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Patient-reported outcomes based on discontinuation or continuous treatment with natalizumab: New York State Multiple Sclerosis Consortium (NYSMSC) study

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ABSTRACT

Background: Patient-reported outcomes (PRO) are increasingly utilized as part of the routine clinical assessment in people with multiple sclerosis (pwMS). The long-term effect of disease modifying therapies (DMTs) and their discontinuation on PRO measures remains largely unknown.

Methods: Two pwMS groups treated with natalizumab were selected from the New York State MS Consortium (NYSMSC) database. The first group utilized long-term follow-up data of pwMS that either still continue natalizumab treatment or discontinued. Minimal requirement of three visits (before natalizumab initiation, during treatment and after discontinuation/latest follow-up) was implemented. The second group consisted of pwMS that completed PRO questionnaire on the day of the infusion and 7 days later PROs were assessed using the LIFEware System™ that assesses limitations in multiple physical and psychosocial domains. Additional physical disability was assessed using Expanded Disability Status Scale (EDSS) and Timed 25-ft walk test (T25FWT). PRO reports were Rasch-transformed, ranging from 0 to 100, with higher scores indicating a better outcome. Linear mixed-effect models and paired analyses were utilized.

Results: Within the prospective cohort, 242 pwMS were followed on average of 6.5 years. Greater number of PRO domains worsened in the 141 pwMS that discontinued natalizumab when compared to 101 pwMS that remained on the drug (10 vs. 2 PRO domains). PwMS that discontinued natalizumab had significant decline in PROs regarding lower extremities, bladder and bower control and psychosocial aspects (feeling lonesome). Contrarily, pwMS that continued natalizumab had significant improvement in bladder and bowel PRO measures. Seven days after the natalizumab infusion, the 67 pwMS from the prospective cohort reported improvement in PRO measures of fatigue (62.8 vs. 66.4, $p = 0.019$), bladder limitations (80.3 vs. 85.0, $p = 0.012$), and feelings of lonesomeness (81.2 vs. 88.0, $p = 0.009$).

Conclusion: Continuous natalizumab treatment provides long-term stability or improvement in PRO measures. Natalizumab also provides short term improvements recorded after the infusion.

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1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating, neuroinflammatory and neurodegenerative disease that mainly affects the young and working population [1]. Over the disease course, people with MS (pwMS) commonly accumulate a plethora of physical and cognitive disabilities that significantly impact the quality of life and reduce life satisfaction [2]. In addition to objective measures which do not fully encompass the impact of the disease, modern clinical assessments of pwMS increasingly adopt implementation of patient-reported outcomes (PRO) measures.

PRO stands for an umbrella term that defines any information regarding the patient's health condition that comes directly from the patient and is not interpreted by the clinician or anyone else. They are commonly administered through standardized and validated questionnaires that can be specific to the disease itself or provide data regarding the general quality of life [3]. PRO measures are recently encouraged by the Food and Drug Administration (FDA) and various professional associations as one of the important ways to measure clinical effect in clinical trials and routine clinical care. In 2009, the FDA published official framework and guidance regarding the inclusion of PRO measures in clinical trials and later specified them into the Prescription Drug User Fee Act (PDUFA) VI/ 21st Century Cures Act. In similar fashion, the Neuro-QoL (Quality of Life in Neurological Diseases) is one of many PRO-based measured that were developed to provide evaluation of the physical, mental and social effects experienced by persons living with neurological diseases [4].

LIFEware System™ is one such short PRO questionnaire that has been previously validated in healthy aging population and in pwMS [5,6]. The domains assessed using the LIFEware system have high intra-rater stability and normative values for individualized patient evaluation have been developed [7]. In addition to assessing the subjective limitations related to the disease, recent studies have demonstrated that early lower-limb PRO indicators can be utilized as a predictive tool that correlate with future worsening in physical disability [8]. Similarly, early PRO measures of fatigue have been associated with future and long-term MS disability progression [9]. In addition to MS, the LIFEware system has been validated in other neurological disease such as stroke [10] and traumatic brain injury [11] and other unrelated non-neurological diseases such coronary disease [12] and orthopedics [13].

Based on this background, we aimed at investigating the effect of natalizumab on long term PRO changes. Two main hypotheses were investigated, 1) pwMS that discontinue natalizumab experience greater worsening in PRO measures when compared to pwMS that continue their treatment, 2) there is significant improvement in PRO measures in the period after natalizumab infusion (7 days after infusion) in pwMS that are still treated with this medication.

2. Materials and methods

2.1. Study populations

The MS population utilized in this two-part analysis were derived from a larger database of the New York State MS Consortium (NYSMSC) [14,15]. Through years, the NYSMSC has enrolled >10.000 unique pwMS with some longitudinal data available since the conception of the database in 1996. The inclusion criteria for this study were: 1) Age >18 years old, 2) diagnosed with MS as per any of the diagnostic criteria (Poser and McDonald criteria as current for each patient at the time of diagnosis) [16], and 3) being currently treated with natalizumab or had previous exposure to natalizumab. On the other hand, the exclusion criteria were: 1) pregnant or nursing mothers at the time of the visit selected for the study, and 2) have major neurological disease in addition to MS. Presence of psychiatric comorbidities such as anxiety or depression were not part of the exclusion criteria. The database excludes clinical visits at the time of relapse (and after 30 days after confirmed relapse) and all disability measures are acquired during stable disability status.

For the retrospective analyses regarding change in PRO measures between pwMS that continue or discontinue natalizumab, several limitations in the data extraction were implemented. Participants were required to have initiated natalizumab treatment at a known time point (initiation visit), have a follow-up preceding the initiation available (visit before initiation), and have used natalizumab for at least one follow-up. Additionally, participants who discontinued natalizumab were required to have a follow-up available after discontinuation (visit after discontinuation). For those who remained on natalizumab throughout the study, the most recent follow-up was used for analysis.

The second prospective analysis included pwMS that were currently treated with natalizumab and agreed to participate in the study. This part of the study was approved by the Institutional Review Board of the University at Buffalo and all participants signed informed consent. PwMS completed the study PRO questionnaire on the day of their infusion and were given another copy of the same questionnaire to fill out 7 days after the infusion. These questionnaires intend to determine the PROs at the end of the natalizumab cycle (just before receiving treatment) and shortly after the natalizumab treatment. Additional information regarding the total number of natalizumab infusions and the time interval between natalizumab infusions were collected.

All pwMS from both analyses were assessed by experienced neurologist and their disability was scored using the Expanded Disability Status Scale (EDSS) score [17]. Based on their clinical presentation and disease history, the pwMS were classified as relapsing-remitting MS (RRMS) or progressive MS (PMS) [18]. Due to the small sample size primary-progressive MS (PPMS) and secondary-progressive MS (SPMS) were considered together. The walking performance as an additional measure of lower extremity limitation was determined using the Timed 25-ft walk (T25FW) test [19]. T25FW is shown in seconds and higher values represent worse walking ability.

2.2. Patient-reported outcome (PRO) measures

The PRO in this study were derived using the LIFEware System™, a short, single-page Likert questionnaire that assesses limitations in multiple physical and psychosocial domains [20]. The full questionnaire has been published elsewhere and available online [8,20]. The three main parts investigated in the LIFEware questionnaire include daily functioning ("getting up from a low seat like a sofa", "climbing a flight of stairs", "standing a long time, like for 30 minutes", "driving an automobile" and "any and extent of pain during the past 3 days"), physical limitations (limitations in right and left upper or lower limb, bowel and bladder continence, fatiguability and vision) and psychosocial limitations ("lonesome or isolated", "pessimistic about future", "uptight, tense or stressed", "panic attacks", "easily irritated or annoyed", "morbid or gloomy thoughts" and "blaming yourself or guilt"). For each answer, scores were Rasch-transformed, allowing for a linear comparison of data points. PRO scores range from 0 to 100, with higher scores indicating a better outcome.

2.3. Statistical analyses

Descriptive statistics were used to summarize pwMS characteristics using mean and standard deviations (SD) for parametric data, while non-parametric data also included the median and interquartile range (IQR). Group comparison between those who discontinued natalizumab and those who continued were conducted using Chi-squared and Independent Samples *t*-tests for parametric categorical and continuous variables respectively, while Wilcoxon signed-ranks tests were used for non-parametric prospective PRO data to compare the visit of natalizumab infusion to PRO data completed at 7 days after natalizumab infusion. Correlations were carried out using Spearman's rank correlations. Linear mixed models were applied to assess the temporal association of

clinical and PRO measures within (dis)continuation status across three time points. Models were fitted using a random term for intercept for each subject and were adjusted for age and disease duration at time of natalizumab initiation. A two-sided *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 28.0 (IBM, Armonk, NY, USA). Matplotlib (v3.7.1) was used for data visualization.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the study population are shown in Table 1. There were total of 642 pwMS that were previously or currently treated with natalizumab included in this analysis. In particular, the population consisted of 72.7% females and had an average age at the time of starting natalizumab of 43.2 years old (SD = 10.3). The average disease duration was 13.3 years (SD = 9.1), age of symptom onset was 29.6 years old (SD = 9.4) and age at diagnosis of 32.9 years old (SD = 9.5) with 2.3 years until diagnosis. They had an average disability at 3.5 EDSS and median lower extremity limitations measured by T25FWT of 6.1 s. The PRO measures of limitations in every category are also described in Table 1 (0–100 score scale). On average, the pwMS had highest limitation in "able to stand for more than 30 minutes" (59.7 points) and lowest reported limitation in the "experiencing panic" category (91.4 points).

Overall, there was longitudinal data available for 242 pwMS treated with natalizumab within the NYSMSC database and shown in Table 2. Both the 141 pwMS that discontinued their natalizumab treatment and 101 that continued natalizumab were followed for similar amount of time (77.7 and 74.8 months, respectively). In addition to being significantly shorter time on natalizumab treatment, the 141 pwMS that discontinued their treatment were significantly older at the time of the start of the natalizumab use (44.8 vs. 42.2 years old, $p = 0.031$) when compared to pwMS that remained on natalizumab. There were no additional demographic, clinical and disability-based differences

Table 1
Demographics of all natalizumab users in NYSMSC.

Demographic and clinical characteristics	Total sample (*n* = 642)
Female, *n* (%)	467 (72.7%)
Age at symptom onset, mean (SD)	29.6 (9.4)
Age at diagnosis, mean (SD)	32.9 (9.5)
Age at start natalizumab, mean (SD)	43.2 (10.3)
Disease duration at start natalizumab, mean (SD)	13.3 (9.1)
Disease course at start natalizumab, *n* (%)	
RRMS	569 (90.5%)
SPMS	49 (7.8%)
PPMS	11 (1.7%)
EDSS at start natalizumab, mean (SD)	3.5 (1.9)
T25FW at start natalizumab, mean (SD) – median (IQR)	10.2 (19.8)–6.1 (4.5)
PROs at start natalizumab – mean (SD) – median (IQR)	
Getting up	75.2 (24.5)–70 (30)
Climbing stairs	68.5 (28.0)–70 (65)
Standing	59.7 (34.8)–70 (65)
Driving	84.4 (29.8)–100 (30)
RUL	85.1 (19.9)–100 (30)
LUL	85.8 (18.6)–100 (30)
RLL	74.8 (25.8)–80 (40)
LLL	75.1 (25.2)–80 (40)
Bowel	87.0 (19.0)–100 (20)
Bladder	79.0 (21.9)–80 (30)
Fatigue	61.6 (24.5)–60 (25)
Vision	79.3 (20.7)–80 (30)
Lonesome	86.1 (22.5)–100 (30)
Pessimism	78.0 (27.1)–100 (30)
Tense	67.1 (28.3)–70 (50)
Panic	91.4 (19.2)–100 (0)
Annoy	70.9 (26.4)–70 (50)
Morbid	88.6 (21.3)–100 (30)
Guilt	84.7 (23.9)–100 (30)

EDSS - Expanded Disability Status Scale, T25FW – Timed 25-Foot Walk, RRMS – relapsing-remitting multiple sclerosis, SPMS – secondary progressive multiple sclerosis, PPMS – primary progressive multiple sclerosis, PRO – patient reported outcomes, RUL– right upper limb, LUL – left upper limb, RLL – right lower limb, LLL – left lower limb, *n* – number, SD – standard deviation, IQR – interquartile range.
Note: This table represents all pwMS who ever reported use of natalizumab while being part of the NYSMSC. Some study participants may have started treatment before NYSMSC enrollment. For them, the enrollment visit was used as their start date. Patient reported outcomes (PRO) were calculated using the LIFEware system. Scores were Rasch-transformed, allowing for a linear comparison of data points. PRO scores range from 0 to 100, with higher scores indicating a better outcome.
Disease duration and age are shown in years. T25FW scores are shown in seconds.

Table 2
Comparing baseline clinical and demographical characteristics between natalizumab users who discontinued and continued.

Demographic and clinical characteristics	Discontinued natalizumab (*n* = 141)	Continued natalizumab (*n* = 101)	*p*-value
Female, *n* (%)	103 (73.0%)	75 (74.3%)	0.834
Age at symptom onset, mean (SD)	29.2 (8.3)	28.5 (8.8)	0.547
Age at MS diagnosis, mean (SD)	32.4 (8.7)	32.1 (8.2)	0.778
Age at start natalizumab, mean (SD)	44.8 (10.0)	42.2 (8.1)	**0.031**
Disease duration at start natalizumab, mean (SD)	15.5 (8.1)	13.4 (7.7)	0.066
Time on natalizumab, mean (SD)	14.1 (23.3)	44.4 (40.2)	**<0.001**
Time of follow-up in the study, mean (SD)	77.7 (45.0)	74.8 (42.9)	0.612
Disease course at start natalizumab, *n* (%)			0.357
RRMS	119 (86.9%)	88 (87.1%)	
SPMS	17 (12.4%)	10 (9.9%)	
PPMS	1 (0.7%)	3 (3.0%)	
EDSS at start natalizumab, mean (SD)	3.6 (1.9)	3.3 (2.1)	0.237
T25FW at start natalizumab, mean (SD)	8.9 (10.3)	9.2 (18.6)	0.883
DMT Type after natalizumab discontinuation			
Injectables	51 (36.2%)	NA	NA
Orals	30 (21.3%)		
Infusion	4 (2.8%)		
Off label	12 (8.5%)		
No DMT	44 (31.2%)		

EDSS - Expanded Disability Status Scale, T25FW – Timed 25-Foot Walk, RRMS – relapsing-remitting multiple sclerosis, SPMS – secondary progressive multiple sclerosis, PPMS – primary progressive multiple sclerosis, DMT – disease modifying therapy, *n* – number, SD – standard deviation. P-value lower than 0.05 was considered statistically significant and shown in bold.
To compare patients with multiple sclerosis (pwMS) who discontinued natalizumab treatment to those who continued, several inclusion criteria were applied. Participants were required to have initiated natalizumab treatment at a known time point (start natalizumab), have a follow-up preceding the initiation available, and have used natalizumab for at least one follow-up. Additionally, participants who discontinued natalizumab were required to have a follow-up available after discontinuation. For those who remained on natalizumab throughout the study, the most recent follow-up was used for analysis.
Disease duration and age are shown in years. Time on natalizumab and time of follow-up are shown in months. T25FW scores are shown in seconds.
The following therapies were considered injectables: Avonex, Betaseron, Copaxone, Rebif, Plegridy, Zinbryta. Orals: Aubagio, Tecfidera, Gilenya, Cladribine, Siponimod. Infusion: Tysabri, Ocrevus, Lemtrada. Off label: Cellcept, Cytoxan, Imuran, IVIG, Methotrexate, Novantrone and Rituximab.

between the pwMS that continued or discontinued their natalizumab treatment. Among the pwMS that discontinued natalizumab, 51(36.2%) transitioned to an injectable DMTs (interferon-β or glatiramer acetate), 44 (31.2%) did not start a new DMT, 30 (21.3%) to an oral DMTs, 12 (8.5%) to an off-label DMTs and 4 (2.8%) to infusion-based medication.

3.2. Clinical and PRO measures between pwMS that discontinued or continue natalizumab

The clinic and PRO measures in pwMS that discontinued or continue natalizumab use are shown in Table 3. Among both groups, a steady increase in disability as measured by EDSS and T25FWT was seen. Within pwMS that discontinue natalizumab, the EDSS went from 3.3 before treatment, 3.6 at the start of natalizumab and 4.1 after discontinuation ($p < 0.001$). Numerically smaller but significant increase was seen in the pwMS that continue natalizumab with EDSS of 2.9 before initiation, 3.3 at the time of natalizumab start and 3.5 at the most recent clinical follow-up ($p = 0.002$).

Over the period before, at the time of natalizumab start and after natalizumab discontinuation, a much greater number of domains within the PRO measures worsened within the pwMS that discontinue natalizumab when compared to the pwMS that are still on the drug (10 vs. 2 PRO domains). In particular, the pwMS that discontinued natalizumab had significant decline in PROs regarding lower extremity limitations 1) "getting up from low seat" (77.8 vs. 75.1 vs. 70.4, $p = 0.009$), 2) "climbing stairs" (69.1 vs. 67.2 vs. 62.3, $p = 0.026$) and 3) "standing for

Table 3
Temporal assessment of clinical and PROs in pwMS who discontinued and continued natalizumab.

	Discontinued ($n = 141$)				Continued ($n = 101$)			
	Visit before initiation	Initiation Visit	Visit after discontinuation	Mixed effect *p*-value	Visit before initiation	Initiation Visit	Most recent follow-up	Mixed-effect *p*-value
EDSS, mean (SD)	3.3 (1.9)	3.6 (1.9)	4.1 (2.1)	**<0.001**	2.9 (1.9)	3.3 (2.1)	3.5 (2.0)	**0.002**
T25FW, mean (SD), median (IQR)	7.3 (3.9)–6.1 (3.5)	8.9 (10.3)–6.0 (4.9)	12.6 (23.0)–6.5 (6.4)	**0.003**	6.3 (3.2)–5.2 (2.8)	9.2 (18.6)–5.6 (3.6)	15.8 (35.7)–6.0 (6.2)	**0.003**
Patient-reported outcomes, mean (SD), median (IQR)								
Getting up	77.8 (23.3)–70 (30)	75.1 (24.0)–70 (30)	70.4 (26.9)–70 (30)	**0.009**	79.6 (25.2)–100 (30)	76.7 (23.9)–70 (30)	77.6 (27.2)–70 (30)	0.666
Climbing stairs	69.1 (25.7)–70 (30)	67.2 (25.4)–70.0 (65)	62.3 (30.9)–70 (65.0)	**0.026**	72.5 (28.8)–70 (30)	71.7 (27.2)–70 (30)	69.9 (31.2)–70 (30)	0.898
Standing	61.2 (34.1)–70 (65)	55.8 (34.9)–70 (65)	50.8 (37.0)–35.0 (35.0)	**<0.001**	64.2 (33.2)–70 (65)	64.1 (35.0)–70 (65)	59.9 (35.1)–70 (65.0)	0.170
Driving	85.8 (25.1)–100 (30)	87.3 (24.1)–100 (30)	82.6 (29.5)–100 (30)	0.470	84.6 (30.6)–100 (30)	86.4 (28.5)–100 (22.5)	84.0 (32.4)–100 (30)	0.897
RUL	88.4 (20.3)–100 (20)	86.8 (18.9)–100 (20)	83.9 (19.6)–80 (30)	0.068	89.1 (15.8)–100 (20)	86.0 (19.2)–100 (30)	90.8 (17.3)–100 (20)	0.151
LUL	88.6 (16.1)–100 (20)	89.2 (14.7)–100 (30)	84.8 (19.1)–100 (30)	**0.035**	90.3 (15.3)–100 (20)	87.8 (16.9)–100 (20)	88.7 (17.9)–100 (20)	0.446
RLL	79.9 (20.5)–80 (30)	75.0 (25.1)–80 (40)	71.6 (28.2)–80 (45.0)	**<0.001**	81.3 (22.6)–100 (37.5)	78.6 (22.9)–80 (40)	80.5 (25.4)–80 (30)	0.403
LLL	78.3 (20.1)–80 (37.5)	76.4 (23.2)–80 (40)	73.2 (26.5)–80 (45.0)	**0.015**	80.5 (24.7)–100 (40)	77.1 (26.1)–80 (40)	78.1 (26.4)–80 (40)	0.635
Bowel	89.5 (16.5)–100 (20)	87.2 (17.3)–100 (20)	85.8 (21.0)–100 (20)	**0.049**	91.9 (13.6)–100 (20)	85.8 (20.3)–100 (30)	86.3 (21.6)–100 (20)	**0.009**
Bladder	81.0 (19.9)–80 (30)	78.9 (21.5)–80 (37.5)	73.4 (25.3)–70 (40)	**<0.001**	84.1 (21.9)–100 (30)	77.7 (24.1)–80 (40)	79.9 (25.1)–80 (30)	**0.035**
Fatigue	61.8 (22.4)–60 (25)	62.9 (24.2)–60 (25)	57.8 (23.6)–60 (15.0)	0.192	65.1 (26.5)–70 (25)	66.7 (23.0)–60 (25)	67.7 (23.6)–70 (25)	0.205
Vision	78.8 (16.5)–80 (30)	81.0 (17.3)–80 (30)	78.5 (18.2)–80 (30)	**0.006**	81.8 (20.1)–80 (30)	81.9 (21.6)–80 (30)	83.9 (18.5)–100 (30)	0.450
Lonesome	90.3 (18.4)–100 (0)	91.2 (16.9)–100 (0)	85.8 (24.3)–100 (30)	**0.034**	86.3 (23.2)–100 (30)	84.9 (22.9)–100 (30)	89.4 (19.8)–100 (30)	0.999
Pessimism	79.9 (26.8)–100 (30)	81.0 (23.9)–100 (30)	80.4 (24.3)–100 (30)	0.747	78.2 (25.9)–70 (30)	80.6 (24.8)–100 (30)	84.2 (26.9)–100 (30)	0.227
Tense	68.4 (28.4)–70 (50)	73.1 (24.5)–70 (50)	70.3 (26.9)–70 (50)	0.567	68.4 (28.4)–70 (50)	68.4 (28.2)–70 (50)	70.3 (27.3)–70 (50)	0.813
Panic	92.8 (16.3)–100 (0)	94.3 (13.5)–100 (0)	91.5(17.0)–100 (0)	0.328	90.9 (19.5)–100 (0)	94.3 (17.2)–100 (0)	93.9 (15.4)–100 (0)	0.056
Annoy	69.2 (26.8)–70 (50)	71.6 (24.4)–70 (50)	71.7(25.8)–70 (50)	0.165	68.3 (26.9)–70 (0)	73.0 (25.6)–70 (50)	74.7 (24.5)–70 (0)	0.061
Morbid	90.5 (20.2)–100 (0)	91.7 (17.7)–100 (0)	91.7 (18.2)–100 (0)	0.404	88.2 (21.9)–100 (30)	90.4 (18.9)–100 (22.5)	92.2 (15.9)–100 (0)	0.594
Guilt	87.6 (23.2)–100 (30)	88.0 (22.1)–100 (30)	87.1 (22.9)–100 (30)	0.987	83.5 (25.0)–100 (0)	86.3 (24.4)–100 (30)	89.6 (20.4)–100 (0)	0.141

EDSS - Expanded Disability Status Scale, T25FW – Timed 25-Foot Walk, RRMS – relapsing-remitting multiple sclerosis, SPMS – secondary progressive multiple sclerosis, PPMS – primary progressive multiple sclerosis. P-value lower than 0.05 was considered statistically significant and shown in bold.
Note: To compare patients with multiple sclerosis (pwMS) who discontinued natalizumab treatment to those who continued, several inclusion criteria were applied. Participants were required to have initiated natalizumab treatment at a known time point (initiation visit), have a follow-up preceding the initiation available, and have used natalizumab for at least one follow-up. Additionally, participants who discontinued natalizumab were required to have a follow-up available after discontinuation. For those who remained on natalizumab throughout the study, the most recent follow-up was used for analysis.
Patient reported outcomes (PRO) were calculated using the LIFEware system. Scores were Rasch-transformed, allowing for a linear comparison of data points. PRO scores range from 0 to 100, with higher scores indicating a better outcome.
Linear mixed models were used to assess the temporal association of clinical and PRO measures within (dis)continuation status. Reported statistical significance compare the change, within (dis)continuation status, across the three time points. Mixed-effects models were fit using a random term for intercept for each subject and were adjusted for age and disease duration at time of natalizumab initiation.

more than 30 minutes" (61.2 vs. 55.8 vs. 50.8, $p < 0.001$). Similar findings were seen for PROs related to motor limitations in each extremality, where pwMS that discontinued natalizumab reported decline in left upper extremality (88.6 vs. 89.2 vs. 84.8, $p = 0.035$), right lower extremity (79.9 vs. 75.0 vs. 71.6, $p < 0.001$) and left lower extremity (78.3 vs. 76.4 vs. 73.2, $p = 0.015$). Decline in bowel (89.5 vs. 87.2 vs. 85.8, $p = 0.049$) and bladder control (81.0 vs. 78.9 vs. 73.4, $p < 0.001$) were also reported. Last but not least, pwMS that discontinued natalizumab had decline in PRO measure of feeling lonesome, especially after the drug discontinuation (90.3 vs. 91.2 vs. 85.8, $p = 0.034$).

On the contrary, the pwMS that continue on natalizumab had improvement in bowel and bladder control from the time of the natalizumab start to the latest follow-up (91.9 vs. 85.8 vs. 86.3, $p = 0.009$ and 84.1 vs. 77.7 vs. 79.9, $p = 0.035$, respectively). All remaining measures remained stable throughout the entire follow-up period.

Similar analyses investigating the trajectory of PRO measures between the two groups are shown in Table 4. The decision to continue or discontinue natalizumab had significant effect on the change in right upper extremity limitation ($p = 0.023$), and the rate of reported feelings regarding panic ($p = 0.04$), but favoring pwMS that continue their natalizumab treatment. The differences in these trajectories are shown also in Fig. 1.

3.3. Prospective cohort investigating PRO changes before and after natalizumab infusion (7-days post-infusion)

The demographic and clinical characteristics of the prospective pwMS group that was treated with natalizumab are shown in Table 5.

Table 4
Temporal assessment of the impact of natalizumab (dis)continuation on clinical and patient reported outcomes.

		Discontinued $n = 141$		Continued $n = 101$			Group x time mixed effect model
	Visit before initiation	Initiation Visit	Visit after discontinuation	Visit before initiation	Initiation Visit	Most recent follow-up	*p*-value
EDSS, mean (SD)	3.3 (1.9)	3.6 (1.9)	4.1 (2.1)	2.9 (1.9)	3.3 (2.1)	3.5 (2.0)	0.263
T25FW, mean (SD), median (IQR)	7.3 (3.9)–6.1 (3.5)	8.9 (10.3)–6.0 (4.9)	12.6 (23.0)–6.5 (6.4)	6.3 (3.2)–5.2 (2.8)	9.2 (18.6)–5.6 (3.6)	15.8 (35.7)–6.0 (6.2)	0.210
Patient reported outcomes, mean (SD), median (IQR)							
Getting up	77.8 (23.3)–70 (30)	75.1 (24.0)–70 (30)	70.4 (26.9)–70 (30)	79.6 (25.2)–100 (30)	76.7 (23.9)–70 (30)	77.6 (27.2)–70 (30)	0.157
Climbing stairs	69.1 (25.7)–70 (30)	67.2 (25.4)–70.0 (65)	62.3 (30.9)–70 (65.0)	72.5 (28.8)–70 (30)	71.7 (27.2)–70 (30)	69.9 (31.2)–70 (30)	0.112
Standing	61.2 (34.1)–70 (65)	55.8 (34.9)–70 (65)	50.8 (37.0)–35.0 (35.0)	64.2 (33.2)–70 (65)	64.1 (35.0)–70 (65)	59.9 (35.1)–70 (65.0)	0.136
Driving	85.8 (25.1)–100 (30)	87.3 (24.1)–100 (30)	82.6 (29.5)–100 (30)	84.6 (30.6)–100 (30)	86.4 (28.5)–100 (22.5)	84.0 (32.4)–100 (30)	0.591
RUL	88.4 (20.3)–100 (20)	86.8 (18.9)–100 (20)	83.9 (19.6)–80 (30)	89.1 (15.8)–100 (20)	86.0 (19.2)–100 (30)	90.8 (17.3)–100 (20)	**0.023**
LUL	88.6 (16.1)–100 (20)	89.2 (14.7)–100 (30)	84.8 (19.1)–100 (30)	90.3 (15.3)–100 (20)	87.8 (16.9)–100 (20)	88.7 (17.9)–100 (20)	0.391
RLL	79.9 (20.5)–80 (30)	75.0 (25.1)–80 (40)	71.6 (28.2)–80 (45.0)	81.3 (22.6)–100 (37.5)	78.6 (22.9)–80 (40)	80.5 (25.4)–80 (30)	0.086
LLL	78.3 (20.1)–80 (37.5)	76.4 (23.2)–80 (40)	73.2 (26.5)–80 (45.0)	80.5 (24.7)–100 (40)	77.1 (26.1)–80 (40)	78.1 (26.4)–80 (40)	0.194
Bowel	89.5 (16.5)–100 (20)	87.2 (17.3)–100 (20)	85.8 (21.0)–100 (20)	91.9 (13.6)–100 (20)	85.8 (20.3)–100 (30)	86.3 (21.6)–100 (20)	0.389
Bladder	81.0 (19.9)–80 (30)	78.9 (21.5)–80 (37.5)	73.4 (25.3)–70 (40)	84.1 (21.9)–100 (30)	77.7 (24.1)–80 (40)	79.9 (25.1)–80 (30)	0.350
Fatigue	61.8 (22.4)–60 (25)	62.9 (24.2)–60 (25)	57.8 (23.6)–60 (15.0)	65.1 (26.5)–70 (25)	66.7 (23.0)–60 (25)	67.7 (23.6)–70 (25)	0.067
Vision	78.8 (16.5)–80 (30)	81.0 (17.3)–80 (30)	78.5 (18.2)–80 (30)	81.8 (20.1)–80 (30)	81.9 (21.6)–80 (30)	83.9 (18.5)–100 (30)	0.779
Lonesome	90.3 (18.4)–100 (0)	91.2 (16.9)–100 (0)	85.8 (24.3)–100 (30)	86.3 (23.2)–100 (30)	84.9 (22.9)–100 (30)	89.4 (19.8)–100 (30)	0.170
Pessimism	79.9 (26.8)–100 (30)	81.0 (23.9)–100 (30)	80.4 (24.3)–100 (30)	78.2 (25.9)–70 (30)	80.6 (24.8)–100 (30)	84.2 (26.9)–100 (30)	0.266
Tense	68.4 (28.4)–70 (50)	73.1 (24.5)–70 (50)	70.3 (26.9)–70 (50)	68.4 (28.4)–70 (50)	68.4 (28.2)–70 (50)	70.3 (27.3)–70 (50)	0.841
Panic	92.8 (16.3)–100 (0)	94.3 (13.5)–100 (0)	91.5(17.0)–100 (0)	90.9 (19.5)–100 (0)	94.3 (17.2)–100 (0)	93.9 (15.4)–100 (0)	**0.040**
Annoy	69.2 (26.8)–70 (50)	71.6 (24.4)–70 (50)	71.7(25.8)–70 (50)	68.3 (26.9)–70 (0)	73.0 (25.6)–70 (50)	74.7 (24.5)–70 (0)	0.597
Morbid	90.5 (20.2)–100 (0)	91.7 (17.7)–100 (0)	91.7 (18.2)–100 (0)	88.2 (21.9)–100 (30)	90.4 (18.9)–100 (22.5)	92.2 (15.9)–100 (0)	0.901
Guilt	87.6 (23.2)–100 (30)	88.0 (22.1)–100 (30)	87.1 (22.9)–100 (30)	83.5 (25.0)–100 (0)	86.3 (24.4)–100 (30)	89.6 (20.4)–100 (0)	0.230

EDSS - Expanded Disability Status Scale, T25FW – Timed 25-Foot Walk, RUL– right upper limb, LUL – left upper limb, RLL – right lower limb, LLL – left lower limb, SD – standard deviation, IQR – interquartile range. P-value lower than 0.05 was considered statistically significant and shown in bold.
Patient reported outcomes (PRO) were calculated using the LIFEware system. Scores were Rasch-transformed, allowing for a linear comparison of data points. PRO scores range from 0 to 100, with higher scores indicating a better outcome.
Longitudinal linear mixed models were used to describe the temporal association of clinical measures between (dis)continuation status. Reported statistical significances are of the interaction term (discontinuation status by clinical or PRO measure) representing a difference in the clinical and PRO outcome measure over time -from the visit before natalizumab initiation, to initiation, to the visit after discontinuation or most recent follow-up depending on group-. Mixed-effects models were fit using a random term for intercept for each subject and were adjusted for age and disease duration.

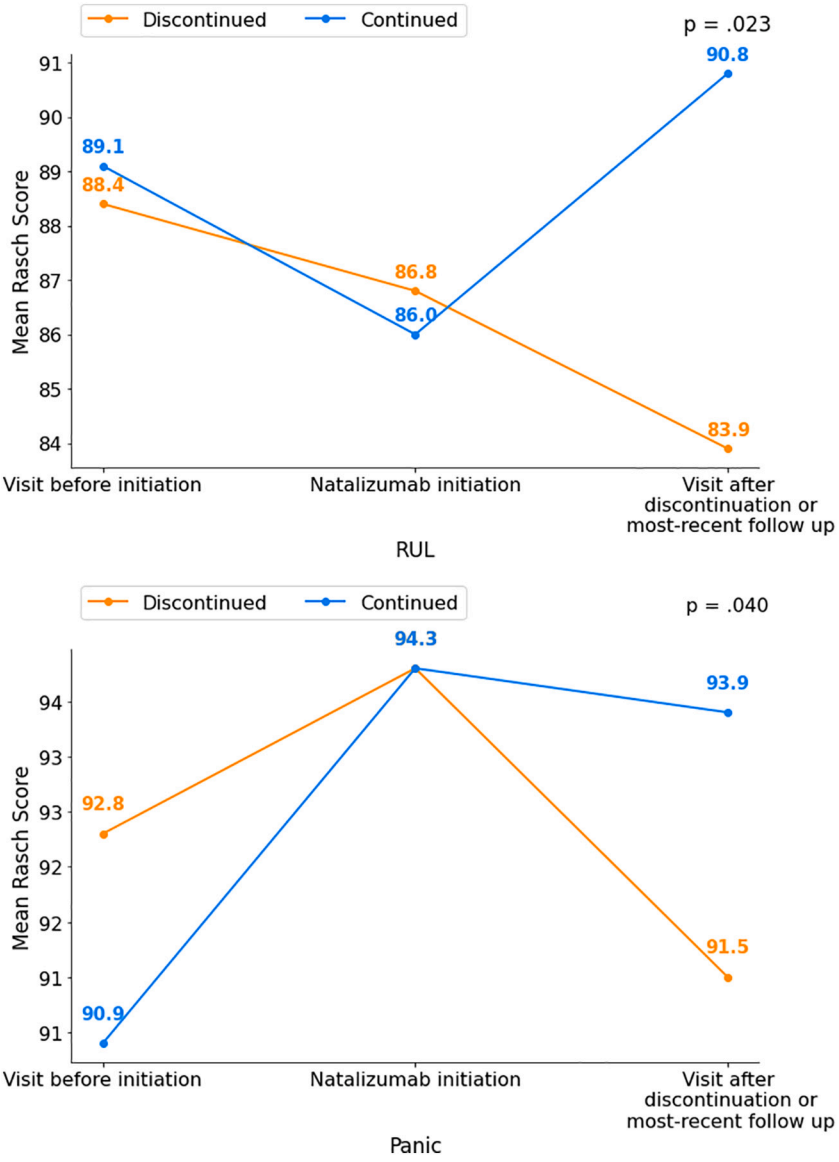

Fig. 1. Differences in longitudinal trajectories in patient reported outcomes in pwMS that discontinue or continue natalizumab during their time in the NYSMSC. PwMS – people with multiple sclerosis Only significant findings are shown.

Total of 67 pwMS were enrolled, with 74.6% being female and average age of 47.5 years old (SD = 12.3) and average age at the time of natalizumab start of 39.7 years old (SD = 10.9). The population had an average age at symptom onset of 31.0 years old (SD = 10.4), average age at MS diagnosis of 32.9 (SD = 10.8) and average disease duration at the time of natalizumab start of 8.8 years (SD = 7.9) and 16.6 years at the time of enrollment (SD = 9.4). The majority of pwMS were RRMS (97.0%) with an average of 69.9 natalizumab infusions and average infusion interval of 6.1 weeks (SD = 1.3). The disability at the time of start of natalizumab as DMT and at the time of enrollment were similar (EDSS of 2.9 and 3.1 and T25FWT of 6.4 and 6.7 s).

The pair-wise comparison of PRO measures when acquired at the time of the natalizumab infusion and 7 days after the infusion are shown in Table 6. After the infusion, the pwMS experienced improvement in PRO measures of fatigue (62.8 vs. 66.4, $p = 0.019$), bladder limitations (80.3 vs. 85.0, $p = 0.012$), and feelings of lonesomeness (81.2 vs. 88.0, $p = 0.009$). Although numerical improvements in other PRO domains were noted, these changes did not reach statistical significance. Bar graph showing the improvement in the PRO domains is shown in Fig. 2.

The PRO score at the time of infusion and 7 days later were not correlated with the total number of infusions and with the interval of the natalizumab infusions. (data not shown).

4. Discussion

The findings from the retrospective and prospective natalizumab groups were multifold. In particular, pwMS that remained on natalizumab treatment experienced improvement in multiple PRO measure when compared to uniform decline in PROs in pwMS that discontinued the treatment and transition to other DMTs. Secondly, receiving natalizumab treatment at the infusion center resulted with significant short-term improvement in multiple PRO measures, encompassing lonesomeness, fatigue and bladder function. The implications of these findings and comparison to the literature are discussed hereafter.

A larger analyses derived from the Australian MS Longitudinal study demonstrated that treatment with natalizumab results with superior improvements on PRO measures (sensory symptoms, feelings of anxiety, sexual dysfunction, bladder problems, difficulty with balance and vision problems) when compared to other DMTs [21]. We further corroborate these findings and show that pwMS that continue natalizumab have

Table 5
Demographic and clinical characteristics of the prospective cohort.

Demographic and clinical characteristics	Prospective cohort ($n = 67$)
Female, *n* (%)	50 (74.6%)
Age at symptom onset, mean (SD)	31.0 (10.4)
Age at diagnosis, mean (SD)	32.9 (10.8)
Age at start natalizumab, mean (SD)	39.7 (10.9)
Disease duration at start natalizumab, mean (SD)	8.8 (7.9)
Age at study enrollment	47.5 (12.3)
Disease duration at study enrollment	16.6 (9.4)
Disease course at start natalizumab, *n* (%)	
RRMS	65 (97.0%)
SPMS	2 (3.0%)
Infusion interval at start natalizumab	4.0 (0.3)
Infusion interval at study enrollment	6.1 (1.3)
Total number of infusions	69.9 (46.8)
EDSS at start natalizumab, mean (SD)	2.9 (1.8)
EDSS at study enrolment, mean (SD)	3.1 (1.9)
T25FW at start natalizumab, mean (SD) – median (IQR)	6.4 (3.8) – 5.6 (2.2)
T25FW at study enrolment, mean (SD) – median (IQR)	6.7 (6.6) – 5.1 (2.1)

RRMS – relapsing-remitting multiple sclerosis, SPMS – secondary progressive multiple sclerosis, EDSS - Expanded Disability Status Scale, T25FW – Timed 25-Foot Walk, SD – standard deviation, IQR – interquartile range.
Note: EDSS and T25FW scores were determined through chart review where a data point closest to natalizumab initiation, and study enrollment was used. Disease duration and age are shown in years, infusion interval is shown in weeks, and T25FW scores are shown in seconds.

Table 6
Short term change in patient-reported outcomes in people with multiple sclerosis treated with natalizumab.

Prospective cohort ($n = 67$)			
Patient reported outcomes, mean (SD), median (IQR)	Visit at infusion	7 days after natalizumab infusion	Paired *p*-value
Getting up	77.5 (26.1)–70.0 (30.0)	77.5 (26.1)–70.0 (30.0)	0.658
Climbing stairs	68.9 (30.6)–70.0 (65.0)	68.4 (30.4)–70.0 (30.0)	0.714
Standing	62.1 (34.0)–70.0 (65.0)	64.2 (33.3)–70.0 (65.0)	0.390
Driving	87.2 (4.3)–100.0 (0.0)	84.6 (4.5)–100.0 (30.0)	0.558
RUL	86.2 (15.8)–80.0 (20.0)	84.8 (17.7)–100.0 (30.0)	0.473
LUL	81.3 (20.8)–80.0 (30.0)	81.6 (23.0)–80.0 (30.0)	0.674
RLL	74.4 (24.1)–80.0 (40.0)	75.8 (23.9)–80.0 (40.0)	0.275
LLL	72.4 (22.9)–70.0 (40.0)	72.2 (27.2)–80.0 (40.0)	0.622
Bowel	86.6 (2.6)–100.0 (30.0)	86.4 (2.6)–100.0 (30.0)	0.664
Bladder	80.3 (20.8)–80.0 (40.0)	85.0 (18.3)–100.0 (30.0)	**0.012**
Fatigue	62.8 (22.4)–70.0 (15.0)	66.4 (22.3)–70.0 (20.0)	**0.019**
Vision	82.1 (15.4)–80.0 (30.0)	81.5 (19.6)–80.0 (30.0)	0.930
Lonesome	81.2 (21.0)–100.0 (30.0)	88.0 (19.6)–100.0 (30.0)	**0.009**
Pessimism	75.7 (23.3)–70.0 (40.0)	77.8 (22.8)–70.0 (30.0)	0.406
Tense	71.0 (21.7)–70.0 (50.0)	73.6 (25.0)–70.0 (50.0)	0.625
Panic	89.8 (16.3)–100.0 (30.0)	92.2 (15.4)–100.0 (0.0)	0.250
Annoy	74.4 (22.5)–70.0 (35.0)	75.0 (23.1)–70.0 (30.0)	0.656
Morbid	89.4 (17.5)–100.0 (30.0)	87.8 (18.4)–100.0 (30.0)	0.560
Guilt	86.4 (17.6)–100.0 (30.0)	84.8 (20.6)–100.0 (30.0)	0.351

RUL– right upper limb, LUL – left upper limb, RLL – right lower limb, LLL – left lower limb, SD – standard deviation, IQR – interquartile range. P-value lower than 0.05 was considered statistically significant and shown in bold.
Note: Patient reported outcomes (PRO) were calculated using the LIFEware system. PRO scores range from 0 to 100, with higher scores indicating a better outcome.
Wilcoxon signed-ranks tests were carried out to compare PROs at the visit of natalizumab infusion to PROs completed 7 days after natalizumab infusion. Due to missing post infusion data for some patients, the analyses are only conducted using those with complete data at both time points. The sample sizes are as follows: $n = 51$ for getting up, climbing stairs, rul, lul, rll, lll, bowel. $n = 50$ for standing, tense, panic, annoy, morbid, guilt. $n = 49$ for bladder, fatigue, vision, lonesome, pessimism. $n = 48$ for driving.

better outcomes in the same exact domains when compared to pwMS that discontinue the drug. Moreover, pwMS that were treated with natalizumab had significantly smaller work productivity loss over time, largely driven by decreasing the absenteeism [21]. The improvement in absenteeism and work productivity was also been seen in 1-yearlong study of natalizumab treated pwMS that had high baseline disease activity [22]. The positive effect of natalizumab on reports of fatigue are also seen in the literature [23,24]. For example, 1-year treatment of natalizumab within the single-arm phase IV TYNERGY study resulted with significant improvement in the fatigue levels, a change that was attributed to improvement in depressive feelings and improvement in sleep quality [23]. The positive impact of natalizumab has been documented even after only 3 consecutive infusions [24]. Moreover, the therapeutic lag of natalizumab is smaller, with the greatest reduction in ARR occurring within the first 3 months of treatment initiation [25,26]. Another study also reported subjective improvement in the sexual dysfunction within 24 weeks of starting natalizumab therapy [27]. In our study, these changes were present despite the fact that almost all pwMS were treated with an extended interval between the infusions. The large NOVA trial (NCT03689972) that investigated the effectiveness and safety of 6-week dosing interval also demonstrated that there were no significant differences resulting from the additional 2-week extension [28]. The EuroQol 5 Dimensions (EQ-5D-5 L) system was the only exception, where higher portion of pwMS in the Q6 dosing experienced worsening when compared to the Q4 interval [28].

One main question from this manuscript is the clinical relevance of the data presented. Since pwMS that are continuously treated with natalizumab exhibited consistent improvement in objective and subjective disease outcomes, even greater efforts towards better safety monitoring and PML stratification are needed. A recent PML-based genetic susceptibility study has been suggested that four specific genetic variants can be associated with 8.7 times greater risk for this severe adverse event [29]. Coupled with extended interval dosing, the determination of the presence or absence of these risk alleles within the C8B, LY9, FCN2 and STXBP2 genes (all genes implicated in the immune system's viral defense mechanisms) could aid the clinical decision making and potentially allowing long-term natalizumab use in pwMS with low PML risk [29]. Moreover, the study demonstrates that the benefit from natalizumab treatment could be multifaceted, with PROs having the potential to capture changes that can be easily measured in the clinical routine.

Two main subjective phenomena related to natalizumab treatment have been reported and investigated in the literature. For example, a recent short survey-based study suggests that pwMS treated with natalizumab report significantly greater rate of having "feel-good experience" when compared to other MS-based DMTs [30]. On the contrary, the multiple studies frequently report of an natalizumab wearing-off effect, finding that is largely inconsistent and not seen in our population. This self-reported "wearing-off' effect does not correlate with the drug concentration or with the saturation of alpha-4 integrin receptors [31]. Interestingly, larger portion of pwMS that were treated every 4 weeks report "wearing off" effect when compared to pwMS treated with extended 6-week interval [31]. The concept of "wearing off" was also

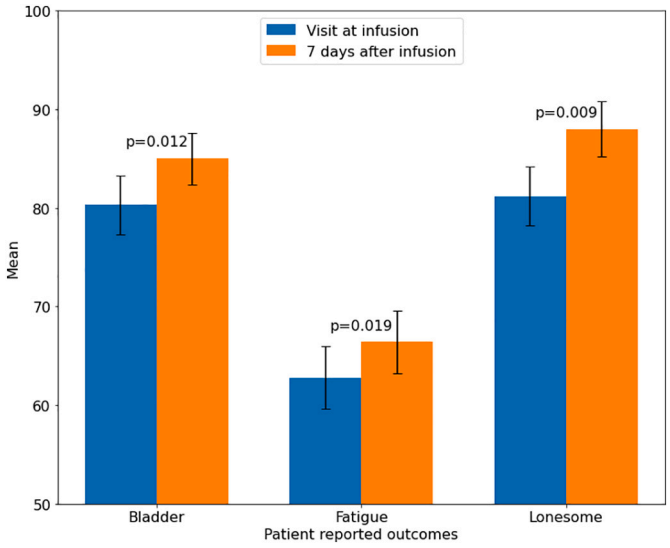

Fig. 2. Bar plots describing changes in patient-reported outcomes in pwMS before and 7 days after natalizumab infusion.
PwMS – people with multiple sclerosis. The y-axis provides the mean Rasch score. Only significant findings are shown.

tested during the COVID-19 pandemic when the intervals were extended from 4-week to 6-week infusions [32]. In a Norwegian group of 30 RRMS pwMS, the extended interval resulted with 50% of pwMS reporting "wearing off" phenomenon with decrease in receptor occupancy in 9 out of 11 leukocyte subtypes (non-statistical decrease) [32]. US-based study also showed that the end of dosing interval is reported in up to two-thirds of pwMS with recrudescence of fatigue, weakness, walking impairment, or cognitive difficulties [33]. The observed improvement in PRO in our study right after the natalizumab infusion could be attributed to this well-described feeling of "feel-good experience". The improvement of all subjective measures and particularly of the lonesomeness category could be attributed to the social interactions with the nursing staff and fellow pwMS at the infusion center. It provides them an opportunity to socialize with people with similar difficulties that could attribute towards greater self-reflection and higher value of the current well-being. The future clinical implementation and the interpretation of longitudinal changes in our PRO measures are currently limited by lack of studies that determine what amount of change is clinically meaningful. In our future studies we should aim at determining the minimal detectable change (MDC) and the minimal clinically important difference (MCID) of the LIFEware questionnaire and each subcomponent of the questionnaire.

Our study does have several limitations worth mentioning. Firstly, the reason for natalizumab discontinuation was not systematically collected in the NYSMSC database and could impact the interpretation regarding the pwMS that discontinue the medication. A large portion of pwMS did not switch to any DMT or switched to moderate efficacy medication (injectable DMTs such as interferon-β or glatiramer acetate). The lack of expected effectiveness, increased risk of severe adverse events and older age may represent the majority of the reasons for these natalizumab discontinuations. This perceived lack of efficacy in the midst of ongoing progression may partially influence the differences in disability trajectories between the pwMS that discontinue natalizumab or remain on the drug. The MS care provider may have already established that the pwMS no longer benefits from natalizumab and decided to discontinue the medication (neurologist indicated change). However, the natalizumab discontinuation due to lack of efficacy is a very rare occurrence in the clinical practice, with most of the discontinuations being indicated to the increased risk of PML (high JCV titer) or due to other safety-related concerns. This limitation can be concretely addressed by randomized discontinuation from the drug, data that is currently not available for the MS literature. Although only numerically lower, the pwMS that remained on natalizumab were less disabled when compared to the discontinuers. The sole fact of lower disability could have contributed to better PRO measures. That said, the same finding could be of favor to natalizumab treatment and its ability to sustain long-term disease stability and prevent further disability progression. Although the PRO questionnaire was administered just before the natalizumab infusion and 7 days after, it did not specifically inquire about presence of wearing off phenomenon. Moreover, these findings are based only one 7-day cycle and should be corroborated over several infusion cycles. Another limitation regarding the prospective part of the study is the lack of differentiation regarding the source of the positive effect (drug vs. social environment). Lastly, the study did include small percentage of progressive pwMS that were exposed to natalizumab. Due to the small sample size, we were not able to perform phenotype-specific analysis. Interestingly, in the phase 3 trial of natalizumab use in progressive MS (ASCEND trial) where natalizumab failed to reach the main efficacy outcomes, it did show that it improved mental health-related QoL [34]. These findings remain as the most concrete evidence of natalizumab improving the PRO even in the progressive stage of the disease.

In conclusion, pwMS that are able to continue their long-term natalizumab treatment have improvement or stable trajectory in PRO measures when compared to the significant decline seen in pwMS that discontinue natalizumab. PwMS treated with natalizumab experience improvement in fatigue, lower lonesomeness and bladder problems right after their infusion. These findings further consolidate the positive impact of natalizumab on subjective well-being.

Disclosures

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CRediT authorship contribution statement

Dejan Jakimovski: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Katelyn S. Kavak:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – review & editing, Visualization, Supervision, Project administration. **Karen Zakalik:** Investigation, Data

curation, Writing – review & editing, Project administration. **Corey McGraw:** Investigation, Writing – review & editing, Project administration. **Malcolm Gottesman:** Investigation, Writing – review & editing, Project administration. **Patricia K. Coyle:** Investigation, Data curation, Writing – review & editing, Project administration. **Robert Zivadinov:** Investigation, Writing – review & editing, Project administration. **Bianca Weinstock-Guttman:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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