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Influence of personalized extended interval dosing on the natalizumab wearing-off effect - a sub-study of the NEXT-MS trial

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ABSTRACT

Background and objectives: Wearing-off symptoms during natalizumab treatment in multiple sclerosis are characterized by an increase of MS-related symptoms prior to natalizumab administration. The influence of extended interval dosing (EID) on wearing-off symptoms are important to consider, as this might cause hesitancy in initiating or continuing EID.

Methods: Participants of the NEXT-MS trial, in which treatment intervals are adjusted based on drug concentrations, were divided into two groups: an extended group containing participants with at least one week of additional interval extension, and a group with a fixed interval during the trial (range 4–7 weeks). Changes in the occurrence, frequency, onset, and severity of wearing-off symptoms were evaluated.

Results: 255 participants were included (extended group $n = 171$, fixed group $n = 84$). The odds on occurrence of wearing-off symptoms in the extended group did not increase after extending the treatment interval. Additional

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analyses for frequency, onset, and severity of wearing-off symptoms showed no changes over time. Mean decrease in natalizumab drug concentration did not influence the frequency of wearing-off symptoms.
Discussion: Wearing-off symptoms were not reinforced by further extending the natalizumab interval. Wearing-off symptoms might increase in a minority of patients after EID, although our data support the view that wearing-off symptoms appear to be unrelated to the decrease in natalizumab trough drug concentrations.

1. Introduction

Wearing-off is a common phenomenon experienced by persons with multiple sclerosis (MS) using natalizumab [1–4]. Wearing-off symptoms are usually described as an increase of MS-related symptoms, mostly fatigue, in the run-up to the next treatment. Wearing-off symptoms usually disappear in the first days after infusion of natalizumab, and re-occur in a cyclical manner towards the end of a new treatment round [1–4]. In another research cohort, the wearing-off phenomenon was not associated with increased radiological or clinical disease activity, suggesting wearing-off symptoms do not reflect decreased efficacy of natalizumab [5]. Still, although wearing-off symptoms are mostly rated as mild, the majority of persons (54–67%) experience wearing-off symptoms at some point during treatment with natalizumab, causing inconvenience and possibly increased burden of treatment [1,2,4].

Extended interval dosing (EID) of natalizumab is increasingly used in daily practice to optimize treatment convenience, to reduce the risk of progressive multifocal leukoencephalopathy (PML), and to lower healthcare costs [6–9]. Hesitancy towards EID due to wearing-off symptoms can prevent persons from adopting or continuing an extended treatment regimen [10]. Longitudinal prospective data on wearing-off symptoms after switching to EID are currently lacking. Our aim was to longitudinally study the occurrence of wearing-off symptoms, and to investigate any changes in frequency, onset, or severity of wearing-off symptoms after further extending the natalizumab treatment interval.

2. Methods

2.1. Study design and participants

This was a sub-study of the NEXT-MS trial, an investigator-initiated prospective phase IV nonrandomized multicenter trial studying natalizumab personalized EID in which treatment intervals are adjusted based on trough drug concentrations [10]. Inclusion criteria were adults with a diagnosis of relapsing-remitting MS according to the 2017 McDonald criteria who had thus far received six or more consecutive natalizumab infusions, and provided written informed consent [11]. The NEXT-MS trial contained three study groups: personalized EID with a target trough drug concentration of 10 μg/mL (EID10), a subgroup of personalized EID with a target of 5 μg/mL (EID5), and standard interval dosing of 4 weeks (SID). Subcutaneous administration of natalizumab was added to the NEXT-MS trial protocol after approval by the European Medicines Agency in 2021 [10,12]. For this sub-study, participants were divided into two groups: an extended group containing all participants with at least one week of additional interval extension during the monitoring period of the NEXT-MS trial compared to the start of the trial, and a group with no new interval extension during the trial (range 4–7 weeks) [10]. Participants were included when data regarding wearing-off symptoms were available at baseline and year 1.

2.2. Study procedures and outcomes

Clinical and radiological results of the first phase of the NEXT-MS trial were reported separately, as all participants were asked to participate in the second phase of the study with an amended study protocol [10]. The occurrence of the natalizumab wearing-off phenomenon and changes over time with extended dosing was one of the secondary outcomes, and these results are reported here. A questionnaire about wearing-off symptoms was sent via Castor EDC (Castor Electronic Data Capture 2019) at baseline, year 1, and year 2. Participants were allowed to complete the questionnaire on paper on request. The questionnaire evaluated the natalizumab wearing-off phenomenon, similar to the questionnaires previously used by our study group (supplementary material) [1,13]. In short, participants were asked at baseline if they ever experienced the wearing-off phenomenon (never, sometimes, usually or always). Participants could specify which wearing-off symptoms occur, their severity, and duration of wearing-off symptoms (pre- and post natalizumab treatment). At year 1 and 2, the questions focused on experienced wearing-off symptoms only in the last year (supplementary material). As the median FU duration of the first phase of the NEXT-MS trial was shorter (87 weeks) than the initially planned FU (104 weeks), only questionnaires at baseline and year 1 were evaluated in this sub-study. When participants discontinued the study due to self-reported wearing-off symptoms, the wearing-off questionnaire was provided in retrospect. Natalizumab trough drug concentrations were measured throughout the study according to the NEXT-MS trial protocol [10].

2.3. Statistical analyses

Baseline characteristics and natalizumab treatment intervals of both study groups were described (means with standard deviation, medians with interquartile range (IQR), or frequencies with percentages). Values were compared between groups using the Chi-Square test for categorical variables, the *t*-test for normally distributed continuous variables, and the Mann-Whitney *U* test for non-normally distributed continuous variables. Occurrence, frequency, onset, and severity of wearing-off symptoms in both study groups at baseline and during follow-up (year 1) were described separately. Frequency of wearing-off symptoms (baseline vs year 1) was also investigated per interval extension group (weeks) and per mean decrease (quartiles) in natalizumab trough concentration after interval extension. Mean decrease in natalizumab concentration was calculated between baseline and year 1 (year 1 – baseline) and divided into quartiles.

Next, changes in occurrence of wearing-off symptoms over time during the first year within the extended and fixed group were analyzed. The answers ‘sometimes’, ‘usually’, and ‘always’ (second question supplementary material) were combined to dichotomize the occurrence of wearing-off symptoms. Generalized Estimating Equations (GEE) analyses were performed for both groups separately with time included as an independent variable (exchangeable correlation matrix). Sex, age, body mass index (BMI), EDSS score, treatment duration, and weeks of interval extension were explored as effect modifiers by including each as independent variable, as well as the interaction with time, and were explored as confounders thereafter. Data were stratified in case of a significant interaction. Confounders were added stepwise to the model when there was >10% difference in β-value compared to the previous model. Frequency, onset, and severity of symptoms were analyzed similarly as ordinal logistic outcome variables for participants with wearing-off symptoms in the extended group. Finally, differences in wearing-off symptoms between the extended and fixed group over time were analyzed, with participants as subject variable and time as within-subject variable (exchangeable correlation matrix). Study group and time were added to the model as independent variables, as well as the interaction between study group and time. Sex, age, body mass index (BMI), EDSS score, and treatment duration were explored as effect

modifiers and confounders. A p-value <0.05 based on two-tailed statistical tests was considered statistically significant. Statistical analyses were performed in SPSS statistic software version 28.0 (IBM, Armonk, NY). Figures were designed in GraphPad Prism version 9.3.1 for Windows (GraphPad software, San Diego, California USA) and R statistical software version 4.0.3.

2.4. Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the medical ethics committee (VUMC Ethics committee number 2019.552). Oral and written informed consent was obtained from all participants. The NEXT-MS trial protocol was registered online (ClinicalTrials.gov: NCT04225312) [10].

3. Results

3.1. Participants

In the NEXT-MS trial, 376 participants started with the study [10]. For this study, 171 participants of the extended group and 84 participants of the fixed group with an available baseline and year 1 wearing-off questionnaire were included (Fig. 1).

Characteristics of the selected participants at baseline are presented in Table 1.

Median natalizumab treatment duration was 4.4 years and 13% of participants had an extended treatment interval at baseline. Natalizumab trough drug concentrations were lower and BMI was higher in the fixed group at baseline (Table 1). Six participants (2.5%) of the extended group dropped out due to self-reported wearing-off symptoms after (further) extending their treatment interval. Three out of four participants who dropped out before the first year completed the wearing-off questionnaire in retrospect.

3.2. Wearing-off symptoms at baseline and year 1

At baseline, 117 participants (46%) experienced wearing-off symptoms during previous treatment with natalizumab (extended group 42%, fixed group 55%; Fig. 2).

Table 1
Baseline characteristics of included participants.

	Extended group (n = 171)	Fixed group (n = 84)	Total (n = 255)	p-value
Age, years	41.4 ± 11.4	41.6 ± 10.0	41.5 ± 11.0	0.87
Sex, female	131 (76.6)	66 (78.6)	198 (77.3)	0.73
Body weight, kilograms	74.4 ± 14.1	79.6 ± 18.1	76.1 ± 15.7	**0.023**
Body mass index, kg/m^2	24.6 ± 4.3	26.8 ± 6.1	25.3 ± 5.1	**0.004**
Time since diagnosis, years	11.1 (5.6–16.9)	11.2 (5.5–15.5)	11.1 (5.6–16.4)	0.72
Duration of NTZ treatment, years	4.1 (1.6–8.7)	4.7 (1.9–9.7)	4.4 (1.7–8.9)	0.58
EDSS score	3.0 (2.0–4.0)	3.0 (2.0–5.4)	3.0 (2.0–4.5)	0.26
NTZ trough concentrations, µg/mL	25.0 (18.5–38.0)	13.0 (8.5–20.5)	22.3 (13.5–32.0)	**<0.001**
Treatment interval				**<0.001**
-4 weeks	151 (88.3)	71 (84.5)	222 (87.1)	
-5 weeks	10 (5.8)	3 (3.6)	13 (5.1)	
-6 weeks	7 (4.1)	10 (11.9)	17 (6.7)	
-7 weeks	3 (1.8)	–	3 (1.2)	

The extended group contains all participants with at least one week of interval extension during the monitoring period of the NEXT-MS trial compared to the start of the trial. The fixed group contains all participants with no new interval extension during the trial (range 4–7 weeks). Values were compared between groups using the Chi-Square test for categorical variables, the t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. EDSS = Expanded Disability Status Scale; NTZ = natalizumab.

At year 1, 111 participants (44%) experienced wearing-off symptoms in the last year (extended group 40%; fixed group 50%). Wearing-off symptoms were similar to previous studies and consisted mainly of fatigue (baseline 32%, year 1 37%), occurred most frequently 3–7 days before treatment (baseline 48%, year 1 62%), and were mostly rated as mild (baseline 63%, year 1 68%, Fig. 3).

The majority of participants in the extended group never

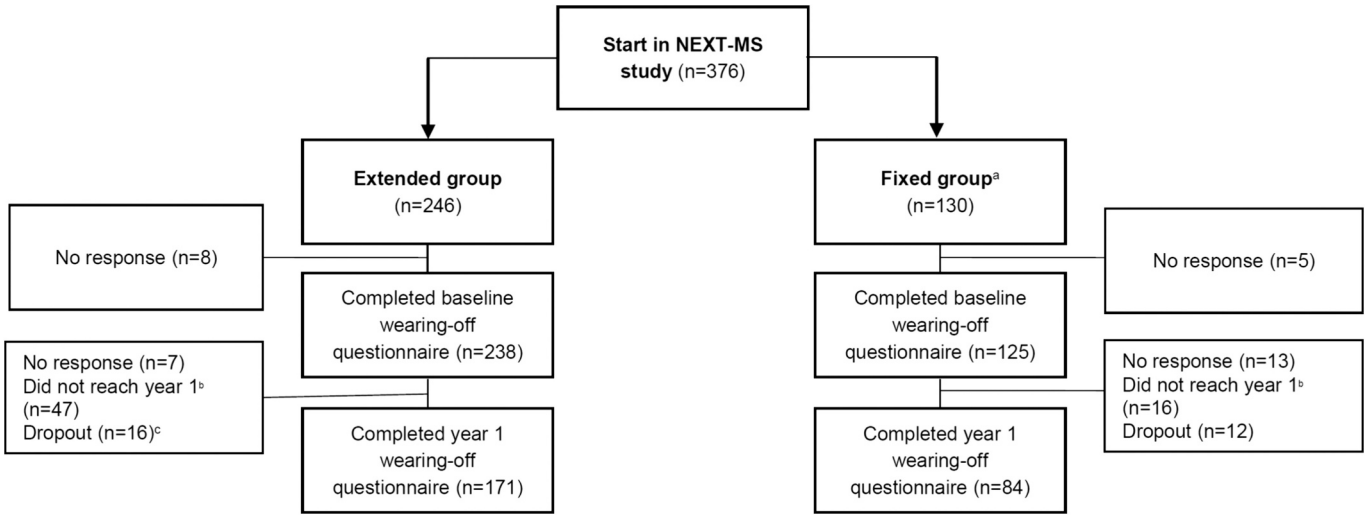

Fig. 1. Flowchart of the inclusion process and overview of completion of questionnaires.
[a]In the fixed group (n = 130), 60 participants (46%) chose for the 4 week treatment interval, 54 participants (42%) were on a 4 week treatment interval in one of the EID groups due to low natalizumab trough concentrations at baseline, and 16 participants (12%) were on EID before the study and had no further interval extension during the study.
[b]Questionnaires were not available due to not reaching the time point yet as the NEXT-MS trial continued with a new study phase before the trial was completed [10].
[c]Six participants dropped out due to wearing-off symptoms within the first year, of whom four participants did not complete the year 1 questionnaire. Wearing-off questionnaires were completed in retrospect by three participants and were added to the analyses (n = 171). Overall response rate for the questionnaires at baseline was 97% in the extended group and 96% in the fixed group. The response rate at year 1 was 96% in the extended group, and 87% in the fixed group.

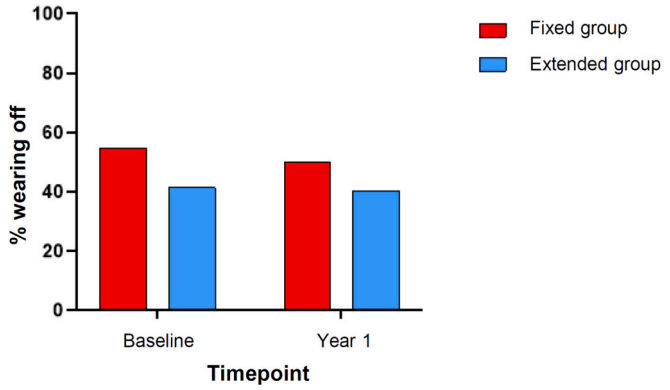

Fig. 2. Percentage of participants with wearing-off symptoms at baseline and year 1.
The answers 'sometimes', 'usually', and 'always' (second question supplementary appendix) were combined to dichotomize the occurrence of wearing-off symptoms.

experienced wearing-off symptoms at baseline and year 1 (Fig. 2). In the extended group, 26 participants (15%) reported an increase in occurrence of wearing-off symptoms in the first year, while 39 participants (23%) reported a decrease of wearing-off symptoms compared to baseline (Fig. 3). In participants with wearing-off symptoms in the extended group, symptoms started sooner and were rated more severe in 25% (Fig. 3).

3.3. Natalizumab treatment intervals and drug trough concentrations

Treatment intervals in the extended group at year 1 ranged between 5 and 9 weeks with a median treatment interval of 6 weeks (IQR 5–6 weeks). Frequency of wearing-off symptoms per amount of additional weeks added to the treatment interval during the study (range 0–4 weeks) was stable or decreased in most participants (Fig. 4A). In the extended group, baseline median natalizumab drug trough concentration was 25.0 μg/mL (IQR 18.5–38.0 μg/mL). At year 1, median natalizumab drug trough concentration was 9.8 μg/mL (IQR 6.5–14.0 μg/mL). Mean decrease in natalizumab drug trough concentration between year 1 and baseline was 17.9 μg/mL ± 12.1 μg/mL. When dividing mean decrease in natalizumab concentration into quartiles, no clear increase in frequency of wearing-off symptoms was present in all quartiles at year 1 (Fig. 4B).

3.4. Changes in wearing-off symptoms over time with fixed- and extended dosing

Within the extended group, GEE analyses showed the odds on occurrence of wearing-off symptoms did not change over time at year 1 compared to baseline (Exp(β) 0.95, 95% CI 0.70–1.31, $p = 0.76$). There were no relevant effect modifiers or confounders. Additional analyses with ordinal outcome variables for frequency (Exp(β) 1.16, 95% CI 0.87–1.57, $p = 0.32$; corrected for sex: Exp(β) 1.14, 95% CI 0.84–1.55, $p = 0.39$), onset (Exp(β) 0.71, 95% CI 0.39–1.29, $p = 0.26$; corrected for treatment interval: Exp(β) 0.74, 95% CI 0.40–1.35, $p = 0.32$), and severity (Exp(β) 0.71, 95% CI 0.40–1.28, $p = 0.26$) of wearing-off symptoms showed no changes over time (Fig. 3). Within the fixed group, the odds on occurrence of wearing-off symptoms did not change over time at year 1 compared to baseline, and there were no relevant effect modifiers or confounders (Exp(β) 0.83, 95% CI 0.57–1.20, $p = 0.32$).

GEE analyses showed a lower odds on occurrence of wearing-off symptoms in the extended group compared to the fixed group (Exp(β) 0.59, 95% CI 0.35–0.99, $p = 0.047$) that did not change over time as the overall p-value of the interaction with time was not significant ($p = 0.57$). There were no relevant effect modifiers or confounders.

4. Discussion

We prospectively studied personalized EID of natalizumab in MS and found that occurrence of wearing-off symptoms does not increase over time after further extending the natalizumab treatment interval. Characteristics of wearing-off symptoms were comparable before and after further extending the natalizumab treatment interval in most participants.

After the COVID-19 pandemic, conflicting retrospective data on the occurrence of wearing-off symptoms after start of EID were shared. One study reported EID did not result in different frequency of wearing-off symptoms compared to SID [14], while another study reported an increase of wearing-off symptoms after start of EID, especially with presence of pre-existing wearing-off symptoms [15]. In our prospective study, we found that occurrence, frequency, onset, and severity of wearing-off symptoms did not increase over time after further extending the natalizumab treatment interval. Frequency of wearing-off symptoms per interval extension group was stable or decreased in most participants. Another study regarding wearing-off symptoms after interval extension in ocrelizumab treatment patients showed comparable results [16]. In our study, although interval extension of 4 weeks increased frequency of wearing-off symptoms in two out of five participants, mean decrease in the highest quartile of natalizumab drug concentration only increased frequency of wearing-off symptoms in 11%. Furthermore, we found a lower odds on occurrence of wearing-off symptoms in the extended group compared to the fixed group. This might be explained by the nonrandomized study design of the NEXT-MS trial, in which participants were allowed to choose their study group [10]. In the fixed group, 46% of participants chose for SID, and this might be due to wearing-off symptoms before start of the study. However, 42% of participants in the extended group experienced previous wearing-off symptoms at some point during treatment with natalizumab, which did not withhold them from extending their treatment interval. On the other hand, six participants (3%) of the extended group discontinued the NEXT-MS trial due to wearing-off symptoms after (further) extending their treatment interval. The occurrence of possible wearing-off symptoms under both SID and EID and possible changes in frequency, onset, and severity of wearing-off symptoms in a minority of patients can be discussed by physicians when initiating EID of natalizumab, together with any hesitancy patients might have to further extend the natalizumab treatment interval due to wearing-off symptoms.

Even though we did not see an increase in wearing-off symptoms after additional interval extension of natalizumab, it remains unclear whether a biological pathway is the underlying cause of the wearing-off phenomenon. In a previous study, higher EDSS scores were associated with wearing-off symptoms, mainly sphincterial function of the bladder/bowel functional system [14], and a positive association between natalizumab wearing-off symptoms and body weight or body mass index (BMI) was found repeatedly [1,3]. One study suggested wearing-off symptoms were associated with lower receptor occupancy of natalizumab on leukocytes in patients with higher BMI, possibly due to increased secretion of serum cytokines [3]. However, this hypothesis was not confirmed, as no correlation between serum cytokines concentration and wearing-off symptoms was found in another study [4]. Natalizumab serum concentrations and α4-integrin receptor saturation were also similar between patients with and without wearing-off symptoms in one of our earlier cross-sectional cohorts [1]. Wearing-off symptoms were also reported in patients using ocrelizumab, with BMI found as the only predicting factor [13]. EID of ocrelizumab was also not associated with wearing-off symptoms [13]. Still, wearing-off symptoms occur frequently and can cause hesitancy in starting with EID [10]. It is reassuring that we found no increase in wearing-off symptoms in the majority of patients after further extending the treatment interval.

Limitations of this study include the nonrandomized study design. In

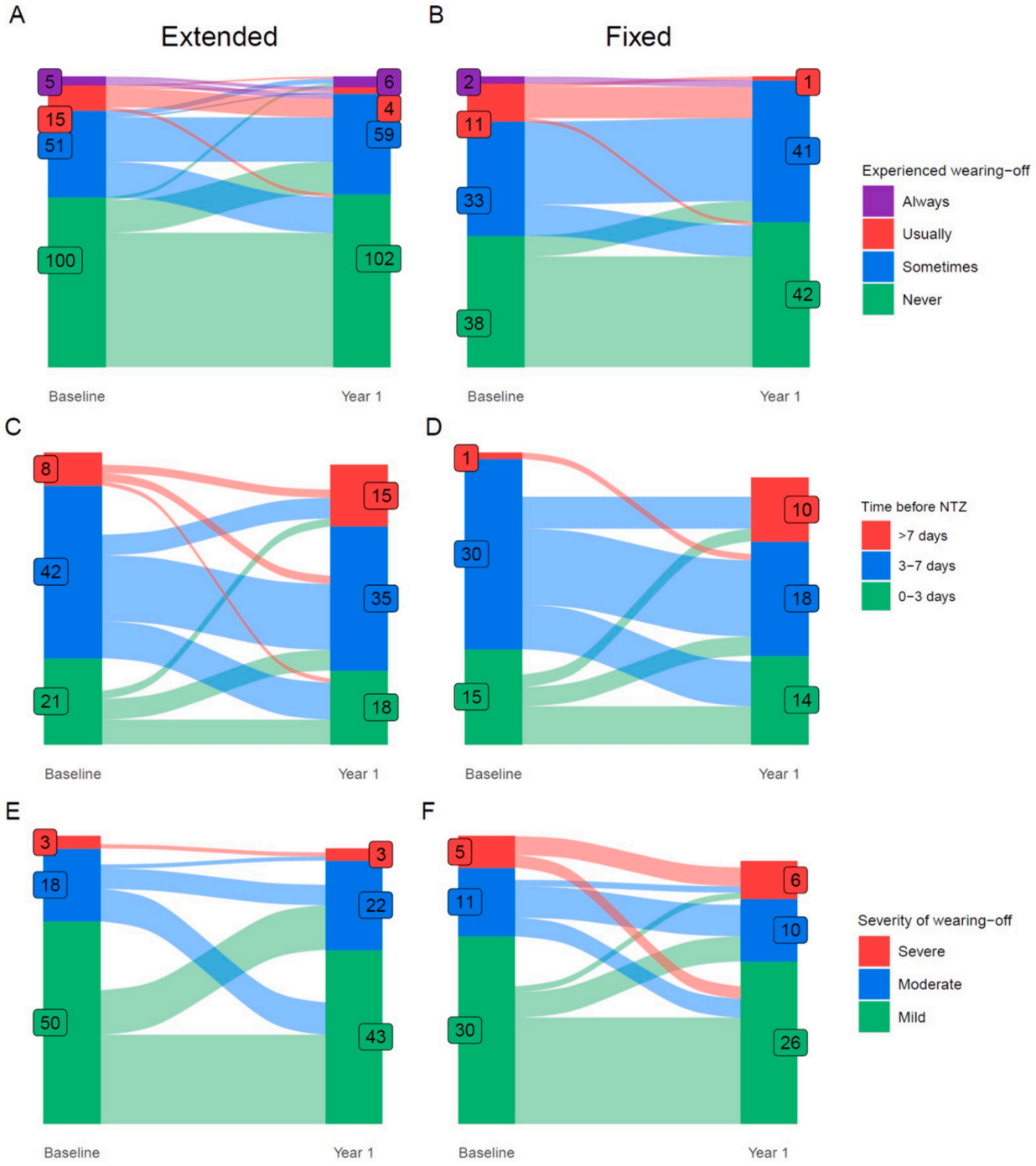

Fig. 3. Changes in wearing-off symptoms over time in the extended and fixed groups.
Values represent number of participants.
A, B: Frequency of wearing-off symptoms were evaluated as never, sometimes, usually, or always (second question supplementary material). An increase of symptoms was defined as a change from never to sometimes, sometimes to usually etc. A decrease of symptoms was defined as a change from always to usually, usually to sometimes etc. Present and stable was defined as wearing-off symptoms (sometimes, usually, always) that were stable over time. Absent and stable was defined as no wearing-off symptoms (never) that were stable over time. Wearing-off symptoms at year 1 were compared to baseline. Five participants completed the year 1 questionnaires after switching to subcutaneous administration of natalizumab (extended group $n = 2$; fixed group $n = 3$), of whom one participant had an increase in occurrence of wearing-off symptoms (extended group $n = 1$), two participants had a decrease in occurrence of wearing-off symptoms (extended group n = 1, fixed group n = 1), and two participants had absent wearing-off symptoms that were stable over time (fixed group n = 2).
C, D: Start of wearing-off symptoms were evaluated as 0–3 days before NTZ, 3–7 days before NTZ, or > 7 days before NTZ (fourth question supplementary material).
E, F: severity of wearing-off symptoms were evaluated as mild, moderate, or severe (sixth question supplementary material). Extended group (A, C, E); Fixed group (B, D, F).
Questions specifying duration and severity of wearing-off symptoms (C-F) were only answered when participants experienced wearing-off symptoms (second question supplementary material was answered with sometimes, usually or always).

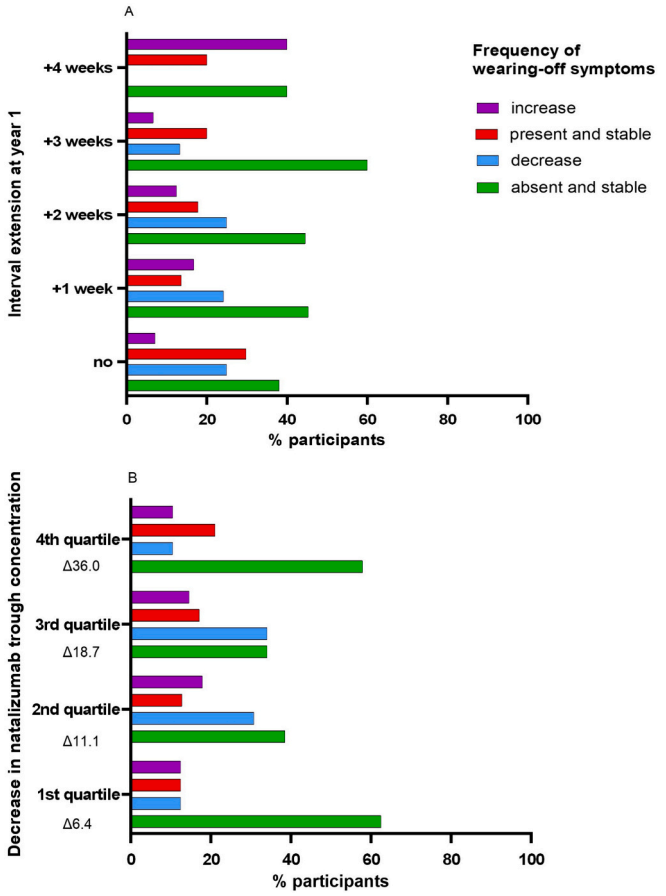

Fig. 4. Changes in frequency of wearing-off symptoms between baseline and year 1 per interval extension group (A) and per delta change in natalizumab drug concentration (B).
Increase of wearing-off symptoms was defined as a change from never to sometimes, sometimes to usually etc. Decrease of wearing-off symptoms was defined as a change from always to usually, usually to sometimes etc. Present and stable was defined as wearing-off symptoms (sometimes, usually, always) that were stable over time. Absent and stable was defined as no wearing-off symptoms (never) that were stable over time (second question supplementary material). Wearing-off symptoms at year 1 were compared to baseline.
A: Participants per interval extension group: no $n = 84$, +1 week $n = 95$, +2 weeks $n = 56$, +3 weeks $n = 15$, +4 weeks $n = 5$.
B: Mean decrease (Δ) in natalizumab drug trough concentrations in μg/mL (year 1 – baseline) was calculated and divided into quartiles. The highest quartile represents the greatest decrease between year 1 and baseline natalizumab drug concentrations. Participants of the extended group were divided per Δ natalizumab quartile: 1st quartile range 1.05–8.5 μg/mL ($n = 40$), 2nd quartile range 8.7–13.7 μg/mL ($n = 39$), 3rd quartile range 13.8–25.5 μg/mL ($n = 41$), 4th quartile range 26.0–52.0 μg/mL ($n = 38$).

addition, wearing-off symptoms remain subjective and probably overlap with MS-related symptoms in general, making it difficult to distinguish these symptoms. A questionnaire specifically asking about wearing-off might influence patient's perspective and awareness of wearing-off symptoms. Strengths of our study are evaluation of prospectively collected longitudinal data in a larger than previously studied cohort of patients on EID, with evaluation of changes in natalizumab trough drug concentration and treatment interval.

In conclusion, wearing-off symptoms were not reinforced by (further) extending the natalizumab treatment interval. Wearing-off symptoms might increase in some patients after interval extension, although our data support the view that wearing-off symptoms appear to be unrelated to the decrease in natalizumab trough drug concentration.

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CRediT authorship contribution statement

A.A. Toorop: Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **M.H.J. Wessels:** Project administration, Investigation, Data curation. **L.M.Y. Gelissen:** Project administration, Investigation, Data curation. **E. Hoitsma:** Writing – review & editing, Investigation. **E.M.P.E. Zeinstra:** Writing – review & editing, Investigation. **L.C. van Rooij:** Writing – review & editing, Investigation. **C.E.P. van Munster:** Writing – review & editing, Investigation. **A. Vennegoor:** Writing – review & editing, Investigation. **J.P. Mostert:** Writing – review & editing, Investigation, Conceptualization. **B.H.A. Wokke:** Writing – review & editing, Investigation. **N.F. Kalkers:** Writing – review & editing, Investigation. **E.L.J. Hoogervorst:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualization. **J.J.J. van Eijk:** Writing – review & editing, Investigation. **C.M. Roosendaal:** Writing – review & editing, Investigation. **J. J. Kragt:** Writing – review & editing, Investigation. **M. Eurelings:** Writing – review & editing, Investigation. **J. van Genugten:** Writing – review & editing, Investigation. **J. Nielsen:** Writing – review & editing, Investigation. **L.G.F. Sinnige:** Writing – review & editing, Investigation. **M.E. Kloosterziel:** Writing – review & editing, Investigation. **E.P.J. Arnoldus:** Writing – review & editing, Investigation. **G.W. van Dijk:** Writing – review & editing, Investigation. **W.H. Bouvy:** Writing – review & editing, Investigation. **E.M.M. Strijbis:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **B.W. van Oosten:** Writing – review & editing, Investigation, Conceptualization. **B. A. de Jong:** Writing – review & editing, Investigation. **B.I. Lissenberg-Witte:** Writing – review & editing, Formal analysis, Data curation. **T. Rispens:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **B.M.J. Uitdehaag:** Writing – review & editing, Investigation, Conceptualization. **J. Killestein:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Z.L.E. van Kempen:** Writing – original draft, Resources, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

A.A. Toorop: nothing to disclose.
M.H.J. Wessels: nothing to disclose.
L.M.Y. Gelissen: nothing to disclose.
E. Hoitsma: has accepted (speaker and congress) fees from Merck Serono, Biogen Idec, Roche, and Sanofi Genzyme.
E.M.P.E. Zeinstra: reports advisory boards/consultancy fees for Merck, Novartis, Genzyme and Roche.
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C.E.P. van Munster: nothing to disclose.
A. Vennegoor: nothing to disclose.
J.P. Mostert: nothing to disclose.
B.H.A. Wokke: nothing to disclose.
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Data availability

Anonymized data will be shared upon reasonable request with any qualified investigator.

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Appendix A. Supplementary data

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