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Review article

Severe disease exacerbations in patients with multiple sclerosis after discontinuing fingolimod



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ABSTRACT

Discontinuation of fingolimod in patients with multiple sclerosis (MS) can lead to disease reactivation. In this review, we describe cases of severe exacerbations in patients with MS following discontinuation of fingolimod, including three cases from our center. We consider potential mechanisms of disease reactivation after cessation of fingolimod, and the evidence supporting this rebound effect. We conclude that discontinuation of fingolimod results in the return of disease activity, which then leads to severe exacerbations (i.e., rebounds) in a clinically significant proportion of patients. Lastly, we consider disease-modifying treatment options for patients who discontinue fingolimod.

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1. Introduction

The availability of highly effective disease-modifying treatments (DMTs) has profoundly improved the management of patients with relapsing-remitting multiple sclerosis (RRMS). For instance, fingolimod nearly halves the frequency of relapses, and natalizumab reduces the relapse rate by approximately 70% [1]. However, the benefits of these therapies can be accompanied by serious complications, which were not observed with first-line DMTs (i.e., interferon beta, glatiramer acetate). On one hand, modern DMTs have increased the risk of opportunistic infections, including the potentially life-threatening viral disease, progressive multifocal leukoencephalopathy (PML) [2]. On the other hand, discontinuation of DMTs can cause severe disease reactivation, which can result in debilitating, and often irreversible,

disease progression. These factors cause dilemmas in clinical decision making, when treatment discontinuation is considered.

In this review, we describe cases of severe disease reactivation in patients with MS, following fingolimod discontinuation, including cases from our center. Moreover, we consider possible mechanisms of disease reactivation after fingolimod cessation and the evidence supporting the rebound effect. Lastly, we consider DMT options for patients who discontinue fingolimod treatment.

2. Cases of severe disease reactivation after fingolimod discontinuation

Since 2012, over twenty cases of severe disease reactivation following fingolimod discontinuation have been described

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Table 1 – Multiple sclerosis patients with disease reactivation following fingolimod withdrawal.

Gender	Age (years)	Reason for discontinuation	Time to first relapse (months)	Lymphocyte recovery	Multiple new lesions (>10)	Treatment during relapse	DMT after relapse	References
F	47	SPMS	5	N/S	Yes	MP	None	[3]
F	30	Genital herpes	3	N/S	Yes	MP	Natalizumab	[3]
M	53	Completion of RCT	3	N/S	No	MP	None (PPMS)	[4]
M	60	Completion of RCT	4	N/S	No	MP plus oral taper	None (PPMS)	[4]
F	~35	Breast cancer	1.5	Yes	Yes	MP, rituximab	Rituximab	[14]
F	~30	Planned pregnancy	1.5	Yes	No (9)	MP	Fingolimod	[14]
F	~28	Planned pregnancy	1	Yes	Yes	MP plus oral taper	Rituximab	[14]
F	~45	Adverse effects	1.5	Yes	Yes	MP and dexamethasone, rituximab	Dimethyl fumarate	[14]
F	~35	Patient decision	1.5	No	Yes	MP	Fingolimod	[14]
F	20	Lymphopenia	3	No	Yes	MP plus oral taper	Dimethyl fumarate	[20]
F	41	SAH	3	No	Yes	MP, PE	Fingolimod	[20]
F	30	Increased transaminases	3	No	Yes	MP, PE	Dimethyl fumarate	[20]
M	53	Melanoma	3	Yes	Yes	MP	Natalizumab	[8]
F	31	Planned pregnancy	2	N/S	N/S	MP	N/S	[9]
F	44	Lymphopenia	3	Yes	No	MP, intrathecal triamcinolone	Dimethyl fumarate	[30]
F	36	Angina pectoris	2	Yes	No	MP	Dimethyl fumarate	[30]
F	29	Viral neuritis	4	No	Yes	MP plus oral taper	Interferon-beta	[33]
F	36	Lymphopenia	2	Yes	Yes	MP	Glatiramer acetate	[34]
F	19	Lack of efficacy	2	Yes	Yes	MP, PE	Cyclophosphamide	[34]
F	33	Patient decision	3	Yes	Yes	MP	Cyclophosphamide	[36]
F	31	Planned pregnancy	3	N/S	Yes	MP	None, relapse during pregnancy	[37]
F	36	Lymphopenia	2	Yes	Yes	MP plus oral taper	N/S	[38]
F	32	Lymphopenia	1	Yes	Yes	MP, immune adsorption	Natalizumab	[39]

Age, at fingolimod discontinuation; DMT, disease modifying therapy; F, female; M, male, MP, intravenous methylprednisolone; N/S, not specified; PE, plasma exchange; SAH, subarachnoid hemorrhage; SPMS, secondary progressive multiple sclerosis; UTI, urinary tract infection.

(summarized in Table 1). These patients often experienced a profound worsening of the neurological state, typically accompanied by the appearance of numerous gadolinium-enhancing (Gd+) lesions on brain magnetic resonance images (MRIs; Fig. 1). Although these exacerbations were nearly exclusively observed in patients with RRMS, one case of severe disease reactivation occurred in a patient that had discontinued fingolimod due to entrance into the secondary progressive phase of MS (SPMS) [3]. Moreover, in a recent report, Davion et al. [4] described two patients with primary progressive MS who experienced significant exacerbations after discontinuing fingolimod, upon completion of the INFORMS study. Those two patients exhibited single Gd+ lesions in strategic locations: the brainstem and the spinal cord.

In our center, we observed three patients with MS who experienced significant disease reactivation following fingolimod cessation (Table 2). We present these case studies below.

2.1. Patient 1

After starting fingolimod therapy at the age of 34 years, this female patient experienced complete clinical remission over a 3-year period (EDSS = 5.0). However, the treatment was discontinued, due to lymphopenia complicated by several urinary tract infections. Two months later, the patient relapsed with right hemiparesis and ataxia (EDSS = 6.5).

Treatment with intravenous methylprednisolone (MP) could not provide functional improvement. Within the next 2 weeks, she developed tetraparesis, bulbar syndrome, dysarthria, and respiratory insufficiency, which required transient mechanical ventilation (EDSS = 9.5). On the MRI, numerous Gd+ lesions were detected in the brain and cervical spinal cord (Fig. 1A–C). After ruling out neuroinfection (including a negative finding in a cerebrospinal fluid DNA study for the JC virus), we administered intravenous MP again, and a plasma exchange. This treatment resulted in an improvement (EDSS = 7.5), but despite subsequent treatment with cyclophosphamide, we observed further debilitating deterioration (EDSS = 9.0). A long-term follow-up examination showed that her functional state had not improved.

2.2. Patient 2

After 3 years of treatment with no change in the disability score (EDSS = 4.5), this 25-year-old woman decided to discontinue fingolimod due to several upper respiratory tract and urinary tract infections. Two months after withdrawal, she was admitted due to a significant exacerbation, with lower limb paresis and ataxia (EDSS = 6.0). A brain MRI showed multiple Gd+ lesions. She received intravenous MP and improved after physical therapy (EDSS = 3.0). She refused to receive any alternative DMTs.

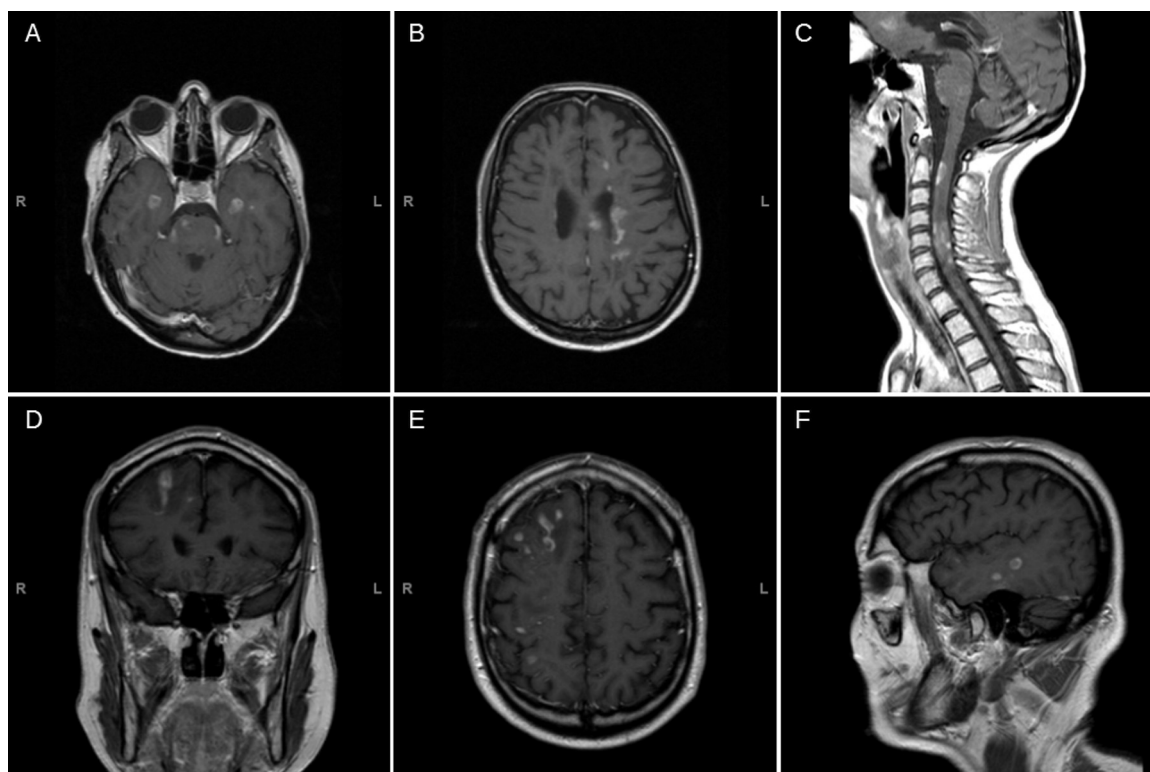


Fig. 1 – T1-weighted magnetic resonance images after gadolinium (Gd) administration in patients with severe exacerbations after discontinuation of fingolimod. (A–C) (patient 1) – Gd+ lesions are located in both brain hemispheres and in the cervical spinal cord; (D–F) (patient 3) – multiple Gd+ lesions are located in both brain hemispheres, including a large cluster of lesions in the right frontal lobe.

2.3. Patient 3

After more than 10 years of fingolimod treatment, this 53-year-old man discontinued treatment due to an episode of atrial fibrillation (EDSS = 1.5 at treatment initiation; after several relapses, he entered SPMS with EDSS = 6.0; Table 2). Atrial fibrillation occurred during treatment with MP for a minor deterioration, with no change in the functional state (left lower limb weakness, EDSS = 6.0). Two months later, he was re-admitted due to left upper limb weakness (EDSS = 6.0). A brain MRI showed multiple Gd+ lesions in both hemispheres, including a large cluster of lesions in the right frontal lobe (Fig. 1D–F). After ruling out neuroinfection (including a negative finding in a cerebrospinal fluid DNA study for the JC virus), the patient was given intravenous MP with an oral taper, which resulted in an improvement (EDSS = 5.5).

3. Rebound effect

It is understandable that withdrawing immunosuppressive agents in patients with immune-mediated diseases can lead to disease recurrence. For instance, this has been observed in myasthenia gravis [5] and psoriasis [6], and it is one of the reasons for transplant rejection. In some patients, the level of reactivation can surpass pretreatment activity levels; thus, it is often referred to as a 'rebound' effect. This effect has also been discussed in the context of severe disease reactivation

following discontinuation of both natalizumab and fingolimod [7–9]. According to our understanding, we might expect that rebound reactivation would increase disease activity indices, like annualized relapse rates (ARRs) and the number of Gd+ lesions, to levels above those observed before a given treatment. However, a precise, widely accepted definition of rebound has not been established for patients with RRMS; thus, it is difficult to conduct further investigations of this issue. The most useful definition would encompass both clinical and neuroimaging measures. In addition, it would preferably include some laboratory parameters, like restoration of lymphocyte counts or specific lymphocyte subpopulations, at specified time windows after treatment cessation.

Based on studies performed to date, it can be concluded that discontinuation of both fingolimod and natalizumab can lead to reactivation of disease, but the indices of disease activity did not surpass those of the pretreatment period. Although O'Connor et al. [10] noted a return of disease activity after withdrawal of natalizumab, they did not observe a rebound in terms of the clinical relapse activity ($n = 1886$) or in the number of Gd+ lesions ($n = 341$), compared to placebo treatment. Similar results were reported by Sorensen et al. [11], despite the fact that, in that study, over 20% of patients who discontinued natalizumab fulfilled the clinical criteria of a rebound (ARRs higher than pretreatment rates). Likewise, among 421 patients who discontinued fingolimod, after a mean follow-up of 153 days, the mean ARR and the number of Gd+ lesions were comparable to baseline values [12]. On the

Table 2 – Demographic, clinical and radiological data of patients 13.

Patient no.	Gender	Age (years)	Reason for discontinuation	Months to first relapse	Lymphocyte recovery	ARR pretreatment	ARR on fingolimod	ARR posttreatment	>10 new lesions	Treatment during relapse	DMT after relapse
1.	F	37	Refractory UTIs	2	Yes	0.4	0	3.0	Yes	MP, PE	Cyclophosphamide
2.	F	25	Patient decision	2	Yes	1.0	0.3	1.0	Yes	MP	None, patient decision
3.	M	53	Atrial fibrillation	2	No	2.0	0.5	3.0	Yes	MP	None, diagnosis of SPMS

Age, at fingolimod discontinuation; ARR, annualized relapse rate; DMT, disease modifying treatment; F, female; M, male; MP, intravenous methylprednisolone; PE, plasma exchange; SPMS, secondary progressive multiple sclerosis; UTI, urinary tract infection.

other hand, two cohort studies on patients with MS who discontinued fingolimod reported rebound disease activity after fingolimod cessation in 7.7% (2/26) and 10.9% (5/46) of patients [13,14]. In the study by Gunduz et al. [13], the criteria for a rebound were not put forward clearly, and the post-discontinuation disease activity in two patients was described as severe relapses, “suggesting a rebound effect”. In the study by Hatcher et al. [14], rebound was defined as new, severe neurological symptoms accompanied by multiple new or Gd+ lesions that exceeded baseline activity.

One might consider whether the reported disease reactivation following discontinuation of highly-effective treatments, used predominantly in patients with more aggressive disease course, is the result of a clear-cut contrast between disease activity during the treatment and post-treatment periods. Interestingly, one study reported that, among patients with a high pretreatment disease activity that showed a good response to interferon-beta, 65% experienced at least one severe relapse after treatment discontinuation [15].

In patients who discontinued natalizumab, those of younger ages that showed high pretreatment disease activity were at a greater risk of significant exacerbations after discontinuation than the other patients [7]. However, no factors are known to predict the response to fingolimod discontinuation.

In conclusion, discontinuations of fingolimod and natalizumab result in the return of disease activity. Moreover, in a clinically significant proportion of patients, discontinuation leads to severe exacerbations that could be described as rebounds.

4. Potential mechanisms of disease reactivation following fingolimod discontinuation in MS

It is thought that fingolimod acts in MS by interfering with lymphocyte egress from secondary lymphoid tissues by binding to and downregulating the expression of lymphocytic sphingosine-1-phosphate receptors 1 (S1P1). Fingolimod selectively retains T cells that express the CCR7 receptor, including central memory cells and CCR7-positive naïve T cells [16]. This retention is reflected by a decrease in peripheral blood lymphocyte count (lymphopenia). Discontinuation of fingolimod is followed by a reconstitution of lymphocyte counts within 4–8 weeks, although in some patients with MS, lymphopenia can be detected for over 2 years after discontinuation [17].

Stopping fingolimod treatment in a relapsing-remitting model of experimental autoimmune encephalomyelitis (EAE) resulted in severe disease recurrence [18]. Recurrence was preceded by an overexpression of S1P1 in lymph node-residing lymphocytes, which prompted their egress. In another EAE study, a similar exacerbating effect was observed on disease severity when fingolimod treatment was stopped [19]. In that study, animals that received both fingolimod and cyclosporine displayed significant exacerbations after only fingolimod was discontinued; in contrast, animals treated with cyclosporine alone throughout the experiment displayed a stable disease course.

In patients with MS, it is conceivable that the reconstitution of the immune system might lead to a return of inflammatory activity within the central nervous system, similar to observations in animal models. This hypothesis was supported by the fact that the majority of patients with severe disease reactivation following fingolimod discontinuation experienced initial symptoms within approximately 3 months of fingolimod cessation, upon the recovery of lymphocyte counts (Table 1). However, we and other authors have observed disease reactivation after fingolimod withdrawal in patients who had remained lymphopenic [14,20]. This finding might be explained by the fact that reactivation of neuroinflammatory activity depends on specific lymphocyte populations, regardless of the general lymphocyte count. For instance, patients with MS that relapsed during fingolimod treatment exhibited significantly higher proportions of central memory T-cells in peripheral blood than patients who remained relapse-free, despite the fact that these groups had comparable lymphocyte counts [21].

The state of clinical disease reactivation following fingolimod cessation, accompanied by immune system reconstitution, has been compared to the immune reconstitution inflammatory syndrome (IRIS) [8,20]. Initially, IRIS was described in patients with HIV-infections. Upon initiation of the highly-active antiretroviral therapy (HAART), the restoration of immune system function led to an exceedingly potent reaction to previously acquired opportunistic infections. For instance, an initially subclinical viral infection, like tuberculosis or cryptococcosis, might present with neurological manifestations upon HAART initiation [22]. Notably, this response was also observed in patients who discontinued natalizumab due to PML; exacerbations were observed for days to weeks after a plasma exchange had been instituted to expedite natalizumab clearance [23]. However, a broader definition of IRIS can include autoimmune reactions, such as the reactivation of MS following cessation of fingolimod, with no evidence of prior infection [24]. Because IRIS is associated with a rapid restoration of immune function, one might suspect that a tapered discontinuation of fingolimod would lead to a less potent response. This strategy was shown to be beneficial for patients who discontinued natalizumab [25]. The use of reduced doses of fingolimod has been reported in 8 patients with MS, but evaluating the benefit of this strategy requires a larger trial, which is currently under way [26].

It has been shown that patients with HIV who had a history of IRIS displayed increased serum IL-6 levels [27]. Similarly, in an animal model of stromal keratitis, an increased IL-6 concentration was observed after discontinuing fingolimod, and this increase was associated with recurrence of inflammatory lesions [28]. Moreover, neutralization of this cytokine with a monoclonal antibody resulted in diminished lesion formation. Those findings suggested a potential rescue treatment with IL-6 receptor inhibitors; e.g., tocilizumab has shown promising results in patients with neuromyelitis optica [29].

5. Treatment of rebound syndromes

Despite the fact that patients with rebound syndrome often present with severe clinical manifestations, the only available

treatment options are those used for all relapses. The typical treatment is a high dose of intravenous corticosteroids, with or without an oral taper. Moreover, one patient treated with intrathecal triamcinolone showed improvement [30]. In patients resistant to glucocorticosteroids, some improvement was observed with antibody-depleting strategies, such as plasma exchange and immune adsorption.

6. DMTs after fingolimod

With the growing number of available DMTs, it has become increasingly complex to transition between different agents. To date, there is no evidence in favor of any particular DMT after fingolimod cessation. Thus, different agents have been administered in different centers to patients who experienced severe exacerbation after fingolimod cessation (Table 1).

Because fingolimod has been shown to reduce disease reactivation following natalizumab cessation [31], a reverse approach might be effective. Because both drugs interfere with immune cell trafficking, it seems plausible that natalizumab could act on immune cells that are redistributed from the lymph nodes by restraining them from entering the central nervous system.

Dimethyl fumarate (DMF) is an alternative for patients who agree to receive exclusively oral therapy. However, three cases of severe disease exacerbation have been described in patients who had transitioned from fingolimod to DMF [14,30]. Because teriflunomide is less efficacious, it is not expected to be a good alternative to fingolimod. The same would apply to other first-line agents, namely, interferon beta and glatiramer acetate. Another alternative, rituximab was previously tested in two patients with rebound syndromes after fingolimod cessation [14]. However, one of the patients experienced an exacerbation, despite having received the first infusion before symptom onset. Moreover, that patient continued to develop new lesions, despite receiving subsequent doses.

Another group of DMTs that could offer an alternative approach to patients who discontinue fingolimod are induction agents, such as alemtuzumab or mitoxantrone [32]. These DMTs would be particularly suitable for women planning pregnancy (a frequent reason for discontinuation), because currently, no DMTs are safe for maintained treatment in pregnant women. However, this approach would significantly postpone the time for a safe conception. For instance, the two courses of alemtuzumab are administered 1 year apart, and pregnancy must be delayed for 4 months after the last infusion.

7. Conclusions

Discontinuation of fingolimod can lead to a return of disease activity. In a clinically significant proportion of patients, fingolimod discontinuation will result in severe exacerbations that could be described as rebounds. With the growing use of fingolimod, this issue will become relevant in clinical practice. To address this issue, we need to establish multi-center registries of patients who discontinue fingolimod. That data would facilitate investigations of potential risk factors for

rebound syndromes. Moreover, it would be informative to compare the effectiveness of particular treatment regimens given after fingolimod discontinuation. However, prior to that endeavor, an explicit definition of rebound should be established.

Conflict of interest

AC and TL have been involved in clinical trials funded by Novartis. LS declares no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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