ARTICLE

The natalizumab wearing-off effect

End of natalizumab cycle, recurrence of MS symptoms

Zoé L.E. van Kempen, MD, Djoeke Doesburg, MD, Iris Dekker, MD, Birgit I. Lissenberg-Witte, PhD, Annick de Vries, PhD, Iris A. Claessen, MSc, Anja ten Brinke, PhD, Theo Rispens, PhD, and Joep Killestein, MD, PhD

Neurology® 2019;93:e1579-e1586. doi:10.1212/WNL.0000000000008357

Correspondence
Dr. van Kempen
z.vankempen@amsterdamumc.nl

Abstract

Objective

Natalizumab is effective in treating relapsing-remitting multiple sclerosis (RRMS). However, many patients report an increase of multiple sclerosis symptoms at the end of the natalizumab cycle: a wearing-off effect. The objective of this study was to evaluate the prevalence of the wearing-off effect in patients with standard and extended intervals and to study possible associations with pharmacokinetic/dynamic measurements and patient characteristics in a prospective, monocenter, cross-sectional cohort study.

Methods

Patients with RRMS, with a minimum of 6 natalizumab infusions, were asked to complete 3 questionnaires: the Multiple Sclerosis Impact Scale, the 36-Item Short Form Health Survey, and a general questionnaire regarding the wearing-off effect. Natalizumab concentration and α4-integrin receptor saturation were measured before redosing.

Results

Ninety-three patients were included. A total of 54% experienced a wearing-off effect during natalizumab treatment and 32% experienced a current wearing-off effect at time of measurement. The self-reported wearing-off effect was not associated with natalizumab concentration nor with α4-integrin receptor saturation. The wearing-off effect was more frequently reported in the standard interval group (39%) than in the extended interval group (19%); the duration of symptoms was comparable between both groups. The wearing-off effect was not associated with number of infusions, disease duration, age, or sex.

Conclusion

The wearing-off effect is a frequently reported phenomenon but is unlikely to reflect a non-optimal pharmacokinetic/dynamic state. We did not find risk factors predicting the wearing-off effect.

RELATED ARTICLE

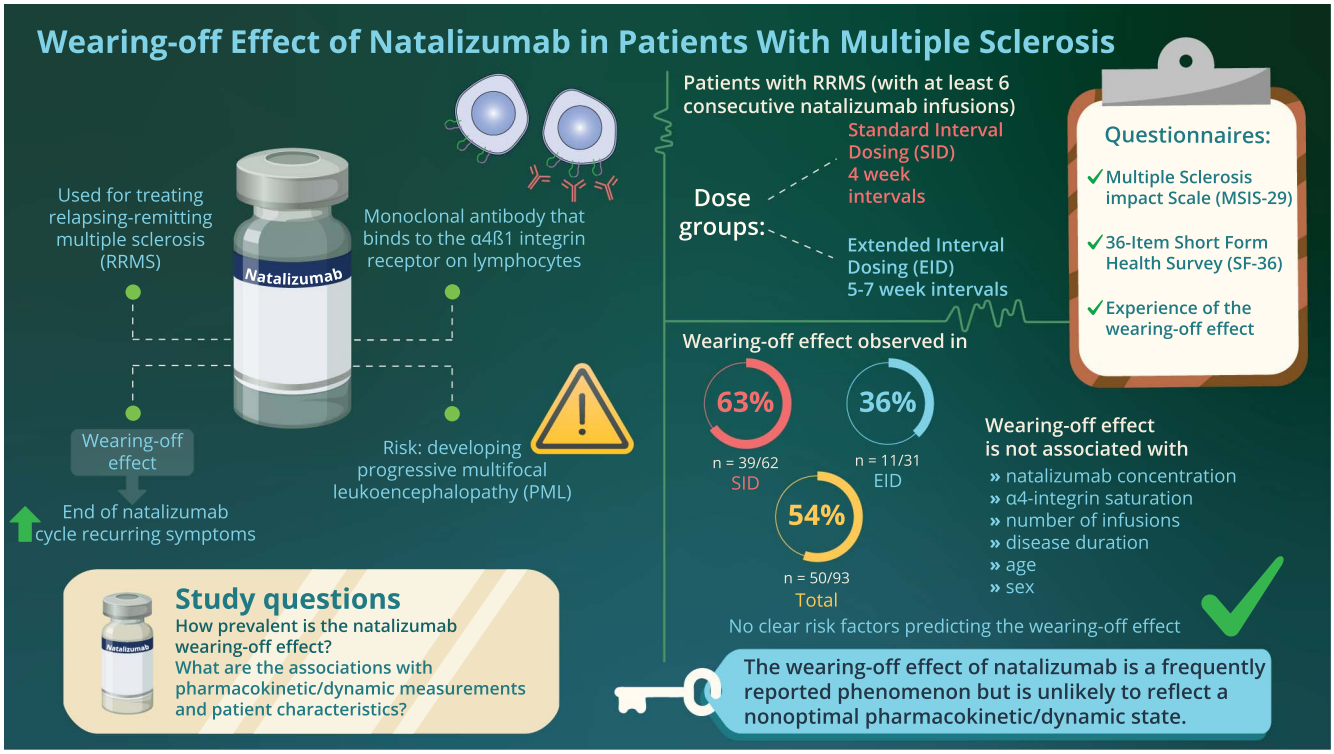
Editorial
Natalizumab wearing-off symptoms: Patients with MS on extended interval dosing may not "mind the gap"
Page 735

From the Amsterdam UMC (Z.L.E.v.K., D.D., I.D., B.I.L.-W., J.K.), Vrije Universiteit Amsterdam; Departments of Neurology (Z.L.E.v.K., D.D., I.D., J.K.) and Radiology & Nuclear Medicine (I.D.), MS Center Amsterdam, Amsterdam Neuroscience; and Departments of Epidemiology and Biostatistics (B.I.L.-W.) and Immunology (A.d.V., I.A.C., A.t.B., T.R.), Landsteiner Laboratory Sanquin Research, Amsterdam, the Netherlands.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CI = confidence interval; **EID** = extended interval dosing; **IgG4** = immunoglobulin G4; **IQR** = interquartile range; **MSIS-29** = Multiple Sclerosis Impact Scale; **OR** = odds ratio; **PBMC** = peripheral blood mononuclear cell; **PML** = progressive multifocal leukoencephalopathy; **RRMS** = relapsing-remitting multiple sclerosis; **SF-36** = 36-Item Short Form Health Survey; **SID** = standard interval dosing.



doi:10.1212/WNL.0000000000008357

Neurology®

Natalizumab, a monoclonal antibody, is effective in the treatment of relapsing-remitting multiple sclerosis (RRMS).[1] Besides the clear effect on disease activity, natalizumab-treated patients report a sustained improvement of physical and psychological health after natalizumab initiation.[2] However, many neurologists prescribing natalizumab are aware of a notable part of patients reporting an increase of symptoms at the end of the natalizumab cycle.[3–5] Patients might mention the natalizumab is wearing off and they are in need of their next infusion. Although this wearing-off effect during natalizumab treatment is widely recognized, research regarding this phenomenon is limited.

Natalizumab concentration peaks directly after infusion, after which an exponential decay sets in.[6] Natalizumab binds to the α4 subunit of the α4β1 integrin receptor on lymphocytes. Saturation of the α4-integrin receptor is concentration-dependent,[6,7] and receptor desaturation (<50%) occurs when the natalizumab concentration falls under 1–2.5 μg/mL.[7,8]

The major disadvantage of natalizumab is the risk of developing progressive multifocal leukoencephalopathy (PML).[9] Besides PML risk stratification and monitoring guidelines,[9] an increasing number of neurologists are extending treatment intervals with the aim of minimizing natalizumab exposure, which hypothetically could reduce PML risk.[10,11]

Extended treatment intervals could lead to unrest in patients experiencing the wearing-off effect, with fear of imminent disease activity or increase of wearing-off symptoms.

The objective of this study was to evaluate the prevalence of the wearing-off effect and to study possible associations with pharmacokinetic and pharmacodynamic measurements and patient characteristics in patients on standard and extended interval dosing in a prospective monocenter setting.

Methods

Patient selection

Patients were recruited at the VU University Medical Center in the Netherlands. All patients with a diagnosis of RRMS according to the applicable panel criteria[12] over 18 years of

age and currently treated with natalizumab with a minimum of 6 consecutive infusions were eligible to participate in this study. A subgroup of patients included in this study also participated in the ongoing trial (ClinicalTrials.gov Identifier: NCT03516526) extending the standard 4-week treatment interval based on individual natalizumab trough concentrations. These patients were treated with a 5- to 7-week interval, referred to as extended interval dosing (EID), whereas the remaining group is referred to as standard interval dosing (SID).

Standard protocol approvals, registrations, and patient consents

Our local institutional review board approved both this study (reference 2017.373) and the EID study (reference 2016-161). Written informed consent was obtained from all patients participating in these studies.

Data collection

Patients completed 3 kinds of questionnaires: the Multiple Sclerosis Impact Scale (MSIS-29),[13] the 36-Item Short Form Health Survey (SF-36),[14] and a questionnaire regarding the patient's experience of a wearing-off effect either at time of blood sampling or in the past during natalizumab treatment. Patients filled in questionnaires at 2 timepoints: in the hospital right before natalizumab infusion (general questionnaire, MSIS-29, and SF-36) and at home 1 week after natalizumab infusion (MSIS-29 and SF-36). Patients were reminded to fill in the second questionnaires by email or text message. Contrary to the MSIS-29, SF-36 scores decrease with greater disability. The MSIS-29 and SF-36 were both adjusted with a statement above the questionnaire asking the patients to evaluate only the prior week, as we specifically aimed to assess a possible difference between the week before natalizumab infusion and the week after natalizumab infusion. The content and items of the questionnaires remained unchanged to the validated questionnaires.

Before natalizumab infusion, blood was drawn to measure natalizumab trough concentration and α4-integrin receptor saturation. Both measurements were performed at Sanquin Laboratory (Amsterdam, the Netherlands). The natalizumab concentration was measured using a crosslinking assay using polyclonal rabbit anti-NTZ F(ab)2 fragments for capture and a mouse anti-IgG4 monoclonal antibody for detection.[16] For testing α4-integrin saturation, peripheral blood mononuclear cells (PBMCs) were isolated from citrated blood samples (Vacuette tubes with sodium citrate; Greiner Bio-One, Kremsmünster, Austria) within 4 hours after blood collection and cryopreserved in liquid nitrogen. The natalizumab binding to α4-integrin on CD8 effector memory and effector cells was analyzed in separate samples by flow cytometry. In brief, PBMCs were first stained with near-IR dead cell stain (Thermo Fisher Scientific Inc., Waltham, MA), after which they were stained with anti-human IgG4-APC (MH164.4; Sanquin) and anti-CD3-PerCP (SK7; BD Biosciences, East Rutherford, NJ), anti-CD4-PECy7 (SK3; BD Biosciences), anti-CD8-BV510 (SK1; Biolegend, San Diego, CA), anti-CD45RO-BV421 (UCHL-1; BD Biosciences), and CCR7-FITC (150,503; BD Biosciences). and measured on a Canto FACS flow cytometer (BD Bioscience). Analysis was performed with Kaluza software (Beckman Coulter, Sharon Hill, PA). To obtain a completely saturated reference sample, PBMCs were postsaturated with saturating concentrations of natalizumab for 15 minutes at room temperature, followed by extensive washing with phosphate-buffered saline to remove natalizumab excess, after which they were analyzed by flow cytometry for maximum natalizumab binding by anti-human immunoglobulin G4 (IgG4). Natalizumab binding was expressed as percentage of background-corrected gMFI relative to that of saturated condition for each sample. To account for the decrease in saturation observed as a result of the cell isolation and cryopreservation procedure, this effect was studied in control experiments, yielding a uniform correction factor of 1.4 for spiked samples as well as patient samples with different levels of saturation; this factor was used to correct all measurements. The interassay variation was 11.7%–17%. As expected, although levels of expression of CD49d vary across individuals, we observed a good correlation between CD49d and saturated levels of natalizumab (Spearman $r = 0.78$).[15]

Patient characteristics (age, sex, body weight, date of diagnosis, and number of natalizumab infusions) were assessed at time of blood sampling. All patients in this study were strictly monitored during natalizumab treatment, with a monthly relapse assessment, frequent Expanded Disability Status Scale scoring, and annual MRI brain scans. Patients positive for the JC virus and patients on EID received 3-monthly MRI brain scans.

Statistics

On the general questionnaire, patients filled in their current experience of a wearing-off effect (at time of blood sampling) and if they had ever experienced a wearing-off effect during natalizumab treatment. For analyses with categorical data (current wearing-off effect and the infusion interval [SID vs EID] or sex), we used a Pearson χ^2 test (minimum expected count was sufficient). We analyzed an association between the current wearing-off effect and the duration of natalizumab treatment or disease duration with the Mann-Whitney *U* test (as normality is not expected) and age or body weight with the independent samples *t* test (normality was proved using Q-Q plots).

The associations between the current experience of a wearing-off effect and natalizumab concentration or α4-integrin receptor saturation were analyzed with a logistic regression analysis. As there was no significant difference in age, sex, disease duration, or treatment duration between the groups with and without a current wearing-off effect, we did not include these covariates as confounders in the regression analyses. As infusion interval (SID vs EID) was a proven

confounder and because body weight influences the concentration,[7] these 2 covariates were added as confounders in the regression analyses. Linearity of the relation was investigated by dividing continuous variables into quartiles. In case of violation, variables were dichotomized using a median split. The association between natalizumab concentration (not normally distributed) and the infusion interval was analyzed using the Mann-Whitney *U* test, and the association between natalizumab α4-integrin receptor saturation (normally distributed) with infusion interval was analyzed using the independent sample *t* test.

Patients filled in MS and general health questionnaires pre and post natalizumab. The scores of the post natalizumab questionnaires were subtracted from the scores of the pre natalizumab questionnaires (delta scores). For analyses with the SF-36, a mean of the transformed scores of the 8 components of this questionnaire was used. To analyze if the experience of a current wearing-off effect was reflected in the questionnaires taken pre and post infusion, the delta scores were compared between patients with and without a current wearing-off effect using a Mann-Whitney *U* test.

SPSS statistics software version 22.0 (IBM, Armonk, NY) was used for the statistical analyses. All reported *p* values are based on 2-tailed statistic tests, with a significance level set at $p < 0.05$.

Data availability

No de-identified patient data will be shared. No related study-related documents will be shared. Anonymized data will be shared by request from any qualified investigator.

Results

In total, 98 patients were eligible for inclusion, of whom 93 were willing to participate. Of all participants, 50 patients (54%) had experienced the wearing-off effect during natalizumab treatment. Thirty patients (32%) experienced a current wearing-off effect at the time of blood sampling. Patient characteristics are presented in table 1.

No linear relation was found between concentration/saturation/body weight and current wearing-off effect, hence we dichotomized these covariates with a median split. Neither the natalizumab concentration (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.19–1.6, $p = 0.28$) nor the α4-integrin saturation (OR 0.94, 95% CI 0.35–2.5, $p = 0.90$) was associated with the reporting of a current wearing-off effect (see figure 1). Median natalizumab concentration was 15.5 (interquartile range [IQR] 10.8–31.8) μg/mL in patients with the current wearing-off effect and 16.0 (IQR 11.0–32.0) μg/mL in patients without a current wearing-off effect. Mean α4-integrin saturation was 70.5% ± 12.3% in patients with and 71.0% ± 12.8% in patients without a current wearing-off effect. The concentration in the SID group (n = 62) was higher in patients without a current wearing-off effect, 29.0 (IQR 15.0–41.3) μg/mL vs 19.0 (IQR 10.3–36.3) μg/mL, but this was not statistically significant (OR 0.98, 95% CI 0.94–1.01, $p = 0.23$). In addition, the saturation was higher in the SID group in patients without a current wearing-off effect; 75.8% ± 12.0% vs 72.3% ± 12.8% (OR 0.98, 95% CI 0.94–1.02, $p = 0.34$). In a post hoc power analysis to show no effect of the concentration in

Table 1 Patient characteristics

	Total, n = 93	Current wearing-off effect, n = 30	No current wearing-off effect, n = 63	*p* Value
Patient characteristics				
Age, y, mean (SD)	40.9 (9.9)	41.0 (9.3)	40.8 (10.3)	0.90
Female, n (%)	71 (76.3)	25 (83.3)	46 (73.0)	0.27
Disease duration, y, median (IQR)	11.0 (8.0–15.0)	11.1 (8.1–15.0)	11.0 (7.9–15.3)	0.91
No. of NTZ infusions, median (IQR)	71 (28–109)	49 (26–93)	74 (30–110)	0.21
Body weight, kg mean (SD)	72.8 (13.9)	74.6 (15.8)	71.9 (13.0)	0.38
Treatment interval				
Standard interval, 4 wk, n (%)	62	24 (38.7)	38 (61.3)	0.060[a]
Extended interval, 5–7 wk, n (%)	31	6 (19.4)	25 (80.6)	
EID, 5 wk, n	12	4	8	
EID, 6 wk, n	16	2	14	
EID, 7 wk, n	3	0	3	

Abbreviations: EID = extended interval dosing; IQR = interquartile range; NTZ = natalizumab.
Characteristics of patients with and without a wearing-off effect at time of blood sampling.
[a] *p* Value of analysis regarding the presence of the wearing-off effect in the standard interval dosing vs EID.

Figure 1 Natalizumab concentration and receptor saturation in patients with and without a wearing-off effect

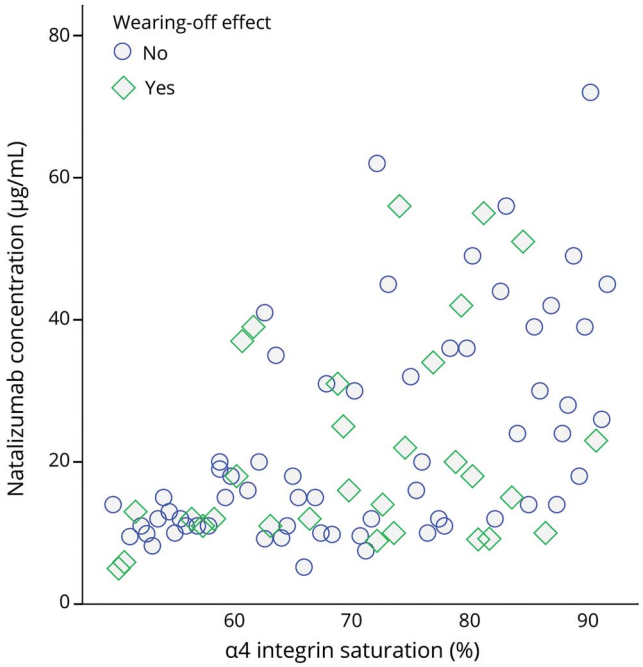
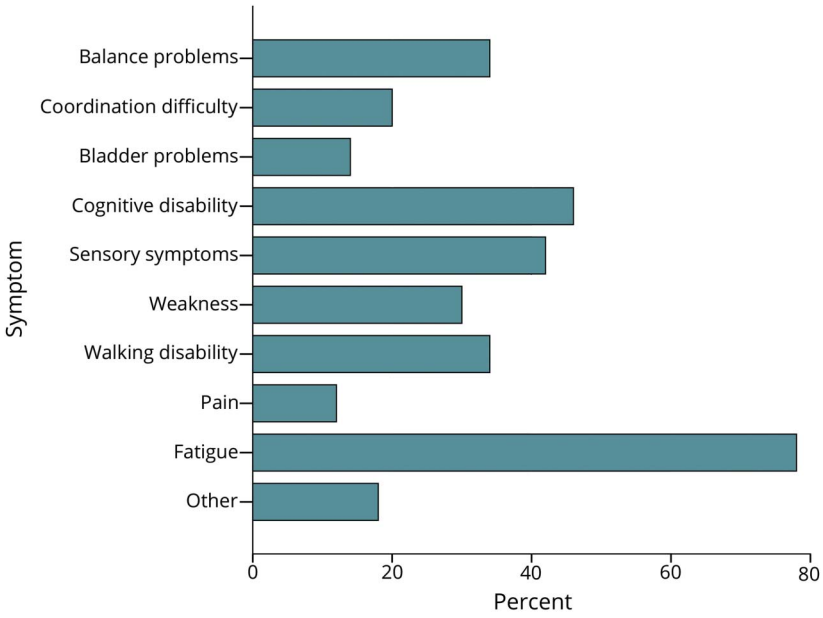


Figure 1 displays a symbol per patient with the corresponding natalizumab concentration (x-axis) and α4-integrin saturation (y-axis). Green diamonds indicate patients with a current wearing-off effect, blue circles indicate patients without a current wearing-off effect. Natalizumab concentration and α4-integrin saturation are trough measurements, sampled before redosing.

a noninferiority design in the SID group, when taking a margin of 10 and an SD of 16, the power is 75%. The concentration was comparable in the EID group in patients with and without the wearing-off effect (12.0 [IQR 10.8–13.3] µg/mL vs 11.0 [IQR 9.9–14.0] µg/mL [OR 0.96, 95% CI 0.69–1.33, p = 0.81]), as was the saturation (63.7% ± 7.8% vs 63.7% ± 10.6%, OR 0.97, 95% CI 0.87–1.08, p = 0.59).

The natalizumab trough concentration and α4-integrin saturation were significantly higher in the SID group compared to the EID group; median concentration was 24.0 (IQR 14.8–39.0) vs 11.0 (IQR 10.0–14.0) and mean saturation was 74.4 ± 12.3 vs 63.7 ± 10.0 (both $p < 0.001$). However, the reported current experience of a wearing-off effect was higher (borderline significance; p = 0.060) in the standard interval group (39%) than in the extended interval group (19%). Eleven patients of the EID group reported the wearing-off effect during natalizumab treatment. In retrospect, we asked these patients if the wearing-off effect changed regarding frequency, duration, or severity when switching from SID to EID. Ten patients filled in this additional questionnaire. Regarding the frequency of the wearing-off effect, 4 patients reported a decrease (of which 3 patients had stopped experiencing a wearing-off effect during EID), 1 patient reported an increase, and 5 patients reported no difference after switching from SID to EID. With respect to duration and severity of the wearing-off effect, 2 patients reported an increase and 5 patients reported no difference of duration and severity of the wearing-off effect (3 patients no longer experienced a wearing-off effect and could not answer these questions). The most frequent reported wearing-off symptom was fatigue (see figure 2).

Figure 2 Reported wearing-off symptoms



Percentages of the wearing-off symptoms in 50 patients with experience of the wearing-off effect during natalizumab treatment.

Table 2 Characteristics of the wearing-off effect

	SID, n = 62	EID, n = 31	Total, n = 93
Ever experience of WOE	39 (62.9)	11 (35.5)	50 (53.8)
Sometimes	29 (74.4)	8 (72.7)	37 (74.0)
Often	6 (15.4)	3 (27.3)	9 (18.0)
Always	4 (10.4)	0	4
Duration WOE before NTZ, d			
Less than 3	4 (10.5)[a]	3 (27.3)	7 (14.3)[a]
3–7	29 (76.3)[a]	7 (63.6)	36 (73.5)[a]
Longer than 7	5 (13.2)[a]	1 (9.1)	6 (12.2)[a]
Disappearance of WOE after NTZ, d			
Directly	9 (24.3)[a]	2 (18.2)	11 (22.9)[a]
Within 3	18 (48.6)[a]	7 (63.6)	25 (52.1)[a]
3–7	9 (24.3)[a]	1 (9.1)	10 (20.8)[a]
After 7	1 (2.7)[a]	1 (9.1)	2 (4.2)[a]
Grade of WOE			
Mild	23 (59.0)	7 (70.0)[a]	30 (61.2)[a]
Moderate	14 (35.9)	3 (30.0)[a]	17 (34.7)[a]
Severe	2 (5.1)	0	2 (4.1)[a]

Abbreviations: EID = extended interval dosing; NTZ = natalizumab; SID = standard interval dosing; WOE = wearing-off effect.
Results of the general questionnaire regarding the wearing-off effect. The number of patients (%) is presented.
[a] Numbers/percentages deviate because of incomplete answers of the questionnaire.

Characteristics of the wearing-off effect are presented in table 2. The duration of the wearing-off symptoms was comparable between the SID and EID (see table 2).

Patients who experienced a current wearing-off had a significant decrease in the scores on the follow-up MSIS-29 compared to patients without a wearing-off effect (median delta score of −8.0 [IQR −18.0 to 2.0] vs −1.0 [IQR −5.5 to 4.5], $p = 0.018$). Furthermore, patients had a significant increase on the follow-up SF-36 compared to patients without a wearing-off effect (median delta score 5.5 [IQR −0.7 to 10.1] vs −0.4 [IQR −5.0 to 2.7], $p = 0.002$). Thus, the results of both questionnaires indicate a significant difference of increase in quality of life after natalizumab infusion in the wearing-off group compared to the patients not experiencing a current wearing-off effect.

Discussion

In this study, over half of patients experienced a wearing-off effect during natalizumab treatment. We show that neither the natalizumab concentration nor the α4-integrin receptor saturation is associated with the experience of a wearing-off effect. Furthermore, we could not identify any risk factors associated with the occurrence of the wearing-off effect during natalizumab treatment.

The current experience of the wearing-off effect was reported more frequently in the SID group than in the EID group (39% vs 19%). This difference might be explained because of the hesitancy patients might feel to participate in a study extending treatment intervals when they experience the need for their next infusion after 4 weeks. An interesting fact is that the duration of the wearing-off effect in EID patients was comparable with the wearing-off effect of SID patients. Furthermore, of 10 patients on EID with experience of the wearing-off effect, more patients reported a decrease of the wearing-off effect than an increase of the wearing-off effect after switching from SID to EID.

Current literature regarding the wearing-off effect in natalizumab-treated patients with MS is scarce and without reporting drug concentrations and receptor saturation. Studies that do address this phenomenon report an incidence of the wearing-off effect of 61%–67%.[3–5] The incidence in our cohort is slightly lower (54%) and we show that the majority of these patients do not experience the wearing-off effect during every cycle. In earlier work, we have shown that intraindividual trough natalizumab concentrations are stable in a set infusion interval.[17] Therefore, we do not suspect fluctuation of the trough natalizumab concentration in patients who sometimes experience the wearing-off effect. By far the most reported wearing-off symptom was fatigue, which is in agreement with other reports.[3–5] Natalizumab led to significant improvement of fatigue symptoms after 1 year of treatment in a one-arm, open-label trial.[18] However, in one of the pivotal trials, fatigue was reported significantly more frequently as an adverse event in the natalizumab group than in the placebo group.[1] As we could not identify any risk factors or pharmacokinetic or pharmacodynamic associations, the wearing-off effect may as well partly or mainly reflect a placebo effect.

Besides a possible placebo effect, cytokines might play a role in fluctuating MS symptoms and have been described in their potential role in the pathophysiology of fatigue in patients with MS.[19] However, as cytokine levels fluctuate and are influenced by many different factors,[20,21] it would be difficult to prove a possible relation between the cytokine profile shifts during a natalizumab cycle in relation to the wearing-off effect.

Our study has several limitations. First, this is a cross-sectional study performed in a relatively small number of patients. However, the inclusion rate in this mono-center study was very high (97%), reducing the chance of inclusion bias. Secondly, as earlier stated, no definite conclusions can be made regarding the prevalence of the wearing-off effect in EID vs SID as it is likely that patients experiencing wearing-

off symptoms would not be willing to extend the treatment interval.

The wearing-off effect is a frequently reported phenomenon but does not reflect a nonoptimal pharmacodynamics/kinetic state. We could not identify risk factors predicting the experience of a wearing-off effect and extended treatment intervals do not result in longer duration of the wearing-off effect.

Acknowledgment

The authors thank all patients included in the study. This research was executed within the VUmc MS Center Amsterdam.

Study funding

Supported by the Brain Foundation Netherlands HA2015.01.05. VUmc MS Center Amsterdam has received financial support for research activities from Bayer Schering Pharma, Biogen, Roche, GlaxoSmithKline, Merck Serono, Genzyme, Novartis, and TEVA.

Disclosure

Z. van Kempen and D. Doesburg report no disclosures relevant to the manuscript. I. Dekker received speaking honoraria from Roche and received funding from the Dutch MS Society, grant 14-358e. B. Lissenberg-Witte, A. de Vries, I. Claessen, and A. ten Brinke report no disclosures relevant to the manuscript. T. Rispens has received speaking fees from Pfizer, AbbVie, and Regeneron, and consulting fees and a research grant from Genmab. J. Killestein has received speaker and consulting fees from Merck-Serono, Biogen, TEVA, Genzyme, Roche, and Novartis. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* December 3, 2018. Accepted in final form May 21, 2019.

Appendix Authors

Name	Location	Role	Contribution
Zoé L.E. van Kempen, MD	Amsterdam UMC, the Netherlands	Author	Conception and design of the study, acquisition of the data, interpretation of data and drafting of the manuscript, statistical analysis, revision of the manuscript critically for intellectual content
Djoeke Doesburg, MD	Amsterdam UMC, the Netherlands	Author	Acquisition of the data, revision of the manuscript critically for intellectual content
Iris Dekker, MD	Amsterdam UMC, the Netherlands	Author	Acquisition of the data, revision of the manuscript critically for intellectual content
Birgit I. Lissenberg-Witte, PhD	Amsterdam UMC, the Netherlands	Author	Statistical analysis, revision of the manuscript critically for intellectual content
Annick de Vries, PhD	Landsteiner Laboratory Sanquin Research, Amsterdam, the Netherlands	Author	Acquisition of the data, revision of the manuscript critically for intellectual content
Iris A. Claessen, MSc	Landsteiner Laboratory Sanquin Research, Amsterdam, the Netherlands	Author	Acquisition of the data, revision of the manuscript critically for intellectual content
Anja ten Brinke, PhD	Landsteiner Laboratory Sanquin Research, Amsterdam, the Netherlands	Author	Acquisition of the data, revision of the manuscript critically for intellectual content
Theo Rispens, MD, PhD	Landsteiner Laboratory Sanquin Research, Amsterdam, the Netherlands	Author	Acquisition of the data, revision of the manuscript critically for intellectual content
Joep Killestein, MD, PhD	Amsterdam UMC, the Netherlands	Author	Conception and design of the study, acquisition of the data, interpretation of data and drafting of the manuscript, statistical analysis, revision of the manuscript critically for intellectual content

References

1. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899–910.
2. 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.
3. Gudesblatt M, Zarif M, Bumstead B, et al. Multiple sclerosis and natalizumab: "between the dose symptoms" [abstract P982]. Mult Scler 2012;18(4 suppl):P982.
4. Katz J, Lathi E, Heyd L. Characterizing the natalizumab "wearing off" effect [abstract]. ACTRIMS meeting 2014; Poster DX36.
5. Ratchford JN, Brock-Simmons R, Augsburger A, et al. Multiple sclerosis symptom recrudescence at the end of the natalizumab dosing cycle. Int J MS Care 2014;16:92–98.
6. Rudick RA, Sandrock A. Natalizumab: alpha 4-integrin antagonist selective adhesion molecule inhibitors for MS. Expert Rev Neurother 2004;4:571–580.
7. Muralidharan KK, Kuesters G, Plavina T, et al. Population pharmacokinetics and target engagement of natalizumab in patients with multiple sclerosis. J Clin Pharmacol 2017;57:1017–1030.
8. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. Neurology 2009;72:402–409.
9. Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol 2017;16:925–933.
10. Bomprezzi R, Pawate S. Extended interval dosing of natalizumab: a two-center, 7-year experience. Ther Adv Neurol Disord 2014;7:227–231.
11. Zhovtis Ryerson L, Frohman TC, Foley J, et al. Extended interval dosing of natalizumab in multiple sclerosis. J Neurol Neurosurg Psychiatry 2016;87:885–889.
12. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162–173.
13. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain 2001;124:962–973.

14. Ware JE, Jr., Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): I: conceptual framework and item selection. Med Care 1992;30:473–483.
15. Ten Brinke A, Claessen I, van Kempen ZLE, Killestein J, Rispens T. Pharmacodynamic assessment of cell-bound natalizumab on PBMC samples stored in liquid nitrogen. J Immunol Methods. 2019;473:112632.
16. Rispens T, Leeuwen Av, Vennegoor A, et al. Measurement of serum levels of natalizumab, an immunoglobulin G4 therapeutic monoclonal antibody. Anal Biochem 2011;411:271–276.
17. van Kempen ZL, Leurs CE, Witte BI, et al. The majority of natalizumab-treated MS patients have high natalizumab concentrations at time of re-dosing. Mult Scler 2018;24:805–810.
18. Svenningsson A, Falk E, Celius EG, et al. Natalizumab treatment reduces fatigue in multiple sclerosis: results from the TYNERGY trial: a study in the real life setting. PLoS One 2013;8:e58643.
19. Heesen C, Nawrath L, Reich C, Bauer N, Schulz KH, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J Neurol Neurosurg Psychiatry 2006;77:34–39.
20. Killestein J, Rep MH, Meilof JF, et al. Seasonal variation in immune measurements and MRI markers of disease activity in MS. Neurology 2002;58:1077–1080.
21. Sospedra M, Martin R. Immunology of multiple sclerosis. Annu Rev Immunol 2005; 23:683–747.