Switch to natalizumab vs fingolimod in active relapsing-remitting multiple sclerosis.

TITLE PAGE

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Running head

Natalizumab vs fingolimod in active MS

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ABSTRACT

Objective

In patients suffering multiple sclerosis activity despite treatment with interferon β or glatiramer acetate, clinicians often switch therapy to either natalizumab or fingolimod. However, no studies have directly compared the outcomes of switching to either of these two agents.

Methods

Using MSBase, a large international, observational multiple sclerosis registry, we identified patients with relapsing-remitting disease experiencing relapses or disability progression within the 6 months immediately preceding switch to either natalizumab or fingolimod. Quasi-randomisation with propensity score-based matching was used to select sub-populations with comparable baseline characteristics. Relapse and disability outcomes were compared in paired, pairwise-censored analyses.

Findings

Out of the 792 included patients, 578 patients were matched (natalizumab n=407, fingolimod n=171). Mean on-study follow-up was 12 months. The annualised relapse rates decreased from 1·5 to 0·2 on natalizumab and from 1·3 to 0·4 on fingolimod, with 50% relative post-switch difference in relapse hazard (p=0·002). A 2·8-times higher rate of sustained disability regression was observed after switch to natalizumab in comparison to fingolimod (p<0·001). No difference in the rate of sustained disability progression events was observed between the groups. The change in overall disability burden (quantified as area under disability-time curve) differed between natalizumab and fingolimod (-0·12 vs. 0·04 per year, respectively, p<0·001).

Interpretation

This study suggests that in active multiple sclerosis during treatment with injectable disease modifying therapies, switch to natalizumab is more effective than switch to fingolimod in reducing relapse rate and short-term disability burden.

TEXT

INTRODUCTION

Injectable disease modifying therapies (DMTs; interferon β or glatiramer acetate) significantly reduce relapse rate and short-term disability progression in multiple sclerosis (MS).[1-6] However, a substantial number of treated patients continue to experience disease activity. The risks are 55-80% for relapses and 33-46% for progression of disability while on injectable DMT over 2 years.[7] In order to maximise the proportion of patients free from disease activity,[8] a common strategy in those with suboptimal treatment response is treatment escalation to agents with presumed higher efficacy. Natalizumab and fingolimod are two agents commonly used for treatment escalation as their efficacy is considered superior to that of the injectable DMTs.[9, 10] However, the evidence concerning the effect of these agents in breakthrough disease is limited. The SENTINEL trial[10] demonstrated superiority of add-on of natalizumab to interferon β-1a versus interferon β-1a alone, and a subgroup analysis of the TRANSFORMS trial[11] showed superior efficacy of switching to fingolimod versus interferon β-1a following failure of prior treatment with interferon β or glatiramer acetate. No study has so far directly compared the efficacy of switch to fingolimod or natalizumab as treatment escalation in the setting of recent treatment failure.[12]

Given practical and financial limitations, it is unlikely that escalation to natalizumab or fingolimod will be directly compared in a randomised head-to-head trial. A feasible alternative strategy is to utilise existing longitudinal registries of clinical outcomes data.[13] MSBase is the largest international, observational registry of MS outcomes, and we previously demonstrated its utility in the analysis of treatment outcomes using propensity-matching to mitigate potential treatment indication bias.[14-16]

The aim of this study was to compare the outcomes of treatment escalation to either natalizumab or fingolimod in MS patients experiencing recent disease activity on injectable DMTs.

PATIENTS AND METHODS

The MSBase registry[17] (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee, and by the local ethics committees in all participating centres (or exemptions granted, according to local regulations). If required, written informed consent was obtained from enrolled patients.

Database and study population

Longitudinal data from 25,960 patients from 66 MS centres in 26 countries were extracted from the MSBase registry in December 2013. For this analysis, we selected patients with relapsing-remitting MS who had switched therapy from interferon β or glatiramer acetate to either natalizumab or fingolimod (treatment gap <3 months; no unified escalation protocol was used) after on-treatment relapse and/or progression of disability documented within the preceding 6 months (i.e. clinical breakthrough activity). The pre-switch disability progression was defined as increase in the Expanded Disability Status Scale (EDSS) by at least 1 step over the year immediately preceding the baseline (no EDSS scores recorded within 30 days of a clinical relapse were included). Minimum 3-month persistence on natalizumab or fingolimod was required. The minimal required dataset consisted of sex, month and year of birth, date of first MS symptoms, dates of clinical relapses, clinical MS course, disability quantified with EDSS recorded at the time of treatment escalation (i.e. the study baseline, -6 to +3 months) and at least one subsequent on-treatment visit with EDSS record. Patients previously participating in randomised trials involving studied agents or receiving teriflunomide, dimethyl fumarate, fingolimod, cladribine, mitoxantrone, natalizumab, rituximab or alemtuzumab before baseline were excluded. Patients were censored at discontinuation or change of therapy or end of follow-up (whichever occurred first). Quality assurance procedures were applied as described elsewhere.[14, 18]

All information was recorded as part of routine clinical practice with real time or near-real time data entry in association with clinical visits. The MSBase protocol stipulates minimum annual updates of the minimum dataset, but patients with less frequent updates were not excluded. Data entry portal was either the iMed patient record system or the MSBase online data entry system.

Study endpoints

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.[19] Confirmation of relapses by increased EDSS was not required. Disability was scored by accredited scorers using EDSS (online Neurostatus certification was required at each centre), excluding any EDSS score recorded within 30 days of a previous relapse. The

EDSS scores were derived from functional scores. Formal assessment of cognitive function or fatigue was not done routinely. MS duration was calculated from the first demyelinating event.

Progression of EDSS was defined as increase of ≥1 EDSS step (≥1·5 EDSS step if baseline EDSS was 0) sustained for ≥6 months. Regression of EDSS was defined as decrease of ≥1 EDSS step (1·5 EDSS step if baseline EDSS was 1·5) sustained for ≥6 months. Burden of disability over the follow-up period was quantified as the area under EDSS-time curve (AUC). The AUC was previously validated as a sensitive summative metric of all disability (transient as well as permanent) experienced by a patient during a follow-up period, with effective use of serial data.[20, 21] The AUC change was calculated relative to the baseline EDSS, between the baseline and a censoring event using the trapezium rule.[20] Median EDSS at 6-12, 12-18 and 18-24 months post-escalation was calculated for patients with available information.

Individual annualised relapse rate (ARR) was calculated as the annualised number of recorded relapses between baseline and a censoring event. Semi-annual relapse rate was also evaluated at 0-6, 6-12, 12-18 and 18-24 months post-baseline.

Where available, categorised evaluations of MRI (within the year preceding baseline) and cerebrospinal fluid (at any timepoint) were reported by the treating neurologists. The availability of MRI data was higher in the natalizumab than fingolimod switch group (Table 1). The proportion of patients with 1-8 lesions was relatively lower in the fingolimod group. However, the difference in proportion of patients with nine or more lesions was small. The observed differences in contrast-enhancing lesion counts and cerebrospinal fluid analysis were only marginal. Due to the high proportion of missing data, the categorised MRI data were not included in the propensity matching, but were adjusted for in all analyses.

Matching and statistical analysis

Matching and statistical analysis was conducted by TK using R (version 3·0·2).[22] The included patients were matched on their propensity of receiving natalizumab or fingolimod using MatchIt package.[23] The propensity score was based on a multivariable logistic regression model with treatment allocation as the outcome variable and the demographic and clinical variables available to treating neurologists at the time of the treatment assignation as the independent variables. These comprised sex, age and disease duration at baseline, EDSS, number of relapses in the 6 or 12 months pre-baseline, evidence of on-treatment MS activity (relapse, progression of disability or both), number of prior DMTs, the DMT used immediately before escalation and country. Given that the baseline MRI information was incomplete (at the time of the treatment decision), this was not included in the propensity-matching procedure but instead it was used to adjust the subsequent

analyses. The missing values of the T2 lesion volume variable (55% in the matched dataset) were imputed based on a model using patient ID, sex, age at baseline, baseline date, MS duration at baseline, treatment group, baseline EDSS, pre-baseline on-treatment MS activity, the last pre-baseline DMT, time from the previous DMT and the duration of the pre-baseline follow-up. We have used multiple imputation with an EMB algorithm (expectation-maximization with bootstrapping, Amelia package for R) to generate 5 imputed datasets. In addition, we have estimated the associations between multiple demographic and clinical variables vs. the availability of the baseline MRI variables with a multivariable logistic regression model.

The individual propensity scores were calculated as the sums of products of the covariates and their corresponding coefficients for the variables with $p \leq 0{\cdot}1$. Patients were then matched in a variable ratio of up to 6:1 using nearest neighbour matching within a caliper of 0·1 standard deviations of the propensity score, without replacement. All subsequent analyses were then structured as paired models with weights assigned to each pair to adjust for multiple inclusion of some patients in several pairs (with 1 being the maximum allowed cumulative weight per patient). Treatment persistence was evaluated as time to censoring/treatment discontinuation with a weighted frailty proportional hazards model (with the frailty term indicating the matched patient sets). The common (pairwise) on-treatment follow-up was determined as the shorter of the two individual follow-up periods for each matched patient pair (pairwise censoring). The purpose of the pairwise censoring was to control attrition bias. Normality of data distribution was assessed and ARR was compared with a weighted negative binomial model with cluster effect for matched patient pairs and adjusted for categorised number of hyperintense T2 lesions on the baseline MRI. Annualised changes in AUC, 6-monthly EDSS and 6-monthly relapse counts were compared with weighted paired t-tests. The proportions of patients free from relapse, with 6-month sustained disability progression and with 6-month sustained disability regression were evaluated with weighted frailty proportional hazards models adjusted for categorised baseline T2 lesion number. Cumulative hazard of relapses was analysed with a weighted frailty proportional hazards model with robust estimation of variance adjusted for categorised baseline T2 lesion number. All primary analyses were also repeated without the adjustment for baseline T2 lesion number. Proportionality of hazards was assessed with Schoenfeld's global test.

Six sensitivity analyses were carried out: (i) using normalised weights to approximate the inferences in the dataset with imputed missing MRI values under Missing Not At Random mechanism[24] (the δ was chosen based on the algorithm described by Heraud-Bousquet and colleagues[25]), (ii) without imputing the missing MRI values while allowing the "missing" value where the information was unavailable, including (iii) only patients with a documented relapse within the 6 months preceding treatment switch (i.e. excluding patients with disability progression only), (iv) all switching patients irrespective

of pre-baseline disease activity, (v) patients with baseline EDSS recorded between -50 to +7 days of study baseline (thus eliminating the immortal time bias) or (vi) adjusted for the baseline EDSS and the number of relapses within the 12 months preceding baseline but not the T2 lesion number. To evaluate robustness to non-recognised confounders of treatment assignation, Rosenbaum bounds based on Hodges-Lehmann Γ were estimated for the analyses of ARR and AUC.[26] Observed differences were considered significant if two-tailed p≤0·05. A power analysis was conducted to define the lower bounds of the minimum effect sizes at α=0.05 detectable in the available dataset at 1-β=0.8. Series of simulations (n=200) were carried out for each or the used statistical models and using the observed distributions of the outcome variables.

Role of the funding source

The study was conducted separately and apart from the guidance of the sponsors.

RESULTS

A total of 792 patients were included in the analysis (Figure 1, Supplementary Table 2). The median on-study follow-up was 21 months (quartiles 12-34) and 14 months (quartiles 8-20) after switching therapy to natalizumab or fingolimod, respectively. Baseline characteristics of the included patients, including previous treatment, are shown in (Table 1 and Supplementary Table 3). Several markers of disease severity differed significantly between the unmatched patient groups. The logistic model, used to estimate propensity scores, showed that higher disability, more relapses recorded within the 12 months preceding treatment escalation and country-specific practice in the Czech Republic and the Netherlands were positively associated with the probability of switching to natalizumab. In contrast, older age and country-specific practice in Spain were positively associated with switch to fingolimod (see Supplementary Table 4). The variable propensity-matching procedures retained 407 (73%) and 171 (74%) patients who switched to natalizumab or fingolimod, respectively. The matching procedure significantly improved the overall match, as indicated by the decrease from 0·39 to 0·01 (97%) in the mean difference in propensity scores (see Figure 2). This was reflected by the improved match on the individual determinants of treatment allocation, including patient age, disability and the number of previously recorded relapses (Table 1). The median difference between baseline date and the date of the baseline EDSS were comparable between the matched cohorts (-83 days [quartiles -145 to -27] for natalizumab vs. -78 days [quartiles -132 to -15] for fingolimod). The

mean on-study visit density in the matched cohorts was 2·86±1·78 visits per year for the natalizumab group and 2·87±1·78 visits per year for the fingolimod group (mean±standard deviation).

Treatment persistence following the baseline did not differ between the compared therapies, with the proportion of patients discontinuing therapy at 24 months reaching 27% and 31% in the natalizumab and fingolimod group, respectively (p=0·9; Figure 3). The proportion of relapse-free patients was higher among those switching to natalizumab than fingolimod (hazard ratio=1·5, 95% confidence interval 1·1-2·2, p=0·02; Figure 4) and the cumulative hazard of relapses was relatively lower in the natalizumab group (hazard ratio=0·6, 95% confidence interval=0·4-0·8, p=0·002). ARR decreased in both groups, with a more prominent drop after switch to natalizumab (1·5 to 0·2) compared to fingolimod (1·3 to 0·4; p=0·002). The difference in ARR was sustained throughout the two years post-switch.

We did not observe any differences in the proportion of patients free from 6-month sustained disability progression (p=0·3) or in the EDSS scores evaluated semi-annually (3·0-3·5; p>0·1). The annualised area under EDSS-time curve was lower among patients switching to natalizumab (-0·12 vs. 0·04, respectively; p<0·001; Figure 5). The negative area under EDSS-time curve in the natalizumab group suggested decrease in disability. This was confirmed by the higher proportion of patients experiencing 6-month sustained regression of disability after switching to natalizumab (20%) compared to fingolimod (11% at 24 months; hazard ratio=2·8, 95% confidence interval=1·7-4·6, p<0·001).

According to the post-hoc power analysis, the lower bounds for the detectable minimum effects were 1.49 (hazard ratio) for treatment persistence, 1·42 (hazard ratio) for the proportion of patients free from relapse, 0·09 relapse per year for ARR, 0.07 EDSS-year for AUC, 2·2 (hazard ratio) for the disability progression hazard and 1·65 (hazard ratio) for the disability regression probability.

John Cunningham (JC) virus status (recorded before the end of the study) was available for 140 patients treated with natalizumab. Among those who discontinued or switched treatment with natalizumab (see Supplementary Table 3), 22 patients were JC virus-positive and 11 patients were JC virus-negative. Among those who continued in treatment with natalizumab, 37 patients were JC virus-positve and 70 patients were JC virus-negative.

The primary analysis, repeated without the adjustment for baseline T2 lesion number, confirmed the outcomes of the primary analysis in full extent. The sensitivity analyses (Supplementary Table 5) replicated the outcomes of the primary analysis when the missingness of the baseline MRI variables was not assumed to be random (for the purpose of multiple imputation) and when no imputation was used and missing MRI values were allowed. The estimated associations between demographic and clinical variables vs. the availability of the baseline MRI are shown in Supplementary Table 6. Sensitivity

analyses in subpopulations with a recent documented relapse (n=622) or irrespective of their recent disease activity (n=1084) also confirmed the findings of the primary analysis in full extent. The sensitivity analysis among patients with the baseline EDSS recorded between -50 to +7 days of the baseline replicated all relapse, disability and persistence outcomes of the primary analysis, with the exception of the proportion of patients free from relapses, where a non-significant trend was observed, which could be attributed to the relatively low power (n=479). Finally, the sensitivity analysis adjusted for the baseline EDSS and the number of relapses within the 12 months preceding baseline validated the outcomes of the primary analysis in full. For the comparisons of ARR and AUC, the results of matching and analysis were resistant to unknown confounders with relative magnitudes of 80% and 10% of the propensity score (Hodges-Lehmann Γ), respectively.

DISCUSSION

We conducted a propensity score-matched analysis of switch to either fingolimod or natalizumab after treatment failure. The ARR was reduced from 1·5 to 0·2 after switching to natalizumab and from 1·3 to 0·4 after switching to fingolimod. The relapse rate was 50% lower after switching to natalizumab than fingolimod, with a corresponding 50% relative increase of the proportion of relapse-free patients on natalizumab. Six-month sustained disability progression rates did not differ between treatments. However, patients switching to natalizumab were 2·8-times more likely to experience a 6-month sustained regression of disability than those switching to fingolimod.

Two prior phase III randomised controlled trials evaluated the efficacy of fingolimod in comparison to placebo (FREEDOMS) or interferon β (TRANSFORMS). The FREEDOMS trial demonstrated superior efficacy of fingolimod on relapse, disability and MRI outcomes (new, enlarging or contrast-enhancing lesions), including 30% reduction of brain atrophy over 24 months.[27] The 12-month TRANSFORMS trial showed superior effect of fingolimod on relapse activity and MRI outcomes compared to intramuscular interferon β-1a.[9] This observation was confirmed in a 12-month trial extension, when the patients originally randomised to interferon β experienced drop in relapse and MRI activity after re-allocation to fingolimod.[28] In a propensity score-matched analysis of the MSBase registry data, we demonstrated that patients switching to fingolimod due to previous on-treatment MS activity experienced less post-switch relapses when compared to those switching to another injectable DMTs.[16] Moreover, we reported a relatively improved short-term disability outcomes in the fingolimod group.

The efficacy of monotherapy with natalizumab was evaluated in the phase III randomised placebo-controlled AFFIRM trial, with the benefit of natalizumab on relapse activity, disability and MRI activity shown over 24 months.[29] In addition, natalizumab was associated with a marked increase in the proportion of patients free from all disease activity.[30] None of

these trials specifically recruited patients switching therapy after treatment failure; both DMT-treated and treatment-naïve patients were included in these trials. A sub-group analysis of TRANSFORMS showed a 61% relative reduction of ARR in patients with high pre-trial disease activity on interferon β switching to fingolimod versus switching to interferon β-1a.[11] The SENTINEL trial evaluated the effect of natalizumab as add-on to interferon β in patients experiencing relapses within the year preceding randomisation.[10] The trial demonstrated superior effect of add-on natalizumab compared to interferon β monotherapy in reducing relapses, disability progression events and MRI activity.

While we did not observe any differences in the rate of sustained disability progression between the compared switch strategies, we found a significantly increased probability of sustained disability regression after switch to natalizumab. A possible interpretation is that, while both strategies of DMT switch are very effective in delaying disability progression, natalizumab is superior in promoting recovery from recently accumulated disability in active MS.[31] This phenomenon is likely responsible for the decrease in overall burden of disability (quantified as the area under EDSS-time curve[20, 21]) among patients switching to natalizumab but not fingolimod. Our findings are in agreement with the post-hoc analysis of the AFFIRM trial, which showed increase in the 2-year probability of EDSS improvement by 69% in the natalizumab cohort (30%) vs. placebo (19%) at two years,[31] an effect further confirmed by other retrospective studies.[32, 33] No similar effect has previously been reported for fingolimod.

Our observed relapse rates on fingolimod were higher compared to the phase III trials (0·4 vs. 0·11-0·21, respectively).[9, 27, 28] This is likely due to the differences in relapse definition, as the pivotal fingolimod studies only considered relapses confirmed by significant changes on neurological examination. In addition, we have selectively included patients with recent activity on DMT (a known predictor of post-switch activity on fingolimod[34]), who had more active disease than the population studied in the fingolimod trials. In contrast, our observed ARR on natalizumab (0·2) was similar to the ARR reported in the AFFIRM trial (0·2, patients with no recent previous DMT) and lower than the ARR reported in the SENTINEL trial (0·34-0·38) despite the high pre-baseline activity.[29]

The main limitation of our study was the follow-up duration, as less than 10% of the patients were followed for more than 2 years post-switch. We will examine the long-term disability outcomes as the exposure to both DMTs in the MSBase cohort increases. No time-dependent variation (that would suggest differential time-dependent treatment response of the two compared switch strategies) in the relapse and disability outcomes was observed, as indicated by Figure 4C and the analyses of disability outcomes satisfied the proportionality of hazards assumption. Generalisation of our findings may be limited by the fact that the studied population was largely recruited from tertiary MS centres. To adjust the analysis for

treatment indication bias, we employed propensity score-matching procedures, which eliminated or reduced known or suspected confounders of treatment allocation. Unlike randomisation, propensity-based matching cannot eliminate unknown confounders. However, we have shown that our analysis was moderately resistant to unknown bias. In addition, our sensitivity analyses confirmed the outcomes of the primary analysis using various inclusion criteria and analysis adjustments. While a proportion of the baseline MRI information was missing, we have shown in a sensitivity analysis that differential availability of this information was unlikely to significantly influence the conclusions drawn. The presumed preferential choice of a therapy that is perceived as more effective for treatment of more severe MS would have confounded the results in favour of fingolimod. Therefore, any potential residual indication bias in our analysis was likely to underestimate rather than overestimate the real difference between the outcomes of the natalizumab and fingolimod switch. Pairwise censoring was applied in order to eliminate attrition bias and to ensure the validity throughout the study of the patient match completed at baseline. Choice of escalation therapy is not only dictated by the DMT efficacy, but is also determined by treatment safety and tolerability. The presence of JC virus antibodies is therefore important information that contributes to the choice of treatment escalation strategy. In this study, we did not evaluate safety and tolerability of the examined therapies, as the availability of this information within the MSBase registry was limited. However, we showed high 2-year treatment persistence on both DMTs.

Both natalizumab and fingolimod significantly reduce relapse activity in patients who switch therapy from interferon β or glatiramer acetate due to recent disease activity, and the rates of confirmed progression of disability events post-switch are highly similar. This analysis suggests that switch to natalizumab is more effective than switch to fingolimod in reducing relapses and promoting reduction of disability. Extended post-escalation follow-up is required to compare the effect of these therapeutic strategies on long-term outcomes.

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Authors' roles and contributions

Tomas Kalincik conceptualised and designed the study, conducted and interpreted the analysis, and drafted, revised and approved the manuscript. Dana Horakova, Timothy Spelman, Vilija Jokubaitis, Maria Trojano, Alessandra Lugaresi, Guillermo Izquierdo, Csilla Rozsa, Pierre Grammond, Raed Alroughani, Pierre Duquette, Marc Girard, Eugenio Pucci, Jeannette Lechner-Scott, Mark Slee, Ricardo Fernandez-Bolanos, Francois Grand'Maison, Raymond Hupperts, Freek Verheul, Suzanne Hodgkinson, Celia Oreja-Guevara, Daniele Spitaleri, Michael Barnett, Murat Terzi, Roberto Bergamaschi, Pamela McCombe, Jose L Sanchez-Menoyo, Magdolna Simo, Tunde Csepany, Gabor Rum, Cavit Boz, Eva Havrdova, and Helmut Butzkueven contributed substantially to data acquisition, interpretation of the analysis, and have revised and approved the manuscript.

Potential conflicts of interests

Alessandra Lugaresi is a Bayer Schering, Biogen Idec, Genzyme, Merck Serono Advisory Board Member. She received travel grants and honoraria from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi Aventis and Teva, research grants from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi Aventis and Teva, travel and research grants from the Associazione Italiana Sclerosi Multipla.

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Celia Oreja-Guevara received honoraria as consultant on scientific advisory boards from Biogen-Idec, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen-Idec, GSK, Teva and Novartis.

Csilla Rozsa has received speaker honoraria from Bayer Schering, Novartis and Biogen Idec, congress and travel expense compensations from Biogen Idec, Teva, Merck Serono and Bayer Schering.

Dana Horakova received speaker honoraria and consulting fees from Biogen Idec, Merck Serono, Teva and Novartis, as well as support for research activities from Biogen Idec.

Daniele LA Spitaleri received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen Idec, Sanofi Aventis, Teva and Merck-Serono.

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Guillermo Izquierdo received speaking honoraria from Biogen-Idec, Novartis, Sanofi, Merck Serono and Teva.

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FIGURE LEGENDS

Figure 1

CONSORT flowchart of patient disposition (primary analysis).

Figure 2

Distribution of propensity scores before (A, C) and after matching (B, D) among patients treated with natalizumab (C, D) or fingolimod (A, B).

Figure 3

Persistence on natalizumab and fingolimod among the matched patients. Results of paired matched analysis without pairwise censoring are shown. Dashed curves indicate 95% confidence intervals.

HR, hazard ratio; CI, confidence interval

Figure 4

Proportion of patients free from clinical relapses (A), overall annualised relapse rate (B) and 6-monthly relapse rate (C) among patients treated with natalizumab or fingolimod. Results of paired matched analyses with pairwise censoring are shown. Dashed curves and error bars indicate 95% confidence intervals.

HR, hazard ratio; CI, confidence interval

Figure 5

Proportions of patients free from disability progression (A) and those with disability regression (B) confirmed at 6 months. Annualised area under disability-time curve (C) showed decrease after escalation to natalizumab but not fingolimod.

Results of paired matched analyses with pairwise censoring are shown. Dashed curves and error bars indicate 95% confidence intervals.

HR, hazard ratio; CI, confidence interval

TABLES

Table 1

Baseline characteristics of the included patients before and after matching

		Unmatched			Matched		
		Natalizumab	**Fingolimod**	**d**[a]	**Natalizumab**	**Fingolimod**	**d**[a]
patients [number (% females)]		560 (73%)	232 (74%)		407 (74%)	171 (74%)	
age, years [mean ± SD]		37 ± 9	38 ± 10	0.14	37 ± 9	38 ± 10	0.11
disease duration, years [mean ± SD]		9.2 ± 6.4	9.3 ± 7.7	0.03	9.4 ± 6.2	9.5 ± 8.0	0.04
relapses 6 months before baseline [mean ± SD]		1.06 ± 0.76	0.77 ± 0.62	0.39	0.98 ± 0.73	0.84 ± 0.60	0.17
relapses 12 months before baseline [mean ± SD]		1.68 ± 1.09	1.20 ± 0.85	0.42	1.53 ± 1.04	1.29 ± 0.86	0.17
patients relapsing within 12 months before baseline [number (%)]		504 (90%)	188 (81%)		356 (87%)	143 (84%)	
disability, EDSS [mean ± SD]		3.5 ± 1.6	3.0 ± 1.7	0.38	3.4 ± 1.5	3.1 ± 1.7	0.11
	[median (quartiles)]	3.5 (2, 4.5)	2.5 (1.5, 4)		3.5 (2, 4)	3 (2, 4)	
countries, [number]		13	9		8		8
time on natalizumab/fingolimod, months[e]	[mean ± SD]	24 ± 15	16 ± 12	0.39	12 ± 7	12 ± 7	0.00
	[median (quartiles)]	21 (12, 34)	14 (8, 20)		11 (6, 17)	11 (6, 17)	
MRI: hyperintense T2 lesions [number (%)]	- missing	280 (50%)	151 (65%)		189 (46%)	114 (67%)	
	- 1-8	150 (27%)	13 (6%)		128 (31%)	9 (5%)	

	- 9+	130 (23%)	68 (29%)	90 (22%)	48 (28%)
MRI: contrast enhancing lesions [number (%)]	- missing	302 (54%)	181 (78%)	210 (52%)	133 (78%)
	- no	171 (31%)	28 (12%)	134 (33%)	22 (13%)
	- yes	87 (16%)	23 (10%)	63 (15%)	16 (9%)
cerebrospinal fluid [number (%)]	- missing	393 (70%)	133 (57%)	269 (66%)	107 (63%)
	- abnormal	148 (26%)	80 (34%)	128 (31%)	50 (29%)
	- normal	19 (3%)	19 (8%)	14 (3%)	14 (8%)

[a]Standardised difference (Cohen d) is shown for continuous variables.

[e]Pairwise-censored on-study follow-up is shown for the matched patients.

EDSS, Extended Disability Status Scale (range 0-10, higher scores indicate greater disability); MRI, magnetic resonance imaging

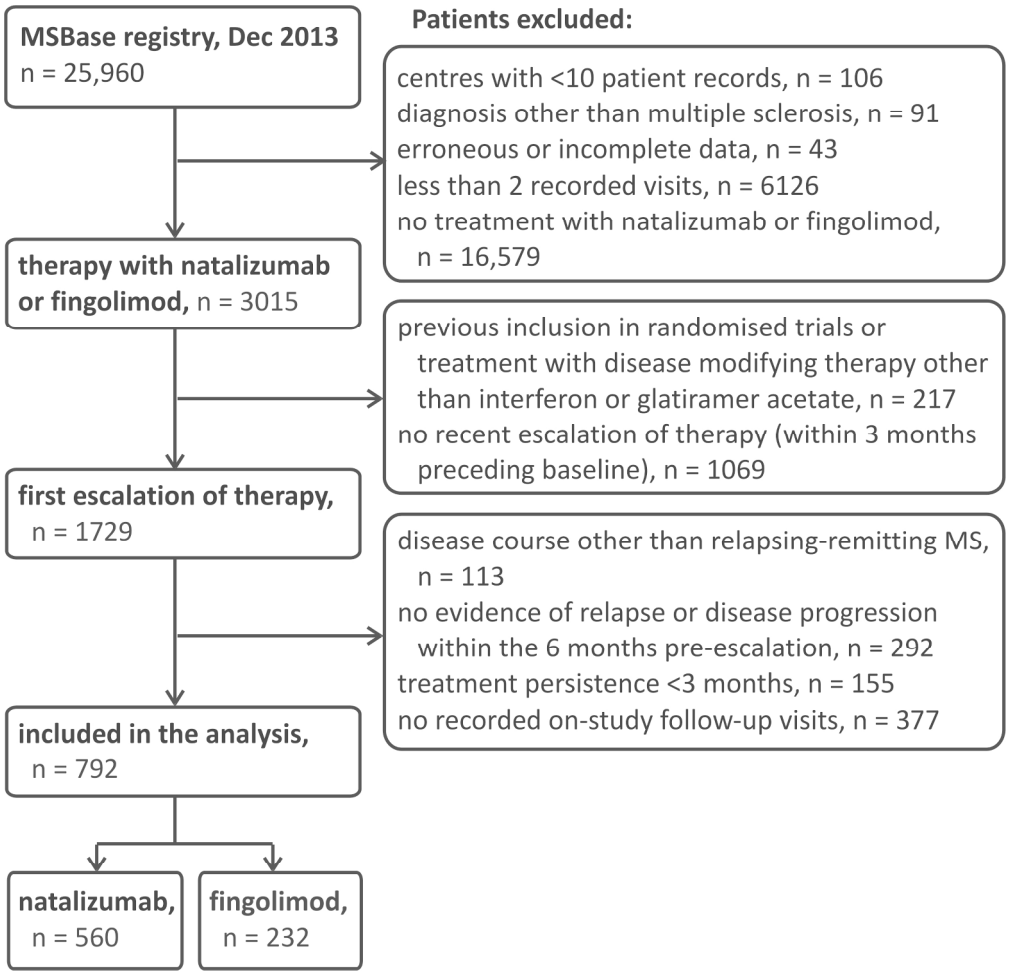


Figure 1: CONSORT flowchart of patient disposition

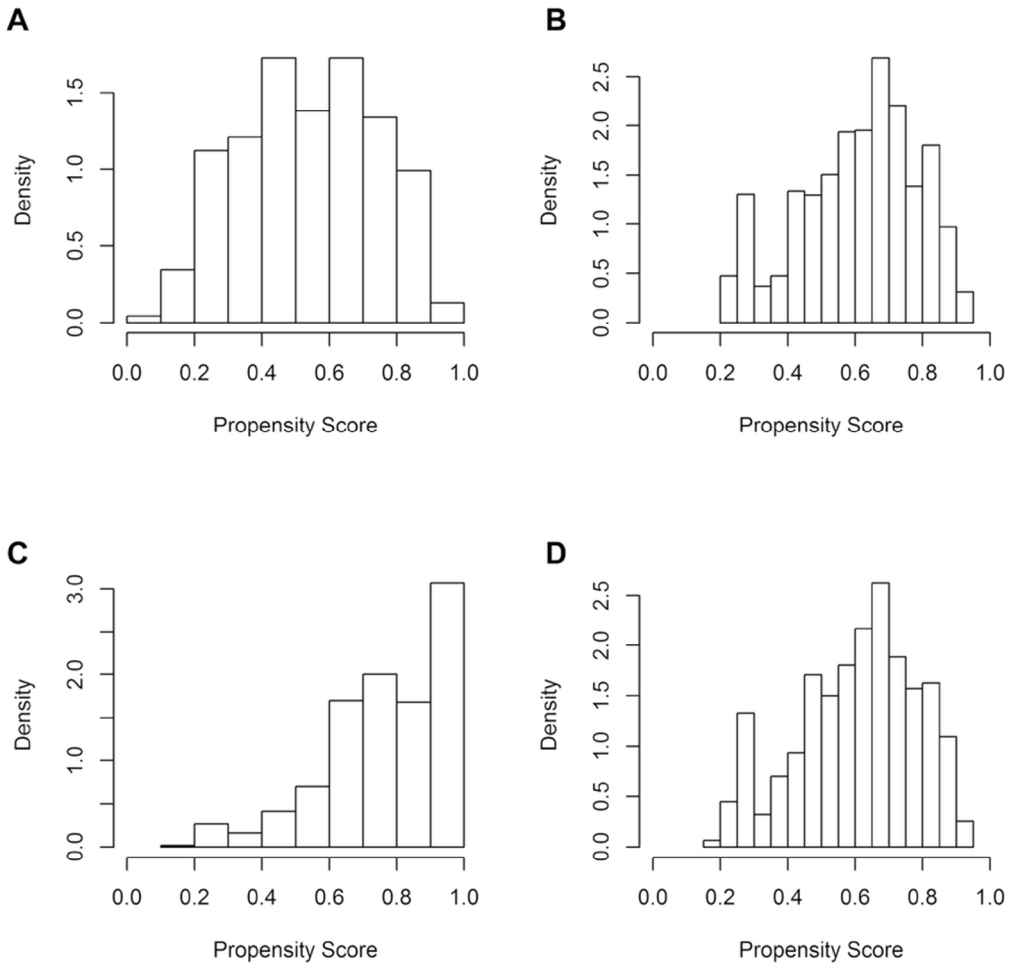
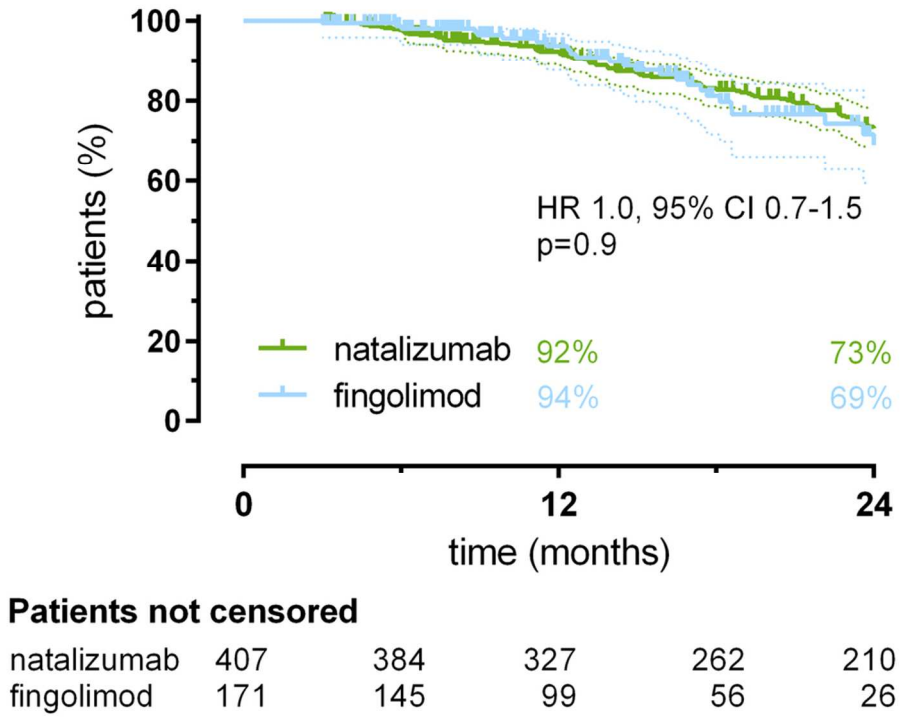


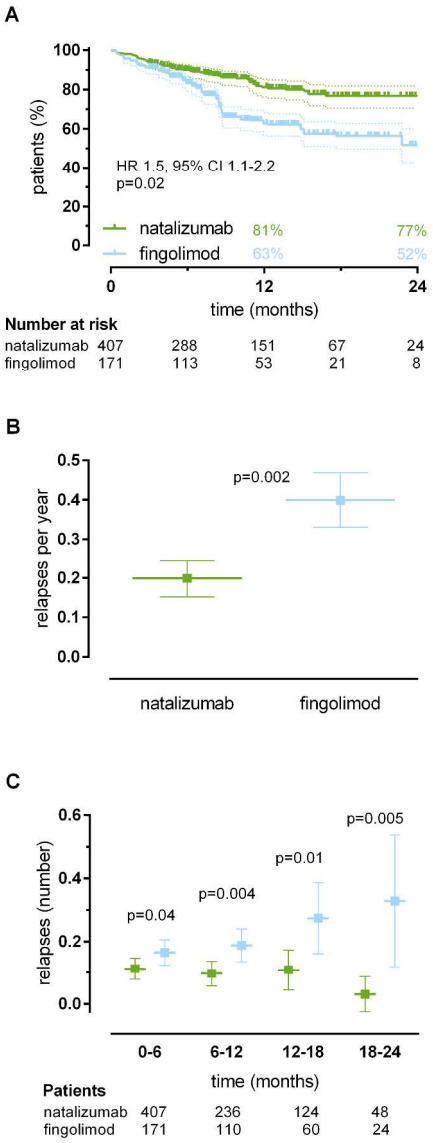
Figure 2: Distribution of propensity scores before and after matching
76x73mm (300 x 300 DPI)



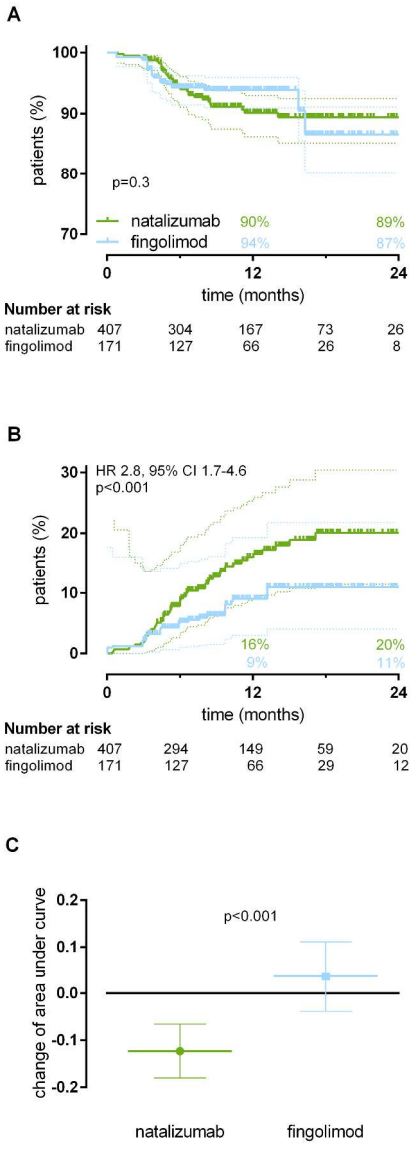
Patients not censored

natalizumab	407	384	327	262	210
fingolimod	171	145	99	56	26

Figure 3: Persistence on natalizumab and fingolimod
92x76mm (300 x 300 DPI)



Proportion of patients free from clinical relapses
250x586mm (300 x 300 DPI)



Proportions of patients free from disability progression
263x644mm (300 x 300 DPI)

Supplementary Table 1
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Supplementary Table 2
Number of eligible patients per MS Centre

Centre	City	Country	Patients
Charles University in Prague	Praha	Czech Republic	77
Kommunehospitalet	Arhus C	Denmark	54
Box Hill Hospital	Melbourne	Australia	49
University of Bari	Bari	Italy	49
The Royal Melbourne Hospital	Melbourne	Australia	48
Ospedale Clinizzato (Ss. Annunziata)	Chieti	Italy	45
Hospital Universitario Virgen Macarena	Sevilla	Spain	44
Jahn Ferenc Teaching Hospital	Budapest	Hungary	41
Centre de Réadaptation déficience Physique Chaudière-Appalache	Levis, PQ	Canada	38
Amiri Hospital	Kuwait City	Kuwait	32
CHUM - Hopital Notre Dame	Montreal	Canada	31
Generale Provinciale Macerata	Macerata	Italy	29
John Hunter Hospital	New Lambton	Australia	27
Flinders Medical Centre	Adelaide	Australia	24
Hospital Universitario Virgen de Valme	Seville	Spain	20
Neuro Rive-Sud	Greenfield Park	Canada	18
Maaslandziekenhuis	Sittard	Netherlands	18
Groene Hart Ziekenhuis	Gouda	Netherlands	14
Liverpool Hospital	Liverpool	Australia	13
Hospital Universitario La Paz	Madrid	Spain	12
AORN San Giuseppe Moscati Avellino	Avellino	Italy	11
Hospital São João	Porto	Portugal	9
Brain and Mind Research Institute	Camperdown	Australia	8
19 Mayis University	Kurupelit	Turkey	7
Péterfy Sandor Hospital	Budapest	Hungary	6
National Neurological Institute C. Mondino	Pavia	Italy	6
Royal Brisbane and Women's Hospital	Brisbane	Australia	5
Hospital de Galdakao-Usansolo	Galdakao	Spain	5
Semmelweis University Budapest	Budapest	Hungary	5
University of Debrecen	Debrecen	Hungary	5
Petz A. County Hospital	Gyor	Hungary	5
BAZ County Hospital	Miskolc	Hungary	5
University Hospital Nijmegen	Nijmegen	Netherlands	5
KTU Medical Faculty Farabi Hospital	Trabzon	Turkey	5
Veszprém Megyei Csolnoky Ferenc Kórház zrt.	Veszprem	Hungary	4
Jewish General Hospital	Montreal	Canada	3
Josa András Hospital	Nyiregyhaza	Hungary	3
The Alfred	Melbourne	Australia	2
Cliniques Universitaires Saint-Luc	Brussels	Belgium	2
Ospedali Riuniti di Salerno	Salerno	Italy	2
Jeroen Bosch Ziekenhuis	Den Bosch	Netherlands	2
FLENI	Buenos Aires	Argentina	1
University of Florence	Florence	Italy	1
Francicus Ziekenhuis	Roosendaal	Netherlands	1
New York University Langone Medical Center	New York	United States	1

Supplementary Table 3
Study cohort characteristics: pre-study disease activity and therapy

	Unmatched		Matched	
	Natalizumab	Fingolimod	Natalizumab	Fingolimod
disease activity within 6 months preceding baseline, number (%)				
relapses	248 (44%)	88 (38%)	171 (42%)	73 (43%)
progression of disability	100 (18%)	70 (30%)	88 (22%)	42 (25%)
relapses and disability progression	212 (38%)	74 (32%)	148 (36%)	56 (33%)
previous disease modifying agents, number (%)				
1	323 (58%)	142 (61%)	239 (59%)	102 (60%)
2-3	226 (40%)	85 (37%)	159 (39%)	66 (38%)
4-5	11 (2%)	5 (2%)	9 (2%)	3 (2%)
last disease modifying agent before escalation, number (%)				
interferon β-1a, intramuscular	91 (16%)	46 (20%)	62 (15%)	26 (15%)
interferon β-1a, subcutaneous	205 (37%)	82 (35%)	161 (40%)	68 (40%)
interferon β-1b	115 (21%)	49 (21%)	85 (21%)	34 (20%)
glatiramer acetate	149 (27%)	55 (24%)	99 (24%)	43 (25%)
post-study disease modifying therapy, number (%)[a]				
continuing treatment	359 (64%)	195 (84%)	230 (57%)	141 (82%)
treatment switch[b]				
to interferon β	13 (2%)	0	11 (3%)	0
to glatiramer acetate	27 (5%)	1 (0.4%)	23 (6%)	1 (0.6%)
to dimethyl fumarate	0	1 (0.4%)	0	1 (0.6%)
to fingolimod	46 (8%)	0	46 (11%)	0
to natalizumab	1 (0.2%)	8 (3%)	1 (0.2%)	8 (5%)
enrolment in randomised trial	1 (0.2%)	0	1 (0.2%)	8 (0.2%)
discontinuation of treatment[d]	113 (20%)	27 (12%)	94 (23%)	20 (12%)

[a]Recorded at the last study entry, prior to pairwise censoring.
[b]Switch to other disease modifying therapy within three months of discontinuing on-study therapy (natalizumab or fingolimod).
[c]Discontinuation of disease modifying therapy for at least three months.

Supplementary Table 4
Determinants of allocation to natalizumab or fingolimod

	Coefficient	Standard error	P-value
Intercept	0.13	0.59	0.8
sex			
[male]	0.08	0.21	0.7
age	-0.03	0.01	0.03
disease duration	0.003	0.02	0.8
disability	0.24	0.07	10^{-4}
relapses 6 months before baseline	0.34	0.26	0.·2
relapses 12 months before baseline	0.33	0.14	0.02
recent disease activity			
[progression of disability]	reference		
[relapse]	0.01	0.35	1.0
[progression of disability or relapse]	-0.09	0.34	0.8
number of previous immunomodulators	-0.05	0.13	0.7
therapy immediately preceding baseline			
[glatiramer acetate]	reference		
[interferon β-1a, intramuscular]	-0.26	0.29	0.4
[interferon β-1a, subcutaneous]	-0.16	0.25	0.5
[interferon β-1b]	0.16	0.28	0.6
country			
[Australia]	reference		
[Argentina]	-19	6523	1.0
[Belgium]	18	4612	1.0
[Canada]	0.29	0.3	0.3
[Czech Republic]	0.8	0.34	0.02
[Denmark]	18	857	1.0
[Spain]	-1.5	0.31	10^{-6}
[Hungary]	18	734	1.0
[Italy]	0.46	0.27	0.092
[Kuwait]	-0.56	0.43	0.2
[The Netherlands]	1.27	0.48	0.009
[Portugal]	18	2118	1.0
[Turkey]	-1.18	0.68	0.08
[United States]	18	6523	1.0

The table demonstrates the results of multivariable logistic regression model evaluating associations between allocation to natalizumab or fingolimod and the considered potential confounders of treatment indication (i.e. the determinants of propensity score). Positive coefficients signify positive association with allocation to natalizumab.

Supplementary Table 5
Sensitivity analyses

1. Analysis with imputation under Missing Not At Random mechanism

	Natalizumab	Fingolimod	P-value
patients			
unmatched	560	232	
matched	407	171	
treatment discontinuation, hazard ratio (95% CI)	1.08 (0.62-1.38)		n/s
relapse outcomes			
proportion free from clinical relapses, hazard ratio (95% CI)	1.51 (1.08-2.10)		0.02
cumulative hazard of relapses, hazard ratio (95% CI)	0.58 (0.51-0.81)		0.001
annualised relapse rate, mean ± SD	0.20 ± 0.46	0.36 ± 0.67	0.0007
disability outcomes			
area under EDSS-time curve, mean ± SD	-0.12 ± 0.71	0.04 ± 0.58	10^{-5}
proportion with EDSS progression, hazard ratio (95% CI)	1.39 (0.59-1.56)		n/s
proportion with EDSS regression, hazard ratio (95% CI)	2.92 (1.80-4.74)		10^{-5}

2. No imputation of the missing MRI data ("missing" value allowed)

	Natalizumab	Fingolimod	P-value
patients			
unmatched	560	232	
matched	407	171	
treatment discontinuation, hazard ratio (95% CI)	1.08 (0.62-1.38)		n/s
relapse outcomes			
proportion free from clinical relapses, hazard ratio (95% CI)	1.47 (1.04-2.07)		0.03
cumulative hazard of relapses, hazard ratio (95% CI)	0.53 (0.37-0.75)		0.0004
annualised relapse rate, mean ± SD	0.20 ± 0.46	0.36 ± 0.67	0.0002
disability outcomes			
area under EDSS-time curve, mean ± SD	-0.12 ± 0.71	0.04 ± 0.58	0.002
proportion with EDSS progression, hazard ratio (95% CI)	1.42 (0.80-2.53)		n/s
proportion with EDSS regression, hazard ratio (95% CI)	2.09 (1.29-3.38)		0.003

3. Patients with a documented relapse within the 6 months preceding treatment switch

	Natalizumab	Fingolimod	P-value
patients			
unmatched	460	162	
matched	311	131	
treatment discontinuation, hazard ratio (95% CI)	1.32 (0·92-1·90)		n/s
relapse outcomes			
proportion free from clinical relapses, hazard ratio (95% CI)	1.48 (1.03-2.12)		0.03
cumulative hazard of relapses, hazard ratio (95% CI)	0.50 (0.34-0.75)		0.0009
annualised relapse rate, mean ± SD	0.18 ± 0.47	0.31 ± 0.61	10^{-5}
disability outcomes			
area under EDSS-time curve, mean ± SD	-0.13 ± 0.64	-0.01 ± 0.57	0.02
proportion with EDSS progression, hazard ratio (95% CI)	0.88 (0.50-1.56)		n/s
proportion with EDSS regression, hazard ratio (95% CI)	2.57 (1.52-4.36)		0.0004

4. Patients irrespective of pre-baseline recent disease activity

	Natalizumab	Fingolimod	P-value
patients			
unmatched	697	387	
matched	524	237	
treatment discontinuation, hazard ratio (95% CI)	0.87 (0.57-1.32)		n/s
relapse outcomes			
proportion free from clinical relapses, hazard ratio (95% CI)	1.46 (1.09-1.96)		0.01
cumulative hazard of relapses, hazard ratio (95% CI)	0.58 (0.42-0.80)		0.0008
annualised relapse rate, mean ± SD	0.19 ± 0.48	0.36 ± 0.70	0.0001
disability outcomes			
area under EDSS-time curve, mean ± SD	-0.09 ± 0.55	0.02 ± 0.60	0.0004
proportion with EDSS progression, hazard ratio (95% CI)	0.98 (0.60-1.61)		n/s
proportion with EDSS regression, hazard ratio (95% CI)	1.66 (1.09-2.52)		0.02

5. Patients with baseline EDSS recorded between -50 to +7 days of treatment initiation

	Natalizumab	Fingolimod	P-value
patients			
unmatched	348	131	
matched	217	91	
treatment discontinuation, hazard ratio (95% CI)	0.90 (0·55-1·46)		n/s
relapse outcomes			

proportion free from clinical relapses, hazard ratio (95% CI)	1.39 (0.91-2.12)		n/s
cumulative hazard of relapses, hazard ratio (95% CI)	0.56 (0.36-0.88)		0.01
annualised relapse rate, mean ± SD	0.23 ± 0.50	0.39 ± 0.68	0.006
disability outcomes			
area under EDSS-time curve, mean ± SD	-0.19 ± 0.52	-0.06 ± 0.58	0.02
proportion with EDSS progression, hazard ratio (95% CI)	0.92 (0.33-2.53)		n/s
proportion with EDSS regression, hazard ratio (95% CI)	2.33 (1.25-4.33)		0.008

6. Analyses adjusted for baseline EDSS and relapse counts within 12 months prior to baseline

	Natalizumab	**Fingolimod**	**P-value**
patients			
unmatched	506	241	
matched	364	165	
treatment discontinuation, hazard ratio (95% CI)	0.94 (0·63-1·39)		n/s
relapse outcomes			
proportion free from clinical relapses, hazard ratio (95% CI)	1.51 (1.08-2.11)		0.01
cumulative hazard of relapses, hazard ratio (95% CI)	0.59 (0.38-0.91)		0.02
annualised relapse rate, mean ± SD	0.20 ± 0.48	0.35 ± 0.64	0.001
disability outcomes			
area under EDSS-time curve, mean ± SD	-0.12 ± 0.65	-0.02 ± 0.63	0.03
proportion with EDSS progression, hazard ratio (95% CI)	1.27 (0.71-2.26)		n/s
proportion with EDSS regression, hazard ratio (95% CI)	2.49 (1.57-3.95)		0.0001

CI, confidence interval; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; SD, standard deviation

Supplementary Table 6
Associations between the availability of baseline MRI variables and other variables

		coefficient	standard error	p value
sex	[female]	reference		
	[male]	-0.16	0.1762	0.3
age at baseline		-0.022	0.0096	0.02
MS duration at baseline		-0.019	0.01598	0.2
therapy [natalizumab]		0.44	0.1948	0.02
baseline date		0.0003	0.00014	0.01
baseline disability		0.0668	0.053	0.2
pre-study MS activity	[progression]	reference		
	[relapse]	0.9943	0.35	0.005
	[relapse & progression]	1.206	0.36	0.0007
pre-study relapses (6-months)		0.0587	0.14	0.7
pre-study relapses (12 months)		-0.1788	0.12	0.1
pre-study therapy	[interferon β-1a IM]	reference		
	[interferon β-1b]	0.0354	0.25	0.9
	[glatiramer acetate]	0.1042	0.25	0.8
	[interferon β-1a SC]	0.0885	0.22	0.7
time from last pre-study thrapy		0.0143	0.0031	10^{-6}
number of previous therapies		0.0107	0.12	0.9
pre-study follow-up duration		-0.00016	0.00007	0.03

Outcome variable: indicator variable for the availability of baseline MRI information
Model: multivariable logistic regression