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Natalizumab extended interval dosing: what about wearing-off effect?

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ABSTRACT

Background: Up to two thirds of patients with multiple sclerosis (MS) under natalizumab report a resurgence of symptoms at the end of the natalizumab cycle (wearing-off (WO) effect). At the outbreak of COVID-19, in line with the international recommendations for MS management, our centre switched all clinically stable patients on natalizumab therapy for more than one year from standard interval dosing (SID) to extended interval dosing (EID) with every six weeks infusions. This study aimed to evaluate the impact of EID in WO in MS patients under natalizumab.

Methods: An observational retrospective study in patients with MS under natalizumab on EID was conducted. A questionnaire regarding current (on EID) and past (on SID) experience of WO effect was applied.

Results: Seventy-six patients were included. No significant differences were found in the annual relapse rate after the switch to EID ($p = 0.083$). However, there was a significant increase in the proportion of patients complaining of WO from 38.2% to 56.6% ($p = 0.001$). Moreover, patients with WO on SID, referred a significant increase in severity ($p = 0.019$) and duration of WO symptoms ($p = 0.029$), due to an anticipation of the symptoms relative to the day of natalizumab infusion ($p = 0.019$), when switching to EID. Symptoms improved with treatment maintenance in 23.3% of patients; instead, a reduction in interval dosing was needed in 54.8% with symptom improvement.

Conclusion: WO affects a significant proportion of MS patients under natalizumab. Its prevalence, severity, and duration increase on EID, therefore despite clinical effectiveness maintenance of this posology should be individualized.

1. Introduction

Natalizumab is a highly effective monoclonal antibody treatment for relapsing-remitting multiple sclerosis (MS). It binds to α4 integrin on the cell surface of leukocytes, reducing their migration into the central nervous system (CNS). [1] Despite the clear effect on disease activity, up to two thirds of patients with MS under natalizumab report a resurgence of symptoms at the end of the natalizumab cycle, that resolve shortly after receiving their following natalizumab infusion, an effect that has been designated as wearing-off (WO). [2] Research regarding this phenomenon is limited and there is no consensus on its pathophysiology. Some support a pharmacodynamic mechanism [3,4], while others propose a cytokine-mediated effect, and there are still who claim a nocebo effect. [5] This treatment is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare, but potentially lethal opportunistic CNS infection caused by John Cunningham virus. [6] It was approved with a standard interval dosing (SID) of 300 mg administered by intravenous infusion once every 4 weeks, but to mitigate PML risk, extended interval dosing (EID), in which the time interval between doses is extended from 4 weeks to 5 or more weeks, has been proposed [7]. Studies assessing EID have been presenting good outcomes in reducing PML risk [6] without reducing efficacy [8]. However, little is known regarding the impact of EID on WO.

At the outbreak of COVID-19, in line with the international recommendations for MS management, our centre switched all clinically stable patients on natalizumab therapy for more than one year from SID to EID with every six weeks infusions. The aim of this study was to evaluate the impact of EID in prevalence, severity, and duration of WO in MS patients under natalizumab.

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2. Methods

2.1. Subjects

All patients from our centre with MS receiving natalizumab on EID from November 2021 through May 2022 were selected and included if they had received two or more consecutive treatment cycles on EID. Patients who were cognitively impaired sufficiently to interfere with the completion of a questionnaire were excluded from participation. Recruited patients were asked to fill in a questionnaire. All patients are usually routinely monitored with biannual assessments and annual brain magnetic resonance imaging; their files were reviewed at the time of enrolment, and demographic and clinical variables were collected.

2.2. Questionnaire

The questionnaire was divided into two parts regarding their current (on EID) and past (on SID) experience of a WO effect. The questionnaire included a first question about the presence of WO symptoms; if answered positively, additional questions about this phenomenon were given – description, frequency, intensity, time, duration of WO symptoms, and for those reporting WO on EID: need to switch back to SID because of WO symptoms and improvement with switching back to SID. A translated version of the original questionnaire can be found as supplementary material.

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software version 28. The demographic and disease characteristics were compared between those who never experienced WO effect and those who have ever experienced it on SID. Relapse rate and WO prevalence, frequency, intensity, time, and duration were compared before and after switching from SID to EID. Categorical variables are represented using frequencies and were compared through chi-square test, if non-paired samples, or McNemar (2 categories) or McNemar-Bowker (>2 categories) tests, if paired samples. For discrete variables, normality was ascertained using the Kolmogorov-Smirnov test. Normally distributed variables are represented using mean values and were compared through a *t*-test. Non-normally distributed variables are represented using median values and were compared through a Mann-Whitney *U* test, if non-paired samples, or Wilcoxon test, if paired samples. Statistical differences were considered significant if $p < 0.05$ using a two-sided comparison.

2.4. Ethics

The present research was approved by the Ethics Board of Coimbra University Hospital Centre. Written informed consent was obtained from all the participants after the aims and procedures of the investigation were fully explained by a member of the study group.

3. Results

Seventy-seven patients were eligible for inclusion, of whom 76 agreed to participate. From those, 29 reported to have ever experienced WO on SID. Patients' demographics and clinical characteristics are summarized in Table 1. No significant differences were found in patients' characteristics between those who have never experienced WO and those who have experienced this phenomenon, namely in body mass index (BMI), annual relapse rate (ARR), and expanded disability status scale (EDSS). The questionnaire was applied on average 20 months after the switch from SID to EID.

No significant differences were found in the ARR after switching to EID ($p = 0.083$). However, there was a significant increase in the proportion of patients complaining of WO from 38.2% to 56.6% ($p = 0.001$). The most common symptoms reported to occur at the end of the dosing cycle were fatigue, weakness, and sensory disturbances. (Table 2).

A subanalysis including only those with WO on SID, also found no significant differences in the ARR after switching to EID (p = 0.083). Four patients presented a relapse on EID, one of them had already presented a relapse on SID. All of them reported WO both on SID and EID.

Among those reporting WO symptoms on SID, the greatest proportion reported having moderate intensity WO symptoms, that recur every cycle, starting 4–7 days before natalizumab infusion and ending 1–3 days after it. Switching from SID to EID, a significant increase in severity ($p = 0.019$) and duration of WO symptoms ($p = 0.029$), due to an anticipation of the symptoms relative to the day of natalizumab infusion (p = 0.019), was observed. Frequency and time for resolution after natalizumab administration were nevertheless similar between

Table 1
Patients' demographics and disease characteristics according to the presence of wearing-off effect on standard interval dosing.

	All $n = 76$	With WO $n = 29$	Without WO $n = 47$	p
Female, %	76.3	76.6	75.9	0.942
Age* in years, mean ± SD	39.7 ± 13.1	38.9 ± 13.7	41.0 ± 12.3	0.504
BMI mean ± SD	24.2 ± 4.0	24.1 ± 4.2	24.3 ± 3.6	0.866
Phenotype				
Relapsing-remitting, %	97.4	100	95.7	0.260
Secondary progressive, %	2.6	0	4.3	
Disease duration* in years, median (IQR)	7.0 (9.0)	8.0 (11.0)	6.0 (7.5)	0.383
Natalizumab therapeutic duration* in years, median (IQR)	3.0 (4.0)	3.0 (5.0)	3.5 (2.0)	0.759
ARR, median (IQR)	0 (0)	0 (0)	0 (0)	0.203
Relapses, n	1	1	0	0.203
EDSS, median (IQR)	1.5 (1.5)	1.5 (1.0)	1.8 (1.5)	0.371
Follow-up** in months, median (IQR)	22.0 (3.0)	22.0 (4.0)	21.0 (3.0)	0.094

WO: wearing-off, SD: standard deviation, IQR: interquartile range, ARR: annual relapse rate, EDSS: Expanded Disability Status Scale.
* At the beginning of extended interval dosing.
** Between the beginning of extended interval dosing and the application of the questionnaire.

Table 2
Clinical disease activity and wearing off effect on standard interval dosing versus extended interval dosing.

	SID n = 76	EID n = 76	p
ARR, median (IQR)	0 (0)*	0 (0)	0.083
Relapses, n	1*	4	0.083
Wearing-off symptoms, %	38.2	56.6	**0.001**
Fatigue, %	72.4	76.7	–
Weakness, %	41.4	39.5	–
Sensory symptoms, %	41.4	32.6	–
Imbalance, %	21.4	25.6	–
Coordination difficulties, %	20.7	20.9	–
Pain, %	20.7	20.9	–
Dizziness, %	20.7	20.9	–
Walking difficulties, %	17.2	23.3	–
Cognitive difficulties, %	10.3	11.6	–
Depressive symptoms, %	6.9	11.6	–
Blurry vision, %	6.9	4.7	–
Dysphagia, %	3.4	4.7	–
Bladder symptoms, %	3.4	4.7	–
Bowel symptoms, %	0	2.3	–

SID: standard interval dosing, EID: extended interval dosing, ARR: annual relapse rate, IQR: interquartile range, n: absolute number of patients.
* In the previous year.

posologies. (Table 3)

Among those reporting WO symptoms on EID, symptoms improved with treatment maintenance in 23.3% of patients; instead, a reduction in interval dosing was needed in 54.8% (in four of them because of relapses). In 47.8% interval dosing was switched back to 4 weeks and in 52.2% to 5 weeks with symptom improvement in all.

There were no cases of PML.

4. Discussion

Up to two thirds of patients with MS receiving natalizumab notice a recurrence of symptoms at the end of their dosing cycle. In our study, WO prevalence on SID (38.2%) was in the lower range of what has been reported in other studies (42.5%–63%). [3,2,5].

Although common, WO is still a poorly understood phenomenon. Initial studies didn't find any risk factor associated with the occurrence of WO [2], concluding it was unlikely to reflect a nonoptimal pharmacokinetic/dynamic state and proposing a cytokine-mediated or a nocebo effect [5]. More recently, a study using a more advanced technique observed a lower natalizumab receptor occupancy in patients complaining about WO symptoms and related this phenomenon to higher BMI. [3] Nevertheless, in line with other studies [2,5], in our cohort no significant differences were found in patients' characteristics between those who have never experienced WO and those who have experienced this phenomenon, namely in BMI.

The main worry about WO is that it might reflect a subclinical reactivation of the disease, although disease activity and progression assessed by EDSS score, new lesions in brain magnetic resonance, ARR, and serum neurofilament light chain (NF-L) levels have been shown to be similar between those with and without WO. [3,2] Consistent with these results, in our cohort no significant differences were found in EDSS or ARR between these two groups.

In agreement with other studies, by far the most frequent WO was fatigue [3,2,5] and in the greatest proportion of cases on SID, symptoms were reported to start 4–7 days before natalizumab infusion [5] and resolve 1–3 days after it [2,5]. However, contrary to other studies that report mild symptoms [2,5] occurring sometimes in most patients, in our cohort, the greatest proportion reported having moderate symptoms, that recur every cycle.

The most fearful adverse effect associated with natalizumab is PML, a rare, but potentially lethal disease [9], and to mitigate this risk, EID has been proposed [7]. Although recent studies have been demonstrating a reduced PML risk [6] without reduced efficacy [8] on EID, few have been evaluating the effect of EID on WO symptoms, and some are limited by possible selection bias [2,5]. In an era where EID is such a promising strategy, our study tries to explore this gap.

Like Bringeland et al. [10], we found a significant increase in the proportion of patients complaining of WO from SID (38.2%) to EID (56.6%). This may be explained by the reduction of natalizumab receptor occupancy in EID compared to SID observed by Foley et al. [4]. Additionally, among those who already complained about WO on SID, switching to EID significantly increased the severity and duration of WO symptoms due to an anticipation of the symptoms relative to the day of natalizumab infusion. Given that patients who experience WO already have lower natalizumab receptor occupancy [3] and EID was shown to reduce natalizumab receptor occupancy [4], EID could potentially increase the risk of disease activity. [3] In line with the most recent randomized control trial comparing SID to EID [8], no significant differences were found in the ARR after switching to EID, even in those who already experienced WO on SID. However, the four relapses registered on EID were observed in patients already reporting WO on SID and then on EID. Moreover, although among those reporting WO on EID, symptoms improved with treatment maintenance in 23.3% without a posology adjustment, a phenomenon that was already described in a previous study [2], a significant proportion (54.8%) required a reduction in interval dosing, with symptom improvement in all of them.

These findings suggest that EID may not be the ideal regimen for every MS patient on natalizumab. Evidence of a pharmacodynamic mechanism explaining WO symptoms that may be worsened on EID leads to fearing disease activity, though subclinical. Further research is needed to address that question; an interesting study would be to measure NF-L levels during WO symptoms and compare it to baseline levels, both on SID and EID. Moreover, even though disease activity may not be at risk, WO has a negative impact on the quality of life of these patients [2]. Therefore, a more appropriate approach would include a personalized dosing interval of natalizumab therapy.

This study did have some limitations. First, there is the small sample size. Additionally, the recall bias – this is a retrospective study, relying on what people remember feeling while on SID (about 22.0 months before). Finally, the process of explaining the study to participants may have biased them to more likely report WO symptoms. Nevertheless, although our study was not randomized, selection bias was avoided as all clinically stable patients on natalizumab therapy for more than one year followed in our centre were temporarily switched to EID due to extraordinary circumstances. Also, all except one patient agreed to participate.

Table 3
Wearing-off effect characteristics on standard interval dosing versus extended interval dosing.

	SID $n = 29$	EID n = 29	p
Frequency			0.075
Sporadically, %	20.7	11.1	
Sometimes, %	24.1	11.1	
Often, %	17.2	7.4	
Always, %	37.9	70.4	
Intensity			**0.019**
Mild, %	44.8	22.2	
Moderate, %	48.3	37.0	
Severe, %	6.9	40.7	
Starting day (before natalizumab infusion)			**0.019**
1–3, %	34.5	18.5	
4–7, %	55.2	33.3	
>7, %	10.3	48.1	
Ending day (after natalizumab infusion)			0.513
< 1, %	27.6	34.6	
1–3, %	62.1	57.7	
4–7, %	3.4	3.8	
>7, %	6.9	3.8	
Duration (days)			**0.029**
1–3, %	20.7	14.8	
4–7, %	51.7	25.9	
>7, %	27.6	59.3	

SID: standard interval dosing, EID: extended interval dosing.

5. Conclusion

WO affects a significant proportion of MS patients under natalizumab. Despite clinical effectiveness maintenance, its prevalence, severity, and duration increase on EID, and therefore, we recommend that this posology should be individualized. Further investigation to elucidate the cause of WO and possible association with disease activity, namely on EID, is needed to ultimately guide dosing decisions.

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CRediT authorship contribution statement

Catarina Bernardes: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Catarina Fernandes:**

Writing – review & editing, Data curation. **Carolina Cunha:** Writing – review & editing, Data curation. **Carla Nunes:** Writing – review & editing. **Carmo Macário:** Writing – review & editing. **Lívia Sousa:** Writing – review & editing. **Sónia Batista:** Writing – review & editing. **Inês Correia:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

Inês Correia, Carla Nunes, Carmo Macário, and Sónia Batista have received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Bristol Myers Squibb, Roche, and Janssen. Lívia Sousa has received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, and Roche. Catarina Bernardes, Catarina Fernandes and Carolina Cunha have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.122930.

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