Rebound Syndrome in Patients With Multiple Sclerosis After Cessation of Fingolimod Treatment

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IMPORTANCE The appropriate sequencing of agents with strong immune system effects has become increasingly important. Transitions require careful balance between safety and protection against relapse. The cases presented herein highlight that rebound events after ceasing fingolimod treatment may happen even with short washout periods (4 weeks) and may perpetuate despite steroid treatment or the immediate use of fast-acting immune therapies, such as rituximab.

OBJECTIVE To describe rebound syndrome in patients with multiple sclerosis (MS) after cessation of fingolimod treatment.

DESIGN, SETTING, AND PARTICIPANTS Clinical and demographic data were extracted from electronic medical records from the University of California, San Francisco, Multiple Sclerosis Center from January 2014 to December 2015. Magnetic resonance images were reviewed by MS neurologists (J.S.G., E.W., B.N., and E.C.H.). Rebound syndrome was defined as new severe neurological symptoms after ceasing fingolimod treatment, with the development of multiple new or enhancing lesions exceeding baseline activity. We reviewed the PubMed database from January 2010 to December 2015 for similar cases of severe disease reactivation after ceasing fingolimod treatment using search terms fingolimod and either rebound or reactivation. Participants were included if they stopped receiving fingolimod between January 2014 and December 2015. Five patients were identified who experienced rebound after ceasing fingolimod treatment.

EXPOSURES Each patient received treatment with oral fingolimod for various durations.

MAIN OUTCOMES AND MEASURES Occurrence of rebound after ceasing fingolimod treatment.

RESULTS The mean (SD) age of the 5 female patients presented in this case series was 35.2 (6.4) years. Of the 46 patients that stopped fingolimod treatment within the 2-year period, 5 (10.9%) experienced severe relapse 4 to 16 weeks after ceasing fingolimod treatment. Despite varying prior severity of relapsing-remitting course, all participants experienced unexpectedly severe clinical relapses accompanied by drastic increases in new or enhancing lesions seen on magnetic resonance imaging evidenced by a median (range) increase of 9 (0–30) new gadolinium-enhancing lesions and a median (range) of 9 (0–30) new T2 lesions. New lesion development persisted for 3 to 6 months despite treatment with corticosteroids (n = 3) and initiation of B-cell depleting therapy (n = 2). In addition, 11 patients were identified through literature review reported as having severe relapses consistent with a rebound syndrome and similar features to our 5 cases.

CONCLUSIONS AND RELEVANCE These cases provide evidence for a fingolimod rebound syndrome at a clinically relevant frequency, highlighting the need to determine the best methods for sequencing or discontinuing MS therapies. A large prospective registry or population-based study would be helpful to confirm this rebound phenomenon and to determine contributing factors, including immune biomarkers, that increase risk for this syndrome.

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A major concern when using therapies for multiple sclerosis (MS) that have a significant effect on immune pathways is their possible rebound effects after discontinuation. Rebound syndrome after stopping natalizumab treatment has been well documented and described as a return of disease activity exceeding predrug activity approximately 8 to 24 weeks after cessation.\(^1\)\(^2\)

Potential rebound activity after fingolimod discontinuation is less understood. Recent reports have described patients with increases in clinical and radiographic disease activity after cessation,\(^3\)\(^4\)\(^5\)\(^6\) but the frequency of these events and common features across these cases have not been summarized. The time-frame of risk for these events, predisposing factors, and associations with pharmacokinetics and immune system markers are not established, although 1 study\(^6\) suggested high levels of prefingolimod disease activity as a common factor.

Our case series highlights clinical rebound syndrome confirmed on magnetic resonance imaging (MRI) within 4 to 16 weeks after ceasing fingolimod treatment in 5 of 46 patients with varying levels of prior disease severity. These cases represent approximately 10.9% of the patients stopping fingolimod treatment at our center. In addition, we review cases of severe reactivation in the literature to date.

**Methods**

We reviewed medical records of all patients from the University of California, San Francisco, Multiple Sclerosis Center who discontinued fingolimod treatment between January 2014 and December 2015 as part of an ongoing study approved by the University of California, San Francisco, Human Research Protection Program of the effects of MS treatments. Informed consent was waived because of minimal risk to the patients and because only deidentified data and MRIs were included. Rebound syndrome was defined as new severe neurological symptoms after ceasing fingolimod treatment with the development of multiple new or enhancing lesions exceeding baseline activity. Of note, rituximab was used off-label as a rescue therapy in some patients who had previously failed multiple US Food and Drug Administration-approved medications or who were positive for John Cunningham virus antibodies and/or because it was thought to be important to prescribe patients a drug with a quick onset of action. Magnetic resonance imaging reports and images were reviewed by 4 MS neurologists (J.S.G., E.W., B.N., and E.C.H.). We further reviewed the PubMed database for similar cases of severe disease reactivation after ceasing fingolimod treatment using the search terms fingolimod and either rebound or reactivation.

**Results**

Forty-six patients from the University of California, San Francisco, Multiple Sclerosis Center stopped receiving fingolimod treatment for various reasons between January 2014 and December 2015, the most common reasons being pregnancy, adverse effects, and breakthrough disease activity. Of these 46 patients, 5 (10.9%) experienced a severe clinical event consistent with a rebound syndrome. We present detailed cases of these 5 patients (Table 1).

**Case 1**

A woman in her mid-30s with an 18-year history of relapsing-remitting MS (RRMS) experienced a brainstem relapse while taking fingolimod, her first relapse for 4 years while taking this therapy. Prior medications—interferon-beta, glatiramer acetate, and natalizumab—were discontinued for disease activity or adverse effects.

**Table 1. Five Cases of Fingolimod Rebound**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Reason for Discontinuation</th>
<th>Time to Rebound, wk</th>
<th>ARR Prior to Fingolimod</th>
<th>ARR During Fingolimod</th>
<th>Lymphocyte Count During Rebound, /μL</th>
<th>Gadolinium+ Lesions (New T2 Lesions), No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Breast cancer; brainstem relapse</td>
<td>6</td>
<td>NA</td>
<td>0.25</td>
<td>960(^{a})</td>
<td>NA 1 (&gt;10) 10 (10)</td>
</tr>
<tr>
<td>2</td>
<td>Attempt pregnancy</td>
<td>4</td>
<td>1.0</td>
<td>0.55</td>
<td>1320</td>
<td>0 (5) 0 (1) 9 (9)</td>
</tr>
<tr>
<td>3</td>
<td>Attempt pregnancy</td>
<td>4</td>
<td>0.60</td>
<td>0.33</td>
<td>1070</td>
<td>0 (0) 1 (7) 2 (25)</td>
</tr>
<tr>
<td>4</td>
<td>Adverse effects</td>
<td>12</td>
<td>0.45</td>
<td>0</td>
<td>990</td>
<td>2 (NA) 0 (0) &gt;10 (&gt;10)</td>
</tr>
<tr>
<td>5</td>
<td>Self-discontinuation</td>
<td>12</td>
<td>0.8</td>
<td>0</td>
<td>70(^{b})</td>
<td>0 (2) 0 (NA) &gt;30 (&gt;30)</td>
</tr>
</tbody>
</table>

Abbreviations: ARR, annualized relapse rate; NA, not applicable.

SI conversion factor: To convert lymphocyte count to \(\times 10^9/\text{L}\), multiply by 0.001.

\(^{a}\) CD4, 346; CD8, 288; CD19, <10.

\(^{b}\) CD4, 3; CD8, 7; CD19, 4.
Given the severity of the brainstem event (John Cunningham virus serum antibody negative and polymerase chain reaction negative in cerebrospinal fluid) and prior recurrence of breast cancer while taking fingolimod, the patient was switched to rituximab and received her first infusion (1 g) after a 6-week washout (total lymphocyte count [TLC] at cessation, 470 000 000/μL [to convert to 10⁹/L, multiply by 0.001]). The next day, she developed new symptoms of nausea, shoulder and back pain, constipation, increased leg weakness, and fatigue. A brain MRI demonstrated 10 new enhancing lesions compared with an MRI 2 months prior (Figure 1). Despite high-dose corticosteroids and B-lymphocyte depletion (CD19+ counts, <1%), she continued to form new brain lesions throughout the next 3 months. She received a second course of high-dose corticosteroids, and during the following 6 months with continued B-cell depletion, no new lesions developed.

Case 2
A woman in her early 30s with a 4-year history of RRMS (Expanded Disability Status Scale score, 1.0; pretreatment annualized relapse rate [ARR], 1.0) discontinued fingolimod treatment after 2 years (ARR, 0.5; TLC, 380 000 000/μL) to attempt pregnancy. Six weeks later, peripheral lymphocyte counts returned to normal. She developed new upper extremity pain, left face and right hand numbness, and 9 new enhancing brain and cervical spine lesions compared with MRI from 20 days prior (Figure 2). Symptoms improved after a course of high-dose corticosteroids. The patient postponed pregnancy and restarted fingolimod treatment.

Case 3
A woman in her late 20s with a 12-year history of RRMS receiving fingolimod for 3 years (ARR, 0.33) experienced a severe relapse 4 weeks after ceasing fingolimod treatment (TLC, 1 070 000 000/μL) to attempt pregnancy. Prior therapies included interferon-beta and glatiramer acetate (ARR, 0.60). Symptoms at time of relapse were diplopia and numbness in the feet and left face in the context of normal peripheral lymphocyte counts. A brain MRI showed 25 new lesions (2 enhancing) compared with MRI from 11 months prior. Diplopia improved with 3 days’ intravenous high-dose methylprednisolone and short oral taper, but throughout the next 6 months, the patient continued to experience balance problems, bilateral hand weakness, and right hemibody numbness. A sec-
Rebound Syndrome in Patients With Multiple Sclerosis After Fingolimod

We report 5 well-documented cases of severe disease reactivation 4 to 16 weeks after ceasing fingolimod treatment consistent with a rebound syndrome (Table 1). We identified 11 similar cases in the literature for further evidence of a stereotypical phenomenon occurring in patients with varying disease duration and clinical history (Table 2). The frequency of 10.9% at our center is clinically relevant and indicates that there is a need for further prospective study to better understand who is at risk and how to best treat these events.

There were limitations to this study, including the retrospective design of the study and the limited availability of immune phenotype data. Although the sample size was modest, it was inclusive of all cases of fingolimod treatment discontinuation over a 2-year period.

Fingolimod, a sphingosine-1-phosphate receptor modulator, sequesters lymphocytes in lymph nodes, preventing entry into clinical worsening, she was found to have ongoing brain lesion enhancement consistent with active demyelination and a urinary tract infection; she improved with intravenous steroids and antibiotics.

Four weeks after the second discontinuation of fingolimod, white blood cell counts returned to normal, and she received 2 rituximab (1-g) infusions separated by 2 weeks. A brain MRI 4 weeks after the end of the 2 rituximab doses (CD19 B-cell counts, <1%) demonstrated persistent although reduced areas of enhancement and no new lesions compared with MRI from 3 months prior.

Literature Review

Of the 19 articles identified from a PubMed search using the described terms, 8 articles detailed a total of 11 cases consistent with a rebound phenomenon. All reviewed cases had similar features to those reported in this series and demonstrated onset of reactivation phenomenon between 4 weeks and 4 months, with varied prefingolimod clinical activity, disability, and treatment history.

Discussion

We report 5 well-documented cases of severe disease reactivation 4 to 16 weeks after ceasing fingolimod treatment consistent with a rebound syndrome (Table 1). We identified 11 similar cases in the literature for further evidence of a stereotypical phenomenon occurring in patients with varying disease duration and clinical history (Table 2). The frequency of 10.9% at our center is clinically relevant and indicates that there is a need for further prospective study to better understand who is at risk and how to best treat these events.

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Fingolimod, a sphingosine-1-phosphate receptor modulator, sequesters lymphocytes in lymph nodes, preventing entry into

Table 2. Published Reports of Severe Disease Reactivation After Ceasing Fingolimod

<table>
<thead>
<tr>
<th>Source</th>
<th>Cases</th>
<th>Response to Steroids</th>
<th>Lymphocyte Counts During Rebound</th>
<th>Time Until Rebound After Ceasing Fingolimod, wk</th>
<th>New MRI Lesions (Enhancing Lesions), No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Masi et al,5 2015</td>
<td>F, 32 y</td>
<td>No</td>
<td>Normal</td>
<td>4</td>
<td>NA*</td>
</tr>
<tr>
<td>Berger et al,6 2015</td>
<td>M, 29 y, F, 15 y, F, 41 y, F, 22 y</td>
<td>Partial; Partial No; No4</td>
<td>Below normal</td>
<td>4-16</td>
<td>Range: 20-120 (11-45)</td>
</tr>
<tr>
<td>La Mantia et al,7 2014</td>
<td>F, 36 y</td>
<td>Yes</td>
<td>Normal</td>
<td>8</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Sempere et al,8 2013</td>
<td>F, 31 y</td>
<td>Partial</td>
<td>NA</td>
<td>11</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Beran et al,9 2013</td>
<td>F, 31 y</td>
<td>Yes</td>
<td>NA</td>
<td>5</td>
<td>NA6</td>
</tr>
<tr>
<td>Piscolla et al,10 2013</td>
<td>F, 19 y</td>
<td>None given; PLEX with good recovery</td>
<td>Normal</td>
<td>12.5</td>
<td>&gt;35 (&gt;25)</td>
</tr>
<tr>
<td>Hakiki et al,11 2012*</td>
<td>F, 33 y</td>
<td>Yes</td>
<td>Normal</td>
<td>12</td>
<td>&gt;25 (&gt;25)</td>
</tr>
<tr>
<td>Havla et al,4 2012</td>
<td>M, 45 y</td>
<td>Partial</td>
<td>Normal</td>
<td>12</td>
<td>&gt;20 (&gt;20)</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; MRI, magnetic resonance imaging; NA, not applicable; PLEX, plasma exchange.

* Exact number not given in this article but described as “increased lesion load.”
* No response to steroids; given PLEX with good recovery.
* No response to steroids; given PLEX with minimal response.
* Exact number not given in this article but described as “numerous.”
* The 5 other cases reported in this article did not fit our predetermined criteria for rebound syndrome as defined in the Methods section.

Case 4

A woman in her mid-40s with a 17-year history of RRMS (ARR, 0.45) remained relapse-free for 2.5 years while taking fingolimod but elected to switch medications owing to adverse effects (TLC, 1560 000 000/μL). After a 12-day washout, she started taking dimethyl fumarate.

Severe relapse occurred 12 weeks after ceasing fingolimod treatment with Lhermitte sign, left-sided arm and leg pain, facial muscle spasms, and blurred vision. Magnetic resonance imaging at this time showed more than 10 new enhancing lesions, including a brainstem lesion. She partially recovered after 2 days’ intravenous high-dose methylprednisolone followed by a single dose of oral dexamethasone (160 mg) but had residual cognitive deficits.

Three months after relapse onset, she received 2 rituximab (1-g) infusions separated by 2 weeks. Symptoms improved within the first month (CD19 B-cell counts, <1%), but contrast enhancement persisted in 5 brain lesions 6 months after rituximab treatment.

Case 5

A woman in her mid-30s with a 15-year history of RRMS was previously treated for 3 years with interferon beta-1a, followed by 11 months with natalizumab (ARR, 0.8). Symptom progression occurred while taking these medications, and the presence of John Cunningham virus antibodies prompted a change to fingolimod 3 months after natalizumab treatment cessation (no relapses during washout).

After 10 relapse-free months with fingolimod, she self-discontinued (TLC, 410 000 000/μL) and experienced an aggressive relapse 12 weeks later, with escalating fatigue, confusion, and paraparesis. A brain MRI showed more than 30 gadolinium-enhancing lesions consistent with demyelination (not indicative of progressive multifocal leukoencephalopathy).

The patient clinically improved with high-dose pulse steroids and resumed fingolimod treatment for 4 weeks. After

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the central nervous system. Peripheral lymphocyte counts in these patients remain depressed while taking the medication. With a half-life of 6 to 9 days, normal levels of peripheral lymphocyte return within 4 to 8 weeks after cessation. Lymphocyte reentry into the central nervous system may precipitate rebound phenomena, and the timing of the earliest rebound events described at 4 weeks is consistent with this hypothesis.

These cases highlight that rebound events may occur with short washout periods (4 weeks) and perpetuate despite steroid treatment or acute treatment with a fast-acting immune therapy, such as rituximab. Thus, the most effective treatment of rebound syndrome is not clear. Most of our cases did not immediately respond to steroids, and new lesions continued to form despite B-cell depletion in some cases. In the literature, a severe relapse after fingolimod discontinuation refractory to 2 courses of steroids has been reported to be responsive to selective immunosuppression.5

It is also of interest to know who may be at greatest risk to have rebound. Differential lymphocyte subset repopulation may play a role in patients that experience rebound. Although our data set did not allow us to fully address this because not all cases had subsets measured, data on relapses occurring during fingolimod treatment suggest that different ratios of lymphocyte subsets may affect disease activity. In our series, cases 1 and 5 were particularly severe. We observed that in these 2 cases, CD8 cells were the first to recover, while CD4 and CD19 were persistently low throughout the timespan of these rebounds. However, these data are speculative, and prospective analysis is needed.

Conclusions

Appropriate sequencing of agents with strong immune system effects has become increasingly important. Transitions require a careful balance between safety and protection against relapse. A large prospective registry would be helpful to confirm rebound phenomena and incidence.

Our observed frequency of fingolimod rebound at the University of California, San Francisco, is of clinical concern, and of our cases also highlight unique considerations for women trying to conceive. A 2-month washout period is mandatory to prevent teratogenicity, and these women are unlikely to start another agent. Severe relapses may interrupt pregnancy attempts. Careful consideration needs to be given to rebound phenomena in this subset of patients in future studies.

It is worth noting that phase 2 clinical trials typically do not build in a phase of observation after discontinuing study drug. Clinical trials designed to include lymphocyte subset testing and at least a 2- to 3-month observation phase with clinical and MRI follow-up of patients who discontinue study drugs could provide valuable information to clinicians prescribing and transitioning patients to and from these drugs.

REFERENCES

1. West TW, Cree BA. Natalizumab dosage suspension: are we helping or hurting? Ann Neurol. 2010;68(3):395-399.