MSJ Experimental Translational Clinical

Original Research Paper

Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: Results from MS PATHS

Multiple Sclerosis Journal—Experimental, Translational and Clinical

April–June 2021, 1–13

DOI: 10.1177/20552173211004634

Carrie M Hersh, Bernd Kieseier, Carl de Moor, Deborah M Miller, Denise Campagnolo, James R Williams, Kathryn C Fitzgerald, Kuangnan Xiong, Marisa P McGinley, Megan Hyland, Richard A Rudick, Tjalf Ziemssen and Irene Koulinska

Abstract

Background: Optimizing multiple sclerosis treatment warrants understanding of changes in physical, mental, and social health.

Objective: To assess the impact of natalizumab on Quality of Life in Neurological Disorders (Neuro-QoL) scores.

Methods: Annualized change in T-scores and likelihood of ≥5-point improvement over baseline were calculated for each Neuro-QoL domain after natalizumab initiation. Comparisons with ocrelizumab-treated patients were conducted after propensity score weighting and adjustment for relevant co-medications, year, and drug-year interaction.

Results: Among 164 natalizumab patients analyzed, 8 of 12 Neuro-QoL domains improved significantly, with greater improvement in patients with abnormal baseline Neuro-QoL. In the subgroup comparison of natalizumab-treated ($n = 145$) and ocrelizumab-treated ($n = 520$) patients, significant improvement occurred in 9 of 12 and 4 of 12 domains, respectively. The difference between groups was statistically significant for positive affect and well-being ($p = 0.02$), sleep ($p = 0.003$), and satisfaction with social roles and activities (SRA) ($p = 0.03$) in the overall population and for emotional and behavioral dyscontrol ($p = 0.01$), participation in SRA ($p = 0.0001$), and satisfaction with SRA ($p = 0.02$) in patients with abnormal baseline Neuro-QoL.

Conclusions: Natalizumab can produce clinically meaningful improvements in mental and social health. Such improvements are unlikely to be primarily driven by expectation bias, as their magnitude exceeded improvements with another high-efficacy therapy, ocrelizumab.

Keywords: Natalizumab, Neuro-QoL, fatigue, sleep, depression, multiple sclerosis

Date received: 2 February 2021; accepted: 3 March 2021

Introduction

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disease typically characterized by progressive physical and cognitive worsening with a substantial impact on different aspects of personal and social life. Health-related quality of life (HRQoL) is lower in MS patients compared with the general population and patients with other chronic diseases.[1–5]

Natalizumab, a monoclonal antibody against very-late-activation antigen 4, reduces central inflammatory activity in MS and can lead to improvements in HRQoL in both real-world and clinical-trial settings.[6–10] Many natalizumab-treated patients anecdotally report a "feel-good effect," which has not been well characterized clinically or physiologically. Patient interview-based studies suggest that the "feel-good effect" might reflect improved depression and fatigue and an overall perception of well-being and energy.[11,12]

In the current study, we investigated the patient-reported experience with natalizumab using Neuro-QoL (Quality

Correspondence to:
Irene Koulinska,
Biogen, 225 Binney Street Cambridge, MA 02142, USA.
james.williams@biogen.com

Carrie M Hersh,
Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV, USA

Bernd Kieseier, Carl de Moor,
Biogen, Cambridge, MA, USA, at the time of these analyses

Biogen, Cambridge, MA, USA

Deborah M Miller, Mellen Center, Cleveland Clinic Main Campus, Cleveland, OH, USA

Denise Campagnolo, **James R Williams**, Biogen, Cambridge, MA, USA

Kathryn C Fitzgerald, Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

Kuangnan Xiong, Biogen, Cambridge, MA, USA, at the time of these analyses

Marisa P McGinley, Mellen Center, Cleveland Clinic Main Campus, Cleveland, OH, USA

Megan Hyland, Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA

Richard A Rudick, Biogen, Cambridge, MA, USA, at the time of these analyses

Tjalf Ziemssen, Department of Neurology, Multiple Sclerosis Center and Neuroimmunological Laboratory, University Clinic Carl-Gustav Carus, Dresden, Germany

Irene Koulinska, Biogen, Cambridge, MA, USA, at the time of these analyses

of Life in Neurological Disorders), a comprehensive self-reported battery of assessments across 12 neurological domains related to physical, mental, and social health[13] previously validated in patients with MS.[14]

We conducted several sensitivity analyses to better understand the clinical meaningfulness of our findings. First, we assessed the magnitude of improvement in individual Neuro-QoL domains by using a predefined threshold of clinical meaningfulness. Then, we investigated whether patients with baseline impairment in each Neuro-QoL domain were more likely to experience improvement than patients without baseline impairment. Last, we sought to understand whether expectation bias, which can occur when patients switch to a new therapy, may be primarily responsible for the observed improvements in Neuro-QoL with natalizumab. To this end, we compared the effect of natalizumab on Neuro-QoL to that of another high-efficacy therapy for MS—ocrelizumab—in a subgroup of patients with balanced baseline characteristics.

Methods

Study population

Data were collected using the previously validated Multiple Sclerosis Performance Test (MSPT)[15,16] at routine patient visits in the large real-world MS cohort known as MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) as of August 2019.[17] At each visit, patient demographics and disease history, use of disease-modifying therapy (DMT), PDDS (Patient Determined Disease Steps),[18] and neuroperformance outcomes were collected along with a computer-adaptive version of the Neuro-QoL. Patients consented to the sharing of pseudoanonymized data with the network investigators and sponsor, and it was approved by all site institutional review boards. We identified patients who initiated natalizumab after enrollment in MS PATHS and had at least one Neuro-QoL assessment in the prior year. Baseline assessment was defined as the last Neuro-QoL measurement recorded within one year prior to the patient's first reporting being on natalizumab.

Neuro-QoL assessments

Patients completed computer-adaptive Neuro-QoL assessments for the following 12 domains: physical function (upper and lower extremities), physical symptoms (sleep disturbance and fatigue), emotional health (anxiety, depression, positive affect and well-being, emotional and behavioral dyscontrol, and stigma), cognitive health, and social abilities (participation in social roles and activities; satisfaction with social roles and activities). As a result of MSPT reconfiguration in April 2019, two of the Neuro-QoL domains—(1) positive affect and well-being and (2) emotional and behavioral dyscontrol—were removed. All longitudinal time points were utilized in this analysis.

In the Neuro-QoL, standardized T-scores for each domain are derived from patient responses on a five-point scale related to their feelings or functioning in the prior seven days. Specific questions can be accessed at http://www.neuroqol.org. A Neuro-QoL T-score of 50 for each domain represents the average in a reference population. A clinical reference population was used for stigma, fatigue, emotional and behavioral dyscontrol, and sleep-disturbance measures; a general reference population was used for the remaining domains. For positively worded concepts (lower- and upper-extremity function, positive affect and well-being, cognition, participation in social roles and activities, and satisfaction with social roles and activities), a T-score $\geq$50 is better than average; for negatively worded concepts (anxiety, depression, emotional and behavioral dyscontrol, fatigue, sleep disturbance, and stigma), a T-score $\leq$50 is better than average.

Outline of analyses and outcome definitions

To better understand the clinical relevance of any improvements in Neuro-QoL observed in the primary population of natalizumab-treated patients, we conducted several subanalyses, including an assessment of clinically meaningful change, an evaluation of a clinically relevant patient subgroup, and an assessment of potential expectation bias (Figure 1). A clinically meaningful change for each domain was defined as $\geq$5-point change ($\geq$0.5 standard deviation (SD)) in T-score from baseline, previously identified as the threshold of discrimination of a minimally important difference using different quality-of-life tools in chronic diseases.[19]

Patients with baseline Neuro-QoL impairment were considered a clinically relevant subpopulation, as Neuro-QoL improvements in such patients would be more clinically meaningful than improvements in patients with normal baseline scores. Thus, we hypothesized that Neuro-QoL improvements would be greater in patients with baseline Neuro-QoL impairment than in the overall study population. Baseline Neuro-QoL impairment was defined as a T-score $\geq$55 for negatively worded domains or

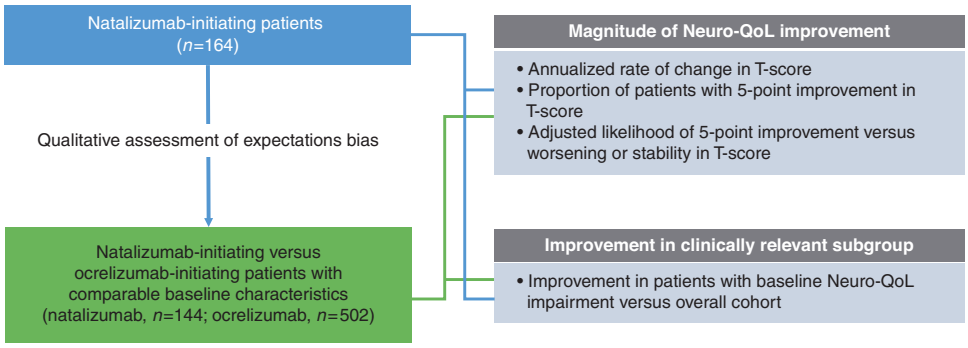

Figure 1. Outline of analyses and patient subgroups. Neuro-QoL: quality of life in neurological disorders.

T-score ≤45 for positively worded domains, as suggested by the general guidelines for interpretation of Neuro-QoL T scores.[20]

A subgroup comparison between natalizumab- and ocrelizumab-initiating patients aimed to gain qualitative understanding of the impact of expectation bias on Neuro-QoL improvements when patients switch to high-efficacy therapies. While the specific contribution of expectation bias versus effectiveness cannot be parsed out in this study, we conceptualized that should natalizumab-related improvements in Neuro-QoL be driven primarily by expectation bias, their magnitude should be the same as or less than improvements observed with another high-efficacy therapy. Therefore, we compared patients who initiated either natalizumab or ocrelizumab in MS PATHS. Patients reporting primary progressive MS and those with prior exposure to ocrelizumab or natalizumab were excluded.

Statistical analysis

The change in Neuro-QoL T-scores for each domain was assessed with a multivariate-adjusted mixed-effects regression model that included year and the following baseline covariates: age, sex, race, education, prior DMT by category (i.e. injectables [interferons or glatiramer acetate], orals [teriflunomide, fingolimod, or dimethyl fumarate], infusions [alemtuzumab], or no DMT), PDDS score, MS duration, and the number of patient-reported relapses in the prior 12 months. Statistical significance was defined as $p < 0.05$.

The percentage of patients with ≥5-point improvement or worsening in T-scores by the last available Neuro-QoL was calculated.

Analyses in natalizumab- and ocrelizumab-treated patients were conducted with multivariate mixed-effects regression models after propensity score modeling and adjustment for year, drug-year interaction, and relevant co-medications (i.e. antidepressants, sleep medicines, stimulants for fatigue, and opioids for pain) as potential effect modifiers. The propensity score of natalizumab treatment was estimated based on eight baseline characteristics (age, sex, race, education, prior DMT use, PDDS score, MS duration, and the number of patient-reported relapses in the prior 12 months) and was used to generate stabilized inverse-probability weighting (IPW) after trimming the outer 2% of the propensity scores. Absolute standardized differences of ≤0.1 were achieved for baseline variables. Baseline characteristics before and after IPW with trimming are shown in Supplementary Tables 1–3.

The logistic-regression model comparing the likelihood of ≥5-point improvement in T-scores between natalizumab and ocrelizumab further adjusted for the use of relevant co-medications (antidepressants, sleep medicines, stimulants for fatigue, and/or opioids) and follow-up duration on treatment.

Results

Overall cohort

Baseline characteristics. A total of 164 natalizumab-treated patients met the selection criteria for this analysis. Patient baseline characteristics prior to natalizumab initiation are shown in Table 1. Mean (SD) patient age was 39.2 (9.6) years. Most patients (62%) reported either normal functioning or mild disability on the PDDS, and approximately a quarter (26%) had moderate disability or gait disability. Median MS disease duration was five years. The average number of relapses reported since the last visit (or in the year prior to the patient's enrollment into MS PATHS) was 0.9 (SD 0.9), with 39% of

Table 1. Baseline characteristics of natalizumab-treated patients in the overall study cohort.

Variable	Natalizumab-treated patients ($n = 164$)
Female, *n* (%)	136 (83)
Race (white), *n* (%)	135 (82)
Years of education, mean (SD)	14.5 (2.6)
Age, mean (SD), year	39.2 (9.6)
PDDS, mean (SD)[a]	1.4 (1.5)
Normal	61 (37)
Mild disability	41 (25)
Moderate disability	17 (10)
Gait disability	26 (16)
Early cane	10 (6)
Late cane, bilateral support, wheelchair scooter	4 (3)
MS disease duration (years), mean (SD)[a]	7.4 (6.8)
MS disease duration (years), *n* (%)[a]	
0–4	77 (47)
5–9	27 (16)
10–14	31 (19)
≥15	24 (15)
Relapses since prior visit, mean (SD)[b]	0.9 (0.9)
Relapses since prior visit, *n* (%)[b]	
0	64 (39)
1	57 (35)
≥2	40 (24)
Prior DMT(s), *n* (%)[b,c]	
Injectable	40 (24)
Oral	32 (20)
Infusion	1 (1)
Not taking any medication	83 (51)
Not taking any medication listed	5 (3)

[a]Data were missing for five patients.
[b]Data were missing for three patients.
[c]Injectables: interferons and glatiramer acetate; orals: teriflunomide, fingolimod, and dimethyl fumarate; infusions: alemtuzumab.
DMT: disease-modifying therapy; MS: multiple sclerosis; PDDS: Patient Determined Disease Steps; SD: standard deviation.

patients reporting no relapses. Most patients in this cohort initiated natalizumab either as a switch from interferons, glatiramer acetate, or orals (44% combined) or reported not taking a DMT prior to natalizumab (51%).

The mean time (SD) since first visit after natalizumab initiation to the last available Neuro-QoL assessment was 6 (6) months, and the mean (SD) number of assessments was 2.3 (1.6). The baseline assessment took place on average (SD) 4.8 (2.4) months before the first assessment on natalizumab, ranging from 0.2 to 10.8 months.

Adjusted annualized rate of change in T-scores for each Neuro-QoL domain. Statistically significant improvements were seen in 8 of 12 Neuro-QoL domains in the overall natalizumab-treated population; the trend toward improvement in three other domains (emotional and behavioral dyscontrol, participation in social roles and activities, and upper extremity function) did not reach statistical significance (Table 2).

Clinically meaningful change in Neuro-QoL T-scores. The proportion of patients who exhibited a ≥5-point change in T-scores for each Neuro-QoL domain

Table 2. Adjusted annualized rates of change in Neuro-QoL T-scores across all domains, overall population and patients with baseline Neuro-QoL impairment.

	Overall population ($n = 164$)[a]		Patients with baseline impairment		
Neuro-QoL domain	Rate (CI)[b]	p value	n, %	Rate (CI)[b]	p value
Positively worded domains					
Positive affect and well-being	2.67 (1.46, 3.88)	<0.0001	23 (15)	10.72 (4.51, 16.92)	<0.01
Satisfaction with social roles and activities	1.38 (0.54, 2.22)	<0.01	76 (46)	2.58 (1.43, 3.73)	<0.0001
Cognitive function	1.10 (0.02, 2.22)	0.05	89 (54)	2.33 (0.55, 4.11)	0.01
Participation in social roles and activities	0.46 (−0.59, 1.51)	0.39	82 (50)	2.67 (1.22, 4.11)	<0.001
Upper extremity function	0.33 (−0.63, 1.28)	0.49	81 (49)	1.33 (−0.18, 2.84)	0.08
Lower extremity function	−0.07 (−0.58, 0.71)	0.84	63 (38)	0.16 (−1.09, 1.40)	0.80
Negatively worded domains					
Sleep disturbance	−1.85 (−3.00, −0.70)	<0.01	75 (46)	−4.50 (−6.49, −2.51)	0.001
Emotional and behavioral dyscontrol	−1.41 (−2.97, 0.15)	0.08	56 (37)	−5.35 (−8.23, −2.46)	<0.001
Anxiety	−1.41 (−2.66, −0.17)	0.03	69 (42)	−3.42 (−5.31, −1.53)	<0.001
Depression	−1.24 (−2.18, −0.30)	0.01	33 (20)	−2.99 (−6.12, 0.14)	0.05
Fatigue	−1.24 (−2.27, −0.22)	0.02	70 (43)	−2.88 (−4.53, −1.22)	<0.01
Stigma	−1.22 (−2.18, −0.26)	0.01	37 (23)	−2.64 (−5.20, −0.09)	0.04

[a]Due to reconfiguration of the Multiple Sclerosis Performance Test during the course of this study, 14 of the 164 patients did not provide responses to two of the Neuro-QoL domains—(1) positive affect and well-being and (2) emotional and behavioral dyscontrol—resulting in a total of 150 individual patient responses for these two domains.
[b]Rate and CI are based on a multivariate-adjusted mixed-effects regression model.
CI: confidence interval; Neuro-QoL: Quality of Life in Neurological Disorders.

following the initiation of natalizumab is shown in Figure 2. In the overall population (Figure 2(a)), over 50% of patients remained stable in each of the assessed domains. A greater proportion of patients reported clinically meaningful improvement than worsening in all domains except lower extremity function and participation in social roles and activities, in which an equal number of patients reported improvement and worsening. The highest percentage of patients with ≥5-point improvement was seen in sleep disturbance (32%), anxiety (27%), emotional and behavioral dyscontrol (26%), stigma (24%), and positive affect and well-being (24%).

Subgroup of patients with baseline impairment in Neuro-QoL domains

The number of patients with perceived impairment in Neuro-QoL domains at baseline ranged from 20% (33 of 164) for depression to 54% (89 of 164) for cognitive function (Table 2). Statistically significant improvements following natalizumab initiation were observed in 10 of 12 Neuro-QoL domains; annualized rates of improvement in each such domain were greater than rates in the overall cohort (Table 2).

Clinically meaningful improvement (≥5 points) in the subgroup of patients with baseline impairment in Neuro-QoL domains is analyzed in Figure 2(b). The percentage of patients with clinically meaningful improvement was higher in most domains than in the overall cohort. The percentage of patients with meaningful improvement was highest in those with baseline impairment in positive affect and well-being (43%), emotional and behavioral dyscontrol (39%), sleep disturbance (36%), and anxiety (33%).

Subgroup of natalizumab- and ocrelizumab-treated patients

After propensity score trimming, 144 natalizumab and 502 ocrelizumab patients were available for analysis. The average (SD) time from the first visit after natalizumab or ocrelizumab initiation to the last available Neuro-QoL assessment was 6 (6) months for both drugs. The average (SD) number of

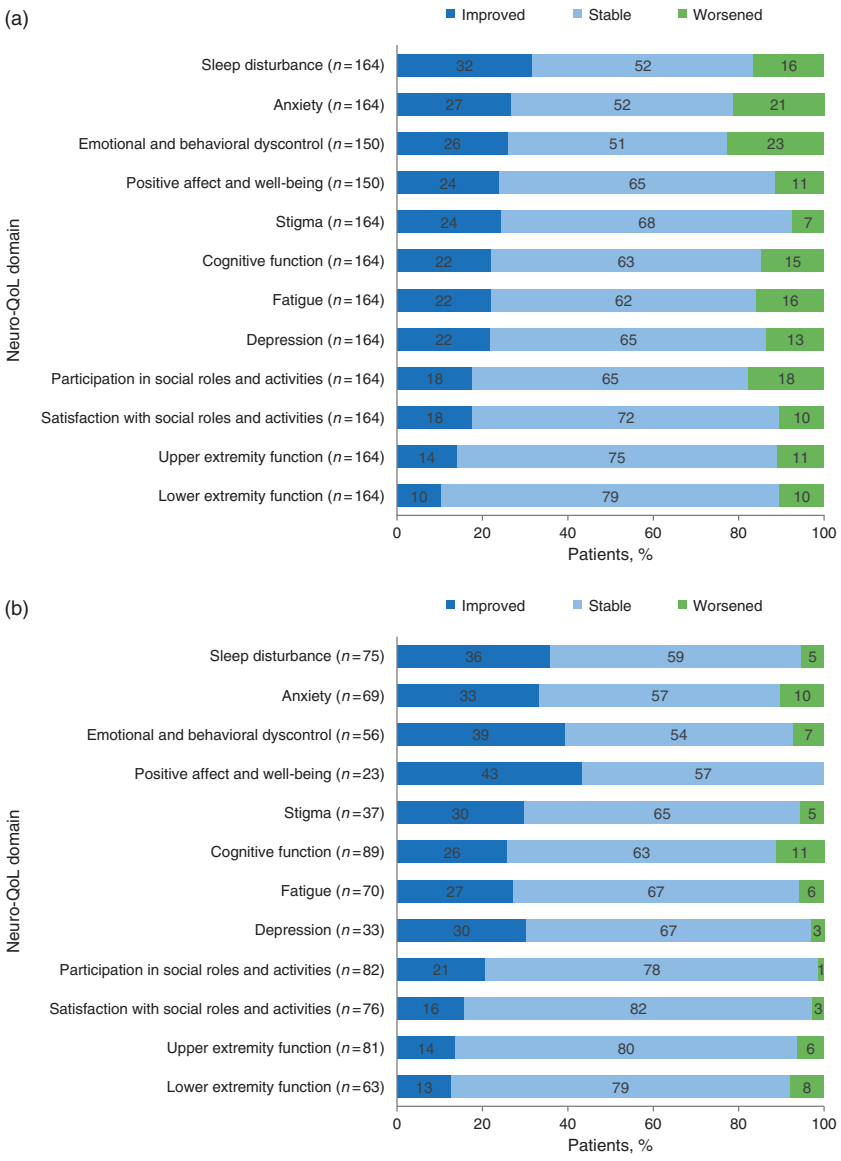

Figure 2. Clinically meaningful change in Neuro-QoL T-scores in (a) the overall population and (b) patients with Neuro-QoL impairment at baseline.
Neuro-QoL: Quality of Life in Neurological Disorders.

assessments was 2.3 (1.6) for natalizumab and 2.0 (1.3) for ocrelizumab. The baseline assessment took place on average (SD) 4.8 (2.4) months before the first assessment on natalizumab and 6 (2.4) months before the first assessment on ocrelizumab.

In natalizumab patients (Table 3), statistically significant improvement was observed in 9 of 12 Neuro-QoL domains. The three domains with the greatest improvement remained the same as in the overall natalizumab cohort: positive affect and well-being, sleep disturbance, and anxiety.

In ocrelizumab patients, statistically significant improvement was observed in 4 of 12 Neuro-QoL domains; the domains with the greatest improvement were anxiety, depression, and positive affect and well-being.

Overall, annualized improvement rates were greater with natalizumab than with ocrelizumab, reaching statistical significance for three domains: positive affect and well-being ($p = 0.02$), sleep disturbance ($p = 0.003$), and satisfaction with social roles and activities ($p = 0.03$).

Table 3. Adjusted annualized rate of T-score change for Neuro-QoL domains, subgroup of natalizumab and ocrelizumab patients.

	Natalizumab ($n = 144$)[a]		Ocrelizumab ($n = 502$)[a]		Natalizumab minus ocrelizumab	
Neuro-QoL domain	Rate (CI)	p value	Rate (CI)	p value	Rate (CI)	p value
Positively worded domains						
Positive affect and well-being	2.30 (1.11, 3.49)	<0.001	0.66 (0.06, 1.26)	0.03	1.65 (0.32, 2.98)	0.02
Satisfaction with social roles and activities	1.34 (0.46, 2.21)	<0.01	0.24 (−0.22, 0.69)	0.30	1.10 (0.12, 2.09)	0.03
Cognitive function	1.33 (0.27, 2.39)	0.02	0.24 (−0.30, 0.78)	0.39	1.09 (−0.10, 2.28)	0.33
Participation in social roles and activities	0.79 (−0.29, 1.87)	0.15	−0.10 (−0.65, 0.45)	0.71	0.89 (−0.31, 2.10)	0.15
Upper extremity function	0.35 (−0.60, 1.30)	0.47	−0.24 (−0.72, 0.24)	0.32	0.59 (−0.47, 1.66)	0.28
Lower extremity function	−0.14 (−0.91, 0.63)	0.72	−0.19 (−0.58, 0.21)	0.35	0.05 (−0.82, 0.91)	0.92
Negatively worded domains						
Sleep disturbance	−2.27 (−3.39, −1.14)	<0.001	−0.33 (−0.91, 0.24)	0.25	−1.93 (−3.20, −0.67)	0.003
Emotional and behavioral dyscontrol	−1.96 (−3.17, −0.75)	<0.01	−1.03 (−1.65, −0.42)	<0.01	−0.93 (−2.29, 0.44)	0.18
Anxiety	−1.54 (−2.99, −0.10)	0.04	−0.28 (−1.02, 0.47)	0.47	−1.27 (−2.89, 0.35)	0.12
Depression	−1.42 (−2.40, −0.44)	<0.01	−0.63 (−1.13, −0.13)	0.02	−0.79 (−1.89, 0.31)	0.16
Fatigue	−1.30 (−2.29, −0.31)	0.01	−0.73 (−1.24, −0.23)	<0.01	−0.57 (−1.67, 0.54)	0.31
Stigma	−1.24 (−2.41, −0.07)	0.04	−0.40 (−0.10, 0.21)	0.20	−0.84 (−2.16, 0.48)	0.21

[a]Due to Multiple Sclerosis Performance Test reconfiguration during the course of the study, the number of patients providing responses to two of the Neuro-QoL domains (positive affect and well-being and emotional and behavioral dyscontrol) in this subgroup analysis is 466 for ocrelizumab and 135 for natalizumab.
CI: confidence interval; Neuro-QoL: Quality of Life in Neurological Disorders.

In the subset of patients with baseline Neuro-QoL impairment, both natalizumab and ocrelizumab performed better than in the respective overall populations, leading to statistically significant improvements in 10 and 8 Neuro-QoL domains, respectively (Table 4). Rates of improvement were higher overall with natalizumab, with the difference between treatment groups reaching statistical significance in three domains: emotional and behavioral dyscontrol ($p = 0.01$), participation in social roles and activities ($p = 0.0001$), and satisfaction with social roles and activities ($p = 0.02$).

Among patients with baseline Neuro-QoL impairment, the percentage with clinically meaningful ($\geq$5-point) improvement was numerically higher among natalizumab- than ocrelizumab-treated patients in 7 of 12 Neuro-QoL domains and the same for natalizumab and ocrelizumab in three of the remaining five domains (Figure 3). The adjusted likelihood of $\geq$5-point improvement was higher in magnitude with natalizumab than with ocrelizumab for 6 of 12 Neuro-QoL domains; however, these differences did not reach statistical significance (Figure 4).

Discussion

Patient-reported outcomes (PROs) are of growing importance to clinicians, patients, payers, and regulators, as they provide a broader overall assessment of MS disease state and progression than clinical and radiological measures alone.[21] Further, PROs facilitate optimized patient management, as they relate not only to the choice of DMT but also to symptomatic treatment or ancillary services for mental health and depression.

We conducted a comprehensive assessment of natalizumab's effect on mental, emotional, cognitive, and physical aspects of quality of life in a real-world setting. To this end, we utilized systematically collected standardized Neuro-QoL assessments, defined a clinically meaningful threshold and patient subpopulations, and analyzed outcomes against a reference subgroup of patients receiving another high-efficacy MS therapy.

Following treatment with natalizumab, we observed statistically significant improvements in annualized T-scores relative to baseline in 8 of 12 Neuro-QoL domains. The only domain in which the rate of change did not indicate improvement was lower extremity function, a finding that may reflect the relatively short mean follow-up period (six months). In this context, the subjective perception of improvement in mobility may require longer treatment than improvements in emotional or mental health.

Sensitivity analyses supported the clinical meaningfulness of the Neuro-QoL findings. The subset of patients with baseline Neuro-QoL impairment exhibited higher rates of improvement than the overall cohort, with statistically significant improvement observed in 10 of 12 domains. Furthermore, the proportion of patients in this subgroup exhibiting $\geq$5-point improvement (0.5 SD) in T-score was higher relative to the overall cohort for most domains.

The demonstrated improvements in Neuro-QoL in the overall study population and in patients with baseline Neuro-QoL impairment support the strong positive impact of natalizumab on various aspects of HRQoL. However, the magnitude of observed effects may be impacted by expectation bias when a patient starts a high-efficacy therapy like natalizumab. While the precise contribution of expectation bias to our findings cannot be quantified, we explored whether a similar impact on Neuro-QoL was observed with another high efficacy therapy that is likely to involve a similar level of expectation related to instituting a more effective therapy. To this end, we used as a reference comparator a population of patients initiating ocrelizumab in the same cohort. Ocrelizumab is a monoclonal antibody targeting CD20 on B cells and has demonstrated strong efficacy in relapsing-remitting MS, as well as lower rates of clinical and MRI progression than placebo in primary progressive MS.[22,23] In the subgroup of ocrelizumab- and natalizumab-treated patients with balanced baseline characteristics, statistically significant improvement was observed in 9 of 12 Neuro-QoL domains with natalizumab and in 4 of 12 Neuro-QoL domains with ocrelizumab. Annualized rates of improvement tended to be greater with natalizumab than with ocrelizumab in both the overall subgroup of patients and those with baseline Neuro-QoL impairment. Analysis of the likelihood of $\geq$5-point improvement in T-scores (versus stability or worsening) among those with baseline Neuro-QoL impairment favored natalizumab over ocrelizumab for six domains despite not reaching statistical significance. These overall results suggest that the strong positive patient experience with natalizumab described in this study was not driven entirely by expectation bias based on initiation of a high-efficacy DMT.

Table 4. Adjusted annualized rate of T-score change for Neuro-QoL domains, subgroup of natalizumab and ocrelizumab patients with baseline Neuro-QoL impairment in individual domains.

	Natalizumab		Ocrelizumab		Natalizumab minus ocrelizumab	
Neuro-QoL domain	Rate (CI)	*p* value	Rate (CI)	*p* value	Rate (CI)	*p* value
Positively worded domains						
Positive affect and well-being	5.06 (2.74, 7.38)	<0.0001	3.12 (1.90, 4.33)	<0.0001	1.94 (−0.67, 4.56)	0.14
Participation in social roles and activities	2.63 (1.89, 3.37)	<0.0001	0.94 (0.54, 1.33)	<0.0001	1.70 (0.86, 2.54)	0.0001
Satisfaction with social roles and activities	2.17 (1.10, 3.23)	0.0001	0.72 (0.28, 1.28)	<0.01	1.39 (0.21, 2.56)	0.02
Cognitive function	1.59 (0.27, 2.91)	0.02	0.72 (0.04, 1.40)	0.39	0.87 (−0.61, 2.36)	0.25
Upper extremity function	1.49 (0.15, 2.84)	0.03	0.28 (−0.32, 0.88)	0.36	1.21 (−0.26, 2.68)	0.11
Lower extremity function	0.43 (−0.73, 1.60)	0.46	0.28 (−0.20, 0.76)	0.26	0.15 (−1.11, 1.41)	0.81
Negatively worded domains						
Emotional and behavioral dyscontrol	−5.95 (−8.53, −3.37)	<0.01	−2.03 (−3.16, −0.90)	<0.001	−3.92 (−6.67, −1.17)	0.01
Anxiety	−3.98 (−5.65, −2.31)	<0.0001	−2.34 (−3.12, −1.56)	<0.0001	−1.64 (−3.49, 0.20)	0.08
Sleep disturbance	−3.59 (−5.21, −1.98)	<0.0001	−2.05 (−2.84, −1.26)	<0.0001	−1.54 (−3.34, 0.25)	0.09
Fatigue	−2.97 (−4.89, −1.06)	<0.01	−1.47 (−2.41, −0.53)	<0.01	−1.50 (−3.63, 0.63)	0.17
Stigma	−2.70 (−3.70, −1.70)	<0.0001	−2.31 (−2.90, −1.72)	<0.0001	−0.39 (−1.55, 0.77)	0.51
Depression	−1.62 (−3.84, 0.60)	0.14	−4.15 (−11.42, 3.12)	0.09	2.53 (−0.38, 5.44)	0.08

CI: confidence interval; Neuro-QoL: Quality of Life in Neurological Disorders.

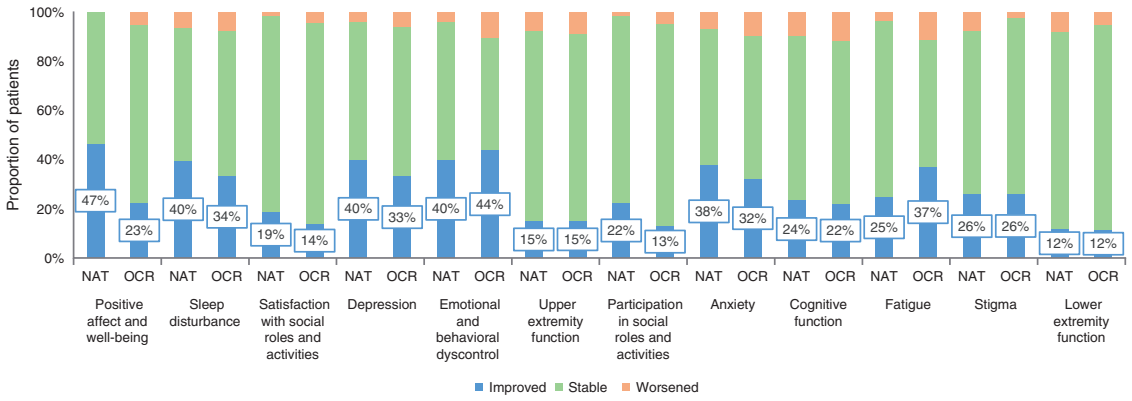

Figure 3. Clinically meaningful change in Neuro-QoL T-scores for natalizumab- and ocrelizumab-treated patients with Neuro-QoL impairment at baseline.
NAT: natalizumab; Neuro-QoL: Quality of Life in Neurological Disorders; OCR: ocrelizumab.

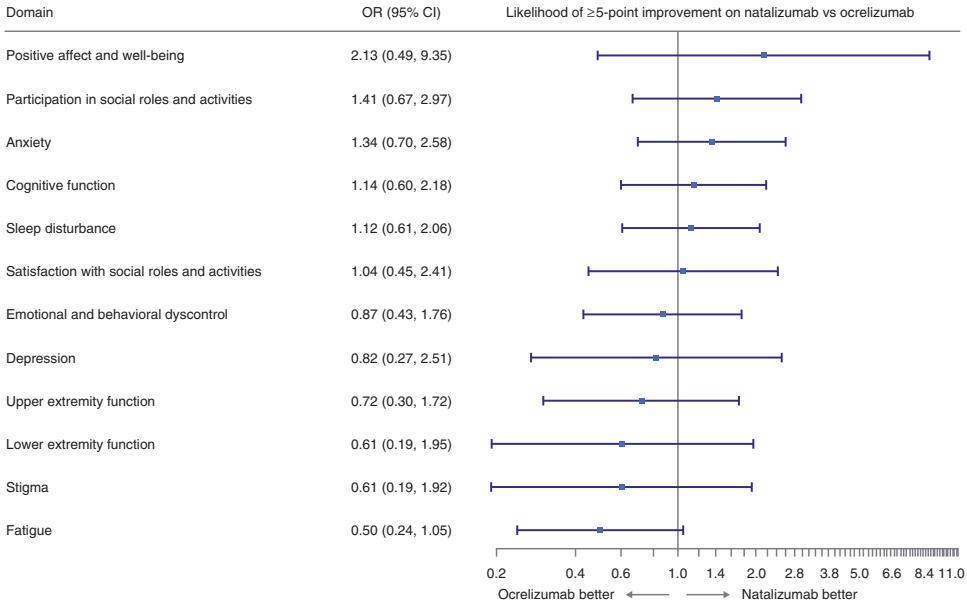

Figure 4. Adjusted likelihood of ≥5-point improvement versus worsening and stability in natalizumab- and ocrelizumab-treated patients with baseline impairment in Neuro-QoL domains.
CI: confidence interval; Neuro-QoL: Quality of Life in Neurological Disorders; OR: odds ratio.

Prior studies have consistently demonstrated improvements or stability relative to baseline across physical and psychosocial functioning in natalizumab-treated patients; however, the emphasis has been primarily on PRO instruments measuring fatigue and depression.[6–8,24–27] In one study, natalizumab was reported to exert positive effects on daytime sleepiness via its effect on fatigue.[25] In the current study, the overall impact of natalizumab on sleep disturbance, positive affect and well-being, emotional and behavioral dyscontrol, and participation/satisfaction with social roles and activities appeared to extend beyond what could be driven by its effect on depression and fatigue. To this effect, our findings may better reflect a perception of overall well-being and energy. This could be related to a natalizumab-induced decrease in inflammatory markers implicated in sleep disturbance, depression, and fatigue in both CSF and in plasma.[28–33] However, direct evidence linking the biological effects of natalizumab with its effect on these symptoms is lacking, and the contribution

of these findings in defining the anecdotal "feel-good effect" of natalizumab needs to be further studied.

There are limitations to this study. The data were collected as part of routine clinical care rather than following a predefined schedule for baseline and follow-up visits and were therefore observational and potentially subject to residual confounding. We did not account for the potential impact of relapses on Neuro-QoL worsening (observed in a minority of patients), the use of extended interval dosing versus standard interval dosing of natalizumab, or the possible "wearing-off" effect of natalizumab during the infusion cycle.[34] Our choice of a $\geq$5-point threshold for clinical meaningfulness was based on results from a literature review of studies computing the minimally important difference for HRQoL instruments for chronic diseases and suggesting that this difference approximates half an SD.[19] We applied this threshold to each of the Neuro-QoL domains; however, there is currently no consensus regarding what constitutes a clinically relevant change in these patient-reported outcomes. Finally, while propensity score–based modeling was used to balance baseline characteristics between natalizumab- and ocrelizumab-treated patients, we could not account for unmeasured covariates.

The follow-up time for natalizumab- and ocrelizumab-treated patients was comparable between the two groups, averaging six months, and was included as a covariate in the statistical models. While one cannot exclude the possibility that additional cumulative benefits or loss of benefits could be observed with a longer treatment duration, prior studies have demonstrated a quick onset of action for both natalizumab and ocrelizumab, as well as sustained effects of natalizumab on PROs starting at three months and continuing through three years of follow-up.[8,10,24,35,36] In addition, given that the average (SD) time of follow-up for both natalizumab and ocrelizumab was 6 (6) months, we do not anticipate that relapses or the use of extended interval dosing would have had a major impact on the study findings.

This analysis has several strengths in design, notably, the use of standardized data from a real-world patient cohort, the ability to adjust for use of co-medications acting as potential effect modifiers, and the incorporation of several sensitivity analyses aimed at understanding the clinical meaningfulness of the findings. The results support a strong positive impact of natalizumab on various aspects of physical, mental, cognitive, and emotional quality of life in addition to its known effect on clinical and radiological outcomes. They also highlight the value of quantitative standardized real-world data in complementing clinical profiles of therapies beyond randomized clinical trials.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CMH: speaking and consulting fees from Biogen, Genentech, Genzyme, EMD Serono, and Novartis; research support paid to her institution from Biogen, Genentech, and the Patient-Centered Outcomes Research Institute (PCORI); BK, KX, RAR, IK: employees of Biogen at the time of these analyses and may have received stock/stock options in Biogen; CdM, DC, JRW: employees of and may hold stock/stock options in Biogen; DMM: served as a consultant for Roche and has received royalties from the Cleveland Clinic for licensing MSPT-related technology; KCF: funded by a Career Transition Fellowship from the National MS Society (NMSS); MPM: served on scientific advisory boards for Genentech, Genzyme; received research support from Novartis; receives funding from a KL2 (KL2TR002547) grant from Clinical and Translational Science Collaborative of Cleveland, from the National Center for Advancing Translational Sciences (NCATS) component of the NIH; MH: research support paid to her institution from Biogen and PCORI; TZ: personal compensation from Bayer, Biogen, Celgene, Novartis, Roche, Sanofi, and Teva for consulting services; additional financial support for research activities from BAT, Bayer, Biogen, Novartis, Sanofi, and Teva.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Biogen funded the study and was involved in the study design, data collection, data analysis, and preparation of the manuscript.

ORCID iDs

Carrie M Hersh https://orcid.org/0000-0002-5716-5645
Deborah M Miller https://orcid.org/0000-0002-8026-1854
Kathryn C Fitzgerald https://orcid.org/0000-0003-3137-0322
Marisa P McGinley https://orcid.org/0000-0002-7463-6787
Tjalf Ziemssen https://orcid.org/0000-0001-8799-8202
Irene Koulinska https://orcid.org/0000-0002-4918-4045

Supplemental material

Supplemental material for this article is available online.

References

1. Rudick RA, Miller D, Clough JD, et al. Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. *Arch Neurol* 1992; 49: 1237–1242.
2. Riazi A, Hobart JC, Lamping DL, et al. Using the SF-36 measure to compare the health impact of multiple sclerosis and Parkinson's disease with normal population health profiles. *J Neurol Neurosurg Psychiatry* 2003; 74: 710–714.
3. Burden of illness of multiple sclerosis: part II: quality of life. The Canadian burden of illness study group. *Can J Neurol Sci* 1998; 25: 31–38.
4. Amtmann D, Bamer AM, Kim J, et al. People with multiple sclerosis report significantly worse symptoms and health related quality of life than the US general population as measured by PROMIS and NeuroQoL outcome measures. *Disabil Health J* 2018; 11: 99–107.
5. Schriefer D, Haase R, Kullmann JS, et al. Health-related quality of life and the relationship to treatment satisfaction in patients with multiple sclerosis: insights from a large observational study. *Patient Prefer Adherence* 2020; 14: 869–880.
6. Wilken J, Kane RL, Sullivan CL, et al. Changes in fatigue and cognition in patients with relapsing forms of multiple sclerosis treated with natalizumab: the ENER-G study. *Int J MS Care* 2013; 15: 120–128.
7. Perumal J, Fox RJ, Balabanov R, et al. Outcomes of natalizumab treatment within 3 years of relapsing-remitting multiple sclerosis diagnosis: a prespecified 2-year interim analysis of STRIVE. *BMC Neurol* 2019; 19: 116.
8. Stephenson JJ, Kern DM, Agarwal SS, et al. Impact of natalizumab on patient-reported outcomes in multiple sclerosis: a longitudinal study. *Health Qual Life Outcome* 2012; 10: 155.
9. Rudick RA, Miller D, Hass S, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol* 2007; 62: 335–346.
10. Planche V, Moisset X, Morello R, et al. Improvement of quality of life and its relationship with neuropsychiatric outcomes in patients with multiple sclerosis starting treatment with natalizumab: a 3-year follow-up multicentric study. *J Neurol Sci* 2017; 382: 148–154.
11. Vartanian T, Berkovich R, Foley J, et al. Characterizing the positive experience reported by natalizumab-treated patients with relapsing multiple sclerosis. In: *European Charcot Foundation 2019 Annual Symposium*, Baveno, Italy, 21 November 2019.
12. Foley J, Berkovich R and Gudesblatt M. Natalizumab-treated patients with relapsing-remitting multiple sclerosis report better "feel-good" outcomes in key physical, emotional, and cognitive domains compared to other disease-modifying therapies. *Int J MS Care* 2020; 22(2 suppl): 87.
13. Cella D, Lai JS, Nowinski CJ, et al. Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology. *Neurology* 2012; 78: 1860–1867.
14. Miller DM, Bethoux F, Victorson D, et al. Validating Neuro-QoL short forms and targeted scales with people who have multiple sclerosis. *Mult Scler* 2016; 22: 830–841.
15. Rhodes JK, Schindler D, Rao SM, et al. Multiple Sclerosis Performance Test: technical development and usability. *Adv Ther* 2019; 36: 1741–1755.
16. Rao SM, Galioto R, Sokolowski M, et al. Multiple Sclerosis Performance Test: validation of self-administered neuroperformance modules. *Eur J Neurol* 2020; 27: 878–886.
17. Mowry EM, Bermel R, Williams JR, et al. Harnessing real-world data to inform decision-making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). *Front Neurol* 2020; 11: 632.
18. Learmonth YC, Motl RW, Sandroff BM, et al. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol* 2013; 13: 37.
19. Norman GR, Sloan JA and Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; 41: 582–592.
20. Neuro-QoL™ score cut points, www.healthmeasures.net/score-and-interpret/interpret-scores/neuro-qol/neuro-qol-score-cut-points (Accessed 20 January 2021).
21. D'Amico E, Haase R and Ziemssen T. Review: patient-reported outcomes in multiple sclerosis care. *Mult Scler Relat Disord* 2019; 33: 61–66.
22. Stahnke AM and Holt KM. Ocrelizumab: a new b-cell therapy for relapsing remitting and primary progressive multiple sclerosis. *Ann Pharmacother* 2018; 52: 473–483.
23. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017; 376: 209–220.
24. Foley JF, Nair KV, Vollmer T, et al. Long-term natalizumab treatment is associated with sustained improvements in quality of life in patients with multiple sclerosis. *Patient Prefer Adherence* 2017; 11: 1035–1048.
25. Penner IK, Sivertsdotter EC, Celius EG, et al. for the TYNERGY trial investigators. Improvement in fatigue during natalizumab treatment is linked to improvement in depression and day-time sleepiness. *Front Neurol* 2015; 6: 18.
26. Holmen C, Piehl F, Hillert J, et al. A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis. *Mult Scler* 2011; 17: 708–719.
27. Kamat SA, Rajagopalan K, Stephenson JJ, et al. Impact of natalizumab on patient-reported outcomes in a clinical practice setting: a cross-sectional survey. *Patient* 2009; 2: 105–112.

28. Mellergard J, Edstrom M, Vrethem M, et al. Natalizumab treatment in multiple sclerosis: marked decline of chemokines and cytokines in cerebrospinal fluid. *Mult Scler* 2010; 16: 208–217.
29. Rockstrom MD, Chen L, Taishi P, et al. Tumor necrosis factor alpha in sleep regulation. *Sleep Med Rev* 2018; 40: 69–78.
30. D'Antono B and Bouchard V. Impaired sleep quality is associated with concurrent elevations in inflammatory markers: are post-menopausal women at greater risk? *Biol Sex Differ* 2019; 10: 34.
31. Huang Y, Jiang Y and Zhu M. The relationship between global sleep score and inflammatory markers in obese adults from the United States. *Nat Sci Sleep* 2019; 11: 317–324.
32. Ming H, Tian A, Liu B, et al. Inflammatory cytokines tumor necrosis factor-alpha, interleukin-8 and sleep monitoring in patients with obstructive sleep apnea syndrome. *Exp Ther Med* 2019; 17: 1766–1770.
33. Wang M, Wei J, Yang X, et al. The level of IL-6 was associated with sleep disturbances in patients with major depressive disorder. *Neuropsychiatr Dis Treat* 2019; 15: 1695–1700.
34. van Kempen ZLE, Doesburg D, Dekker I, et al. The natalizumab wearing-off effect: end of natalizumab cycle, recurrence of MS symptoms. *Neurology* 2019; 93: e1579–e1586.
35. Boyko OV, Choroshilova II, Petrov SV, et al. [Changes in the quality of life in patients with multiple sclerosis treated with ocrelizumab]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2019; 119: 120–127.
36. Barkhof F, Kappos L, Wolinsky JS, et al. Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis. *Neurology* 2019; 93: e1778–e1786.