Analysis of Lymphocyte Counts and Infection Rates With Fingolimod in Patients With Primary Progressive Multiple Sclerosis Over the INFORMS Trial

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Introduction

- Fingolimod 0.5 mg is a once-daily oral sphingosine 1-phosphate (S1P) receptor modulator for treatment of relapsing forms of multiple sclerosis (MS)[1]
- Therapeutic effects of fingolimod are mediated primarily via functional antagonism of S1P1 receptors on lymphocytes[2]
  - Reduced circulating absolute lymphocyte count (ALC) due to inhibition of egress from lymph nodes is an expected pharmacodynamic effect of fingolimod treatment[2,3]
- Clinical trial data from patients with relapsing MS who received fingolimod have not demonstrated an association between reduced ALC and infection rates relative to placebo, although these comparisons were limited to a maximum of 2 years[4]
- Long-term effects of fingolimod were evaluated in the INFORMS trial, a Phase 3, double-blind, randomized study assessing efficacy and safety of fingolimod vs placebo over 36-60 months in patients with primary progressive MS (PPMS)[5]

Objective

- Assess whether extent of reduced ALC is associated with differences in infection rates in patients with PPMS who participated in INFORMS

Methods

Study design

- Enrolled patients were aged 25-65 years with a clinical diagnosis of PPMS, ≥1 year of disease progression, and at least two of: positive brain magnetic resonance imaging (MRI) scan, positive spinal cord MRI or positive cerebrospinal fluid[5]
- Patients were randomized 1:1 to oral fingolimod or placebo for 36-60 months[5]
  - A small cohort of patients was initially randomized to fingolimod 1.25 mg (n=147); however this group was switched to fingolimod 0.5 mg once this was the dose selected for regulatory approval
- ALC was measured at baseline and each study visit, and 3 months after the end of treatment[5]
  - Study drug was interrupted for patients with confirmed on-study ALC <0.2 ×10^9/L[5]
  - Recovery of ALC was assessed for all patients who discontinued fingolimod and had at least one follow-up assessment[5]

Analyses

- Summary statistics were calculated for ALC, and number and percentage of patients with ALC <0.2 ×10^9/L (by visit and by year)
- Rates of infection-related adverse events (AEs) per 100 patient-years were assessed post hoc for subgroups of patients stratified by on-study nadir ALC, as well as for the overall fingolimod and placebo groups
  - Frequency of infection-related AEs was calculated as percentage of patients experiencing between 0 and ≥10 events

Results

Patients

- In total, 336 patients received fingolimod 0.5 mg (exposure: 908.1 patient-years) and 487 patients received placebo (exposure: 1423.5 patient-years)
- Demographics and baseline characteristics were similar between treatment groups (**Table 1**)[5]

Reduction in ALC on treatment

- Mean (standard deviation) ALC was 1.8 (0.5) ×10^9/L at baseline and 0.6 (0.2) ×10^9/L at 2 weeks after fingolimod initiation (**Figure 1**)
  - Mean ALC reductions remained stable during the 4-year treatment period (**Figure 1**)
- Long-term fingolimod treatment did not appear to be associated with increased risk of ALC falling below the study drug interruption threshold of <0.2 ×10^9/L (**Figure 1**)
  - From 2 months, the proportion of patients with ALC <0.2 ×10^9/L at any visit was low (2.5-6.8%)
  - Only one patient discontinued fingolimod owing to reduced ALC

Recovery of ALC following treatment discontinuation

- At month 3 following treatment discontinuation, the ALC in 81.3% of patients (n/N=74/91) recovered to approximately 75% of mean baseline value (1.4 [0.6] ×10^9/L; **Figure 2**)

Overall safety profile

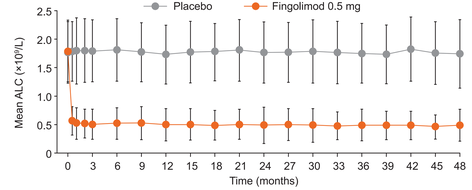
- Rates (95% confidence interval [CI]) of infection-related AEs per 100 patient-years were similar with fingolimod and placebo (53.6 [46.9-61.0] vs 51.9 [46.5-57.7]; **Table 2**)
  - Rates were also similar when stratifying patients according to nadir ALC subgroup
- With fingolimod, there was no apparent relationship between nadir ALC and frequency of infection-related AEs (**Figure 3A**)
- With fingolimod, there was no apparent relationship between nadir ALC and rates (95% CI) per 100 patient-years of infection-related AEs; rates were broadly similar to those for the overall fingolimod and placebo groups
  - Any infection-related AE: 38.1-66.3 in nadir ALC subgroups; overall fingolimod group, 53.6 (46.9-61.0); placebo, 51.9 (46.5-57.7; **Figure 3B**)
  - Respiratory tract infections: 6.8-24.9 in nadir ALC subgroups; overall fingolimod group, 16.4 (13.5-19.7); placebo, 18.1 (15.6-20.9; **Figure 3C**)
  - Herpes infections: 0.0-4.2 in nadir ALC subgroups; overall fingolimod group, 2.5 (1.6-3.8); placebo, 2.5 (1.7-3.5; **Figure 3C**)
- This trend was supported by data from patients who received fingolimod 1.25 mg
  - No association was observed between the incidences of overall infection and nadir ALC
  - Nadir ALC <0.2 ×10^9/L: 60 (29.9-107.3), n=27; nadir ALC 0.3-0.4 ×10^9/L: 124.7 (71.3-202.4), n=28; nadir ALC >0.7 ×10^9/L: 46.2 (1.17-257.6), n=5

Table 1. Demographics and baseline characteristics

Characteristic	Fingolimod 0.5 mg (n=336)	Placebo (n=487)
Age, years	48.5 (8.6)	48.5 (8.3)
Sex, n (%)		
Male	173 (51)	252 (52)
Female	163 (49)	235 (48)
Race, n (%)		
Caucasian	324 (96)	467 (96)
Black	7 (2)	6 (1)
Asian	0	4 (1)
Other	5 (1)	10 (2)
Disease duration since diagnosis, years	2.80 (2.6)	2.91 (2.3)
Disease duration since onset of first symptom, years	5.8 (2.5)	5.9 (2.4)
EDSS score	4.70 (1.03)	4.66 (1.03)
History of DMT use		
Treatment-naïve	272 (81)	372 (76)
Any interferon beta	36 (11)	66 (14)
Natalizumab	3 (1)	2 (<1)
Glatiramer acetate	26 (8)	33 (7)
Other MS medicines	19 (6)	36 (7)
Normalized brain volume, cm^3	n=335 1490.9 (86.5)	n=483 1491.7 (84.9)
Total volume of T2 lesions, mm^3	n=336 9442.7 (10 179.7)	n=485 10 038.2 (13 030.9)
Number of Gd+ lesions	n=336 0.3 (1.10)	n=484 0.3 (1.03)

Data are mean (SD) unless stated otherwise
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; SD, standard deviation

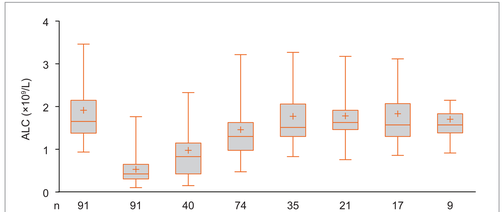
Figure 1. Reduction in ALC while on treatment



Time on fingolimod 0.5 mg, months	0	0.5	1	2	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
n	336	320	318	319	320	301	291	282	270	264	254	251	238	233	230	227	171	123	89	59
Percentage of patients with count <0.2 ×10^9/L	–	0.9	3.1	2.5	2.5	4.7	6.2	6.4	4.4	4.2	3.9	4.4	4.2	5.6	5.7	5.3	4.7	4.9	3.4	6.8

Data are mean ± standard deviation
ALC, absolute lymphocyte count

Figure 2. Recovery of ALC following treatment discontinuation



ALC (×10^9/L)	Baseline (study entry)	Last value on fingolimod	1-45	46-135 (Month 3)	136-270 (Month 6)	271-540 (Month 12)	541-900 (Month 24)	901-1260 (Month 36)
Mean	1.8	0.5	0.9	1.4	1.7	1.8	1.7	1.5
Median	1.7	0.4	0.8	1.3	1.5	1.6	1.6	1.6

Days after fingolimod discontinuation

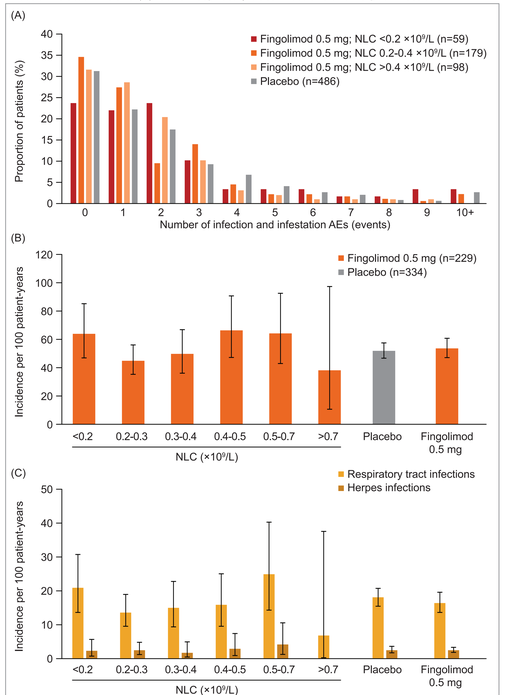
Non-uniform time axis; +, mean; middle bar, median; box, Q1-Q3 interval; whisker, range
ALC, absolute lymphocyte count

Table 2. Infection-related AE rates by nadir ALC

Number of patients (incidence per 100 patient-years)	Fingolimod 0.5 mg, nadir ALC <0.2 ×10^9/L (n=59)	Fingolimod 0.5 mg, nadir ALC 0.2-0.4 ×10^9/L (n=179)	Fingolimod 0.5 mg, nadir ALC >0.4 ×10^9/L (n=98)	Fingolimod 0.5 mg, all patients (n=336)	Placebo, all patients (n=487)
Any infection or infestation[a]	**45 (63.9)**	**117 (46.3)**	**67 (64.5)**	**229 (53.6)**	**334 (51.9)**
Nasopharyngitis	1 (0.5)	3 (0.6)	1 (0.4)	5 (0.5)	11 (0.7)
Urinary tract infection	11 (6.7)	29 (6.1)	10 (4.2)	50 (5.7)	79 (5.9)
Upper respiratory tract infection	8 (4.9)	20 (4.1)	9 (3.9)	37 (4.2)	58 (4.2)
Influenza	3 (1.7)	12 (2.4)	14 (6.6)	29 (3.2)	43 (3.1)
Bronchitis	6 (3.5)	7 (1.4)	3 (1.2)	16 (1.7)	21 (1.4)
Gastroenteritis	2 (1.1)	9 (1.7)	3 (1.2)	14 (1.5)	23 (1.6)
Sinusitis	6 (3.5)	5 (1.0)	3 (1.2)	14 (1.5)	14 (1.0)
Oral herpes	3 (1.7)	6 (1.2)	4 (1.7)	13 (1.4)	23 (1.6)
Herpes zoster	1 (0.5)	5 (1.0)	4 (1.6)	10 (1.1)	9 (0.6)
Tooth infection	0 (0.0)	8 (1.6)	2 (0.8)	10 (1.1)	5 (0.3)
Cystitis	1 (0.5)	6 (1.2)	2 (0.8)	9 (1.0)	18 (1.2)
Onychomycosis	1 (0.5)	4 (0.8)	2 (0.8)	7 (0.7)	11 (0.7)
Rhinitis	2 (1.1)	3 (0.6)	3 (1.2)	8 (0.8)	17 (1.2)
Gastroenteritis viral	0 (0.0)	4 (0.8)	3 (1.2)	7 (0.7)	9 (0.6)
Respiratory tract infection	1 (0.5)	4 (0.8)	2 (0.8)	7 (0.7)	12 (0.8)
Folliculitis	0 (0.0)	4 (0.8)	2 (0.8)	6 (0.6)	10 (0.7)
Pharyngitis	2 (1.1)	3 (0.6)	0 (0.0)	5 (0.5)	14 (1.0)
Lower respiratory tract infection	0 (0.0)	3 (0.6)	1 (0.4)	4 (0.4)	12 (0.8)

[a]Infections/infestations occurring in ≥2% of patients in the placebo group or in any of the fingolimod 0.5 mg groups
AEs were coded using the Medical Dictionary for Regulatory Activities version 17.1 terminology
AE, adverse event; ALC, absolute lymphocyte count

Figure 3. (A) Proportion of patients experiencing infection-related AEs, (B) rate of overall infection-related AEs and (C) rate of respiratory tract infections and herpes infections



Error bars show 95% confidence intervals
AE, adverse event; NLC, nadir lymphocyte count

Conclusions

- Fingolimod-associated reductions in ALC (to <0.2 ×10^9/L) did not appear to be associated with an increased risk of infection in patients with PPMS
- These data demonstrate that there was no relationship between the magnitude of ALC reduction with fingolimod and rate of infection-related AEs, respiratory tract infections or herpes infections

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