Fingolimod after natalizumab and the risk of short-term relapse

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ABSTRACT

Objective: To determine early risk of relapse after switch from natalizumab to fingolimod; to compare the switch experience to that in patients switching from interferon-β/glatiramer acetate (IFN-β/GA) and those previously treatment naive; and to determine predictors of time to first relapse on fingolimod.

Methods: Data were obtained from the MSBase Registry. Relapse rates (RRs) for each patient group were compared using adjusted negative binomial regression. Survival analyses coupled with adjusted Cox regression were used to model predictors of time to first relapse on fingolimod.

Results: A total of 536 patients (natalizumab-fingolimod [n = 89]; IFN-β/GA-fingolimod [n = 350]; naive-fingolimod [n = 97]) were followed up for a median 10 months. In the natalizumab-fingolimod group, there was a small increase in RR on fingolimod (annualized RR [ARR] 0.38) relative to natalizumab (ARR 0.26; $p = 0.002$). RRs were generally low across all patient groups in the first 9 months on fingolimod (RR 0.001–0.13). However, 30% of patients with disease activity on natalizumab relapsed within the first 6 months on fingolimod. Independent predictors of time to first relapse on fingolimod were the number of relapses in the prior 6 months (hazard ratio [HR] 1.59 per relapse; $p = 0.002$) and a gap in treatment of 2–4 months compared to no gap (HR 2.10; $p = 0.041$).

Conclusions: RRs after switch to fingolimod were low in all patient groups. The strongest predictor of relapse on fingolimod was prior relapse activity. Based on our data, we recommend a maximum 2-month treatment gap for switches to fingolimod to decrease the hazard of relapse.

Classification of evidence: This study provides Class IV evidence that RRs are not higher in patients with multiple sclerosis switching to fingolimod from natalizumab compared to those patients switching to fingolimod from other therapies. *Neurology*® 2014;82:1204–1211

GLOSSARY

ARR = annualized relapse rate; **CI** = confidence interval; **EDSS** = Expanded Disability Status Scale; **GA** = glatiramer acetate; **HR** = hazard ratio; **IFN** = interferon; **IQR** = interquartile range; **IRR** = incidence-rate ratio; **MS** = multiple sclerosis; **PML** = progressive multifocal leukoencephalopathy; **RR** = relapse rate.

Fingolimod (Gilenya, Novartis, Basel, Switzerland), a functional antagonist of sphingosine-1-phosphate receptors,[1,2] is a relatively new therapeutic option for treatment of relapsing-remitting multiple sclerosis (MS). Fingolimod has been shown to significantly reduce relapse rate (RR) and new lesion development in clinical trials against placebo and in a head-to-head study against interferon β-1a.[3–5] It has become a common choice for patients failing first-line therapies and those newly engaging with MS therapy in jurisdictions where this is permitted, such as the United States and Australia. It has also become a common switch choice prescribed to patients who have previously been on natalizumab, particularly those who have been on natalizumab for more than

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24 months and test positive for anti-JC-virus antibodies, an identified higher-risk group for progressive multifocal leukoencephalopathy (PML).

Recently, however, a small number of cases of severe MS relapses and radiologic "rebound" occurring shortly after initiation of fingolimod in patients previously treated with natalizumab[6–9] have been reported. Proposed mechanisms include differential inhibition of regulatory T-cell proliferation[6] in patients with high intrinsic relapse activity and differential pharmacokinetics of natalizumab, which may take between 3 and 6 months to wash out,[10] and fingolimod, reported to significantly reduce CNS inflammation and achieve steady-state kinetics at 2 months postinitiation.[2,11] However, case reports suffer from reporting bias, and severe exacerbations of MS rarely occur even in patients on highly active MS treatments.

We therefore used the independent MSBase Registry dataset to examine and compare dynamics of RR change in 3 populations of patients starting fingolimod therapy: namely, patients switching from natalizumab, patients switching from interferon-β/glatiramer acetate (IFN-β/GA), or patients commencing fingolimod as initial therapy. To assess potential evidence for rebound post-natalizumab, we further assessed RR change in the natalizumab to fingolimod switch population, comparing RRs in these 89 patients before commencing natalizumab, during natalizumab therapy, during washout, and on fingolimod therapy. Furthermore, we used survival analysis to determine factors influencing time to first relapse on fingolimod.

METHODS

Standard protocol approvals, registrations, and patient consents. ***Ethics.*** All patients gave written informed consent to participate in the MSBase Registry (www.msbase.org) and Human Research Ethics Committee approval or waivers were obtained from all participating centers, according to applicable local laws and regulations.

Clinical cohort. Patients in the MSBase Registry who were prescribed fingolimod were selected for study. Data were extracted from the Registry in February 2013.

Extracted data were recorded as part of routine clinical practice according to the MSBase observational protocol.[12] The MSBase protocol mandates minimum annual updates; however, patients receiving fingolimod typically attend appointments with their treating neurologists every 3 months in their first year of treatment and every 6 months thereafter, therefore visit frequency in this population was much higher. Data entry was performed in real-time or near real-time at most participating centers. MS-related outcomes data were captured using either the iMed electronic medical record system or the MSBase online data entry system. Date of onset was recorded for each clinical relapse, whether self-reported or physician-confirmed. A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse. Expanded Disability Status Scale (EDSS) scores were recorded by accredited scorers (online Neurostatus certification was required at each center). Disease duration was calculated from the first clinical manifestation, and disease phenotype was assessed by treating physicians.

The MSBase Registry contained clinical data of 733 patients prescribed fingolimod from 23 MS centers in 10 countries: Australia, Spain, Canada, Kuwait, the Netherlands, Italy, Turkey, Argentina, Denmark, and the United States. A total of 536 of these had a minimum follow-up period of 3 months post-fingolimod commencement and were included in the analysis. Some patients from participating centers were involved in the original fingolimod phase II and phase III[3,13] clinical trials, and therefore patient follow-up on fingolimod ranged up to 9.5 years. Patients switching treatment were defined as those on a prior treatment for at least 6 months and who had a maximum 6-month gap between cessation of prior treatment and commencement of fingolimod.

Statistical analyses. Patients were stratified by prior treatment (natalizumab, IFN-β/GA, or none) and RRs were determined.

RRs were compared using negative binomial regression and results were expressed as incidence-rate ratios (IRR) with 95% confidence interval (CI). Unless otherwise stated, the negative binomial regression model was adjusted for sex, age at fingolimod start, disease duration, gap in treatment, and EDSS at fingolimod start. Kaplan-Meier estimates were used to estimate median time to first relapse post-fingolimod initiation. Cox proportional hazards regression was used to model predictors of time to first relapse post-fingolimod initiation. Results are expressed as hazard ratios (HR) with 95% CI. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. The multivariable Cox model was adjusted for significant predictors on univariate analysis. The model was also adjusted for baseline covariates identified a priori including patient group, sex, age at fingolimod start, disease duration, latitude, and an interaction term for age/disease duration. Data assessing time to first relapse were censored at the patients' most recent clinic visit date if a relapse had not yet occurred. One-way analysis of variance and Kruskal-Wallis rank sum test with Bonferroni post hoc adjustments and χ^2 tests were used to test for differences between continuous, nonparametric, or categorical variables, respectively. Spearman rank correlation was used to assess the correlations with annualized RRs.

All statistical analyses were performed using Stata version 12.0 software package (StataCorp, College Station, TX). All reported p values are 2-tailed and for each analysis $p < 0.05$ was considered significant, with the exception of Bonferroni-deflated p values.

RESULTS

Primary research question. Does switching from natalizumab to fingolimod (0.5 mg daily) result in short-term relapse exacerbation? This study provides Class IV evidence that RRs remained relatively stable in patients switching from natalizumab to fingolimod in the first 9 months of fingolimod use (quarterly RR range 0.079–0.13) relative to RR in the 15 months prior to fingolimod use (quarterly RR range 0.045–0.11). These RRs were not significantly different from those of patients switching from IFN-β/GA over the same observation period ($p = 0.460$). However, the annualized RR in this cohort increased to 0.38 on fingolimod from 0.26 on natalizumab ($p = 0.002$),

most likely reflecting a difference in efficacy of the 2 medications.

Baseline characteristics. A total of 536 patients from the MSBase Registry who initiated fingolimod were included in this analysis. Of these, 97 patients were naive to treatment prior to fingolimod start, 350 patients switched from any one of the IFN-β preparations or GA, and 89 patients switched from natalizumab (second-line treatment). Fewer than 5% of patients switching therapy had a treatment gap of greater than 4 months. Those patients switching from IFN-β/GA to fingolimod had a median time off treatment of 1 day (interquartile range [IQR] 0–16). For natalizumab to fingolimod switches, patients had a median washout period of 79 days (IQR 57–96) from last infusion. A single patient was prescribed prophylactic methylprednisolone for the latter 2 months of a 5-month washout period in the natalizumab-fingolimod group. Patients were followed up on fingolimod for a median of 10.3 months (range 3.0–114) totaling 524.6 person-years with 163 post-fingolimod initiation relapses reported for 111 patients.

Table 1 summarizes demographic and baseline clinical characteristics of the 3 fingolimod patient groups. Patients who were treatment naive at fingolimod start were younger than those switching from natalizumab ($p = 0.003$). Disease duration at treatment start differed between all patient groups ($p < 0.0001$ for all comparisons). In addition, patients switching from natalizumab to fingolimod had a higher baseline EDSS (median 4, IQR 2–6) than those who were previously treatment naive (median 1.5, IQR 0–3; $p < 0.0001$), or switching from IFN-β/GA (median 2.5, IQR 1.5–4; $p < 0.0001$). There were no statistically significant differences in baseline EDSS scores between the treatment-naive and IFN-β/GA groups.

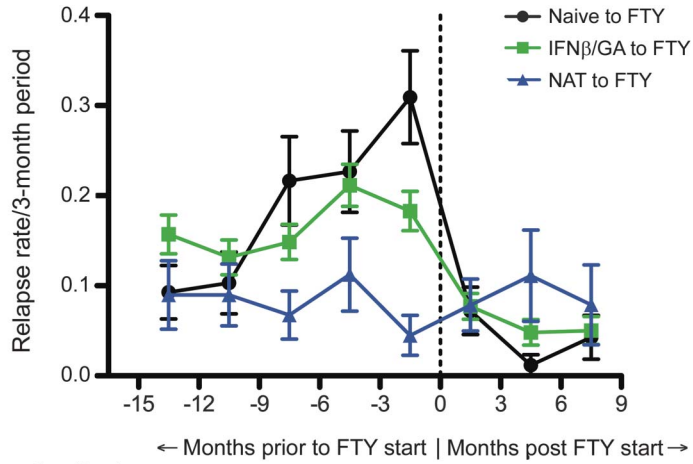
RRs post-fingolimod commencement. To determine whether there was an increase in relapse activity after fingolimod initiation, RRs during each 3-month period in the 15 months preceding fingolimod initiation and in the 9-month period post-fingolimod initiation were determined (figure 1). Three-month RRs in the IFN-β/GA-fingolimod and naive-fingolimod patient groups

Table 1 Baseline patient characteristics and relapse activity post-fingolimod start by patient group

	All groups (n = 536)	Naive to fingolimod (n = 97)	IFN-β/GA to fingolimod (n = 350)	Natalizumab to fingolimod (n = 89)	*p* Value between groups
Female, n (%)	377 (70.3)	62 (63.9)	255 (72.9)	60 (67.4)	0.188[a]
Age at MS onset, y, mean (SD)	30.0 (9.9)	30.6 (10.3)	29.9 (9.8)	29.9 (9.7)	0.826[b]
Age at fingolimod start, y, mean (SD)	40.3 (11.0)	38.0 (12.2)[c]	40.2 (10.8)	43.2 (9.7)[c]	0.005[b]
Disease duration at fingolimod start, y, median (IQR)	8.6 (4.2–14.2)	4.3 (1.7–9.8)[c]	8.7 (4.4–13.7)[c]	12.8 (7.7–17.2)[c]	<0.0001[d]
EDSS at fingolimod start, median (IQR)	2.5 (1.5–4.5)	1.5 (0–3.5)[c]	2.5 (1.5–4)[e]	4 (2–6)[c,e]	<0.0001[d]
Location, n (%)					
Australia	304 (56.7)	44 (45.4)	196 (56.0)	64 (71.9)	
Canada	36 (6.7)	7 (7.2)	26 (7.4)	3 (3.4)	
Italy	42 (7.8)	3 (3.1)	36 (10.3)	3 (3.4)	
Kuwait	46 (8.6)	14 (14.4)	30 (8.6)	2 (2.2)	
Spain	84 (15.7)	19 (19.6)	48 (13.7)	17 (19.1)	
Other	24 (4.5)	10 (10.3)	14 (4.0)	0 (0)	
Follow-up time, patient-years	524.6	167.0	300.9	56.7	
Follow-up months, median (IQR)	10.3 (6.2–14.9)	12.3 (8.0–28.2)[c]	10.0 (6.4–14.9)[c]	7.6 (4.2–12.3)[c]	<0.0001[d]
Prior treatment duration, y, median (IQR)	—	—	2.96 (1.58–5.66)	2.65 (1.90–3.26)	
Patients relapsing on fingolimod, n (%)					
First 3 months	41 (7.6)	7 (7.2)	27 (7.7)	7 (7.9)	0.983[d]
3–6 months	18 (4.4)	1 (1.2)[c]	12 (4.5)	5 (9.3)[c]	0.01[d]
6–9 months	16 (5.2)	3 (4.3)	10 (5.0)	3 (7.9)	0.894[d]
Total follow-up	111 (20.7)	18 (18.6)	75 (21.4)	18 (20.2)	0.813[d]

Abbreviations: EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN = interferon; IQR = interquartile range; MS = multiple sclerosis.
[a] Pearson χ^2 test.
[b] One-way analysis of variance with Bonferroni post hoc test.
[c] Significant comparisons.
[d] Kruskal-Wallis rank sum test with Bonferroni post hoc test.
[e] Significant comparisons.

Figure 1 Relapse rate by patient group pre- and post-fingolimod initiation



Number of patients

Naive to FTY	97	97	97	97	97	97	85	70
IFNβ/GA to FTY	350	350	350	350	350	350	269	199
NAT to FTY	89	89	89	89	89	89	54	38

Relapse rates (mean ± SEM) per 3-month interval in the 15 months preceding fingolimod (FTY) start and in the 9 months following fingolimod initiation by patient group. This figure demonstrates that the relapse rate of patients switching from natalizumab (NAT) remains relatively stable on fingolimod, with no short-term exacerbation of relapse rate. Patients switching from interferon-β (IFNβ)/glatiramer acetate (GA) or who were previously treatment naive have a marked decrease in relapse rate on fingolimod.

progressively increased in the period prior to fingolimod initiation, then decreased markedly on treatment to levels between 0.01 and 0.08 per quarter. Quarterly RRs in the natalizumab-fingolimod group ranged between 0.045 and 0.11 in the 15 months preceding fingolimod start and remained relatively stable, increasing slightly to between 0.079 and 0.13 during the first 9 months of fingolimod use. We did not find any significant differences in quarterly (i.e., 3-monthly) RRs between groups, with the exception of the 3–6 months post-fingolimod commencement between natalizumab to fingolimod switchers and naive to fingolimod commencements ($p = 0.016$), potentially due to the very low RR reported for the latter group in this interval. We did not find any differences between the proportion of patients relapsing at 3 months, or over the entire observation period between patient groups (table 1). Furthermore, no individuals experienced more than 2 relapses in the first 6 months of fingolimod use. Table 2 illustrates relapse risk matrices for the first 6 months of fingolimod use in the natalizumab to fingolimod switch group.

Table 2 Relapse risk matrices for the natalizumab to fingolimod switch group

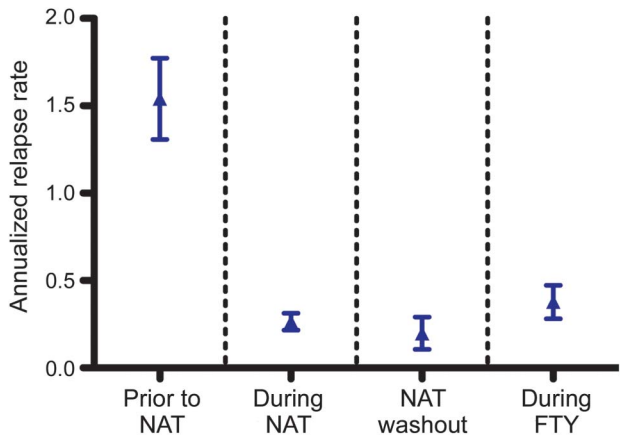
	Number of relapses in first 6 months of fingolimod use		
	0	1+	Total
Natalizumab to fingolimod, numbers relapsing, n (%) of relapses prior 6 months			
0	39 (72.2)	5 (9.3)	44 (81.5)
1+	7 (13.0)	3 (5.5)	10 (18.5)
Total	46 (85.2)	8 (14.8)	54 (100)
Natalizumab to fingolimod, percentage at risk, n (%) of relapses prior 6 months			
0	88.6%	11.4%	
1+	70.0%	30.0%	

To assess whether disease rebound occurred in the natalizumab-fingolimod patient group, annualized RRs (ARR) were determined for the observation period (up to 2 years) prior to natalizumab start, on natalizumab, during natalizumab washout, and on fingolimod (figure 2). We found an increase in the annualized RR on fingolimod in this group with ARR increasing from 0.26 on natalizumab to 0.38 on fingolimod (IRR 1.84; 95% CI 1.25–2.70; $p = 0.002$, adjusted for sex, age at fingolimod start, and disease duration), but this remained substantially lower than the ARR prior to natalizumab start in this group (1.54). We found no correlation between relapse activity prior to natalizumab start and relapse activity on fingolimod (r^2 −0.06; $p = 0.599$). Additionally, we did not find an association between natalizumab exposure length and fingolimod RR (r^2 −0.03; $p = 0.7613$).

Using relapse treatment (ambulatory, hospitalization, or none) as a proxy for relapse severity, we did not find any differences by patient group in the severity of relapses occurring in the first 3 months of treatment use ($p = 0.590$) or over the entire observation period ($p = 0.283$). Of all relapses recorded, 85% were mild to moderate, requiring either no treatment (22%) or ambulatory treatment (63%). The remaining 15% of relapses requiring hospitalization were evenly distributed across patient groups and across the entire observation period, with no clustering at fingolimod treatment start or in the natalizumab to fingolimod group.

Predictors of time to first relapse after fingolimod commencement. At the date of data extract, fewer than 25% of patients had experienced a first relapse on fingolimod. Univariate predictors of time to first relapse included treatment gap and the number of relapses in the preceding 6 months. There was no association between baseline EDSS and time to first relapse on univariate analysis (data not shown). Adjusted Cox proportional regression analyses showed that patient group was not independently predictive of time to first relapse (IFN-β/GA-fingolimod HR = 1.26 [95% CI 0.67–2.39], $p = 0.474$; natalizumab-fingolimod HR = 1.18 [95% CI 0.45–3.11], $p = 0.735$; comparisons vs naive-fingolimod; figure 3A). Our analysis had 90% power at the level of $\alpha = 0.05$ to detect a difference between groups of 4.7% and 3.3%, respectively, relative to the naive-fingolimod group.

Figure 2 Annualized relapse rates in the natalizumab to fingolimod patient group



Annualized relapse rates (mean ± SEM) prior to natalizumab (NAT) start, during natalizumab use, during natalizumab washout, and during fingolimod (FTY) use. This figure demonstrates that while there is an increase in disease activity on fingolimod relative to natalizumab (negative binomial regression incidence-rate ratio 1.84, $p = 0.002$), there is no evidence of disease rebound in this population as assessed by annualized relapse rate.

Rather, adjusted analyses revealed that the strongest independent predictor of time to first relapse on fingolimod was the number of relapses experienced in the 6 months prior to fingolimod start (HR = 1.60 per each relapse, $p = 0.002$). In addition, we found that patients who had a gap in treatment of 2–4 months were more likely to have a relapse on fingolimod than switchers without treatment gap, $p = 0.040$, whereas a 0–2 months gap was not a significant predictor compared to the same reference group. We did not find an effect of sex, age at fingolimod start, disease duration, or latitude on time to first fingolimod relapse in the adjusted analysis (figure 3B).

DISCUSSION Several studies have raised concern that interruption of natalizumab treatment can result in disease rebound (profound disease activation to pre-natalizumab levels),[14–16] even when subsequent immunotherapy has been prescribed.[6,7,17,18]

In the present study, all patients in the natalizumab-fingolimod group were treated with natalizumab as a second-line therapy, having failed on prior treatment. Although we could not formally assess the reasons for natalizumab discontinuation in this cohort, the likely rationale for switching patients who were stable on natalizumab to fingolimod was the increased risk of PML in patients who were positive for anti-JC virus antibodies and on treatment for more than 24 months.[19] In our study, the median duration of natalizumab exposure was 2.65 years.

Our interpretation of the presented data is that patients followed up in the longitudinal MSBase clinical practice registry who switch from natalizumab to fingolimod do not typically experience a marked increase in relapse activity after commencing fingolimod treatment. Indeed, in contrast to a prior report,[20] we found that fingolimod was able to control disease activity in those patients switching from natalizumab to fingolimod, with 85% of patients remaining relapse-free in the first 6 months of fingolimod use. We did find, however, that ARR in this cohort after fingolimod commencement was higher than during natalizumab therapy, but remained very substantially below the pre-natalizumab ARR in this cohort. Quarterly relapse activity in this cohort peaked in the 3–6 months interval, after fingolimod start, equivalent to 5–9 months after natalizumab discontinuation, and one possible explanation could be found in the pharmacokinetics of both natalizumab and fingolimod.[2,10,11]

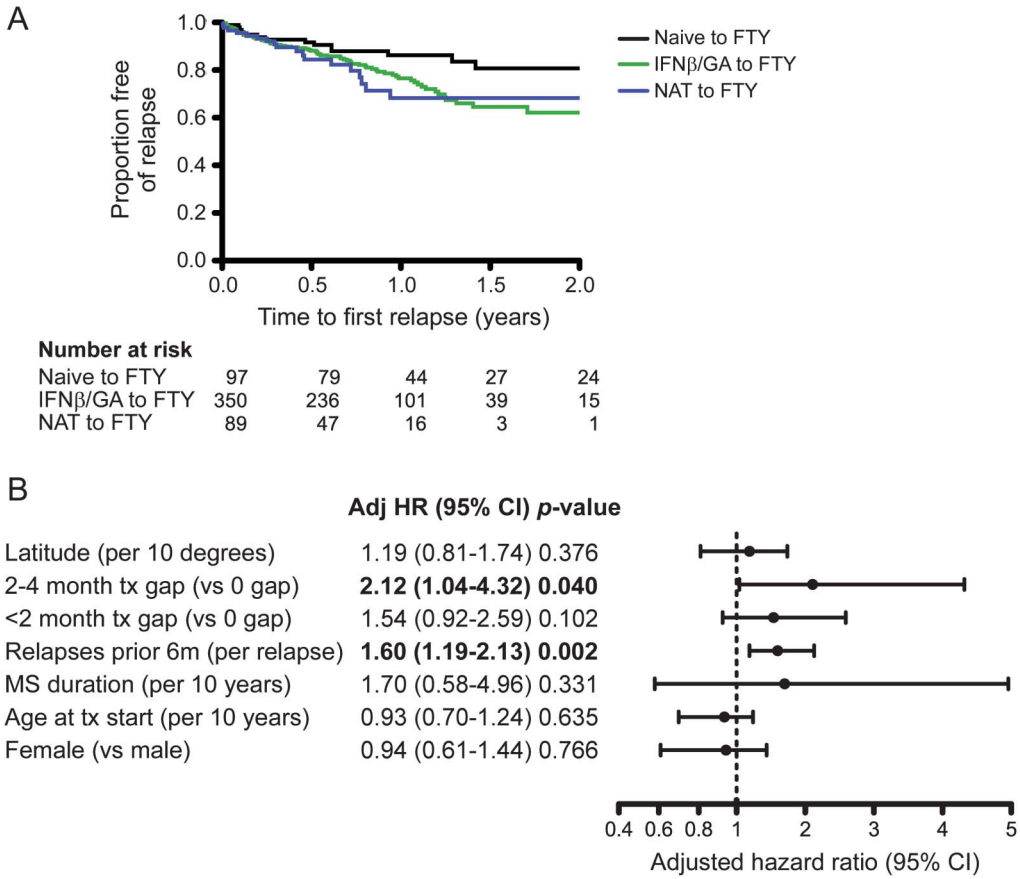
At no point did RRs on fingolimod come close to RRs prior to natalizumab start, and therefore we did not find evidence of disease rebound as assessed by clinical relapse activity in this cohort, consistent with past studies of natalizumab discontinuation.[21–23] It has been suggested that radiologic rebound in patients who discontinue natalizumab treatment occurs in patients with short natalizumab exposure,[8,14] although this was not confirmed in other studies.[22,23] While the MSBase cohort study does not systematically evaluate MRI data, we found RR in the natalizumab-fingolimod switch group was not influenced by duration of natalizumab exposure or relapse activity prior to natalizumab start.

In a recent study of 22 Italian patients who were switched to fingolimod after testing positive for anti-JC virus antibodies, it was reported that relapses, mostly mild, occurred in 27% of patients, and combined clinical and radiologic reactivation occurred in 50% of patients.[24] In our approximately 4-fold larger cohort, we report recurrent relapse activity in 20% of natalizumab-fingolimod switch patients, a lower number, but likely within the expected range of observation error.

Another recent report from the same Italian group described 3 patients with early disease onset who had severe relapses within 1 month of fingolimod start having switched from natalizumab.[7] In our cohort, only 15% of all relapses recorded required hospitalization, and these were equally distributed between all patient groups and across the observation period. However, our results do not exclude the possibility that a small subset of patients could be vulnerable to paradoxical severe exacerbation after fingolimod start, potentially due to underlying disease heterogeneity.

To determine the drivers of time to first relapse on fingolimod, we employed an adjusted Cox regression paradigm. We found that the strongest independent predictor of time to first relapse on fingolimod was relapse activity in the 6 months prior to treatment start, with each relapse in the preceding 6 months increasing the hazard of relapse on fingolimod by 1.6-fold. In other

Figure 3 Time to first relapse on fingolimod



(A) Kaplan-Meier survival estimates for median time to first relapse on fingolimod (FTY) by patient group. There are no significant differences in time to first relapse on treatment between patient groups. Adjusted Cox regression: interferon-β (IFNβ)/glatiramer acetate (GA)-fingolimod hazard ratio (HR) = 1.26 (95% confidence interval [CI] 0.67–2.39), $p = 0.474$; natalizumab (NAT)-fingolimod HR = 1.18 (95% CI 0.45–3.11), $p = 0.735$; comparisons vs naive-fingolimod. (B) Multivariable Cox regression analysis of factors potentially associated with time to first relapse on fingolimod. Analysis of patients (n = 536) treated with fingolimod for a minimum 3 months (median 10.3 months) totaling 524.6 person-years. Patients who had not relapsed were censored at their most recent clinic visit. Analysis was adjusted for sex, age at fingolimod start, disease duration, latitude, patient group, prior relapses, treatment gap, and an interaction term for age/disease duration. Analysis reveals that the strongest predictor of time to first relapse is prior relapse activity. A treatment gap of 2–4 months was also associated with an increased hazard of first relapse relative to no gap. Scaled Schoenfeld Residual $p = 0.9051$. MS = multiple sclerosis.

words, those patients with relapse activity on prior treatment, irrespective of prior treatment identity (including those who were treatment naive), are most likely to continue to relapse on fingolimod. This is consistent with a previous report that showed that prestudy relapse number was significantly associated with on-study RR in phase III clinical trials.[25]

The timing of natalizumab-fingolimod switch remains an important issue. There are currently no guidelines for the optimal period between natalizumab cessation and fingolimod start, but a period of 3 to 6 months has frequently been recommended.[26,27] Moreover, in certain countries, including Italy, a minimum 3-month washout period is mandated before fingolimod treatment can begin, whereas in other countries, such as Australia, there is a degree of flexibility and a period of 8 weeks washout is often used. Our data suggest that a treatment gap of 2–4 months was an independent predictor of increased relapse risk on fingolimod vs no treatment gap, whereas a treatment gap of 1 day to 2 months was not. A limitation of the present analysis was that our natalizumab-fingolimod cohort was too small to test the effect of treatment gap in this group in isolation; therefore, this result should be treated with caution. However, our study suggests that a treatment gap of less than 2 months between prior treatment (including natalizumab) cessation and fingolimod commencement reduces the risk of disease reactivation, consistent with a recent report.[28]

In this study, the largest of its kind to date, we found no evidence to support the occurrence of clinical rebound in patients switching from natalizumab to fingolimod. Recent case reports of disease rebound in patients undergoing this switch could represent

selection bias for reporting severe exacerbations, could be related to long treatment gaps, or could represent a fingolimod-specific side effect in a small subpopulation of patients with MS, with mechanisms of action yet to be fully elucidated. Relapse activity was well-controlled in this patient group and similar to patients switching to fingolimod from IFN-β/GA or those commencing fingolimod as first disease-modifying therapy for MS. The main risk factor for time to relapse on fingolimod is recent prior relapse activity. Our data support choosing a short switch period (2 months or less) between prior treatment and fingolimod to decrease the hazard of relapse on fingolimod.

AUTHOR CONTRIBUTIONS

Dr. Jokubaitis was involved in study conceptualization and design, performed the data analysis and interpretation, drafted and revised the manuscript, and aided in obtaining funding. Dr. Li aided in data analysis and interpretation and in drafting and revising the manuscript. Dr. Kalincik aided in data analysis and interpretation and aided in revising the manuscript. Dr. Izquierdo aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Hodgkinson aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Alroughani aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Lechner-Scott aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Lugaresi aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Duquette aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Girard aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Barnett aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Grand'Maison aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Trojano aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Slee aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Giuliani aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Shaw aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Boz aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Spitaleri aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. Dr. Verheul aided in revising the manuscript for intellectual content and contributed to the acquisition of data and study supervision. J. Haartsen was involved in study conceptualization, aided in revising the manuscript for intellectual content, and contributed to the acquisition of data. Dr. Liew aided in revising the manuscript for intellectual content and helped to obtain study funding. Dr. Butzkueven was involved in study conceptualization and design, data interpretation, revised the manuscript, contributed to the acquisition of data, study supervision, and helped to obtain funding.

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