

A comparison of multiple sclerosis disease activity after discontinuation of fingolimod and placebo

Patrick Vermersch, Ernst-Wilhelm Radue, Norman Putzki, Shannon Ritter, Martin Merschhemke and Mark S Freedman

Multiple Sclerosis Journal –
Experimental, Translational
and Clinical

July–September 2017: 1–10

DOI: 10.1177/
2055217317730096

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Abstract

Background: Cases of higher-than-expected disease activity have been reported following fingolimod discontinuation.

Objective: The objective of this paper is to assess the risk of substantially higher-than-expected disease activity post-study drug discontinuation (SDD) at the individual patient level using data from the Phase III, placebo-controlled FREEDOMS and FREEDOMS II trials.

Methods: Baseline gadolinium-enhancing T1-lesion volumes were used to statistically model the expected level of MRI disease activity post-SDD. Patients exceeding this level were classed as “MRI outliers.” Patients with an unusually high increase in Expanded Disability Status Scale score, hospitalization for relapse, severe relapse, or relapse with incomplete recovery post-SDD were classed as “clinical outliers.”

Results: In FREEDOMS, the number of MRI outliers post-SDD was 2/69 (2.9%), 1/65 (1.5%) and 7/83 (8.4%) for the placebo, fingolimod 0.5 mg, and fingolimod 1.25 mg groups, respectively. In FREEDOMS II, the corresponding numbers were 4/72 (5.6%), 6/79 (7.6%) and 3/73 (4.1%). The number of clinical outliers across both trials was low. No consistent evidence of placebo vs fingolimod, dose-related or inter-trial patterns was discernable.

Conclusion: The low number of clinical and MRI outliers and lack of any discernible pattern within and between trials, including between placebo and fingolimod, argues against a systematic risk of higher-than-expected recurrence of disease activity following discontinuation of fingolimod.

Keywords: Fingolimod, multiple sclerosis, discontinuation, rebound, safety

Date received: 21 December 2016; accepted: 19 July 2017

Introduction

Recurrence of disease activity following cessation of disease-modifying therapy (DMT) in patients with relapsing–remitting multiple sclerosis (RRMS) is to be expected. However, concern may be raised when the level of recurrent disease activity exceeds that observed prior to starting therapy, a phenomenon often referred to as “rebound effect” or “rebound syndrome.”

The risk of a rebound effect has been comprehensively discussed in the context of withdrawal from natalizumab.^{1–8} In a series of 68 patients undergoing natalizumab treatment interruption, seven (10%) experienced severe disease “flares.”⁵ A separate analysis of 47 cases of withdrawal from natalizumab

found that 18 patients (38.3%) had either radiological or clinical disease activity that exceeded the pre-treatment period.⁸

Sorensen et al. (2014), however, who systematically evaluated a large, unselected cohort of 375 patients who discontinued natalizumab therapy, highlighted some of the issues associated with the study of “rebounds.”⁷ Their results show that, although the average relapse rate increased at Month 3 after discontinuation of natalizumab, it never reached the same magnitude as before natalizumab therapy. In addition, these authors pointed out that the relapse activity observed after natalizumab discontinuation includes a period in which the patients were essentially untreated, whereas the pre-natalizumab activity

Correspondence to:
Patrick Vermersch
University of Lille,
Department of Neurology,
Hôpital Roger Salengro,
CHRU Lille, 2 Rue Emile
Laine, Lille cedex, 59037,
France.
[patrick.vermersch@
univ-lille2.fr](mailto:patrick.vermersch@univ-lille2.fr)

Patrick Vermersch,
University of Lille, CHU
Lille, LIRIC – INSERM
U995, FHU Imminent,
France

Ernst-Wilhelm Radue,
Medical Image Analysis
Center, University Hospital
Basel, Switzerland

Norman Putzki,
Novartis Pharmaceuticals
Corporation, USA



Shannon Ritter,
Novartis Pharmaceuticals
Corporation, USA

Martin Merschhemke,
Novartis Pharma AG,
Switzerland

Mark S Freedman,
University of Ottawa, The
Ottawa Hospital Research
Institute, Canada

data were obtained for a period in which the vast majority of patients were on an active treatment.⁷

Recently, individual case reports of an unexpectedly high level of disease activity have been reported in relation to the withdrawal of fingolimod, a DMT that significantly reduces the frequency of relapses and of magnetic resonance imaging (MRI) lesion activity in patients with RRMS.^{9–16} These case reports now raise the question of whether there is a systematic risk of higher-than-expected disease activity following withdrawal of fingolimod.

The objective of this analysis is to explore the patterns of unexpectedly high disease activity observed at an individual patient level following fingolimod cessation. The individual risk of unexpectedly high disease activity post-study drug discontinuation (SDD) is addressed using data from two similarly designed Phase III clinical trials: FREEDOMS¹⁷ and FREEDOMS II.¹⁸ The identification of individuals with higher-than-expected post-SDD disease activity is based on specific criteria relating to clinical (severe relapses) and MRI measures. For the purpose of this analysis, patients meeting these criteria were referred to as “outliers.” This outlier analysis allows a scientifically robust comparison of unexpectedly high disease activity following withdrawal of fingolimod vs withdrawal of placebo within each clinical trial and at the individual patient level.

Group-level relapse rates and MRI measures following discontinuation of fingolimod vs placebo will also be presented to support and complement these individual-patient-level results.

Materials and methods

FREEDOMS and FREEDOMS II had very similar placebo-controlled study designs and inclusion criteria. This allowed the exploration of two aspects of disease activity following treatment withdrawal: (a) the frequency and severity of higher-than-expected disease activity within each treatment group of FREEDOMS and FREEDOMS II, and (b) the consistency of the pattern of any higher-than-expected disease activity across the two studies.

Both studies were conducted in compliance with the tenets of the Declaration of Helsinki. Approvals were obtained from the independent ethics committees or institutional review boards and all patients provided written informed consent before enrollment into the trials.

In both FREEDOMS and FREEDOMS II, disease activity data, including relapses and MRI scans, were collected for at least three months after withdrawal (follow-up data at three-month follow-up visit, with a visit window of Day 46 to Day 104) and were collected beyond this point in time and up to seven months (210 days) after SDD when available. The number of patients available for follow-up at 90 days and 210 days in each study are outlined in Supplementary Table e1.

MRI analysis

To analyze and compare MRI disease activity following SDD at the individual patient level, baseline gadolinium (Gd)-enhancing T1-lesion volume data from each study were used to generate prediction intervals assuming a normal distribution, and were derived as: $\text{mean} \pm z(\alpha/2) \times \text{standard deviation (SD)}$. An outlier was defined as a patient with an increase in Gd-enhancing T1-lesion volume outside the upper boundary of the modeled 95% (two-sided) prediction limits. In this way, individual patients with MRI disease activity after SDD that exceeded that predicted from (unbiased) baseline data and the degree to which disease activity exceeded that predicted within each study could be identified. Outliers' rates and characteristics were also assessed at baseline and at end of treatment as a comparison.

Gd-enhancing volume, rather than number of Gd-enhancing lesions, was used in this analysis for both clinical and methodological reasons. On the clinical side, this approach accounts for the possibility that overall volume, and therefore inflammatory disease activity, may vary for any given number of lesions. In particular, large lesions that coalesce would actually lead to a reduction in lesion count, making lesion volume potentially more indicative of disease progression than count. Increased activity due to multiple lesions, which will lead to a large accumulated volume, can still be captured by this method. On the methodological side, using Gd-enhancing volume allows for a more robust analysis due to more homogeneously distributed data, with confidence intervals that make the identification of outliers possible.

The number of outliers, based on the next available MRI scan following SDD, was assessed in the MRI analysis set of both studies. This analysis set included all randomized patients who received at least one dose of study drug and had at least one valid post-baseline MRI scan at Month 3 or later. It should be noted that among all patients included in our analyses, only very few had received the study

drug treatment for a very short course. There were two, three and six patients in FREEDOMS and one, one, and seven patients in FREEDOMS II who received placebo, fingolimod 0.5 mg and 1.25 mg, respectively, for seven days or less. While it could be argued that a potential rebound effect after fingolimod discontinuation in this subgroup is unlikely to occur, the inclusion of these patients on short exposure was not considered to have the potential to affect the overall conclusion of this study, given the small numbers and balanced distribution.

Since the elimination of fingolimod may take up to two months, and typically normal peripheral lymphocyte counts are reached within one to two months,¹⁹ all data up to 30 days after SDD are considered to be on treatment.

Clinical analysis

For clinical outcomes, an outlier was defined as a patient who experienced one or more severe relapses defined as one of the following: any hospitalization due to a relapse, any relapse assessed as “severe” by the study investigator, any relapse with incomplete recovery or unusual increase in Expanded Disability Status Scale (EDSS) score compared to prior EDSS score (defined as ≥ 3 for patients with a prior EDSS score of 0; ≥ 2 for patients with a prior EDSS score from 1 to 5; and ≥ 1 for patients with a prior EDSS score > 5) with “prior” defined as the latest EDSS measure on treatment—i.e. around SDD and up to 30 days after SDD. All severe relapses, including those occurring immediately after discontinuation, are considered up to seven months (210 days) after SDD.

Results at the treatment group level using pooled data from the clinical development program, including the Phase II (extension) study FTY720D2201E1 (up to 60 months after treatment initiation), the

one-year interferon (IFN) β -1a-controlled TRANSFORMS study, and the two-year placebo-controlled FREEDOMS study, are also presented here to complement these individual-patient-level results.

Results

The outlier analysis for both the clinical and MRI outcomes was based on the data from the intention-to-treat (ITT) populations of FREEDOMS ($n = 1272$) and FREEDOMS II ($n = 1083$), which were identical to the respective safety populations. In FREEDOMS, the number of patients in the placebo, fingolimod 0.5 mg, and fingolimod 1.25 mg was 418, 425, and 429, respectively.¹⁷ The corresponding numbers for FREEDOMS II were 355, 358, and 370.^{17,18} For reference, the group-level baseline disease characteristics relevant to these studies are presented in Table 1 (overall ITT population) and Table 2 (patients who discontinued treatment, by treatment group).

MRI outliers

At baseline, the mean volume of Gd-enhancing T1 lesions was similar in each group ($137.0 \pm 373.7 \text{ mm}^3$, $158.2 \pm 536.4 \text{ mm}^3$, and $153.7 \pm 488.8 \text{ mm}^3$ in the placebo, fingolimod 0.5 mg, and fingolimod 1.25 mg groups, respectively). The 95% prediction upper boundary was 1253.2 mm^3 in FREEDOMS and 818.8 mm^3 in FREEDOMS II.

In FREEDOMS, the number (%) of individuals who, following SDD, had Gd-enhancing lesion volumes above the upper boundary of the modeled 95% prediction limit was 2/69 (2.9%) for placebo, 1/65 (1.5%) for fingolimod 0.5 mg and 7/83 (8.4%) for fingolimod 1.25 mg (Figure 1(a)). The numbers (%) for FREEDOMS II were 4/72 (5.6%), 6/79 (7.6%) and 3/73 (4.1%) for the placebo, fingolimod 0.5 mg and fingolimod 1.25 mg groups, respectively (Figure 1(b)). Baseline disease characteristics of these MRI

Table 1. Baseline disease characteristics from FREEDOMS and FREEDOMS II.

Variable at baseline, mean (SD)	FREEDOMS ($N = 1272$)	FREEDOMS II ($N = 1083$)
Time since first symptoms, years	8.2 (6.60)	10.6 (8.02)
No. relapses in previous year	1.5 (0.77)	1.5 (0.93)
No. relapses in previous two years	2.1 (1.19)	2.3 (1.67)
EDSS	2.40 (1.32)	2.44 (1.32)
No. Gd+ T1 lesions	1.6 (4.53)	1.3 (3.41)
Gd+ T1-lesion volume, mm^3	176.54 (549.31)	118.23 (357.425)

Parentheses are standard deviations. EDSS: Expanded Disability Status Scale; Gd+: gadolinium enhancing; N = number of participants randomized; No: number of.

Table 2. Baseline disease characteristics of premature withdrawals (pooled data from FREEDOMS and FREEDOMS II).

Variable at baseline, mean (SD)	FTY 1.25 mg (<i>N</i> = 799) (<i>N</i> [*] = 276)	FTY 0.5 mg (<i>N</i> = 783) (<i>N</i> [*] = 196)	Placebo (<i>N</i> = 773) (<i>N</i> [*] = 238)	Total (<i>N</i> = 2355) (<i>N</i> [*] = 710)
Time since first symptoms, years	10.0 (7.57)	8.6 (6.32)	9.6 (6.89)	9.5 (7.03)
No. relapses in previous year	1.5 (1.04)	1.4 (0.80)	1.5 (0.79)	1.5 (0.90)
No. relapses in previous two years	2.3 (2.10)	2.2 (1.19)	2.2 (1.36)	2.2 (1.65)
EDSS	2.54 (1.37)	2.37 (1.32)	2.64 (1.35)	2.53 (1.36)
No. Gd+ T1 lesions	1.4 (4.65)	1.9 (7.20)	1.5 (3.23)	1.6 (5.11)
Gd+ T1-lesion volume, mm ³	130.64 (477.47)	180.01 (703.63)	189.95 (442.95)	164.27 (539.33)

EDSS: Expanded Disability Status Scale; FTY: fingolimod; Gd+: gadolinium enhancing; *N* = number of participants randomized. *N*^{*} = number of patients who prematurely discontinued treatment; No: number of.

outliers and their reasons for discontinuation are provided in Tables 3 and 4. Figure 1 also displays numbers and rates of outliers at baseline and end of treatment. As shown in Figure 1(a) and (b), no fingolimod patient post-SDD showed Gd-enhancing lesion volume exceeding that measured at the other time points.

Clinical outliers

Baseline disease characteristics of those experiencing a severe relapse are provided in Supplementary Tables e2 and e3, along with reasons for discontinuation. In FREEDOMS, the number of clinical outliers (patients who experienced one or more severe relapses during the SDD period as defined in Methods) was 10/228 (4.4%), 8/201 (4.0%) and 19/230 (8.3%) for placebo, fingolimod 0.5 mg and fingolimod 1.25 mg, respectively (Figure 2(a)). The rates in FREEDOMS II were 8/193 (4.1%), 7/201 (3.5%), and 8/223 (3.6%) in the placebo, fingolimod 0.5 mg and fingolimod 1.25 mg groups, respectively (Figure 2(b)).

Comparison with group-level data

The potential risk of rebound effect following withdrawal of fingolimod has also been assessed at the treatment-group level using pooled data from the Phase II and Phase III clinical development program.²⁰ Annual relapse rates (ARRs) in patients prematurely discontinuing study drug were similar across groups: 0.23 for placebo, 0.18 for fingolimod 0.5 mg ($p = 0.9366$ vs placebo) and 0.21 for fingolimod 1.25 mg ($p = 0.7280$ vs placebo), respectively (Supplementary Table e4). Additionally, mean Gd-enhancing lesion counts recorded 15–90 days after SDD were similar to baseline counts in both fingolimod groups.²⁰

Discussion

This analysis at the individual-patient level revealed that few patients in each treatment arm of FREEDOMS and FREEDOMS II experienced severe relapses, or had MRI disease activity outside of predicted limits following discontinuation of fingolimod 0.5 mg, fingolimod 1.25 mg, or placebo.

In the FREEDOMS and FREEDOMS II clinical trials, fingolimod reduced the frequency of relapses by approximately 50% and reduced MRI lesion activity by up to 82% vs placebo.^{17,18} Fingolimod is frequently used in patients with previous treatment failure or more aggressive disease, and any disease activity following the discontinuation of fingolimod could represent the expected consequences of withdrawal from an effective medication. However, the present study demonstrates that the number of outliers (individuals with higher-than-expected recurrence of disease activity after SDD) was small across all treatment groups in both of these large, placebo-controlled studies. Overall, the individual risk of unexpectedly high recurrence of clinical or MRI disease activity after SDD was similar between placebo- and fingolimod-treated patients. As shown in Figure 1 for MRI outliers and in Figure 2 for severe relapses, there was no discernable pattern in terms of frequency, treatment arm, association with dose, or consistency across two large clinical trials of similar design. For example, the small numerical increase observed for the number of severe relapses post-SDD in the fingolimod 1.25 mg group compared to the other groups in the FREEDOMS trial was not replicated in the FREEDOMS II trial. In fact, while numbers were higher for fingolimod 1.25 mg group for MRI outliers and clinical outliers in the FREEDOMS trial as compared to placebo and the 0.5 mg group, the exact opposite was true for the

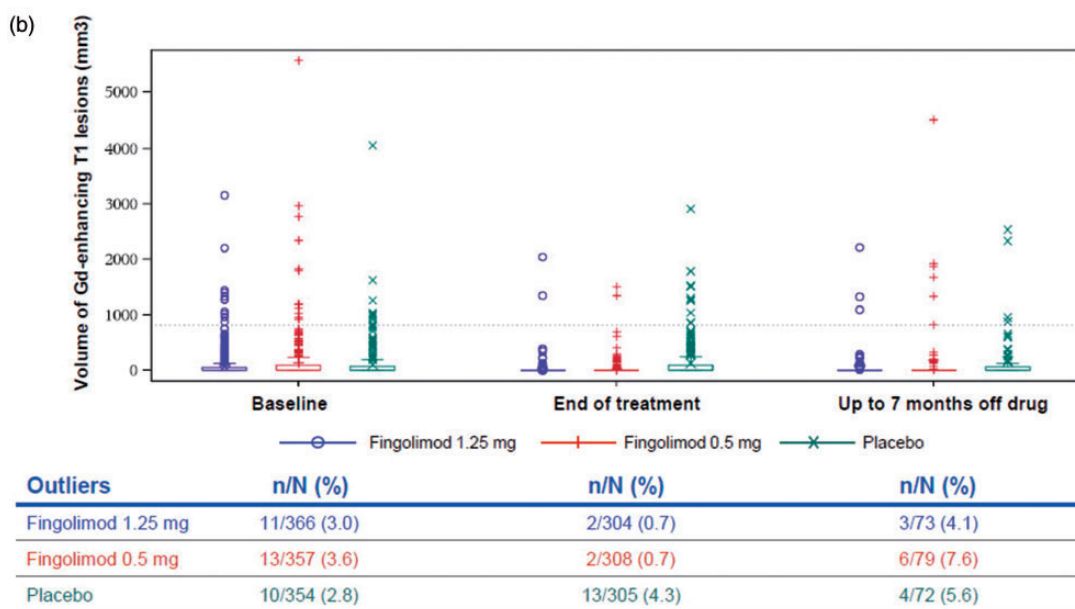
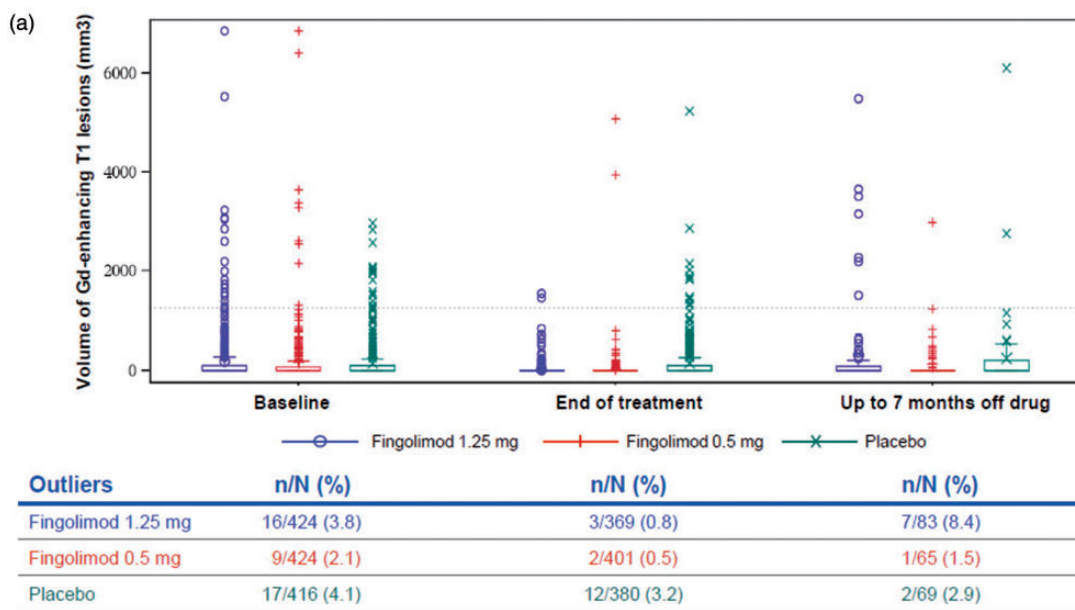


Figure 1. Number of gadolinium (Gd)-enhancing lesion volume observations outside of modelled 95% (two-sided) prediction limits in FREEDOMS (a) and FREEDOMS II (b).

The dotted line depicts the 95% prediction limit ((a) 1253.2 mm³; (b) 818.8 mm³). *n*: number of patients with Gd-enhancing T1-lesion volume above the 95% upper limit (i.e. magnetic resonance imaging outliers); *N*: total number of patients included in the analysis. All data up to 30 days after study drug discontinuation (SDD) are considered to be on treatment. Data after SDD are considered up to seven months (210 days). Data during steroid use are not presented.

FREEDOMS II trial, where the numbers in the fingolimod 1.25 mg group were smaller for both instances as compared to placebo. This absence of any dose-dependent pattern across the two similar studies suggests that these observations are rather reflective of the underlying variability of disease

activity, as opposed to being reflective of any “rebound effect.”

Such variability is further illustrated by the similar range of disease activity observed after drug cessation compared to the existing range at baseline.

Table 3. Gd+ lesion volume outliers from FREEDOMS.

Patient ^a	Treatment	Reason for discontinuation	Time since first symptoms (years)	No. relapses in previous year	No. relapses in previous two years	EDSS at baseline	No. Gd+ T1 lesions		Gd+ T1 volume (mm ³)		Days between SDD and next MRI scan
							At baseline	At first visit after SDD	At baseline	At first visit after SDD	
1	Placebo	AE	4	1	1	5.5	4	41	163.1	6103.1	40
2	FTY 1.25 mg	COM	7.5	2	4	4.5	0	63	0	5487.9	87
3	FTY 1.25 mg	WC	19.5	1	1	1	0	11	0	3651	104
4	FTY 1.25 mg	UTE	6.9	2	3	3	2	2	74.4	3510.8	124
5	FTY 1.25 mg	PV	12.2	5	7	2.5	0	15	0	3147.4	121
6	FTY 0.5 mg	ALV	9.7	1	2	1	2	12	80.1	2978.6	89
7	Placebo	UTE	15.6	2	3	3	15	26	2832.6	2758.2	41
8	FTY 1.25 mg	WC	0.5	2	2	1.5	5	19	309	2269	100
9	FTY 1.25 mg	UTE	0.8	1	1	2	2	2	297.6	2186	157
10	FTY 1.25 mg	AE	1.4	1	2	4	13	11	975.7	1505	111

^aPatients with high disease activity at first visit after discontinuation in order of volume of Gd+ lesions.

AE: adverse event; ALV: abnormal laboratory value; COM: completed study drug per protocol; EDSS: Expanded Disability Status Scale; FTY: fingolimod; Gd+: gadolinium-enhancing; No: number of; MRI: magnetic resonance imaging; PV: protocol violation; SDD: study drug discontinuation; UTE: unsatisfactory therapeutic effect; WC: withdrew consent.

In fact, the highest activity levels for patients in the fingolimod 1.25 mg or 0.5 mg group were observed at baseline, both in FREEDOMS and FREEDOMS II (which was actually not always the case in the placebo group, since in FREEDOMS the highest level of disease activity was observed after placebo discontinuation). Altogether these findings support the notion that individual cases of “high” disease activity are to be expected as part of the natural unpredictability of the disease course regardless of treatment history.

Finally, the individual-patient-level data presented here are in line and complement results from the group-level analysis, which demonstrate that annual relapse rates and Gd-enhancing lesion counts were similar in post-SDD patients from the fingolimod groups compared to those from the placebo group.²⁰

Of note, as shown in Tables 2 and 3, baseline disease characteristics varied widely among the individuals with MRI disease activity outside the predicted limits. This was the same for individuals experiencing severe relapse (“clinical outliers,” see Supplementary Tables e1 and e2). Therefore, this analysis suggests limited ability of baseline disease characteristics to predict future individual episodes of more severe disease activity following discontinuation of fingolimod or placebo for that matter.

The recurrence of high disease activity after discontinuation of immunomodulatory agents for MS is a topic of ongoing debate, which entails a number of challenges. Firstly, it is accepted that MS is characterized by extreme variability in disease course and progression and that relapses occur unpredictably with a frequency that varies both within and between individuals.²¹ Therefore, a key point about referring to the recurrence of any disease activity after discontinuation as high disease activity or even “rebound effect” is to define it appropriately. While some correctly use the term “rebound effect” only for a recurrence of disease activity that substantially exceeds the level of prior to treatment (baseline) or that of a control group, depending on setup, others use the term rebound effect or rebound syndrome to refer to the expected recurrence of any disease activity. Secondly, it is often impossible to define the true underlying individual baseline, as the natural disease course in the individual patient is usually already influenced (reduced) by other treatments before switching to a new drug. Only in exceptional cases will an observational baseline of a long enough untreated period be available for an unbiased comparison. Simply comparing the recurring disease

Table 4. Gd+ lesion volume outliers from FREEDOMS II.

Patient ^a	Treatment	Reason for discontinuation	Time since first symptoms (years)	No. relapses in previous year	No. relapses in previous two years	EDSS at baseline	No. Gd+ T1 lesions		Gd+ T1 volume (mm ³)		Days between SDD and next MRI scan
							At baseline	At first visit after SDD	At baseline	At first visit after SDD	
1	FTY 0.5 mg	UTE	9.8	1	2	1.5	6	19	526.4	4517.9	93
2	Placebo	UTE	13.2	1	2	3	0	33	0	2543.6	48
3	Placebo	UTE	3.2	3	4	3.5	8	13	815.5	2331.9	78
4	FTY 1.25 mg	COM	7.7	1	2	0	2	13	661	2220.3	149
5	FTY 0.5 mg	COM	16.1	2	3	3.5	0	12	0	1931.4	50
6	FTY 0.5 mg	ALV	5.8	1	1	1	33	16	5570.3	1877	71
7	FTY 0.5 mg	COM	24.4	1	2	2.5	4	9	372	1685.3	99
8	FTY 0.5 mg	ATPR	6.6	2	4	2	5	12	105.9	1336.1	109
9	FTY 1.25 mg	ALV	6.2	0	2	1.5	12	17	755.4	1333.4	170
10	FTY 1.25 mg	WC	9.4	4	6	1.5	4	6	400.6	1093	117
11	Placebo	UTE	7.2	4	6	2.5	9	8	812.6	958.5	104
12	Placebo	WC	10.3	1	3	3	3	4	117.3	878.4	43
13	FTY 0.5 mg	ALV	2.1	1	1	2	0	1	0	826.9	55

^aPatients with high disease activity at first visit after discontinuation in order of volume of Gd+ lesions.

ALV: abnormal laboratory value; ATPR: abnormal test procedure result; COM: completed study drug per protocol; EDSS: Expanded Disability Status Scale; FTY: fingolimod; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging; SDD: study drug discontinuation; No: number of; UTE: unsatisfactory therapeutic effect; WC: withdrew consent.

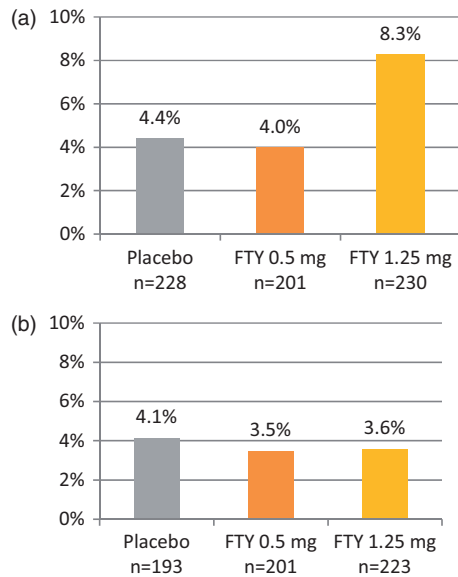


Figure 2. Incidence of severe relapses^a following discontinuation of fingolimod or placebo in FREEDOMS (a) and FREEDOMS II (b).

^aSevere relapses defined as any one of the following: any hospitalization for a relapse, any relapse assessed as “severe” by the study investigator, any relapse with incomplete recovery or unusual increase in Expanded Disability Status Scale (EDSS) score (defined as ≥ 3 for patients with a prior EDSS score of 0; ≥ 2 for patients with a prior EDSS score from 1 to 5; and ≥ 1 for patients with a prior EDSS score > 5) with “prior” defined as the latest EDSS measure on treatment—i.e. around study drug discontinuation (SDD) and up to 30 days after SDD. All severe relapses, including those occurring immediately after discontinuation, are considered up to seven months (210 days) after SDD.

FTY: fingolimod.

activity after discontinuation of an effective drug (and during a time frame when the patient is left completely untreated) to the last clinical or MRI observational time point (“snapshot”) prior to that treatment (while the patient was still receiving alternative treatment) certainly does not constitute a meaningful assessment.

This is the strength of the methodological approach presented here: (1) We use the baseline activity of the patients building the entire cohort to model boundaries of what can be expected as a typical (i.e. within limits) disease activity of patients constituting this cohort; (2) we then compare the likelihood of participants falling out of these limits between the treatment groups. This approach allows us to

delineate in a scientifically robust way true outliers, namely patients with disease activity substantially exceeding the disease activity of what could have been expected. This should lead to a more reliable estimate than assessing individual disease activity changes based on an arbitrarily chosen time point. The fact that there is no difference in that regard between the treatment arms (i.e. placebo and fingolimod), along with the lack of any discernible pattern, or dose-response relationship within- and between-study analyses, provides solid evidence that isolated cases of high disease activity after fingolimod treatment discontinuation are likely to be attributable to the natural MS disease course.

This interpretation is illustrated by the fact that the individual with the largest increase in post-discontinuation Gd-enhancing T1 volume for both trials (i.e. the pooled group) was a placebo-treated patient (increase from 163.1mm^3 to 6103.1mm^3 ; Gd-enhancing T1-lesion number increasing from 4 at baseline to 41 after discontinuation; Table 3, FREEDOMS). This individual, along with the placebo-treated patient ranking second in the FREEDOMS II trial in regard to the measured disease activity after discontinuation (number of Gd-enhancing T1 lesions at baseline was 0 as compared to 33 after discontinuation, and Gd-enhancing T1 volume was 0.0mm^3 at baseline as compared to 2543.6mm^3 after discontinuation from placebo) also contradicts the idea that there would be a simple correlation between baseline disease activity and disease activity after discontinuation in individual patients.

The clinical experience with fingolimod is approximately 453,000 patient-years exposure as of July 17, 2017.²² Random episodes of “high” or “unusual” activity have been shown to be part of the natural multiple sclerosis disease course which can occur at any time and independent of any prior withdrawal.²¹ This analysis strengthens the evidence that any episodes of unexpectedly high disease activity following the discontinuation of fingolimod are more likely to reflect the variable disease course of RRMS rather than a systematic risk of a true “rebound effect.”

Strengths and limitations

While the pooled data from the Phase II and Phase III clinical development program exploring group-level results in terms of ARR and Gd-enhancing T1-lesion count post-SDD were a pre-planned prospective analysis (which was included in the original

submission documents for Gilenya), the findings related to the individual “outliers” have been added post hoc. They however followed a very rigorous pre-specified analysis planning using placebo-controlled clinical trial data in a very large patient cohort. It should also be noted that in none of the single case reports (or small case series) published was there a prospective planning to evaluate “rebound effect,” nor was that term adequately applied^{9–16} (for example, disease activity in patients on DMT was compared to that of patients left untreated for a substantial period of time), a fact that was already critically mentioned by Sorensen *et al.*⁷ In addition, none of those case reports included a control, which makes observational bias more likely, especially considering the large variability of MS disease activity.

It could also be argued that our results apply to a subset of the overall MS population, as defined by the trial inclusion and exclusion criteria. Given the magnitude of the FREEDOMS and FREEDOMS II trials and the related baseline characteristics, we are confident that these findings reflect that of a typical RRMS population. We nevertheless cannot fully exclude that some patients included in the “rebound” case reports^{9–16} may have particular baseline characteristics differentiating them from our study population, which may put them at increased risk; we therefore encourage authors of such reports to carefully evaluate whether their patients exhibited specific characteristics that would have excluded them from the above-mentioned fingolimod clinical trials. However, the fact remains that a control group should still be included to be able to differentiate potential compound-specific effects from the natural disease course and avoid observational bias.

Finally, we acknowledge that in the absence of any clearly defined parameters for identifying clinical outliers, the criteria used in this study have a degree of subjectivity. We however feel that they are conservative and the identified threshold would overestimate rather than underestimate the number of patients with a high level of disease activity following SDD. Furthermore, the same criteria were used for all treatment groups and across both studies, and therefore, were deemed useful for the purpose of this analysis.

Based on this evaluation there is no suggestion of an increased risk of high disease activity after fingolimod discontinuation vs placebo.

Acknowledgements

The authors would like to thank patients from whom data were taken for analysis. They would also like to thank Paul Coyle, Rishard Salie (formerly of Novartis) and Marie-Catherine Mousseau (Novartis) for writing assistance, scientific editorial review and coordinating author reviews.

Conflicts of interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Prof. P Vermersch has received honoraria and consulting fees from Biogen Idec, Genzyme-Sanofi, Bayer, Novartis, Merck Serono, Roche, GSK and Almirall; and research support from Biogen Idec, Genzyme-Sanofi, Bayer and Merck Serono. Prof. E-W Radue has received research support from: Biogen Idec, Merck-Serono, Novartis and Actelion. Prof. MS Freedman has received honoraria or consultation fees from Bayer Healthcare, Biogen-Idex, Chugai, EMD Canada, Genzyme, Novartis, Sanofi-Aventis and Teva Canada Innovation. He is a member of the following company advisory boards, board of directors or other similar group for Bayer Healthcare, Biogen-Idex, Hoffman La-Roche, Merck Serono, Novartis, Opexa and Sanofi-Aventis. He is a participant in Genzyme’s company-sponsored speaker’s bureau. N Putzki, S Ritter and M Merschhemke are employees of Novartis.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Novartis Pharma AG, Basel, Switzerland.

Supplementary material

Supplementary material is available for this article online.

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