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Effect of switching from intramuscular interferon β-1a to oral fingolimod on time to relapse in patients with relapsing–remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS

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ABSTRACT

Background: In the absence of controlled, parallel-group studies, statistical methods developed to estimate treatment effects in patients receiving alternative/rescue treatment in clinical trials may be used to estimate the effects of multiple sclerosis (MS) therapy switch using available clinical trial data.
Objective: To use TRANSFORMS data and parametric models to assess the time to first confirmed relapse in MS patients who switched from intramuscular interferon β-1a (IFNβ-1a IM) 30 μg/mL once weekly to oral fingolimod 0.5 or 1.25 mg once daily vs. remaining on IFNβ-1a IM.
Methods: Post hoc analyses were conducted using data from the intent-to-treat population. The Branson and Whitehead switch model with iterative parameter estimation was used to estimate the ratio of the observed time to first confirmed relapse over the estimated time.
Results: Log-linear regression model results showed that fingolimod 0.5 and 1.25 mg prolonged time to relapse, with an estimated median time to first relapse of 5.07 years ($P = 0.0026$ vs. IFNβ-1a IM) and 4.11 years ($P = 0.0113$), respectively, versus 2.26 years with IFNβ-1a IM. The estimated ratio of observed time to first confirmed relapse to the estimated time had the patient remained on IFNβ-1a IM was 2.09 (95% CI, 1.45–3.04) for switching to fingolimod 0.5 mg and 1.84 (95% CI, 1.30–2.65) for switching to fingolimod 1.25 mg.
Conclusion: During the extension, time to first confirmed relapse was approximately doubled in patients switching from IFNβ-1a IM to fingolimod. These analytic methods may be useful in evaluating treatment switch effects in clinical trials with extension data.

1. Introduction

Prevention or delay of relapse is a major treatment goal of disease-modifying therapy (DMT) for patients with multiple sclerosis (MS) [1–3]. To evaluate efficacy, clinical trials of DMTs in patients with MS routinely examine treatment effects on relapse rates as a primary measure [4]. These trials are often designed with a core treatment phase, wherein patients are randomized to the investigational drug or control [5–11]; upon

Abbreviations: DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; IFNβ-1a, interferon beta-1a; IM, intramuscular; MS, multiple sclerosis; TRANSFORMS, Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing–Remitting Multiple Sclerosis.

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completion of the core phase, patients originally randomized to the control group may be offered the opportunity to receive the investigational drug during an extension phase [12–14].

From a study design perspective, it would be preferable to prospectively re-randomize patients at the time of a treatment switch to evaluate comparative outcomes after changing therapy. This would entail some patients switching from the control to the investigational treatment, some remaining on the control and some continuing on with the investigational treatment. However, even basic clinical trial designs in MS are operationally challenging to execute, and such an approach is not common practice.

In the absence of controlled, parallel-group studies designed to evaluate relapse-related outcomes after a DMT switch, statistical methods originally developed to estimate treatment effects in patients receiving alternative or rescue treatment in clinical trials may have applicability in estimating the effects of such a therapy switch based on the available clinical trial and extension data [15]. Fingolimod is an oral, once-daily sphingosine 1-phosphate receptor modulator approved (at a dose of 0.5 mg/day) in the United States and more than 70 other countries for treatment of relapsing forms of MS. In the pivotal, 12-month, phase 3 Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS; NCT00340834) study, fingolimod 0.5 or 1.25 mg daily demonstrated superiority to IFNβ-1a intramuscular (IM) in reducing the rate of relapse and extending the time to first confirmed relapse [10]. In a 1-year extension of TRANSFORMS, patients switching from IFNβ-1a IM treatment to fingolimod 0.5 or 1.25 mg daily exhibited further within-group annualized relapse rate (ARR) reductions compared with the previous 12-month core phase, suggesting that switching to fingolimod may provide additional clinical benefit in patients receiving IFNβ-1a IM [13].

The current analysis used data from the IFNβ-1a IM treatment group in the TRANSFORMS core study to predict the time to first confirmed relapse had the patient not switched to fingolimod during the extension phase and compared it with the actual observed time to first confirmed relapse after switching from IFNβ-1a IM to fingolimod.

2. Materials and methods

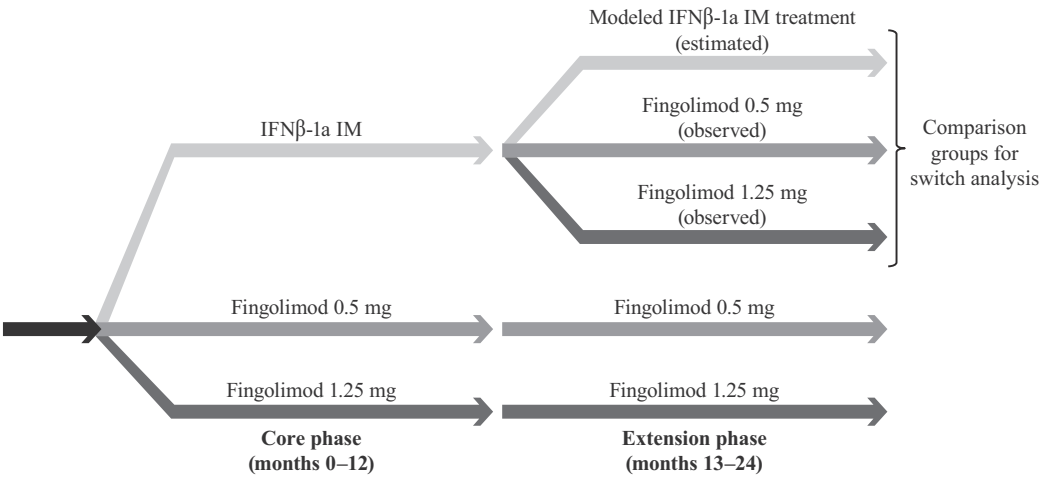
2.1. Study design

TRANSFORMS (N = 1292) was a 12-month, phase 3, randomized, double-blind, double-dummy study of fingolimod 0.5 or 1.25 mg once daily versus IFNβ-1a IM 30 μg once weekly [10] with an optional 1-year extension (Fig. 1) [13]. In the extension study, patients receiving IFNβ-1a IM during the core phase of the original study were randomly reassigned to fingolimod 0.5 or 1.25 mg, and patients receiving fingolimod during the core phase continued treatment at the previously assigned dose. Key inclusion criteria were age 18 to 55 years and diagnosis of MS according to revised McDonald criteria [16] with a relapsing–remitting course, ≥1 documented relapse in the previous year or ≥2 relapses in the previous 2 years, and an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 [17]. Relapse was defined as new, worsening, or recurrent neurologic symptoms ≥30 days after onset of a preceding relapse without fever or infection, with at least a half-point increase on the EDSS, a ≥1-point increase in 2 functional system scores, or a ≥2-point increase in 1 functional system score (excluding bowel/bladder and cognition).

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki, and the study protocol was approved by each institution. All patients gave written informed consent.

2.2. Analysis

These post hoc analyses were based on 24-month data (core + extension) for patients in the intent-to-treat population. Log-linear regression models were employed to better describe the relationship between time to first confirmed relapse and treatment. The analyses started with an assumption of a Weibull distribution for time to relapse, known as an accelerated failure time model. The survival function S(t) was estimated from the data set and plotted as log(−log(S(t)))



IFN=interferon; IM=intramuscular.

Fig. 1. Design of TRANSFORMS study and switch analysis.

versus log(t). Resultant plots were approximately linear, justifying the Weibull distribution assumption. The LIFEREG procedure within SAS software (SAS Institute Inc., Cary, NC) was used to estimate the median time to relapse during core phase. Predicted time to first confirmed relapse was calculated using the log-linear regression model assuming Weibull distribution for time to confirmed relapse, with treatment as a lone explanatory variable (Model 1). A second model with treatment, country, number of relapses in the 2 years before enrollment in the core phase, and core phase baseline EDSS score as explanatory variables was used for prediction of time to first confirmed relapse and treatment comparisons. Statistical comparisons of estimated median time to first relapse were performed using z-test. No adjustment was made for multiplicity.

The Branson and Whitehead switch model with iterative parameter estimation [15] was used to estimate the time to relapse during the extension phase in patients who switched from IFNβ-1a IM to fingolimod 0.5 or 1.25 mg, had these patients not switched treatment and instead remained on IFNβ-1a IM. Each patient contributed a single event (i.e., the first relapse) to the analysis, and the time origin was the time of randomization. The model assumes that relapse rate is constant except for the effects of switching to fingolimod, and the rate of the "slowing down" of relapse was denoted by $\exp(-\eta)$. An initial estimate of $\exp(-\eta)$ was obtained by comparing the groups as randomized using a parametric accelerated failure time model. For a given initial point estimate of $\exp(-\eta)$, the estimated times to relapse of patients who switched from IFNβ-1a IM to fingolimod 0.5 mg or 1.25 mg were transformed using the following formula:

$$\begin{aligned}\text{Estimated time to relapse} &= \text{time to fingolimod switch} \\ &\quad + \exp\left(-\eta_j\right) \\ &\quad \times (\text{observed time to relapse} \\ &\quad - \text{time to fingolimod switch}),\end{aligned}$$

where $j = 1$ or 2 to indicate 0.5 or 1.25 mg group.

Using these transformed times to relapse and the original observed time to relapse for all other patients, the groups were once again compared using the parametric survival analysis. This analysis led to another estimate for $\exp(-\eta)$. This estimate was used in a second transformation of the relapse times of patients who switched treatment in the control group. Once the entire process was repeated several times, the value of $\exp(-\eta)$ used in the transformation was close to the value used in the previous iteration (within 10^{-5}). At that point, the procedure was considered to have converged.

Ratios of the observed time over the estimated time to relapse were calculated; ratios >1 indicate a greater time to relapse with fingolimod after switching from IFNβ-1a IM compared with remaining on IFNβ-1a IM. Four sensitivity analyses were performed. The first assumed a generalized gamma distribution in replacement of a Weibull distribution to test the effects of nature of the data. The second sensitivity analysis excluded the first 1.5, 3, and 6 months of core phase data to account for long-lasting trends in the treatment effect. The third excluded patients who did not enter the extension phase. The fourth ignored relapses during the core phase for patients who had relapsed in the extension phase.

3. Results

The intent-to-treat population included 431 patients who were randomized to IFNβ-1a IM during the core phase; 341 entered the extension, with 167 switching to fingolimod 0.5 mg and 174 switching to fingolimod 1.25 mg. After switching, 31 patients experienced a confirmed relapse, including 16 (9.5%) who switched to fingolimod 0.5 mg and 15 (8.6%) who switched to fingolimod 1.25 mg.

Estimates of Weibull regression parameters for treatments based on core phase data are shown in Table 1. Results obtained from the Weibull regression model demonstrated that fingolimod 0.5 mg ($P < 0.0001$) and fingolimod 1.25 mg ($P = 0.0010$) were associated with a longer time to first confirmed relapse during the core phase compared with IFNβ-1a IM (Fig. 2). The estimated median times to relapse were 2.26 years for IFNβ-1a IM, 5.07 years for fingolimod 0.5 mg ($P = 0.0026$ vs. IFNβ-1a IM), and 4.11 years for fingolimod 1.25 mg ($P = 0.0113$ vs. IFNβ-1a IM).

The estimated delay in time to relapse ranged from 3.1 to 184.4 days for patients switching from IFNβ-1a IM to fingolimod 0.5 mg and from 5.5 to 142.8 days for patients switching from IFNβ-1a IM to fingolimod 1.25 mg. The ratio of the observed time to first confirmed relapse after the switch to fingolimod to the estimated time to relapse if the patient had remained on IFNβ-1a IM was 2.09 (95% CI, 1.45–3.04) for patients switching from IFNβ-1a IM to fingolimod 0.5 mg and 1.84 (95% CI, 1.30–2.65) for patients switching from IFNβ-1a IM to fingolimod 1.25 mg.

Sensitivity analyses of the observed time over the estimated time to relapse demonstrated consistent results. Using the generalized gamma distribution to relax the proportionality assumption, fingolimod 0.5 mg ($P < 0.0001$) and fingolimod 1.25 mg ($P = 0.0007$) were superior to IFNβ-1a IM in delaying the first confirmed relapse during the core phase. The estimated median times to relapse were 1.95 years for IFNβ-1a IM, 4.18 years for fingolimod 0.5 mg ($P = 0.0021$ vs. IFNβ-1a IM), and 3.49 years for fingolimod 1.25 mg ($P = 0.0075$ vs. IFNβ-1a IM; Fig. 3). Among the patients who experienced relapse after switching, the estimated delay in time to relapse ranged from 3.3 to 195.0 days for patients switching to fingolimod 0.5 mg

Table 1
Weibull regression estimates for log (time to first confirmed relapse) during core phase, intent-to-treat population.

Treatment	Estimate	Standard error	95% CI	*P* value
Model 1[a]				
Fingolimod 0.5 mg	0.8462	0.1886	0.4765–1.2159	<0.0001
Fingolimod 1.25 mg	0.6021	0.1802	0.2489–0.9552	0.0008
IFNβ-1a IM (reference)	0	NA	NA	NA
Model 2[b]				
Fingolimod 0.5 mg	0.8095	0.1897	0.4377–1.1812	<0.0001
Fingolimod 1.25 mg	0.6010	0.1828	0.2428–0.9592	0.0010
IFNβ-1a IM (reference)	0	NA	NA	NA

IFN = interferon; IM = intramuscular; NA = not applicable.
[a] Model 1 has treatment, country, number of relapses in the 2 years before enrollment, and core baseline Expanded Disability Status Scale for patients as explanatory variables.
[b] Model 2 has only treatment as the explanatory variable.

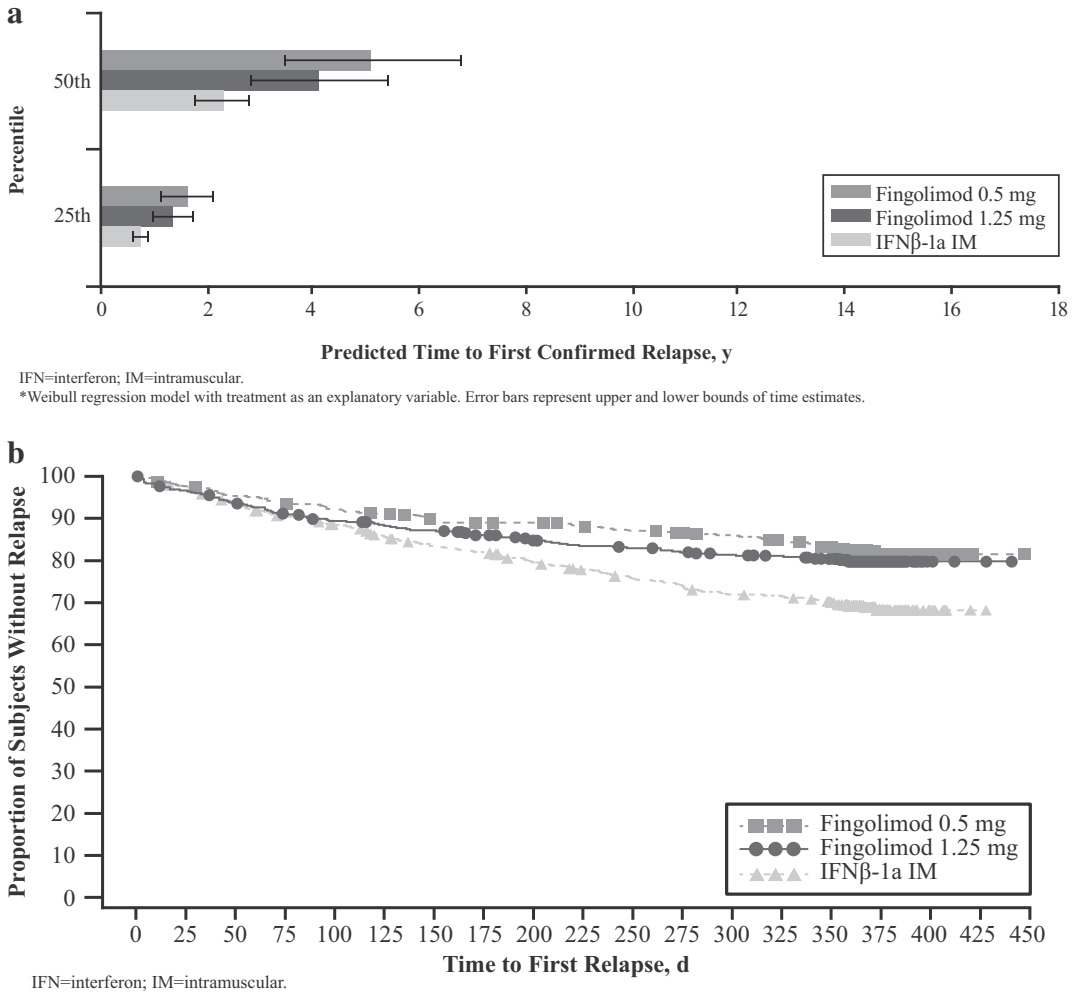


Fig. 2. Predicted time to first confirmed relapse calculated using core phase data and Weibull regression model (a)* and Kaplan–Meier plot of time to first relapse in the core phase (b).

and from 5.4 to 139.7 days for patients switching to fingolimod 1.25 mg. Estimated ratios of observed time to relapse after switching to the estimated time to relapse without switching were 2.23 (95% CI, 1.50–3.32) for fingolimod 0.5 mg and 1.81 (95% CI, 1.19–2.70) for fingolimod 1.25 mg. Further sensitivity analysis excluding data from progressively longer periods of the early core phase continued to indicate a delay in time to first confirmed relapse associated with switching to fingolimod versus remaining on IFNβ-1a IM (Table 2). By excluding the patients who did not enter the extension phase,

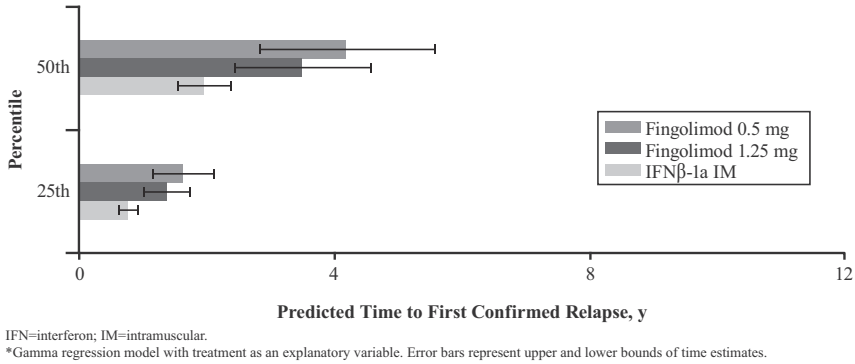


Fig. 3. Predicted time to first confirmed relapse calculated using core phase data and the generalized gamma regression model.*

Table 2
Sensitivity analysis of the ratio of the observed time to first confirmed relapse to the estimated time to first relapse had the patient not switched to fingolimod.

Data exclusion (core phase)	Treatment group	
	IFNβ-1a IM to fingolimod 0.5 mg	IFNβ-1a IM to fingolimod 1.25 mg
No exclusions	2.09	1.84
Months 0–1.5	1.80	1.72
Months 0–3	1.59	1.68
Months 0–6	1.36	1.42

IFN = interferon; IM = intramuscular.

the estimated ratios were 2.24 and 1.96, for fingolimod 0.5 mg and 1.25 mg, respectively. Finally, by ignoring the relapses during the core phase for patients who also had relapse in extension phase (17, 19, and 40 patients in fingolimod 0.5 mg, fingolimod 1.25 mg, and IFNβ-1a IM groups, respectively), the estimated ratios of observed time to relapse after switching to the estimated time to relapse without switching were 1.82 for fingolimod 0.5 mg and 1.63 for fingolimod 1.25 mg.

4. Discussion

In this analysis of the TRANSFORMS trial and extension data, the median time to first relapse was approximately doubled in patients treated with fingolimod 0.5 or 1.25 mg versus IFNβ-1a IM during the core phase; during the extension phase, the observed time to first confirmed relapse after switching from IFNβ-1a IM to fingolimod 0.5 or 1.25 mg was also approximately double the estimated time to relapse had the patient remained on IFNβ-1a IM. These results support the superior efficacy of fingolimod 0.5 and 1.25 mg over IFNβ-1a IM in terms of time to first confirmed relapse during the 1-year core phase and the positive impact of switching from fingolimod to IFNβ-1a IM on time to relapse during the 1-year extension phase. These results further complement previous findings demonstrating a benefit of switching therapy from IFNβ-1a IM to fingolimod [18]. Among patients who switched from IFNβ-1a IM to fingolimod 0.5 or 1.25 mg at the start of the extension phase, ARRs were reduced by 30% and 36%, respectively, during the 12-month extension period compared with the previous 12-month core phase [13]. Furthermore, subgroup analysis of the TRANSFORMS core phase data showed that among patients with a history of IFNβ treatment, fingolimod 0.5 and 1.25 mg significantly reduced ARR by approximately 58% and 39%, respectively, compared with IFNβ-1a IM [18].

Previous analyses of TRANSFORMS core phase data support the idea that the effect of fingolimod on relapse reduction is most apparent in patients with disease activity despite prior treatment with other DMTs [19]. In the proposed model, estimated time to relapse was delayed in all 31 patients who experienced a relapse after switching to fingolimod, compared with if they had continued to receive IFNβ-1a IM. However, the results were based on a modeling approach with an assumption of delay in relapse with switching. Thus, it should not be assumed that every patient switching to fingolimod would experience a delay in relapse compared with continued treatment with IFNβ-1a IM. Although the estimated delay in relapse occurrence ranged from 3 to 184 days for patients switching to the approved 0.5 mg dose of fingolimod, it was not possible to analyze the delay with respect to reason for switching because all patients who received IFNβ-1a IM during the core phase were switched to fingolimod.

To directly address switching outcomes, a preferred study design would include double-blinded re-randomization at the time of a switch, resulting in patients continuing on experimental treatment, switching from control to experimental treatment, or remaining on control treatment. The current modeling of TRANSFORMS core and extension trial data allowed for retrospective evaluation of the effects of remaining on IFNβ-1a IM in the absence of a prospectively designed, double-blinded switch study. This represents one of the earliest applications of the Branson and Whitehead switch model to examine treatment effects in this manner, and may provide a valuable means to evaluate trial extension switch data for other MS therapies by allowing estimation of the treatment benefit in trials that include a rescue treatment for patients in the placebo group for ethical reasons.

Key limitations to this analysis are the 24-month study duration and assumptions inherent in the Branson and Whitehead model that minimize the potential effects of some typical features of trial populations on the model. The model assumes that relapse rate is constant except for the effects of switching, but long-term studies have shown that clinical trial populations have slowly declining relapse rates during continued follow-up, regardless of treatment [20,21]. However, the natural decline in relapse rates during a single year of follow-up and the impact on the rate ratio between groups is likely to have a minimal effect in the assumed model. As suggested by the findings of the sensitivity analysis, the natural decline in relapse rate was not of a great enough magnitude to explain the doubling of time to first confirmed relapse seen after switching to fingolimod in the current analysis.

5. Conclusions

In summary, this report suggests that switching from IFNβ-1a IM to fingolimod 0.5 or 1.25 mg will delay relapse compared with remaining on IFNβ-1a IM. These analytic methods may help clinicians better understand the treatment effects observed after switching therapies, and may be useful in evaluating trial extension switch data for other MS treatments.

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