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REVIEW

Fingolimod Rebound: A Review of the Clinical Experience and Management Considerations

Brian Barry · April A. Erwin · Jessica Stevens · Carlo Tornatore

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ABSTRACT

Because the treatment of multiple sclerosis (MS) may span decades, the need often arises to make changes to the treatment plan in order to accommodate changing circumstances. Switching drugs, or the discontinuation of immunomodulatory agents altogether, may leave patients vulnerable to relapse or disease progression. In some cases, severe MS disease activity is noted clinically and on MRI after treatment withdrawal. When this disease activity is disproportionate to the pattern observed prior to treatment initiation, patients are said to have experienced *rebound*. Of the US Food and Drug Administration (FDA)-approved agents to treat MS, the drugs most commonly implicated in rebound are natalizumab and fingolimod. In this review based on the reported cases and data from clinical trials, we characterize disease rebound after fingolimod cessation. We also outline fingolimod rebound management considerations, summarizing what evidence is available to help clinicians mitigate the risk of rebound, switch therapies, and treat rebound events when they occur. The commonly encountered situation of fingolimod discontinuation prior to pregnancy is also discussed.

Keywords: Disease-modifying therapy; Fingolimod; Multiple sclerosis; Rebound; Relapse

Key Summary Points

Multiple sclerosis is a complex inflammatory disease of the central nervous system (CNS).

Fingolimod's mechanism of action includes not only diminished trafficking of inflammatory cells through the CNS but also altering the phenotypic profile of the trafficking cells to a less inflammatory state.

Withdrawal of fingolimod can result in a recurrence of MS-related disease activity which has been characterized as "rebound".

Treatment or prevention of rebound includes the use of corticosteroids, plasma exchange, and B cell depleting therapies.

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B. Barry · J. Stevens · C. Tornatore (✉)
Georgetown University Medical Center, Washington, DC, USA
e-mail: tornatoc@gunet.georgetown.edu

A. A. Erwin
The Neuromedical Group, Baton Rouge, LA, USA

INTRODUCTION TO REBOUND IN MULTIPLE SCLEROSIS

Relapsing–remitting multiple sclerosis (MS) is characterized by relapses, defined as a new neurologic deficit or episode of neurologic worsening lasting longer than 24 h in the absence of fever or infection [1]. Although good recovery to previous functional baseline is a common outcome after a relapse, in many cases recovery is incomplete and relapses result in the accumulation of disability [2]. Relapses are presumed to be caused by a new or enlarging demyelinating plaque at the site of an inflammatory event within the central nervous system (CNS) [3, 4]. Disease-modifying therapies (DMTs) for relapsing–remitting MS decrease the frequency of relapses and patients are well served by a treatment approach that emphasizes prevention of relapses.

In a patient with active MS, any interruption in treatment, such as when switching therapies, leaves the patient vulnerable to relapses [5]. Reasons for treatment changes include adverse effects, treatment failure, disease progression, comorbidities, life cycle events such as pregnancy and lactation, and evolving patient preferences. Severe disease reactivation after the withdrawal of DMT that exceeds a patient's pre-DMT baseline is considered a rebound event, although there is no consensus definition of severe disease reactivation [6–8]. As fulminant MS rebound events resembling immune reconstitution inflammatory syndrome (IRIS) have been reported with the withdrawal of treatment in MS [9, 10], it is important for the clinician to be aware of the circumstances when patients are at risk for severe disease reactivation.

Of the DMTs used for MS, the therapies most associated with rebound are natalizumab and fingolimod. Natalizumab is a monoclonal antibody that interferes with lymphocyte entry into the CNS by blocking α4 integrin-mediated lymphocyte migration into the brain and spinal cord [11, 12]. Rebound clinical events and MRI changes have been widely reported after the discontinuation of natalizumab [9, 13, 14], although an analysis of clinical trial data of subjects who discontinued natalizumab showed no increase in rebound events when compared to placebo-treated subjects [15].

Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator that became the first US Food and Drug Administration (FDA)-approved oral therapy for multiple sclerosis in 2010 [16]. Randomized clinical trials have documented the efficacy of fingolimod in decreasing relapse rates in patients with MS [17–19]. There are multiple sites of action that may contribute to fingolimod's efficacy in MS [20]. Fingolimod decreases the trafficking of autoreactive lymphocytes into the CNS by blocking S1P1-dependent egress of lymphocytes out of lymph nodes [21]. This results in a drop of peripheral blood lymphocyte counts to approximately 30% of baseline levels and a drop in peripheral blood neutrophil counts to approximately 80% of baseline levels during the period of administration, with levels returning to the normal range 1–2 months after fingolimod cessation [16]. Fingolimod affects both B cell and T cell populations, as well as costimulatory molecule profiles in the peripheral blood [22]. Reported effects include decreases in subtypes of memory B cells and naïve T cells that have been implicated in MS pathogenesis, as well as increased levels of naïve B cells and memory conventional and regulatory T cells that may help with normal immune system function and downregulation of autoimmune responses [22].

Although the mechanisms of action of natalizumab and fingolimod are distinct, the "anti-trafficking" strategy shared by both natalizumab and fingolimod reduces CNS entry of lymphocytes, and may help explain why a rebound phenomenon may occur when these drugs are stopped [23]. Though further study is needed, fingolimod has a more complex mechanism of action than a simple anti-trafficking function, likely augmenting beneficial processes while preventing disadvantageous processes within the immune system. In a small analytic study of messenger RNA expression in peripheral blood $CD4^+$ cells, for example, fingolimod treatment was associated with altered transcription levels of 890 different genes [24]. Many of these genes affect cytokine secretion, Toll-like receptor expression, and cell adhesion

molecules that may be involved in T cell functions that suppress inflammation and autoimmunity.

In this paper, we characterize rebound after fingolimod discontinuation, distinguishing it from expected disease reactivation, and comment on management considerations for patients who are stopping fingolimod. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

REPORTS OF DISEASE REBOUND AFTER FINGOLIMOD DISCONTINUATION

Reported cases of unexpected increases in clinical and MRI activity after discontinuation of fingolimod began accumulating in 2012 [10, 25–35], with some including reports of tumefactive lesions on MRI [36–40]. While these cases exhibit a significant amount of clinical heterogeneity, a recently published case series has demonstrated three different MRI patterns of post-fingolimod rebound: tumefactive lesions, a punctated pattern with innumerable small T2 and gadolinium (Gd)-enhancing lesions, and a pattern more typical of classical MS [40].

A rapid reentry of lymphocytes into the CNS upon drug discontinuation has been hypothesized to explain fingolimod rebound [41], but the phenomenon does not appear solely due to a repopulation of peripheral lymphocytes, as rebound has been noted even when lymphocyte counts have remained depressed [33, 41, 42]. Animal data has suggested a possible mechanism, as experimental withdrawal of fingolimod resulted in overexpression of lymphocytic S1P1 receptors leading to lymphocyte egress from lymph nodes and an increase in severity of relapse symptoms [43]. Another group has reported increased S1P1 immunoreactivity on hypertrophic astrocytes in tumefactive plaques at autopsy in a patient who died after cyclophosphamide was administered for a catastrophic rebound relapse [44]. They hypothesize that the withdrawal of fingolimod resulted in astrocytic overexpression of S1P1 and a downstream inflammatory response, possibly mediated by NF-κB activation and release of inflammatory cytokines and nitric oxide. Overall, however, when compared to natalizumab, fingolimod rebound is relatively less well characterized [8], and it has been argued that severe relapses after fingolimod cessation constitute expected reactivation of disease rather than true rebound [7].

The comparison of rebound rates after fingolimod discontinuation across retrospective cohorts is limited by the lack of a consensus applied definition of rebound and variation in the populations studied. Nevertheless, reported severe relapse rates range from about 10% to 25% (Table 1). In one center, 5/46 patients (10.9%) who discontinued fingolimod had a severe relapse within 4 months [42]. Another group analyzed patients who stopped fingolimod after a relapse-free interval of at least 6 months and noted that 10/100 patients had severe disease reactivation [8]. Out of these 10 patients, five were considered to have true rebound, as investigators noted that the relapse activity was more severe than the patients' pre-fingolimod baseline. In another cohort analyzing the subset of patients who discontinued fingolimod and did not immediately resume another DMT, 8/31 patients (25.8%) had a severe relapse within 6 months [45].

In contrast to these cohorts, a post hoc analysis of MRI and clinical data of study drug discontinuation subjects from the fingolimod phase III placebo-controlled trials FREEDOMS and FREEDOMS II reported no difference in severe relapse rates or Gd-enhancing lesion volume on MRI between those who discontinued fingolimod and those who stopped placebo [7]. Clinical relapse data was collected up to 7 months after stopping fingolimod or placebo. Combined across the two trials, data was available in the fingolimod 0.5 mg dose group for 152/402 subjects (38%) at 90 days and 69/402 subjects (17%) at 210 days [46]. A severe relapse rate of 4.0% was reported in FREEDOMS and 3.5% in FREEDOMS II after stopping fingolimod 0.5 mg, compared to rates of 4.4% and 4.1%, respectively, for placebo. An increased relapse rate of 8.3% was noted in the high dose

Table 1 Severe relapse rates after fingolimod discontinuation

Series	Definition of severe relapse	Duration of follow-up	Time to relapse after discontinuation	Severe relapse rate
Hatcher et al. [42]	Severe symptoms with multiple new or enhancing MRI lesions	1–4 months	Mean 7.6 weeks	10.9% (5/46)
Frau et al. [8]	Increase in EDSS $\geq$ 2 OR $\geq$ 2 relapses in 6-month study period	6 months	Not reported	10% (10/100)[a]
Uygunoglu et al. [45]	(1) More than 5 Gd-enhancing lesions or single tumefactive lesion AND (2) clinical and MRI activity worse than pre-fingolimod treatment course AND (3) increased of at least 1 point on EDSS	6 months	Median 3 months	25.8% (8/31)[b]
Vermersch et al. [7]	Any "severe" relapse as assessed by investigator, any relapse with hospitalization, incomplete recovery, or unusual EDSS increase from baseline[c]	Up to 7 months[d]	Mean 15 weeks[e]	4.0% (8/201 FREEDOMS), 3.5% (7/201, FREEDOMS II)

EDSS Expanded Disability Status Scale, *Gd* gadolinium

[a] 5/10 (5% of total) of these severe relapse cases met investigators' criteria for rebound, defined as a severe reactivation with a severity never before experienced by the patient prior to fingolimod

[b] Only patients adherent to standard treatment protocol for fingolimod for at least 6 months, and who were available for follow-up for at least 6 months, and did not receive any subsequent DMT for 3 months were included. A total of 303 patients discontinued fingolimod in this cohort

[c] EDSS criteria defined as increase $\geq$ 3 if prior EDSS 0, $\geq$ 2 if prior EDSS 1–5, $\geq$ 1 for prior EDSS greater than 5

[d] 37.8% of subjects available at 90 days following discontinuation, 17.2% of subjects available at 210 days

[e] Calculated from pooled data of fingolimod 0.5 mg dose group from FREEDOMS and FREEDOMS II available in supplementary materials to Vermersch et al. [46]

fingolimod 1.25 mg group in FREEDOMS but not FREEDOMS II, in which severe relapses were seen in only 3.6% of subjects.

Among those with MRI data, there was no difference in Gd-enhancing lesion volume among those who discontinued placebo and fingolimod. The next available MRI scan after study drug discontinuation was compared to a threshold calculated from normative data obtained from an analysis of MRIs obtained at the beginning of the study, but few subjects exceeded the upper threshold of the model. At the fingolimod 0.5 mg dose, only 1/65 (1.5%) subject MRIs were outliers in FREEDOMS and 6/79 studies (7.6%) were outliers in FREEDOMS II. These rates were comparable to the 2/69 studies (2.9%) and 4/72 studies (5.6%) seen in the placebo group. Surprisingly, the MRI study with the largest calculated volume of Gd-enhancement (6103.1 mm^3) was performed 40 days after a patient discontinued placebo.

While the lack of available follow-up data in a majority of these patients has been criticized as a weakness [8], this data is the only published comparison of patients who discontinued fingolimod to an untreated, matched patient population. Although the lack of extended follow-up time likely results in overall underestimated severe relapse rates in both placebo and fingolimod discontinuation groups compared to other cohorts (Table 1), availability of patient data at 7 months after study drug discontinuation was the same for placebo and fingolimod groups [46]. It is possible that more subtle

relapses were not captured in this cohort, although the authors also report a similar overall annualized relapse rate (ARR) between those who discontinued fingolimod 0.5 mg (0.18, 95% CI 0.07–0.33) and placebo (0.23, 95% CI 0.07–0.33) [46]. It is also plausible that episodes of severe rebound demyelination, such as the case reports of severe relapses due to tumefactive plaques after fingolimod cessation [36–40], are sufficiently rare not to be captured in these clinical trials.

CONSIDERATIONS FOR PREVENTION AND MANAGEMENT OF REBOUND DISEASE AFTER CESSATION OF FINGOLIMOD

Risk Factors for Rebound

No definitive risk factors for the development of severe relapses after fingolimod have been established, but pre-fingolimod baseline high ARR has been proposed to be a risk factor for rebound disease after stopping fingolimod [41, 45]. In one cohort, baseline ARR seemed to be a risk factor, as those who developed a severe relapse had a baseline ARR of 1.5 compared to 0.8 in those who did not [45]. Notably, 3/8 of these patients had breakthrough disease activity while on fingolimod. In a cohort with stable disease on fingolimod (relapse-free for at least 6 months), baseline ARR was not found to be risk factor for rebound [8]. Nevertheless, it is advisable to be vigilant for severe relapses after stopping treatment in a patient who had breakthrough disease on fingolimod, even if such a situation might not represent true disease rebound.

Timing of Rebound Events

When they occur, the timing of severe relapses after stopping fingolimod appears somewhat predictable, with events occurring approximately within 2–4 months after stopping fingolimod [47]. A review of the initial case reports noted that the relapses occurred between 4 and 16 weeks after stopping fingolimod [42]. A separate review of cases with tumefactive lesions ranged in onset from 3 to 18 weeks after fingolimod cessation [38]. Multiple authors [23, 42] have noted that this timeline is consistent with the average elimination half-life of fingolimod of 6–9 days [16, 48] with normalization of lymphocyte count after 1–2 months [16].

Treatment of Rebound Events

Several treatment strategies have been employed to manage severe relapses and rebound after fingolimod cessation including corticosteroids, plasma exchange, and anti-CD20 B cell depletion with rituximab or ocrelizumab [38]. Responses to treatment with corticosteroids appear to range from no improvement to complete treatment response [42]. In a case of a severe rebound event refractory to two rounds of methylprednisolone, selective immune adsorption was used with good reported success [49]. There is also a single case of successful treatment of a rebound event in a patient with primary progressive MS with cladribine [50].

Reported outcomes are also variable after B cell depletion. Rituximab has been used with a good outcome [38]. In the series published by Hatcher et al., however, one case featured clinical worsening 1 day after rituximab infusion after a 6-week fingolimod washout [42]. Two other cases featured persistent Gd-enhancing lesions despite treatment with steroids and rituximab. In a separate report, two patients with rebound disease after fingolimod cessation were noted to have clinical worsening and new Gd-enhancing MRI lesions 1 week after initiation of ocrelizumab [51]. More data is needed regarding the utility of B cell depletion as a potential therapeutic option for MS rebound.

Choice of Next Therapy

Several strategies have been proposed to mitigate risk when discontinuing fingolimod. Tapered withdrawal of fingolimod has been suggested [33, 35], although this approach is untested. Monthly pulses of intravenous

steroids have been offered as an option to bridge to the next therapy [41]. A 3-day course of pulse methylprednisolone 10 days after stopping fingolimod has also been proposed [38]. Shortening of washout periods for natalizumab and fingolimod has been suggested to avoid rebound [52], but the safety and efficacy of this approach is unknown.

There is limited evidence regarding how the choice and timing of the next therapy after fingolimod affects the risk of disease rebound. Switching from fingolimod to natalizumab prior to lymphocyte repopulation has been proposed, since rapid entry of lymphocytes into the CNS may contribute to rebound, and natalizumab could interrupt this process [33]. A case of severe disease reactivation 19 days after infusion of rituximab 1 g after a 6-week fingolimod washout has been reported, suggesting that a 6-week washout period may be too long in some patients [53]. In one cohort, 9/36 patients with highly active MS who switched from fingolimod to alemtuzumab had significant disease activity during the first year of alemtuzumab treatment [54], but larger cohorts have found alemtuzumab to be an effective option after fingolimod [55, 56].

Considerations for Pregnancy

Pregnancy planning is a frequent reason for fingolimod discontinuation. Fingolimod has been associated with birth defects in animal studies [16], and it is recommended that fingolimod be stopped prior to conception [57], although the ideal timing of cessation remains unclear. As a result of the possibility of teratogenicity, a 2-month washout period has been recommended [42]. In a cohort described by Meinl et al., relapses during pregnancy were seen 12–20 weeks after stopping fingolimod [58]. There have also been reports of fulminant rebound with significantly worsening of disability during early pregnancy with cessation of fingolimod [59]. This includes a report of death in one patient due to septic shock after receiving intravenously administered methylprednisolone, immunoglobulins (IVIG), and cyclophosphamide for deteriorating neurological status [59].

Switching from fingolimod to rituximab or ocrelizumab prior to pregnancy has been proposed as a strategy to decrease risk of relapse during pregnancy [57]. A waiting period of 6–-12 months after fingolimod cessation prior to attempting pregnancy has been proposed in patients unwilling to switch therapy to B cell depletion prior to pregnancy [57]. Caution should be used during a prolonged washout, as this strategy may increase the overall length of time that the patient is at risk for relapses while off DMT, and multiple sequential relapses are possible as part of a relapse event. In the cohort reported by Frau et al., multiple relapses were seen in 4/5 patients with rebound disease over a 6-month period after stopping fingolimod, although this was not a cohort of pregnant patients [8].

Proposed Treatment Algorithm

Given all the above, the authors believe that the treatment algorithm (Fig. 1) is supported by literature.

CONCLUSIONS

There are several general challenges when studying disease rebound in MS. The definition of rebound requires that the rebound event be more severe than the patient's pretreatment baseline. It is often difficult to ascertain a pretreatment baseline, as patients are often previously treated with another DMT, masking their "untreated" baseline [7]. Also, as a result of the unpredictable nature of MS relapses, it is possible that some patients will have unprecedented severe relapses decades into their disease course. Additionally, clinical severity may not always be proportional to imaging severity, as large and numerous enhancing lesions on MRI may cause mild symptoms, and small MRI lesions may cause clinically severe disease depending on their anatomic location. For the purpose of future research classification, MRI-based definitions of severity may be more useful, since all cases of fulminant demyelination should have marked imaging changes, even if clinical changes are relatively less pronounced.

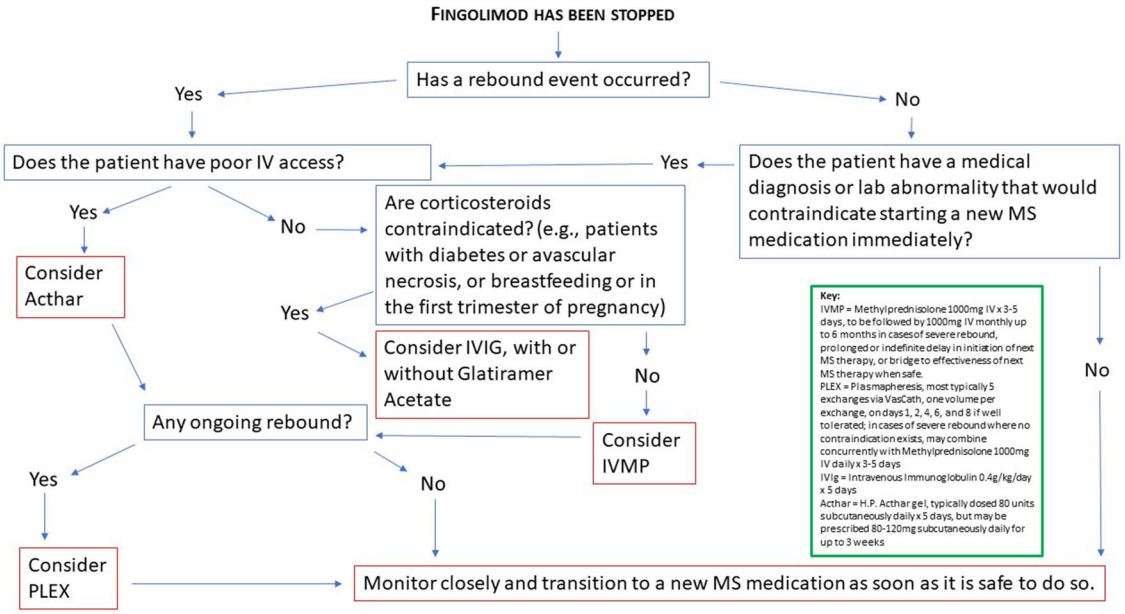

Fig. 1 Proposed treatment algorithm for fingolimod rebound

While cases of fulminant rebound events after the discontinuation of fingolimod may be easy to identify, several clinical management questions remain. It is not known whether the reported cases of fulminant and tumefactive disease rebound represent the far end of a spectrum of expected disease reactivation after stopping therapy, or a distinct, but rare, neurologic event. Since the incidence of these most severe events has not been established, it is challenging to counsel patients on the specific risks of stopping therapy. No optimal strategy for prevention or treatment of severe relapses after fingolimod cessation has been established, and future work is needed to identify the ideal timing of next DMT. Nevertheless, it is important to recognize the possibility of a severe relapse when stopping fingolimod as part of a pause in MS therapy.

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REFERENCES

1. Berkovich R. Treatment of acute relapses in multiple sclerosis. Neurotherapeutics. 2013;10(1):97–105.

2. Lublin F, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology. 2003;61(11):1528–32.

3. Lassmann H, Bruck W, Lucchinetti C. The immunopathology of multiple sclerosis: an overview. Brain Pathol. 2007;17(2):210–8.

4. Frischer J, Weigand S, Guo Y, et al. Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. Ann Neurol. 2015;78(5):710–21.

5. Berkovich R. Clinical and MRI outcomes after stopping or switching disease-modifying therapy in stable MS patients: a case series report. Mult Scler Relat Disord. 2017;17:123–7.

6. Sorensen P, Koch-Henriksen N, Petersen T, Ravnbord M, Oturai A, Sellebjerg F. Recurrence or rebound of clinical relapses after discontinuation of natalizumab therapy in highly active MS patients. J Neurol. 2014;261:1170–7.

7. Vermersch P, Radue E-W, Putzki N, Ritter S, Merschhemke M, Freedman MS. A comparison of multiple sclerosis disease activity after discontinuation of fingolimod and placebo. Mult Scler J Exp Transl Clin. 2017;3:205521731773009.

8. Frau J, Sormani M, Signori A, et al. Clinical activity after fingolimod cessation: disease reactivation or rebound? Eur J Neurol. 2018;25(10):1270–5.

9. Miravalle A, Jensen R, Kinkel R. Immune reconstitution inflammatory syndrome in patients with multiple sclerosis following cessation of natalizumab therapy. Arch Neurol. 2011;68(2):186–91.

10. Beran RG, Hegazi Y, Schwartz RS, Cordato DJ. Rebound exacerbation multiple sclerosis following cessation of oral treatment. Mult Scler Relat Disord. 2013;2(3):252–5.

11. Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against α4β1 integrin. Nature. 1992;356:63–6.

12. Polman C, O'Connor P, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899–910.

13. Vellinga M, Castelijns J, Barkhof F, et al. Post-withdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. Neurology. 2008;70:1150–1.

14. Kerbrat A, Le Page E, Leray E, et al. Natalizumab and drug holiday in clinical practice: an observational study in very active relapsing remitting multiple sclerosis patients. J Neurol Sci. 2011;308(1–2):98–102.

15. O'Connor P, Goodman A, Kappos L, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. Neurology. 2011;76(22):1858–65.

16. Gilenya [prescribing information] East Hanover, NJ: Novartis; Revised January 2019.

17. Cohen J, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402–15.

18. Kappos L, Radue E, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401.

19. Calabresi P, Radue E, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545–56.

20. Dev K, Mullershausen F, Mattes H, et al. Brain sphingosine-1-phosphate receptors: implication for FTY720 in the treatment of multiple sclerosis. Pharmacol Ther. 2008;117(1):77–93.

21. Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. Br J Pharmacol. 2009;158(5):1173–82.

22. Claes N, Dhaeze T, Fraussen J, et al. Compositional changes of B and T cell subtypes during fingolimod treatment in multiple sclerosis patients: a 12-month follow-up study. PLoS One. 2014;9(10):e111115.

23. Giovannoni G, Hawkes C, Waubant E, Lublin F. The 'Field Hypothesis': rebound activity after stopping disease-modifying therapies. Mult Scler Relat Disord. 2017;15:A1–2.

24. Friess J, Hecker M, Roch L, et al. Fingolimod alters the transcriptome profile of circulating CD4+ cells in multiple sclerosis. Sci Rep. 2017;7:42087.

25. Gross C, Baumgartner A, Rauer S, Stitch O. Multiple sclerosis rebound following herpes zoster infection and suspension of fingolimod. Neurology. 2012;79(19);2006–7.

26. Havla J, Pellkofer H, Meinl I, Gerdes L, Hohlfeld R, Kumpfel T. Rebound of disease activity after withdrawal of fingolimod (FTY720) treatment. Arch Neurol. 2012;69(2):262–4.

27. Ghezzi A, Rocca M, Baroncini D, et al. Disease reactivation after fingolimod discontinuation in two multiple sclerosis patients. J Neurol. 2013;260:327–9.

28. Hakiki B, Portaccio E, Giannini M, Razzolini L, Pastò L, Amato M. Withdrawal of fingolimod treatment for relapsing–remitting multiple sclerosis: report of six cases. Mult Scler J. 2012;18(11):1636–9.

29. Piscolla E, Hakiki B, Pastò L, Razzolini L, Portaccio E, Amato MP. Rebound after fingolimod suspension in a pediatric-onset multiple sclerosis patient. J Neurol. 2013;260:1675–7.

30. Sempere A, Berenguer-Ruiz L, Feliu-Rey E. Rebound of disease activity during pregnancy after withdrawal of fingolimod. Eur J Neurol. 2013;20:e109–10.

31. La Mantia L, Prone V, Marazzi M, Erminio C, Protti A. Multiple sclerosis rebound after fingolimod discontinuation for lymphopenia. Neurol Sci. 2014;35:1485–6.

32. Gündüz T, Kürtüncü M, Eraksoy M. Severe rebound after withdrawal of fingolimod treatment in patients with multiple sclerosis. Mult Scler Relat Disord. 2017;11:1–3.

33. Czlonkowska A, Smolinski L, Litwin T. Severe disease exacerbations in patients with multiple sclerosis after discontinuing fingolimod. Neurol Neurochir Pol. 2017;51(2):156–62.

34. Alroughani R, Almulla A, Lamdhade S, Thussu A. Multiple sclerosis reactivation postfingolimod cessation: is it IRIS? BMJ Case Rep. 2014;2014. https://doi.org/10.1136/bcr-2014-206314.

35. Fragoso Y, Adoni T, Gomes S, et al. severe exacerbation of multiple sclerosis following withdrawal of fingolimod. Clin Drug Investig. 2019;39:909.

36. Salam S, Mihalova T, Siripurapu R. Severe tumefactive rebound of multiple sclerosis following fingolimod cessation. BMJ Case Rep. 2016;2016. https://doi.org/10.1136/bcr-2016-215596.

37. Faissner S, Hoepner R, Lukas C, Chan A, Gold R, Ellrichmann G. Tumefactive multiple sclerosis lesions in two patients after cessation of fingolimod treatment. Ther Adv Neurol Disord. 2015;8:233–8.

38. Sánchez P, Meca-Lallana V, Vivancos J. Tumefactive multiple sclerosis lesions associated with fingolimod treatment: report of 5 cases. Mult Scler Relat Disord. 2018;25:95–8.

39. Sato K, Niino M, Kawashima A, Yamada M, Miyazaki Y, Fukazawa T. Disease exacerbation after the cessation of fingolimod treatment in Japanese patients with multiple sclerosis. Intern Med. 2018;57(18):2647–55.

40. Lapucci C, Baroncini D, Cellerino M, et al. Different MRI patterns in MS worsening after stopping fingolimod. Neurol Neuroimmunol Neuroinflamm. 2019;6(4):e566.

41. Berger B, Baumgartner A, Rauer S, et al. Severe disease reactivation in four patients with relapsing-remitting multiple sclerosis after fingolimod cessation. J Neuroimmunol. 2015;282:118–22.

42. Hatcher SE, Waubant E, Nourbakhsh B, Crabtree-Hartman E, Graves JS. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. JAMA Neurol. 2016;73(7):790–4.

43. Cavone L, Felici R, Lapucci A, et al. Dysregulation of sphingosine 1 phosphate receptor-1 (S1P1) signaling and regulatory lymphocyte-dependent immunosuppression in a model of post-fingolimod MS rebound. Brain Behav Immun. 2015;50:78–86.

44. Giordana M, Cavalla P, Uccelli A, et al. Overexpression of sphingosine-1-phosphate receptors on reactive astrocytes drives neuropathology of multiple sclerosis rebound after fingolimod discontinuation. Mult Scler J. 2018;24(8):1133–7.

45. Uygunoglu U, Tutuncu M, Altintas A, Saip S, Siva A. Factors predictive of severe multiple sclerosis disease reactivation after fingolimod cessation. Neurologist. 2018;23(1):12–6.

46. Vermersch P, Radue E-W, Putzki N, Ritter S, Merschhemke M, Freedman MS. A comparison of multiple sclerosis disease activity after discontinuation of fingolimod and placebo. Supplemental materials. Mult Scler J Exp Transl Clin. 2017;3(3):2055217317730096.

47. Yoshii F, Moriya Y, Ohnuki T, Ryo M, Takahashi W. Neurological safety of fingolimod: an updated review. Clin Exp Neuroimmunol. 2017;8(3):233–43.

48. Kovarik J, Schmouder R, Barilla D, Riviere G, Wang Y, Hunt T. Multiple-dose FTY720: tolerability,

pharmacokinetics, and lymphocyte responses in healthy subjects. J Clin Pharmacol. 2004;44(5):532–7.

49. De Masi R, Accoto S, Orlando S, et al. Dramatic recovery of steroid-refractory relapsed multiple sclerosis following fingolimod discontinuation using selective immune adsorption. BMC Neurol. 2015;15:125.

50. Alvarez-Gonzalez C, Adams A, Mathews J, et al. Cladribine to treat disease exacerbation after fingolimod discontinuation in progressive multiple sclerosis. Ann Clin Transl Neurol. 2017;4(7):506–11.

51. Schmidt S, Schulten T. Severe rebound after cessation of fingolimod treated with ocrelizumab with coincidental transient aggravation: report of two cases. Ther Adv Neurol Disord. 2019;12:1–6.

52. Pardo G, Jones D. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. J Neurol. 2017;264(12):2351–74.

53. Holmøy T, Torkildsen Ø, Zarnovicky S. Extensive multiple sclerosis reactivation after switching from fingolimod to rituximab. Case Rep Neurol Med. 2018;2018;5190794.

54. Willis M, Pearson O, Zsolt I, et al. An observational study of alemtuzumab following fingolimod for multiple sclerosis. Neurol Neuroimmunol Neuroinflamm. 2017;4(2):e320.

55. Huhn K, Bayas A, Doerck S, et al. Alemtuzumab as rescue therapy in a cohort of 50 relapsing-remitting MS patients with breakthrough disease on fingolimod: a multi-center observational study. J Neurol. 2018;265:1521.

56. Alcala C, Gascon F, Perez-Miralles F, et al. Treatment with alemtuzumab or rituximab after fingolimod withdrawal in relapsing-remitting multiple sclerosis is effective and safe. J Neurol. 2019;266:726–34.

57. Langer-Gould AM. Pregnancy and family planning in multiple sclerosis. Continuum (Minneap Minn). 2019;25:773–92.

58. Meinl I, Havla J, Kumpfel T, Hohlfeld R. Recurrence of disease activity during pregnancy after cessation of fingolimod in multiple sclerosis. Mult Scler J. 2018;24(7):991–4.

59. Novi G, Ghezzi A, Pizzorno M, et al. Dramatic rebounds of MS during pregnancy following fingolimod withdrawal. Neurol Neuroimmunol Neuroinflamm. 2017;4(5):e377.