Impact of Fingolimod Discontinuation Strategy on Recurrence of Disease Activity in Individuals With Multiple Sclerosis

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ABSTRACT

BACKGROUND: For individuals with multiple sclerosis (MS), treatment interruption can result in relapse/recurrence of the disease activity. Currently, there are no consensus guidelines about whether an abrupt stop with a short washout period or gradual tapering is better for fingolimod (Gilenya) cessation. We investigated the impact of the fingolimod discontinuation strategy on the recurrence of disease activity and the rebound occurrence of symptoms during washout.

METHODS: This was a retrospective, observational, multicenter study of individuals with MS in Egypt and Kuwait. The charts of patients on fingolimod therapy were screened to collect data on the impact of drug cessation strategies on disease activity and relapse occurrence. Disease relapse after cessation was defined as a relapse that occurred in the previous 12 months despite using a first-line treatment option or 2 relapses in the previous 12 months.

RESULTS: In a cohort of 100 patients, 58 had an abrupt cessation and 42 had a gradual tapering. Compared with abrupt cessation, gradual tapering was associated with a significantly lower rate of disease relapse (4.8% vs 81%, respectively; $P = .001$). Abrupt cessation also resulted in increased MRI findings of new lesions (24.1%; $P = .29$), enhancing lesions (32.8%; $P = .5$), and enlarging lesions (6.9%; $P = .59$); however, none of the MRI findings were significant. Other risk factors showed no significant association with disease relapse after fingolimod cessation.

CONCLUSIONS: Gradual fingolimod tapering is highly recommended to decrease the risk of rebound and severe disease reactivation. A prolonged washout should be avoided for lymphocyte recovery.

Int J MS Care. 2024;26:329-340. doi:10.7224/1537-2073.2023-050

Multiple sclerosis (MS) is a highly prevalent autoimmune disease. MS is a global challenge, affecting more than 2.9 million people worldwide, and its prevalence continues to rise.[1] The disease involves immune-mediated attacks on the central nervous system (CNS) and is characterized by demyelination, inflammation, and degenerative changes.[2] In addition to a significant impact on individuals' quality of life, it also has a considerable economic burden, ranked second among all chronic conditions in direct costs. In the United States, the total financial burden is estimated to be $2.5 billion, and individual lifetime costs exceed $4 million.[3]

Fingolimod (Gilenya) is an oral disease-modifying drug (DMD) that works through in vivo phosphorylation, resulting in the formation of fingolimod phosphate. This phosphorylated form resembles the important, naturally found sphingosine 1-phosphate (S1P). S1P has at least 5 receptor subtypes ($S1P_{1-5}$).[4] SIP_1 is significantly expressed in B and T lymphocytes and plays a critical role in the immune system because it regulates the egress of lymphocytes from lymphoid tissues into blood circulation.[4] Through high-affinity receptor binding, fingolimod phosphate can activate lymphocyte $S1P_1$ and induce subsequent SIP_1 down-regulation, thus inhibiting lymphocyte egress and reducing auto-aggressive lymphocyte infiltration into the CNS.[4]

Treatment interruption in patients with active MS can be caused by comorbidities, disease progression, adverse events (AEs), treatment failure, and life cycle events such as pregnancy.[5] This interruption can result in relapse/recurrence of the disease activity.[6] After the withdrawal of a DMD (eg, fingolimod or natalizumab [Tysabri]), severe disease reactivation exceeding the pre-DMD baseline can be referred to as a rebound event even though no consensus definition of severe disease reactivation has been approved yet.[7-9] Many reports have described increased clinical and radiographic disease activity after fingolimod cessation.[9,10] Still, the

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TABLE 1. Univariate Analysis of Factors That May Be Associated With Relapse Occurrence During Washout

		Relapses during washout			*P*	OR	95% CI	
		No	Yes	Total			Lower	Upper
Age, years	20-40	35.00	38.00	73.00	.32	0.63	0.26	1.55
	›40	16.00	11.00	27.00				
	Total	51.00	49.00	100.00				
Sex	Female	35.00	42.00	77.00	.042*	0.37	0.14	0.99
	Male	16.00	7.00	23.00				
	Total	51.00	49.00	100.00				
Age at onset, years	18-50	42.00	40.00	82.00	.93	1.05	0.38	2.91
	‹18	9.00	9.00	18.00				
	Total	51.00	49.00	100.00				
Disease duration, months	‹120	28.00	24.00	52.00	.55	1.27	0.58	2.78
	≥120	23.00	25.00	48.00				
	Total	51.00	49.00	100.00				
Vitamin D levels	Insufficient	40.00	36.00	76.00	.56	1.31	0.52	3.30
	Sufficient	11.00	13.00	24.00				
	Total	51.00	49.00	100.00				
Comorbidities	No	41.00	48.00	89.00	.005*	0.09	0.01	0.70
	Yes	10.00	1.00	11.00				
	Total	51.00	49.00	100.00				
Smoking	No	33.00	41.00	74.00	.031*	0.36	0.14	0.93
	Yes	18.00	8.00	26.00				
	Total	51.00	49.00	100.00				
Duration of fingolimod treatment	‹30 months	28.00	22.00	50.00	.32	1.49	0.68	3.29
	≥30 months	23.00	27.00	50.00				
	Total	51.00	49.00	100.00				
Start or switch?	Start	12.00	15.00	27.00	.43	0.70	0.29	1.69
	Switch	39.00	34.00	73.00				
	Total	51.00	49.00	100.00				
Fingolimod discontinuation	Abrupt	11.00	47.00	58.00	‹ .001*	0.01	0.00	0.06
	Gradual	40.00	2.00	42.00				
	Total	51.00	49.00	100.00				
IVMP	No	42.00	46.00	88.00	0.08	0.30	0.08	1.20
	Yes	9.00	3.00	12.00				
	Total	51.00	49.00	100.00				
On another DMD	Yes	1.00	2.00	3.00	0.39	2.13	0.19	24.24
	No	50.00	47.00	97.00				
	Total	51.00	49.00	100.00				
Relapses before fingolimod	Abrupt	41.00	1.00	42.00	0.63	1.20	0.09	5.40
	Gradual	38.00	4.00	42.00				
	Total	79.00	5.00	84.00				
Fingolimod failure	Abrupt	8.00	20.00	28.00	.07	3.20	0.09	10.67
	Gradual	18.00	1.00	19.00				
	Total	26.00	21.00	47.00				

DMD, disease-modifying drug; IVMP, intravenous methylprednisolone.
Note: P ‹ .05 was considered significant.
*Data analyzed using χ^2 test.

frequency and common features of disease reactivation have not been discussed.[11]

Results of a previous study revealed that the risk of rebound disease after discontinuation of a DMD is highest in younger patients with recent relapses or MRI activity.[12] Results of another study demonstrated that neither age nor disease subtype strongly influenced rebound.[13]

In 2018, the US Food and Drug Administration warned of potential worsening following fingolimod cessation,[14] leading to the suggestion of various strategies to mitigate the risk of fingolimod discontinuation. These included tapered withdrawal (not tested yet),[15] monthly pulses of intravenous methylprednisolone (IVMP) as a bridge to the subsequent therapy,[10] a 3-day course of pulse IVMP 10 days after stopping fingolimod,[15] and shorter washouts.[16] However, the safety and efficacy of these approaches have not yet been fully described.[5]

No consensus guidelines concerning the method of fingolimod cessation, whether abrupt, short washout, or gradual tapering, exist. Due to the growing evidence of a possible rebound after fingolimod cessation,[9,17] our centers started to adopt a more cautious tapering strategy whenever feasible (ie, the discontinuation is not due to significant AEs or unplanned pregnancy) to observe the pattern of disease reactivation following discontinuation. Our objective is to investigate the influence of the gradual tapering of fingolimod on the recurrence of disease activity and the rebound occurrence of disease symptoms during the washout.

METHODS

Study Design and Procedures

We conducted a retrospective, observational, comparative, multicenter study to collect data on individuals with MS receiving fingolimod. The study protocol was approved by the research and ethics committees of the included centers in Egypt and Kuwait (Kasr Al-Ainy MS unit of Cairo University, Egypt; MS unit at Al-Amiri Hospital, Kuwait; N-105-2021).

We screened medical records for patients receiving fingolimod between January 2011 and October 2020. Data on the impact of cessation strategies on disease activity were extracted. Baseline data, including patients' demographics, MS disease history, fingolimod use–related data, Expanded Disability Status Scale (EDSS) score before fingolimod use, and baseline laboratory values, were also collected.

Patients receiving fingolimod were divided into 2 study groups: abrupt cessation and gradual tapering. Abrupt cessation was used in nonoptimal situations such as unplanned pregnancy, the emergence of AEs related to fingolimod use, or other patient-related factors; gradual tapering was used in cases of family planning or as a response to the drug's failure for that particular person. There were 2 strategies for gradual tapering. In the Egyptian centers, patients were placed on every other day dosing for 2 weeks, then 3 times weekly for 2 weeks, then twice weekly for 2 weeks. In Kuwait, patients had every other day dosing over 1 month. The washout for switching DMDs was scheduled to last 6 weeks, but varied due to factors such as delayed conception, logistic causes, or persistence of lymphopenia for long periods.

Eligibility Criteria

Individuals on fingolimod therapy between January 2011 to October 2020 who met the French health authority's label indications were included in the study. Included were all patients who had highly active disease and started fingolimod as first DMD or received it after another first-line DMD due to at least 1 disease relapse that occurred in the previous 12 months, or 2 relapses that occurred in the previous 12 months and were associated with at least 1 lesion on brain MRI without passing through a complete neurological recovery.[18]

In addition, all patients with relapsing-remitting MS or secondary progressive MS treated with fingolimod therapy at any of the included centers were included in our study if they stopped fingolimod therapy, had a washout of less than 60 days, and were older than 20 years. Patients treated with fingolimod for less than 6 months were excluded because of the inability to assess disease stability or treatment failure in such a short period of time.

Study Objectives and Data Collection

The primary objective of this study was to compare the effect of gradual tapering vs abrupt cessation of fingolimod on the recurrence and rebound of MS disease activity during the washout. Secondary objectives were to observe MRI findings after the washout and determine the associated risk factors for relapses during the washout. Disease rebound for MS has been defined as severe disease reactivation exceeding the pre-DMD baseline.[7-9]

Data collected from each patient's chart included baseline demographics and clinical characteristics (age, sex, smoking status, comorbidities, vitamin D levels, disease characteristics, and recovery rate from relapses), fingolimod discontinuation strategy and causes, laboratory values (including mean total leukocyte count [TLC] and mean lymphocyte count [MLC]), clinical and radiological activity after fingolimod cessation, and disease activity within the study period (including use of IVMP, use of DMDs, relapse occurrence rate, the mean number of relapses, annualized relapse rate [ARR], recovery rate from disease relapses, and MRI findings after the washout period). In addition, data from brain and spinal cord MRIs with contrast after 12 weeks of fingolimod cessation were collected to show any changes in radiological activity (new, enlarging, or enhancing lesions). Disease relapse severity was defined as a relapse that impaired quality of life and required assistance for 3 months or longer due to delayed or incomplete recovery, as per the Canadian MS Working Group's 2013 updated recommendations.[19] MRI lesions were defined as either gadolinium-enhancing lesions, new/enlarging T2 lesions, or stable lesions. Stable lesions were defined as lesions that presented without any change in size or contrast intake. New or enlarged lesions were signs of active disease. MS contrast-enhancing lesions on post contrast MRI were considered markers of the inflammatory responses associated with blood-brain barrier breakdown and markers of suboptimal response to MS medications. We didn't use advanced techniques for automatic

TABLE 2. Multivariate Logistic Regression Predicting Relapse Likelihood During Washout After Fingolimod Discontinuation

Model coefficients-relapses during washout							
						95% CI	
Predictor	Estimate	SE	Z	*P*	OR	Lower	Upper
Sex							
(R: Female)							
Male	−1.03	1.07	−0.968	.33	0.36	0.04	2.88
Comorbidities							
(R: No)							
Yes	−1.44	1.42	−1.02	.31	0.24	0.02	3.81
Smoking							
(R: No)							
Yes	−0.703	1.04	−0.676	.50	0.50	0.06	3.80
Strategy							
(R: Abrupt)							
Gradual	−4.55	0.84	−5.41	<.001	0.01	0.00	0.06

*Note: $P < .05$ was considered significant.

detection of active T2 lesions, but instead compared imaging 6 months and 1 year after treatment with baseline scans.

Statistical Analysis and Sample Size Calculation

We analyzed the collected patient data using IBM SPSS Statistics 26.0 software. Categorical variables were reported as frequency (n) and percentage (%); quantitative variables were reported using descriptive measures such as mean, SD, and range. A χ^2 test was used to determine the association among different risk factors with relapse occurrence during the washout. A P value of less than .05 determined significance. Multivariate logistic regression analysis was used to analyze the relationship between the dependent variable (relapses, yes/no) and multiple predictors or independent variables.

RESULTS

Sociodemographic and Clinical Characteristics of Study Patients

The cohort's mean age (± SD) was 36 (± 8) years. There were 77 women and 23 men, 76 individuals with low/insufficient vitamin D levels, and 26 smokers. Comorbidities were more common in the gradual tapering group (21.4%) than in the abrupt cessation group (3.4%) (P=.005). Baseline EDSS was similar between both groups, with a median value of 2. Half of the cohort was on fingolimod treatment for more than 30 months, and 73 individuals were switched to fingolimod from another DMD. Demographic and baseline disease characteristics were comparable across study groups (**TABLE S1**).

Relapse and Recovery Rates During Fingolimod Therapy

Before fingolimod treatment, 84% of patients had a disease relapse within the previous 2 years; 45% had a relapse after beginning fingolimod therapy. The abrupt cessation group had a higher percentage of patients with an ARR of 1 or 2 during fingolimod therapy (46.6%) compared with the gradual tapering group (34.2%). Rapid recovery rates were comparable across study groups before and after fingolimod therapy. The median EDSS during fingolimod therapy was lower in the abrupt cessation group than in the gradual tapering group (medians 1.5 and 2, respectively) (**TABLE S2**).

Fingolimod Discontinuation Strategies and Laboratory Findings During Washout

Treatment-response failure was the primary cause of drug discontinuation in the abrupt cessation group (48.3%) and the gradual tapering group (45.2%); other causes included pregnancy, drug-related AEs, and other reasons (**TABLE S3**). Causes of fingolimod discontinuation are detailed in **TABLE S4**

Abrupt cessation of fingolimod led to higher TLC and MLC values after the washout than gradual tapering. TLC had a mean difference of 1.8 (SE , 0.3; 95% CI, 1.17-2.40) in the abrupt cessation group and 1.0 (SE, 0.35; 95% CI, 0.03-1.70) in the gradual tapering group. MLC had a difference of 0.5 (SE, 0.08; 95% CI, 0.33-0.67) in the abrupt cessation group and 0.3 (SE, 0.09; 95% CI, 0.10-0.50) in the gradual tapering group (Table S3). The 2 groups also had significant differences in TLC and MLC after the washout. The mean TLC was 6.5 (± 1.9) in the abrupt cessation group and 5.4 (± 1.7) in the gradual tapering group (P=.007); MLC was 1.3 (± 0.5) in the abrupt cessation group and 1 (± 0.5) in the gradual tapering group (P = .04; Table S3).

The gradual tapering group had a significantly higher need for IVMP (21.4%) compared with the abrupt cessation group (5.2%; P = .01). On the other hand, the need for other DMDs was comparable between groups (3.4% vs 2.4%; P = .70, respectively) (Table S3).

Clinical and Radiological Findings

The gradual tapering group had a significantly lower rate of disease relapse compared with the abrupt cessation group (4.8% vs 82.8%; *P*=.001). In the abrupt cessation group, more patients had new lesions (24.1%; *P*=.29), enhancing lesions (32.8%; *P*=0.5), and enlarging lesions (6.9%; *P*=.59) on MRI. The full details of clinical and radiological activity after fingolimod cessation are shown in **TABLE S5**.

Risk Factors Associated With MS Relapse Occurrence

Female sex (OR, 0.37; 95% CI, 0.14-0.99), absence of comorbidities (OR,0.09; 95% CI, 0.01-0.69), nonsmoking (OR,0.36; 95% CI, 0.13-0.93), and abrupt cessation (OR, 0.012; 95% CI, 0.002-0.056) were found to be significant risk factors for MS disease relapse during the washout. Other factors, including age at onset, disease duration, vitamin D levels, duration of fingolimod treatment, switching to or starting on fingolimod, relapses before fingolimod, response failure on fingolimod, use of IVMP, and use of other DMDs had no significance on disease relapse. (**TABLE 1**).

Abrupt cessation was the only statistically significant risk factor for MS disease relapse in the multivariate logistic regression analysis (OR, 0.01; 95% CI, 0.002-0.055; *P*<.001), whereas female sex, absence of comorbidities, and smoking status had no significant risk (OR, 0.36; 95% CI, 0.044-2.89; OR, 0.24; 95% CI, 0.015-3.81; OR, 0.50; 95% CI, 0.06-3.81, respectively) (**TABLE 2**).

DISCUSSION

Forty-nine percent of participants experienced relapses after discontinuing fingolimod, with abrupt cessation associated with a significantly higher rate of relapse occurrence (81%) than gradual tapering (4.8%). Abrupt cessation was also linked to more severe relapses and delayed recovery. Fingolimod prevents auto-aggressive lymphocytes from entering the CNS, and withdrawal leads to a rapid invasion of self-reactive T cells from lymph nodes to the blood, T-cell–dependent B-cell activation, and reduced S1P receptor actions on CNS cells.[4,20] Astrocytic $S1P_1$ overexpression causes the release of inflammatory cytokines and nitric oxide, which may contribute to MS rebound after fingolimod cessation.[21] Gradual tapering may release these inflammatory mediators in lower amounts, resulting in a lower risk of disease relapse (as indicated by our study results).

Another plausible hypothesis is that different types of lymphocytes have varying vulnerabilities for entrapment in secondary lymphoid organs and, thus, for facilitating recovery after fingolimod withdrawal. It has been shown that CD4+ T cells are the most susceptible to entrapment, followed by CD8+ T cells.[4] Hence, CD4+ T cells are the last to recover after fingolimod withdrawal.[22] During this period of consecutive lymphocytes returning to the peripheral circulation, a state of dysregulation may occur when autoreactive cytotoxic CD8+ T cells return to the peripheral circulation earlier than the regulatory CD4+ T cells, leading to inflammation and tissue damage in the CNS.[23] Therefore, gradual discontinuation of fingolimod may help lessen the number of CD8+ cytotoxic T cells released into the CNS and help in the gradual repair of lymphopenia. Moreover, this may support the theory that bridging with other DMDs such as dimethyl fumarate (DMF) may also help mitigate the fingolimod rebound by depleting the CD8+ T-cell population.[24]

New lesions on MRI after washout were found in 19% of the cohort. The development of new MRI lesions did not differ between the abrupt discontinuation and gradual tapering groups. Previous reports have shown increased MRI activity and tumefactive lesions after fingolimod discontinuation.[25] In addition, multiple studies reported multiple enhanced lesions with increased disease activity on brain MRI after fingolimod cessation.[26] It has been suggested that bridging with monthly pulses of intravenous steroids[10] and a 3-day course of pulse IVMP 10 days after stopping fingolimod might mitigate the risk of increased disease activity after fingolimod cessation.[27] In our study, 12% of participants received IVMP, and 3% were bridged with interferon beta. However, the use of IVMP or other DMDs during the washout did not affect relapse occurrence.

Previous studies suggest that baseline ARR should be considered a risk factor for disease relapse after fingolimod discontinuation.[10,28] In a Turkish study by Uygunoglu et al,[28] patients who developed a severe relapse had a baseline ARR of 1.5 compared with that of 0.8 in those who did not. However, baseline ARR was not a risk factor in cases with disease control on fingolimod (relapse-free for at least 6 months). Also, patients who had a breakthrough in fingolimod therapy had a higher risk for severe relapses after fingolimod cessation. Women had a significantly higher relapse occurrence than men, but age did not appear to be a factor. In a study by Frau et al,[9] all of the patients with severe disease reactivation were women and younger than others in the study.

Fingolimod reduces lymphocyte count by 76% of the baseline value, which recovers to 80% by 3 months. Rapidly switching to another DMD without considering lymphocyte recovery can increase the risk of infection. Thus, considering lymphocyte recovery time is crucial when managing discontinuation of fingolimod. Nagy et al[29] reported that patients with lower lymphocyte counts before fingolimod therapy who were pretreated with mitoxantrone were at a higher risk for prolonged lymphopenia. They also found that patients with low peripheral TLC (especially < 500/μL lymphocytes) at the time of fingolimod cessation might be at a higher risk for disease exacerbation.[29] In our study, no patient had a true rebound, possibly because the mean TLC was 4.6 (± 1.6) at the time of drug discontinuation and 6.1 (± 1.9) after the washout.

Sato et al investigated the clinical and laboratory status of patients with MS who switched from fingolimod to DMF.[30] Patients with disease exacerbations and patients without exacerbations all had significantly higher TLCs 4 weeks after fingolimod cessation than at baseline.[30] Based on this, the researchers suggested that lower values of TLCs at fingolimod cessation should be considered a risk factor for MS

PRACTICE POINT

Analysis of fingolimod discontinuation in Egyptian and Kuwaiti individuals with multiple sclerosis showed that although abrupt cessation was used more frequently, gradual tapering had a lower rate of disease relapse. ■

exacerbations. Therefore, gradual discontinuation of fingolimod therapy, such as tiered dosage reduction or alternate-day administration, may reduce the incidence of disease exacerbation after discontinuation. These recommendations align with our study results and hypothesis that using gradual tapering for fingolimod discontinuation would decrease the risk of rebound or severe disease reactivation.

To avoid disease rebound, we only included patients with a washout of less than 60 days in our study. In our clinical practice, patients with a longer washout (> 60 days) have experienced more relapses or worsened disease status, especially those with highly active disease who require dose escalation or treatment adjustment. This observation is supported by Członkowska et al,[31] who described severe disease reactivation in 3 patients with MS after 2 months of fingolimod discontinuation.[31] Pardo and Jones also recommend a short washout after fingolimod cessation to avoid disease rebound,[16] but the safety and efficacy of this approach are not well-defined.

CONCLUSIONS

In our study, over 80% of patients with MS who abruptly stopped fingolimod therapy experienced disease relapse and increased disease activity. To avoid disease relapse, our study suggests using gradual tapering with a short washout when discontinuing fingolimod. As our study only included patients with a washout of less than 60 days, additional research is needed to investigate the association between washout duration and disease relapse after fingolimod cessation. Disease monitoring and strict follow-up, especially during the first 2 months, are highly recommended for patients discontinuing fingolimod for any reason. ■

ACKNOWLEDGMENTS: The authors thank the study patients, hospital staff, and investigators for their active participation. Medical writing assistance and editorial support were provided by Ahmed Salah Hussein, MD, of RAY, a contract research organization. We also extend our gratitude to Dr Reham Elgarhy and Dr Fady Adel for their efforts.

DECLARATION OF CONFLICTING INTEREST: The authors declare no conflicts of interest.

PRIOR PRESENTATION: The abstract was published as an oral presentation at the 7th Middle East North African Committee for Treatment and Research in Multiple Sclerosis Congress; November 11-12, 2022; Cairo, Egypt.

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TABLE S1. Baseline Demographic Data and Clinical Characteristics of Study Participants

	Mean	SD
Age, years	36	8
Age at onset, years	25	8
Disease duration, months	125	63
Fingolimod treatment, months	30	20

	Abrupt (n = 58)	Gradual (n = 42)	Total (N = 100)	*P*
Age, years				.763
20-40	43 (74.1%)	30 (71.4%)	73 (73.0%)	
› 40	15 (25.9%)	12 (28.6%)	27 (27.0%)	
Sex				.519[a]
Female	46 (79.3%)	31 (73.8%)	77 (77.0%)	
Male	12 (20.7%)	11 (26.2%)	23 (23.0%)	
Age at onset, years				.768[a]
18-50	47 (81%)	35 (83.3%)	82 (82.0%)	
‹ 18	11 (19%)	7 (16.7%)	18 (18.0%)	
Disease duration, months				.733[a]
‹ 120	31 (53.4%)	21 (50%)	52 (52.0%)	
≥ 120	27 (46.6%)	21 (50%)	48 (48.0%)	
Comorbidities				.005[a]
No	56 (96.6%)	33 (78.6%)	89 (89.0%)	
Yes	2 (3.4%)	9 (21.4%)	11 (11.0%)	
Smoking				.337[a]
No	45 (77.6%)	29 (69%)	74 (74.0%)	
Yes	13 (22.4%)	13 (31%)	26 (26.0%)	
Vitamin D levels				.663[a]
Insufficient	45 (77.6%)	31 (73.8%)	76 (76.0%)	
Sufficient	13 (22.4%)	11 (26.2%)	24 (24.0%)	
Baseline EDSS				.29[7b]
Median (IQR)	2 (1.0)	2 (1.8)	2 (1.4)	
Range	1-6	0-6.5	0-6.5	
Duration of fingolimod				.418[a]
‹ 30 months	31 (53.4%)	19 (45.2%)	50 (50.0%)	
≥ 30 months	27 (46.6%)	23 (54.8%)	50 (50.0%)	
DMD history				.353[a]
Switch	41 (70.7%)	32 (76.2%)	73 (23.0%)	
Naive	17 (29.3)	10 (23.8%)	27 (27.0%)	

DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale.
Note: $P < .05$ was considered significant.
[a]Data analyzed using χ^2 test.
[b]Data analyzed using Mann-Whitney *U* test.

TABLE S2. Relapse and Recovery Rates Before and After Fingolimod Prescription

	Abrupt (n = 58)	Gradual (n = 42)	Total (N = 100)	*P*
Relapses (2 years before fingolimod)				.655[a]
0	11 (19.0%)	5 (11.9%)	16 (16.0%)	
1	27 (46.6%)	25 (59.5%)	52 (52.0%)	
2	15 (25.9%)	7 (16.7%)	22 (22.0%)	
3	2 (3.4%)	3 (7.1%)	5 (5.0%)	
4	2 (3.4%)	1 (2.4%)	3 (3.0%)	
6	1 (1.7%)	1 (2.4%)	2 (2.0%)	
ARR before fingolimod				<.001[a]
0	11 (19.0%)	3 (7.1%)	14 (14.0%)	
1	37 (63.8%)	21 (50.0%)	58 (58.0%)	
2	7 (12.1%)	2 (4.8%)	9 (9.0%)	
3	1 (1.7%)	1 (2.4%)	2 (2.0%)	
Missing	2 (3.4%)	15 (35.7%)	17 (17.0%)	
Recovery (2 years before fingolimod)				.106[a]
No relapses	11 (19.0%)	5 (11.9%)	16 (16.0%)	
Delayed	17 (29.3%)	21 (50.0%)	38 (38.0%)	
Rapid	30 (51.7%)	16 (38.1%)	46 (46.0%)	
EDSS before fingolimod				.297[b]
Median (IQR)	2 (1.0)	2 (1.8)	2 (1.4)	
Range	1-6	0-6.5	0-6.5	
Relapses on fingolimod				.714[a]
No	31 (53.4%)	24 (57.1%)	55 (55.0%)	
Yes	27 (46.6%)	18 (42.9%)	45 (45.0%)	
ARR on fingolimod				.186[a]
0	31 (53.4%)	27 (65.9%)	58 (58.6%)	
1	24 (41.4%)	10 (24.4%)	34 (34.3%)	
2	3 (5.2%)	4 (9.8%)	7 (7.1%)	
Missing	0	1 (1.7%)	1 (1.7%)	
Recovery on fingolimod[c]				.447[a]
Delayed	10 (17.2%)	10 (23.8%)	20 (20.0%)	
No	31 (53.4%)	24 (57.1%)	55 (55.0%)	
Rapid	17 (29.3%)	8 (19.0%)	25 (25.0%)	
Last EDSS on fingolimod				.222[b]
Missing	1 (1.7%)	0	1 (1.0%)	
Median (IQR)	1.5 (2.3)	2 (3)	2 (3)	
Range	0-6.5	0-7	0-7	

ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale.
Note: $P < .05$ was considered significant.
[a]Data analyzed using χ^2 test.
[b]Data analyzed using Mann-Whitney *U* test.
[c]Delayed recovery is defined as required ≥ 3 months for assistance. Delayed or incomplete recovery is defined as period over ≥ 3 months.

TABLE S3. Characteristics of Fingolimod Discontinuation and Washout

	Abrupt (n = 58)	Gradual (n = 42)	Total (N = 100)	*P*
Discontinuation reason				.762[a]
Adverse event	6 (10.3%)	7 (16.7%)	13 (13.0%)	
Others	7 (12.1%)	6 (14.3%)	13 (13.0%)	
Pregnancy	17 (29.3%)	10 (23.8%)	27 (27.0%)	
Treatment failure	28 (48.3%)	19 (45.2%)	47 (47.0%)	
TLC at discontinuation				.288[b]
Missing	3 (5.2%)	4 (9.5%)	7 (7.0%)	
Mean (SD)	4.7 (1.5)	4.4 (1.5)	4.6 (1.5)	
Range	1.2-7.9	1.8-8.6	1.2-8.6	
LC at discontinuation				.196[b]
Missing	3 (5.2%)	5 (11.9%)	8 (8.0%)	
Mean (SD)	0.8 (0.4)	0.7 (0.4)	0.7 (0.4)	
Range	0.1-1.8	0.2-2.2	0.1-2.2	
TLC after washout				.007[b]
Missing	4 (6.9%)	10 (23.8%)	14 (14.0%)	
Mean (SD)	6.5 (1.9)	5.4 (1.7)	6.1 (1.9)	
Range	2.6-10.4	3-10.4	2.6-10.4	
LC after washout				.043[b]
Missing	4 (6.9%)	10 (23.8%)	14 (14.0%)	
Mean (SD)	1.3 (0.5)	1 (0.5)	1.2 (0.5)	
Range	0.4-3.1	0.4-2.8	0.4-3.1	
IVMP				.014[a]
No	55 (94.8%)	33 (78.6%)	88 (88.0%)	
Yes	3 (5.2%)	9 (21.4%)	12 (12.0%)	
Other DMD				.757[a]
No	56 (96.6%)	41 (97.6%)	97 (97.0%)	
Yes	2 (3.4%)	1 (2.4%)	3 (3.0%)	

DMD, disease modifying drug; IVMP, intravenous methylprednisolone; LC, lymphocyte count; TLC, total leukocyte count.
Note: $P < .05$ was considered significant.
[a]Data analyzed using χ^2 test.
[b]Data analyzed using Mann-Whitney *U* test.

TABLE S4. Detailed Reasons for Fingolimod Cessation

	Abrupt (n = 58)	Gradual (n = 42)	Total (N = 100)
Pregnancy			
Unplanned	4 (6.9%)	0 (0.0%)	4 (4.0%)
Planned	13 (22.4%)	10 (23.8%)	23 (23.0%)
Treatment failure			
Relapse	28 (48.3%)	8 (19.0%)	36 (36.0%)
Passing to progression	0 (0.0%)	11 (26.2%)	11 (11.0%)
Adverse event			
Elevated LFT	2 (3.4%)	2 (4.8%)	4 (4.0%)
Lymphopenia, grade 4	2 (3.4%)	0 (0.0%)	2 (2.0%)
Fatigue	0 (0.0%)	1 (2.4%)	1 (1.0%)
Seizures	0 (0.0%)	1 (2.4%)	1 (1.0%)
Cystoid macular edema	1 (1.7%)	0 (0.0%)	1 (1.0%)
Rash	1 (1.7%)	0 (0.0%)	1 (1.0%)
Other			
Fear of COVID-19 infection	3 (5.2%)	0 (0.0%)	3 (3.0%)
Financial issues	1 (1.7%)	0 (0.0%)	1 (1.0%)
HTLV positive	0 (0.0%)	1 (2.4%)	1 (1.0%)
Leukopenia	0 (0.0%)	1 (2.4%)	1 (1.0%)
Lymphopenia, leukopenia	0 (0.0%)	2 (4.8%)	2 (2.0%)
Nonadherence	1 (1.7%)	0 (0.0%)	1 (1.0%)
Patient decision	2 (3.4%)	4 (9.5%)	6 (6.0%)
Recurrent UTI	0 (0.0%)	1 (2.4%)	1 (1.0%)

HTLV, human T-cell lymphotropic virus; LFT, liver function test; UTI, urinary tract infection.

TABLE S5. Clinical and Radiological Activity After Fingolimod Cessation by Strategy

	Abrupt (n = 58)	Gradual (n = 42)	Total (N = 100)	*P*
Relapses				< .001
No	10 (17.2%)	40 (95.2%)	50 (50.0%)	
Yes	48 (82.8%)	2 (4.8%)	50 (50.0%)	
Number of relapses				< .001
0	10 (17.2%)	40 (95.2%)	50 (50.0%)	
1	42 (72.4%)	1 (2.4%)	43 (43.0%)	
2	6 (10.3%)	0 (0.0%)	6 (6.0%)	
3	0 (0.0%)	1 (2.4%)	1 (1.0%)	
Recovery[B]				< .001
Delayed	11 (19.0%)	1 (2.4%)	12 (12.0%)	
No	11 (19.0%)	40 (95.2%)	51 (51.0%)	
Rapid	36 (62.1%)	1 (2.4%)	37 (37.0%)	
MRI findings				
Stationary				.004
No	28 (48.3%)	7 (16.7%)	35 (35.0%)	
Yes	27 (46.6%)	33 (78.6%)	60 (60.0%)	
N/A	3 (5.2%)	2 (4.8%)	5 (5.0%)	
New lesions				.295
No	41 (70.7%)	35 (83.3%)	76 (76.0%)	
Yes	14 (24.1%)	5 (11.9%)	19 (1.09%)	
N/A	3 (5.2%)	2 (4.8%)	5 (5.0%)	
Enhancing lesions				.500
No	36 (62.1%)	35 (83.3%)	71 (71.0%)	
Yes	19 (32.8%)	5 (11.9%)	24 (24.0%)	
N/A	3 (5.2%)	2 (4.8%)	5 (5.0%)	
Enlarging lesions				.586
No	51 (87.9%)	39 (92.9%)	90 (90.0%)	
Yes	4 (6.9%)	1 (2.4%)	5 (5.0%)	
N/A	3 (5.2%)	2 (4.8%)	5 (5.0%)	

N/A, not assessed.

[a]Data analyzed using χ^2 test. $P < .05$ was considered significant.

[b]Delayed or incomplete recovery is defined as period of ≥ 3 months. Stable lesions were defined as the same lesions presented without any change in size or contrast intake. Contrast-enhancing lesions post contrast MRI were considered markers of inflammatory responses associated with blood-brain barrier breakdown and suboptimal response to multiple sclerosis medications.