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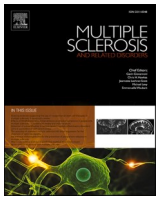

Original article

Switching to natalizumab or fingolimod in multiple sclerosis: Comparative effectiveness and effect of pre-switch disease activity

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ABSTRACT

Background: Patients with relapsing-remitting multiple sclerosis (RRMS) who experience relapses on a first-line therapy (interferon, glatiramer acetate, dimethyl fumarate, or teriflunomide; collectively, "BRACETD") often switch to another therapy, including natalizumab or fingolimod. Here we compare the effectiveness of switching from a first-line therapy to natalizumab or fingolimod after ≥1 relapse.
Methods: Data collected prospectively in the MSBase Registry, a global, longitudinal, observational registry, were extracted on February 6, 2018. Included patients were adults with RRMS with ≥1 relapse on BRACETD therapy in the year before switching to natalizumab or fingolimod. Included patients received natalizumab or fingolimod for ≥3 months after the switch.
Results: Following 1:1 propensity score matching, 1000 natalizumab patients were matched to 1000 fingolimod patients. Mean (standard deviation) follow-up time was 3.02 (2.06) years after switching to natalizumab and 2.58 (1.64) years after switching to fingolimod. Natalizumab recipients had significantly lower annualized relapse rate (relative risk=0.66; 95% confidence interval [CI], 0.59–0.74), lower risk of first relapse (hazard ratio

Abbreviations: ARR, annualized relapse rate; BRACETD, Betaseron, Rebif, Avonex, Copaxone, Extavia, Tecfidera, Aubagio; CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IPTW, inverse-probability-of-treatment-weighting; MRI, magnetic resonance imaging; OFSEP, Observatoire Français de la Sclérose en Plaques; RR, relative risk; RRMS, relapsing-remitting multiple sclerosis; RRR, relapse rate ratio; SD, standard deviation.

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[HR]=0.69; 95% CI, 0.60–0.80), and higher confirmed disability improvement (HR=1.27; 95% CI, 1.03–1.57) than fingolimod recipients. No difference in confirmed disability worsening was observed.
Conclusions: Patients with RRMS switching from BRACETD demonstrated better outcomes with natalizumab than with fingolimod.

1. Introduction

Multiple sclerosis (MS) is a heterogeneous disease with a number of approved disease-modifying therapies (DMTs). In many countries, first-line DMTs include the injectable and oral therapies interferon beta-1b (Betaseron®, Extavia), interferon beta-1a (Rebif®, Avonex®), glatiramer acetate (Copaxone®), teriflunomide (Aubagio®), and dimethyl fumarate (Tecfidera®), together, referred to as BRACETD. In patients who experience MS disease activity on a first-line therapy, clinicians often switch to another treatment to achieve optimal disease control (Giovannoni et al., 2016; Grand'Maison et al., 2018). Both natalizumab and fingolimod are frequent choices for patients switching therapy after MS disease activity on BRACETD (Grand'Maison et al., 2018). The effectiveness of each therapy has been demonstrated in clinical trials and real-world studies (Kappos et al., 2010; Polman et al., 2006; Izquierdo et al., 2017; Butzkueven et al., 2014). One randomized, controlled head-to-head trial of these 2 therapies commenced, but recruitment was stopped early for economic reasons. An analysis of the 108 patients who were enrolled showed lower T1 gadolinium-enhancing lesion accumulation and lower relapse rate in patients randomized to natalizumab vs fingolimod over a maximum of 36 weeks of follow-up (Butzkueven et al., 2017). High-quality comparative real-world data generation is highly economical compared with randomized trials, and is often the only practical way of providing outcome information for many MS treatment switch decisions (Kalincik and Butzkueven, 2016; Trojano et al., 2017).

Several matched or adjusted comparative effectiveness analyses have assessed outcome differences between natalizumab and fingolimod (Barbin et al., 2016; Baroncini et al., 2016; Kalincik et al., 2015; Lorscheider et al., 2018; Prosperini et al., 2017; Carruthers et al., 2014). Collectively, the evidence suggests that natalizumab is more effective than fingolimod; however, differences have not been observed in all cohorts, and point estimates of the magnitude of the differences vary between studies.

This study estimates potential effectiveness differences between natalizumab and fingolimod in patients from MSBase, a large global database, who switched from a BRACETD therapy after ≥1 relapse in the preceding year. Through the use of multiple statistical approaches and subgroup analyses, this analysis evaluated the robustness of the comparative effectiveness estimates in treatment switchers. In particular, we examine the influence of recent on-treatment pre-switch relapse activity on comparative effectiveness of the 2 switch therapies.

2. Methods

2.1. Data source

All patients contributing to this study were sourced from MSBase, a global, longitudinal, observational registry for MS (Butzkueven et al., 2006). Established in 2004, the registry prospectively collects disease-related information from consenting patients at MS treatment centers using an internet-based, physician-owned and -operated system (www.msbase.org; registered with the World Health Organization International Clinical Trials Registry Platform, identification number ACTRN12605000455662). Data for the analysis were extracted from MSBase on February 6, 2018. Informed consent from all patients according to local laws is required for participation in MSBase, and the project has received human research ethics committee approval or exemption at each contributing center.

2.2. Included patients

Adult patients with relapsing-remitting multiple sclerosis (RRMS) previously treated with BRACETD were included in the analysis. Eligible patients had ≥1 relapse on BRACETD therapy within the 12 months prior to switching to either natalizumab or fingolimod (the index therapy) and remained on the index therapy for ≥3 months following the switch. A minimum dataset of variables was also required to derive the propensity score employed in matching and weighting, including demography, baseline Expanded Disability Status Scale (EDSS) score, pre-baseline treatment, and relapse history. Patients with non-BRACETD DMT use prior to switching were excluded from the analysis. Patients participating in randomized clinical trials involving fingolimod, natalizumab, teriflunomide, dimethyl fumarate, alemtuzumab, rituximab, cladribine, or mitoxantrone were also excluded.

2.3. Definitions and outcomes

The baseline (or index date) was defined as the start date of the index switch to natalizumab or fingolimod. A treatment switch was defined as a treatment gap of ≤6 months between discontinuation of the prior BRACETD and initiation of the index switch product. The primary analysis compared the following on-index therapy outcomes: annualized relapse rate (ARR), time to first relapse, time to first 6-month confirmed disability worsening, and time to first 6-month confirmed disability improvement. Confirmed disability worsening events were defined as EDSS score increases ≥0.5 point for patients with a baseline EDSS score >5.5, increases ≥1.0 point for those with a baseline score between 1.0 and 5.5 (inclusive), and increases ≥1.5 points for those with a baseline score of 0.0, confirmed ≥24 weeks later. Confirmed disability improvement events were defined as EDSS score decreases ≥0.5 point for patients with a baseline score >5.5, decreases ≥1.0 point for those with a baseline score between 1.5 and 5.5 (inclusive), and decreases of 1.0 point for those with a baseline score of 1.0, confirmed ≥24 weeks later. For confirmation of either worsening or improvement, EDSS scores recorded ≤30 days after the onset of a relapse were excluded.

2.4. Statistical analysis

Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation (SD) as appropriate. For the primary analysis, patients switching to either natalizumab or fingolimod following a relapse on pre-index BRACETD were propensity score matched to form balanced pairs. The propensity score was derived using a logistic regression in which the dependent variable was the switched treatment group and the independent variables included known correlates of the study outcomes selected a priori, including age, sex, country, disease duration, baseline EDSS, pre-switch treatment history, pre-baseline relapse activity, and index year. Standardized differences were then used to assess the balance of each variable between the 2 switch treatment arms. ARR was compared using a generalized Poisson estimating equation clustering on the matched pair. Time to first relapse, 6-month confirmed disability worsening, and 6-month confirmed disability improvement in the matched sample were compared using a univariate marginal Cox model. Hazard proportionality for each model was assessed via analysis of scaled Schoenfeld residuals. Kaplan-Meier survival and failure curves were used to visualize time-to-event outcome. Three sensitivity analyses were conducted for each outcome model: (1) adjusting by index year, (2)

pairwise censoring the matched pair, and (3) adjusting for index year and pairwise censoring.

As an internal validation, a further sensitivity analysis to check for the impact of the loss of patients who could not be matched, the primary analysis was rerun on the full unmatched sample using the derived propensity score as a weight in a series of inverse-probability-of-treatment-weighting (IPTW) outcome models. Three scenarios were trialed for each outcome: (1) IPTW adjusting the unmatched sample with no trimming, (2) removing patients with nonoverlapping propensity scores, and (3) excluding patients with a stabilized IPTW in excess of the third quartile of the weight distribution.

Three subgroup analyses were run based on the following pre-baseline relapse criteria: (1) exactly one relapse in the 12 months before baseline, (2) ≥2 relapses in the 12 months before baseline (i.e. patients with highly active disease), and (3) exactly one relapse in the 12 months before baseline and ≥1 relapse in the 13–24 months before baseline. These patient subgroups were first identified from the unmatched sample and then separately propensity score matched.

For all analyses, $p < 0.05$ was considered significant. All analyses were conducted in Stata version 15 (StataCorp).

3. Results

3.1. Patients

A total of 1307 patients who switched from BRACETD to natalizumab and 1349 patients who switched from BRACETD to fingolimod following relapse met the inclusion criteria (Table 1). After propensity score matching, 1000 natalizumab patients were successfully matched on a 1:1 basis to 1000 fingolimod patients. The matched sample demonstrated good balance in the distribution of baseline confounders between the switched treatment arms with standardized differences <0.20 for all characteristics (Table 1). No difference in the treatment gap between discontinuation of pre-index BRACETD and initiation of natalizumab (mean [SD] = 26.27 [34.49] days) or fingolimod (mean [SD] = 23.83 [34.78] days) was observed (standardized difference = 0.070). However, follow-up time on natalizumab (mean [SD] = 3.02 [2.06] years) was longer than follow-up time on fingolimod (mean [SD] = 2.58 [1.64] years; standardized difference = 0.237).

3.2. Relapse outcomes

Switching to natalizumab was associated with a reduction in ARR relative to switching to fingolimod (0.189 vs 0.285; Table 2). This translated into a 34% reduction (relative risk [RR] = 0.66; 95%

Table 1
Baseline characteristics before and after matching.

Parameter	Overall population before matching			Matched patients		
	Natalizumab (*n* = 1307)	Fingolimod (*n* = 1349)	Standardized difference	Natalizumab (*n* = 1000)	Fingolimod (*n* = 1000)	Standardized difference
Age, mean (SD), y	36.67 (9.83)	37.71 (9.63)	−0.107	37.10 (10.02)	37.59 (9.41)	−0.050
Sex, *n* (%)						
Female	957 (73.2)	949 (70.4)	0.064	734 (73.4)	721 (72.1)	−0.029
Male	350 (26.8)	400 (29.7)		266 (26.6)	279 (27.9)	
Country, *n* (%)						
Australia	214 (16.4)	170 (12.6)	−0.075	193 (19.3)	148 (14.8)	−0.057
Canada	107 (8.2)	119 (8.8)		96 (9.6)	95 (9.5)	
Czech Republic	181 (13.9)	232 (17.2)		174 (17.4)	212 (21.2)	
Spain	137 (10.5)	127 (9.4)		122 (12.2)	105 (10.5)	
Hungary	152 (11.6)	1 (0.1)		0 (0.0)	1 (0.1)	
Italy	171 (13.1)	246 (18.2)		161 (16.1)	168 (16.8)	
Turkey	62 (4.7)	284 (21.1)		62 (6.2)	102 (10.2)	
Other	283 (21.7)	170 (12.6)		192 (19.2)	169 (16.9)	
MS disease duration, mean (SD), y	8.51 (6.48)	9.32 (6.99)	−0.120	8.84 (6.67)	9.02 (6.85)	−0.026
Pre-index DMTs, *n* (%)						
1	705 (53.9)	720 (53.4)	−0.056	522 (52.2)	514 (51.4)	−0.027
2	371 (28.4)	360 (26.7)		276 (27.6)	278 (27.8)	
3	140 (10.7)	141 (10.5)		115 (11.5)	109 (10.9)	
≥4	91 (7.0)	128 (9.5)		87 (8.7)	99 (9.9)	
Proportion of disease on treatment, mean (SD)	0.57 (0.27)	0.61 (0.27)	−0.153	0.58 (0.27)	0.60 (0.27)	−0.065
Last pre-index DMT, *n* (%)						
Intramuscular interferon beta-1a	253 (19.4)	229 (17.0)	−0.050	173 (17.3)	186 (18.6)	−0.011
Subcutaneous interferon beta-1b	260 (19.9)	289 (21.4)		209 (20.9)	190 (19.0)	
Glatiramer acetate	314 (24.0)	321 (23.8)		222 (22.2)	224 (22.4)	
Subcutaneous interferon beta-1a	423 (32.4)	430 (31.9)		342 (34.2)	331 (33.1)	
Dimethyl fumarate	41 (3.1)	37 (2.7)		38 (3.8)	37 (3.7)	
Teriflunomide	16 (1.2)	43 (3.2)		16 (1.6)	32 (3.2)	
Baseline EDSS score, median (Q1, Q3)	3.5 (2.0, 4.5)	2.5 (1.5, 4.0)	0.408	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.178
Number of relapses in the past 12 months, mean (SD)	1.47 (2.07)	1.85 (1.00)	0.435	1.68 (0.83)	1.59 (0.77)	0.116
Number of relapses in the past 24 months, mean (SD)	2.07 (1.10)	2.71 (1.44)	0.500	2.45 (1.19)	2.25 (1.14)	0.167
Number of relapses treated with steroids in the past 12 months, mean (SD)	1.07 (0.82)	1.29 (1.01)	0.249	1.19 (0.91)	1.15 (0.89)	0.048
Number of relapses treated with steroids in the past 24 months, mean (SD)	1.46 (1.14)	1.84 (1.37)	0.303	1.68 (1.22)	1.57 (1.20)	0.084
Index year, *n* (%)						
≤2007	96 (7.3)	14 (1.0)	−0.964	29 (2.9)	14 (1.4)	−0.619
2008–2012	806 (61.7)	325 (24.1)		615 (61.5)	325 (32.5)	
≥2013	405 (31.0)	1010 (74.9)		356 (35.6)	661 (66.1)	

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Table 2
Annualized relapse rates and relative risks of relapse on natalizumab or fingolimod after matching.

Duration of follow-up	Natalizumab ARR (95% CI)	Fingolimod ARR (95% CI)	*p*-value	RR (95% CI)	*p*-value
All available follow-up	0.189 (0.173–0.205)	0.285 (0.265–0.306)	<0.001	0.66 (0.59–0.74)	<0.001
1 year	0.251 (0.220–0.285)	0.340 (0.303–0.379)	0.004	0.74 (0.62–0.87)	<0.001
2 years	0.219 (0.197–0.243)	0.325 (0.298–0.354)	<0.001	0.69 (0.61–0.79)	<0.001
3 years	0.209 (0.190–0.229)	0.305 (0.282–0.330)	<0.001	0.72 (0.64–0.81)	<0.001
4 years	0.202 (0.184–0.220)	0.295 (0.273–0.318)	<0.001	0.73 (0.65–0.82)	<0.001
5 years	0.194 (0.178–0.211)	0.289 (0.266–0.308)	<0.001	0.75 (0.67–0.84)	<0.001

ARR, annualized relapse rate; CI, confidence interval; RR, relative risk.

confidence interval [CI], 0.59–0.74) in relapse risk relative to fingolimod over the full follow-up period. This reduction in ARR favoring natalizumab was consistently observed over 1–5 years of follow-up (Table 2).

Patients who switched to natalizumab had a 31% reduction in the risk of first relapse relative to those who switched to fingolimod (hazard ratio [HR] = 0.69; 95% CI, 0.60–0.80) (Fig. 1A). Censoring the matched pairs to correct for on-treatment follow-up differences returned an almost identical reduction in first-relapse rate favoring natalizumab (HR = 0.68; 95% CI, 0.56–0.81). Results were also similar with pairwise censoring and adjustment by index year (HR = 0.63; 95% CI, 0.53–0.76).

3.3. Disability outcomes

No difference between treatment groups was observed in the rate of remaining free of 6-month confirmed disability worsening while on treatment (HR = 1.14 for natalizumab vs fingolimod; 95% CI, 0.88–1.47) (Fig. 1B). Similarly, no difference was observed after pairwise censoring of the matched pairs (HR = 0.93; 95% CI, 0.69–1.26) or adjustment by index year (HR = 0.86; 95% CI, 0.63–1.18).

Patients switching to natalizumab were 1.27 times more likely than those switching to fingolimod to exhibit 6-month confirmed disability improvement (HR = 1.27; 95% CI, 1.03–1.57) (Fig. 1C). However, this difference was reduced when the matched sample was pairwise censored, accounting for differences in follow-up time (HR = 1.16; 95% CI, 0.97–1.28 vs fingolimod). Pairwise censoring with adjustment by index year also reduced the difference in confirmed disability improvement between patients switching to natalizumab and fingolimod (HR = 1.12; 95% CI, 0.89–1.20).

3.4. Sensitivity analysis

Eligible fingolimod patients excluded from the matched sample (n = 349) were older at baseline, were more likely to be male, and had a longer disease duration, a lower baseline EDSS, and less pre-switch relapse activity than unmatched natalizumab patients (n = 307; Supplementary Table 1). In the IPTW analysis of unmatched groups, the observed reduction in first-relapse rate favoring natalizumab in the matched sample was not significant when the unmatched model was IPTW adjusted without trimming (HR = 0.88; 95% CI, 0.74–1.04; Supplementary Table 2). A reduction in the risk of first relapse favoring natalizumab was once again observed when the IPTW model was trimmed to exclude stabilized weights above the third quartile (HR = 0.65; 95% CI, 0.53–0.76).

Differences in confirmed disability worsening varied from significant (HR = 1.39; 95% CI, 1.02–1.90) in the non-trimmed IPTW model to nonsignificant in the trimmed models (Supplementary Table 2). Confirmed disability improvement generally followed IPTW relapse models, with the significant improvement favoring natalizumab observed in the matched sample falling marginally outside of significance on the untrimmed model (HR = 1.24; 95% CI, 0.98–1.58). However, this improvement was significant once the IPTW model was trimmed at the third quartile of stabilized weights (HR = 1.31; 95% CI, 1.05–1.65; Supplementary Table 2).

3.5. Subgroup analyses

In the subgroup of patients with exactly 1 relapse in the 12 months prior to the study baseline, 484 pairs of natalizumab and fingolimod patients were matched (Supplementary Table 3). Patients who switched to natalizumab had a significantly lower ARR (0.17; 95% CI, 0.15–0.19) than patients who switched to fingolimod (0.23; 95% CI, 0.21–0.26), with a relative risk of 0.71 (95% CI, 0.60–0.84). Switching to natalizumab was also associated with a significant reduction in the risk of first relapse relative to fingolimod (HR = 0.73; 95% CI, 0.59–0.91; Fig. 2A). No significant differences in confirmed disability worsening or improvement were observed (Table 3).

In the highly active subgroup (≥2 relapses in the 12 months before baseline), which included 427 pairs of patients, natalizumab exhibited benefits over fingolimod in terms of both ARR (0.23 [95% CI, 0.20–0.26] for natalizumab vs 0.36 [95% CI, 0.33–0.40] for fingolimod) (RR = 0.64; 95% CI, 0.55–0.74) and time to first relapse (HR = 0.58; 95% CI, 0.48–0.72; Fig. 2B). No statistically significant difference in confirmed disability worsening was observed (Table 3). However, confirmed disability improvement was significantly more likely with natalizumab than with fingolimod (HR = 1.42; 95% CI, 1.04–1.94). As in the primary analysis, this difference was no longer significant once pairwise censoring was applied (Table 3).

Finally, in the subgroup reporting 1 relapse in the 12 months prior to switching and ≥1 relapses in months 13–24 prior to switching, 217 pairs of natalizumab and fingolimod patients were analyzed. Patients who switched to natalizumab again exhibited a significantly lower ARR (0.21; 95% CI, 0.17–0.24) than patients who switched to fingolimod (0.29; 95% CI, 0.25–0.33) (RR for natalizumab vs fingolimod = 0.72; 95% CI, 0.57–0.90). Although there was no significant difference in time to first relapse on the unadjusted modeling of the matched sample (Fig. 2C), a reduction in first-relapse rate in the natalizumab arm was observed once pairwise censoring was applied to the model (HR = 0.68; 95% CI, 0.47–0.98). For this subgroup, there was no significant difference between natalizumab and fingolimod in confirmed disability worsening or improvement (Table 3).

4. Discussion

This comparative effectiveness analysis investigated clinical outcomes for patients switching from a BRACETD therapy to either natalizumab or fingolimod due to on-treatment disease activity. Overall, patients who switched to natalizumab had lower relapse rates and greater time to first relapse than patients who switched to fingolimod. These differences remained consistent with a number of statistical approaches and subgroup analyses, supporting the robustness of the results. The most pronounced differences, a 36% reduction in relapse risk and a 42% increase in the cumulative probability of confirmed disability improvement, were observed in the subgroup of patients with ≥2 relapses on a BRACETD therapy in the prior year, suggesting that the improvement in efficacy with natalizumab relative to fingolimod is greatest in patients with high disease activity prior to the treatment switch.

Limited differences in disability outcomes between patients who switched to natalizumab or fingolimod were observed. Confirmed

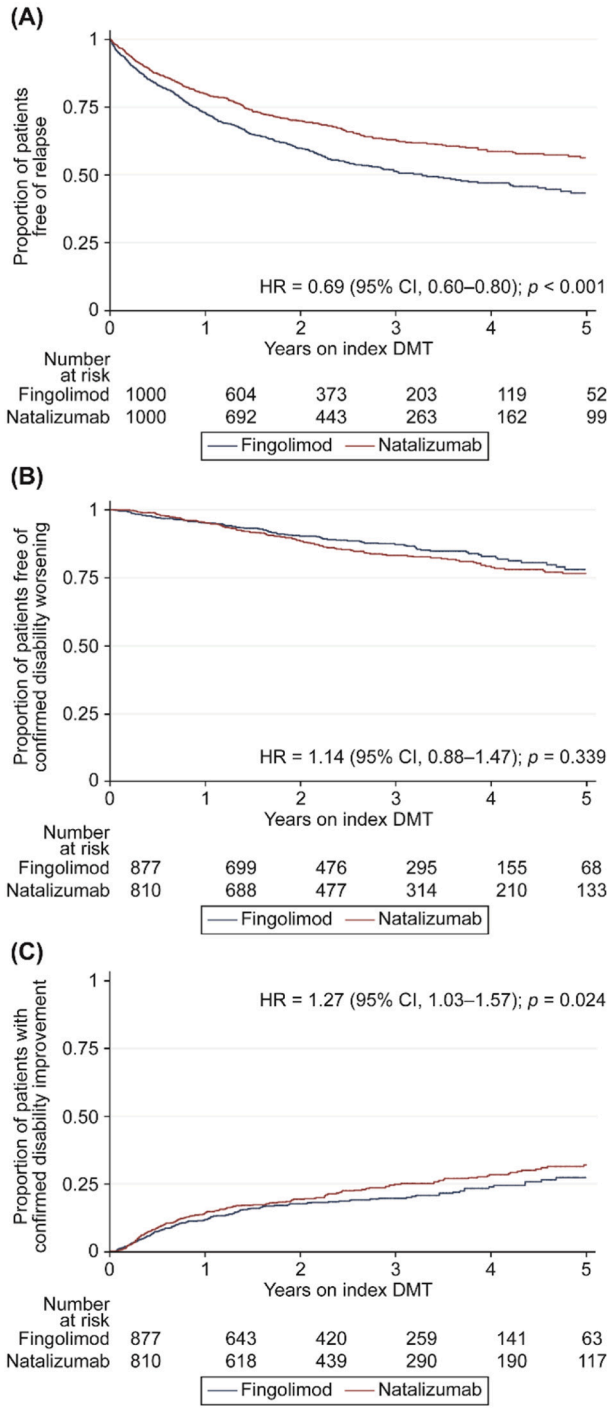

Fig. 1. Relapse, confirmed disability worsening, and confirmed disability improvement. KM curves for (**A**) time to first relapse, (**B**) time to first 6-month confirmed disability worsening event, and (**C**) time to first 6-month confirmed disability improvement event in propensity score–matched natalizumab and fingolimod patients. The x-axis is truncated at 5 years based on the limited numbers of patients at later time points. HR shows risk of first relapse, first confirmed disability worsening event, or first confirmed disability improvement event for natalizumab vs fingolimod. CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio; KM, Kaplan-Meier.

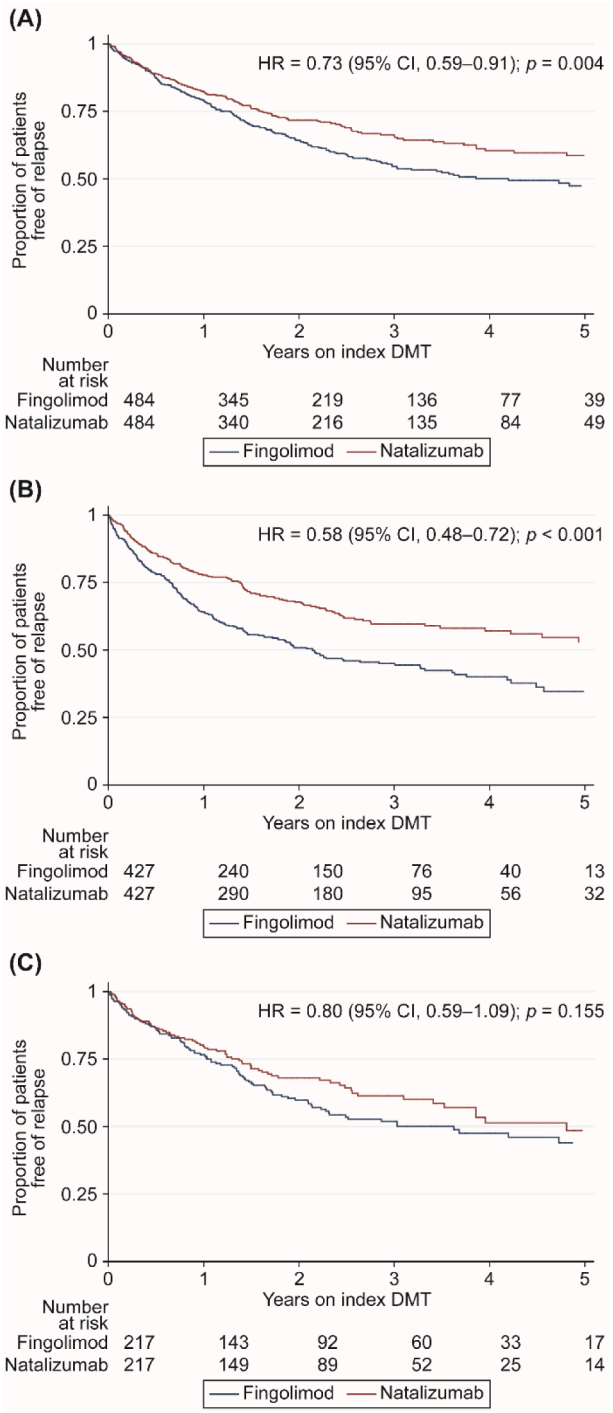

Fig. 2. Time to relapse by prior disease activity subgroup. Analyses of time to first relapse in subgroups with (**A**) 1 relapse in the year prior to switching, (**B**) ≥2 relapses in the year prior to switching, or (**C**) 1 relapse in the 12 months prior to switching and ≥1 relapse in months 13–24 prior to switching. The x-axis is truncated at 5 years based on the limited numbers of patients at later time points. HR shows risk of first relapse for natalizumab vs fingolimod. CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio.

disability improvement was significantly more likely for patients switching to natalizumab vs fingolimod in the primary analysis of patients with ≥1 pre-switch relapse and in the subgroup of patients with ≥2 prior relapses. However, this difference was no longer significant when pairwise censoring was applied, indicating that differences in follow-up time may have contributed to the disability improvement outcome. With a longer follow-up time, greater differences in disability outcomes might have been seen. These results are consistent with a number of previous reporting trends toward less 6-month confirmed disability worsening and more 6-month confirmed disability improvement with natalizumab than with fingolimod (Baroncini et al., 2016;

Table 3
Subgroup analyses of 6-month confirmed disability worsening and improvement after matching.

	Subgroup 1: 1 relapse in the year prior to switching		Subgroup 2: ≥2 relapses in the year prior to switching		Subgroup 3: 1 relapse in the year prior to switching and ≥1 relapse in months 13–24 prior to switching	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
6-month confirmed disability worsening						
Univariate	1.12 (0.77–1.63)	0.546	1.00 (0.68–1.47)	0.990	1.45 (0.84–2.51)	0.179
Pairwise censored	0.90 (0.57–1.33)	0.518	1.13 (0.66–1.86)	0.400	1.22 (0.66–2.28)	0.528
Pairwise censored and adjusted by index year	0.83 (0.54–1.28)	0.410	1.12 (0.68–1.84)	0.657	1.14 (0.61–2.13)	0.689
6-month confirmed disability improvement						
Univariate	1.15 (0.85–1.56)	0.365	1.42 (1.04–1.94)	0.027	1.12 (0.71–1.76)	0.635
Pairwise censored	1.05 (0.77–1.34)	0.220	1.37 (0.99–1.91)	0.081	1.06 (0.69–1.70)	0.798
Pairwise censored and adjusted by index year	0.98 (0.75–1.31)	0.167	1.27 (0.91–1.71)	0.204	1.06 (0.68–1.69)	0.771

CI, confidence interval; HR, hazard ratio.

Kalincik et al., 2015; Prosperini et al., 2017; Guger et al., 2018; Lanzillo et al., 2017; Curti et al., 2019).

These results confirm and expand upon a previous analysis from MSBase using 2013 data that showed benefits for natalizumab over fingolimod in patients switching from interferon beta or glatiramer acetate after an on-treatment relapse or disability worsening event (Kalincik et al., 2015). The current analysis extends the results to include additional typical first-line therapies (teriflunomide and dimethyl fumarate), many more patients, and a longer duration of follow-up. Minor differences in the results of these 2 analyses could be explained in part by the differences in inclusion criteria, in particular pre-switch therapies.

The results of registry studies comparing outcomes between fingolimod and natalizumab treatments can vary. Sources of this variation were examined recently in a multi-registry collaboration including the Danish registry, the French Observatoire Français de la Sclérose en Plaques (OFSEP), and the MSBase registry (Andersen et al., 2021). The relevant registry data were pooled and harmonized. Then, the authors replicated individual prior registry studies – the Danish registry data again showed no differences in relapse metrics between natalizumab and fingolimod, whereas the OFSEP and MSBase replications again favored natalizumab. A pooled cohort analysis was consistent with the OFSEP and MSBase results. The authors hypothesized that differences between the study populations could be very important. The Danish patients were older and had a much lower pre-index relapse rate (ARR 0.76 in prior 12 months) than either the MSBase (ARR 1.35) or OFSEP (1.62) patients. Interestingly, the relapse rate ratio (RRR) of natalizumab to fingolimod was also greatest in the OFSEP cohort (RRR 0.47), compared with MSBase (RRR 0.62) and the Danish registry (RRR 1.12).

In this study, we have replicated and confirmed these results in a single cohort drawn from only 1 registry source, MSBase, by evaluating subgroups with 1 relapse (minimal disease activity) or ≥2 relapses (high disease activity) in the year prior to switching. We also examined a subgroup with 1 relapse in the 12 months prior to switching and ≥1 relapse in months 13–24 prior to switching (prolonged disease activity). The high-disease-activity subgroup showed the greatest RRR with natalizumab vs fingolimod and also the greatest difference in confirmed disability improvement, favoring natalizumab.

Results from our IPTW and propensity score-matching methods were similar and replicate results from another recent study (Lefort et al., 2022). The authors used the above 3-registry dataset to demonstrate that matching vs weighting methodologies had no material effects on the study results.

In a third study using the same 3-registry dataset, Sharmin and colleagues formally examined baseline covariates that influence relapse outcomes in the natalizumab vs fingolimod comparisons (Sharmin et al., 2021). They again confirmed that baseline relapse rate was a key determinant of the size of the therapeutic difference favoring natalizumab.

One limitation of our analysis was the lack of sufficient MRI data to assess radiological outcomes such as new MRI lesion number of new gadolinium-enhancing lesion activity. The comparison of MRI outcomes in real-world settings can be challenging due to variability in MRI timing and non-standardized reporting. The randomized, head-to-head REVEAL trial demonstrated that patients with active RRMS who initiated natalizumab accumulated fewer gadolinium-enhancing lesions or new or newly enlarging T2 lesions over 24 weeks compared with those who initiated fingolimod (Butzkueven et al., 2017). However, this study was terminated early, precluding examination of the primary endpoint or other MRI outcomes beyond 24 weeks. Four additional real-world studies, all from Italy, compared composite outcomes of clinical and radiological disease activity for natalizumab and fingolimod and identified significant benefits with natalizumab over 2 years of follow-up (Baroncini et al., 2016; Prosperini et al., 2017; Preziosa et al., 2017; Totaro et al., 2015).

The relatively short follow-up time and the difference in follow-up duration for natalizumab and fingolimod (3.0 vs 2.6 years) could also have influenced outcomes, particularly with regard to disability worsening and improvement, for which additional follow-up time for 6-month confirmation was required. Given that natalizumab follow-up duration was longer, more events could have been observed in the natalizumab group. We applied pairwise censoring to account for this difference and limit attrition bias, but this also limited the number of observable events by generally shortening follow-up time.

Reasons for switching to natalizumab or fingolimod were not systematically collected, and we do not know the extent to which certain characteristics such as anti–JC virus serostatus may have contributed to these decisions. Finally, safety outcomes were not compared in this analysis. The established safety profiles of natalizumab and fingolimod must also be considered when considering benefits and risks for individual patients.

5. Conclusion

These updated results from the MSBase registry support the superior effectiveness of natalizumab over fingolimod in patients switching from a BRACETD therapy following on-treatment relapse. We confirm and extend results of recent studies showing that the greatest relapse outcome differences favoring natalizumab over fingolimod occurs among those with very high relapse activity in the year prior to switching. These findings may be useful to clinicians weighing the benefits and risks of switching from BRACETD therapies to either natalizumab or fingolimod.

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Declaration of Competing Interest

Dr Spelman has received honoraria for consultancy and funding for travel from Biogen and Novartis. Dr Horakova has received speaker honoraria and consulting fees from Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva, as well as support for research activities from Biogen and the Czech Ministry of Education (project Progres Q27/LF1). Dr Alroughani has received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche, and Sanofi Genzyme. Dr Kalincik has served on scientific advisory boards for Biogen, Merck, Novartis, Roche, and Sanofi Genzyme and a steering committee for Genzyme's Brain Atrophy Initiative; has received conference travel support and/or speaker honoraria from Bio-CSL, Biogen, Merck, Novartis, Sanofi Genzyme, Teva, and WebMD Global; and has received research support from Biogen. Dr Terzi has received travel grants from Bayer Schering, Merck, Novartis, and Teva and has participated in clinical trials by Novartis, Roche, and Sanofi. Dr Grammond has served on advisory boards for Biogen, Genzyme, Merck, Novartis, and Teva Neuroscience and as a consultant for Merck; has received payments for lectures from Merck, Teva Neuroscience, and the Canadian Multiple Sclerosis Society; and has received grants for travel from Novartis and Teva Neuroscience. Dr Patti has received speaker honoraria or advisory board fees from Almirall, Bayer, Biogen, Celgene,

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Supplementary materials

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