ANNALS of Clinical and Translational Neurology
Open Access
ANA American Neurological Association since 1875

RESEARCH ARTICLE

Comparative efficacy of switching to natalizumab in active multiple sclerosis

Timothy Spelman[1], Tomas Kalincik[1], Annie Zhang[2], Fabio Pellegrini[3], Heinz Wiendl[4], Ludwig Kappos[5], Larisa Tsvetkova[6], Shibeshih Belachew[2], Robert Hyde[2], Freek Verheul[7], Francois Grand-Maison[8], Guillermo Izquierdo[9], Pierre Grammond[10], Pierre Duquette[11], Alessandra Lugaresi[12], Jeannette Lechner-Scott[13], Celia Oreja-Guevara[14], Raymond Hupperts[15], Thor Petersen[16], Michael Barnett[17], Maria Trojano[3,a], Helmut Butzkueven[1,18,a] & on behalf of the MSBase Investigators and the TOP investigators

[1]Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia
[2]Biogen Idec Inc., Cambridge, Massachusetts
[3]Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy
[4]Department of Neurology, University of Münster, Münster, Germany
[5]Department of Neurology, University Hospital Basel, Basel, Switzerland
[6]Biogen Idec Int BV, Badhoevedorp, The Netherlands
[7]Groene Hart Ziekenhuis, Gouda, The Netherlands
[8]Neuro Rive-Sud, Hôpital Charles LeMoyne, Quebec, Canada
[9]Hospital Universitario Virgen Macarena, Sevilla, Spain
[10]Center de réadaptation déficience physique Chaudière-Appalache, Levis, Canada
[11]Hôpital Notre Dame, Montreal, Quebec, Canada
[12]MS Center, Department of Neuroscience, Imaging and Clinical Sciences, University "G. d'Annunzio", Chieti, Italy
[13]John Hunter Hospital, Newcastle, Australia
[14]University Hospital San Carlos, Madrid, Spain
[15]Orbis Medical Centre, Sittard-Geleen, The Netherlands
[16]Kommunehospitalet, Arhus C, Denmark
[17]Brain and Mind Research Institute, Sydney, Australia
[18]Department of Neurology, Eastern Health, Monash University, Box Hill, Australia

Correspondence
Timothy Spelman, Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia. Tel: 61 3 9342 4406; Fax: 61 3 9349 5997; E-mail: tim@burnet.edu.au

Funding Information
The work was supported by the NHMRC Career Development Award (Clinical) to H. B. (ID628856), NHMRC Early Career Fellowship (1071124), NHMRC Project Grant (1032484), NHMRC Center for Research Excellence (Grant ID 1001216), and the MSBase Foundation. The MSBase Foundation is a not-for-profit organization that receives support from Merck Serono, Biogen Idec, Novartis Pharma, Bayer-Schering, Sanofi-Aventis, and BioCSL. The TYSABRI Observational Program (TOP) is fully funded by Biogen Idec. Biogen Idec provided writing assistance for the development of this manuscript.

Abstract

Objective: To compare treatment efficacy and persistence in patients who switched to natalizumab versus those who switched between glatiramer acetate (GA) and interferon-beta (IFNβ) after an on-treatment relapse on IFNβ or GA using propensity score matched real-world datasets. **Methods**: Patients included were registered in MSBase or the TYSABRI Observational Program (TOP), had relapsed on IFNβ or GA within 12 months prior to switching to another therapy, and had initiated natalizumab or IFNβ/GA treatment $\leq$6 months after discontinuing prior therapy. Covariates were balanced across post switch treatment groups by propensity score matching at treatment initiation. Relapse, persistence, and disability measures were compared between matched treatment arms in the total population (n = 869/group) and in subgroups defined by prior treatment history (IFNβ only [n = 578/group], GA only [n = 165/group], or both IFNβ and GA [n = 176/group]). **Results**: Compared to switching between IFNβ and GA, switching to natalizumab reduced annualized relapse rate in year one by 65–75%, the risk of first relapse by 53–82% (mean follow-up 1.7–2.2 years) and treatment discontinuation events by 48–65% (all $P \leq 0.001$). In the total population, switching to natalizumab reduced the risk of confirmed disability progression by 26% (P = 0.036) and decreased the total disability burden by 1.54 EDSS-years ($P < 0.0001$) over the first 24 months post switch.

All statistical analyses were performed independently by the MSBase Foundation statistician, Tim Spelman.

Received: 8 October 2014; Revised: 9 December 2014; Accepted: 8 January 2015

Annals of Clinical and Translational Neurology **2015; 2(4): 373–387**

doi: 10.1002/acn3.180

[a]Equal contribution.

Interpretation: Using large, real-world, propensity-matched datasets we demonstrate that after a relapse on IFNβ or GA, switching to natalizumab (rather than between IFNβ and GA) led to superior outcomes for patients in all measures assessed. Results were consistent regardless of the prior treatment identity.

Introduction

For multiple sclerosis (MS) patients with relapse on first-line interferon-beta (IFNβ) or glatiramer acetate (GA) therapy, switching to another immunomodulatory therapy is a potentially useful treatment strategy.[1–4] There is some evidence that switching between IFNβ and GA and among different IFNβ therapies can improve patient treatment response.[5–7] On the other hand, natalizumab (TYSABRI®) is also recommended for patients with relapse on IFNβ and/or GA therapy.[8,9] Improvements in disability status and ambulation have been reported in single-arm observational studies of patients who switched to natalizumab after experiencing high disease activity while on another disease-modifying therapy (DMT), usually IFNβ/GA.[10,11] In a single center retrospective analysis by Rio and colleagues,[6] relapse rates in a IFNβ/GA treatment failure population declined significantly after switch to another IFN/GA product or switch to natalizumab, but these two switch groups were not compared. Another two-center 24-month observational study showed that patients who switched to natalizumab (n = 106) or IFNβ/GA (n = 161) after first-line (IFNβ/GA) treatment failure were more likely to remain free of relapse, disability progression, and magnetic resonance imaging (MRI) disease activity than those who switched between IFNβ and GA formulations,[12] with all treatment effects nonsignificant in year 1 but significant in year 2.

These treatment comparisons are challenging to interpret because treatment assignations are nonrandom; and bias may be introduced due to differing patient characteristics. Typically, patients switching to natalizumab would be expected to have more severe disease than patients switching between IFNβ or GA treatments, with resultant bias against natalizumab in outcome analyses. Given the limited observational evidence and lack of randomized controlled trial evidence, we examined treatment outcomes of switch to natalizumab versus switch between IFNβ and GA therapy after IFNβ/GA failure using patients (n = 869/group) matched by disease severity and demographic variables at the time of switch.

The aims of this study were to compare relapse rate, treatment persistence, and disability progression in multiple sclerosis (MS) patients who switched therapy after failure on Betaferon®, Betaseron®, Rebif®, Avonex®, Copaxone®, or Extavia® (BRACE) treatments using propensity matched samples from the MSBase Observational Registry and the TYSABRI Observational Program (TOP), two distinct real-world cohorts with contemporaneous recruitment, according to prospectively defined protocols. We decided to apply propensity score matching, a powerful statistical technique for correcting multiple baseline covariate imbalances in nonrandomly selected cohorts.[13–15] Recently, this technique was successfully used to aid comparisons of IFNβ treatment persistence and disease outcomes using observational data from the MSBase registry.[16]

Materials and Methods

Patient sources

MSBase registry

Patients in the BRACE treatment arms of this study were sourced from the international online MSBase Registry. The MSBase Registry was established in 2004 to collect disease-related information from consenting patients attending MS clinics. As of 4 April 2013, a total of 21,348 people with MS across 60 clinics in 26 countries were participating in MSBase. The registry's member centers, almost exclusively large academic MS centers, follow a defined minimum dataset protocol to prospectively collate outcomes data using an internet-based, physician owned and operated system www.msbase.org.[17] Each center enters patient data either in the offline iMed© local electronic database or the online MSBase registry data entry system during routine clinic visits and intermittently uploads codified datasets to the MSBase server. Physicians record clinical information such as date of MS onset, diagnostic

category, Kurtzke Expanded Disability Status Scale (EDSS) score, relapse onset dates and characteristics, cerebral MRI, and other investigations, and commit to minimum annual follow-up. A clinical attack is defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 h, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous attack, also previously applied in an MSBase relapse phenotype analysis.[18,19] Records are classified as complete and eligible for analyses if they meet a minimum required dataset. Quality of EDSS assessment is monitored by Neurostatus certification of investigators. Informed consent (as required by local laws and regulations) is provided by each participant in MSBase. At each contributing center the project has Human Research Ethics Committee approval or exemption.

TYSABRI observational program

Patients treated with natalizumab were sourced from TOP (Biogen Idec, Cambridge, MA). TOP is an ongoing, open-label, multinational, multicenter, prospective, observational study conducted in clinical practice settings in Europe, Australia, Canada, and Argentina.[11] Patients are recruited within 3 months of commencing natalizumab. Data are collected at regular clinical visits every 6 months. Data entry is web-based. The primary endpoint is long-term safety (incidence and type of serious adverse events). Secondary endpoints include measures of MS disease activity (including the occurrence of clinical relapses and change in EDSS score). In TOP, a clinical relapse is also defined as new or recurrent neurological symptoms, not associated with fever, lasting for ≥24 h and followed by a period of 30 days of stability or improvement. Study endpoints are assessed uniformly across sites. To assure standardized examinations and consistent definitions for the EDSS Functional System (FS) scores, participating physicians are provided a copy of the interactive Neurostatus Training DVD-ROM, and Neurostatus certification is highly recommended. Investigators not previously certified are offered the same online certification (http://www.neurostatus.net) available to MSBase investigators. To reduce the risk of entry error with EDSS score reporting, electronic case report forms (CRFs) were designed to automatically generate queries for data inconsistencies, including data that were out of range or otherwise invalid. The CRF calculates an EDSS score based on the Kurtzke FS and ambulation scores that were entered. The same EDSS calculator was used to assist MSBase investigators. Data quality control procedures were checked for consistency across data sets. Site-based verification and correction was used for residual data queries. At the time of extraction, there were 4821 patients participating in TOP across 16 countries. The TOP study design is in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all enrolled patients provided written informed consent.

Study design

Patients and subgroups

Participants in MSBase or TOP who relapsed in the 12 months prior to switching to natalizumab or a BRACE therapy and who initiated the new treatment ≤6 months after discontinuation of the prior BRACE therapy were included in this study. Treatment efficacy was initially compared between patients who switched from any BRACE therapy to natalizumab and those who switched between different BRACE therapies. Additional comparisons were performed using three subgroups of patients (based on prior BRACE treatment): (1) those with only prior IFNβ therapy exposure who switched to either natalizumab or GA; (2) those with only prior GA therapy exposure who switched to natalizumab or IFNβ; and (3) those with both prior GA and IFNβ therapy exposure who switched to natalizumab or another IFNβ therapy. Propensity score matching was performed separately for the total patient population and each subgroup (Fig. 1).

Efficacy measures

The primary efficacy outcomes assessed were annualized relapse rate (ARR), time to first relapse on therapy, time to treatment discontinuation and time to confirmed disability progression. An area under the disability/time curve (AUC) analysis was conducted as a secondary, exploratory outcome. Confirmed disability progression events were defined as ≥3-month confirmed increases of ≥0.5 points for patients with a baseline EDSS score >5.5, ≥1.0 point for those with a baseline EDSS score between 1.0 and 5.5, inclusive, and ≥1.5 points for those with a baseline EDSS score of 0. EDSS scores recorded within 30 days after the onset of a relapse were excluded. A minimum of three visits (including baseline) at which an EDSS was formally recorded were, by definition, required to be able to assess confirmed disability progression. Thus, this analysis was limited to patients with a minimum of three EDSS scores reported. As this decreased the number of matched pairs available, comparisons of the time to confirmed disability progression were not performed across treatment arms in the subgroup analyses.

As an exploratory analysis, AUC comparisons were performed from baseline through 24 months of treatment. AUC values were derived for both the natal-

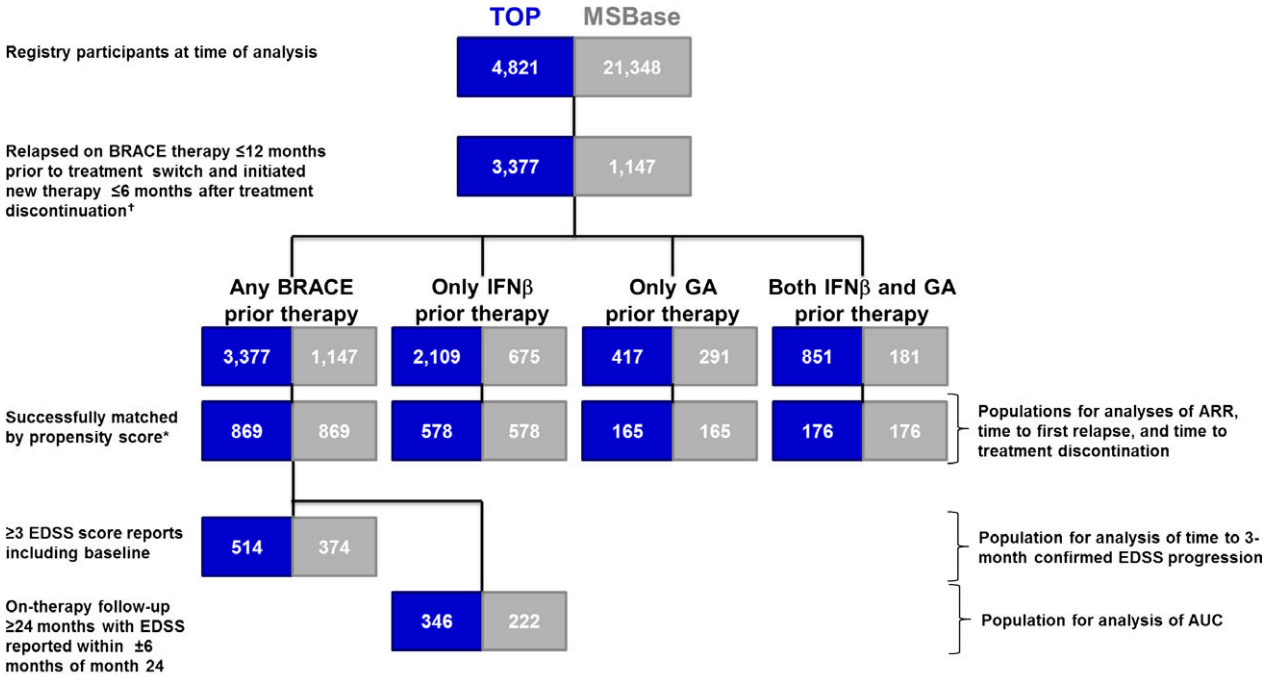


Figure 1. Study profile.

izumab and BRACE treatment arms to estimate each patient's total study experience with respect to disability burden after switching treatment. Only propensity-matched patients who remained on the new therapy ≥24 months after switching and who had an EDSS score recorded within ±6 months of the 24-month postbaseline mark were included in this analysis. This limited the number of matched pairs available. Therefore, AUC measures were not compared in the subgroup analyses.

Statistical analyses

The data from both registries were combined according to a prespecified protocol. Categorical variables were summarized using frequency and percentage. Continuous variables were assessed for significant departures from normality using a Shapiro–Wilk test of skew and summarized using mean and standard deviation (SD) or standard error, or median and interquartile range (IQR) as appropriate. All baseline covariates common to and available from both registries were used to calculate propensity scores. These included gender, age, disease duration, baseline EDSS, number of DMT initiations, duration of DMT use as a proportion of disease duration, total relapses and total steroid-treated relapses in the 12 and 24 months preceding baseline. Prior DMTs reported were Betaferon® (Bayer Pharma AG, Berlin, Germany), Betaseron® (Bayer Pharma AG, Berlin, Germany), Rebif® (Merck KGaA, Darmstadt, Germany), Avonex® (Biogen Idec Inc., Cambridge, Massachusetts), Copaxone® (Teva Pharmaceuticals, North Wales, PA, USA) or Extavia® (Novartis AG, Basel).

Propensity scores were calculated for each individual patient and represented the probability that a patient from either registry would have commenced natalizumab treatment based purely on pretreatment baseline characteristics. This propensity score was derived from a logistic regression model, in which receipt of natalizumab was the outcome variable and the pretreatment characteristics formed the explanatory variables. Patients from each treatment arm were matched, based on high similarity of propensity score, on a 1:1 basis using a 5-to-1 digit matching algorithm with a 0.01 calliper.[20] Success of matching was assessed using both paired tests and analysis of standardized differences. Imbalance was defined as an absolute value of the standardized difference equal or greater than 0.20.[21,22] Wilcoxon rank-sum and chi-square tests were used to compare unmatched baseline characteristics by treatment arm as appropriate. Wilcoxon signed-rank and McNemar tests were used to compare baseline characteristics in the matched data for continuous variables and proportions, respectively. Standardized differences were calculated for both unmatched and matched comparisons, permitting direct comparison of different

baseline characteristics with the same standardized units. Baseline for these analyses was defined as the date the patient initiated the new treatment after BRACE therapy discontinuation. Post hoc Rosenbaum sensitivity analyses across all outcomes were conducted to test the sensitivity of our propensity-matched models to unobserved heterogeneity.[23–28]

Comparative analyses of time to first relapse on treatment, time to treatment discontinuation, and time to confirmed disability progression between natalizumab and BRACE comparator groups were performed using a Cox Marginal Model, clustered for the matched pair. Hazard proportionality was assessed via analysis of scaled Schoenfeld residuals and for all models presented in this report, hazard proportionality was satisfied. A competing risks extension of the Cox time-to-event model was used to further assess for the influence of informative censoring on event ascertainment, for example the influence of differences in follow-up time (censoring at last observed assessment) by treatment arm on observing relapse or discontinuation events.

In order to perform AUC analyses, for each patient all EDSS scores recorded within the 24-month interval were plotted, and the inter-EDSS serial disability area was calculated as the product of the difference between observed and baseline EDSS and the time elapsed between two successive EDSS assessments (Fig. 2). This quantity could take positive values (for disability area recorded above baseline EDSS) or negative values (area contributed by EDSS recorded below baseline EDSS). These inter-EDSS AUC values were then summed to produce a cumulative AUC across the 24-month on-treatment interval. This approach to calculating AUC presumes that EDSS change between two successive assessments is not a constant, linear change as has been assumed in comparable studies[29–31] but rather an event-based step up or down in EDSS, more consistent with the attack/relapse course of MS. As a sensitivity analysis we compared the performance of our AUC approach with that calculated using the trapezoidal rule,[32,33] which presumes a steady, linear change in EDSS between assessment points. The standardized 24-month AUC values were compared across propensity score matched treatment arms with quantile median regression using Censored Least Absolute Deviations (CLAD)[34,35] to adjust for the matched pairs. A quantile regression of the median was preferred to simple linear regression of the mean because the distribution of standardized 24-month AUC values was significantly skewed and resistant to transformation. A Cochran-Armitage test was used to check for nonlinearity in the associations between AUC and treatment arm. Data were extracted and compiled on 4 April 2013. To test for potential ascertainment bias secondary to unequal frequency of EDSS assessment points and/or unequal time between assessments by switch therapy arm, we conducted a sensitivity analysis limiting the serial disability-time analysis to just that subset of patients who recorded exactly five assessments (at baseline, 6, 12, 18, and 24 months). Consistent with the real-world nature of the data, temporal assessments were not always made exactly on the 6-month mark, thus we analysed a series of time ranges around each of the 6, 12, 18, and 24 month points – namely 1, 1.5, and 2 months. Informative censoring was minimized through application of pairwise censoring. This involved censoring both members of the propensity-matched natalizumab-BRACE pair at the earliest censor point recorded by either member of the pair. All analyses were undertaken using Stata version 12 (StataCorp, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria).

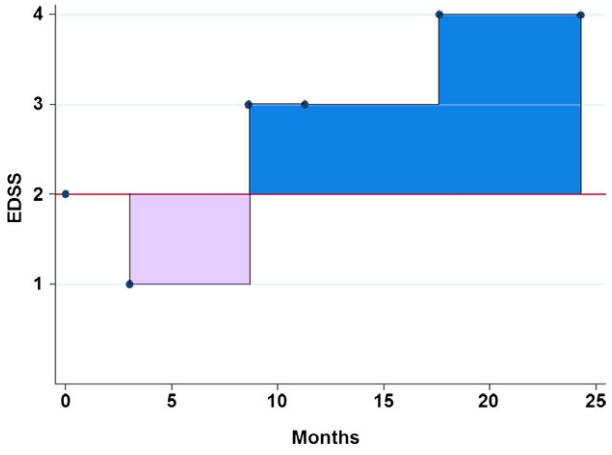


Figure 2. Example of a cumulative AUC measurement from a sample 24-month EDSS/time plot. The red line represents baseline EDSS. Dots indicate individual EDSS measurements. The area above baseline EDSS (blue) minus the area below baseline EDSS (pink) equals the cumulative summed AUC. AUC, area under the disability/time curve; EDSS, Expanded Disability Status Scale.

Results

Patients with relapse on any BRACE therapy who switched to another BRACE therapy or to natalizumab

Patients

Of the 3377 patients in TOP who met inclusion criteria and switched from BRACE to natalizumab and the 1147 patients in MSBase who met inclusion criteria and switched between BRACE treatments, 869 were successfully paired by propensity score. Distribution plots of propensity scores by switch arm for both the unmatched and matched sample are presented in

Table 1. Prematching comparison of baseline characteristics by switch group.

Variable (at baseline)	Total population		Prior therapy with IFNβ		Prior therapy with GA		Prior therapy with IFNβ and GA	
	NTZ	IFNβ/GA	NTZ	GA	NTZ	IFNβ	NTZ	IFNβ
n	3377	1147	2109	675	417	291	851	181
Female, %	72.0	79.4	70.4	77.6	75.3	81.1	74.2	83.4
P-value	<0.001		<0.001		0.0681		0.0084	
Standardized difference[1], %	−17.5		−16.5		−14.1		−22.8	
Age, median (IQR)	37 (30, 44)	37 (31, 45)	37 (29, 44)	37 (30, 44)	38 (30, 45)	37 (31, 45)	37 (31, 44)	38 (32, 45)
P-value	0.048		0.064		0.8939		0.2146	
Standardized difference[1], %	−7.3		−8.9		1.2		−12.8	
Disease duration, median (IQR)	6.9 (3.4, 11.9)	6.4 (3.2, 11.6)	6.3 (3.1, 11.6)	5.8 (2.8, 11.0)	6.6 (2.8, 11.5)	6.0 (3.1, 11.3)	7.9 (4.7, 11.7)	8.1 (5.3, 13.4)
P-value	0.104		0.114		0.7113		0.0991	
Standardized difference[1], %	2.6		3.2		3.9		−12.5	
Proportion disease duration on DMT, median (IQR)	0.5 (0.3, 0.8)	0.4 (0.2, 0.6)	0.6 (0.3, 0.8)	0.4 (0.2, 0.6)	0.4 (0.2, 0.7)	0.3 (0.2, 0.6)	0.6 (0.3, 0.8)	0.4 (0.2, 0.6)
P-value	<0.001		<0.0001		0.1483		<0.0001	
Standardized difference[1], %	45.6		47.3		13.0		53.3	
Number of DMT starts mean (SD)	1.5 (0.8)	1.4 (0.7)	1.3 (0.6)	1.4 (0.7)	1.0 (0.3)	1.4 (0.7)	2.4 (0.7)	2.2 (5.7)
P-value	0.743		0.0016		<0.0001		0.0051	
Standardized difference[1], %	0.4		−15.9		−74.1		22.8	
Number of DMT starts/disease duration, mean (SD)	0.3 (0.5)	0.4 (0.4)	0.3 (0.4)	0.4 (0.5)	0.36 (0.66)	0.37 (0.43)	0.42 (0.43)	0.35 (0.34)
P-value	0.094		0.0057		0.0001		0.0056	
Standardized difference[1], %	−5.3		−13.6		−2.3		16.8	
Baseline EDSS, median (IQR)	3 (2, 4.5)	2.5 (2, 4)	3 (2, 4)	2.5 (2, 4)	3.5 (2, 4.5)	2.5 (2, 4)	3.5 (2, 4.5)	3 (2, 4.5)
P-value	<0.001		0.0001		0.0004		0.262	
Standardized difference[1], %	16.2		15.6		24.6		7.1	
Total relapse onsets last 12 months, mean (SD)	2.0 (1.0)	1.6 (0.9)	2.0 (1.0)	1.6 (0.8)	2.0 (1.0)	1.7 (0.9)	2.0 (1.1)	1.7 (0.9)
P-value	<0.001		<0.0001		<0.0001		<0.0001	
Standardized difference[1], %	38.2		43.2		28.9		35.8	
Total steroid-treated relapses last 12 months, mean (SD)	1.7 (1.1)	0.9 (0.9)	1.7 (1.1)	0.9 (0.9)	1.6 (1.1)	1.0 (0.9)	1.7 (1.1)	1.0 (0.9)
P-value	<0.001		<0.0001		<0.0001		<0.0001	
Standardized difference[1], %	70.7		74.3		64.3		66.4	
Total relapse onsets last 24 months, mean (SD)	2.9 (1.5)	2.4 (1.4)	2.9 (1.5)	2.3 (1.3)	2.8 (1.4)	2.6 (1.4)	3.1 (1.6)	2.5 (1.6)
P-value	<0.001		<0.0001		0.0053		<0.0001	
Standardized difference[1], %	34.5		39.1		18.7		35.9	
Total steroid-treated relapses last 24 months, mean (SD)	2.3 (1.5)	1.3 (1.3)	2.3 (1.5)	1.3 (1.3)	2.2 (1.5)	1.4 (1.3)	2.5 (1.7)	1.5 (1.5)
P-value	<0.001		<0.0001		<0.0001		<0.0001	
Standardized difference[1], %	70.1		74.3		62.9		61.0	

NTZ, natalizumab; IFNβ, interferon-beta; GA, glatiramer acetate; IQR, interquartile range; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale.

[1]Imbalance defined as an absolute value ≥20%.

Figure S1 for the primary any BRACE switch analysis group. As expected, baseline covariates were markedly different between treatment groups in the unmatched sample, with greater disease severity demonstrated in the patients switching to natalizumab (Table 1); no significant differences were demonstrated after propensity score matching (Table 2). For the propensity score matched patients, mean (SD) follow-up from baseline was 2.24 years (2.47) in the BRACE group compared to 1.95 years (1.23) in the natalizumab group ($P = 0.002$). Mean (SD) time between on-treatment assessments was 6.33 (3.91) months in the BRACE group and 6.30 (1.83) months in the natalizumab group ($P = 0.753$).

Table 2. Propensity-matching comparison of baseline characteristics by switch group.

Variable (at baseline)	Total population		Prior therapy with IFNβ		Prior therapy with GA		Prior therapy with IFNβ and GA	
	NTZ	IFNβ/GA	NTZ	GA	NTZ	IFNβ	NTZ	IFNβ
n	869	869	578	578	165	165	176	176
Female, %	77.2	78.9	76.5	76.1	80.0	78.8	83.0	83.5
P-value	0.412		0.9455		0.8957		0.8815	
Standardized difference[1], %	−4.2		6.6		5.5		15.2	
Age, median (IQR)	38 (31, 45)	37 (31, 45)	38 (31, 44)	37 (30, 43)	38 (30, 45)	38 (32, 46)	39 (32, 46)	38 (32, 45)
P-value	0.518		0.8507		0.8458		0.6841	
Standardized difference[1], %	3.2		3.7		6.5		−15.9	
Disease duration, median (IQR)	6.8 (3.4, 12.0)	6.2 (3.0, 11.6)	6.3 (3.2, 11.9)	5.8 (2.8, 11.2)	6.4 (3.1, 10.3)	5.5 (2.6, 10.3)	8.0 (4.8, 12.6)	8.1 (5.3, 13.4)
P-value	0.340		0.1739		0.3567		0.2384	
Standardized difference[1], %	2.0		6.4		−6.9		−19.2	
Proportion disease duration on DMT, median (IQR)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	0.3 (0.1, 0.5)	0.3 (0.1, 0.6)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)
P-value	0.434		0.5014		0.2818		0.5272	
Standardized difference[1], %	−4.1		−5.0		−19.1		18.3	
Number of DMT starts mean (SD)	1.4 (0.7)	1.4 (0.7)	1.2 (0.6)	1.3 (0.7)	1.0 (0.2)	1.2 (0.5)	2.2 (0.5)	2.2 (0.4)
P-value	0.178		0.4431		0.5637		0.7179	
Standardized difference[1], %	3.9		−9.8		−18.9		1.3	
Number of DMT starts/disease duration, mean (SD)	0.4 (0.6)	0.4 (0.4)	0.3 (0.4)	0.4 (0.4)	0.3 (0.5)	0.4 (0.5)	0.3 (0.3)	0.4 (0.3)
P-value	0.533		0.1832		0.1288		0.3834	
Standardized difference[1], %	1.1		−10.6		11.0		19.4	
Baseline EDSS, median (IQR)	3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2, 4)	2.5 (2, 4)	3 (2, 4)	3 (2, 4.5)
P-value	0.138		0.6519		0.2375		0.4605	
Standardized difference[1], %	6.6		8.5		8.2		−14.1	
Total relapse onsets last 12 months, mean (SD)	1.6 (0.7)	1.6 (0.9)	1.59 (0.77)	1.61 (0.94)	1.76 (0.85)	1.84 (0.95)	1.64 (0.87)	1.69 (0.92)
P-value	0.670		0.7929		0.5135		0.7494	
Standardized difference[1], %	−1.9		7.0		−18.8		−4.9	
Total steroid-treated relapses last 12 months, mean (SD)	0.9 (0.8)	1.0 (0.9)	0.98 (0.83)	0.97 (0.92)	1.15 (0.87)	1.19 (0.97)	0.96 (0.82)	1.00 (0.91)
P-value	0.090		0.2891		0.5899		0.8566	
Standardized difference[1], %	−6.2		−1.5		−8.4		−6.2	
Total relapse onsets last 24 months, mean (SD)	2.4 (1.2)	2.4 (1.3)	2.4 (1.2)	2.4 (1.3)	2.6 (1.3)	2.6 (1.4)	2.5 (1.3)	2.5 (1.6)
P-value	0.407		0.9629		0.7601		0.7484	
Standardized difference[1], %	2.3		8.5		−19.2		15.7	
Total steroid-treated relapses last 24 months, mean (SD)	1.3 (1.1)	1.4 (1.2)	1.4 (1.1)	1.4 (1.3)	1.6 (1.3)	1.6 (1.3)	1.5 (1.2)	1.5 (1.5)
P-value	0.198		0.5144		0.9086		0.8427	
Standardized difference[1], %	−4.3		−1.5		−9.5		−0.9	

NTZ, natalizumab; IFNβ, interferon-beta; GA, glatiramer acetate; IQR, interquartile range; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale.

[1]Imbalance defined as an absolute value ≥20%.

Relapse rate

During the first 12 months after treatment switch, ARR was higher in patients who switched to another BRACE therapy (mean, 0.58; SD, 0.86) than in those who switched to natalizumab (mean, 0.20; SD, 0.52) ($P < 0.0001$), representing a 66% relative reduction in ARR for patients who switched to natalizumab. This difference was sustained over subsequent years (Table 3). Over the study period, patients who switched to natalizumab had a 54% reduction in the risk of first relapse (hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.39–0.53; $P < 0.001$) (Fig. 3A). When the analysis was limited to the first 12 months after treatment switch, the

risk of first on-treatment relapse was reduced by 65% for patients who switched to natalizumab (HR, 0.35; 95% CI, 0.28–0.44; $P < 0.001$).

Treatment persistence

For patients who switched to natalizumab there was a 60% reduction in the risk of further treatment discontinuation (HR, 0.40; 95% CI, 0.34–0.47; $P < 0.001$) (Fig. 3B). Limiting the model to the first 12 months after treatment switch increased the effect size. Patients who switched to natalizumab had a 74% reduction in the risk of treatment discontinuation (HR, 0.26; 95% CI, 0.20–0.34, $P < 0.001$). Despite longer mean follow-up in the BRACE treatment arm, competing risks models for both the time to first relapse and treatment discontinuation confirmed that this difference did not significantly influence the estimated HRs. Forty-one (4.7%) of the 869 matched patients who switched to natalizumab tested positive for anti-JCV antibodies at least once during the follow-up period.

Disability progression

Of the 869 propensity score matched pairs, a total of 374 patients in the BRACE arm and 514 patients in the natalizumab arm met the minimum requirement of three reported EDSS scores (including baseline) and were included in the disability progression analysis. There were no significant differences in baseline characteristics between the groups. Patients who switched to natalizumab had a 26% reduction in the risk of 3-month confirmed disability progression (HR, 0.74; 95% CI, 0.55–0.97; $P = 0.036$) (Fig. 3C). There was no significant difference in time to confirmed disability progression when this analysis was limited to the first 12 months after treatment switch (HR, 0.86; 95% CI, 0.51–1.44; $P = 0.561$).

Of the 1738 propensity score matched patients in the total study population, 568 had the minimum on-treatment follow-up of 24 months required for inclusion in the AUC analysis. There were no significant differences in any of the baseline characteristics between the treatment groups, however, ascertainment of EDSS during the 24-month interval was significantly more frequent in the BRACE arm compared with the natalizumab arm. Within the 24-month AUC analysis time window, the mean (SD) number of visits with an EDSS score reported was 4.75 (1.72) in the BRACE arm and 3.67 (0.65) in the natalizumab arm ($P = 0.0001$).

Patients switching from BRACE to natalizumab had significantly less total disability burden, as measured by standardized 24-month AUC values, compared to patients who switched between BRACE therapies. The mean cumulative AUC was decreased by 0.64 EDSS-years in the natalizumab treatment arm compared to the BRACE treatment arm (natalizumab: mean [SD], −3.30 [1.65] EDSS-years; BRACE: −2.66 [1.70] EDSS-years; $P < 0.0001$). On quantile regression, median standardized 24-month AUC was decreased by 1.54 EDSS-years (95% CI −2.30, −0.78) ($P < 0.0001$) in patients who switched to natalizumab compared to those who switched to BRACE treatments. In a sensitivity analysis, AUC was measured using the trapezoidal rule[24–26]; median standardized 24-month AUC was decreased by 1.01 EDSS-years in the natalizumab group compared to the BRACE group ($P = 0.001$) when this method was employed. For comparison, time to first 3-month confirmed disability progression was also assessed over the same 24-month time window and in the subset of patients used in the AUC analysis (including only propensity-matched patients who remained on the new therapy ≥24 months after switching). In this group, patients who switched to natalizumab had a 45% reduction in the risk of 3-month confirmed disability progression (HR, 0.55; 95% CI, 0.35–0.88; $P = 0.012$). To test this result for potential ascertainment bias secondary to unequal frequency of EDSS assessment points and/or unequal time between assessments by treatment arm, we reran this model limiting the analysis to just the subset of patients who recorded exactly five visits (at baseline, 6, 12, 18, and 24 months) within the 24-month consideration period. Applying, successively, a 1, 1.5, and 2-month time range buffer around each 6-month assessment point we observed a significant decrease in median standardized 24-month AUC of 1.68 EDSS-years (95% CI −2.51, −0.69), 1.59 EDSS-years (95% CI −2.47, −0.72), and 1.56 EDSS-years (95% CI −2.35, −0.75), respectively, in the natalizumab switch arm relative to the BRACE switchers. These results are consistent with the primary analysis with only a marginal broadening of the CIs around the point estimates consistent with the loss of sample associated with each sensitivity analyses. This suggests that the results of the primary analysis are relatively resistant to any ascertainment bias conferred by the minor imbalances in 24-month EDSS assessment frequency and time between assessments.

Subgroup analyses by prior BRACE treatment

After propensity scores were used to match patients in TOP and MSBase independently in each prior treatment subgroup, there were no significant differences in the baseline characteristics between treatment arms in any subgroup (Table 2). Mean (SD) follow-up in subgroup 1 (patients with only prior IFNβ therapy who switched to GA or natalizumab) was 2.24 (2.30) years in the GA

Table 3. Annualized relapse rates by treatment group and postbaseline year[1].

	Total population		Prior therapy with IFNβ		Prior therapy with GA		Prior therapy with IFNβ and GA	
	No. of patients	ARR, mean (SD)	No. of patients	ARR, mean (SD)	No. of patients	ARR, mean (SD)	No. of patients	ARR, mean (SD)
Year 1								
Natalizumab	607	0.20 (0.52)	439	0.16 (0.50)	112	0.21 (0.47)	125	0.14 (0.39)
BRACE	497	0.58 (0.86)	369	0.54 (0.86)	113	0.60 (0.82)	95	0.55 (0.78)
P-value		<0.0001		<0.0001		<0.0001		<0.0001
Year 2								
Natalizumab	372	0.18 (0.38)	269	0.19 (0.50)	63	0.24 (0.50)	75	0.21 (0.50)
BRACE	333	0.48 (0.59)	257	0.43 (0.75)	95	0.38 (0.70)	61	0.48 (1.03)
P-value		<0.0001		<0.0001		0.1721		0.0475
Year 3								
Natalizumab	189	0.16 (0.28)	143	0.03 (0.18)	31	0.03 (0.18)	29	0.07 (0.26)
BRACE	219	0.39 (0.46)	167	0.29 (0.56)	81	0.10 (0.32)	40	0.30 (0.65)
P-value		<0.0001		<0.0001		0.2533		0.0517
Year 4								
Natalizumab	59	0.14 (0.25)	62	0.00 (0.00)	10	0.10 (0.32)	6	0.00 (0.00)
BRACE	166	0.36 (0.42)	133	0.21 (0.49)	78	0.22 (0.47)	27	0.26 (0.59)
P-value		0.0002		0.0009		0.4361		0.2946

IFNβ, interferon-beta; GA, glatiramer acetate; ARR, annualized relapse rate.
[1]Patients were only included in the analysis for a given year if they were both on-treatment and followed up through the entire the year.

group compared with 1.98 (1.23) years in the natalizumab group; in subgroup 2 (patients with only prior GA therapy who switched to IFNβ or natalizumab) it was 1.69 (2.01) years in the IFNβ group compared with 1.73 (1.17) years in the natalizumab group; in subgroup 3 (patients with both prior IFNβ and GA therapy who switched to another IFNβ or natalizumab) it was 1.82 (1.94) years in the IFNβ group compared with 1.79 (1.13) years in the natalizumab group.

In all subgroups, on-treatment ARR in the first 12 months after switching treatment was lower in patients who switched to natalizumab compared to those who switched to another BRACE therapy; the relative reduction in ARR was 70% in subgroup 1, 65% in subgroup 2, and 75% in subgroup 3. ARR remained lower in the natalizumab group in subsequent years in all subgroups (Table 3). Patients who switched to natalizumab also had a lower risk of first relapse and a lower risk of treatment discontinuation compared to patients who switched to another BRACE therapy in all subgroups. Figures 4, 5 display the Kaplan–Meier curves of time to first relapse and treatment discontinuation for each prior treatment subgroup; relative risk reductions and rate increases associated with each treatment decision are included in the text on each figure.

Sensitivity analyses

To assess the sensitivity of our propensity matched models to potential confounding secondary to imbalance of baseline MRI metrics, we remodeled treatment arm as a predictor of first on-treatment relapse, switch therapy discontinuation and 3-month confirmed disability progression incorporating baseline cerebral MRI metrics, where available, as adjusting covariates in the Cox marginal model. The reduction in the rate of first on-treatment relapse associated with natalizumab relative to BRACE observed in the matched primary analysis (HR 0.46, 95% CI 0.39–0.53, reference = BRACE) was strongly resistant to the influence of MRI lesion type and frequency with only marginal changes in the adjusted hazard ratio (aHR) point estimate and associated CI observed (aHR 0.47, 95% CI 0.35–0.62 adjusted for ≥1 T1 Gd+ lesions; aHR 0.48, 95% CI 0.37, 0.62 adjusted for ≥9 T2 hyperintense lesions and aHR 0.46, 95% CI 0.31–0.68 adjusted for all of ≥1 T1 Gd+, ≥9 T2 hyperintense, ≥1 infratentorial, ≥1 juxtacortical and ≥2 periventricular lesions). A similar preservation of the effect size estimated in the primary analysis was further observed when both the time to switch therapy discontinuation and disability progression models were extended to adjust for baseline MRI data. The MRI-adjusted model of both the treatment discontinuation and disability progression models returned adjusted HR point estimates that differed by only 0.01 (treatment discontinuation: aHR 0.39. 95% CI 0.26–0.59 compared with a primary analysis estimate of HR 0.40, 95% CI 0.34–0.47; disability progression: aHR 0.75, 95% CI 0.54–0.98 adjusted model, HR 0.74, 95% CI 0.55–0.98 primary analysis).

Using post hoc Rosenbaum sensitivity analyses of our propensity-matched relapse, persistence and progression

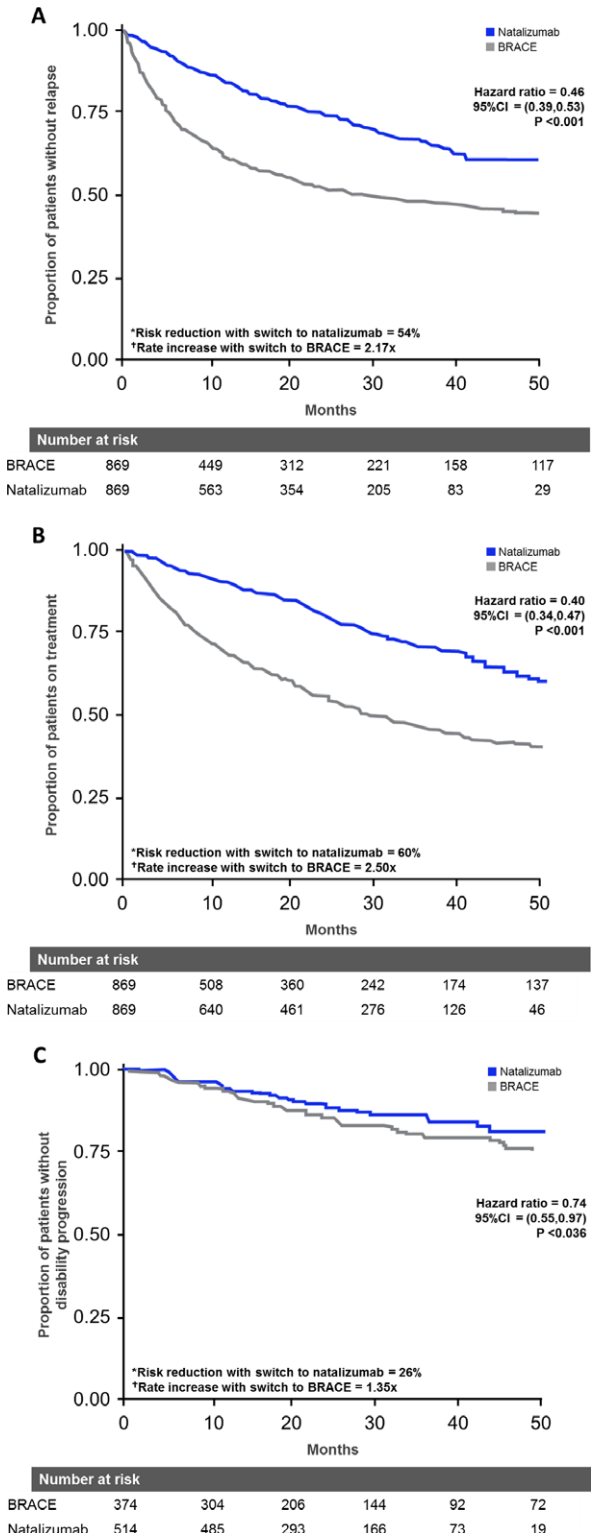


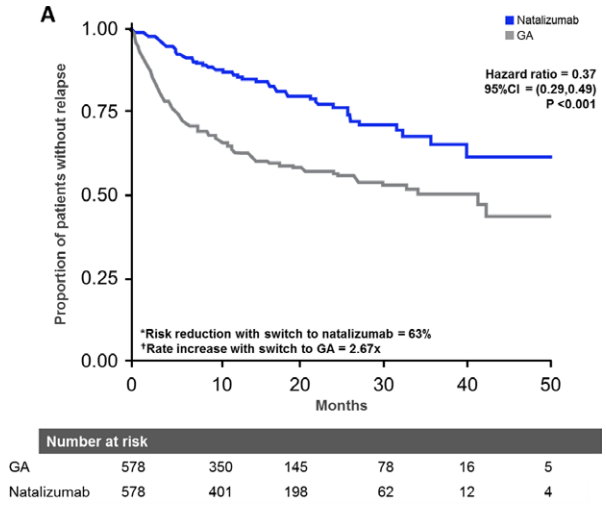
Figure 3. Time to (A) first relapse, (B) treatment discontinuation, or (C) 3-month confirmed disability progression after treatment switch. *Reference group switched to BRACE. †Reference group switched to natalizumab.

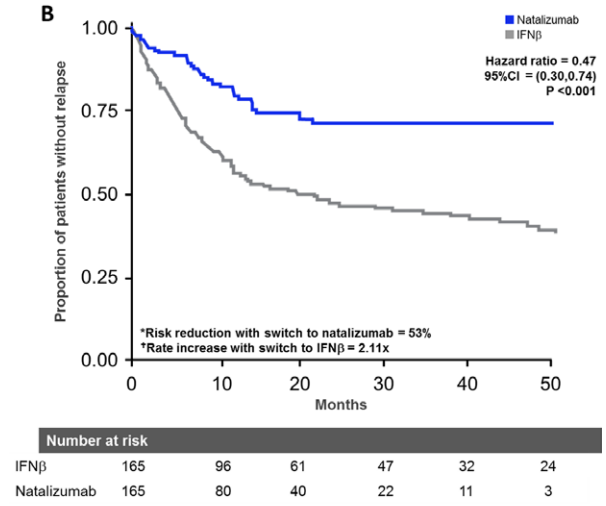
models we estimated that an unobserved confounder would need to produce a minimum 3.01-, 2.75-, and 3.18-fold increase in the rate of relapse, discontinuation, and progression, respectively, in order to reject the inference of a treatment effect in favor of selection effects. These represent improbably large differences in the context of the point estimates and associated CIs observed, thus we can conclude that our observation of efficacy and persistence differentials by switch treatment arm are reasonably robust to unmeasured influences.

Discussion

There are no head-to-head randomized clinical trials comparing efficacy outcomes between patients who switch to natalizumab or to another BRACE therapy after a BRACE treatment failure, so that this question can currently only be examined in real-world datasets, including cohort studies such as MSBase and TOP. Using propensity score matched samples from MSBase registry and TOP observational dataset, we demonstrated that superior outcomes were achieved in patients who switched to natalizumab after an on-treatment relapse. Compared to patients who switched between BRACE therapies, patients who switched to natalizumab had significantly reduced risks of further relapse occurrence, treatment discontinuation, and disability progression. Cumulative 24-month total disability burden, assessed using an exploratory AUC analysis, was also significantly lower in patients who switched to natalizumab. Subgroup analyses demonstrated that similar relapse and treatment discontinuation results are observed regardless of the type of prior BRACE treatment. Whilst the relative reduction in ARR associated with natalizumab was similar across all three prior treatment subgroups (ranging from 65% to 75%), the comparative hazard of first relapse on switch therapy associated with natalizumab relative to BRACE was greatest in those patients previously exposed to *both* IFNβ and GA (Fig. 4). This same subgroup also recorded the greatest differential in switch therapy discontinuation rates across all three subgroups (Fig. 5). This suggests that there may be identifiable subsets of patients who respond differently to IFNβ and/or GA. However, regardless of the identity or sequence of prior BRACE exposure, natalizumab treatment initiation was observed to be consistently associated with an efficacy advantage relative to BRACE switches.

Smaller studies have demonstrated results broadly consistent with these findings. Lanzillo and colleagues performed an adjusted analyses of 12-month outcomes after natalizumab or Rebif® initiation (n = 42/group, mixed pretreated and treatment-naïve at baseline) and showed better relapse, MRI, and disability outcomes in the natalizumab group.[36] In a prospective, observational propensity-score





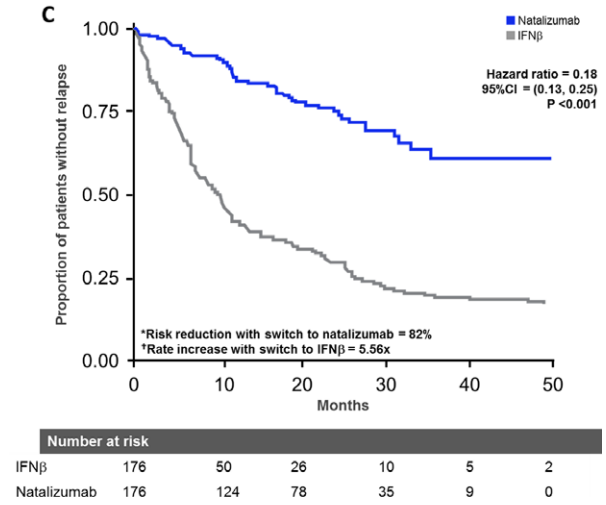
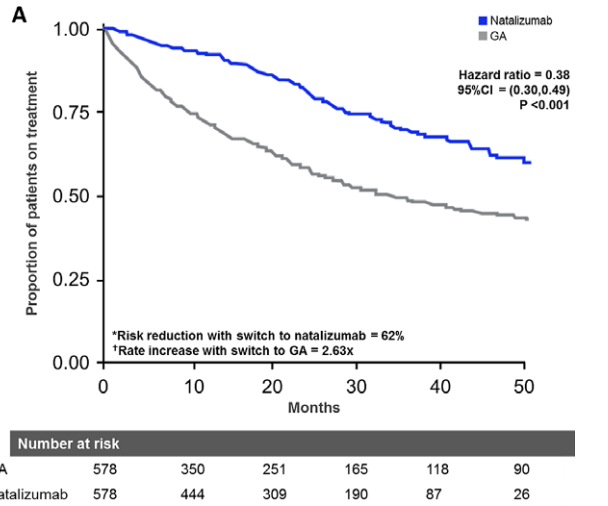
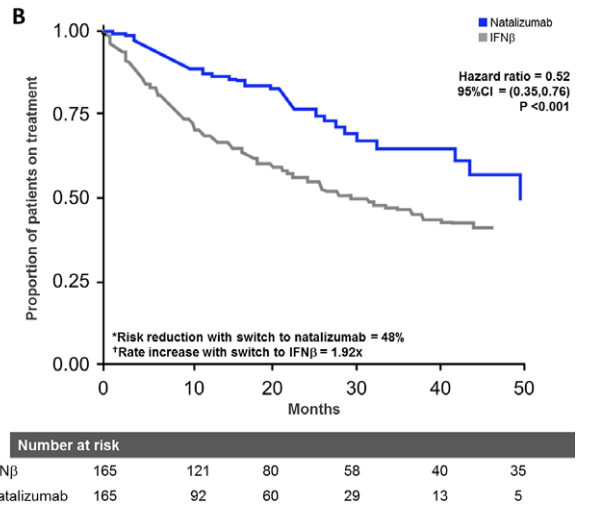


Figure 4. Time to first relapse after treatment switch by prior treatment subgroup, (A) IFNβ, (B) GA, or (C) IFNβ and GA. *Reference group switched to BRACE. †Reference group switched to natalizumab. IFNβ, interferon-beta; GA, glatiramer acetate.





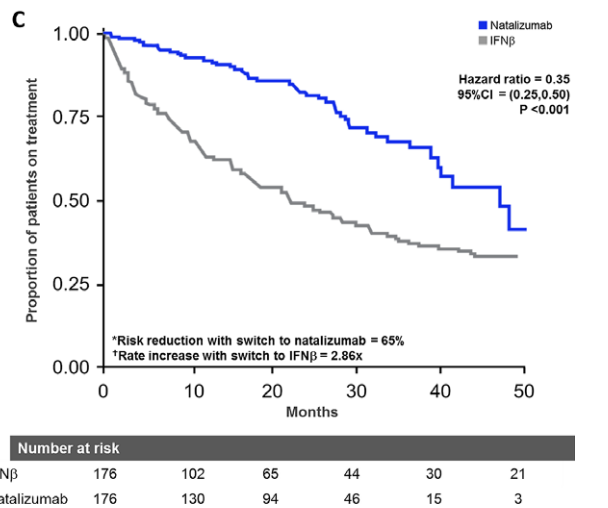


Figure 5. Time to treatment discontinuation after treatment switch by prior treatment subgroup, (A) IFNβ, (B) GA, or (C) IFNβ and GA. *Reference group switched to BRACE. †Reference group switched to natalizumab. IFNβ, interferon-beta; GA, glatiramer acetate.

adjusted but unmatched study of 267 relapsing-remitting MS patients in two Italian centers, Prosperini et al. demonstrated that patients who escalated to natalizumab (n = 106) after first-line treatment failure on IFNβ or GA had a significantly higher probability of remaining relapse free, disability progression free, and MRI activity free over the next 24 months after switching treatment compared to patients who switched between IFNβ and/or GA formulations (n = 161).[12] These investigators controlled for some of the imbalance in baseline disease characteristics by deriving a propensity score of treatment assignation and adjusting for it, but a propensity matching approach such as the one detailed here has previously been demonstrated to provide superior control of confounding factors and thus superior attribution of treatment benefit compared to nonmatched multivariable regression models. This is true even when regression models are fully adjusted for all available baseline characteristics.[14,15] Unlike randomized controlled trials, propensity score based approaches cannot adjust for confounder imbalance in baseline characteristics that have *not* been recorded. However, propensity matching as a variety of pseudo-randomization has been demonstrated to both reduce selection bias[20] and closely approximate the risk estimates derived from randomized trials,[37] including in the MSBase dataset.[16]

The AUC serial disability time plots, albeit exploratory, were attempted to capture and estimate the total burden of complex disability trajectories commonly observed for relapsing MS patients in a clinical practice setting. Compared with the more commonly used summary measures such as the time to first confirmed disability progression analysis, which we have also presented herein, an AUC analysis arguably permits better estimation of a patient's total study duration experience[29] with respect to disability progression and thus superior attribution of any differences observed between treatment groups. Since these serial disability plots explicitly attempt to capture and quantify the total changes in a patient's on-treatment course, the use of an AUC disability metric is proposed to be more clinically meaningful than summary measures of EDSS change. In our analyses, treatment persistence was markedly longer after switch to natalizumab then switch to IFNβ/GA. These results are consistent with an analysis of U.S. claims database which also showed that patients who switched to natalizumab demonstrated greater treatment persistence compared to those who switched to an alternative DMT.[38]

While this study focused on treatment efficacy and persistence, these are not the only important factors for clinicians to consider when weighing these treatment options. Treatment safety, in particular the risk of natalizumab-associated progressive multifocal leukoencephalopathy (PML), must also be assessed. Although not addressed here, evaluation of comparative natalizumab treatment benefits in clinical practice needs to be balanced with appropriate risk-stratification for PML, including testing for JC virus antibody status, to optimize informed and personalized treatment decisions.

The strongest results of our study concern the efficacy differentials observed in time to first relapse and treatment persistence favoring natalizumab. Although a comparable advantage was further observed with regards to confirmed disability progression, this result is less robust as it applies to that subset of the larger eligible sample who recorded a minimum of three prospective EDSS assessments. Furthermore, our study only considers switches from BRACE to natalizumab and not alternate switch scenarios such as natalizumab to newer era oral disease-modifying drugs (DMDs). Generalization of the efficacy advantages observed in this study for patients who switched to natalizumab may be limited by the characteristics of this patient population (most were recruited from large tertiary MS centers) and by the potential for treatment indication bias that may not have been adjusted for in the matched datasets. Propensity score matching was employed in this study to eliminate or reduce known or suspected confounders of treatment allocation. However, unlike true randomization, propensity matching cannot eliminate confounding secondary to imbalance of unknown or unmeasured confounders, and this remains a major limitation of this study. However, it would be expected that any residual bias would not favor the natalizumab cohort, as the known baseline variables in the unmatched populations indicated that those switching to natalizumab had much worse disease (Table S1). Whilst subgroup and sensitivity analyses consistently demonstrated comparable efficacy advantages for patients who switched to natalizumab, future analyses adjusting for an expanded set of baseline characteristics, such as lesion number and distribution on baseline cerebral MRI, would be useful to corroborate these observations.

In the absence of randomized clinical trials, propensity-matching techniques can estimate the benefits associated with various treatment decisions in a clinical practice setting. Using a large real-world dataset, we have shown that patients who relapse on BRACE therapies have better outcomes if they switch to natalizumab rather than switching to another BRACE therapy. This extends to relapse rates, treatment persistence and, in the largest cohort examined, rates of first disability progression events.

Acknowledgments

MSBase study group co-investigators and contributors: From the MS-Centrum Nijmegen, Nijmegen, The Netherlands Cees Zwanikken; from Hospital S. Joao, Porto, Por-

tugal, Maria Edite Rio; Veszprem Megyei Csolnoky Ferenc Korhaz, Veszprem, Hungary, Imre Piroska; from Jewish General Hospital, Montreal, Canada, Fraser Moore; from Josa Andras Hospital, Nyiregyhaza, Tunde Erdelyi; The Alfred Hospital and Monash University, Melbourne, Australia, Olga Skibina; from Cliniques Universitaires Saint-Luc, Brussels, Belgium, Vincent Van Pesch; from Ospedali Riuniti di Salerno, Salerno, Italy, Gerardo Iuliano; from Jeroen Bosch Ziekenhuis, Den Bosch, The Netherlands, Erik van Munster; from FLENI, Buenos Aires, Argentina, Marcela Fiol, Jorge Correale and Celica Ysrraelit; from Department NEUROFARBA, Section of Neurosciences, University of Florence, Florence, Italy, Maria Pia Amato; from Francicus Ziekenhuis, Roosendaal, The Netherlands, Leontien den Braber-Moerland; from New York University Langone Medical Center, New York, USA, Joseph Herbert and Iliya Kister; from Hopital Tenon, Paris, France, Etienne Roullet; from Jahn Ferenc Teaching Hospital, Budapest, Hungary, Krisztian Kasa; from Central Clinical Emergency Military Hospital, Bucharest, Romania, Carmen-Adella Sirbu; from the Geelong Hospital, Geelong, Australia, Cameron Shaw; from HIGA Gral. San Martin, La Plata, Argentina, Santiago Vetere; from the Westmead Hospital, Sydney, Australia, Steve Vucic; from the Clinic of Neurology Clinical Center, Skopje, Macedonia, Tatjana Petkovska-Boskova; from the Bombay Hospital Institute of Medical Sciences, Mumbai, India, Bhim Singhal; from the Instituto de Neurociencias, Cordoba, Argentina, Elizabeth Alejandra Bacile Bacile; from the Hospital Ecoville, Brazil, Walter Oleschko Arruda; from the Center hospitalier del'Universite de Montreal, Hopital Notre-Dame, Canada, Elaine Roger and Pierre Despault; from the Royal Melbourne Hospital, Australia, Mark Marriott, Anneke Van der Walt, John King, Jill Byron and Lisa Morgan; from Box Hill Hospital, Monash University, Australia, Jodi Haartsen; from Department of Neuroscience and Imaging, University "G. d'Annunzio", Italy, Giovanna De Luca, Valeria Di Tommaso, Daniela Travaglini, Erika Pietrolongo, Maria di Ioia, Deborah Farina and Luca Mancinelli; from Hospital Italiano, Argentina, Juan Ignacio Rojas and Liliana Patrucco; from Ospedale di Macerata, Italy, Elisabetta Cartechini and Giorgio Giuliani; from John Hunter Hospital, Australia, David Williams and Lisa Dark; from Buenos Aires, Argentina, Aldo Savino; and from Sheba Medical Center, Tel Hashomer, Israel, Joab Chapman; from Assaf Harofeh Medical Center, Beer-Yaakov, Israel, Shlomo Flechter; from Hospital Italiano, Buenos Aires, Argentina, Edgardo Cristiano; from Centro Internacional de Restauracion Neurologica, Havana, Cuba. Jose Antonio Cabrera-Gomez; from INEBA, Buenos Aires, Argentina, Maria Laura Saladino; from Hospital Fernandez, Buenos Aires, Argentina, Norma Deri; from Craigavon Area Hospital, Portadown, U.K., Orla Gray; from St Vincent's Hospital, Melbourne, Australia; Mark Paine; and from Mater Dei Hospital, Malta; Norbert Vella; Samir Méchati, Eric Bianchi, Alexandru Bulla and Matthieu Corageoud. No compensation has been received for the persons who have made substantial contributions to the work but do not qualify as authors. Nolan Campbell of Biogen Idec provided editorial assistance which involved reference management, coordination of author feedback and manuscript versioning management. Patrick Campbell of Biogen Idec provided minor graphic design assistance with a subset of figures during the development of this manuscript.

Author Contributions

T. Spelman conceptualized and designed the study, conducted and interpreted the analysis and drafted, revised and approved the manuscript. H. Butzkueven conceptualized the study and drafted, revised and approved the manuscript. T. Kalincik and S. Belachew conceptualized the study and revised and approved the manuscript. A. Zhang, F. Pellegrini, H. Wiendl, L. Kappos, L. Tsvetkova, R. Hyde, F. Verheul, F. Grand-Maison, G. Izquierdo, P. Grammond, P. Duquette, A. Lugaresi, J. Lechner-Scott, C. Oreja-Guevara, R. Hupperts, T. Petersen, M. Barnett, and M. Trojano contributed substantially to data acquisition, interpretation of the analysis and have revised and approved the manuscript.

Conflict of Interest

Alessandra Lugaresi is a Bayer Schering, Biogen Idec, Genzyme/Sanofi, Merck Serono Advisory Board Member. She received travel grants and honoraria from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi and Teva and research grants from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva. Prof Lugaresi has also received travel and research grants from the Associazione Italiana Sclerosi Multipla and was a Consultant of "Fondazione Cesare Serono". Annie Zhang is an employee of Biogen Idec Inc. Celia Oreja-Guevara reports no conflicts of interest. Fabio Pelligrini received honoraria for speaking and personal compensation for consulting services from Biogen Idec. Francois Grand' Maison received an honorarium for organizing a CME event for Biogen Idec in 2013 and received consultation fees from Biogen Idec as well as from Novartis and Genzyme in 2013 and 2014. Freek Verheul reports no conflicts of interest. Guillermo Izquierdo received consulting fees from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi, and Teva. Heinz Wiendl received compensation for

serving on scientific advisory boards for Bayer Healthcare, Biogen Idec, Genzyme, Merck Serono, Novartis, and Sanofi; speaker honoraria and travel support from Bayer Schering AG, Bayer Vital GmbH, Biogen Idec, CSL Behring, Fresenius Medical Care, Genzyme, GlaxoSmithKline, GW, Merck Serono, Novartis, and Sanofi; compensation as a consultant from Biogen Idec, Merck Serono, Novartis, and Sanofi; research support from Bayer Vital GmbH, Biogen Idec, Merck Serono, Novartis, Sanofi Germany, and Sanofi U.S. Helmut Butzkueven received compensation for serving on scientific advisory boards and as a consultant for Biogen Idec and Novartis; speaker honoraria from Biogen Idec Australia, Merck Serono Australia, and Novartis Australia; travel support from Biogen Idec Australia and Merck Serono Australia; research support from CASS Foundation (Australia), Merck Serono Australia, the Royal Melbourne Hospital Friends of the Neurosciences Foundation, and the University of Melbourne. Jeannette Lechner Scott reports no conflicts of interest. Larisa Tsvetkova is an employee of Biogen Idec Inc. Maria Trojano received honoraria for consultancy and/or speaking from Biogen Idec, Genzyme-Sanofi, Merck Serono, Novartis, and Roche; research grants from Biogen Idec, Merck Serono, Novartis, and Teva. Michael Barnett has received honoraria for participation in advisory boards and travel sponsorship from Novartis, BioCSL, Genzyme and Biogen Idec. Pierre Duquette has received honoraria for organizing CME events and has obtained funding to attend meetings from Biogen Idec, EMD Serono, TEVA Neuroscience, Novartis, and Genzyme, has received funding for investigator-initiated trials with Biogen Idec, EMD Serono and Novartis, and has received peer-review funding from CIHR and from the MS Society of Canada. Pierre Grammond is a Novartis, Teva-neuroscience, Biogen Idec advisory board member, consultant for Merck Serono, received payments for lectures by Merck Serono, Teva-Neuroscience and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis. Raymond Hupperts received honoraria as consultant on scientific advisory boards from Merck-Serono, Biogen-Idec, Genzyme-Sanofi and Teva, research funding from Merck-Serono and Biogen-Idec, and speaker honoraria from Sanofi-Genzyme. Robert Hyde is an employee of Biogen Idec Inc. Shibeshih Belachew is an employee of Biogen Idec Inc. Thor Petersen received funding or speaker honoraria from Biogen Idec, Merck Serono, Novartis, Bayer Schering, Sanofi-Aventis, Roche, and Genzyme. Tim Spelman received honoraria for consultancy and funding for travel from Biogen Idec Inc. Tomas Kalincik received compensation for travel from Novartis, Biogen Idec, Sanofi Aventis, Teva and Merck Serono.

References

1. Caon C, Din M, Ching W, et al. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. Eur J Neurol 2006;13:471–474.
2. Coyle PK. Switching algorithms: from one immunomodulatory agent to another. J Neurol 2008;255 (suppl 1):44–50.
3. Carra A, Onaha P, Luetic G, et al. Therapeutic outcome 3 years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. Eur J Neurol 2008;15:386–393.
4. Caon C. Maximising therapeutic outcomes in patients failing on current therapy. J Neurol Sci 2009;277(suppl 1): S33–S36.
5. Panitch H, Goodin D, Francis G, et al. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. J Neurol Sci 2005;239:67–74.
6. Rio J, Tintore M, Sastre-Garriga J, et al. Change in the clinical activity of multiple sclerosis after treatment switch for suboptimal response. Eur J Neurol 2012;19:899–904.
7. Gajofatto A, Bacchetti P, Grimes B, et al. Switching first-line disease-modifying therapy after failure: impact on the course of relapsing-remitting multiple sclerosis. Mult Scler 2009;15:50–58.
8. Putzki N, Yaldizli O, Maurer M, et al. Efficacy of natalizumab in second line therapy of relapsing-remitting multiple sclerosis: results from a multi-center study in German speaking countries. Eur J Neurol 2010;17:31–37.
9. Kappos L, Bates D, Edan G, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol 2011;10:745–758.
10. Belachew S, Phan-Ba R, Bartholomé E, et al. Natalizumab induces a rapid improvement of disability status and ambulation after failure of previous therapy in relapsing-remitting multiple sclerosis. Eur J Neurol 2011;18:240–245.
11. Butzkueven H, Kappos L, Pellegrini F, et al. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. J Neurol Neurosurg Psychiatry 2014;85:1190–1197. doi: 10.1136/jnnp-2013-306936.
12. Prosperini L, Gianni C, Leonardi L, et al. Escalation to natalizumab or switching among immunomodulators in relapsing multiple sclerosis. Mult Scler 2012; 18:64–71.
13. Rosenbaum PR, Rubin DB. The central role of propensity scores in observational studies for causal effects. Biometrika 1983;70:41–55.
14. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33–38.

15. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265–2281.
16. Kalincik T, Spelman T, Trojano M, et al. Persistence on therapy and propensity matched outcome comparison of two subcutaneous interferon beta 1a dosages for multiple sclerosis. PLoS One 2013;8:e63480.
17. Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. Mult Scler 2006;12:769–774.
18. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–127.
19. Kalincik T, Buzzard K, Jokubaitis V, et al. Risk of relapse phenotype recurrence in multiple sclerosis. Mult Scler 2014;20:1511–1522. doi: 10.1177/1352458514528762.
20. Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Proceedings of the Twenty-sixth Annual SAS Users group international conference. 2001;26:214–226.
21. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates Publishers, 1988.
22. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–3107.
23. DiPrete TA, Gangl M. Assessing bias in the estimation of causal effects: Rosenbaum bounds on matching estimators and instrumental variables estimation with imperfect instruments. Sociol Methodol 2004;34:271–310.
24. Keele L. An overview of rbounds: an R package for Rosenbaum bounds sensitivity analysis with matched data. White Paper. Columbus, OH, 2010. p. 1–15.
25. Rosenbaum PR. Observational studies. 2nd ed. New York, NY: Springer, 2002.
26. Rosenbaum PR. "Observational study." In: Everitt BS, Howell DC, eds. Encyclopedia of statistics in behavioral science. Vol. 3. New York: John Wiley and Sons, 2005. p. 1451–1462.
27. Nannicini T. A simulation-based sensitivity analysis for matching estimators. Stata J 2007;7:334–350.
28. Ichino A, Mealli F, Nannicini T. From temporary help jobs to permanent employment: what can we learn from matching estimators and their sensitivity? J Appl Econ 2008;23:305–327.
29. Liu C, Blumhardt LD. Randomised, double blind, placebo controlled study of interferon beta-1a in relapsing-remitting multiple sclerosis analysed by area under disability/time curves. J Neurol Neurosurg Psychiatry 1999;67:451–456.
30. Liu C, Blumhardt LD. Benefits of glatiramer acetate on disability in relapsing-remitting multiple sclerosis. An analysis by area under disability/time curves. The Copolymer 1 Multiple Sclerosis Study Group. J Neurol Sci 2000;181:33–37.
31. Liu C, Blumhardt LD. Disability outcome measures in therapeutic trials of relapsing-remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. J Neurol Neurosurg Psychiatry 2000;68:450–457.
32. Yeh ST. Using trapezoidal rule for the area under a curve calculation. NESUG. Collegeville, PA: GlaxoSmithKline, 2002.
33. Tallarida RJ, Murray RB. Manual of pharmacologic calculations with computer programs. New York: Springer-Verlag, 1981.
34. Jolliffe D, Krushelnytskyy B, Semykina A. Censored least absolute deviations estimator: CLAD. Stata Tech Bull 2000;58:13–16.
35. Honore B, Khan S, Powell JL. Quantile regression under random censoring. J Econom 2002;109:67–105.
36. Lanzillo R, Quarantelli M, Bonavita S, et al. Natalizumab vs interferon beta 1a in relapsing-remitting multiple sclerosis: a head-to-head retrospective study. Acta Neurol Scand 2012;126:306–314.
37. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am J Epidemiol 2006;163:262–270.
38. Halpern R, Agarwal S, Borton L, et al. Adherence and persistence among multiple sclerosis patients after one immunomodulatory therapy failure: retrospective claims analysis. Adv Ther 2011;28:761–775.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of propensity scores by treatment arm prior to (A) and after (B) propensity matching.
Table S1. Baseline characteristics of unmatched patients by switch group.

