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No Increase in Symptoms Toward the End of the Ocrelizumab Infusion Cycle in Patients With Multiple Sclerosis

Symptom Burden on Ocrelizumab: A Longitudinal Study (SymBOLS)

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Abstract

Background and Objectives

Some patients with multiple sclerosis (MS) receiving ocrelizumab (OCR) report worsening symptoms toward the end of the 6-month infusion cycle ('wearing off'). The objective of our study was to comprehensively assess changes in symptom burden across 2 consecutive OCR infusion cycles.

Methods

SYMptom Burden on Ocrelizumab, a Longitudinal Study (SymBOLS; NCT04855617) was an investigator-initiated, 2-center study of patients with MS starting or receiving OCR. Patients' symptoms were assessed with NeuroQoL short forms, SymptoMScreen, and Work Productivity and Activity Impairment Questionnaire at the start-cycle, mid-cycle, and end-cycle time points in each of the 2 infusion cycles. Symptom scores at the 3 time points within each cycle were compared with repeated-measures ANOVA or the Friedman rank-sum test for non-normal variables. The proportions of patients with a meaningful symptomatic change from the start to the end of each infusion cycle were calculated, and patients whose symptoms improved, worsened, and stayed the same from the start to the end of the cycle were compared with respect to demographic and clinical characteristics.

Results

One hundred three patients with MS provided longitudinal data for analyses (mean age [SD]: 46.7 [12.2] years, 68% female, 33% non-White, disease duration: 15.5 [5] years, 41% with the Extended Disability Status Scale score >3). On a group level, NeuroQoL and SymptoMScreen scores mostly remained stable or even improved slightly toward the end of each cycle. On an individual level, symptoms remained unchanged across either cycle for most patients, and meaningful symptom worsening from the start to the end of the cycle was no more common than improvement. Meaningful change in symptoms in both cycles was very rare and generally in the direction of improvement toward the end cycle. Despite the lack of evidence for symptom worsening with a longer time from infusion, 54% of patients endorsed feeling of "wearing off" at least sometimes, most commonly as an increase in fatigue.

Discussion

Our prospective study failed to uncover evidence for the worsening of symptoms with a longer time from OCR infusion. These findings cast doubt on the existence of wearing off as a physiologic phenomenon in OCR-treated patients with MS. The perception of wearing off is likely the result of natural fluctuations in MS symptoms and attribution bias.

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Introduction

Ocrelizumab (OCR), an anti-CD20 monoclonal antibody approved for the treatment of relapsing and primary progressive multiple sclerosis (MS),[1,2] is given as an IV infusion every 6 months. Patients treated with OCR often describe "wearing off"—worsening of their MS symptoms, especially fatigue—toward the end of the infusion cycle.[3] A recent study found that 61% of OCR-treated patients responded in the affirmative to the question "I have wearing off at least sometimes before OCR infusion."[4] Of interest, similar rates of wearing off have also been reported with natalizumab, a monthly infusible therapy for MS with a completely different mechanism of action.[5-9]

Methodologically, the use of a leading question, "Do you feel worse toward the end of the cycle?" to define "wearing off" is problematic because it implicitly communicates the expectation of wearing off and is also liable to induce acquiescence bias, the tendency of responders to agree with the question.[10] Another concern is that patients with symptomatic worsening around the time of reinfusion may attribute their worsening to the drug's wearing off (attribution bias), whereas symptom worsening early in the cycle would be attributed to other causes.[11]

Our investigator-initiated study, designed to assess changes in MS symptoms throughout the OCR infusion cycle, deployed several strategies to minimize these potential sources of bias. Ab initio, we assumed the null hypothesis that symptoms are as likely to improve as to worsen from the start to the end of the treatment cycle. Disproving this hypothesis would provide evidence for the existence of wearing off. We were careful not to disclose the expectation of "wearing off" to the study participants. We prospectively assessed MS-related symptoms at prespecified time points in the infusion cycle using validated patient-reported outcome measures. We defined "meaningful change" in symptom severity based on the thresholds of symptom severity that patients with MS and their clinicians considered to be clinically meaningful.[12]

Methods

SYMptom Burden on Ocrelizumab, a Longitudinal Study (SymBOLS; NCT04855617) was a prospective study of patients with MS who were initiated on OCR or were receiving OCR for >12 months. All patients received neurologic care at the NYU Multiple Sclerosis Comprehensive Care Center (NYU) in New York City, NY, and the Elliot Lewis Center for Multiple Sclerosis Care (ELC) in Wellesley, MA. OCR treatments were provided per routine clinical care. Inclusion criteria for the study were age 18–80 years, diagnosis of multiple sclerosis (revised 2017 criteria[13]), Extended Disability Status Scale (EDSS) score of 0–7 (wheelchair bound), ability to read and understand English, and provide informed consent. Exclusion criteria for the study were cognitive impairment limiting the ability to consent or fill out the electronic surveys; an uncontrolled psychiatric illness; active substance abuse disorder; major systemic medical comorbidities (such as nonskin cancer or chronic infection); a history of severe traumatic brain injury or stroke; pregnancy, breastfeeding, or planning to become pregnant during the study period; chemotherapy within 6 months of the first on-study infusion; treatment with alemtuzumab or a B-cell–depleting therapy other than OCR within 12 months of the first on-study infusion; and clinical relapse within 3 months of the first on-study infusion. Consecutive patients who met our criteria were invited to participate in the study. The enrollment period was from November 2020 to September 2021.

Before each of the 2 on-study OCR infusions, patients underwent routine clinical examination by their treating neurologist, and their medical history and Neurostatus EDSS score were obtained by a study clinician. Serum samples for neurofilament light chain levels (NfL) and OCR concentration were collected before each infusion. The serum NfL level, a validated biomarker for neuroaxonal damage in MS,[14,15] was analyzed using Quanterix Simoa Platform (Frontage Laboratories, Inc., Exton PA). Ocrelizumab concentration in serum samples was assessed with a validated ELISA with a lower limit of quantitation of 250 ng/mL[16] (PPD Laboratory Services, Wilmington, NC). All participants received study questionnaires through email links to a secure, HIPAA-compliant REDCap database[17] hosted by NYU Langone Health. Patients' symptoms were assessed during 2 infusion cycles to ascertain whether the pattern of symptom change remained consistent from one cycle to the next. Study questionnaires were emailed to the participants 4 weeks after each infusion (start-cycle questionnaire), 12 weeks after each infusion (mid-cycle questionnaire), and 22 weeks after each infusion (end-cycle questionnaire), i.e., at study weeks 4, 12, and 22 (first cycle) and 28, 36, and 46 (second cycle). Participants had 14 days to complete each survey. If the questionnaires were not completed within 7 days, a study coordinator contacted the patient by phone to encourage timely completion. All the infusion cycle questionnaires included the following instruments:

- Quality of Life in Neurologic Disorders (NeuroQoL) short forms: They are freely available, patient-reported outcome measures with excellent psychometric properties[18] that have been widely used in MS research.[12,19,20] The following NeuroQoL short forms were collected in our study: Fatigue, Upper Extremity Function—Fine Motor (Arm Function), Lower Extremity Function—Mobility (Leg Function), Sleep Disturbance, Cognitive Function, Positive Affect and Well-Being, Ability to Participate in Social Roles and Activities, Communication, Anxiety, Depression, and Emotional and Behavioral Dyscontrol.
- SymptoMScreen is a validated tool for the rapid assessment of symptoms across 12 domains commonly affected in MS: Mobility, Dexterity, Body pain, Spasticity,

Sensory function, Bladder function, Fatigue, Vision, Dizziness, Cognition, Depression, and Anxiety.[21] Each domain is scored on a 7-point Likert scale ranging from 0 (unaffected) to 6 (total limitation).
- Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis V2.0 (WPAI:MS), a tool for assessing the impact of MS on work productivity,[22] asks whether the participant is currently working for pay, the hours of work missed due to MS (absenteeism), or were impaired because of MS (presenteeism).
- The medical screening questionnaire asked about MS relapses, hospitalizations, adverse events related to OCR, new medications, procedures and medical diagnoses, and prior infections, including, after March 2020, COVID-19 infection.

So as not to bias patients' responses, we assiduously avoided the phraseology of "wearing off" or "symptom worsening" in any written or oral communications during recruitment and the longitudinal phase of the study. After patients filled out their last end-cycle questionnaire (week 46), they were emailed a study completion questionnaire (SCQ) that specifically asked about their perception of "wearing off." The SCQ was the only study document to mention wearing off explicitly and was the same as the published questionnaire used in the prior study of OCR wearing off.[4]

Standard Protocol Approvals, Registrations, and Patient Consents

All patients signed informed consent before participation in the study. The study was approved by NYU Langone Health Institutional Review Board.

Statistical Analyses

The characteristics of patients, including demographics and clinical characteristics, were first summarized using descriptive statistics in mean (SD) or median (interquartile ranges [IQRs]) for continuous variables or percentages (counts) for categorical variables. All the continuous outcome variables were checked for normality before the statistical analyses. The raw scores for NeuroQoL domains were transformed into T scores and treated as continuous variables. Missing data were not imputed. Because a prior study[4] suggested that BMI may be a covariate associated with the probability of "wearing off," an assessment for imbalance in BMI across groups was included in the primary analysis.

NYU and ELC patients were compared with respect to baseline demographic and clinical characteristics and outcome scores using the unpaired t test or Wilcoxon test for continuous variables and the χ^2 test for categorical variables. We then examined the changes in NeuroQoL domains, SymptoMScreen (total and domain specific), and WPAI across 3 time points (start, mid, and end cycle) within each infusion cycle using a nonparametric Friedman rank-sum test. Where statistical significance was observed, we further performed a post hoc pairwise comparison with Bonferroni correction using the Wilcoxon signed-rank test to identify the difference. Sensitivity analyses excluding patients who experienced COVID-19 during the study were also performed.

"Meaningful symptom change" across the infusion cycle on NeuroQoL Fatigue, Sleep, Arm, and Leg function domains was defined as a change in the symptom severity category based on thresholds for "none," "mild," "moderate," and "severe" symptom severity as agreed on by patients with MS and clinicians.[12] Thus, any patient who switched from a lower severity category at the start cycle to a higher severity category at the end cycle was considered to have a "meaningful symptom worsening" for that cycle. Any patient who changed from a higher severity category at the start cycle to a lower severity category at the end cycle was considered to have "meaningful symptom improvement" for that cycle. Any patients who stayed within their severity category throughout the cycle were classified as "unchanged" symptom severity.

For SymptoMScreen, thresholds for clinically meaningful change have not been defined. Prior work has shown that ~20% of patients with MS have mean SymptoMScreen score worsening by ≥0.5 points over a 1–2 year period.[11] Mean SymptoMScreen score changes below the 0.5-point threshold from one visit to the next in neurologically stable patients with MS likely represent expected fluctuations of MS symptoms and measurement noise. Therefore, in this work, we chose the ≥0.5-point change in the mean SymptoMScreen score as a threshold likely to reflect meaningful worsening or improvement and calculated the number of patients whose mean SymptoMScreen score changed by ≥0.5 points from the start to the end of each cycle.

We compared 3 groups whose symptoms "worsened," "improved," or remained "unchanged" in any of the 4 NeuroQoL domains and on the SymptoMScreen scale with respect to a large number of demographic and clinical variables. A χ^2 test was used for categorical variables. Repeated-measures ANOVA was used for continuous variables or the Friedman rank-sum test for non-normal continuous variables. A value of $p < 0.05$ was considered significant for the Wilcoxon signed-rank test and the Friedman rank-sum test. For post hoc multiple comparisons, we elected a preassigned p/number of comparisons (Bonferroni correction) as the threshold for significance, and therefore, a p value of <0.017 (0.05/3) was used as a definition of statistical significance for n = 3 time points.

We also compared patients based on their self-perception of "wearing off" on the SCQ. Patients who self-reported wearing off "sometimes, usually," or "always" were compared with patients who reported never having wearing off. We also examined the predictors of self-reported wearing off using the logistic regression model in univariate and multivariate analyses. Odds ratios with 95% CI are reported, and statistical differences with $p < 0.05$ were considered significant using a

2-sided test. All statistical procedures were performed using R (R-project.org).

The sample size for our trial was based on an estimated standardized mean difference of outcome variables between preinfusion and postinfusion. Using a 2-sided paired *t* test at a type I error rate of 0.05, we calculated that a sample of 100 patients with data for at least 2 time points would provide 95% statistical power or more to detect the mean NeuroQoL T scores change by more than 10 (60–50) with an SD of 30 points from preinfusion and postinfusion.

Data Availability

Anonymized data are available on reasonable request from qualified investigators.

Results

Patient Characteristics

The flowsheet for the study and the number of questionnaires filled out at each time point in the study are shown in eFigure 1 (links.lww.com/CPJ/A454). Of the 111 patients who filled out the initial questionnaire, 103 completed both the start-cycle (week 4) and the end-cycle (week 22) questionnaires. Thus, the evaluable cohort comprised 103 individuals, who were included in all subsequent analyses. Eighty-nine patients (86%) also filled out start-cycle (week 28) and end-cycle (week 46) questionnaires in cycle 2, allowing us to compare patterns of symptom change across both cycles in this subset.

Demographic and disease-related characteristics for the total cohort, as well as for patients from NYU (n = 43) and ELC (n = 60) MS Centers, are shown in Table 1. Only 6 patients were naive to OCR, whereas others have been on OCR for >1 year (mean duration of treatment was 2.6 years). Because the number of OCR-naive patients was smaller than expected (possibly a result of the COVID-19 pandemic, which began in the early months of the enrollment period), we were unable to compare treatment-naive and non-naive patients statistically. The exclusion of 6 OCR-naive patients from analyses did not change our results (data not shown).

NYU patients were, on average, more than a decade younger, less disabled, had a shorter time to last relapse, had fewer comorbidities, and were more ethnically diverse compared with ELC patients. The race/ethnicity characteristics of the participants were broadly representative of the catchment areas of our centers.[23] There were no statistical differences between the 2 centers with respect to sex, body mass index (BMI), duration on OCR, and prevalence of COVID-19 during the study. There were no statistical differences in any of the domains of NeuroQoL, SymptoMScreen, and WPAI between NYU and ELC patients (eTable 1, links.lww.com/CPJ/A455), and the data from the 2 centers were therefore combined for the purposes of analyses.

During the study, no relapses were recorded for any participant in either center. The disability remained stable: the initial and final EDSS scores were highly correlated (correlation coefficient >0.9, $p < 0.001$).

Comparisons Across Infusion Cycles on NeuroQoL, SymptoMScreen, and WPAI Questionnaires

The medians (IQR) for all NeuroQoL domains, SymptoMScreen (total and domain specific), and WPAI items for the 3 time points in cycle 1 and cycle 2 are presented in Table 2. The nonparametric Friedman rank-sum tests showed no statistically significant changes on any of the NeuroQoL domain scores across the 3 time points in either cycle 1 or cycle 2, with a single exception of the Sleep domain in cycle 1 ($p = 0.03$ by the Friedman test) for which the post hoc analysis revealed an improvement in sleep quality from week 4 (start cycle) to week 22 (end cycle) ($p = 0.007$). SymptoMScreen scores also did not change significantly across either cycle 1 or cycle 2, except for the Sensory domain of cycle 1, Dexterity domain of cycle 2, and Depression score in cycle 2 (Friedman test: $p = 0.024$, $p = 0.048$, and $p = 0.007$, respectively). The post hoc analysis showed that the difference in the depression score over time was due to the improvement from week 36 to week 46 ($p = 0.005$), whereas the difference between any 2 time points in the Sensory and Dexterity domains did not attain significance. Fatigue, consistently identified as the most common symptom of wearing off in MS,[5-8] showed no change across the 3 time points in either the first or the second cycle on either NeuroQoL or SymptoMScreen scales.

For WPAI, the Friedman test revealed that scores for all 4 questions did not change significantly throughout cycle 1. In cycle 2, there were significant changes in presenteeism ($p = 0.006$) and absenteeism ($p = 0.001$) in the subset of employed patients (n = 33). The post hoc analysis showed a 10% worsening between week 28 (start cycle) to week 46 (end cycle) for both presenteeism ($p = 0.002$) and absenteeism ($p < 0.001$) in the employed patients.

Sensitivity analyses of temporal trends in NeuroQoL, SymptoMScreen, and WPAI that excluded patients who were infected with COVID-19 during the study (n = 25) did not change any of the conclusions.

Meaningful Symptom Changes From the Start to the End of the Infusion Cycle

NeuroQoL scores in Fatigue, Sleep, Arm, and Leg domains were classified into "None," "Mild," "Moderate," and "Severe" categories[12] for each participant and were then compared at the start- and end-cycle time points. The results for Fatigue, Sleep, Arm, and Leg domains are presented as 8 Sankey diagrams—2 per cycle for each of the 4 domains—in Figure 1.

For the Fatigue domain in cycle 1 (Figure 1A), there were 98 patients with evaluable start- and end-cycle questionnaires, of whom 13.2% worsened from the start to the end of the cycle

Table 1 Demographic and Clinical Characteristics of Patients in the Total Cohort and the 2 Contributing Centers

Variables	All patients (N = 103)	ELC (N = 60)[a]	NYU (N = 43)[a]	*p* Value[b]
Age in years	46.49 (12.24)	51.77 (10.76)	39.12 (10.29)	<0.001
Female (%)	70 (68%)	43 (72%)	27 (63%)	0.3
Race/Ethnicity (%)				<0.001
White	69 (67%)	55 (92%)	14 (33%)	
African ancestry	17 (17%)	2 (3.3%)	15 (35%)	
Hispanic/Latino	14 (14%)	3 (5.0%)	11 (26%)	
Others	3 (2.9%)	0 (0%)	3 (7.0%)	
Body mass index (SD)	28.17 (5.97)	27.84 (5.10)	28.62 (7.06)	0.8
Smoking status				0.8
Current	7 (6.8%)	4/60 (6.7%)	3 (7.0%)	
Former	23 (22%)	15/60 (25%)	8 (19%)	
Never	73 (71%)	41/60 (68%)	32 (74%)	
Disease duration in years (SD)	15.53 (10.80)	18.65 (11.23)	11.19 (8.54)	<0.001
Disease subtype				<0.001
Primary progressive MS	18 (17%)	16 (27%)	2 (4.7%)	
Secondary progressive MS	23 (22%)	17 (28%)	6 (14%)	
Relapsing-remitting MS	62 (60%)	27 (45%)	35 (81%)	
Years from the last relapse to enrollment	7.36 (7.22)	10.43 (8.10)	3.34 (2.55)	<0.001
Missing	29	18	11	
Naive to Ocrevus (%)	6 (5.8%)	3 (5.0%)	3 (7.0%)	0.7
Ocrelizumab duration in weeks	134.03 (54.89)	138.83 (49.45)	127.19 (61.83)	0.2
Missing	6	3	3	
COVID-19 during study	25 (24%)	12 (20%)	13 (30%)	0.2
EDSS at baseline ≤3 (%) 3.23 (2.09)	61 (59%) 3.23 (2.09)	29 (48%) 3.77 (2.03)	32 (74%) 2.60 (2.01)	0.008 0.002
EDSS at 24th week ≤3 (%) 3.16 (2.07)	64 (62%) 3.16 (2.07)	28 (52%) 3.70 (2.07)	36 (72%) 2.58 (1.93)	0.035 0.005
EDSS at 48th week ≤3 (%) 3.24 (2.08)	53 (60%) 3.24 (2.08)	26 (51%) 3.59 (2.07)	27 (71%) 2.79 (2.05)	0.056 0.093
Total # comorbidities				0.004
0	26 (25%)	8 (13%)	18 (42%)	
1	23 (22%)	15 (25%)	8 (19%)	
2 or more	54 (52%)	37 (62%)	17 (40%)	
Do you have increase in symptoms before you receive OCR?				0.7
Always	2 (2.2%)	1 (1.9%)	1 (2.6%)	
Never	44 (48%)	27 (52%)	17 (44%)	
Sometimes	31 (34%)	18 (35%)	13 (33%)	
Usually	13 (14%)	6 (12%)	7 (18%)	
Missing	12	8	5	

Continued

Table 1 Demographic and Clinical Characteristics of Patients in the Total Cohort and the 2 Contributing Centers *(continued)*

Variables	All patients (N = 103)	ELC (N = 60)[a]	NYU (N = 43)[a]	*p* Value[b]
Self-report wearing off (includes: sometimes/often/always)	44 (48%)	27 (52%)	17 (44%)	0.4
Missing	12	8	4	

Abbreviations: EDSS = Expanded Disability Status Scale score; ELC = Elliot Lewis Center for Multiple Sclerosis; NYU = NYU Multiple Sclerosis Care Center; OCR = ocrelizumab. Comorbidities included self-reported cardiovascular, psychiatric (depression or other mental illness), endocrine (including diabetes), gastrointestinal, oncologic (systemic cancer), pulmonary, systemic autoimmune rheumatologic diseases, other significant medical problems, and surgical history. For the 6 OCR-naive patients, prior disease-modifying therapy was natalizumab (2), fingolimod (1), and none (3).
[a] Mean (SD); n/N (%).
[b] Comparison between 2 centers using the Wilcoxon rank-sum test, Pearson χ^2 test, and Fisher exact test.

(6 patients from "none" to "mild" and 7 from "mild" to "severe"), 19% improved from the start to the end of the cycle (all of them from either "mild" to "none" or from "moderate" to "mild"), and the remaining 67.3% stayed in the same fatigue severity category. Similarly, for cycle 2, 11.6% worsened (from either "none" to "mild" or "mild" to "severe"), and 17.4% improved (from "mild" to "none" or from "moderate" to "mild"), and the remaining 71% remained "unchanged" (Figure 1B). Four patients improved in both cycles, 4 improved in one cycle and worsened in the other, and none worsened in both cycles.

In the Sleep domain (Figures 1, C and D), 19.4% of patients improved from the start to the end of cycle 1, and 7% improved toward the end of the cycle in cycle 2; 10.2% worsened from the start to the end of cycle 1, and 14% worsened in cycle 2. Consistent improvement in Sleep toward the end of both cycles was recorded by 3 patients and consistent worsening by 1. With regard to Leg function (Figures 1, E and G), 9.2% of patients improved from the start to the end of cycle 1 and 6% in cycle 2. Worsening from the start to the end of the cycle was reported by 15% in cycle 1 and 14% in cycle 2. No patient showed improvement or worsening in Leg function in both cycles. In the Arm domain (Figure 1, G and H), 10.2% of patients improved from the start to the end of cycle 1 and 9.3% in cycle 2. Worsening was reported by 5% in cycle 1 and 11.6% in cycle 2. Improvement in Arm function in both cycles was recorded for 1 patient and worsening by none. No patient showed worsening for more than 1 domain in both cycles, whereas 8 patients showed improvement in 2 or more domains in both cycles.

Similar results were obtained with SymptoMScreen: mean scores worsened by more than 0.5 points from the start to the end of cycle 1 in 10% and improved in 13.9%, whereas in cycle 2, 9.3% of patients worsened, and 11.6% improved. Only 1 patient worsened by >0.5 points in the mean SymptoMScreen score in both cycles, whereas 3 patients improved by >0.5 points in both cycles.

Because of the small number of patients with meaningful worsening or improvement across 2 cycles on either NeuroQoL or SymptoMScreen, we could not perform logistic regression to identify predictors of consistent symptom improvement or worsening.

Comparing Patients With Improvement, Worsening, and No Change in Symptoms Across the Infusion Cycle

Comparisons among the patients whose symptoms meaningfully improved, worsened, or remained unchanged on the 4 NeuroQoL domains (Fatigue, Sleep, Arm, and Leg Function) in either cycle are summarized in eTable 2 (links.lww.com/CPJ/A455). There were only a few differences with borderline significance between these groups in cycle 1 or cycle 2, mostly because of the "no change group." None of the differences were sustained in both cycles. Notably, there were no differences in OCR serum concentration among patients whose symptoms improved, worsened, or remained the same in either cycle for any domain. NfL concentration was similar in the 3 subgroups for 6 of 8 comparisons and was marginally higher in those whose Sleep improved toward the end of cycle 1 and marginally lower in those whose Sleep worsened toward the end of cycle 2. BMI was similar across the 3 subgroups. Patients who reported wearing off on the SCQ were not more likely to show a change in symptoms on NeuroQoL domains than those who did not.

These conclusions were largely replicated with SymptoMScreen, as shown in eTable 3 (links.lww.com/CPJ/A455). The only difference between the groups sustained in both cycles was that White patients were less likely to show symptom changes than the other racial groups in both cycles 1 and 2 (p = 0.024 and 0.006, respectively), possibly because of their lower baseline symptom burden than in other race/ethnic groups. Again, there were no statistically significant differences among those whose symptoms improved, worsened, or remained unchanged with respect to OCR concentrations or BMI. NfL levels were similar across 3 subgroups in cycle 1 and were elevated in those whose symptoms worsened in cycle 2, but only for NfL levels measured at 24 weeks (end of the first cycle) and not 48 weeks (end of the second cycle). Taken together, our data do not suggest any relationship between symptom worsening and NfL levels or OCR serum concentration.

Comparing Patients With and Without Self-Report of Wearing Off

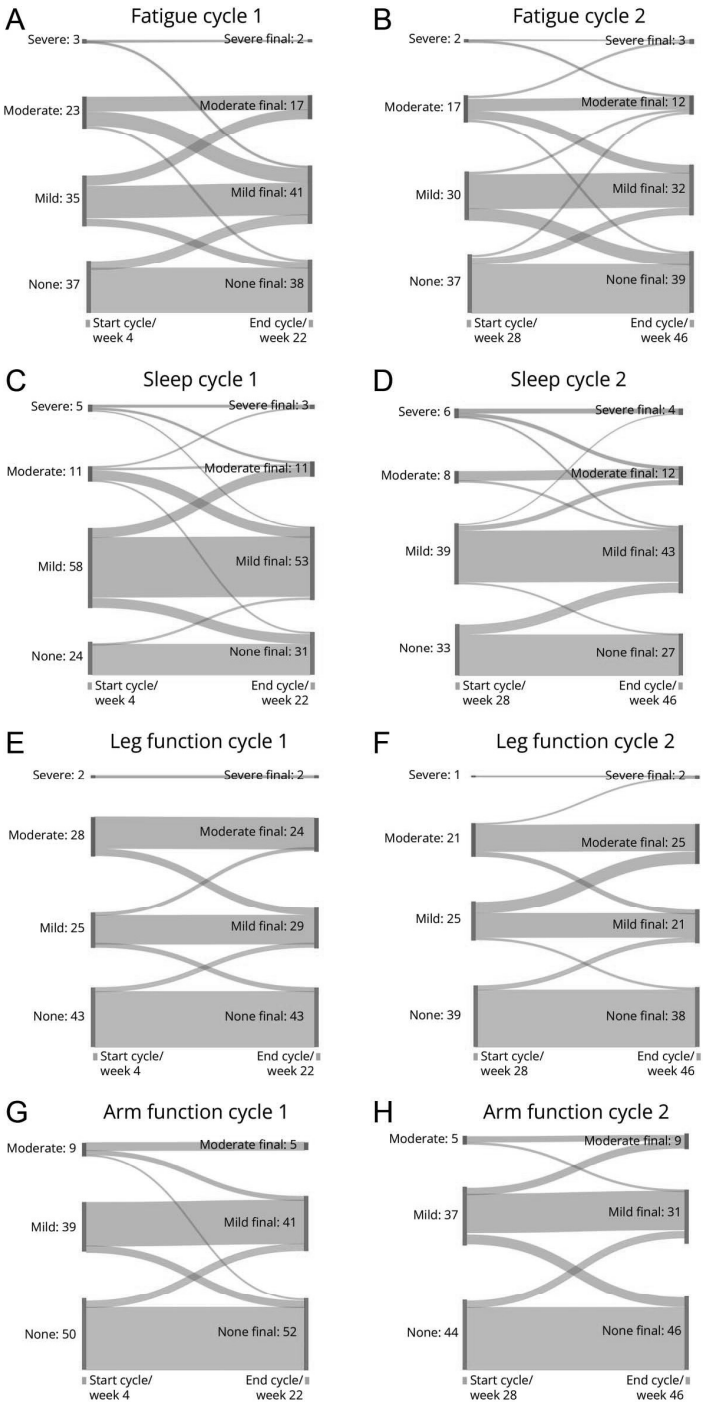
Of the 99 participants who filled out the study completion questionnaire (SCQ), 54 (54.5%) reported that they "sometimes" (n = 34), "usually" (n = 16), or "always" (n = 4) experienced an

Table 2 NeuroQoL, SymptoMScreen, and WPAI Median Scores and Interquartile Ranges (IQRs) at Each Time Point in the Infusion Cycle

	Cycle 1				Cycle 2			
SymptoMScreen	Week 4 N = 85[a]	Week 12 N = 85[a]	Week 22 N = 85[a]	*p* Value[b]	Week 28 N = 75[a]	Week 36 N = 75[a]	Week 46 N = 75[a]	*p* Value[b]
Walking	2 (0, 3)	1 (0, 3)	1 (0, 3)	0.489	2 (0, 3)	2 (0, 3)	1 (0, 3)	0.830
Hand function/dexterity	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.551	1 (0, 2)	1 (0, 2)	1 (0, 2)	**0.048**
Spasticity and stiffness	2 (0, 3)	2 (1, 3)	2 (1, 2)	0.344	2 (1, 3)	2 (1, 3)	1 (0, 3)	0.197
Bodily pain	1 (0, 2)	1 (0, 3)	1 (0, 2)	0.266	1 (0, 3)	1 (0, 3)	1 (0, 2)	0.357
Sensory	1 (1, 2)	1 (1, 2)	1 (1, 2)	**0.024**	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.090
Bladder control	1 (0, 3)	1 (0, 2)	1 (0, 2)	0.241	1 (0, 2)	1 (0, 3)	2 (0, 3)	0.572
Fatigue	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.614	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.489
Vision	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.290	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.590
Dizziness	1 (0, 1)	0 (0, 1)	0 (0, 1)	0.255	0 (0, 1)	0 (0, 1)	1 (0, 1)	0.442
Cognitive function	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.155	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.752
Depression	1 (0, 2)	1 (0, 1)	0 (0, 2)	0.106	0 (0, 2)	1 (0, 2)	0 (0, 2)	**0.007**
Anxiety	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.351	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.361
Symptom screen total	14 (7, 26)	14 (7, 23)	13 (6, 22)	0.119	12 (6, 22)	15 (7, 24)	14 (6, 24)	0.771
NeuroQoL	Week 4 N = 85[a]	Week 12 N = 85[a]	Week 22 N = 85[a]	*p* Value[b]	Week 28 N = 82[a]	Week 36 N = 82[a]	Week 46 N = 82[a]	*p* Value[b]
Social score	45 (41, 53)	45 (42, 53)	46 (42, 60)	0.124	46 (41, 60)	46 (41, 60)	46 (41, 60)	0.41
Anxiety score	50 (42, 57)	50 (42, 56)	48 (36, 56)	0.097	48 (42, 56)	48 (36, 56)	49 (36, 57)	0.441
Depression score	45 (37, 51)	45 (37, 52)	45 (37, 51)	0.840	43 (37, 51)	45 (37, 51)	43 (37, 51)	0.644
Emotional score	47 (37, 53)	45 (32, 54)	45 (32, 54)	0.270	45 (32, 53)	42 (32, 51)	46 (32, 53)	0.995
Fatigue score	47 (40, 55)	46 (40, 52)	47 (38, 52)	0.124	46 (40, 52)	46 (38, 52)	46 (38, 52)	0.635
Lower extremity score	47 (39, 59)	47 (39, 59)	47 (39, 59)	0.864	48 (40, 59)	47 (38, 59)	49 (38, 59)	0.469
Positive score	53 (47, 58)	53 (49, 63)	55 (50, 63)	0.078	54 (48, 61)	54 (51, 63)	55 (48, 63)	0.480
Sleep score	52 (44, 58)	50 (44, 57)	50 (39, 56)	**0.030**	49 (42, 56)	49 (42, 55)	50 (42, 56)	0.683
Upper extremity score	54 (39, 54)	54 (37, 54)	54 (37, 54)	0.678	54 (38, 54)	44 (39, 54)	54 (36, 54)	0.094
Social satisfaction score	46 (41, 51)	46 (43, 51)	46 (42, 52)	0.225	46 (43, 50)	46 (43, 54)	45 (42, 53)	0.721
Cognitive score	50 (40, 59)	50 (43, 56)	51 (44, 59)	0.093	51 (45, 63)	51 (44, 59)	51 (42, 59)	0.153
WPAI	Week 4 N = 33[a]	Week 12 N = 33[a]	Week 22 N = 33[a]	*p* Value[b]	Week 28 N = 32[a]	Week 36 N = 32[a]	Week 46 N = 32[a]	*p* Value[b]
% Work time missed due to health	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.564	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.702
% Impairment in work due to health	10 (0, 20)	10 (0, 20)	0 (0, 10)	0.241	0 (0, 30)	10 (0, 40)	10 (0, 42)	**0.006**
% Overall work impairment due to health	10 (0, 22)	10 (0, 20)	0 (0, 17)	0.354	0 (0, 30)	10 (0, 40)	10 (0, 50)	**0.001**
WPAI	Week 4 N = 88[a]	Week 12 N = 88[a]	Week 22 N = 88[a]	*p* Value[b]	Week 28 N = 86[a]	Week 36 N = 86[a]	Week 46 N = 86[a]	*p* Value[b]
% Activity impairment due to health	30 (8, 60)	20 (10, 50)	30 (10, 52)	0.073	30 (10, 58)	30 (2, 50)	30 (10, 50)	0.841

Abbreviation: WPAI = Work Productivity and Activity Impairment Questionnaire.
Post hoc comparisons show significant differences for the following time points: NeuroQoL sleep score in cycle 1 improved from week 4 to week 22 (mean ± SD 50.47 ± 9.79 vs 48.36 ± 9.56, $p = 0.007$), SymptoMScreen depression score in cycle 2 improved from week 36 to week 46 (1.07 ± 1.23 vs 0.84 ± 1.10, $p = 0.005$), and WPAI scores on "% impairment while working due to health" in employed patients worsened from week 28 to week 46 (13.12 ± 18.91 vs 22.50 ± 27.59, adjusted $p = 0.002$) and "% overall work impairment due to health" in employed patients also worsened from week 28 to week 46 (14.22 ± 20.15 vs 25.78 ± 29.28, adjusted $p = 0.0005$).
[a] Median (IQR).
[b] Friedman rank-sum test. Significant *p* values ($p < 0.05$) are shown in bold.

Figure 1 Changes in Symptom Severity From the Start of the Cycle to the End of the Cycle in Fatigue, Sleep, Leg, and Arm NeuroQoL Domains



The symptom severity category for the start cycle is shown on the left of each diagram, and the severity category at the end cycle is on the right.

increase in symptoms before OCR infusion. These patients constituted the "self-reported wearing-off group." The 3 most common symptoms to worsen in this group were fatigue (37 patients), spasticity (28 patients), and walking difficulty (26 patients). The remaining 45 (45.5%) patients who reported never experiencing an increase in symptoms at the end cycle constituted the "no self-reported wearing-off group." The 2 groups were compared with respect to baseline clinical characteristics and demographics, as

shown in eTable 4 (links.lww.com/CPJ/A455). In univariate logistic regression, those with wearing off were younger and more likely to have EDSS score >3 at baseline (OR = 3.2, 95% CI [1.4–7.7], p value = 0.006) and at week 24 (OR = 2.7, 95% CI [1.16–6.48], p value = 0.021), had lower OCR concentration before infusion, and higher median NeuroQoL, SymptoMScreen, and WPAI scores on nearly all domains/responses (all OR > 1, p values < 0.05; eTable 4). In a multivariate logistic regression model, younger age (p = 0.004) at baseline and higher EDSS score (p = 0.029) at baseline were independent predictors of self-reported wearing off.

Discussion

In SymBOLS, a prospective, 2-center study of 103 neurologically stable OCR-treated patients, symptom burden assessed with NeuroQoL and SymptoMScreen either remained stable throughout the infusion cycles or improved slightly toward the end of the cycle (Table 2). Meaningful worsening from the start to the end of the cycle was no more common than meaningful improvement (Figure 1). Worsening toward the end of the cycle in both cycles was recorded by just 1 patient in a single NeuroQoL domain (Sleep), whereas end-of-cycle improvement in the 2 cycles was reported by 8 patients. The only trend for worsening toward the end of the cycle was a 10% increase in absenteeism and presenteeism in a subset of employed patients (in the second cycle alone).

Despite the lack of demonstrable symptomatic worsening with a longer time from infusion, more than half of our participants responded affirmatively to the question, "Have you ever experienced wearing off?". The distribution of responses was similar to that of a prior study of wearing off with OCR,[4] in which 39% "Never" had wearing off (vs 48% in ours), 44% had it "Sometimes" (vs 34% in our study), 10% had wearing off "Usually" (vs 14% in our study), and 6% "Always" (vs 2% in our study). Other points of similarity between the 2 studies are that neither study observed a correlation between serum NfL levels and self-reported wearing off, and neither showed statistically significant differences in symptom severity before and after infusion among those who perceived wearing off and those who did not. In both studies, patients with self-reported wearing off had a higher symptom burden than those who did not. Factors predicting the self-report of wearing off in multivariate analyses in our cohort were younger age and higher disability. However, unlike the Dutch study, we did not observe that a higher BMI increases the odds ratio of self-perceived wearing off. This may be due to the average BMI of our patients being several points higher than the average BMI of the Dutch patients.[4] In our study, there were no differences in BMI among patients whose symptoms worsened, improved, or stayed the same in either cycle for either NeuroQoL or SymptoMScreen (eTables 2 and 3, links.lww.com/CPJ/A455). Thus, we found no evidence of a significant confounding effect of BMI.

The 2 studies of wearing off with OCR cast doubt on the existence of wearing off as a physiologic phenomenon defined by consistent worsening of symptoms toward the end of the infusion cycle and consistent improvement with reinfusion. The common perception of wearing off is probably mostly due to natural fluctuations in MS symptoms,[11] which are liable to be attributed to "wearing off of the drug" when they coincide with the time for reinfusion. Conversely, any symptom improvement after infusion could be plausibly attributed to the treatment effect. However, our data show that symptom improvement and worsening occur independently of the time from the infusion and are, therefore, unlikely to be due to infusion. Several additional lines of evidence argue against "physiologic wearing off" with OCR. There is no evidence for disease reactivation toward the end of the cycle,[1,2,4,24] and moreover, there was no relation between extending the dosing interval between infusions and the frequency of wearing off in the Dutch study. Rather, patients tended to report worsening symptoms within a few days of infusion, independent of whether the infusion interval was extended or not.[4] Thus, patients should not be dissuaded from extending the interval between OCR infusions—when clinically appropriate—for the fear of wearing off, nor is it likely that shortening the time from infusions will have a measurable impact on symptom burden. Finally, serum NfL, a highly sensitive marker of neuroaxonal damage[14,15] and subclinical MS activity,[25] was similar in those who perceived wearing off and those who did not, which suggests that self-reported wearing off is not the result of subclinical disease activity.

The perception of wearing off in the absence of a measurable uptick in disease activity has been documented in other neurologic conditions as well. For example, more than one-third of patients with migraine reported wearing off with monthly or quarterly injections of CGRP receptor monoclonals in observational studies,[26] but rigorous analyses of trial data fail to disclose any evidence for a decrease in drug efficacy with a longer time from injection.[27,28] It seems likely that migraineurs, as patients with MS, attribute any headache close to the reinjection time to the decreasing drug effect. The diminishing expectation of drug efficacy can be referred to as the "wo-cebo effect," which needs to be differentiated from physiologic wearing off that is consistent with the drug's pharmacokinetics, such as the disease reactivation after desaturation of alpha4 integrin receptor with natalizumab,[29] an increase in the infection rate toward the end of the IV immunoglobulin infusion cycle in patients with immunodeficiency,[30] or, most dramatically, "off" symptoms in Parkinson disease with levodopa therapy.[31]

The main limitation of our study is its relatively small size and duration. A longer study with more patients might have detected consistent wearing off in at least some patients, although their number would be expected to be quite small. It is also possible that using more sensitive tools for functional assessment, such as wearable devices that monitor activity on a day-to-day basis,[32] would allow one to uncover subtle changes in function across the cycle that lie below the threshold of even the best patient-reported outcome

measures. The possibility of selection bias must also be acknowledged. If patients with consistent wearing off are more likely to discontinue OCR soon after starting on it, they could be underrepresented in our sample. However, this would unlikely have a major impact on the results because the rates of OCR discontinuation in clinical trials and real-world practice are less than 5% over a 1–2 year period.[1,33] It is also possible that patients who declined participation—very few did—or failed to participate after the initial enrollment (see the flowchart in eFigure 1, links.lww.com/CPJ/A454) would show a different pattern of responses than the study completers. Finally, although our 2-center study design allowed us to ascertain that responses from the 2 different demographic areas were very similar (eTable 1, links.lww.com/CPJ/A455), the extent to which our results are generalizable to patients with MS receiving care outside of specialized referral centers is unknown. Patients followed by referral centers tend to be younger[34] and more rapidly disabled,[35] which may lead to higher rates of self-reported wearing off in our sample than in the general MS population.

In conclusion, in our prospective study of patients with MS treated with OCR, symptom fluctuations were common but unrelated to time from the infusion. Future studies should seek to improve our understanding of the causes of symptom fluctuation in MS, a question that has not received sufficient attention to date.

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Disclosure

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No Increase in Symptoms Toward the End of the Ocrelizumab Infusion Cycle in Patients With Multiple Sclerosis: Symptom Burden on Ocrelizumab: A Longitudinal Study (SymBOLS)

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