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ORIGINAL RESEARCH ARTICLE

Multiple Sclerosis Relapses Following Cessation of Fingolimod

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Abstract

Background There is growing interest in the issue of disease reactivation in multiple sclerosis following fingolimod cessation. Relatively little is known about modifiers of the risk of post-cessation relapse, including the delay to commencement of new therapy and prior disease activity.

Objective We aimed to determine the rate of relapse following cessation of fingolimod and to identify predictors of relapse following cessation.

Methods Data were extracted from the MSBase registry in March 2019. Inclusion criteria were (a) clinically definite relapsing multiple sclerosis, (b) treatment with fingolimod for ≥ 12 months, (c) follow-up after cessation for ≥ 12 months, and (d) at least one Expanded Disability Status Scale score recorded in the 12 months before cessation.

Results A total of 685 patients were identified who met criteria. The mean annualised relapse rate was 1.71 (95% CI 1.59, 1.85) in the year prior to fingolimod, 0.50 (95% CI 0.44, 0.55) on fingolimod and 0.43 (95% CI 0.38, 0.49) after fingolimod. Of these, 218 (32%) patients experienced a relapse in the first 12 months. Predictors of a higher relapse rate in the first year were: younger age at fingolimod cessation, higher relapse rate in the year prior to cessation, delaying commencement of new therapy and switching to low-efficacy therapy.

Conclusions Disease reactivation following fingolimod cessation is more common in younger patients, those with greater disease activity prior to cessation and in those who switch to a low-efficacy therapy.

Key Points

In patients with multiple sclerosis treated with fingolimod, there is a risk of disease relapse following cessation of this treatment.

This study investigated the risk factors associated with an increased disease relapse.

Disease reactivation following fingolimod cessation is more common in younger patients, those with greater disease activity prior to cessation and those who switch to a low-efficacy therapy.

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1 Introduction

Fingolimod (Gilenya®; Novartis Pharma AG, Basel, Switzerland) is a sphingosine 1-phosphate receptor modulator that was approved for the treatment of relapsing-remitting multiple sclerosis in 2010 [1, 2]. Data from clinical trials have demonstrated the effectiveness and generally favourable safety profile of fingolimod in relapsing-remitting multiple sclerosis [3]. A systematic review of the research literature confirmed that fingolimod was associated with improved outcomes compared with the pre-treatment period [4]. Fingolimod is considered to be more effective than glatiramer acetate or the beta-interferons and less effective than natalizumab in limiting the frequency of relapses, even though some heterogeneity among the studies of comparative effectiveness remains to be resolved [5–10].

There has been growing concern regarding the risk of disease reactivation following the cessation of fingolimod, which culminated in the issuing of an US Food and Drug

Administration alert in 2018 [11]. A recent review identified case reports of 52 patients who had experienced a severe rebound following cessation of fingolimod [12]. The recent iMuST study found that 26% of patients were at risk of relapsing within 6 months following fingolimod cessation [13]. While there is some evidence that patients with high disease activity prior to the start of fingolimod treatment, and those that show a good therapeutic response to treatment might be at a higher risk, a clear set of risk factors of post-fingolimod relapse has not yet been established [14–16].

The primary objective of this study was to compare relapse rates in the 12 months prior to fingolimod cessation to the 12 months after fingolimod cessation. The secondary objective was to investigate risk factors of relapse following the cessation of fingolimod.

2 Methods

2.1 Participants

Data were extracted from the MSBase registry in March 2019. Inclusion criteria were: (a) a diagnosis of clinically definite relapse-onset multiple sclerosis [17], (b) treatment with fingolimod for at least 12 months, (c) at least one Expanded Disability Status Scale (EDSS) score recorded within the 12 months prior to fingolimod cessation and (d) clinical follow-up for at least 12 months following fingolimod cessation. All data were entered into the iMed patient record system or the MSBase online system as part of routine clinical practice. Data quality assurance procedures were performed as described elsewhere [18]. The number of patients from each clinical centre are shown in Table S1 of the Electronic Supplementary Material (ESM).

2.2 Clinicodemographic Variables

Key clinicodemographic variables were extracted from MSBase, including age at fingolimod cessation, sex, disease duration (from first symptom of multiple sclerosis) at time of fingolimod cessation, treatment duration at time of fingolimod cessation, number of relapses in the year prior to fingolimod commencement, number of relapses in the year prior to fingolimod cessation, number of relapses in the year following fingolimod cessation, last recorded EDSS score prior to fingolimod cessation (excluding scores within 28 days of relapse), and confirmed pregnancy in the year following fingolimod cessation (including pregnancies confirmed in the 28 days prior to cessation). Recommencement of a disease-modifying therapy was extracted and stratified into low-efficacy (glatiramer acetate, interferon-β, dimethyl fumarate, teriflunomide) or high-efficacy (mitoxantrone, natalizumab, cladribine, fingolimod, alemtuzumab, autologous stem cell transplantation, daclizumab, ocrelizumab, ofatumumab, rituximab, siponimod) therapies [20]. The number of severe relapses (relapses that significantly affected activities of daily living as reported by patients or required hospitalisation) in the year prior to fingolimod commencement (*before fingolimod*), the year prior to fingolimod cessation (*on fingolimod*) and the year following fingolimod cessation was also extracted (*after fingolimod*).

2.3 Statistical Analyses

All statistical analyses were performed in *R* (version 3.6.0). The annualised relapse rate (ARR) was computed by taking the mean of the number of relapses observed over a 12-month period. Bootstrapped bias corrected and accelerated confidence intervals (CIs) were computed at the 95% level. Multivariable negative binomial regression models were used to investigate predictors (risk factors) of the number of relapses occurring in the first year after fingolimod. The following predictors were included: age at fingolimod cessation, disease duration at fingolimod cessation, fingolimod treatment duration, number of relapses in year prior to cessation, last recorded EDSS score prior to fingolimod cessation, confirmed pregnancy in the year following fingolimod cessation, efficacy class of new therapy commenced in first 12 months following cessation (high, low or none) and time to recommencement of therapy (0–2 months, 2–4 months, 4–6 months, 6–8 months, 8–10 months, 10–12 months, > 12 months). Raw and exponentiated model parameters were computed with 95% confidence intervals. The overall significance of model terms was performed using sequential likelihood ratio tests. Cox proportional hazards regression models were computed to investigate the risk of relapse following fingolimod cessation. The same predictors were entered as for the negative binomial models described above.

3 Results

3.1 Sample Characteristics

Data were available from 1869 patients who met the criteria of fingolimod cessation following at least 12 months treatment. Of these, 704 patients were excluded because the post-cessation follow-up time was less than 12 months. Of these patients, 241 patients were excluded because they switched to a randomised controlled trial with unrecorded therapy and 31 were excluded because of a diagnosis of primary progressive multiple sclerosis or neuromyelitis optica. In addition, 208 patients were then excluded because they did not have a recorded EDSS score within

12 months prior to fingolimod cessation. The final sample comprised 685 patients (Table 1).

The most common reason for treatment cessation was lack of effectiveness ($n = 234$, 34%) followed by pregnancy planning or confirmation ($n = 106$, 15%), lack of tolerance ($n = 117$, 17%), and convenience, no adherence or scheduled stop ($n = 85$, 12%). Cessation reason was unrecorded for 143 patients (21%).

The majority of patients commenced another therapy within 12 months of fingolimod cessation ($n = 593$, 87%). Of these, the majority of patients had commenced a high-efficacy therapy ($n = 409$, 60%) compared to a low-efficacy therapy ($n = 184$, 27%). The most common therapy commenced within 12 months of fingolimod cessation was natalizumab ($n = 218$, 32%) followed by dimethyl fumarate ($n = 99$, 14%), rituximab ($n = 51$, 7%), glatiramer acetate ($n = 40$, 6%), teriflunomide ($n = 33$, 5%) and alemtuzumab ($n = 23$, 3%). Other therapies, commenced by fewer than ten patients each, were autologous stem cell transplant, interferon-beta, cladribine, daclizumab, and mitoxantrone. A significant number of patients recommenced fingolimod ($n = 92$, 13%).

3.2 Relapse Rates

Of the overall sample, 218 (32%) had at least one relapse in the first year following cessation. The frequency distribution of the time to first relapse occurring in the first year following treatment cessation is shown in Fig. 1. The majority of these patients had one relapse ($n = 160$, 73%), followed by two ($n = 47$, 22%), three ($n = 5$, 2%), four ($n = 4$, 2%) and five ($n = 2$, 1%) relapses. The ARR in the year prior to fingolimod commencement was 1.71 (95% CI 1.59, 1.85) (Table 2 and Fig. 2). The ARR in the year prior to fingolimod cessation was significantly lower 0.50 (95% CI 0.44, 0.55) and remained consistent in the year following fingolimod cessation 0.43 (95% CI 0.38, 0.49). The difference between ARRs during and after fingolimod was not statistically significant (mean difference [M_{diff}] = − 0.06, 95% CI − 0.14, 0.01).

A similar pattern emerged when the 72 participants were excluded who became pregnant in the year following fingolimod cessation. Of the remaining patients, 170 (28%) had at least one relapse in the first year. The ARR in the year prior to fingolimod commencement was 1.74 (95% CI 1.60, 1.88). The ARR in the year prior to

Table 1 Sample characteristics

Variable	Total sample (n =685)	No relapse in 12 months following cessation ($n = 467$)	Any relapse in 12 months following cessation ($n = 218$)
Clinicodemographic			
Age at fingolimod cessation (years)	39.56 (9.88)	40.75 (10.05)	37.02 (9.01)
Female, *n* (%)	539 (79)	356 (76)	183 (84)
Disease duration at cessation (years)	12.31 (7.23)	12.61 (7.19)	11.67 (7.30)
Treatment duration at cessation (years)	2.51 (1.32)	2.52 (1.32)	2.49 (1.34)
No. of relapses year prior to cessation	0.54 (0.42)	0.45 (0.70)	0.60 (0.77)
Last EDSS prior to cessation	3.05 (2.50)	3.17 (2.11)	2.81 (1.82)
Pregnancy within 12 months, *n* (%)	72 (11)	47 (10)	25 (12)
New therapy within 12 months, *n* (%)			
None	92 (13)	70 (15)	22 (10)
Low efficacy	184 (27)	117 (25)	67 (31)
High efficacy	409 (60)	280 (60)	129 (59)
Delay to new therapy (months), *n* (%)			
0–2	322 (47)	240 (51)	82 (38)
2–4	108 (16)	60 (13)	48 (22)
4–6	48 (7)	25 (5)	23 (11)
6–8	25 (4)	13 (3)	12 (6)
8–10	19 (3)	12 (3)	7 (3)
10–12	22 (3)	11 (2)	11 (5)
> 12	141 (21)	106 (23)	35 (16)

Point and interval estimates are mean (SD), unless specified otherwise

EDSS Expanded Disability Status Scale

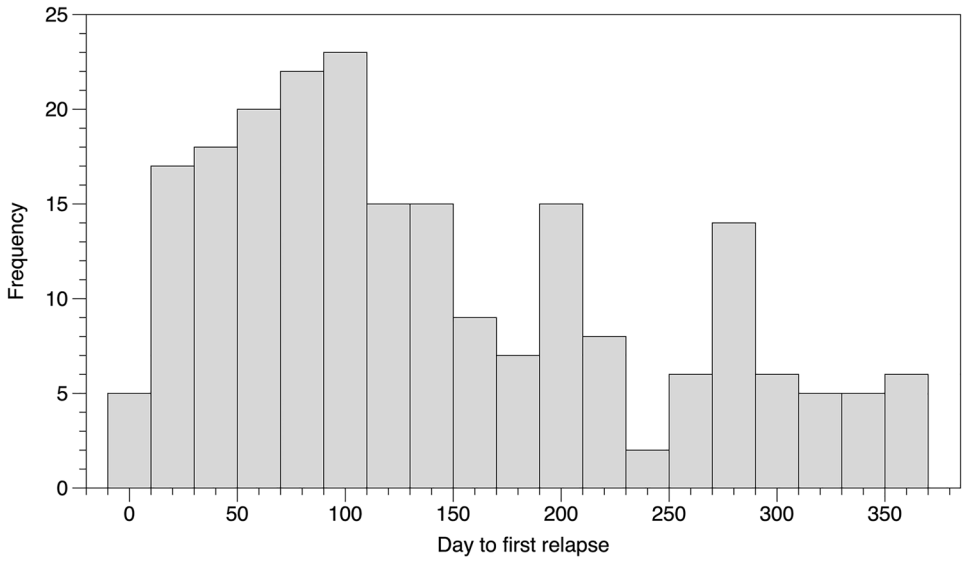

Fig. 1 Frequency distribution of relapses occurring in the first year following treatment cessation

Table 2 Annualised relapse rates (ARR) [95% CI]

	ARR [95% CI]		
Cohort	Before treatment	During treatment	After cessation
All ($n = 685$)	1.71 [1.59, 1.85]	0.50 [0.44, 0.55]	0.43 [0.38, 0.49]
Switch to new therapy (12 months)			
None ($n = 92$)	1.38 [1.09, 1.73]	0.28 [0.17, 0.42]	0.26 [0.16, 0.36]
Low efficacy ($n = 184$)	1.38 [1.17, 1.60]	0.33 [0.24, 0.41]	0.51 [0.40, 0.62]
High efficacy ($n = 409$)	1.95 [1.79, 2.13]	0.62 [0.54, 0.69]	0.44 [0.36, 0.51]
Time to switch (months)			
0–2 ($n = 322$)	1.87 [1.68, 2.07]	0.58 [0.50, 0.67]	0.38 [0.27, 0.42]
2–4 ($n = 108$)	1.72 [1.43, 2.03]	0.52 [0.39, 0.67]	0.53 [0.41, 0.65]
4–6 ($n = 48$)	1.21 [0.81, 1.68]	0.29 [0.13, 0.48]	0.71 [0.46, 0.98]
6–8 ($n = 25$)	1.72 [0.96, 2.64]	0.44 [0.16, 0.84]	0.80 [0.44, 1.37]
8–10 ($n = 19$)	1.74 [1.11, 2.32]	0.32 [0.11, 0.58]	0.84 [0.32, 1.68]
10–12 ($n = 22$)	1.23 [0.64, 2.18]	0.23 [0.05, 0.36]	0.86 [0.45, 1.41]
12+ ($n = 141$)	1.60 [1.35, 1.88]	0.42 [0.31, 0.54]	0.28 [0.20, 0.38]

ARRs were computed as the total number of relapses observed over the specific 12-month period divided by the number of patients. 'Switch to new therapy' shows the ARRs stratified by the efficacy of the new therapy commenced within 12 months of fingolimod cessation. 'Time to switch' shows the ARRs stratified by the time to commencement of any new therapy following fingolimod cessation

fingolimod cessation was substantially lower (0.52, 95% CI 0.46, 0.58) and has further decreased in the year following fingolimod cessation (0.42, 95% CI 0.37, 0.48). The difference between the ARRs during and after fingolimod was statistically significant ($M_{\text{diff}} = -0.12$, 95% CI -0.14, -0.05). Full details of this sub-cohort are shown in Table S2 of the ESM. The same pattern was observed when considering only the 544 patients who recommenced therapy within the first 12 months (Table S4 of the ESM). The ARR was higher in the year prior to commencement (1.75, 95% CI 1.60, 1.90), lower in the year prior to cessation (0.51, 95% CI 0.46, 0.58) and stable over the year following commencement (0.47, 95% CI 0.41, 0.54). The difference between these latter two ARRs was not statistically significant ($M_{\text{diff}} = -0.05$, 95% CI -0.14, 0.04).

A sensitivity analysis was performed to investigate the ARRs in the year following fingolimod separately for relapses that occurred prior to treatment recommencement (i.e. during the washout period) and for relapses after treatment recommencement. The ARR was 0.20 (95% CI 0.16, 0.24) for relapses prior to treatment recommencement and

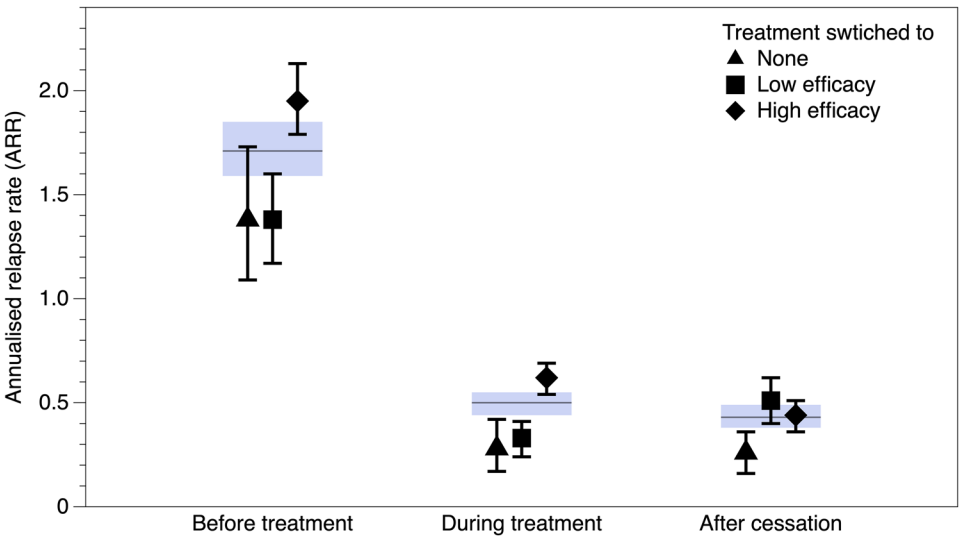

Fig. 2 Annualised relapse rates (ARR) during the 12 months before treatment commencement (before treatment), 12 months before treatment cessation (during treatment) and 12 months after treatment cessation (after cessation). The black line shows the mean relapse rate for the whole cohort, with the shaded area indicating a 95% bootstrapped bias corrected and accelerated confidence intervals. Points with whiskers show the relapse rates stratified by the class of immunotherapy started in the 12 months following cessation (high efficacy, low efficacy or none)

0.24 (95% CI 0.19, 0.27) for relapses following treatment recommencement.

3.3 Predictors of Relapse

Negative binomial regression models were used to investigate the predictors of relapse in the first year following fingolimod cessation. Statistically supported predictors included sex, age at fingolimod cessation, ARR in the year prior to cessation, efficacy class of newly commenced therapy and the time to commencing new therapy (Table 4). Being male was associated with a lower number of relapses, as was being older at the time of fingolimod cessation. Compared with patients who commenced a new therapy within 2 months of fingolimod cessation, delay to new therapy up to 12 months was associated with a greater relapse rate. Patients who waited > 12 months to commence therapy had a comparable relapse rate to those who commenced within 2 months, most likely owing to unmeasured reasons for the extended delay to the next treatment start (such as a low underlying risk of disease reactivation). Annualised relapse rates over the 12-month follow-up were computed, stratified by the delay to new therapy (Fig. 3). Evaluation of ARRs calculated separately within each 2-month period showed that the frequency of relapses that occurred off treatment during the first 2 months after discontinuing fingolimod was comparable to ARRs reported on fingolimod (0.38, 95% CI 0.21, 0.56; Table 5). Thereafter, the off-treatment ARR increased considerably, exceeding the ARR on fingolimod. In contrast, the on-treatment ARR remained consistently low after discontinuing fingolimod, with the exception of the ARR recorded during the first 2 months. This is likely because of high underlying disease activity among those patients who opted to commence another treatment

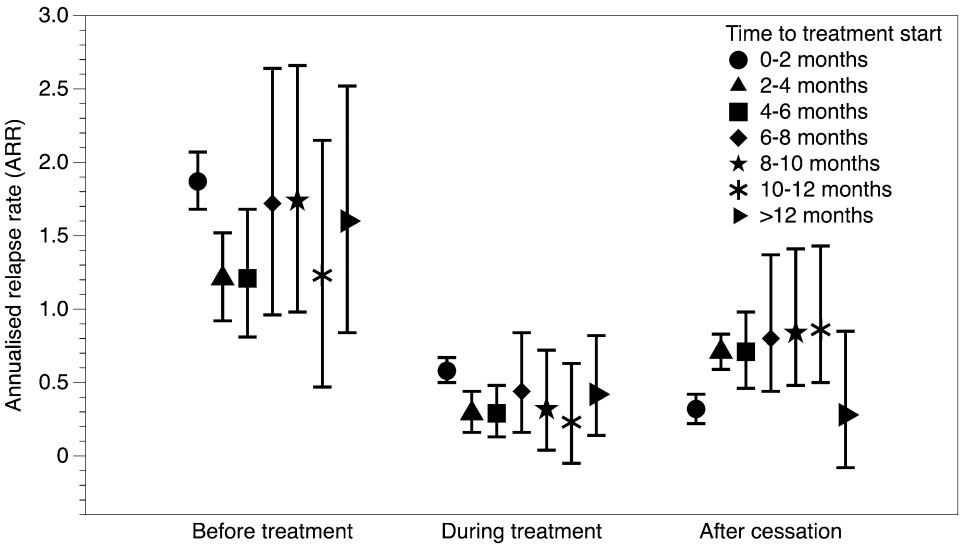

Fig. 3 Annualised relapse rates (ARR) 12 months before treatment commencement (before treatment), 12 months before treatment cessation (during treatment) and 12 months after treatment cessation (after cessation) stratified by the time until recommencement of therapy

immediately after they stopped fingolimod. A post-hoc analysis revealed that switching to a low-efficacy therapy was associated with a higher relapse rate ($p = 0.02$) compared with a high-efficacy therapy. Similarly, because of unmeasured confounding, there was no strong evidence for a difference between no therapy and high-efficacy therapy ($p = 0.99$) nor low-efficacy therapy ($p = 0.63$).

The negative binomial models were then computed separately for the number of relapses in the first year prior to recommencement of therapy and following recommencement of therapy (Table S9 of the ESM). For relapses that occurred prior to recommencement of therapy (i.e. during 'washout'), only the time to recommencing therapy were predictors. The risk of relapse increased 2–4 months after fingolimod cessation (IRR = 6.18, 95% CI 3.31, 12.09) to 10–12 months after fingolimod cessation (IRR = 12.60, 95% CI 6.01, 26.97). In contrast, only the ARR in the year prior to treatment cessation (IRR = 1.27, 95% CI 1.01, 1.58) and switching to a low-efficacy therapy (IRR = 1.86, 95% CI 1.27, 2.70) were predictive of relapses after recommencement of therapy.

3.4 Severe Relapses

Rates of severe relapses for the whole sample were computed (Table 3) as well as for those who recommenced therapy within 12 months (Table S3 of the ESM). Of the overall sample, 16 (2%) patients had a severe relapse in the first 12 months following fingolimod cessation. Nine (1%) patients had a severe relapse in the year prior to cessation. No patients had a severe relapse both in the year prior and the year following cessation. Logistic regression models failed to converge, owing primarily to the relatively small number of patients with severe relapses. Univariate tests revealed that patients who had a severe relapse in the first year following cessation were younger at fingolimod cessation [mean (SD) 33.73 (9.63) years] compared with those who did not [39.70 (9.85) years]. The ARR in the year prior to cessation was also higher in those who experienced a severe relapse [0.77 (0.42)] compared with those who did not [0.54 (0.41)]. All patients who experienced a severe relapse had started either a high-efficacy ($n = 8$) or low-efficacy ($n = 8$) therapy with 12 months of fingolimod cessation, and eight patients experienced a severe relapse prior to re-commencing therapy. Full details of these 16 patients are included in Table S8 of the ESM.

3.5 Freedom from Relapses After Discontinuing Fingolimod

A survival analysis was performed to investigate the risk of relapse following fingolimod cessation. Being older at fingolimod cessation was associated with a lower risk of relapse (Table 4). A greater number of relapses in the year prior to cessation was associated with a higher risk of release. Delaying recommencement of therapy from 2 to 6 months, compared with beginning within 2 months, was also associated with a greater risk of relapse. These results were comparable when the patients who became pregnant within 12 months following fingolimod cessation were excluded

Table 3 Severe relapse rates

	ARR [95%]		
Cohort	Before treatment	During treatment	After cessation
All ($n = 685$)	0.05 [0.03, 0.07]	0.02 [0.01, 0.03]	0.02 [0.01, 0.04]
Switch to new therapy (12 months)			
None ($n = 92$)	0.05 [0.01, 0.12]	0.01 [0.00, 0.03]	–
Low efficacy ($n = 184$)	0.04 [0.02, 0.08]	0.01 [0.00, 0.02]	0.04 [0.02, 0.08]
High efficacy ($n = 409$)	0.05 [0.03, 0.08]	0.03 [0.01, 0.04]	0.02 [0.01, 0.04]
Time to switch (months)			
0–2 ($n = 322$)	0.04 [0.02, 0.07]	0.02 [0.01, 0.03]	0.03 [0.01, 0.04]
2–4 ($n = 108$)	0.07 [0.02, 0.16]	0.04 [0.01, 0.07]	0.04 [0.00, 0.09]
4–6 ($n = 48$)	0.02 [0.00, 0.06]	0.02 [0.00, 0.06]	0.02 [0.00, 0.06]
6–8 ($n = 25$)	–	–	0.08 [0.00, 0.02]
8–10 ($n = 19$)	0.11 [0.00, 0.21]	0.05 [0.00, 0.16]	0.05 [00.0, 0.16]
10–12 ($n = 22$)	0.14 [0.00, 0.41]	0	0.05 [0.00, 0.14]
12+ ($n = 141$)	0.05 [0.01, 0.09]	0.01 [0.00, 0.02]	–

ARRs were computed as the total number of relapses observed over the specific 12-month period divided by the number of patients. 'Switch to new therapy' shows the ARRs stratified by the efficacy of the new therapy commenced within 12 months of fingolimod cessation. 'Time to switch' shows the ARRs stratified by the time to commencement of any new therapy following fingolimod cessation

ARRs annualised relapse rates

Table 4 Predictors of relapse after fingolimod cessation (all patients)

Term	Exp(B) [95% CI]	
	Number of relapses	First relapse
Clinicodemographic		
Sex (male)	**0.62 [0.43, 0.87]**	0.89 [0.67, 1.18]
Age at cessation	**0.96 [0.94, 0.98]**	**0.97 [0.95, 0.98]**
Disease duration at cessation	1.01 [0.99, 1.03]	1.01 [0.99, 1.03]
Treatment duration	1.02 [0.93, 1.12]	1.02 [0.93, 1.12]
ARR year before cessation	**1.29 [1.10, 1.51]**	**1.36 [1.18, 1.56]**
EDSS before cessation	1.02 [0.95, 1.09]	1.00 [0.94, 1.07]
Pregnancy post-fingolimod	1.35 [0.90, 1.99]	0.88 [0.58, 1.33]
Switch to new therapy (12 months)[a]		
Switched to no treatment	0.89 [0.45, 1.80]	1.49 [0.84, 2.65]
Switched to low efficacy	**1.47 [1.12, 1.94]**	**1.52 [1.17, 1.98]**
Time to switch[b] (months)		
2–4	**1.63 [1.16, 2.27]**	**1.67 [1.22, 2.27]**
4–6	**2.31 [1.51, 3.46]**	**2.08 [1.38, 3.14]**
6–8	**2.29 [1.34, 3.74]**	**1.56 [0.88, 2.76]**
8–10	**2.07 [1.13, 3.57]**	**1.45 [0.75, 2.76]**
10–12	**1.96 [1.10, 3.33]**	**1.71 [0.93, 3.15]**
12+	0.79 [0.44, 1.32]	0.83 [0.50, 1.37]

Parameters under "Number of relapses" are from negative binomial model predicting relapse count in the first 12 months after cessation of fingolimod. Parameters under "First relapse" are derived from the Cox proportional hazards model

Bold values indicate CIs that do not capture the null hypothesis value

ARR annualised relapse rate, *EDSS* Expanded Disability Status Scale

[a]Switch to high-efficacy treatment is used as the reference class

[b]Switched to new therapy at 0–2 months is used as the reference class

from the analysis. The relapse incidence by epoch and treatment status was also computed (Table 5).

3.6 Disability Outcomes

The median EDSS score was 2.00 before fingolimod (median absolute deviation [MAD] = 1.48), 2.50 (MAD = 2.22) on fingolimod, and 3.00 (MAD = 2.22) after fingolimod cessation. The median change in EDSS score was 0 (MAD = 0.74). Approximately 20% of patients ($n = 136$) experienced an increase of 1 or more EDSS score points following fingolimod cessation. A logistic regression analysis was performed to investigate the predictors of EDSS score progression. An increase in the EDSS score was associated with older age at fingolimod cessation (odds ratio = 1.05, 95% CI 1.01, 1.08), higher ARR in the year following fingolimod cessation (odds ratio = 2.17, 95% CI 1.64, 3.00) and a lower EDSS score in the year prior to fingolimod cessation (odds ratio = 0.63, 95% CI 0.55, 0.72). There was no evidence for an effect of disease duration, treatment duration, ARR in the year prior to fingolimod cessation, pregnancy following fingolimod cessation, time to recommencement of therapy or

Table 5 Relapse incidence by time interval and treatment status

Time interval (months)	No. of relapses		ARR [95% CI]	
	On treatment	Not on treatment	On treatment	Not on treatment
0–2	19	34	0.72 [0.25, 1.19]	0.39 [0.20, 0.57]
2–4	32	41	0.49 [0.24, 0.76]	0.81 [0.45, 1.18]
4–6	23	23	0.30 [0.12, 0.48]	0.60 [0.26, 0.95]
6–8	27	14	0.33 [0.15, 0.51]	0.43 [0.11, 0.76]
8–10	29	14	0.34 [0.16, 0.52]	0.49 [0.13, 0.83]
10–12	31	8	0.35 [0.17, 0.52]	0.32 [0.01, 0.62]

Relapse rates are given as ARRs with 95% CIs in square brackets. ARRs were computed as the total number of relapses observed over the specific 12-month period divided by the number of patients. 'Time interval' indicates time from fingolimod cessation

ARRs annualised relapse rates

efficacy of the new therapy. The full results of this analysis are included in Table S11 of the ESM.

4 Discussion

The results of this MSBase study indicate that the average relapse rate did not increase following fingolimod cessation in patients with relapsing remitting multiple sclerosis. This was also true for the rate of severe relapses, which occurred in a small number of patients at similar rates to the treatment and pre-treatment epochs. Being male or older at the time of fingolimod cessation was associated with a lower risk of relapse, while a higher relapse rate in the year prior to fingolimod cessation was associated with greater risk of relapse in the first 12 months after the cessation of fingolimod. Importantly, delaying the commencement of immunotherapy beyond 2 months after stopping fingolimod was associated with an increased risk of relapse in the first 12 months. Patients who switched to a high-efficacy therapy achieved better control of clinical disease activity than the patients who switched to a low-efficacy therapy.

These findings are consistent with the iMuST study [13] who found that 26% of the studied 100 patients were at risk of experiencing relapse within 6 months following fingolimod cessation. The risk was slightly greater in our cohort (32%); however, we recorded relapses over a longer period [12 months] and the risk in our cohort was consistent with the 33% reported by Landi and colleagues [21]. The proportion of patients with severe relapses reported in our study was lower than in the iMuST study. This difference is most likely due to the differences in definitions of severe relapse: we defined severe relapses as relapses that significantly affected activities of daily living or required hospitalisation, whereas iMuST defined severe relapses as those associated with at least a 2-point EDSS score increase, or as two or more relapses occurring within 6 months following fingolimod cessation. Over 12 months after fingolimod treatment, 8.4% of patients in our study experienced two or more relapses.

The results of the present study are also in keeping with an earlier MSBase study that evaluated relapse activity in patients who discontinued natalizumab [22]. In the included 536 patients, only a marginal increase in relapse frequency was reported after switching from natalizumab to fingolimod. This increase was more pronounced in patients with more relapses before commencing fingolimod after natalizumab, and with a longer gap between natalizumab and fingolimod.

The association of a longer duration of the 'washout period' after discontinuation of fingolimod with more pronounced clinical reactivation of multiple sclerosis presents a salient point. In particular, patients whose washout period after fingolimod exceeds 2 months have a considerably higher relapse risk. This association is stronger than any other predictor of post-fingolimod clinical activity, which is particularly important to the small subgroup of patients who experience rebound activity with severe/catastrophic relapses [12]. Planned early recommencement of disease-modifying therapy after fingolimod therefore represents an accessible strategy to mitigate the risk of rebound activity.

The observational nature of the data analysed is a limitation of this study. One should therefore bear in mind that our aim was not to draw causal inferences regarding the effect of fingolimod cessation, but to document relapse rates in this population. However, conducting this study in a large observational international registry allowed us to answer the question of disease reactivation after the cessation of fingolimod in the largest cohort yet studied. Second, some clinical data were unavailable, which precluded certain analyses. Specifically, we were unable to study radiological evidence of disease reactivation and lymphocyte counts were not recorded for patients in our study. Third, the relapses did not require confirmation of their severity with EDSS scores. However, we unified the studied timeframe by requiring a conservative minimum on-treatment follow-up of 12 months and a post-fingolimod follow-up of 12 months. Fourth, through sensitivity analyses, we have studied influences of other potential confounders: excluding patients who became pregnant during the post-fingolimod epoch and limiting the analysis to patients who recommenced therapy within 12 months of cessation. Finally, catastrophic relapses have been reported after discontinuation of fingolimod, this study did not enable a focused analysis of specifically these rare but devastating events.

5 Conclusions

This study suggests that discontinuation of fingolimod is safe for most patients, given it is followed by prompt commencement of another therapy within 2 months. Because our individual predictive markers of disease reactivation after fingolimod are limited, especially for the very rare cases of catastrophic events, increased vigilance and early reinstitution of an alternative immunotherapy of equal, but preferably higher effectiveness, is strongly recommended.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-022-01129-7.

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Declarations

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Conflict of interest Charles Malpas, Sifat Sharmin, Olga Skibina and Sara Eichau report no conflicts of interest. Izanne Roos received conference travel support and/or speaker honoraria from Biogen, Novartis, Roche, Merck and Sanofi-Genzyme and has received research support from MSIF, ARSEP and the University of Melbourne. Katherine Buzzard received honoraria and consulting fees from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck, CSL and Grifols. Helmut Butzkueven served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck, Novartis and Biogen. Ludwig Kappos received research support from Acorda, Actelion, Allozyne, BaroFold, Bayer HealthCare, Bayer Schering, Bayhill Therapeutics, Biogen, Elan, European Union, Genmab, Gianni Rubatto Foundation, GlaxoSmithKline, Glenmark, MediciNova, Merck , Novartis, Novartis Research Foundation, Roche, Roche Research Foundation, Sanofi-Aventis, Santhera, Swiss MS Society, Swiss National Research Foundation, Teva Neuroscience, UCB and Wyeth. Francesco Patti received speaker honoraria or advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Myalin, Novartis, Roche, Sanofi-Genzyme and TEVA. He received research funding from Ministero Italiano della Universit‡ e della Ricerca Scientifica, Fondazione Italiana Sclerosi Multipla, Biogen and Merck. Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme. Dana Horakova received speaker honoraria and consulting fees from Biogen, Merck, Teva, Roche, Sanofi Genzyme and Novartis, as well as support for research activities from Biogen and the Czech Ministry of Education (project Progres Q27/LF1). Eva Kubala Havrdova received speaker honoraria and consultant fees from Actelion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi and Teva, and support for research activities from the Czech Ministry of Education (project Progres Q27/LF1). Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva. Suzanne Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering. Pierre Grammond is a Merck, Novartis, Teva-neuroscience, Biogen and Genzyme advisory board member, a consultant for Merck, received payments for lectures by Merck, Teva-Neuroscience and Canadian Multiple Sclerosis Society, and received grants for travel from Teva-Neuroscience and Novartis. Jeannette Lechner-Scott accepted travel compensation from Novartis, Biogen and Merck. Her institution receives the honoraria for talks and advisory board commitment from Bayer Health Care, Biogen, Genzyme Sanofi, Merck, Novartis and Teva, has been involved in clinical trials with Biogen, Novartis and Teva. Tomas Kalincik served on scientific advisory boards for Roche, Celgene, Sanofi-Genzyme, Novartis, Merck and Biogen, served on a steering committee for Brain Atrophy Initiative by Sanofi-Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Genzyme-Sanofi, Teva, BioCSL and Merck and received research support from Biogen.

Ethics approval Patient data were obtained from the international MSBase cohort study (WHO ICTRP ID: ACTRN12605000455662) (19). The study was approved by the Melbourne Health Research Ethics Committee and local ethics committees where relevant. All procedures in this study were in accordance with the 1964 Helsinki Declaration (and its amendments).

Consent to participate Not applicable as data were collected retrospectively.

Consent for publication Not applicable.

Availability of data and material The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions Charles B. Malpas, Izanne Roos and Tomas Kalincik: conception and design of the study, acquisition, analysis, and interpretation of data, drafting and reviewing the manuscript. Sifat Sharmin: conception and design of the study, analysis, and interpretation of data, drafting and reviewing the manuscript. Katherine Buzzard, Olga Skibina, Helmut Butzkueven, Ludwig Kappos, Francesco Patti, Raed Alroughani, Dana Horakova, Eva Kubala Havrdova, Guillermo Izquierdo, Sara Eichau, Suzanne Hodgkinson, Pierre Grammond and Jeannette Lechner-Scott: conception and design of the study, acquisition, and interpretation of data, drafting and reviewing the manuscript. Charles Malpas conducted the primary statistical analyses.

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