. Frequencies and rates of lymphopenia and of the most common[a] infection-related adverse events in PREFER*MS*

	Fingolimod (n=433)		iDMTs (n=428)	
	Frequency, n (%)	Rate, n/patient-year	Frequency, n (%)	Rate, n/patient-year
Lymphopenia[b]	30 (6.9)	0.087	1 (0.2)	0.005
Decreased lymphocyte count[b]	23 (5.3)	0.066	0 (0.0)	0.000
Any infection	160 (37.0)	0.586	98 (22.9)	0.592
Nasopharyngitis	41 (9.5)	0.121	22 (5.1)	0.113
Sinusitis	28 (6.5)	0.081	21 (4.9)	0.108
Upper respiratory tract infection	27 (6.2)	0.077	21 (4.9)	0.108
Urinary tract infection	23 (5.3)	0.066	16 (3.7)	0.082

[a]At least 5% of patients in either treatment group.
[b]Terms used by the investigators.

- In 7 patients (1.6%), pneumonia (n=2) and bacteremia, *Campylobacter* gastroenteritis, cellulitis, pneumonia (influenza), acute pyelonephritis, tooth abscess and viral infection (all n=1) were reported.
- In 6 of these patients, there was no evidence of total ALC below 0.2 × 10^9/L at any study visit.
- No serious infection-related AEs were reported in the iDMT group.
- Differences in treatment exposure may contribute to the numerical difference in serious infection-related AEs between groups.

Conclusions

- Consistent with its mechanism of action, fingolimod reduced ALCs and was associated with a higher frequency of lymphopenia compared with iDMTs.
- Reported rates of infection-related AEs were similar in the fingolimod and iDMT groups.
- No association was observed between the incidence of infection-related serious AEs and reduced ALCs in the fingolimod group.

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Disclosures

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