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Duration of natalizumab therapy and reasons for discontinuation in a multiple sclerosis population

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Abstract

Objective: To determine multiple sclerosis patient characteristics that predict a shorter duration of natalizumab treatment.

Methods: The Tysabri Outreach: Unified Commitment to Health database was reviewed to identify patients treated with natalizumab at our centers. Cox proportional hazards models were used to evaluate patient characteristics associated with shorter treatment durations on natalizumab. Associations were also assessed with respect to specific reasons for stopping natalizumab.

Results: We identified 554 patients who began and stopped natalizumab treatment during the observation period. The average disease duration at natalizumab initiation was 7.6 years, and the average number of infusions was 30. The multivariable Cox proportional hazards model identified greater age ($P = 0.035$), longer disease duration ($P < 0.001$), progressive relapsing multiple sclerosis phenotype ($P = 0.003$), current smoking ($P = 0.031$), and greater depression ($P = 0.026$) as significant predictors for natalizumab discontinuation. Greater disability levels ($P = 0.022$) and gadolinium-enhancing lesions on baseline magnetic resonance imaging ($P < 0.001$) were significantly associated with longer natalizumab treatment. Individuals with progressive relapsing multiple sclerosis had a 14-fold increased hazard of discontinuing natalizumab due to inflammatory events ($P < 0.001$) than those with relapsing–remitting multiple sclerosis. Smokers had an 80% increased hazard of discontinuation due to intolerance ($P = 0.008$).

Conclusions: Our results suggest that smoking, depression, and a progressive relapsing multiple sclerosis phenotype are associated with shorter natalizumab treatment durations.

Keywords: Multiple sclerosis, disease-modifying therapies, natalizumab, outcome measurement, treatment response

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Introduction

A wide array of disease-modifying therapies (DMTs) are available for the treatment of multiple sclerosis (MS). However, treatment response varies significantly between patients, and there is uncertainty surrounding both the optimal DMT choice for any given patient and the general philosophy of DMT management.[1] As such, there has been interest in predicting an individual's response to particular DMTs before they are started, often referred to as personalized treatment.[2]

Natalizumab is a monoclonal antibody that antagonizes the alpha-4 integrin receptor on circulating leukocytes.[3] The disruption of alpha-4 integrin binding to vascular cell adhesion molecule-1 inhibits leukocyte migration into the central nervous system and leads to a profound reduction in relapses and gadolinium-enhancing (GdE) lesions as detected by magnetic resonance imaging (MRI).[4,5] The use of natalizumab is limited by concerns about an increased risk of progressive multifocal leukoencephalopathy (PML), but the development of the John Cunningham virus (JCV) antibody assay and identification of other PML risk factors facilitate the safe use of natalizumab in a subpopulation of MS patients.

While natalizumab is a highly effective DMT, there are other high efficacy options including

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alemtuzumab and ocrelizumab.[6–8] As such, the ability to discriminate which patients are more likely to discontinue natalizumab treatment early would be useful in clinical decision-making. To investigate this question, we collected and analyzed the data for patients initiating and discontinuing natalizumab at two tertiary referral MS centers.

Methods

The Tysabri Outreach: Unified Commitment to Health (TOUCH) program is a risk minimization plan in which only prescribers and patients who are enrolled can prescribe and receive natalizumab.[9] The TOUCH program maintains a database of all patients who receive natalizumab and includes the dates of all infusions. We queried the TOUCH database to identify all patients starting and stopping natalizumab at the Cleveland Clinic Mellen Center and Lou Ruvo Center for Brain Health between 1 December 2005 and 25 January 2018. Individuals continuing natalizumab beyond 25 January 2018 were not included. Patient data were manually collected from the TOUCH database and the electronic medical record including age, sex, race, date of first and last natalizumab infusions, total infusion number, smoking status (current/former or never), years of education, number of prior DMTs, relapses in the year prior to natalizumab initiation, baseline performance scale (PS; a measure of MS-related disability validated against the expanded disability status scale),[10] patient health questionnaire 9 (PHQ9; a measure of depression),[11] timed 25 foot walk (T25FW), and 9 hole peg test (9HPT) scores,[12] as well as the presence of new T2 or GdE lesions on baseline brain MRI. MS phenotype at the time of natalizumab initiation was determined based on a standardized progress note template that is updated by the clinician at every visit and indicates the patient's current phenotype. The phenotype from the visit immediately prior to natalizumab initiation was used as specified by the treating neurologist.

Reasons for natalizumab discontinuation were also determined through review of the electronic medical record and classified as either inflammatory activity (relapses, new T2 or GdE lesions on MRI), disability progression, PML risk, intolerance, or other. Patients were counted as stopping due to PML risk when the progress notes stated that concern for PML was the dominant reason for discontinuation. This was inclusive of patients stopping due to JCV seropositivity, duration of natalizumab treatment, or general anxiety about the possibility of PML. Single imputation was performed to handle missing data.

Descriptive statistics were calculated to characterize the cohort. Univariable Cox proportional hazards models were constructed to determine which baseline patient characteristics were associated with shorter duration of natalizumab therapy. A multivariable Cox proportional hazards model inclusive of all predictors was also used to evaluate duration of natalizumab therapy. The component predictors were narrowed based on their significance level to build a parsimonious multivariable model of time on natalizumab. Given that natalizumab is primarily indicated for patients with relapsing–remitting multiple sclerosis (RRMS) and that RRMS patients made up the majority of our cohort, we also conducted this analysis in a subset containing only patients with that phenotype.

In addition, we wished to determine if predictors differed based on the reason for natalizumab discontinuation. To evaluate this, Cox proportional hazards models were used to determine hazard ratios (HRs) based on patient characteristics associated with specific reasons for natalizumab discontinuation.

Finally, we completed a post-hoc analysis of the frequency of natalizumab neutralizing antibodies in smokers versus non-smokers. The laboratory data for all patients were reviewed to determine if they ever had neutralizing antibody testing within our system, and if so, whether they ever had a positive test. A chi square test was performed to determine the presence of an association between smoking history and the development of neutralizing antibodies to natalizumab.

As this study was for hypothesis generation, adjustments were not made for multiple comparisons. Our local institutional review board approved the study protocol. All analyses were conducted in R version 3.5.2 (https://www.r-project.org).

Results

Review of the TOUCH database identified 554 MS patients who received and discontinued natalizumab at our centers. The mean age was 41.1 years and 75.6% of patients had RRMS. The patients received an average of 30 infusions with a range of 1–140. The characteristics of the cohort at the time of natalizumab initiation are summarized in Table 1. Within the cohort, 305 (55.1%, average number of infusions 41.1) discontinued because of the risk of PML, 98 (17.7%, average number of infusions 11.5) due to intolerance, 36 (6.5%, average number of infusions 18.7) due to disability progression, and

Table 1. Cohort characteristics at the time of natalizumab initiation.

Baseline characteristics	$n = 554$
Age, mean (SD)	41.1 (10.7)
Women, *n* (%)	376 (67.9%)
Race, *n* (%)	
African American	95 (17.1%)
Caucasian	443 (80.0%)
Hispanic	10 (1.8%)
Other	6 (1.1%)
MS phenotype, *n* (%)	
Relapsing–remitting	419 (75.6%)
Secondary progressive	105 (19.0%)
Primary progressive	9 (1.6%)
Progressive relapsing	21 (3.8%)
Disease duration (years), mean (SD)	7.6 (7.1)
JCV positive, *n* (%)	216 (40.0%)
Total natalizumab Infusions, mean (SD)	30.1 (27.3)
Current smokers, *n* (%)	148 (26.7%)
Prior DMTs, mean (SD)	3.0 (1.6)
Prior year relapses, mean (SD)	0.5 (0.7)
Patients with prior year relapse, *n* (%)	235 (42.4%)
Baseline PS, mean (SD)	15.2 (9.0)
Baseline PHQ9, mean (SD)	9.2 (7.1)
9HPT (seconds), mean (SD)	31.5 (13.3)
T25FW (seconds), mean (SD)	9.3 (9.7)
Assistive device	
Independent	378 (68.2%)
Unilateral	62 (11.2%)
Bilateral	82 (14.8%)
Wheelchair	32 (5.8%)
New T2 lesions on baseline MRI, *n* (%)	215 (38.8%)
New GdE lesions on baseline MRI, *n* (%)	227 (41%)

SD: standard deviation; DMT: disease-modifying therapy; PS: performance scale; PHQ9: patient health questionnaire 9; T25FW: timed 25 foot walk; 9HPT: 9 hole peg test; GdE: gadolinium-enhancing; MRI: magnetic resonance imaging.

28 (5.0%, average number of infusions 17.1) due to inflammatory disease. The remaining 87 patients (15.7%, average number of infusions 21.2) stopped natalizumab for other reasons such as payer denials or the inconvenience of monthly infusions.

Univariable Cox proportional hazards models revealed that longer disease duration at natalizumab initiation (HR 0.984, 95% confidence interval (CI) 0.972–0.996; $P = 0.001$) and GdE on baseline brain MRI (HR 0.710, 95% CI 0.584–0.864; $P = 0.001$) were associated with longer treatment times on natalizumab. The only significant predictors of shorter treatment duration were MS phenotype and smoking. Individuals with a progressive relapsing multiple sclerosis (PRMS) phenotype had more than twice the hazard of an earlier natalizumab discontinuation (HR 2.067, 95% CI 0.28–1.17; $P < 0.001$) than those with a RRMS phenotype. Discontinuation according to MS phenotype is demonstrated in a Kaplan–Meier survival curve in Figure 1. Notably, smokers had a 22% increased hazard of early natalizumab cessation (HR 1.223, 95% CI 1.012–1.477; $P = 0.037$) (see Figure 2). Full results of the univariable analyses are shown in Table 2.

The inclusive multivariable Cox proportional hazards model predicting total time on natalizumab therapy revealed that the hazard of earlier natalizumab discontinuation increased by 1.2% (HR 1.012, 95% CI 1.001–1.022; $P = 0.0351$) for each year of increasing age at natalizumab initiation. Similar to

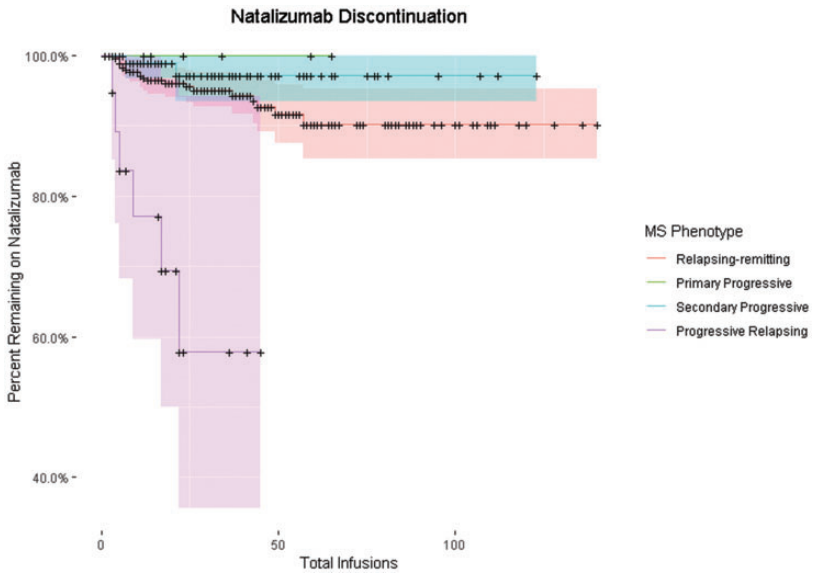

Figure 1. Kaplan–Meier curve of time on natalizumab by multiple sclerosis phenotype among 554 discontinuers of the medication.

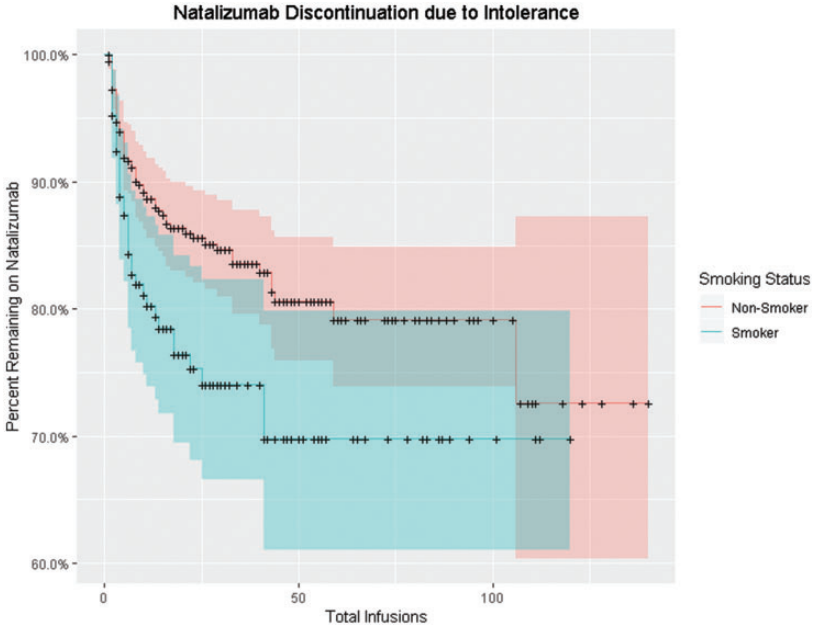

Figure 2. Kaplan–Meier curve of time on natalizumab by smoking status among 554 discontinuers of the medication.

the univariable analysis, PRMS was associated with a more than two-fold increased risk of earlier discontinuation. Higher depression scores and smoking were also associated with a shorter time on natalizumab in the multivariable models, whereas longer disease duration, higher self-reported disability levels, and GdE lesions on baseline brain MRI were predictive of longer periods on natalizumab. The results of the parsimonious model that included only significant predictors were similar. Table 3 shows the full results for both models.

When the inclusive multivariable Cox proportional hazards model was applied only to patients with RRMS, greater age at initiation slightly increased the risk of earlier natalizumab discontinuation.

Table 2. Hazard of shorter duration of natalizumab treatment by patient characteristics based on univariable Cox proportional hazard models.

Predictor	Hazard ratio (95% CI)	*P* value
Age	1.004 (0.996–1.012)	0.376
Women	1.121 (0.937–1.341)	0.212
Race (white ref.)		
African American	1.161 (0.930–1.450)	0.187
Hispanic	1.352 (0.721–2.534	0.347
Other	1.907 (0.851–4.273)	0.117
MS phenotype (RRMS ref.)		
Secondary progressive	0.963 (0.778–1.194)	0.732
Primary progressive	1.250 (0.645–2.421)	0.509
Progressive relapsing	2.067 (1.328–3.217)	0.001*
Disease duration	0.984 (0.972–0.996)	0.011*
JCV positive	0.936 (0.789–1.111)	0.451
Current smoker	1.223 (1.012–1.477)	0.037*
Prior DMTs	0.989 (0.933–1.048)	0.703
Prior year relapses	0.910 (0.805–1.029)	0.134
PS	0.993 (0.952–1.036)	0.743
PHQ9	1.008 (0.997–1.02)	0.154
9HPT	0.998 (0.992–1.005)	0.600
T25FW	1.005 (0.994–1.015)	0.394
Assistive device (independent ref.)		
Unilateral	1.051 (0.803–1.376)	0.717
Bilateral	1.06 (0.831–1.341)	0.658
Wheelchair	1.239 (0.863–1.779)	0.246
New T2 lesions on baseline MRI	1.057 (0.890–1.254)	0.527
New GdE lesions on baseline MRI	0.754 (0.635–0.895)	0.001*

HR: hazard ratio; CI: confidence interval; ref: reference level; RRMS: relapsing–remitting multiple sclerosis; DMT: disease-modifying therapy; PS: performance scale; PHQ9: patient health questionnaire 9; 9HPT: nine hole peg test; T25FW: timed 25 foot walk; MRI: magnetic resonance imaging.
* indicates that the hazard ratio is significantly different from 1 at a significance threshold of $p<0.05$.

Interestingly, women with RRMS were more than 25% more likely to discontinue natalizumab earlier compared to men (HR 1.258, 95% CI 1.007–1.571; $P = 0.044$). A greater number of GdE lesions on baseline MRI was again predictive of longer time on natalizumab. The parsimonious model had similar results, with women's predilection to stopping natalizumab earlier being slightly more prominent. The full results are shown in Table 3, alongside those for the entire cohort.

The results of the multivariable Cox proportional hazards models predicting natalizumab discontinuation for specific reasons (inflammatory disease, disability progression, PML risk, and intolerance) are shown in Table 4. The only patient characteristic that significantly predicted discontinuation due to inflammatory disease was having a progressive relapsing phenotype. Individuals with PRMS had more than a 14-fold higher hazard of stopping natalizumab (HR 14.77, 95% CI 4.76–45.79; $P < 0.001$) due to inflammatory disease than those with RRMS.

In light of the striking results with respect to PRMS, we further investigated the reasons for discontinuation among the different MS phenotypes. In the 21 PRMS patients, six (28.5%) stopped natalizumab due to inflammatory disease, and three (14.3%) discontinued due to disability progression as compared to RRMS, in which 20 patients (4.8%) stopped due to inflammatory disease and 11 (2.6%) stopped due to disease progression. Among patients with secondary progressive multiple sclerosis (SPMS), two (1.9%) stopped due to inflammatory disease and 20 (19.0%) due to disability progression, while no primary progressive multiple sclerosis (PPMS) patients stopped due to inflammatory disease

Table 3. Inclusive and parsimonious Cox proportional hazard models predicting risk of natalizumab discontinuation.

	Entire cohort				RRMS patients only			
	Inclusive model		Parsimonious model		Inclusive model		Parsimonious model	
Predictor	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	1.01 (1.001–1.022)	0.035*	1.010 (0.999–1.020)	0.065	1.016 (1.003–1.028)	0.015*	1.012 (1.000–1.024)	0.058
Woman	1.150 (0.952–1.390)	0.147			1.258 (1.007–1.571)	0.044*	1.267 (1.029–1.560)	0.026*
Race (white ref.)								
African American	1.115 (0.877–1.418)	0.376			1.256 (0.951–1.661)	0.109		
Latino	1.154 (0.589–2.260)	0.676			1.193 (0.560–2.543)	0.647		
Other	1.569 (0.636–3.872)	0.329			1.733 (0.608–4.941)	0.304		
MS phenotype (RRMS ref.)								
Secondary progressive	1.010 (0.771–1.324)	0.941	1.036 (0.804–1.336)	0.785				
Primary progressive	0.935 (0.450–1.943)	0.857	0.955 (0.482–1.893)	0.896				
Progressive relapsing	2.024 (1.273–3.220)	0.003*	2.078 (1.326–3.256)	0.001*				
Disease duration	0.972 (0.957–0.986)	<0.001*	0.975 (0.961–0.989)	<0.001*	0.964 (0.945–0.983)	<0.001*	0.968 (0.950–0.986)	<0.001*
JCV positive	0.888 (0.736–1.073)	0.218			0.823 (0.665–1.020)	0.076		
Current smoker	1.243 (1.020–1.513)	0.031*	1.228 (1.013–1.489)	0.036*	1.225 (0.992–1.562)	0.059		
Prior DMTs	1.009 (0.946–1.077)	0.779			1.001 (0.928–1.079)	0.985		
Prior year relapses	0.962 (0.839–1.103)	0.581			0.961 (0.828–1.116)	0.605		
PS	0.981 (0.966–0.997)	0.022*	0.986 (0.973–1.000)	0.045*	0.985 (0.966–1.003)	0.108		
PHQ9	1.020 (1.002–1.039)	0.026*	1.016 (1.000–1.033)	0.044*	1.019 (0.999–1.039)	0.066		
9HPT	0.996 (0.987–1.004)	0.294			0.991 (0.979–1.003)	0.142		
T25FW	1.002 (0.990–1.015)	0.699			1.008 (0.992–1.024)	0.318		
Assistive device (none ref.)								
Unilateral	1.136 (0.818–1.578)	0.447			1.071 (0.722–1.588)	0.735		
Bilateral	1.150 (0.831–1.592)	0.398			1.180 (0.773–1.800)	0.443		
Wheelchair	1.412 (0.909–2.192)	0.125			1.429 (0.791–2.580)	0.237		
Baseline MRI new T2 lesions	1.206 (0.996–1.461)	0.056			1.163 (0.943–1.435)	0.158		
Baseline MRI new GdE lesions	0.710 (0.584–0.864)	<0.001*	0.726 (0.602–0.876)	0.0001*	0.717 (0.577–0.891)	0.003*	0.726 (0.593–0.890)	0.002*

HR: hazard ratio; CI: confidence interval; ref.: reference level; RRMS: relapsing–remitting multiple sclerosis; DMT: disease-modifying therapy; PS: performance scale; PHQ9: patient health questionnaire 9; 9HPT: nine hole peg test; T25FW: timed 25 foot walk; MRI: magnetic resonance imaging.
* indicates that the hazard ratio is significantly different from 1 at a significance threshold of $p<0.05$.

Table 4. Results of inclusive cox proportional hazards models predicting natalizumab discontinuation for specific reasons.

	Inflammatory disease		Disability progression		PML risk		Intolerance	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	0.99 (0.94–1.04)	0.688	1.00 (0.96–1.04)	0.985	1.01 (1.00–1.03)	0.130	1.03 (1.00–1.05)	0.032*
Women	0.85 (0.36–1.99)	0.712	0.64 (0.29–1.44)	0.284	1.22 (0.94–1.58)	0.135	1.46 (0.91–2.33)	0.119
Race (white ref.)								
African American	0.61 (0.16–2.20)	0.449	1.46 (0.56–3.85)	0.436	0.95 (0.68–1.33)	0.772	1.67 (0.96–2.90)	0.069
Hispanic	2.90 (0.34–24.54)	0.329	1.6×10^{-7} (0–∞)	0.998	1.65 (0.66–4.14)	0.289	4.9×10^{-8} (0–∞)	0.995
Other	3.36 (0.27–41.73)	0.346	1.6×10^{-7} (0–∞)	0.998	1.79 (0.39–8.29)	0.459	2.11 (0.37–12.00)	0.401
MS phenotype (RRMS ref.)								
Secondary progressive	0.75 (0.14–4.12)	0.742	4.41 (1.54–12.67)	0.006*	1.02 (0.70–1.49)	0.924	1.82 (0.43–1.58)	0.558
Primary progressive	2.9×10^{-8} (0–∞)	0.999	1.23 (0.19–8.20)	0.829	0.39 (0.09–1.71)	0.211	0.90 (0.11–7.21)	0.922
Progressive relapsing	14.77 (4.76–45.79)	<0.001*	2.45 (0.51–11.74)	0.264	2.01 (0.92–4.44)	0.080	1.67 (0.64–4.37)	0.293
Disease duration	0.95 (0.87–1.04)	0.290	0.92 (0.86–0.98)	0.011	0.98 (0.96–1.00)	0.066	0.94 (0.90–0.97)	0.001*
JCV positive	1.85 (0.78–4.35)	0.160	0.85 (0.36–1.99)	0.708	1.40 (1.09–1.80)	0.009*	0.52 (0.31–0.86)	0.011*
Current smoker	1.34 (0.55–3.25)	0.523	1.23 (0.55–2.80)	0.611	0.93 (0.70–1.24)	0.606	1.80 (1.17–2.78)	0.008*
Prior DMTs	1.25 (0.94–1.66)	0.122	1.20 (0.92–1.57)	0.182	0.99 (0.90–1.08)	0.801	0.99 (0.86–1.14)	0.879
Prior year relapses	0.97 (0.54–1.75)	0.923	0.38 (0.14–1.06)	0.064	0.93 (0.77–1.11)	0.409	1.04 (0.76–1.44)	0.790
PS	1.02 (0.95–1.09)	0.637	0.97 (0.91–1.03)	0.369	1.00 (0.97–1.02)	0.732	0.99 (0.95–1.03)	0.532
PHQ9	0.98 (0.89–1.07)	0.585	1.04 (0.96–1.12)	0.382	1.00 (0.97–1.02)	0.797	0.99 (0.95–1.04)	0.811
9HPT	1.03 (0.99–1.07)	0.205	1.04 (1.02–1.06)	<0.001*	1.00 (0.99–1.01)	0.589	0.91 (0.88–0.94)	<0.001*
T25FW	1.03 (0.99–1.07)	0.160	0.98 (0.94–1.03)	0.446	0.98 (0.96–1.00)	0.047*	1.02 (1.00–1.04)	0.095
Assistive device (none ref.)								
Unilateral	0.62 (0.14–2.79)	0.535	3.43 (1.10–10.71)	0.034*	0.87 (0.53–1.44)	0.592	1.09 (0.48–2.46)	0.843
Bilateral	0.31 (0.05–2.10)	0.230	2.34 (0.73–7.52)	0.153	1.22 (0.77–1.94)	0.392	1.27 (0.63–2.58)	0.507
Wheelchair	8.2×10^{-8} (0–∞)	0.997	2.41 (0.47–12.34)	0.292	1.15 (0.60–2.20)	0.672	4.31 (1.78–10.49)	0.001*
Baseline MRI new T2 lesions	1.23 (0.51–2.97)	0.646	1.74 (0.69–4.37)	0.241	1.43 (1.11–1.86)	0.007*	0.72 (0.44–1.17)	0.187
Baseline MRI new GdE lesions	1.63 (0.67–3.97)	0.283	0.08 (0.02–0.39)	0.001	0.72 (0.55–0.94)	0.016*	0.55 (0.34–0.88)	0.014*

HR: hazard ratio; CI: confidence interval; ref.: reference level; RRMS: relapsing–remitting multiple sclerosis; DMT: disease-modifying therapy; PS: performance scale; PHQ9: patient health questionnaire 9; 9HPT: nine hole peg test; T25FW: timed 25 foot walk; MRI: magnetic resonance imaging.
* indicates that the hazard ratio is significantly different from 1 at a significance threshold of $p<0.05$.

and two (22.0%) discontinued due to disability progression.

Individuals with SPMS were more than four times more likely to stop natalizumab due to disability progression than those with RRMS (HR 4.41, 95% CI 1.54–12.67; $P = 0.006$). Those with PPMS and PRMS were also more likely to stop due to disability progression, but these findings did not reach significance. Surprisingly, each additional year of disease duration reduced the hazard of discontinuing due to disability progression. Individuals using an assistive device were also more likely to stop natalizumab due to disability progression than those without an assistive device. However, this finding was only significant for those using unilateral support, for whom there was a nearly three-fold increased hazard of stopping natalizumab due to disability progression (HR 3.43, 95% CI 1.10–10.71; $P = 0.034$).

As expected, individuals who were JCV antibody seropositive had a 40% increased hazard of stopping natalizumab due to the risk of PML (HR 1.40, 95% CI 1.09–1.80; $P = 0.047$). For each 1-second increase in the T25FW, there was a 2% reduction in the odds of stopping natalizumab due to PML risk.

Interestingly, smoking was associated with an 80% increased hazard of stopping natalizumab due to intolerance (HR 1.80, 95% CI 1.17–2.78; $P = 0.008$). Individuals in wheelchairs had more than a four-fold increased hazard of stopping natalizumab due to intolerance (HR 4.31, 95% CI 1.78–10.49; $P = 0.001$). In addition, with each year of increasing age at the time of natalizumab initiation, there was an increased hazard of discontinuing natalizumab due to intolerance by 3% (HR 1.03, 95% CI 1.00–1.05; $P = 0.032$). Characteristics that predicted a decreased hazard of stopping natalizumab due to poor tolerance included disease duration (HR 0.94, 95% CI 0.90–0.97; $P = 0.001$), JCV antibody seropositivity (HR 0.52, 95% CI 0.31–0.86; $P = 0.011$), higher 9HPT scores (HR 0.91, 95% CI 0.88–0.94; $P < 0.001$), and the presence of GdE lesions on the baseline MRI (HR 0.55, 95% CI 0.34–0.88; $P = 0.014$).

Finally, with respect to the post-hoc analysis of the relationship between smoking and neutralizing antibodies to natalizumab, there were 380 patients with neutralizing antibody testing. Of these, 94 (24.7%) were smokers and 286 (75.3%) were non-smokers. There was at least one positive neutralizing antibody test in five smokers (5.3%) and in 14 non-smokers (4.9%). The chi square testing revealed no significant relationship between smoking and the development of neutralizing antibodies ($P = 1.0$).

Discussion

Our analysis evaluated real-world data for 554 MS patients receiving natalizumab, including their duration on treatment and reasons for discontinuation. These results can be applied to the clinical setting to identify patients who are likely to remain on natalizumab longer, suggesting greater success in MS treatment. Alternative treatments can be considered in patients with characteristics predictive of early natalizumab discontinuation, thereby reducing an individual's time to finding effective therapy.

The use of DMT is typically recommended for individuals with relapsing forms of MS, including within the guidelines from the American Academy of Neurology.[13] Interestingly, we found that individuals with PRMS were more likely to discontinue natalizumab early than those with RRMS. As with other available DMTs, there is little evidence regarding the use of natalizumab in patients with PRMS. In our study, the majority of natalizumab discontinuations by PRMS patients were due to inflammatory events. This is surprising given the impressive efficacy seen in the AFFIRM[4] and SENTINEL[5] natalizumab trials, as well as general clinical experience suggesting natalizumab has high efficacy in suppressing MS-related inflammatory activity. Due to the paucity of data in the PRMS population, it is unclear if these findings would extend to other DMTs. Notably, there were only 21 patients with PRMS in our study, so our results need to be interpreted with caution, particularly given that resistance to natalizumab's anti-inflammatory mechanism of action in PRMS would be counterintuitive. Additional research to confirm our findings with natalizumab and to investigate the response of PRMS patients to other DMTs is warranted.

Another notable finding in our study was the relationship between tobacco use and natalizumab. Numerous studies, dating back to the 1960s, showed an increased risk of MS in smokers.[14–16] Furthermore, a dose–response relationship between smoking and the risk of MS was previously demonstrated,[17] and smoking was also shown to increase the risk of clinically definite MS in patients with a clinically isolated syndrome.[18] Tobacco is also known to worsen the clinical course of MS and

increase the risk of SPMS. For instance, Ramanujam et al. studied 728 smokers with RRMS and discovered that each year of smoking after MS diagnosis accelerated evolution to SPMS by 4.9%.[19]

In our study, smokers were found to have a significantly increased hazard of natalizumab discontinuation, both in the univariable and multivariable models. Although smoking is known to increase the risk of relapses in natalizumab-treated patients,[20] our study found that the discontinuations were driven by natalizumab intolerance. The underlying pathophysiological mechanism behind fewer smokers tolerating natalizumab is uncertain, and it is also unclear if this finding might extend to alternative DMTs. Smoking is known to increase the risk of neutralizing antibodies to interferons[20] and natalizumab, which could affect both tolerance and efficacy.[21] No association was seen between neutralizing antibodies and a history of tobacco use in our study, which suggests another mechanism may be at play. The lack of a relationship in our study might also be attributed to irregular testing for natalizumab neutralizing antibodies, the smaller sample size of patients who had neutralizing antibody testing, and the fact that patients were not necessarily tested at the time of natalizumab discontinuation. Additional research is needed to examine failure rates of the other DMTs in smokers versus non-smokers. If tobacco use is found generally to make patients less tolerant of immunomodulatory treatments, this finding could partially explain the more rapid disability progression observed in smokers with MS.

In addition to smoking, another comorbidity, depression, was significantly associated with shorter durations of natalizumab treatment. The effect of depression appeared more global than that for smoking as it was not associated with any specific reason for natalizumab discontinuation. Comorbidities are known to be associated with worse outcomes in MS patients.[22–24] This effect is not completely understood and there may be some contribution from early discontinuation of DMTs, as was seen in our cohort. Our results underscore the importance of counseling MS patients regarding appropriate management of their comorbidities.

Some limitations of this study deserve mention. First, the data were collected from two tertiary MS referral centers with similar treatment approaches. As such, the patient sample and management decisions may not be completely generalizable. Furthermore, the retrospective nature of the study is prone to missing data and other limitations. For instance, it is notable that while neurologists at our center use the Lublin criteria to classify MS phenotype, the retrospective nature of this analysis means that such criteria were not strictly enforced. Thus, the results of our analysis pertaining to phenotype must be interpreted with caution. Our study also involved multiple comparisons, which can increase the risk of chance findings, and so the results should be primarily interpreted as hypothesis generating. Additional research specifically aimed at investigating the notable findings from this study is needed for verification purposes.

The restriction of our dataset to patients who discontinued natalizumab is also a shortcoming, as it would have been preferable to include all natalizumab-treated patients in the analysis. However, our data cover 13 years of natalizumab infusions and, therefore, are expected to include patients with long durations of natalizumab treatment. For instance, there were 68 patients (12.3%) who received more than 5 years of natalizumab infusions, and 49 patients (8.8%) who received more than 6 years. Thus, the characteristics of patients successfully treated for extended periods are represented in the survival models, but the results are primarily applicable to patients who ultimately discontinue natalizumab.

Personalization of DMT choice in MS remains challenging. Considerable effort was previously expended to predict response to interferon beta,[25–27] but these methods typically required a medication trial to anticipate long-term responses. The DMT landscape has rapidly changed in the interim and the importance of early effective treatment is increasingly being recognized.[28] The current study is an attempt to identify characteristics a priori that may indicate a lower likelihood of success with natalizumab. The goal is that such methodology, especially if applied to a wider range of DMTs, will allow for faster identification of effective therapy for individuals with MS. Based on our study, careful consideration should be given when prescribing natalizumab to patients with comorbidities such as smoking and depression, as well as to patients with PRMS, but these results require further verification in a larger, multicenter cohort.

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Conflict of Interests

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