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Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis

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The comparative effectiveness of fingolimod versus interferon beta/glatiramer acetate was assessed in a multicentre, observational, prospectively acquired cohort study including 613 patients with relapsing multiple sclerosis discontinuing natalizumab in the Italian iMedWeb registry. First, after natalizumab suspension, the relapse risk during the untreated wash-out period and during the course of switch therapies was estimated through Poisson regression analyses in separated models. During the wash-out period an increased risk of relapses was found in patients with a higher number of relapses before natalizumab treatment (incidence rate ratio = 1.31, $P = 0.0014$) and in patients discontinuing natalizumab due to lack of efficacy (incidence rate ratio = 2.33, $P = 0.0288$), patient's choice (incidence rate ratio = 2.18, $P = 0.0064$) and adverse events (incidence rate ratio = 2.09, $P = 0.0084$). The strongest independent factors influencing the relapse risk after the start of switch therapies were a wash-out duration longer than 3 months (incidence rate ratio = 1.78, $P < 0.0001$), the number of relapses experienced during and before natalizumab treatment (incidence rate ratio = 1.61, $P < 0.0001$; incidence rate ratio = 1.13, $P = 0.0118$, respectively) and the presence of comorbidities (incidence rate ratio = 1.4, $P = 0.0097$). Switching to fingolimod was associated with a 64% reduction of the adjusted-risk for relapse in comparison with switching to interferon beta/glatiramer acetate (incidence rate ratio = 0.36, $P < 0.0001$). Secondly, patients who switched to fingolimod or to interferon beta/glatiramer acetate were propensity score-matched on a 1-to-1 basis at the switching date. In the propensity score-matched sample a Poisson model showed a significant lower incidence of relapses in patients treated with fingolimod in comparison with those treated with interferon beta/glatiramer acetate (incidence rate ratio = 0.52, $P = 0.0003$) during a 12-month follow-up. The cumulative probability of a first relapse after the treatment switch was significantly lower in patients receiving fingolimod than in those receiving interferon beta/glatiramer acetate ($P = 0.028$). The robustness of this result was also confirmed by sensitivity analyses in subgroups with different wash-out durations (less or more than 3 months). Time to 3-month confirmed disability progression was not significantly different between the two groups (Hazard ratio = 0.58; $P = 0.1931$). Our results indicate a superiority of fingolimod in comparison to interferon beta/glatiramer acetate in controlling disease reactivation after natalizumab discontinuation in the real life setting.

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Abbreviations: BRACE = Betaferon®, Betaseron®, Rebif®, Avonex®, Copaxone® or Extavia®; EDSS = Expanded Disability Status Scale; IFNβ = interferon beta; IRR = incidence rate ratio

Introduction

The handling of treatment sequencing in relapsing multiple sclerosis patients who must discontinue natalizumab for efficacy or tolerability reasons or because they have a high risk of developing progressive multifocal leukoencephalopathy, is one of the main issues in patient management that neurologists are facing today. After natalizumab discontinuation, there is a risk of disease reactivation (Killestein *et al.*, 2010; West *et al.*, 2010; Borriello *et al.*, 2011, 2012; Havla *et al.*, 2011; Kaufman *et al.*, 2011; Kerbrat *et al.*, 2011; Magraner *et al.*, 2011; O'Connor *et al.*, 2011; Rossi *et al.*, 2013; Cohen *et al.*, 2014) which correlates with the wash-out duration and disease activity before (O'Connor *et al.*, 2011) and during (Jokubaitis *et al.*, 2014) natalizumab treatment. The risk seems to be higher after 3 months of wash-out, with a peak between 4 and 7 months (O'Connor *et al.*, 2011;

Cohen *et al.*, 2014), but a high rate of recurrence of clinical activity has been demonstrated as early as 4–8 weeks after the last natalizumab infusion in a more recent randomized study (Fox *et al.*, 2014).

Switching from natalizumab to first-line Betaferon®, Betaseron®, Rebif®, Avonex®, Copaxone® or Extavia® (BRACE) or fingolimod may be reasonable options for preventing disease reactivation, but results of published studies are not conclusive and often discordant (Stuve *et al.*, 2009; Havla *et al.*, 2011, 2013; Magraner *et al.*, 2011; O'Connor *et al.*, 2011; Borriello *et al.*, 2012; Centonze *et al.*, 2012; Rinaldi *et al.*, 2012; Laroni *et al.*, 2013; Rossi *et al.*, 2013; Sempere *et al.*, 2013; Clerico *et al.*, 2014; Cohen *et al.*, 2014; Fox *et al.*, 2014; Jokubaitis *et al.*, 2014).

The randomized Restore study (Fox *et al.*, 2014) and the Italian prospective spontaneous observational study TY-STOP (Clerico *et al.*, 2014) have proved the superiority of continuing natalizumab in comparison with its interruption despite switching to first-line BRACE or methylprednisolone.

The effect of fingolimod in preventing disease reactivation after natalizumab discontinuation has been evaluated by a number of small size observational studies (Rinaldi *et al.*, 2012; Havla *et al.*, 2013; Laroni *et al.*, 2013; Sempere *et al.*, 2013). Two of them (Havla *et al.*, 2013; Laroni *et al.*, 2013) suggested patients who switched to fingolimod within 6 months after natalizumab had reduced annualized relapse rates compared with those who remained untreated or who switched to intramuscular interferon beta (IFNβ)-1a or glatiramer acetate, whereas two other studies (Rinaldi *et al.*, 2012; Sempere *et al.*, 2013) reported increased severe relapses in patients switching to fingolimod during the 3–4 months after natalizumab discontinuation. Two more recent and larger observational studies (Cohen *et al.*, 2014; Jokubaitis *et al.*, 2014) provided results in favour of disease activity stabilization in patients with an early switch to fingolimod after natalizumab. Although fingolimod seems to be the most attractive option available so far, no direct comparative effectiveness study of fingolimod versus placebo or versus BRACE has yet been carried out. Hence to date, there are no conclusive guidelines nor is there any consensus underpinning practice as regards the best currently available treatment option and the safest wash-out duration for relapse risk reduction after natalizumab suspension.

In a large unselected cohort of prospectively-followed Italian patients with relapsing-remitting multiple sclerosis discontinuing natalizumab therapy, we directly compared the effectiveness of fingolimod versus BRACE in controlling clinical disease reactivation after natalizumab suspension. Moreover, we evaluated clinical and demographic factors influencing the relapse risk during both the untreated wash-out period and the course of treatment switch.

Materials and methods

Database and study population

This was a large, multicentre, observational, prospectively acquired cohort study. Longitudinal data from 26 086 patients from 45 Italian multiple sclerosis centres were extracted from the iMedWeb registry in December 2013. Inclusion criteria for the subsequent analysis comprised patients with a diagnosis of multiple sclerosis (Polman *et al.*, 2011), at least six natalizumab infusions before discontinuation, and the availability of a minimal data set consisting of: sex, date of birth, date of multiple sclerosis onset, dates of clinical relapses occurring in the year preceding natalizumab initiation, during natalizumab treatment and after natalizumab suspension, immunomodulant and/or immunosuppressive therapies before natalizumab treatment (yes/no), reasons for natalizumab discontinuation, dates of start and type of treatment switch after natalizumab, Expanded Disability Status Scale (EDSS) score recorded at the time of the first and last natalizumab infusions, and during the treatment switch. Any invalid or inconsistent entries were identified and excluded in a series of automated filtering steps. Patients were censored at the end of follow-up. Patients who stopped natalizumab treatment owing to the occurrence of progressive multifocal leukoencephalopathy were excluded from the analysis. The final population entering the analysis included 613 patients from 24 Italian sites (Fig. 1).

During the post-natalizumab suspension follow-up, the decision on whether, how, and when to restart alternative treatment was the responsibility of the treating neurologist at each participating centre. Of the total cohort of 613 patients, 433 patients received at least one disease-modifying drug prescription during the follow-up. The time interval between natalizumab cessation and switching to another therapy or the end of follow-up period for patients who did not start other therapies was considered as an untreated wash-out period. This made it possible to estimate the risk of relapse during the wash-out period in the entire study population ($n = 613$). The factors influencing relapse risk after starting switching therapies were evaluated in 433 patients, 135 of whom switched to fingolimod and 298 to BRACE ($n = 160$ any formulation of IFNβ, $n = 138$ glatiramer acetate) (Fig. 1). The comparative effectiveness of fingolimod versus BRACE for relapse risk was assessed in propensity score-matched groups. Finally, the comparative effect on disability progression was also estimated in propensity score-matched patients. Confirmed disability progression was defined as $\geqslant$3-month confirmed increase of $\geqslant$1.0 point EDSS score compared to the EDDS value at the time of the switch in therapy

Statistical analyses

In descriptive analyses, continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables were expressed as percentages. The risk of relapses during the untreated wash-out period and after switching therapy was estimated through a Poisson regression analysis in separated models. Incidence rates were expressed as number of events/100 patients/month and the risk of relapses was reported as incidence rate ratio (IRR).

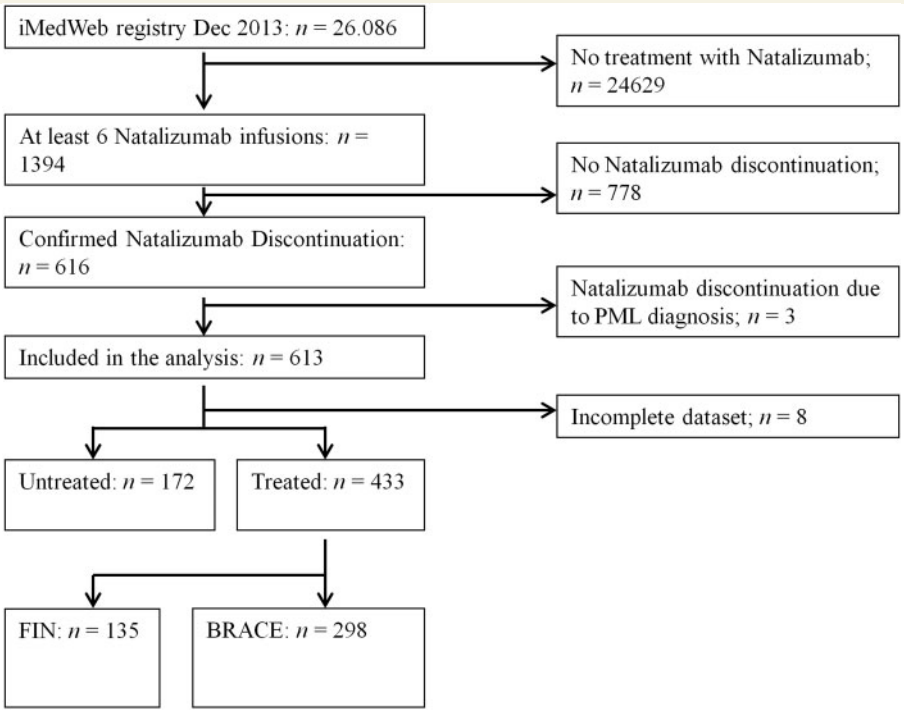

Figure 1 Flow-chart showing patients selection. FIN = fingolimod; PML = progressive multifocal leukoencephalopathy.

To evaluate the risk of relapses during the untreated wash-out period the following covariates, evaluated at the time of the last infusion of natalizumab, were included in the model: sex, age, disease duration, EDSS, comorbidity (thyroid dysfunction/allergy/headache/other) (yes/no), immunomodulant exposure prior to natalizumab (yes/no), immunosuppressive exposure prior to natalizumab (yes/no), number of relapses in the year before natalizumab and during natalizumab, number of natalizumab infusions and reasons for natalizumab suspension (progressive multifocal leukoencephalopathy concern, pregnancy, adverse event, patient's choice or lack of efficacy of the natalizumab treatment).

The factors influencing the relapse risk after starting switching therapies were then estimated including the following covariates, evaluated at the time of the switch in therapy, in the model: sex, age, disease duration, EDSS, comorbidity (thyroid dysfunction/allergy/headache/other) (yes/no), immunomodulant exposure prior to natalizumab (yes/no), immunosuppressive exposure prior to natalizumab (yes/no), number of relapses in the year before natalizumab, during natalizumab and during the wash-out period, number of natalizumab infusions, switching therapy (fingolimod/BRACE), wash-out length (0-3 versus >3 months). To assess the effect of different durations of the untreated wash-out on treatment response, we applied a wash-out cut-off of 3 months.

To compare the effectiveness of switching therapies on clinical disease reactivation we evaluated the relapse risk in two groups of patients: those who switched to fingolimod and those who switched to BRACE. Furthermore, to allow for an unbiased comparison, these patients were propensity score-matched on a one-to-one basis, at the time of the switch (Parsons *et al.*, 2004; Yanovitzky *et al.*, 2005). A five-to-one greedy matching algorithm was used to identify a unique matched BRACE-treated patient for each fingolimod-treated patient according to the propensity score. Adequacy of balance for the covariates in the matched sample was assessed via the standardized mean difference between the two groups, considering differences of $<10\%$ as a good balance (Austin *et al.*, 2007). Overlapping of propensity score between the two groups was also checked. The propensity score was calculated by a logistic regression model using the probability of receiving fingolimod as a dependent variable and including the following covariates at the time of the treatment switch: sex, age, disease duration, EDSS, comorbidity (thyroid dysfunction/allergy/headache/other–yes/no), previous immunomodulant exposure (yes/no), previous immunosuppressive exposure (yes/no), number of natalizumab infusions, occurrence of relapse (yes/no) before and during natalizumab and during the wash-out period. In the matched sample, a Poisson model was used to allow a comparison between patients treated with fingolimod or BRACE in terms of the risk of relapses after the treatment switch. Since the wash-out duration was markedly different between patients switching to fingolimod and those receiving BRACE, this covariate was not included in the propensity score procedure, but *ad hoc* sensitivity analyses were performed: propensity score matching (including the same covariates) was applied to two subgroups of patients, those who received fingolimod or BRACE within 3 months, and those with a wash-out period of >3 months after natalizumab discontinuation, the Poisson models were performed to estimate the incidence of relapses in both subgroups. Probabilities of relapses during the wash-out period and after switching to fingolimod or BRACE were calculated using the Kaplan-Meier method. Comparison of the relapse risk between patients treated with fingolimod or BRACE was performed using the log-rank test.

Comparison of time to confirmed disability progression was obtained by a time-to-event Cox regression model. *P*-values were 2-sided, and values <0.05 were considered to be statistically significant. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc.).

Results

At the time of data extraction 1394 patients had received at least six infusions of natalizumab, and 616 of 1394 patients had definitively stopped the treatment. Three patients were excluded as the reason for discontinuation was diagnosis of progressive multifocal leukoencephalopathy (Fig. 1). The demographic and clinical characteristics of the whole study population are shown in Table 1. Patients had received a mean of 23.59 ($\pm$11.10) natalizumab infusions. The mean annualized relapse rates were significantly reduced at the time when natalizumab was stopped (0.35 ± 1.27) in comparison with annualized relapse rates in the year before natalizumab (1.21 ± 1.06); the mean EDSS score remained stable during natalizumab treatment (3.53 ± 1.69 at natalizumab start versus 3.54 ± 1.57 at natalizumab stop, *P* = not significant). The main reasons for discontinuation were: progressive multifocal leukoencephalopathy concerns in 58.56%, adverse events in 18.43%, patient's choice in 12.23%, lack of efficacy in 6.69% and confirmed pregnancy in 4.08% of patients. One hundred and nineteen patients (19.4%) experienced at least one clinical relapse after stopping natalizumab during the untreated wash-out period. The median of untreated wash-out duration was 2.5 (q1–q3 = 1–5.3) months for the total population and 5.1 (q1–q3 = 3.5–10.5) months for patients who switched to fingolimod and 1.4 (q1–q3 = 0.9–3.1) months in patients who switched to BRACE.

The Poisson regression analysis (Table 2) demonstrated that the clinical disease activity before natalizumab treatment was associated with an increased risk in disease reactivation during the wash-out period (IRR = 1.31, $P = 0.0014$). Furthermore, a higher risk of relapse during the wash-out was found in patients discontinuing natalizumab due to lack of efficacy (IRR = 2.33, $P = 0.0288$), patient's choice (IRR = 2.18, $P = 0.0064$) and adverse events (IRR = 2.09, $P = 0.0084$) in comparison with those stopping natalizumab due to progressive multifocal leukoencephalopathy concerns.

Figure 2A shows the cumulative probability of the first relapse during the untreated wash-out period after natalizumab suspension. The cumulative probability was 0.25% in the first month, it grew 3-fold in the second and third months (1.08–1.75%) and more than 10 times thereafter (4–6%). At 12 months after natalizumab discontinuation, 22.3% of patients presented at least one relapse.

The Poisson model, which included the covariates evaluated at the time of switching, revealed that the strongest independent factors influencing the risk of relapse after the start of a new therapy were a wash-out duration longer than 3 months (IRR = 1.78, $P < 0.0001$), the number of relapses experienced during and before natalizumab treatment (IRR = 1.61, $P < 0.0001$; IRR = 1.13, $P = 0.0118$, respectively), and the presence of comorbidities (IRR = 1.4, $P = 0.0097$). Switching to fingolimod was associated with a 64% reduction in the risk of relapse in comparison to switching to BRACE (IRR = 0.36, $P < 0.0001$). In addition, increasing age and disease duration, at the switch, were associated with a reduction in risk of relapses (IRR = 0.98, $P = 0.0111$; IRR = 0.98, $P = 0.0444$, respectively), whereas for each infusion of natalizumab there was an increase of 1% in the risk of relapse during the switching treatment (IRR = 1.01, $P = 0.0439$). (Table 3)

Table 4 presents the clinical and demographic characteristics of the two groups of patients receiving fingolimod or BRACE treatments after natalizumab suspension, at the time of the treatment switch. Before propensity score matching, there were significant differences between the two patients groups for all the covariates, except for sex, EDSS, number of patients with relapse during natalizumab, number of patients with previous immunomodulant exposure and with previous immunosuppressive exposure.

After the propensity score matching, the two groups were perfectly balanced for all the covariates (Table 4). Because of no overlapping propensity score, 20.74% of patients receiving fingolimod were excluded from the analyses. This is considered an acceptable percentage of no overlapped cases in propensity score models (Austin *et al.*, 2007). The matched sample was 107 patients for both groups.

The Poisson model performed in the propensity score-matched groups showed a significantly lower incidence of relapses in patients treated with fingolimod in comparison with patients treated with BRACE (IRR = 0.52, $P = 0.0003$) (Table 5).

The cumulative probability of a first relapse after the treatment switch was significantly lower in patients receiving fingolimod than in those receiving BRACE ($P = 0.028$) (Fig. 2B).

The cumulative probability of a first relapse during the first year of post-switching follow-up in patients treated with fingolimod versus those treated with BRACE was 6.10% versus 9.89% at the end of the fourth month, 13.49% versus 20.13% at the end of the eighth month and 15.01% versus 26.84% at 12 months.

Sensitivity analyses in 25 pairs of matched patients with a wash-out duration between 0 and 3 months and in 73 pairs of matched patients with wash-out duration over 3 months confirmed the lower risk of relapses in patients switching to fingolimod in comparison with BRACE (IRR = 0.53, $P = 0.0363$, IRR = 0.41, $P = 0.0013$, respectively) (Table 6).

A confirmed 1.0 point increase of the EDSS score was reached by 22.5% of patients receiving BRACE, and by 11.4% of those receiving fingolimod ($P = 0.06$). However the different rate of confirmed disability progression between the two groups of patients did not reach a statistical significance in the Cox model (Hazard ratio = 0.58,

Table 1 Demographic and clinical baseline characteristics of the entire study population

Variable		Value
Sex (female/male)		439/174
Age at NTZ stop, mean (SD), years		37.5 (9.0)
Disease duration at NTZ stop, mean (SD), years		12.1 (6.9)
EDSS score at NTZ start, mean (SD); median (min–max)		3.5 (1.6); 3.5 (0–8)
EDSS score at NTZ stop, mean (SD); median (min–max)		3.5 (1.7); 3.5 (0–8)
n of NTZ infusions, mean (SD); median (min–max)		23.6 (11.1); 24 (6–84)
ARR in the year before NTZ, mean (SD); median (min–max)		1.2 (1.1); 1 (0–6)
ARR during NTZ, mean (SD); median (min–max)		0.3 (1.3); 0 (0–7)
IM exposure prior to NTZ, *n* (%)	Yes	539 (87.9)
	No	74 (12.1)
IS exposure prior to NTZ, *n* (%)	Yes	129 (21)
	No	484 (79)
Comorbidity, *n* (%) (thyroid dysfunction/allergy/headache/other)	Yes	84 (13.7)
	No	529 (86.3)
Main reasons for discontinuation, *n* (%)	PML concern	359 (58.6)
	Adverse event	113 (18.4)
	Patient's choice	75 (12.2)
	Lack of efficacy	41 (6.7)
	Pregnancy	25 (4.1)

ARR = annualized relapse rate; NTZ = natalizumab; IM = immunomodulant; IS = immunosuppressant; PML = progressive multifocal leukoencephalopathy.

Table 2 Poisson regression analysis: risk of relapses during the wash-out period (*n* = 613)

Variable	Category	IR (95% IR CI)	IRR (95% IRR CI)	*P*
Sex	Male	4.87 (2.83–8.38)	1.1 (0.73–1.65)	0.655
	Female	4.44 (2.87–6.87)	1	
Age at NTZ stop			0.99 (0.97–1.02)	0.486
Disease duration at NTZ stop			1.02 (0.99–1.06)	0.193
EDSS at NTZ stop			0.88 (0.78–1.00)	0.058
Comorbidity	Yes	3.58 (1.85–6.93)	0,59 (0.33–1.06)	0.080
	No	6.04 (4.18–8.72)	1	.
Previous IM exposure	Yes	4.29 (2.98–6.17)	0.85 (0.48–1.51)	0.581
	No	5.04 (2.61–9.74)	1	.
Previous IS exposure	Yes	4.52 (2.61–7.85)	0.95 (0.61–1.46)	0.805
	No	4.78 (3.09–7.40)	1	.
Relapses in the year before NTZ, *n*			1.31 (1.11–1.54)	0.001
n of relapses during NTZ			1.04 (0.85–1.28)	0.706
NTZ infusions, *n*			1.02 (1.00–1.03)	0.093
Main reasons of discontinuation	Adverse event	5.57 (3.23–9.62)	2.09 (1.21–3.62)	0.008
	Patient's choice	5.79 (3.31–10.10)	2.18 (1.25–3.79)	0.006
	Lack of efficacy	6.2 (2.94–13.06)	2.33 (1.09–4.97)	0.029
	Pregnancy	4.09 (1.90–8.81)	1.54 (0.76–3.12)	0.234
	PML concern	2.66 (1.65–4.29)	1	.

IR = incidence rate for 100 person/month; NTZ = natalizumab; PML = progressive multifocal leukoencephalopathy; IM = immunomodulant; IS = immunosuppressant; CI = confidence interval.

95% confidence interval = 0.26–1.31, reference = BRACE; $P = 0.1931$).

Discussion

To date, there are no head-to-head randomized controlled trials or large observational comparative effectiveness studies indicating what is the optimal treatment strategy to prevent the consistently shown risk of disease reactivation for patients who discontinue natalizumab treatment for efficacy or safety issues (Stuve *et al.*, 2009; Killestein *et al.*, 2010; West *et al.*, 2010; Borriello *et al.*, 2011, 2012; Havla *et al.*, 2011; Kaufman *et al.*, 2011; Kerbrat *et al.*, 2011; Magraner *et al.*, 2011; O'Connor *et al.*, 2011; Rinaldi *et al.*, 2012; Rossi *et al.*, 2013).

First, in this study we evaluated clinical and demographic factors influencing the relapse risk during the untreated wash-out period after stopping natalizumab. We confirmed findings of previous studies (O'Connor *et al.*, 2011; Cohen

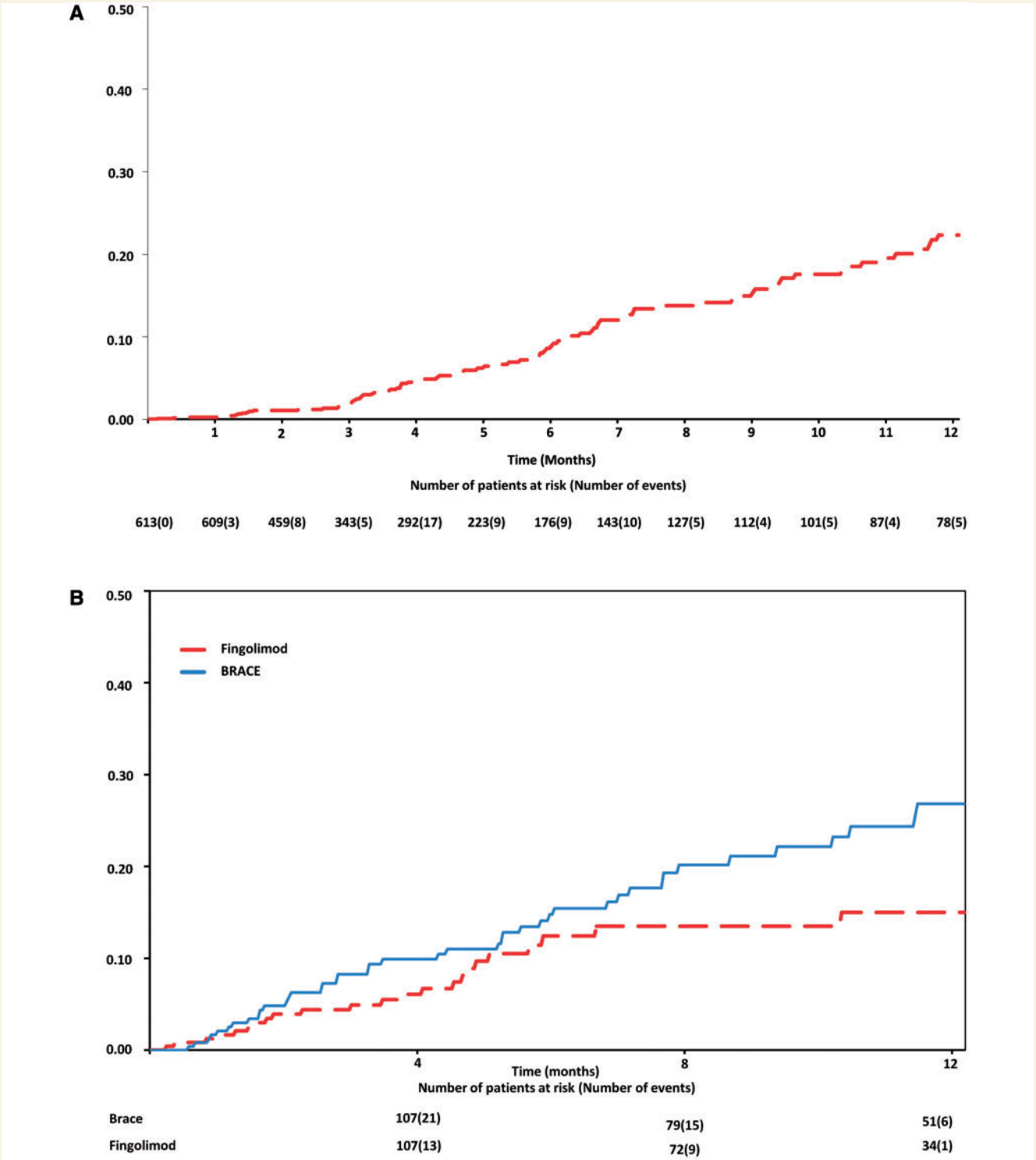

Figure 2 Cumulative probabilities of a first relapse. (**A**) Cumulative probability of a first relapse during the untreated wash-out period after natalizumab discontinuation. (**B**) Cumulative probability of a first relapse after the treatment switch.

et al., 2014; Fox *et al.*, 2014) showing a higher risk of relapse in patients discontinuing natalizumab due to lack of efficacy or the occurrence of adverse events and in patients with high disease activity before natalizumab. In our cohort, the cumulative probability of a first relapse was less than 0.5% during the first month, but it grew 3-fold in the second and third months and more than 10 times thereafter. This is in line with the results of the randomized Restore study (Fox *et al.*, 2014) demonstrating that in patients assigned to the placebo arm (42 patients), after

Table 3 Poisson regression analysis: risk of relapses after the treatment switch (*n* = 433)

Variable	Category	IR (95% IR CI)	IRR (95% IRR CI)	*P*
Sex	Male	6 (4.32–8.24)	0.97 (0.74–1.27)	0.828
	Female	6.2 (4.75–7.95)	1	
Age at switch			0.98 (0.97–1.00)	0.011
Disease duration at switch			0.98 (0.96–1.00)	0.044
EDSS at switch			0.94 (0.88–1.01)	0.097
Comorbidity	Yes	7.2 (5.19–9.88)	1.4 (1.09–1.80)	0.01
	No	5.1 (3.98–6.58)	1	
Previous IM exposure	Yes	6.5 (5.27–8.12)	1.17 (0.81–1.68)	0.408
	No	5.6 (3.78–8.30)	1	
Previous IS exposure	Yes	6.8 (4.87–9.47)	1.26 (0.96–1.65)	0.099
	No	5.4 (4.22–6.91)	1	
Relapses in the year before NTZ, *n*			1.13 (1.03–1.25)	0.012
Relapses during NTZ, *n*			1.61 (1.46–1.78)	<0.0001
Relapses during the wash-out *n*			0.99 (0.79–1.22)	0.898
NTZ infusions, *n*			1.01 (1.00–1.02)	0.044
Wash-out length	>3 months	8.1 (6.09–10.74)	1.78 (1.39–2.30)	<0.0001
	0–3 months	4.5 (3.38–6.08)	1	
Treatment	FIN	3.7 (2.49–5.33)	0.36 (0.25–0.52)	<0.0001
	BRACE	10 (7.97–12.68)	1	

IR = incidence rate for 100 person/month; NTZ = natalizumab; PML = progressive multifocal leukoencephalopathy; IM = Immunomodulant; IS = Immunosuppressant; FIN = fingolimod.

Table 4 Patients characteristics before and after propensity-score matching

Variable	Before propensity-score matching				After propensity-score matching			
	BRACE	FIN	*P**	Standardized difference (%)	BRACE	FIN	*P**	Standardized difference (%)
n	298	135			107	107		
Age at switch mean (SD), years	37.2 (8.8)	39.7 (9.6)	0.011	27.1	38.8 (8.7)	38.6 (9.1)	0.959	−1.1
Sex, male (%)	86 (28.9)	38 (28.1)	0.880	1.6	30 (28.0)	34 (31.8)	0.550	−8.2
Disease duration at switch mean (SD), years	11.9 (7.1)	13.4 (6.5)	0.011	21.8	12.2 (6.8)	12.9 (6.5)	0.375	10.0
EDSS at switch mean (SD)	3.5 (1.7)	3.7 (1.9)	0.1	16.1	3.6 (1.7)	3.8 (1.8)	0.338	12.3
Patients with comorbidity, *n* (%)	57 (19.1)	14 (10.4)	0.023	24.9	14 (13.1)	13 (12.1)	0.837	2.8
Patients with previous IM treatment, *n* (%)	267 (89.6)	120 (88.9)	0.825	2.3	92 (85.3)	93 (86.9)	0.842	−2.7
Patients with previous IS treatment, *n* (%)	61 (20.5)	27 (20.0)	0.910	1.2	20 (18.7)	21 (19.6)	0.862	−2.4
NTZ infusions, *n* mean (SD)	19.4 (11.5)	26.4 (14.1)	<0.0001	54.3	22.4 (11.0)	23.2 (12.1)	0.571	7.7
Patients who relapsed in the year prior to NTZ, *n* (%)	242 (81.2)	84 (62.2)	<0.0001	43.1	71 (66.4)	73 (68.2)	0.771	−3.9
Patients who relapsed during NTZ, *n* (%)	74 (24.8)	43 (31.8)	0.128	−15.6	28 (26.2)	31 (29.0)	0.646	−6.3
Patients who relapsed during the wash-out, *n* (%)	39 (13.1)	44 (32.6)	<0.0001	−47.8	28 (26.2)	26 (24.3)	0.753	4.3

*Mann–Whitney U-test for continuous variables and χ^2 statistic for categorical variables.
FIN = fingolimod; IM = immunomodulant; IS = Immunosuppressant; NTZ = natalizumab; SD = standard deviation.

natalizumab interruption, the total proportion of patients with a relapse was 17%, but most of the relapses occurred after the fourth month. In addition these findings confirm the results of a large observational study reporting an increasing risk of relapse after natalizumab discontinuation, with a peak after 4 months (O'Connor *et al.*, 2011).

Second, using a Poisson model, performed at the time of switching therapies, we demonstrated that younger patients with shorter disease duration and comorbidities are more at risk of relapse after natalizumab suspension. Moreover, we confirmed that a high (O'Connor *et al.*, 2011; Cohen *et al.*, 2014; Fox *et al.*, 2014) disease activity before natalizumab and/or during natalizumab and a wash-out duration of >3 months are strong independent factors influencing the risk of relapse, even after the start of a new therapy. Accordingly, Jokubaitis *et al.* (2014) found that patients with relapses during the 6 months before fingolimod start and patients with a wash-out duration of 2–4 months had

Table 5 Poisson regression analysis: incidence of relapse after switch in propensity score-matched patients

Treatment	*n*	*n* of events	Person-years	IR (95% IR CI)	IRR (95% IRR CI)	*P*
Fingolimod	107	46	890.70	5.16 (3.87–6.89)	0.52 (0.37–0.74)	0.0003
BRACE	107	114	1154.99	9.87 (8.21–11.86)	1	

IR = Incidence for 100 person/month.

Table 6 Sensitivity analysis: Poisson regression analysis performed in the two groups of propensity-score matched patients stratified by wash-out duration (0–3 months; >3 months)

WO duration	Treatment	*n*	*n* of events	Person-Year	IR (95% IR CI)	IRR (95% IRR CI)	*P*
0–3 months	Fingolimod	25	18	46.55	38.70 (24.36–61.37)	0.53(0.30–0.94)	0.036
	BRACE	25	31	42.35	73.20 (51.48–104.10)	1	
>3 months	Fingolimod	73	17	733.28	2.32 (1.44–3.73)	0.41 (0.24–0.69)	0.001
	BRACE	73	60	1048.23	5.72 (4.44–7.37)	1	

WO = wash-out; *n* = number; IR = Incidence for 100 person/month; IRR = Incidence Rate Ratio; CI = Confidence Intervals.

1.6 and 2.12 times increased risk of a post-switching relapse, respectively, in comparison to patients without previous relapses and no treatment gap.

All of these results taken together suggest that more aggressive treatments should be considered early in the disease course for patients with a very active presentation from the disease onset, and that a wash-out duration lasting more than 1–3 months after natalizumab cessation is no longer acceptable in clinical practice.

Most importantly, we demonstrate that, after the adjustment for all the covariates, switching to fingolimod was associated with a 64% reduction in the risk of relapse in comparison to switching to BRACE. Moreover, the results of the Poisson analysis, performed after propensity score matching, strongly confirmed in the two quasi-randomized groups, that fingolimod is more effective than BRACE in reducing the incidence of disease reactivation and the cumulative probability of a first relapse after natalizumab suspension. In this cohort, 6.10% of patients on fingolimod had a first relapse within the first 4 months of treatment, 13.49% at 8 months and 15.01% at 12 months of follow-up, whereas the percentages of patients with a first relapse after switching to BRACE were 9.89%, 20.13% and 26.84%, at the same time points, respectively. The superiority of fingolimod versus BRACE was further confirmed, by sensitivity analyses, in subgroups of patients with different wash-out durations (less than or more than 3 months) and with consequent different relapse risks. Our study confirms the results of a previous head to head randomized controlled trial (Cohen *et al.*, 2013) designed to compare the efficacy of fingolimod versus intramuscular IFNβ-1a in patients with a very active form of multiple sclerosis, despite treatment with IFNβ in the year before the study, and those from other randomized controlled trials (Fox *et al.*, 2014) and observational studies (Havla *et al.*, 2013; Laroni *et al.*, 2013; Rossi *et al.*, 2013; Sempere *et al.*, 2013; Clerico *et al.*, 2014; Cohen *et al.*, 2014; Jokubaitis *et al.*, 2014) aimed to, independently, evaluate the efficacy of fingolimod or BRACE in controlling the disease reactivation after natalizumab suspension. The 1-year randomized controlled trial (Cohen *et al.*, 2013) showed that fingolimod significantly reduced the annualized relapse rates by 52%, compared with IFNβ-1a. Two studies, one randomized and partially controlled (Fox *et al.*, 2014) and one observational (Clerico *et al.*, 2014), analysed multiple sclerosis disease recurrence after natalizumab withdrawal in subpopulations of patients ($n = 175$ and $n = 124$, respectively) with restricted inclusion criteria (patients stable on natalizumab with no clinical or MRI evidence of disease activity) during a follow-up of 6 months and 12 months, respectively. Although these two studies were not designed to determine whether one treatment was better than another, as their main objective was to determine whether multiple sclerosis worsened after stopping natalizumab, they did demonstrate that first-line BRACE are not able to abolish post-natalizumab disease reactivation (Clerico *et al.*, 2014; Fox *et al.*, 2014). Some small size observational studies (Havla *et al.*, 2013; Laroni *et al.*, 2013) found that patients who switched to fingolimod within 6 months of natalizumab discontinuation had reduced annualized relapse rates compared with those who remained untreated or switched to intramuscular IFNβ-1a or glatiramer acetate. Larger size (Cohen *et al.*, 2014; Jokubaitis *et al.*, 2014) observational studies suggested a stabilization of disease reactivation in patients who switched to fingolimod after natalizumab. The French ENIGM study (Cohen *et al.*, 2014), which gathered data from 333 patients with multiple sclerosis who switched from natalizumab to fingolimod, after a mean wash-out duration of 17 weeks, found that 20% of them relapsed

during the first 6 months of fingolimod therapy, but the occurrence of relapse during the wash-out was the only statistically significant prognostic factor for relapse during fingolimod therapy. Jokubaitis *et al.* (2014) from the MSBase platform found a small increase in annualized relapse rates on fingolimod relative to natalizumab treatment in patients switching from natalizumab to fingolimod.

Comi *et al.* (2014), in a *post hoc* analysis of an open label, phase 3b study (FIRST), demonstrated that fingolimod was able to reduce the proportion of patients experiencing relapses after natalizumab but that timing of treatment initiation is critical for achieving an optimal effect.

All these previous studies consistently emphasized that fingolimod has the potential to reduce disease reactivation after natalizumab withdrawal, but this is the first comparative effectiveness study of fingolimod versus BRACE confirming the superiority of fingolimod versus BRACE in a real-world setting.

In this study, as expected in a follow-up lasting 12 months, the rate of confirmed disability progression was not significantly different between the two groups although the confirmed disability progression events were found in 11.4% of patients receiving fingolimod and in 22.5% of patients receiving BRACE.

Some limitations of this study deserve discussion. First, although we have applied sophisticated statistical analysis to reduce possible confounders that could have biased the results, the lack of randomization and blinded evaluation of outcomes remain insurmountable limits common to all observational studies. Second, we only evaluated clinical outcomes, and did not systematically collect radiologic data. The latter is the main limitation of this study, but since the data from randomized controlled trials (Cohen *et al.*, 2010, 2013) consistently provided evidence of a superior efficacy of fingolimod over IFNβ in improving MRI outcomes (number of new Gd-enhancing lesions, active T_2 lesions, and the rate of brain volume loss) across different subgroups of patients with relapsing-remitting multiple sclerosis, including those with high disease activity, the lack of this information might be only responsible for an underestimation of the major effectiveness of fingolimod in comparison to BRACE. In conclusion, our findings confirm the occurrence of a clinical disease reactivation after natalizumab suspension, mainly in patients with multiple sclerosis experiencing a previous high disease activity before and during natalizumab treatment, and the importance of establishing an alternative treatment, promptly, within 30 days, after the suspension. However, the most relevant finding of this prospective comparative study is the demonstration that fingolimod, among currently available disease-modifying drugs, is the best treatment choice for controlling this risk. Comparisons of fingolimod with newer available oral and injectable therapies in the clinical practice setting are eagerly awaited.

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Conflicts of interest

Pietro Iaffaldano has served on scientific advisory boards for Biogen Idec, and has received funding for travel and/or speaker honoraria from Sanofi-Aventis, Biogen Idec, Teva and Novartis. Carlo Pozzilli has served on scientific advisory boards for Novartis, Merck Serono, Biogen Idec, Sanofi-Aventis Genzyme, Almiral and Bayer Schering and has received funding for travel and speaker honoraria from Sanofi-Aventis, Biogen Idec, Bayer Schering, Teva Neurosciences, Merck Serono, Almirall, Genzyme, Actelion and Novartis, and receives research support from Novartis, Merck Serono, Biogen Idec, Bayer Schering and Sanofi-Aventis. Angelo Ghezzi has served on scientific advisory boards for Merck Serono, Biogen Idec, Novartis, Teva; received honoraria for speaking form Merck Serono, Biogen Idec, Genzyme, Almirall and Novartis; received research support from Sanofi Genzyme, Biogen Idec and Merck Serono. Francesco Patti has undertaken advisory activities for Almirall, Bayer, Biogen Idec Italy, Merck Serono, Sanofi Genzyme and Novartis, he has received research support from FISM and MIUR; personal compensation for speaking activities from Bayer, Biogen Idec Italy, Merck Serono, Novartis and TEVA; and travel grants from Bayer, Biogen Idec Italy, Merck

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