2-1-2022

No difference in radiologic outcomes for natalizumab patients treated with extended interval dosing compared with standard interval dosing: Real-world evidence from MS PATHS

Lana Zhovtis Ryerson

Robert T. Naismith

Lauren B. Krupp

Leigh E. Charvet

Shirley Liao

See next page for additional authors

Authors

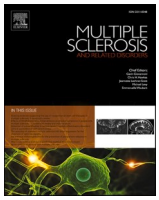
Lana Zhovtis Ryerson, Robert T. Naismith, Lauren B. Krupp, Leigh E. Charvet, Shirley Liao, Elizabeth Fisher, Carl de Moor, James R. Williams, and Nolan Campbell

Multiple Sclerosis and Related Disorders 58 (2022) 103480

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



No difference in radiologic outcomes for natalizumab patients treated with extended interval dosing compared with standard interval dosing: Real-world evidence from MS PATHS

Lana Zhovtis Ryerson [a,*], Robert T. Naismith [b], Lauren B. Krupp [a,c], Leigh E. Charvet [a], Shirley Liao [d], Elizabeth Fisher [e], Carl de Moor [e], James R. Williams [e], Nolan Campbell [e]

[a] New York University Langone Multiple Sclerosis Comprehensive Care Center, 240 East 38th Street, New York, NY 10016, USA
[b] Department of Neurology, Washington University, 660 S. Euclid Ave., St. Louis, MO 63110, USA
[c] Perlmutter Cancer Center at NYU Langone Huntington Medical Group, 789 Park Ave, Huntington, NY 11743, USA
[d] Biogen, 225 Binney St., Cambridge, MA 02142, USA, at the time of this analysis
[e] Biogen, 225 Binney St., Cambridge, MA 02142, USA

A B S T R A C T

Background: Extended interval dosing (EID; average dosing interval approximately every 6 weeks) of natalizumab is associated with significantly lower risk of progressive multifocal leukoencephalopathy than standard interval dosing (SID; every 4 weeks) in patients with relapsing-remitting multiple sclerosis (MS). Real-world studies, though limited, suggest that natalizumab effectiveness is generally maintained in patients who switch to EID after initiation of stable treatment with SID. MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) is a collaborative, multicenter learning health system that generates real-world clinical and MRI data using highly standardized acquisition protocols. We compared MRI outcomes in MS PATHS patients treated with natalizumab EID versus SID. We also compared MRI outcomes in patients treated with natalizumab (EID and/or SID) versus injectable MS platform therapy.

Methods: Natalizumab infusion data from the TOUCH Prescribing Program database and MS PATHS MRI assessment data from seven US sites as of July 23, 2020, were used to identify patients with relapsing-remitting MS who had received natalizumab EID or SID in the interval between two MRI scans (an MRI segment). Patients who received injectable platform MS therapy between two MRI scans were also identified. MRI data were used to determine the incidence rate and odds of developing new or enlarging T2 lesions, annualized percentage change in T2 lesion volume (T2LV), and annualized percentage change in brain parenchymal fraction (BPF). MRI outcomes were compared for 1) natalizumab EID treatment versus natalizumab SID treatment, 2) natalizumab treatment (EID + SID) versus platform therapy, and 3) natalizumab EID versus platform therapy. Propensity score–based weighting or matching were used to balance covariates at the start of MRI segments for all comparisons.

Results: The MRI outcomes observed with natalizumab EID treatment did not differ significantly from those observed with natalizumab SID treatment. The odds ratio for any new or enlarging T2 lesion was 1.07 (95% confidence interval [CI]: 0.93, 1.24; $p = 0.355$), and the rate ratio (95% CI) for new or enlarging T2 lesions was 1.62 (0.93, 2.82; $p = 0.090$). Differences (95% CI) between EID and SID patients in mean annualized percentage change in T2LV and BPF were 1.56% (−3.77%, 6.90%; $p = 0.566$) and −0.11% (−0.25%, −0.10%; $p = 0.096$), respectively. Conversely, when MRI outcomes in natalizumab and platform therapy patients were compared, there were significant differences favoring natalizumab in all assessments: the odds of any new or enlarging T2 lesion (odds ratio: 0.69 [95% CI: 0.64, 0.75]; $p<0.001$), the incidence rate of new or enlarging T2 lesions (rate ratio: 0.47 [95% CI: 0.37, 0.61]; $p<0.001$), annualized percentage change (decrease) in T2LV (difference: −3.68% [95% CI: −7.06%, −0.30%]; $p = 0.033$), and annualized percentage change (increase) in BPF (difference: 0.22% [95% CI: 0.16%, 0.29%]; $p<0.001$). Results of the subgroup comparison of natalizumab EID patients with platform therapy patients were similar to those of the overall-natalizumab-group-versus-platform-therapy comparison.

Conclusions: The results indicate that natalizumab EID and SID provide comparable real-world effectiveness on quantitative MRI metrics. These data further demonstrate that natalizumab EID can provide superior real-world effectiveness to injectable platform therapy on quantitative MRI metrics.

* Corresponding author.
E-mail address: lana.zhovtisryerson@nyulangone.org (L.Z. Ryerson).

https://doi.org/10.1016/j.msard.2021.103480
Received 5 August 2021; Received in revised form 24 November 2021; Accepted 31 December 2021
Available online 2 January 2022

1. Introduction

Natalizumab administered intravenously every 4 weeks (Q4W[1]) is an efficacious treatment for relapsing forms of multiple sclerosis (MS), as demonstrated by randomized clinical trials and real-world evidence (Butzkueven et al., 2020; Capra et al., 2020; Gudesblatt et al., 2018; Horakova et al., 2020; Perumal et al., 2019; Polman et al., 2006; Wiendl et al., 2020). However, Q4W natalizumab dosing is associated with a risk of progressive multifocal leukoencephalopathy (PML) in anti–JC virus (JCV) antibody-positive patients (Bloomgren et al., 2012; Ho et al., 2017). Analyses of the TYSABRI Outreach: United Commitment to Health (TOUCH) Prescribing Program safety database have demonstrated that natalizumab extended interval dosing (EID) with an average dosing interval of approximately every 6 weeks (Q6W) is associated with a significantly lower risk of PML than Q4W dosing (Zhovtis Ryerson et al., 2019). As efficacy data are not captured in the TOUCH database, TOUCH risk assessments cannot assess whether natalizumab effectiveness is maintained with EID. While previous real-world and clinical studies comparing EID with standard interval dosing (SID; every 4 weeks) have found that natalizumab effectiveness is not diminished with EID (Bomprezzi and Pawate, 2014; Chisari et al., 2020; Clerico et al., 2020; van Kempen et al., 2020; Yamout et al., 2018; Zhovtis Ryerson et al., 2016), these studies have generally been limited by a lack of well-matched treatment cohorts and by variable definitions of EID.

Magnetic resonance imaging (MRI) is a sensitive method to monitor disease activity and progression as well as patient response to treatment with MS disease-modifying therapy (DMT) even in the absence of clinical measures of disease activity (Traboulsee et al., 2016). Data from MS patients treated in real-world settings are important for understanding treatment effects beyond randomized controlled trials. However, long-term observational MRI studies can be challenging, as variability over time in scanner hardware, imaging sequences, and image analysis pipelines may make consistent MRI assessment difficult (Tur et al., 2018). Such studies can, however, provide informative, meaningful results when patients are followed systematically with standardized imaging protocols (Tur et al., 2018).

MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) is a learning health system initiated in 2016 and comprised of a collaborative network of 10 health care institutions in the United States, Germany, and Spain (Mowry et al., 2020). MS PATHS provides access to standardized real-world clinical and MRI data, with MRI data collected using highly standardized acquisition protocols that can be integrated into routine clinical practice radiology workflows and used to generate quantitative metrics (Fisher et al., 2020; Kitzler et al., 2020).

In the present study, we compared radiological outcomes for matched cohorts of patients in MS PATHS treated with natalizumab EID or SID. Radiological outcomes for natalizumab-treated patients were also compared with outcomes of matched patients in MS PATHS who received injectable platform therapy in order to provide context for EID-versus-SID comparisons, as well as additional information on the comparative effectiveness of natalizumab EID and SID.

[1] *Abbreviations:* AIC, average infusion cycle; ATT, average treatment effect among the treated; BPF, brain parenchymal fraction; CI, confidence interval; DMT, disease-modifying therapy; EID, extended interval dosing; JCV, JC virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS PATHS, Multiple Sclerosis Partners Advancing Technology and Health Solutions; MSPie, MS PATHS Image Evaluation; OR, odds ratio; PML, progressive multifocal leukoencephalopathy; PS, propensity score; Q4W, every 4 weeks; Q6W, every 6 weeks; RR, rate ratio; SID, standard interval dosing; T2LV, T2 lesion volume; TOUCH, TYSABRI Outreach: United Commitment to Health.

2. Methods

This was an observational retrospective study of patients enrolled at seven MS PATHS clinical care sites in the United States (Cleveland Clinic, Johns Hopkins University, New York University, Lou Ruvo Center, Ohio Health, University of Rochester, and Washington University in St. Louis).

2.1. Analysis population

Patients with a diagnosis of relapsing-remitting MS who were enrolled in MS PATHS in the US were eligible for inclusion. Patients treated with natalizumab or injectable platform therapy (interferon beta-1a, interferon beta-1b, peginterferon beta-1a, or glatiramer acetate) were identified from the MS PATHS database. Patients provided informed consent to share pseudoanonymized data with the network investigators and sponsor in accordance with national and local patient privacy regulations. In addition, patients included in the natalizumab arm provided separate informed consent to merge their MS PATHS records with exact dosing information from the TOUCH database. The availability of exact dosing information from TOUCH was the reason for limiting this analysis to MS PATHS patients in the US.

2.2. Data acquisition

Brain MRI data were collected as part of routine patient care for all patients in MS PATHS and were acquired using standardized image acquisition protocols (3D-MPRAGE and 3D-FLAIR) and Siemens 3T scanners (Mowry et al., 2020). The number of new or enlarging T2 lesions, T2 lesion volume (T2LV), and brain parenchymal fraction (BPF) were analyzed using fully automated MS PATHS Image Evaluation (MSPie) software (Fisher et al., 2020; Kitzler et al., 2020; Tsang et al., 2019).

2.3. Treatment comparisons

Due to variability in patient dosing over time in real-world settings, we determined natalizumab dosing patterns (i.e. EID or SID) between consecutive MRI assessments (Fig. 1). For this study, the interval between two consecutive MRI assessments was defined as an MRI segment. A natalizumab infusion cycle was defined as two consecutive infusions, and the duration of the associated interval was quantified utilizing exact infusion date information from the TOUCH database.

The average duration of all infusion cycles occurring within an MRI segment was defined as the average infusion cycle (AIC) for that segment. MRI segments with an AIC >35 days were defined as EID, and MRI segments with an AIC ≤35 days were defined as SID. Individual natalizumab patients could, over the course of their natalizumab infusion history, have received EID, SID, or both and could therefore contribute either one or both types of MRI segments for analysis.

For all comparisons, covariates were balanced between MRI segments using propensity score (PS) models adjusted for age, MS duration, BPF, and T2LV (all at start of MRI segment); sex; education (≤12 years, >12 to ≤16 years, or >16 years of education); race; and time between MRI scans (segment duration). For comparisons of EID versus SID, natalizumab patients in MS PATHS with ≥1 MRI segment, ≥2 natalizumab infusion cycles (infusion interval >21 days and ≤84 days), and complete covariate information to support PS models were included. For comparisons of natalizumab versus platform therapy, platform patients were required to have received ≥1 of the specified platform DMTs for the entire duration of an MRI segment (with missing drug data and/or treatment gaps allowed) and to have complete covariate information to support PS models.

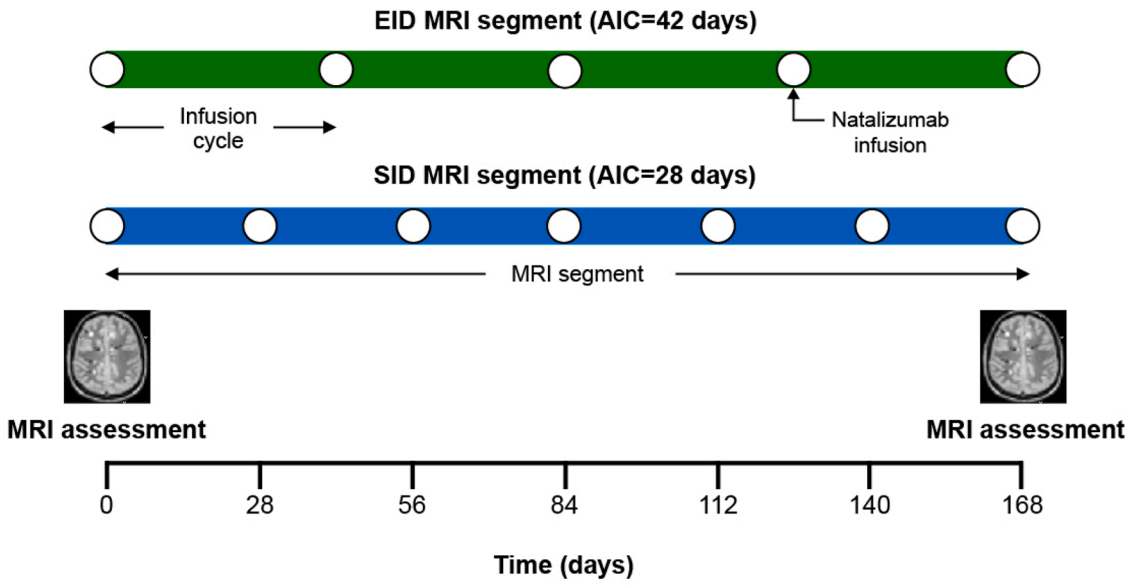


Fig. 1. Hypothetical EID and SID MRI segments.
Hypothetical MRI segments of 24 weeks' (168 days') duration between two consecutive MRI assessments are represented by green and blue bars. Natalizumab infusion cycles are shown as the interval between two infusions (open circles). The upper (green) bar depicts a hypothetical EID MRI segment with an AIC of 42 days. The lower (blue) bar depicts a hypothetical SID MRI segment with an AIC of 28 days. AIC, average infusion cycle; EID, extended interval dosing; MRI, magnetic resonance imaging; SID, standard interval dosing.

2.4. Statistical analyses

For primary analyses of treatment effects in the different patient groups, average-treatment-effect-among-the-treated (ATT) weighting or 1:1 PS methods were used based on which method minimized covariate imbalance. For the primary analysis of natalizumab EID versus SID, radiologic outcomes were compared using ATT weighting to estimate the treatment effect in the EID-treated population. For ATT weighting, EID segments were assigned a weight of 1, and SID segments were weighted proportionally to their PS to resemble the EID population. A secondary analysis was performed using SID segments that were PS matched 1:1 with replacement to all available EID segments.

For the primary analysis of natalizumab versus platform therapy, platform MRI segments were PS matched 1:1 with replacement to all available natalizumab MRI segments (pooled EID and SID segments). A secondary analysis using ATT weighting was also performed, with natalizumab segments given a weight of 1 and platform segments weighted proportionally to their PS to resemble the natalizumab-treated population. A sensitivity analysis comparing outcomes for a subgroup of ATT-weighted MRI segments from EID natalizumab-treated patients with those from platform-treated patients was also performed.

The odds of any new or enlarging T2 lesion and the incidence rates of new or enlarging T2 lesions (defined as the number of new or enlarging T2 lesions per year) were compared using logistic regression and negative binomial regression, respectively, with final adjustment for patient body mass index, T2LV at first MRI, and MRI segment duration (covariates with absolute standardized mean difference >0.1 after ATT weighting or PS matching). Annualized percentage changes in T2LV and BPF were compared using robust linear regression with final adjustment for T2LV at first MRI (covariate with absolute standardized mean difference >0.1 after ATT weighting or PS matching). Between-groups p values were estimated using robust sandwich estimation of standard error.

3. Results

3.1. MS PATHS patient and MRI segment populations

As of July 23, 2020, MS PATHS included data from 15,721 patients with MS. For this analysis, 150 MRI segments from 79 patients met the definition of EID and 1071 segments from 354 patients met the definition of SID. Of these, 98 EID segments from 66 patients and 629 SID segments from 299 patients had all necessary covariate information and were included in the analyses. For comparisons of platform therapy with natalizumab, 145 MRI segments from 82 patients treated with injectable platform therapy were available. Of these, 143 segments from 80 unique patients had non-missing covariate information and were included (Fig. 2).

3.2. MRI outcomes: primary analyses

3.2.1. Analysis of EID versus SID

Prior to ATT weighting, covariate distributions in the EID and SID segment populations were generally well balanced, although three covariates (race, education, and T2LV at start of segment) displayed unadjusted absolute differences >0.1. After ATT weighting, EID and SID segments (effective sample sizes of 98 and 433.85, respectively) were well balanced, with no covariates having an adjusted absolute difference >0.1 (Table 1).

None of the assessed treatment outcomes for ATT-weighted MRI segments differed significantly between patients treated with natalizumab EID and SID. The odds ratio (OR) of any new or enlarging T2 lesion was 1.07 (95% confidence interval [CI]: 0.93, 1.24; $p = 0.335$; Fig. 3). The incidence rate of new or enlarging T2 lesions was 0.96 (95% CI: 0.57, 1.61) for EID and 0.60 (95% CI: 0.35, 1.02) for SID (rate ratio [RR]: 1.62 [95% CI: 0.93, 2.82]; $p = 0.09$). Effect differences (EID minus SID) were small for mean annualized percentage changes in T2LV and BPF (T2LV: 1.56% [95% CI: −3.77%, 6.90%]; $p = 0.566$; BPF: −0.11% [95% CI: −0.25%, 0.02%]; $p = 0.096$; Fig. 4).

3.2.2. Analysis of natalizumab versus platform therapy

Given the similar MRI outcomes for EID and SID described above,

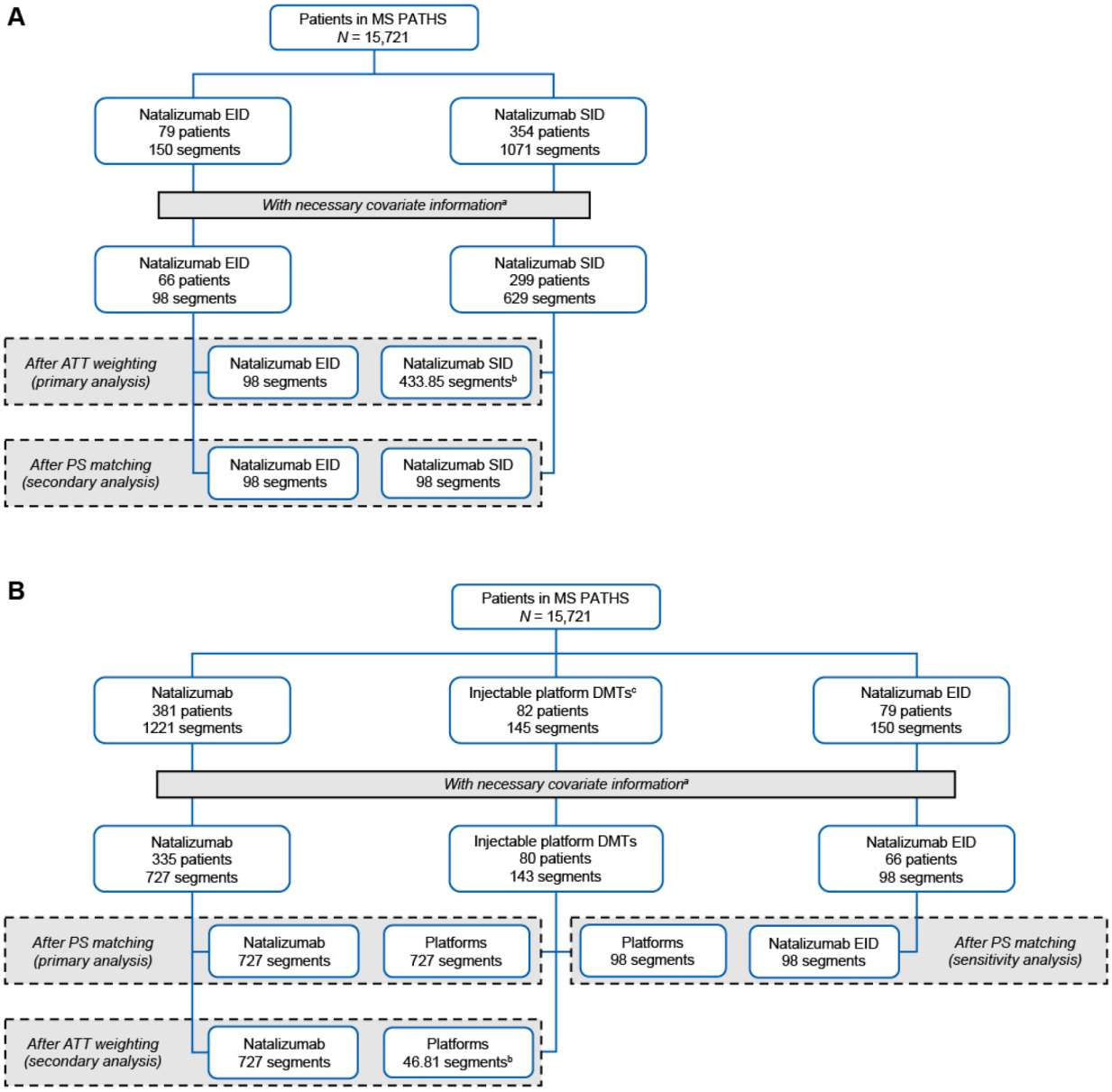


Fig. 2. Flow diagrams of patients included in the analysis of (A) natalizumab EID vs SID and (B) natalizumab or natalizumab EID vs platform DMTs.
[a] Covariates used for PS models are: age, MS duration, BPF, and T2LV (all at start of MRI segment); sex; education (≤12 years, >12 to ≤16 years, or >16 years of education); race; and time between MRI scans (segment duration).
[b]Fractional value due to ATT weighting.
[c]Injectable platform DMTs are interferon beta-1a, interferon beta-1b, peginterferon beta-1a, or glatiramer acetate.
ATT, average effect of treatment on the treated; DMT, disease-modifying therapy; EID, extended interval dosing; PS, propensity score; SID, standard interval dosing.

MRI segments from the EID and SID groups were combined for the comparison of natalizumab with injectable platform DMTs. Thus, MRI outcomes were compared using 727 MRI segments from natalizumab patients and 143 MRI segments from platform therapy patients. Prior to PS matching, 5 of the 10 covariate categories displayed unadjusted absolute differences >0.1 (Table 2). Importantly, natalizumab patients had shorter mean intervals between MRI scans (i.e. shorter MRI segment durations) than injectable platform therapy patients (0.78 [standard deviation (SD) 0.44] years vs 0.89 [SD 0.31] years). After 1:1 PS matching (with replacement of platform segments allowed to achieve the best match for each natalizumab segment), covariate balance was improved; however, three covariates (MS duration and T2LV at start of segment and race) displayed adjusted absolute differences >0.1 and were included in the final outcome models (Table 2).

The odds of any new or enlarging T2 lesion were significantly lower in MRI segments from natalizumab-treated patients than in segments from platform patients (OR: 0.69 [95% CI: 0.64, 0.75]; $p<0.001$; Fig. 3). Similarly, the incidence rate of new or enlarging T2 lesions was significantly lower in MRI segments from natalizumab-treated patients than from patients treated with injectable platform DMTs (natalizumab: 0.61 [95% CI: 0.48, 0.76]; platform: 1.1 [95% CI: 0.87, 1.38]; RR: 0.47 [95% CI: 0.37, 0.61]; $p<0.001$). Mean annualized percentage change in T2LV and BPF both significantly favored segments from natalizumab-treated patients over those from platform patients (effect difference [natalizumab minus platform]: T2LV: −3.68 [95% CI: −7.06, −0.30 ($p = 0.033$)]; BPF: 0.22 [95% CI: 0.16, 0.29 ($p<0.001$)]; Fig. 4).

In the subgroup analysis of MRI outcomes using 98 EID natalizumab and 143 injectable platform DMT segments, covariate distributions before PS matching were unbalanced, with 7 of 10 covariates exhibiting unadjusted absolute differences >0.1 (Table 3). After PS matching with

Table 1
Covariate distribution of MRI segments from patients treated with natalizumab EID or SID before and after ATT weighting (primary analysis).

Covariate, mean (SD)[a]	Before ATT weighting			After ATT weighting		
	Natalizumab EID[b]	Natalizumab SID[c]	Unadjusted absolute difference	Natalizumab EID[b]	Natalizumab SID[d]	Adjusted absolute difference
Age, y	42.24 (10.30)	42.48 (10.33)	0.0237	42.24	42.38	0.0142
Sex[e]	0.276	0.305	0.0297	0.276	0.276	0.0000
Race[f]						
White	0.643	0.801	0.1584	0.643	0.656	0.0131
Black/African American	0.255	0.124	0.1311	0.255	0.244	0.0110
Other	0.102	0.075	0.0273	0.102	0.100	0.0021
Education, y	13.77 (2.55)	14.73 (2.57)	0.3760	13.76	13.76	0.0034
MS duration at start of segment, y	13.66 (9.24)	12.91 (8.04)	0.0875	13.66	13.67	0.0004
T2LV at start of segment, mL	11.05 (10.49)	12.73 (13.21)	0.1410	11.05	11.06	0.0009
BPF at start of segment	0.85 (0.02)	0.85 (0.03)	0.0047	0.85	0.85	0.0001
MRI segment duration, y	0.78 (0.46)	0.78 (0.44)	0.0070	0.78	0.79	0.0201

[a] SDs not provided for binary variables (proportions) and not calculated for ATT-weighted means.
[b] Effective sample size: 98 segments from 66 patients.
[c] Effective sample size: 629 segments from 299 patients.
[d] Effective sample size: 433.85 segments (fractional value due to ATT weighting).
[e] Proportion of male patients.
[f] Proportion of patients.

ATT, average effect of treatment on the treated; BPF, brain parenchymal fraction; EID, extended interval dosing; MRI, magnetic resonance imaging; SD, standard deviation; SID, standard interval dosing; T2LV, T2 lesion volume.

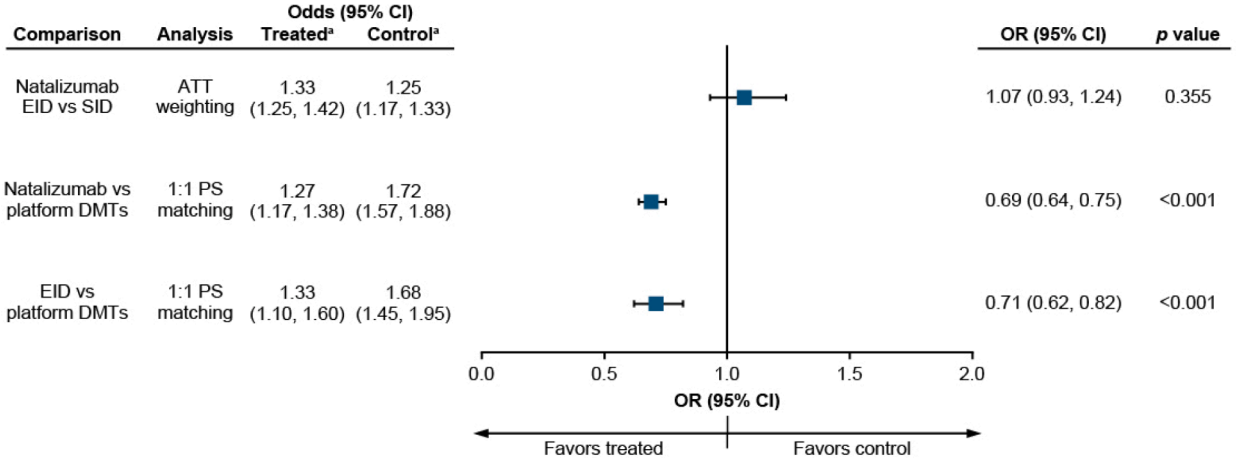


Fig. 3. Odds of any new or enlarging T2 lesion.
Odds of any new or enlarging T2 lesions calculated by logistic regression. *p* values and CIs were based on logistic regression with robust sandwich estimation of standard error. For natalizumab versus platform DMTs, outcome model included further adjustment for race and MS duration and T2LV at start of segment. For EID versus platform DMTs, outcome model included further adjustment for age at start of segment, sex, MS duration at start of segment, BPF at start of segment, segment duration. An OR <1 favors the treated population.
[a] For EID versus SID, treated=EID and control=SID; for natalizumab versus platform DMTs, treated=natalizumab and control=platform; for EID versus platform DMTs, treated=EID and control=platform.
ATT, average effect of treatment on the treated; CI, confidence interval; DMT, disease-modifying therapy; EID, extended interval dosing; MRI, magnetic resonance imaging; OR, odds ratio; PS, propensity score; SID, standard interval dosing.

replacement of platform segments to achieve the best match for each EID segment, covariate balance was slightly improved, but 5 of 10 covariates (age, MS duration, and BPF at start of segment; segment duration; and sex) still displayed an adjusted absolute difference >0.1 and were further adjusted in outcome models (Table 3).

The odds of any new or enlarging T2 lesion were significantly lower with natalizumab EID than with platform therapy (OR: 0.71 [95% CI: 0.62, 0.82]; $p<0.001$; Fig. 3). However, incidence rates of new or enlarging T2 lesions did not differ significantly between natalizumab EID and platform DMTs (natalizumab EID: 0.87 [95% CI: 0.44, 1.71]; platform DMTs: 0.75 [95% CI: 0.43, 1.30]; RR: 0.98 [95% CI: 0.56, 1.72]; $p = 0.952$). The mean annualized percentage change in T2LV significantly favored segments from natalizumab EID patients over those from platform therapy patients (difference: −7.96 [95% CI: −15.05, −0.86]; $p = 0.028$), though the mean annualized percentage change in BPF in segments from natalizumab EID and platform patients did not differ significantly (difference: 0.04 [95% CI: −0.13, 0.21]; $p = 0.653$; Fig. 4).

3.2.3. MRI outcomes: secondary and sensitivity analyses

The Supplementary Appendix provides the results of secondary analyses for EID versus SID and for natalizumab versus platform therapy; Supplementary Tables 1 and 2 present covariate distributions for pre- and post-PS matching (EID versus SID) and pre- and post-ATT weighting (natalizumab versus platform therapy), respectively. (A secondary sensitivity analysis based on ATT weighting of EID versus platform therapy was also performed; however, as covariates remained

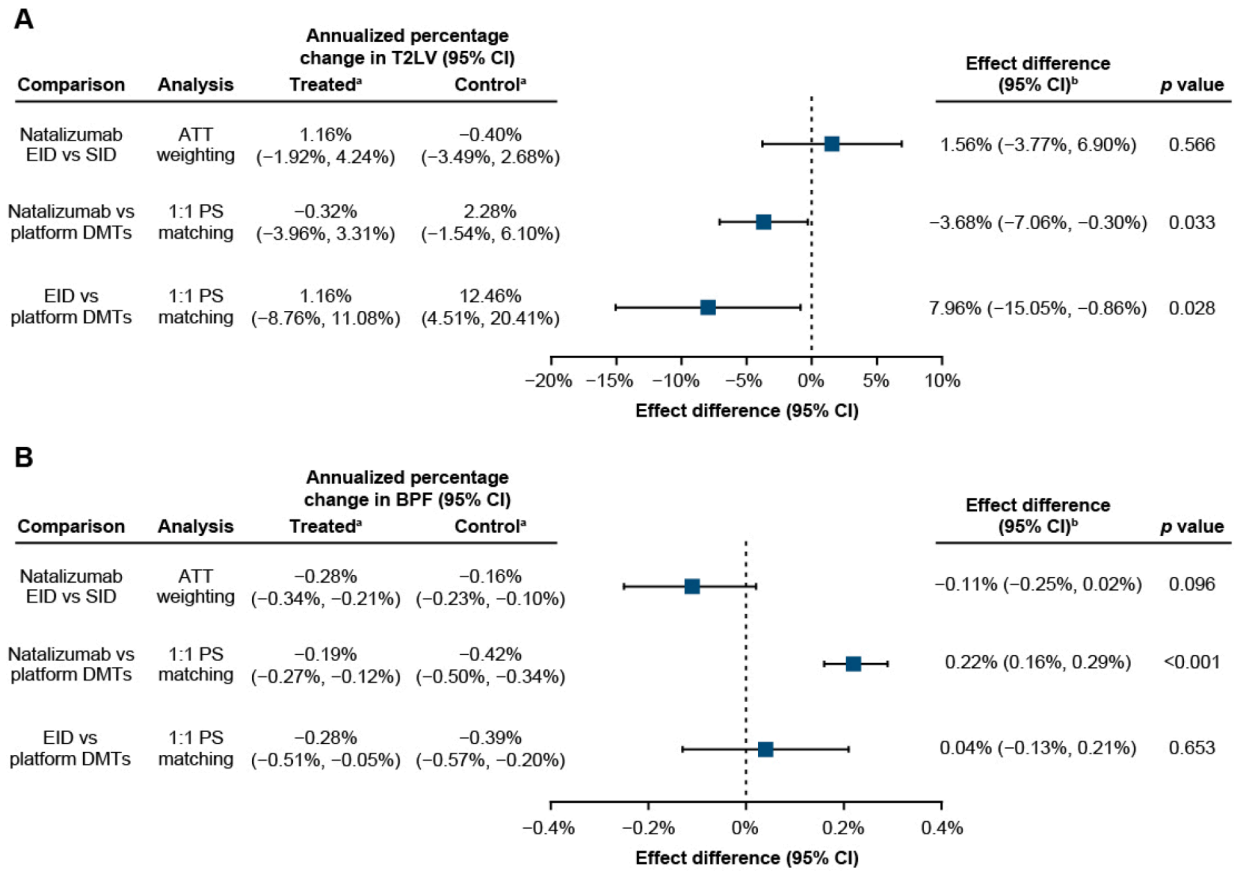


Fig. 4. Mean annualized percentage changes and effect differences in (A) T2LV and (B) BPF in MRI segments after ATT weighting or 1:1 PS matching.
Effect difference intervals that cross the vertical dashed lines (effect difference of 0%) represent non–significantly different effect differences. CIs and *p* values based on linear regression with robust sandwich estimation of standard error.
[a] For EID versus SID, treated=EID and control=SID; for natalizumab versus platform DMTs, treated=natalizumab and control=platform; for EID versus platform DMTs, treated=EID and control=platform.
[b] Effect difference=treated minus control.
ATT, average effect of treatment on treated; BPF, brain parenchymal fraction; CI, confidence interval; DMT=disease- modifying therapy; EID, extended interval dosing; MRI, magnetic resonance imaging; PS=propensity score; SID, standard interval dosing; T2LV, T2 lesion volume.

Table 2
Covariate distribution of MRI segments from patients treated with natalizumab or injectable platform DMTs before and after 1:1 PS matching (primary analysis).

Covariate, mean (SD)[a]	Before PS matching			After PS matching		
	Natalizumab[b]	Platform therapy[c]	Unadjusted absolute difference	Natalizumab[b]	Platform therapy[d]	Adjusted absolute difference
Age, y	42.45 (10.32)	47.72 (10.66)	0.5032	42.45 (10.32)	43.09 (11.64)	0.0627
Sex[e]	0.301	0.245	0.0565	0.301	0.212	0.0894
Race[f,g]						
White	0.780	0.811	–0.0313	0.780	0.607	0.1733
Black/African American	0.142	0.056	0.0857	0.142	0.220	0.0784
Other	0.078	0.133	0.0545	0.078	0.173	0.0949
Education, y	14.60 (2.59)	15.10 (2.49)	0.1965	14.60 (2.59)	14.76 (2.33)	0.0621
MS duration at start of segment, y[g]	13.01 (8.21)	9.77 (7.66)	0.4086	13.0 (8.2)	14.0 (8.4)	0.1149
T2LV at start of segment, mL[g]	12.51 (12.88)	6.95 (6.90)	0.5375	12.51 (12.88)	10.83 (9.01)	0.1300
BPF at start of segment	0.85 (0.02)	0.85 (0.02)	0.0679	0.85 (0.02)	0.85 (0.02)	0.0176
MRI segment duration, y	0.78 (0.44)	0.89 (0.31)	0.3058	0.78 (0.44)	0.75 (0.37)	0.0634

[a] SDs not provided for binary variables (proportions).
[b] Effective sample size: 727 segments from 335 patients.
[c] Effective sample size: 143 segments from 80 patients.
[d] Effective sample size: 727 segments (108 unique) from 72 patients.
[e] Proportion of male patients.
[f] Proportion of patients.
[g] Covariate also adjusted in final outcome models. BPF, brain parenchymal fraction; EID, extended interval dosing; MRI, magnetic resonance imaging; PS, propensity score; SD, standard deviation; SID, standard interval dosing; T2LV, T2 lesion volume.

Table 3
Covariate distribution of MRI segments from patients treated with natalizumab EID or injectable platform DMTs before and after 1:1 PS matching (primary analysis).

Covariate, mean (SD)[a]	Before PS matching			After PS matching		
	Natalizumab EID[b]	Platform therapy[c]	Unadjusted absolute difference	Natalizumab EID[b]	Platform therapy[d]	Adjusted absolute difference
Age, y[e]	42.24 (10.30)	47.72 (10.66)	0.5229	42.24 (10.30)	38.91 (10.08)	0.3296
Sex[e,f]	0.276	0.245	0.0308	0.276	0.082	0.1939
Race[e,g]						
White	0.643	0.811	0.1683	0.643	0.714	0.0714
Black/African American	0.255	0.056	0.1992	0.255	0.184	0.0714
Other	0.102	0.133	0.0308	0.102	0.102	0.0000
Education, y	13.77 (2.55)	15.10 (2.49)	0.5287	13.77 (2.55)	13.86 (2.08)	0.0441
MS duration at start of segment, y[e]	13.66 (9.24)	9.77 (7.66)	0.4593	13.66 (9.24)	10.53 (6.80)	0.4601
T2LV at start of segment, mL[e]	11.05 (10.49)	6.95 (6.90)	0.4616	11.05 (10.49)	10.70 (7.44)	0.0476
BPF at start of segment[e]	0.85 (0.02)	0.85 (0.02)	0.0662	0.85 (0.02)	0.86 (0.02)	0.2308
MRI segment duration, y[e]	0.78 (0.46)	0.89 (0.31)	0.2892	0.78 (0.46)	0.66 (0.37)	0.3319

[a] SDs not provided for binary variables (proportions).
[b] Effective sample size: 98 segments from 66 patients.
[c] Effective sample size: 143 segments from 80 patients.
[d] Effective sample size: 98 segments (40 unique) from 33 patients.
[e] Covariate also adjusted in final outcome models.
[f] Proportion of male patients.
[g] Proportion of patients.
BPF, brain parenchymal fraction; EID, extended interval dosing; MRI, magnetic resonance imaging; PS, propensity score; SID, standard interval dosing; T2LV, T2 lesion volume.

considerably unbalanced after weighting, this analysis was not pursued further.)

The results of the secondary analyses were consistent with the results of the corresponding primary analyses. For EID versus SID, 1:1 PS-matched MRI segments did not differ significantly on any MRI outcome. The incidence rates of new or enlarging T2 lesions were similar for matched MRI segments from patients treated with EID and SID (RR: 0.99 [95% CI: 0.48, 2.03]; $p = 0.970$), as were the odds of any new or enlarging T2 lesion (OR: 0.98 [95% CI: 0.86, 1.12]; $p = 0.755$; Supplementary Table 3). Mean annualized percentage changes in T2LV and BPF also did not differ significantly between treatment groups (Supplementary Table 3). In the secondary analysis of natalizumab versus platform DMTs, there were significant differences in the incidence rate of new or enlarging T2 lesions (RR: 0.65 [95% CI: 0.43, 0.98]; $p = 0.042$) and in mean annualized percentage change in BPF (difference: 0.20 [95% CI: 0.04, 0.36]; $p = 0.016$) as well as numerical differences in the odds of any new or enlarging T2 lesion and the annualized percentage change in T2LV, all favoring natalizumab (Supplementary Table 3).

4. Discussion

In these analyses based on quantitative imaging metrics from MS PATHS, there were no statistically significant differences between natalizumab EID and SID in any of the MRI outcome measures examined, including the number and volume of T2 lesions and brain atrophy. These real-world data are consistent with and extend previous reports that the effectiveness of natalizumab with SID is maintained with EID.

These observations provide important additional information for clinicians considering natalizumab EID as a PML risk mitigation strategy. An analysis of the TOUCH prescribing database concluded that switching from Q4W dosing to an EID interval of approximately Q6W is associated with lower PML risk than continuing Q4W dosing in anti-JCV antibody positive patients (Zhovtis Ryerson et al., 2019). However, the TOUCH dataset does not contain efficacy data, and results of the ongoing randomized controlled phase 3b trial (NOVA, NCT03689972) comparing the effectiveness of natalizumab in patients who switch to Q6W dosing after ≥1 year of Q4W dosing and patients who remain on Q4W dosing are not yet available. Accordingly, comparisons of efficacy between such dosing strategies depend on real-world data sources. The mean AICs for EID and SID observed in this study (40.8 and 29.5 days, respectively) closely approximate Q6W and Q4W dosing intervals and thus are relevant to both the TOUCH PML risk analysis and the NOVA trial. Overall, these results are in accord with previously published real-world analyses utilizing clinical endpoints and less standardized MRI endpoints, which have consistently concluded that natalizumab efficacy is maintained in patients switching from Q4W dosing to EID (Bomprezzi and Pawate, 2014; Chisari et al., 2020; Clerico et al., 2020; van Kempen et al., 2020; Yamout et al., 2018; Zhovtis Ryerson et al., 2016).

MRI outcomes are objective, highly sensitive measures of MS disease activity. Historically, longitudinal real-world comparative analyses of MRI outcomes have been limited due to inconsistent acquisition protocols for MRIs collected in routine clinical practice. Quantitative assessment of T2 lesions and brain volume can be complicated by MRI technical factors, such as changes in scanner hardware and sequence parameters over time or across sites (Tur et al., 2018), and the image analysis methods used to generate quantitative metrics introduce additional measurement error. Longitudinal assessment of brain atrophy is especially difficult since the annual rate of brain atrophy in patients with MS is estimated at 0.5% (Sormani et al., 2014), which necessitates the use of analysis techniques with very high reproducibility to enable accurate detection (Tsang et al., 2019).

A standardized MRI acquisition and fully automated image analysis tool (MSPie) has been developed by the MS PATHS network to overcome the variability seen in real-world longitudinal and multisite imaging studies (Fisher et al., 2020). In a scan-rescan study performed with 30 patients from three sites, each imaged four times within a week on two different scanners at each site, the mean coefficient of variation was 0.16%, which is well within the 0.25% cutoff required to reliably detect a change of 0.5% (Tsang et al., 2019).

This study is limited by the moderate sample sizes in the comparator groups, which were in turn limited by the data available within the MS PATHS network. Included patients often had both EID and SID treatment periods, and MRI dates did not necessarily correspond to treatment starts; thus comparisons were made between MRI segments to utilize all available data. Important consequences of this are that an absence of MRI activity within a segment cannot be interpreted as indicating no MRI activity over the full treatment period, and there is potential for confounding from unmeasured drug exposure dependent changes in disease activity. This study was not powered to address a noninferiority

hypothesis of natalizumab EID relative to SID with a prespecified margin. Consequentially, the absence of statistical differences between EID and SID presented here do not demonstrate equivalent efficacy. With this limitation noted, the comparative effectiveness analyses between natalizumab and injectable platform DMTs within the same MS PATHS network help to contextualize the small numerical differences observed between natalizumab EID and SID across MRI outcomes. For example, while the RR for new or enlarging T2 lesions, the OR for any new or enlarging T2 lesion, and differences in mean annualized percentage changes in T2LV and BPF all numerically favored SID over EID, none of the differences were statistically significant (all $p>0.09$). In contrast, there were significant differences between MRI segments in patients treated with natalizumab (EID and SID combined) and those treated with injectable platform DMTs, all favoring natalizumab (all $p \leq 0.033$). The comparisons of EID with injectable platform DMTs provide additional context, as the relative benefits of natalizumab over platform therapy are well established and have consistently been demonstrated in prior real-world comparative effectiveness analyses (Johnson et al., 2015; Spelman et al., 2016). The sensitivity analyses comparing EID to platform DMTs reported here showed point estimate advantages for EID in three of four outcomes, with significant advantages in two (the odds of any new or enlarging T2 lesion and T2LV). The apparently lower incidence rate for new or enlarging T2 lesions in the platform DMT group may possibly by explained by the covariate imbalance remaining in the EID group after 1:1 PS matching and by the wide CIs in both groups due to the small number of EID and platform samples ($n = 98$ and $n = 40$, respectively).

All nonrandomized data sets are limited by potential selection biases from unmeasured or unadjusted-for covariates. In this analysis, clinical disease covariates, such as relapses or disability progression assessments, were not available to control for potential residual bias from these factors. In addition, the reasons that patients switched to natalizumab EID or remained on SID are unknown and could reflect differences in disease activity between the 2 groups; consistent with this possibility is that prior to covariate adjustment there was considerable imbalance in T2LV between the groups. However, as MRI disease characteristics were accounted for, and as MRI and clinical outcomes of MS diseases are likely to be related, the impact any such biases is likely to be small. With respect to the comparison of natalizumab and platform DMTs, one potential limitation is the difference in disease activity at MRI segment start in these populations. PS matching was utilized to make the comparator population (injectable therapies) resemble the treated population (natalizumab) and produce patient populations with similar MRI activity and, by extension, similar disease activity. It should be noted that platform patients had a longer interval between MRIs than natalizumab patients. To reduce potential confounding from unequal MRI acquisition frequencies in different groups, time between MRIs was included in the PS models used for covariate balancing, and, in addition, the T2LV and BPF outcomes were assessed using annualized rates. However, the possibility of some remaining confounding due to this limitation cannot be excluded. One strength of this analysis is that the comparisons employed different statistical methodologies, and the consistent findings demonstrated that the conclusions were not restricted to or dependent on any one strategy for handling between-groups covariate imbalances.

Overall, our results indicate that natalizumab EID and SID provide comparable real-world effectiveness on quantitative MRI metrics, and they also show that natalizumab provides superior real-world effectiveness compared with injectable platform DMTs. To our knowledge, this represents the first comparative effectiveness analysis of natalizumab EID versus other MS DMTs. These results also support the potential utility of MS PATHS MRI acquisition and image analysis methods to address important, previously unresolved questions related to MS clinical practice. Additional studies of quantitative MRI metrics in MS PATHS will add to our understanding of the comparative effectiveness of DMTs (including natalizumab EID) on radiologic outcomes in real-world patient populations. Future studies will compare the MRI outcome estimates for EID and SID patients in MS PATHS presented here with the results from the ongoing NOVA clinical trial (when they become available) to quantify the accuracy of highly standardized MRI assessments from clinical practice in predicting randomized clinical trial outcomes.

Funding

MS PATHS is supported by Biogen. Biogen provided funding for medical writing support in the development of this manuscript and reviewed and provided feedback on the manuscript to the authors.

CRediT authorship contribution statement

Lana Zhovtis Ryerson: Investigation, Writing – review & editing. **Robert T. Naismith:** Investigation, Writing – review & editing. **Lauren B. Krupp:** Investigation, Writing – review & editing. **Leigh E. Charvet:** Investigation, Writing – review & editing. **Shirley Liao:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Elizabeth Fisher:** Methodology, Writing – review & editing. **Carl de Moor:** Methodology, Writing – review & editing. **James R. Williams:** Methodology, Writing – review & editing. **Nolan Campbell:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

LZR: personal compensation for advisory board activities from Biogen, Genentech, and Novartis; research support from Biogen and Genentech.

RTN: compensation for consulting from Banner Life Sciences, BeiGene, Biogen, Bristol Myers Squibb, Genentech, Genzyme, Janssen, GW Therapeutics, Horizon Therapeutics, Lundbeck, NervGen, Questcor, TG Therapeutics, and Third Rock Ventures.

LBK: research funding (paid to institution) from Biogen; compensation for consulting from Biogen, Cambridge Medical Technologies, Eisai, Everyday Health, Genentech, Gerson Lehman, Janssen, Medergy, Novartis, Roche, and Sanofi; honoraria (invited faculty) from At the Limits; support for meeting attendance from Sanofi; compensation for data safety monitoring and/or advisory board activities from Biogen; royalty payments for use of the Fatigue Severity Scale.

LEC: research support from Biogen.

SL: former employee of and may hold stock in Biogen.

EF, CdM, JRW, NC: employees of and may hold stock/stock options in Biogen.

Acknowledgments

The authors gratefully thank all of the patients who are participating in the MS PATHS initiative. All named authors meet the ICMJE criteria for authorship for this manuscript and take responsibility for the integrity of the work as a whole. The authors were assisted in preparation of the manuscript by John Watson, PhD, of Ashfield MedComms, an Ashfield Health Company (Middletown, CT, USA). Joshua Safran of Ashfield MedComms copyedited and styled the manuscript per journal requirements. The authors had full editorial control of the manuscript and provided final approval of all content.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103480.

References

Bloomgren, G., Richman, S., Hotermans, C., Subramanyam, M., Goelz, S., Natarajan, A., et al., 2012. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N. Engl. J. Med. 366 (20), 1870–1880.

Bomprezzi, R., Pawate, S., 2014. Extended interval dosing of natalizumab: a two-center, 7-year experience. Ther. Adv. Neurol. Disord. 7 (5), 227–231.

Butzkueven, H., Kappos, L., Wiendl, H., Trojano, M., Spelman, T., Chang, I., et al., 2020. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J. Neurol. Neurosurg. Psychiatry 91 (6), 660–668.

Capra, R., Morra, V.B., Mirabella, M., Gasperini, C., Scandellari, C., Totaro, R., et al., 2020. Natalizumab is associated with early improvement of working ability in relapsing-remitting multiple sclerosis patients: WANT observational study results. Neurol. Sci. 42 (7), 2837–2845.

Chisari, C.G., Grimaldi, L.M., Salemi, G., Ragonese, P., Iaffaldano, P., Bonavita, S., et al., 2020. Clinical effectiveness of different natalizumab interval dosing schedules in a large Italian population of patients with multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 91 (12), 1297–1303.

Clerico, M., De Mercanti, S.F., Signori, A., Iudicello, M., Cordioli, C., Signoriello, E., et al., 2020. Extending the interval of natalizumab dosing: is efficacy preserved? Neurotherapeutics 17 (1), 200–207.

Fisher, E., Kober, T., Tsang, A., Corredor-Jerez, R., Liao, S., Benzinger, T.L.S., et al., 2020. Magnetic resonance imaging (MRI) metrics in routine clinical practice: proof of concept in MS PATHS (Multiple Sclerosis Partners Advancing Technology for Health Solutions). Neurology 94 (15 Suppl), 1356.

Gudesblatt, M., Wissemann, K., Zarif, M., Bumstead, B., Fafard, L., Wilken, J., et al., 2018. Improvement in cognitive function as measured by NeuroTrax in patients with relapsing multiple sclerosis treated with natalizumab: a 2-year retrospective analysis. CNS Drugs 32 (12), 1173–1181.

Ho, P.-.R., Koendgen, H., Campbell, N., Haddock, B., Richman, S., Chang, I., 2017. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol 16 (11), 925–933.

Horakova, D., Uher, T., Krasensky, J., Seidl, Z., Ribbens, A., Van Hecke, W., et al., 2020. Long-term effectiveness of natalizumab on MRI outcomes and no evidence of disease activity in relapsing-remitting multiple sclerosis patients treated in a Czech Republic real-world setting: a longitudinal, retrospective study. Mult. Scler. Relat. Disord. 46, 102543.

Johnson, B.H., Bonafede, M.M., Watson, C., 2015. Platform therapy compared with natalizumab for multiple sclerosis: relapse rates and time to relapse among propensity score-matched US patients. CNS Drugs 29 (6), 503–510.

Kitzler, H.H., Jones, S., Blefari, M., Corredor-Jerez, R., Huelnhagen, T., Liao, S., et al., 2020. In-clinic performance of MSPie, an image analysis prototype for automated MRI quantitative point-of-care metrics in MS. Presented at ECTRIMS virtual congress; 2020. P0592.

Mowry, E.M., Bermel, R.A., Williams, J.R., Benzinger, T.L.S., de Moor, C., Fisher, E., et al., 2020. Harnessing real-world data to inform decision-making: multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). Front. Neurol. 11, 632.

Perumal, J., Fox, R.J., Balabanov, R., Balcer, L.J., Galetta, S., Makh, S., et al., 2019. Outcomes of natalizumab treatment within 3 years of relapsing-remitting multiple sclerosis diagnosis: a prespecified 2-year interim analysis of STRIVE. BMC Neurol 19 (1), 116–127.

Polman, C.H., O'Connor, P.W., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D.H., et al., 2006. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 354 (9), 899–910.

Sormani, M.P., Arnold, D.L., De, Stefano, N., 2014. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann. Neurol. 75 (1), 43–49.

Spelman, T., Kalincik, T., Jokubaitis, V., Zhang, A., Pellegrini, F., Wiendl, H., et al., 2016. Comparative efficacy of first-line natalizumab vs IFN-β or glatiramer acetate in relapsing MS. Neurol. Clin. Pract. 6 (2), 102–115.

Traboulsee, A., Simon, J.H., Stone, L., Fisher, E., Jones, D.E., Malhotra, A., et al., 2016. Revised recommendations of the Consortium of MS Centers Task Force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. Am. J. Neuroradiol. 37 (3), 394–401.

Tsang, A., Su, Y.-.C., Perea, R.D., Corredor-Jere, R., Fartaria, M.J., Huelnhagen, T., et al., 2019. Brain volume measurements in multiple sclerosis patients: a novel combination approach for routine clinical assessment in MS paths. Presented at ISMRM; Montreal, Canada; May 11-16, 2019. P3159.

Tur, C., Moccia, M., Barkhof, F., Chataway, J., Sastre-Garriga, J., Thompson, A.J., et al., 2018. Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting. Nat. Rev. Neurol. 14 (2), 75–93.

van Kempen, Z.L.E., Hoogervorst, E.L.J., Wattjes, M.P., Kalkers, N.F., Mostert, J.P., Lissenberg-Witte, B.I., et al., 2020. Personalized extended interval dosing of natalizumab in MS: a prospective multicenter trial. Neurology 95 (6), e745–e754.

Wiendl, H., Spelman, T., Butzkueven, H., Kappos, L., Trojano, M., Su, R., et al., 2020. Real-world disability improvement in patients with relapsing-remitting multiple sclerosis treated with natalizumab in the Tysabri Observational Program. Mult. Scler. 27 (5), 719–728.

Yamout, B.I., Sahraian, M.A., Ayoubi, N.E., Tamim, H., Nicolas, J., Khoury, S.J., et al., 2018. Efficacy and safety of natalizumab extended interval dosing. Mult. Scler. Relat. Disord. 24, 113–116.

Zhovtis Ryerson, L., Foley, J., Chang, I., Kister, I., Cutter, G., Metzger, R.R., et al., 2019. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology 93 (15), e1452–e1462.

Zhovtis Ryerson, L., Frohman, T.C., Foley, J., Kister, I., Weinstock-Guttman, B., Tornatore, C., et al., 2016. Extended interval dosing of natalizumab in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 87 (8), 885–889.