Relapse outcomes in patients with multiple sclerosis treated with fingolimod by previous treatment with injectable disease-modifying therapies

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CONCLUSIONS

- **Across clinical trials, treatment with fingolimod 0.5 mg consistently reduced ARRs compared with placebo and IFNβ-1a IM in patients with RRMS**
- **Among patients who had discontinued previous DMTs before study entry, those who were treated with fingolimod had greater improvements in ARR than those who received placebo or IFNβ-1a IM**
- **The greatest improvements in ARR with fingolimod compared with placebo and IFNβ-1a IM were seen in patients who were treatment-naïve, which may have important implications for treatment selection early in MS**

INTRODUCTION

- Increased relapse frequency early in the course of MS is associated with long-term disability,[1] and higher annualized relapse rates (ARRs) correlate with poorer outcomes[2]
- In phase 3 clinical trials, fingolimod significantly reduced ARRs in patients with relapsing–remitting multiple sclerosis (RRMS) compared with placebo in FREEDOMS and FREEDOMS II, and with interferon (IFN) β-1a IM in TRANSFORMS[3–5]
- Pooling data from FREEDOMS, FREEDOMS II and TRANSFORMS provided a larger study population than was available from the individual studies for *post hoc* analyses of the efficacy of fingolimod in patients with suboptimal response to previous disease-modifying therapies (DMTs)
  - Analyses of patient subgroups (predefined by age, sex, treatment history and baseline disease characteristics) are provided in poster DX18
  - Analyses of patient subgroups according to disease duration are provided in poster DX62

OBJECTIVES

- To assess the effects of oral fingolimod treatment on ARRs in patients with RRMS according to treatment history (categorized as patients who were naïve to previous treatment with IFNβ-1a IM or glatiramer acetate [GA], or who had discontinued previous treatment with these agents)

METHODS

Study designs and participants

- The pooled analyses included patients who had been randomized to receive oral fingolimod 0.5 mg or placebo once daily for 2 years in FREEDOMS and FREEDOMS II,[6,7] or to receive oral fingolimod 0.5 mg once daily or IFNβ-1a IM 30 µg once weekly for 1 year in TRANSFORMS[8]
- Patients were aged 18–55 years, had been diagnosed with RRMS in accordance with the 2005 revised McDonald criteria[9], had one or more confirmed relapses in the previous year or two or more in the previous 2 years, and had a score of 0–5.5 on the Expanded Disability Status Scale (EDSS)

Analyses

- Patient subgroups were defined according to:
  - Whether or not injectable therapies for RRMS had been received before study entry (IFN-treated versus IFN-naïve[a]; GA-treated versus GA-naïve[b])
  - Reasons for discontinuation of previous treatment (unsatisfactory therapeutic effect versus reasons other than unsatisfactory therapeutic effect, and adverse event [AE] versus reasons other than AE)
- Subgroup analyses were performed on the intention-to-treat populations pooled from all three trials
- ARRs were obtained using a negative binomial regression model with study, treatment, subgroup and treatment-by-subgroup as explanatory variables
- 95% CIs are presented and p values indicate the statistical significance of treatment differences; p values were hypothesis generated only and no adjustments were made for multiple comparisons

[a]IFN-naïve patients did not receive an IFN before study entry, but could have received other treatments
[b]GA-naïve patients did not receive GA before study entry, but could have received other treatments

RESULTS

Study population

- In total, 2416 patients were included in the pooled analyses: 1212 in the fingolimod 0.5 mg group, 773 in the placebo group and 431 in the IFNβ-1a IM group. **Table 1** presents patient disposition and study drug exposure
- Baseline demographics and disease characteristics were similar across treatment groups (**Table 2**)

Annualized relapse rates

- Irrespective of treatment status at baseline (i.e. treatment-naïve or previously treated), and of the type of previous DMT, ARRs were significantly lower in patients treated with fingolimod 0.5 mg than in those who received placebo or IFNβ-1a IM (**Figure 1**)
- In patients who were IFN-naïve at baseline, fingolimod significantly reduced ARR relative to placebo (59%; p<0.001) and to IFNβ-1a IM (42%; p=0.001); ARR reductions of 49% versus both placebo (p<0.001) and IFNβ-1a IM (p<0.001) were observed in patients who had previously received IFNβ-1a IM
- Similar results were observed for fingolimod-treated patients who had previously received GA: relative to placebo and to IFNβ-1a IM, fingolimod treatment reduced ARR by 42% (p<0.001) and 44% (p<0.05), respectively. In GA-naïve patients, ARR was reduced by 58% (p<0.001) and 46% (p<0.001), respectively
- Fingolimod therapy led to significant relative reductions in ARR among patients who had discontinued their previous DMT owing to an unsatisfactory therapeutic effect (54% [p<0.001] versus placebo; 53% [p=0.009] versus IFNβ-1a IM), and among those who had discontinued owing to an AE (37% [p=0.002] and 36% [p=0.090], respectively)

Table 1. Patient disposition and study drug exposure (randomized population)

	Placebo (n=773)	IFNβ-1a IM (n=435)	Fingolimod 0.5 mg (n=1214)
Completed study, n (%)	587 (75.9)	386 (88.7)	1039 (85.6)
On study drug	535 (69.2)	380 (87.4)	972 (80.1)
Off study drug	52 (6.7)	6 (1.4)	67 (5.5)
Discontinued from the study, n (%)	186 (24.1)	49 (11.3)	175 (14.4)
Abnormal laboratory value	3 (0.4)	1 (0.2)	29 (2.4)
Abnormal test procedure	2 (0.3)	3 (0.7)	6 (0.5)
Administrative problem	5 (0.6)	7 (1.6)	5 (0.4)
Adverse event	34 (4.4)	9 (2.1)	44 (3.6)
Death	2 (0.3)	0	0
Lost to follow-up	28 (3.6)	4 (0.9)	19 (1.6)
Protocol violation	6 (0.8)	2 (0.5)	7 (0.6)
Consent withdrawn	63 (8.2)	16 (3.7)	50 (4.1)
Condition no longer required study drug	1 (0.1)	0	0
Unsatisfactory therapeutic effect	42 (5.4)	7 (1.6)	15 (1.2)
Drug exposure, days[a]			
Mean (SD)	596 (223)	337 (81)	517 (221)
Median (interquartile range)	719 (497–731)	361 (351–370)	576 (363–723)
Drug exposure, patient-years[b]	1261	398	1716

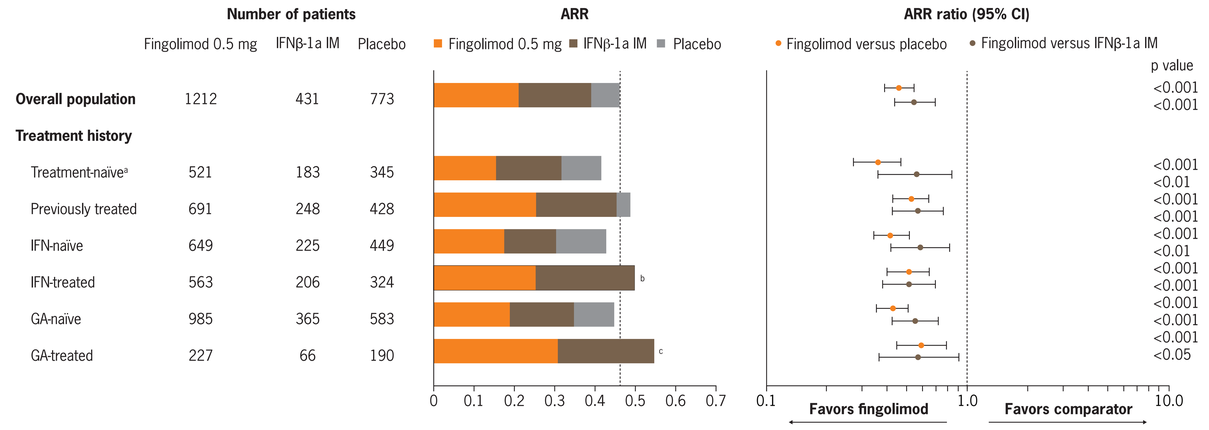
[a]Number of days on study drug
[b]Patient-years calculated as the sum of the number of days on study drug for all patients in the group divided by 365.25 days

Table 2. Baseline demographics and patient characteristics (randomized population)

	Placebo (n=773)	IFNβ-1a IM (n=435)	Fingolimod 0.5 mg (n=1214)
Baseline demographic factors			
Age, years	38.6 (8.6)	36.0 (8.3)	37.8 (8.9)
Sex, female, n (%)	586 (75.8)	295 (67.8)	853 (70.3)
Baseline disease characteristics			
Time since diagnosis, years	5.7 (5.5)	4.9 (5.4)	5.2 (5.3)
Number of relapses within past year	1.5 (0.8)	1.5 (0.8)	1.5 (1.0)
Number of relapses within past 2 years	2.2 (1.3)	2.3 (1.2)	2.2 (1.7)
EDSS score	2.5 (1.3)	2.2 (1.3)	2.3 (1.3)
Number of Gd-enhancing lesions at baseline	1.2 (3.1)	1.1 (2.8)	1.3 (4.1)
Treatment history			
Treatment-naïve,[a] n (%)	345 (44.6)	190 (43.7)	531 (43.7)
Previous MS treatment, n (%)			
Glatiramer acetate	190 (24.6)	67 (15.4)	228 (18.8)
IFNβ-1a SC	143 (18.5)	72 (16.6)	236 (19.4)
IFNβ-1a IM	185 (23.9)	118 (27.1)	313 (25.8)
IFNβ-1b SC	120 (15.5)	69 (15.9)	173 (14.3)
Natalizumab	25 (3.2)	1 (0.2)	25 (2.1)
Other	79 (10.2)	16 (3.7)	87 (7.2)

All values are presented as mean (SD) unless otherwise stated
[a]Treatment-naïve patients were defined as those who had not previously received any drugs for the treatment of MS, according to MS history case report forms

Figure 1. ARRs in patient subgroups defined by treatment history (intention-to-treat population)



ARRs for different treatment groups in the histogram are superimposed
[a]Treatment-naïve patients were defined as those who had not previously received any drugs for the treatment of MS, according to MS history case report forms
[b]ARRs were 0.498 for both IFNβ-1a IM and placebo groups. Only the IFNβ-1a IM ARR is displayed
[c]ARR was 0.547 for the IFNβ-1a IM group and 0.527 for the placebo group. Only the IFNβ-1a IM ARR is displayed

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