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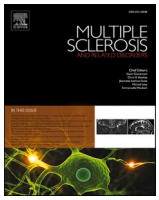

Original article

Benefits of early treatment with natalizumab: a real-world study

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ABSTRACT

Background: The impact of early versus later high-efficacy disease-modifying therapy (DMT) in patients with multiple sclerosis (MS) is uncertain. This study reported the association of early versus later natalizumab treatment with real-world clinical outcomes in MS patients.

Methods: The study included 661 participants diagnosed with MS in 1994 or later from 7 US centers participating in the MS Partners Advancing Technology for Health Solutions (MS PATHS) network. Time to natalizumab treatment between diagnosis and first infusion (TTNT) was determined from the Tysabri Outreach: Unified Commitment to Health (TOUCH) registry. Clinical outcomes were defined using neuroperformance tests included in the Multiple Sclerosis Performance Test. Associations were tested using TTNT as a categorical and continuous variable. Linear mixed models addressed within-subject and within-site clustering.

Results: TTNT varied from 0.1 to 19.8 years (median [interquartile range] 4.2 [1.8, 9.0] years). A significant association between later natalizumab use and worse outcomes was demonstrated for walking speed ($p < 0.001$), processing speed ($p < 0.001$), manual dexterity ($p < 0.001$), brain atrophy ($p = 0.001$), and T2 lesion volume ($p = 0.02$). Covariate-adjusted modelling of a sensitivity population diagnosed with MS in 2006 or later ($n = 424$) demonstrated significant associations between longer TTNT and worse walking speed ($p < 0.05$), processing speed ($p < 0.001$), and manual dexterity ($p < 0.001$).

Conclusion: Later initiation of natalizumab was associated with worse clinical and radiologic imaging outcomes. Thus, high-efficacy DMT may have greater benefit when started earlier in MS patients. These results provide a rationale for randomized controlled trials to further assess the impact of early highly-effective DMT use versus later escalation of therapy.

1. Introduction

Multiple sclerosis (MS[1]) is a chronic autoimmune and neurodegenerative disease characterized by variable severity and progression. Over the past 25 years, numerous disease-modifying therapies (DMTs) have been introduced, offering an array of choices with a range of efficacy profiles and risks. Ideally, MS should be diagnosed promptly and treated early. However, the proper intensity of disease treatment at onset, the selection of individual DMTs, and the sequencing of DMTs are ongoing areas of research. Standardized tools to more accurately predict each

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[1] *Abbreviations:* DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS PATHS, MS Partners Advancing Technology for Health Solutions; MSFC, Multiple Sclerosis Functional Composite; MSPT, Multiple Sclerosis Performance Test; PDDS, Patient-Derived Disease Steps; PML, progressive multifocal leukoencephalopathy; Q1, quintile 1; Q5, quintile 1; RCT, randomized controlled trial; TOUCH, Tysabri Outreach: Unified Commitment to Health; TTNT, time to natalizumab treatment

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patient's prognosis and better data on optimal DMT sequencing are needed to move toward individualized DMT treatment decisions. This, in turn, would improve long-term patient outcomes.

Long-term follow-up of patients from randomized controlled trials (RCTs) has demonstrated the value of early versus later MS treatment. Participants who were initially randomized to placebo and then switched to interferon beta at the end of the double-blind phase of RCTs had worse long-term outcomes than those initially randomized to interferon beta (PRISMS Study Group, 1998; PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group, 2001; Schwid and Bever, 2001). This finding, which was echoed in follow-up studies for other DMTs, led to the recommendation for early rather than later treatment (Cerqueira et al., 2018; Coyle, 2008; Rudick et al., 1999). Early treatment is now generally considered standard practice in the MS field, but controversy remains about treatment sequencing strategy and how intensively to treat the disease at onset. In the absence of definitive evidence, one therapeutic option is to treat early with high-efficacy DMTs (Harding et al., 2019; Stankiewicz and Weiner, 2020) rather than starting with first-line DMTs and escalating to high-efficacy therapy as needed (Ontaneda et al., 2019). A similar controversy was seen with rheumatoid arthritis, with observational studies suggesting the benefits of early high-efficacy therapy (Lard et al., 2002; Verstappen et al., 2003). Eventually, an RCT demonstrated the long-term value of early highly active treatment (Breedveld et al., 2006). In MS, given continued uncertainty about the value of early high-efficacy treatment for long-term outcomes, two large RCTs testing the impact of early high-efficacy versus escalation approaches (ClinicalTrials.gov NCT03535298 [DELIVER-MS] and NCT03500328 [TREAT-MS]) were initiated with funding from the Patient-Centered Outcomes Research Institute. Until the results of these trials are available, clinicians treating MS patients will have to choose between early high-efficacy and escalation approaches based on the available observational evidence.

In the present study, observational data from the Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) network were utilized to examine the effect of early versus later use of a high-efficacy therapy, natalizumab, on clinical and magnetic resonance imaging (MRI) measures. MS PATHS is a technology-enabled network of 10 MS centers in the United States, Germany, and Spain that seeks to generate standardized, quantitative clinical and imaging outcome assessments in a clinical practice setting. Data from MS PATHS were analyzed to determine whether shorter intervals between diagnosis and natalizumab treatment are associated with more favorable clinical and MRI outcomes in a contemporaneous real-world cohort.

2. Methods

2.1. Data sources

In MS PATHS, data are collected as part of routine patient care for all patients with a diagnosis of MS seeking care at 10 institutions: 7 in the US, 2 in Germany, and 1 in Spain. All MS patients at these centers are offered enrollment in MS PATHS. Clinical data collection is through an assessment tool, the Multiple Sclerosis Performance Test (MSPT) (Rhodes et al., 2019). Participants self-administer their own clinical assessment, yielding standardized data including information on use of DMTs, MS history, self-reported disability, quality of life, and quantitative tests of cognition, vision, dexterity, and walking. Brain MRI is acquired using standardized image acquisition protocols on Siemens 3T platforms; brain atrophy and T2 lesion metrics are analyzed using MS PATHS Image Evaluation (MSPie) software (Kitzler et al., 2020).

In the US, patients receiving natalizumab are required to participate in the Tysabri Outreach: Unified Commitment to Health (TOUCH) Prescribing Program. TOUCH is a pharmacovigilance registry established in 2006 to ensure complete ascertainment of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab. PML is an uncommon but potentially fatal complication of natalizumab treatment. Since 2006, all natalizumab infusions occurring in the US have been recorded in TOUCH, with detailed information on timing, allowing for accurate determination of natalizumab exposure. Whereas the TOUCH registry provides accurate, lifetime natalizumab exposure data, MS PATHS has provided quantitative clinical and imaging outcome data since 2016, when the network was initiated. As the TOUCH registry is used only in the US, MS PATHS data for this study were restricted to the 7 US sites: Cleveland Clinic, Johns Hopkins University, New York University, Lou Ruvo Center, Ohio Health, University of Rochester, and Washington University in St. Louis.

The neuroperformance tests included in the MSPT were adaptations of the Multiple Sclerosis Functional Composite (MSFC) components (Rhodes et al., 2019; Rudick et al., 2002). The Processing Speed Test, Manual Dexterity Test, Contrast Sensitivity Test, and Walking Speed Test were adapted from the Symbol Digit Modalities Test (Benedict et al., 2017), 9-Hole Peg Test (Motl et al., 2017), Sloan Low Contrast Letter Acuity Test (Balcer et al., 2017), and 25-Foot Walk Test (Motl et al., 2017), respectively. Results on patient-administered MSPT tests were previously shown to correlate strongly with results on the parallel examiner-administered MSFC tests (Rao et al., 2020; Rao et al., 2017).

2.2. Population

Current or former patients on natalizumab consented to the linking of data collected through the TOUCH registry with data collected during MS PATHS. From this linked population, participants were identified who met the following criteria: (a) $\geq$18 years of age at the time of the first infusion, (b) $\geq$8 years of education, (c) $\geq$1 MS PATHS visit after the first infusion, (d) demographic and neuroperformance testing from MSPT, (e) diagnosis in 1994 or later (ie, after approval and widespread use of DMTs in MS), (f) an interval between MS diagnosis and the first natalizumab infusion of $\leq$20 years, and (g) no missing data on covariates (see below).

2.3. Statistical analysis

The time from MS diagnosis to the first natalizumab infusion, which was termed time to natalizumab treatment (TTNT), was estimated using the first recorded infusion in TOUCH and the self-reported age at diagnosis. The relationship of TTNT to outcomes measured in MS PATHS was assessed via regression modelling. Linear mixed-effects regression models with random intercepts were separately fit for each outcome, including terms for TTNT and covariates. Categorical and continuous forms of TTNT were explored via quintile cutoffs and natural splines with four degrees of freedom, respectively. In order to account for participants' multiple, irregularly timed outcome measurements, within-patient correlation was modelled using a spatial Gaussian error structure. All models included adjustment for age at outcome measurement, sex, race, years of education, smoking status, calendar year of natalizumab initiation, disease duration at outcome measurement, proportion of disease duration on natalizumab, and MS PATHS site.

A sensitivity analysis was conducted to evaluate outcomes for participants with a diagnosis in or after 2006, when natalizumab was approved for clinical use. This subgroup allowed assessment of the impact of the timing of natalizumab initiation in a more contemporary era, after diagnostic criteria were amended to allow earlier diagnosis and when MS patients were increasingly being treated with newer DMTs with greater effectiveness.

The overall significance of the association between treatment interval and outcome was assessed with the F test, with $p \leq 0.05$ set as the significance threshold. The modelled relationship between the treatment interval and outcomes was assessed graphically by plotting least-squares means over the range of the interval, superimposing plots of actual scores for clinical and imaging outcomes as a function of TTNT divided into equal-interval quintiles.

3. Results

A total of 661 participants were included in the study (Fig. 1). Fig. 2 shows the time to the first natalizumab infusion in these participants, which ranged from 0.1 to 19.8 years (median [interquartile range], 4.2 [1.8, 9.0] years).

Table 1 shows participant characteristics stratified by TTNT quintile at the time of MS PATHS assessment. Participants with shorter TTNT were older at diagnosis (average age for quintile 1 [Q1] vs quintile 5 [Q5], 34.9 vs 30.7 years; $p = 0.001$); they were also younger at the first natalizumab infusion (35.6 years for Q1 vs 44.1 years for Q5) and the first MS PATHS MSPT assessment (38.3 years for Q1 vs 48.1 years for Q5) and had shorter disease duration at the last MS PATHS visit (5.36 years for Q1 vs 19.4 years for Q5; all $p < 0.001$). Sex, race, and education were not significantly associated with TTNT.

Clinical disease severity and MRI outcomes are shown in Fig. 3, with smoothed continuous outcome data based on the model described in the Methods section as well as unadjusted observed data plotted as quintiles of TTNT. A consistent pattern across outcome measures for both the adjusted models and the raw scores was observed: greater TTNT was significantly associated with worse outcomes for walking speed ($p < 0.001$), processing speed ($p < 0.001$), manual dexterity ($p < 0.001$), brain atrophy ($p = 0.001$), and T2 lesion volume ($p = 0.020$). Patient-Derived Disease Steps (PDDS) worsening trended in the same direction but was not statistically significant ($p = 0.540$).

Table 2 shows a summary of the raw scores for MS outcomes from MS PATHS assessments stratified by pre-natalizumab treatment interval, as well as the sample size and proportion of missing data for each data element. These data show the magnitude of the range of outcomes from shortest to longest TTNT.

Table 3 presents characteristics of 424 participants diagnosed in 2006 or later. As with the larger cohort, those with shorter TTNT were younger at the first natalizumab infusion (34.5 years for Q1 vs 39.7 years for Q5; $p < 0.01$) and the first MS PATHS MSPT assessment (37.1 years for Q1 vs 39.3 years for Q5; $p < 0.05$) and had shorter disease duration at the last MS PATHS visit (4.93 years for Q1 vs 10.8 years for Q5; $p < 0.001$). Sex, race, and education were not significantly associated with TTNT in this group. Fig. 4 shows smoothed continuous outcome data based on the model as well as unadjusted observed data plotted as quintiles of TTNT. Patterns in this cohort were similar to but less consistent than those observed in the overall population. The covariate-adjusted modelling demonstrated that greater TTNT was significantly associated with decreased walking speed ($p = 0.037$), processing speed ($p < 0.001$), and manual dexterity ($p < 0.001$). There was no statistically significant association between TTNT and PDDS, brain atrophy, or T2 lesions. Table 4 shows a summary of the raw scores for MS outcomes by TTNT, as well as sample size and the proportion of missing data for each data element for the cohort of participants diagnosed in 2006 or later.

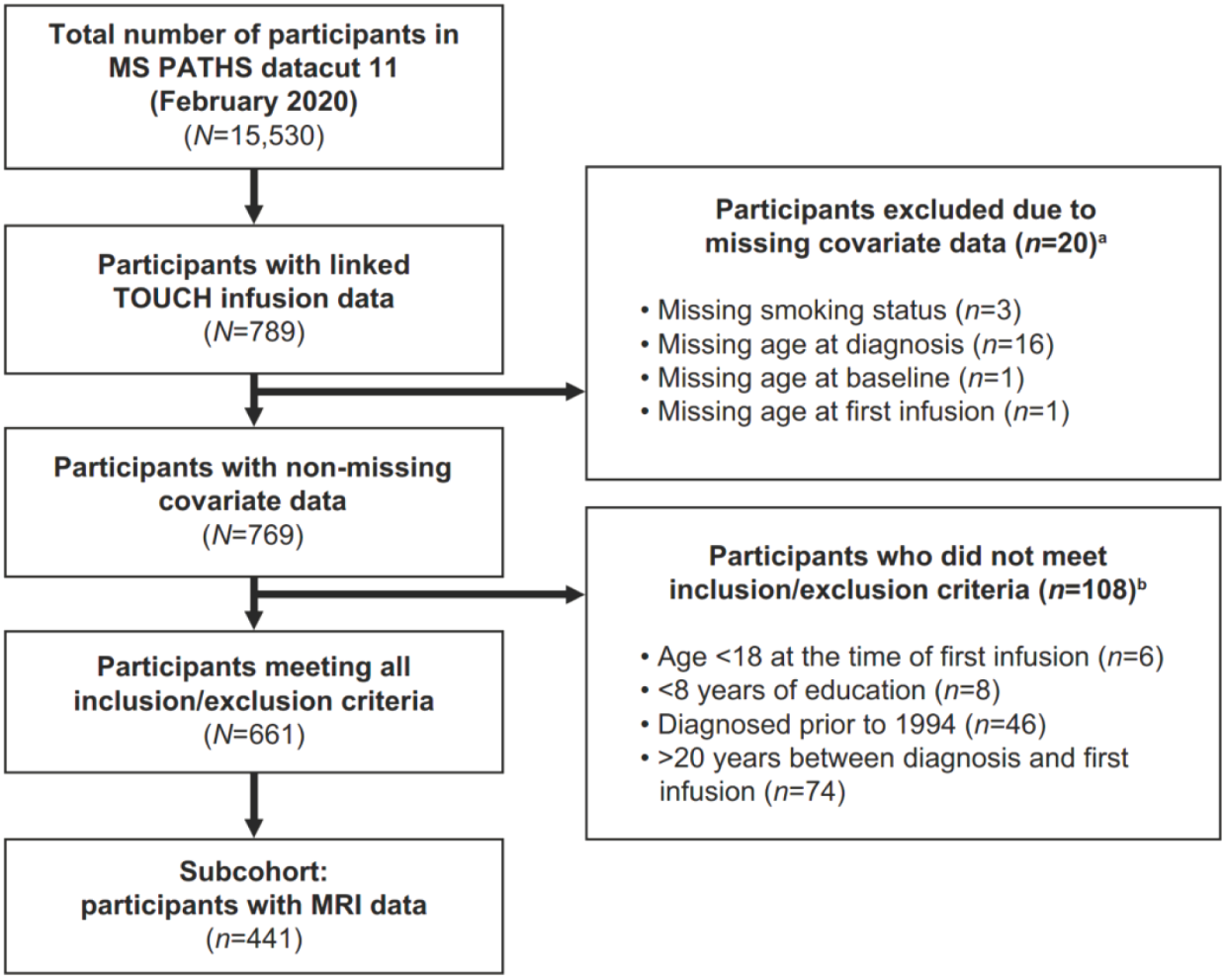

Fig. 1. Participant flow diagram.
[a]Participants could have had missing data for >1 covariate. [b] Participants could have not met >1 inclusion or exclusion criterion.

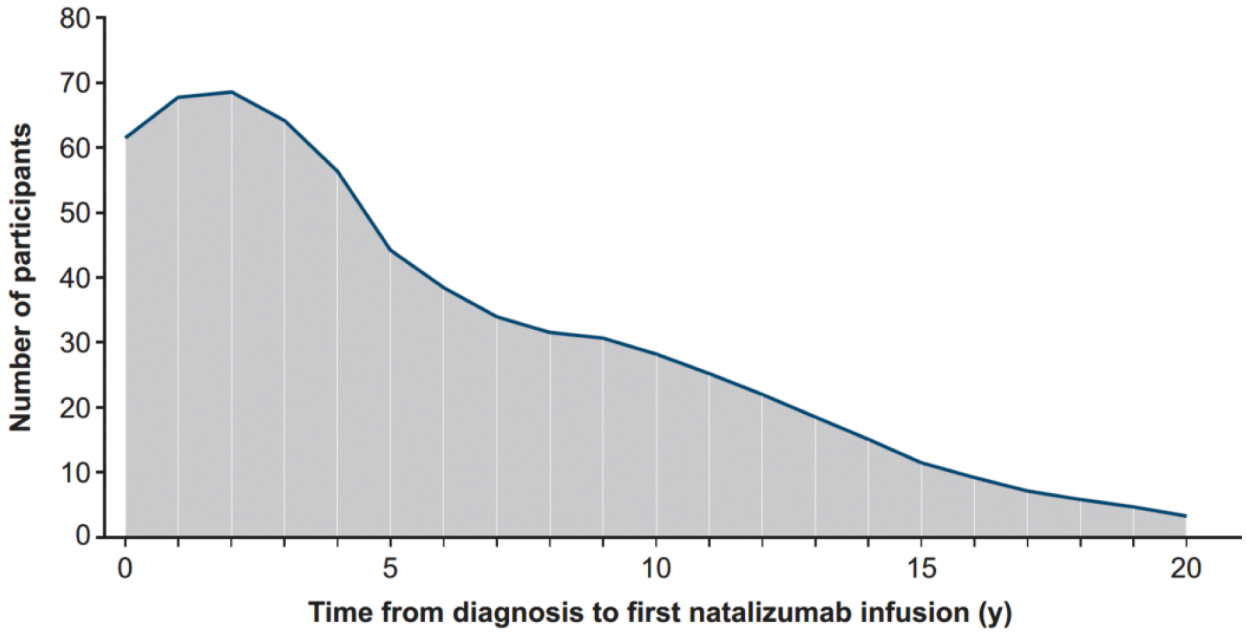

Fig. 2. Distribution of time from multiple sclerosis diagnosis to first natalizumab infusion ($n = 661$).

Table 1
Participant characteristics by TTNT quintile (MS diagnosis in 1994 or later).

Characteristic	Q1 (0.1–1.3 y)	Q2 (1.3–3.1 y)	Q3 (3.1–6.3 y)	Q4 (6.3–10.0 y)	Q5 (10.0–19.8 y)	Overall	*p* value
Number of participants	133	132	132	132	132	661	
Sex, female *n* (%)	98 (73.7)	100 (75.8)	96 (72.7)	98 (74.2)	98 (74.2)	490 (74.1)	0.988
Race, *n* (%)							
White	105 (78.9)	107 (81.1)	102 (77.3)	97 (73.5)	96 (72.7)	507 (76.7)	
Other	28 (21.1)	25 (18.9)	30 (22.7)	35 (26.5)	36 (27.3)	154 (23.3)	0.443
Years of education							
Mean (SD)	14.9 (2.25)	15.2 (2.44)	15.2 (2.52)	14.9 (2.48)	15.2 (2.40)	15.1 (2.42)	0.659
Median (min, max)	15 (11, 20)	16 (8, 20)	16 (9, 20)	16 (9, 20)	16 (11, 20)	16 (8, 20)	
Age at MS diagnosis, y							
Mean (SD)	34.9 (9.32)	33.3 (9.70)	33.6 (10.1)	32.0 (8.42)	30.7 (7.60)	32.9 (9.17)	0.001
Median (min, max)	34 (18, 59)	33 (16, 56)	33 (14, 56)	30 (15, 55)	30 (14, 55)	32 (14, 59)	
Age at first infusion, y							
Mean (SD)	35.6 (9.35)	35.4 (9.71)	38.0 (10.2)	40.0 (8.57)	44.1 (7.87)	38.6 (9.69)	<0.001
Median (min, max)	35.1 (18.1, 59.1)	35.2 (18.4, 59.0)	36.3 (18.3, 60.9)	38.8 (23.7, 63.5)	43.8 (25.7, 70.3)	38.2 (18.1, 70.3)	
Age at first MSPT, y							
Mean (SD)	38.3 (10.2)	38.9 (10.1)	42.4 (10.5)	44.5 (9.2)	48.1 (8.1)	42.4 (10.3)	<0.001
Median (min, max)	38 (18, 65)	39 (18, 62)	41 (22, 71)	43.5 (23, 67)	48 (29, 73)	42 (18, 73)	
Disease duration at last MS PATHS visit, y							
Mean (SD)	5.36 (3.34)	7.64 (3.37)	10.9 (3.60)	14.5 (4.01)	19.4 (3.65)	11.5 (6.15)	<0.001
Median (min, max)	4.71 (0.2, 13.6)	7.14 (2.3, 16.1)	10.7 (3.5, 18.0)	14.2 (7.4, 22.6)	19.6 (11.7, 25.4)	11.0 (0.2, 25.4)	

P values are based on one-way ANOVA assessment of differences across quintiles.
MS, multiple sclerosis; MS PATHS, MS Partners Advancing Technology for Health Solutions; MSPT, Multiple Sclerosis Performance Test; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5; SD, standard deviation; TTNT, time to natalizumab treatment.

4. Discussion

4.1. Context for this work

Over the past 27 years, over a dozen DMTs for MS have been introduced to medical practice. The first DMTs approved were characterized by intramuscular or subcutaneous routes of administration, modest effect sizes, and few serious risks. Over time, neurologists developed a consensus that DMTs should be used in most patients beginning soon after diagnosis. With the approval of natalizumab in 2006, biological drugs with higher effectiveness but also higher risk of serious adverse events were added to the clinical armamentarium. Initiating natalizumab is associated with a significantly lower relapse rate and risk of first on-treatment relapse compared with initiating interferon or glatiramer acetate (Spelman et al., 2016). However, natalizumab is associated with PML, a rare but serious adverse event. This has limited the use of natalizumab to patients with more active forms of MS, and general treatment approaches have been more lenient in tolerating disease activity. However, preventing any form of disability accrual is a widely recognized goal of MS treatment. This highlights the importance of determining whether initiating high-efficacy drugs soon after diagnosis more effectively delays or prevents progressive clinical deterioration than initially using less potent DMTs and escalating to higher-efficacy products only with disease activity or progression. Because there are no definitive data on this question, practice patterns vary. A common practice is to use less potent first-line drugs during a trial period and escalate to high-efficacy drugs in patients who have disease activity or are worsening on treatment.

To provide Class 1 evidence for this question, two multicenter randomized controlled clinical trials are currently being conducted. The

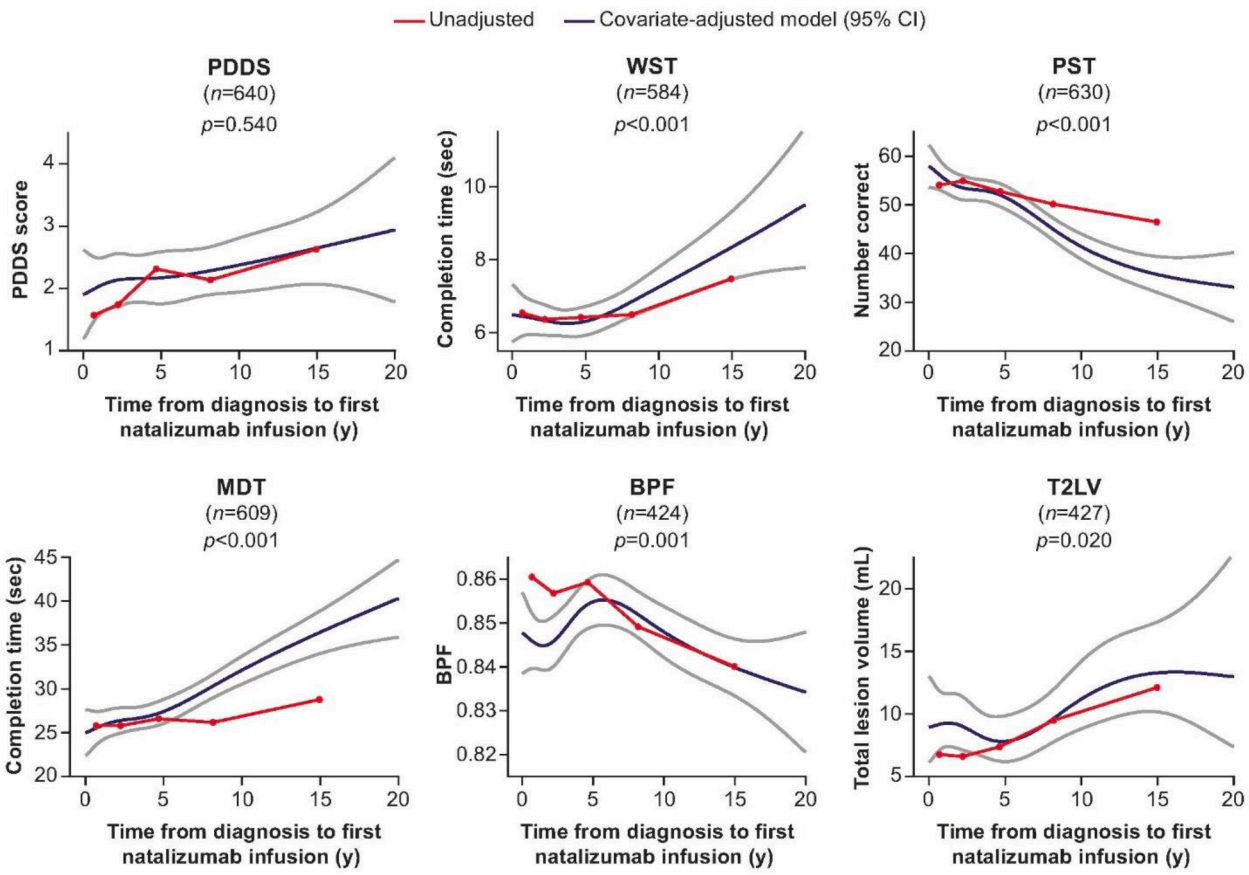

Fig. 3. Clinical and imaging outcomes for participants with a diagnosis in 1994 or later.
Red symbols and lines=unadjusted scores. PDDS, WST, PST, MDT are means; BPF and T2LV are shown as medians based on the data distribution. Blue lines=plots of the models, where time to natalizumab treatment was a continuous variable. BPF, brain parenchymal fraction; CI, confidence interval; LS, least squares; MDT, Manual Dexterity Test; PDDS, Patient-Derived Disease Steps; PST, Processing Speed Test; T2LV, T2 hyperintense lesion volume; WST, Walking Speed Test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

first trial, A Pragmatic Trial to Evaluate the Intermediate-term Effects of Early, Aggressive Versus Escalation Therapy in People With Multiple Sclerosis (TREAT-MS; NCT03500328), is an RCT enrolling 900 patients with relapsing MS to test whether early high-efficacy treatment (including natalizumab) is better than standard MS treatment with escalation to high-efficacy therapy if needed. The primary outcome is time to sustained worsening on the EDSS-Plus (worsening on the Expanded Disability Status Scale [EDSS], the Timed 25-Foot Walk, or the 9-Hole Peg Test). Secondary outcome measures include PDDS, other MSFC elements, brain atrophy, and T2 lesion burden.

The second trial is Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for RRMS (DELIVER-MS; NCT03535298), a pragmatic comparative RCT and parallel observational study in which 800 treatment-naive patients with relapsing MS will receive either high-efficacy treatment or escalation therapy (Ontaneda et al., 2020). The long-term outcome of interest is disability, but the study is powered to assess brain atrophy over 3 years. Secondary endpoints of DELIVER-MS include MSFC, patient-reported outcomes, and other MRI measures.

These two complementary studies will provide class I evidence on the topic of whether to use aggressive therapy earlier rather than maintaining the standard practice of treating with less aggressive therapy and escalating if needed. These studies are important because there is presently inadequate information on this question.

4.2. Findings and implications of this study

This study found that longer TTNT was associated with worse clinical and imaging outcomes at the time of MS PATHS assessment. These general observations were consistent across clinical and imaging outcome measures and were also consistent with a sensitivity analysis focusing on a more contemporary sample of patients. In the aggregate, the data show that shorter TTNT was associated with less severe clinical and radiological manifestations at the time of MS PATHS assessment. These findings are consistent with a recent report from the MSBase and Swedish MS registries (He et al., 2020), which found that patients initiating natalizumab within 2 years of diagnosis had less accumulated disability 6–10 years post diagnosis than patients with greater TTNT.

The most obvious explanation for the findings of the MSBase/Swedish Registry study and the MS PATHS study is that disease pathology and related disability accumulate when patients experience disease activity, which may be more common with moderate-efficacy therapy, and that treatment does not reverse pathology or accumulated disability. Rather, high-efficacy DMTs act by suppressing disease activity, thereby preventing later irreversible disability. This suggests that there is a window of opportunity to prevent disability accumulation, after which future disability is already determined.

The subgroup diagnosed in 2006 or later exhibited less consistent and less robust differences related to TTNT. Notably, no significant relationship between TTNT and MRI outcomes was observed. There are several possible explanations for this finding. First, the sample size was significantly lower for the subgroup diagnosed in 2006 or later than for those diagnosed earlier, and it was even lower for those participants with MRI data. Second, the range of disease duration across the cohort was much narrower for the 2006-and-onward subgroup than for the overall population studied, as was the range of TTNT. The narrower ranges of disease duration and TTNT may have attenuated the observed

Table 2
MS outcomes by TTNT quintile (MS diagnosis in 1994 or later).

Outcome PDDS	Q1 (0.1–1.3 y)	Q2 (1.3–3.1 y)	Q3 (3.1–6.3 y)	Q4 (6.3–10.0 y)	Q5 (10.0–19.8 y)	Overall
n	114	115	121	118	113	581
Mean (SD)	1.57 (1.84)	1.74 (1.99)	2.31 (2.20)	2.14 (2.16)	2.63 (2.30)	2.08 (2.13)
Median (min, max)	1 (0, 7)	1 (0, 7)	2 (0, 7)	1 (0, 7)	2 (0, 7)	1 (0, 7)
Missing, *n* (%)	19 (14.3)	17 (12.9)	11 (8.3)	14 (10.6)	19 (14.4)	80 (12.1)
Walking Speed Test						
n	109	110	107	101	96	523
Mean (SD)[a]	6.54 (2.08)	6.37 (1.97)	6.42 (2.03)	6.50 (2.46)	7.48 (2.75)	6.64 (2.29)
Median (min, max)[a]	6.16 (2.0, 13.2)	5.96 (2.8, 13.5)	6.16 (3.0, 14.8)	5.76 (2.0, 13.8)	6.71 (3.1, 14.9)	6.16 (2.02, 14.9)
Missing, *n* (%)	24 (18.0)	22 (16.7)	25 (18.9)	31 (23.5)	36 (27.3)	138 (20.9)
Processing Speed Test						
n	110	117	117	115	106	565
Mean (SD)[b]	54.1 (13.4)	54.9 (13.3)	52.7 (12.4)	50.2 (12.1)	46.5 (13.6)	51.8 (13.3)
Median (min, max)[b]	54 (7, 83)	55 (11, 79)	53 (26, 83)	50 (23, 76)	46 (16, 82)	52 (7, 83)
Missing, *n* (%)	23 (17.3)	15 (11.4)	15 (11.4)	17 (12.9)	26 (19.7)	96 (14.5)
Manual Dexterity Test						
n	111	110	110	103	102	538
Mean (SD)‡	25.8 (7.26)	25.8 (6.08)	26.6 (6.69)	26.2 (7.19)	28.8 (7.38)	26.6 (6.99)
Median (min, max)[c]	23.7 (16.1, 54.6)	24.8 (15.6, 43.5)	24.9 (16.0, 54.4)	24.4 (16.7, 53.2)	27.2 (16.9, 52.1)	24.9 (15.6, 54.6)
Missing, *n* (%)	22 (16.5)	22 (16.7)	20 (15.2)	29 (22.0)	30 (22.7)	123 (18.6)
Brain atrophy (BPF)						
n	64	62	67	49	72	314
Mean (SD)	0.853 (0.025)	0.857 (0.023)	0.855 (0.018)	0.846 (0.024)	0.835 (0.028)	0.849 (0.025)
Median (min, max)	0.861 (0.764, 0.883)	0.857 (0.776, 0.890)	0.859 (0.799, 0.883)	0.849 (0.783, 0.884)	0.840 (0.766, 0.878)	0.854 (0.764, 0.890)
Missing, *n* (%)	69 (51.9)	70 (53.0)	65 (49.2)	83 (62.9)	60 (45.5)	347 (52.5)
T2 lesion volume						
n	67	69	68	50	72	320
Mean (SD)	9.88 (12.5)	10.7 (12.2)	8.88 (7.27)	14.1 (11.4)	17.5 (15.7)	12.2 (12.6)
Median (min, max)	6.76 (0.4, 74.0)	6.62 (1.0, 63.0)	7.38 (0.6, 30.6)	9.49 (1.6, 46.5)	12.1 (1.4, 88.7)	8.31 (0.373, 88.7)
Missing, *n* (%)	66 (49.6)	69 (52.3)	64 (48.5)	82 (62.1)	60 (45.5)	341 (51.6)

BPF, brain parenchymal fraction; MS, multiple sclerosis; PDDS, Patient-Determined Disease Steps; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5; SD, standard deviation; TTNT, time to natalizumab treatment.

[a] Completion time in seconds.

[b] Number of correct responses on test.

[c] Completion time in seconds.

Table 3
Participant characteristics by TTNT quintile (MS diagnosis in 2006 or later).

Characteristic	Q1 (0.1–0.9 y)	Q2 (1.0–1.8 y)	Q3 (1.8–3.1 y)	Q4 (3.1–5.3 y)	Q5 (5.3–13.2 y)	Overall	*p* value
Number of participants	85	85	84	85	85	424	
Sex, *n* (%)							
Female	65 (76.5)	59 (69.4)	66 (78.6)	59 (69.4)	65 (76.5)	314 (74.1)	0.506
Male	20 (23.5)	26 (30.6)	18 (21.4)	26 (30.6)	20 (23.5)	110 (25.9)	
Race, *n* (%)							
Other	19 (22.4)	16 (18.8)	16 (19.0)	21 (24.7)	30 (35.3)	102 (24.1)	0.0762
White	66 (77.6)	69 (81.2)	68 (81.0)	64 (75.3)	55 (64.7)	322 (75.9)	
Years of education, y							
Mean (SD)	14.9 (2.32)	15.0 (2.30)	15.0 (2.40)	15.3 (2.55)	14.3 (2.43)	14.9 (2.41)	0.122
Median (min, max)	15 (11, 20)	15 (12, 20)	16 (8, 20)	16 (9, 20)	14 (9, 20)	15 (8, 20)	
Age at MS diagnosis, y							
Mean (SD)	34.0 (9.1)	34.4 (9.2)	33.6 (10.3)	33.8 (10.5)	32.0 (7.7)	33.6 (9.4)	0.343
Median (min, max)	34 (18, 59)	34 (17, 55)	33.5 (16, 56)	33 (14, 56)	30 (18, 50)	33 (14, 59)	
Age at first infusion, y							
Mean (SD)	34.5 (9.1)	35.7 (9.1)	36.0 (10.3)	37.8 (10.5)	39.7 (8.0)	36.8 (9.6)	<0.01
Median (min, max)	34.7 (18.1, 59.1)	35.5 (18.6, 55.9)	35.6 (18.4, 59.0)	36.3 (18.3, 60.4)	38.0 (25.0, 57.1)	36.4 (18.1, 60.4)	
Age at first MSPT, y							
Mean (SD)	37.1 (9.66)	38.8 (9.96)	38.9 (10.3)	41.0 (10.3)	40.8 (8.02)	39.3 (9.75)	<0.05
Median (min, max)	38 (18, 59)	39 (19, 65)	39.5 (18, 62)	40 (22, 65)	40 (23, 57)	39 (18, 65)	
Disease duration at last MS PATHS visit, y							
Mean (SD)	4.93 (3.2)	6.36 (3.2)	7.15 (2.6)	9.28 (2.8)	10.8 (1.8)	7.71 (3.5)	<0.001
Median (min, max)	4.41 (0.2, 13.3)	5.35 (1.3, 13.6)	7.07 (2.5, 13.3)	9.44 (3.5, 13.9)	11.0 (6.6, 13.7)	7.74 (0.2, 13.9)	

P values are based on one-way ANOVA assessment of differences across quintiles.
MS, multiple sclerosis; MS PATHS, MS Partners Advancing Technology for Health Solutions; MSPT, Multiple Sclerosis Performance Test; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5; SD, standard deviation; TTNT, time to natalizumab treatment.

impact of TTNT in the two cohorts. Finally, practice patterns have evolved over the course of this study. Starting in 1994, MS DMTs were introduced, and over time, were increasingly used. By 2006, standard practice involved treating most patients with an MS DMT, and starting treatment early after diagnosis. Beginning in 2010, oral DMTs were introduced to MS practice, and these products, some of which were mildly to moderately more effective than injectable therapies, were increasingly substituted for the DMTs introduced during the 1990s. In addition, the routine use of MRI to monitor disease and initiate treatment switches to high-efficacy therapies likely increased over the course

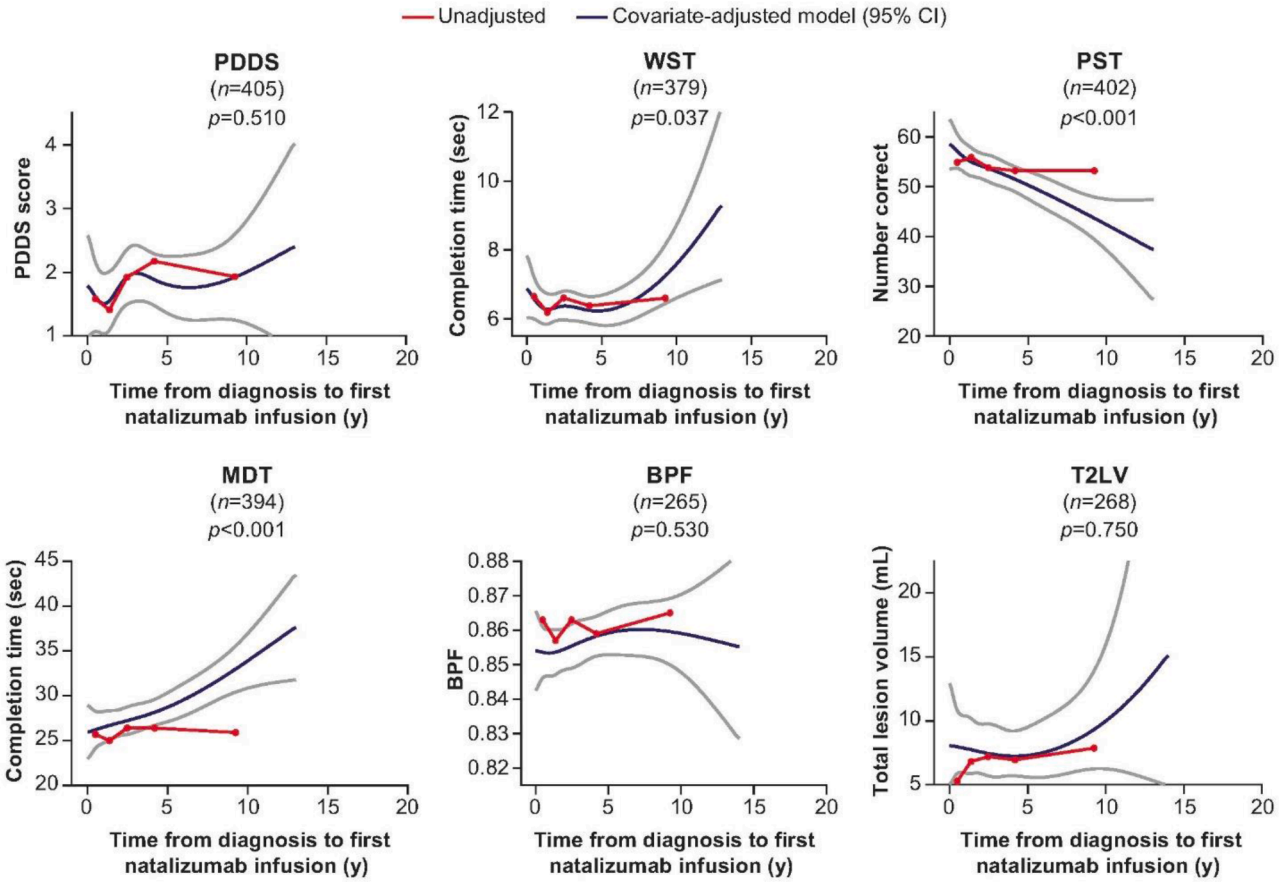

Fig. 4. Clinical and imaging outcomes for participants with a diagnosis in 2006 or later. Red symbols and lines=unadjusted scores.
PDDS, WST, PST, MDT are means; BPF and T2LV are shown as medians based on the data distribution. Blue lines=plots of the models, where time to natalizumab treatment was a continuous variable. BPF, brain parenchymal fraction; CI, confidence interval; MDT, Manual Dexterity Test; PDDS, Patient-Derived Disease Steps; PST, Processing Speed Test; T2LV, T2 hyperintense lesion volume; WST, Walking Speed Test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

of this study. Therefore, high-efficacy treatments may have been used over an increasing proportion of the TTNT interval, which would attenuate differences in TTNT in the 2006-and-onward cohort relative to the overall cohort.

4.3. *Limitations of this work*

One limitation of this study is the lack of quantitative disease severity metrics (clinical and imaging) both at diagnosis and at the time of natalizumab initiation. Such data are not available because MS PATHS was not initiated until 2016, whereas MS diagnosis and initiation of natalizumab preceded 2016 for most participants in the full cohort. Therefore, it was not possible to match disease characteristics for participants with short versus long TTNT. If such matching were possible, this would provide additional insight into the present finding of worse clinical and imaging outcomes with longer TTNT.

Another limitation is the lack of a comparator cohort. While longer TTNT was associated with worse outcomes, this study did not include a comparator group of participants with long disease duration who never initiated natalizumab or other high-efficacy therapies. Such a comparator group might have less severe disease, which would seem to controvert the current results showing worse outcomes with longer TTNT. Alternatively, at least a proportion of such a comparator group may have accumulated disease burden over time, which *would* support the current finding of worse outcomes with longer TTNT.

As with other observational studies, the role of potential confounding factors needs to be considered. Importantly, the decision to treat with natalizumab was determined by individual physicians rather than by randomization, and systematic treatment decision patterns may have biased the results. Since this cohort largely comes from tertiary care centers, it likely includes participants who were referred to treatment centers later in the disease course. Some participants with prolonged TTNT may have already accumulated a substantial degree of subclinical disease burden (eg, lesions visible on MRI) prior to their referral. In these high-risk patients, treating physicians may have attempted to initiate natalizumab in the hopes of preventing disability accumulation. Such a systematic treatment decision pattern would preferentially bias participants with more severe disease to have longer TTNT, which would drive the results in the direction of the observed associations (ie, worse outcomes with longer TTNT). Alternatively, treating physicians may have systematically delayed natalizumab initiation in participants with less severe disease, using an escalation approach in which a high-efficacy therapy such as natalizumab would not be initiated until a rather robust amount of breakthrough disease has occurred. Such a treatment decision pattern would preferentially bias participants with more severe disease to have shorter TTNT, which would drive the results in the direction of the null (ie, less impact for early versus later treatment).

Observational studies may have limited ability to determine from available data whether treatment decisions were affected by systematic bias. While delaying escalation to high-efficacy therapy was more common in the past, in contemporary practice most MS experts advocate rapidly identifying suboptimal response to initial therapy and then switching to another treatment. Given the time horizon of this study, a

Table 4
MS outcomes by time to natalizumab treatment quintile (MS diagnosis in 2006 or later).

Outcome PDDS	Q1 (0.1–0.9 y)	Q2 (1.0–1.8 y)	Q3 (1.8–3.1 y)	Q4 (3.1–5.3 y)	Q5 (5.3–13.2 y)	Overall
n	73	73	72	76	76	370
Mean (SD)	1.58 (1.86)	1.41 (1.67)	1.92 (2.15)	2.17 (2.26)	1.93 (2.06)	1.81 (2.02)
Median (min, max)	1 (0, 7)	1 (0, 7)	1 (0, 7)	2 (0, 7)	1 (0, 7)	1 (0, 7)
Missing, *n* (%)	12 (14.1)	12 (14.1)	12 (14.3)	9 (10.6)	9 (10.6)	54 (12.7)
Walking Speed Test						
n	68	72	69	68	69	346
Mean (SD)[a]	6.65 (2.23)	6.19 (1.81)	6.61 (2.10)	6.38 (2.20)	6.60 (2.34)	6.48 (2.13)
Median (min, max)[a]	6.16 (3.5, 13.2)	5.97 (2.0, 11.7)	6.16 (3.4, 13.5)	5.81 (3.0, 14.8)	5.96 (2.0, 13.8)	5.97 (2.0, 14.8)
Missing, *n* (%)	17 (20.0)	13 (15.3)	15 (17.9)	17 (20.0)	16 (18.8)	78 (18.4)
Processing Speed Test						
n	70	73	73	76	73	365
Mean (SD)[b]	54.9 (11.6)	55.9 (14.7)	53.8 (14.0)	53.2 (11.8)	53.2 (12.9)	54.2 (13.0)
Median (min, max)[b]	55 (19, 76)	57 (7, 83)	55 (11, 79)	53 (26, 78)	55 (31, 83)	55 (7, 83)
Missing, *n* (%)	15 (17.6)	12 (14.1)	11 (13.1)	9 (10.6)	12 (14.1)	59 (13.9)
Manual Dexterity Test						
n	71	72	70	73	71	357
Mean (SD)[c]	25.7 (7.56)	25.0 (5.99)	26.4 (6.41)	26.4 (6.84)	25.9 (6.74)	25.9 (6.71)
Median (min, max)[c]	23.2 (16.1, 47.9)	23.7 (15.6, 54.6)	25.2 (16.7, 43.5)	24.2 (16.0, 54.4)	24.5 (16.7, 50.7)	24.1 (15.6, 54.6)
Missing, *n* (%)	14 (16.5)	13 (15.3)	14 (16.7)	12 (14.1)	14 (16.5)	67 (15.8)
Brain atrophy (BPF)						
n	37	48	35	46	28	194
Mean (SD)	0.858 (0.021)	0.854 (0.025)	0.858 (0.022)	0.857 (0.014)	0.857 (0.024)	0.856 (0.021)
Median (min, max)	0.863 (0.767, 0.883)	0.857 (0.764, 0.890)	0.863 (0.807, 0.888)	0.859 (0.812, 0.883)	0.865 (0.793, 0.882)	0.860 (0.764, 0.890)
Missing, *n* (%)	48 (56.5)	37 (43.5)	49 (58.3)	39 (45.9)	57 (67.1)	230 (54.2)
T2 lesion volume[d]						
n	40	48	36	46	30	200
Mean (SD)	7.4 (6.0)	10.6 (14.3)	11.3 (11.8)	7.6 (6.1)	11.2 (9.4)	9.5 (10.2)
Median (min, max)	5.3 (0.3, 23.7)	6.81 (1.0, 74.0)	7.19 (1.0, 56.4)	6.95 (1.0, 30.6)	7.86 (1.0, 38.3)	6.74 (0.4, 74.0)
Missing, *n* (%)	45 (52.9)	37 (43.5)	48 (57.1)	39 (45.9)	55 (64.7)	224 (52.8)

BPF, brain parenchymal fraction; MS, multiple sclerosis; PDDS, Patient-Determined Disease Steps; Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5; SD, standard deviation; TTNT, time to natalizumab treatment.
[a] Completion time in seconds.
[b] Number of correct responses on test.
[c] Completion time in seconds.
[d] T2 lesion volume in mL.

mixture of prescribing patterns and their associated biases were likely present.

5. Conclusion

With the introduction of numerous MS DMTs, the determination of which DMTs will optimize outcomes for individual patients and when they should be introduced is an important research area. The observational work reported here suggests that later initiation of high-efficacy treatment is associated with worse long-term outcomes. These results and the gaps in knowledge they highlight provide a strong rationale for ongoing RCTs of early highly effective MS treatment.

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