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Clinical short communication

Wearing-off symptoms during standard and extended natalizumab dosing intervals: Experiences from the COVID-19 pandemic

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ABSTRACT

Natalizumab effectively prevents disease activity in relapsing-remitting multiple sclerosis, but many treated patients report subjective wearing-off symptoms at the end of the 4-week interval between infusions. Extended interval dosing (EID) is a promising strategy to mitigate the risk of natalizumab-associated progressive multifocal leukoencephalopathy, but it is unknown whether EID affects wearing-off symptoms. In this observational study, we evaluated if prevalence or intensity of wearing-off symptoms changed when natalizumab dosing intervals were extended from 4 to 6 weeks in 30 treated patients during the outbreak of COVID-19 in Norway. New or increased wearing-off symptoms during EID were reported by 50%. Symptom increase was more frequent among patients with pre-existing wearing-off symptoms during standard dosing compared to patients without such pre-existing symptoms [$p = 0.0005$]. Our observations support the need to study the effect of EID on wearing-off symptoms in randomized controlled trials.

1. Introduction

Natalizumab effectively reduces disease activity in relapsing-remitting multiple sclerosis (RRMS) by binding to $\alpha 4$ integrin on the surface of leukocytes, thereby preventing leukocyte migration into the CNS [1]. Natalizumab is administered intravenously every 4 weeks at standard interval dosing (SID). Many patients report subjective wearing-off symptoms at the end of dosing intervals which improve shortly after infusions [2–4]. We have previously proposed that low natalizumab receptor occupancy (RO) may be a contributing cause to such wearing-off symptoms [4]. Natalizumab RO, defined as the proportion of $\alpha 4$ integrins on the cell surface bound by natalizumab, has been suggested as a biomarker for treatment efficacy [5]. RO may vary between individuals receiving equal natalizumab doses, but is stable over time within each patient if doses are kept unchanged [6]. Accumulating evidence suggests that extended interval dosing (EID) every 6–8 weeks mitigates the risk of natalizumab-associated progressive multifocal leukoencephalopathy (PML), possibly mediated through RO reduction [7]. Whether EID affects wearing-off symptoms is not known.

At the outbreak of COVID-19 in Norway, neurologists at our department advised patients receiving natalizumab to extend dosing intervals from 4 to 6 weeks to minimize contact with the department. We had previously registered wearing-off and measured natalizumab RO in the same patient cohort [4]. Here, we aimed to determine whether EID increased wearing-off symptoms and if symptom increase during EID was associated with pre-existing wearing-off. Further, we aimed to investigate if natalizumab RO measured during SID differed between patients with and without symptom increase during EID.

2. Materials and methods

2.1. Subjects

All RRMS patients over 18 years of age receiving natalizumab at the Department of Neurology, Haukeland University Hospital were invited to participate in this study after written informed consent. The study was approved by the Regional Ethics Committee (REK 2016/579).

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Table 1

Reported change in symptoms during extended interval dosing (EID) of natalizumab in relapsing-remitting multiple sclerosis (RRMS) patients who had previously reported wearing-off symptoms regularly (at the end of every dosing interval), sometimes (at the end of some dosing intervals), or never during standard interval dosing (SID). Numbers are total numbers unless otherwise stated.

	Total	Symptoms during EID	
		Increased	Unchanged
RRMS patients with	30	15 (50%)	15 (50%)
Wearing-off during SID			
• regularly	7	6 (86%)	1 (14%)
• sometimes	5	5 (100%)	0
• never	18	4 (22%)	14 (78%)

2.2. Evaluation during standard and extended interval dosing

All included patients had filled in questionnaires during SID regarding whether they had wearing-off symptoms regularly (at the end of every dosing interval), sometimes (at the end of some dosing intervals), or never, as previously described [4]. Natalizumab RO, defined as the ratio between number of bound natalizumab molecules and total $\alpha 4$ integrin on single cells, had been measured by mass cytometry (Helios) in blood samples collected at the end of a standard dosing interval [4].

At the outbreak of COVID-19, all patients were advised to temporarily switch to EID. After 6 months, patients who had received \geq two consecutive treatment cycles with EID filled in new questionnaires regarding whether they had experienced any changes in wearing-off symptoms during EID. Increase was defined as more pronounced or newly occurred wearing-off symptoms and decrease was defined as less pronounced or disappearance of wearing-off symptoms. The medical

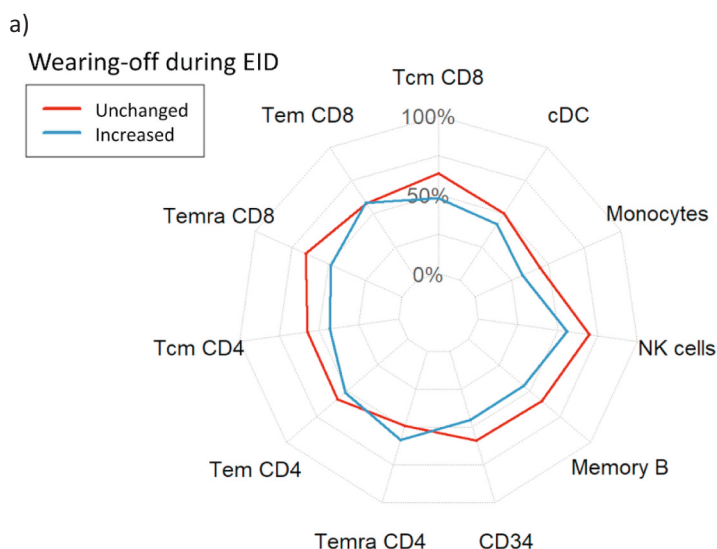
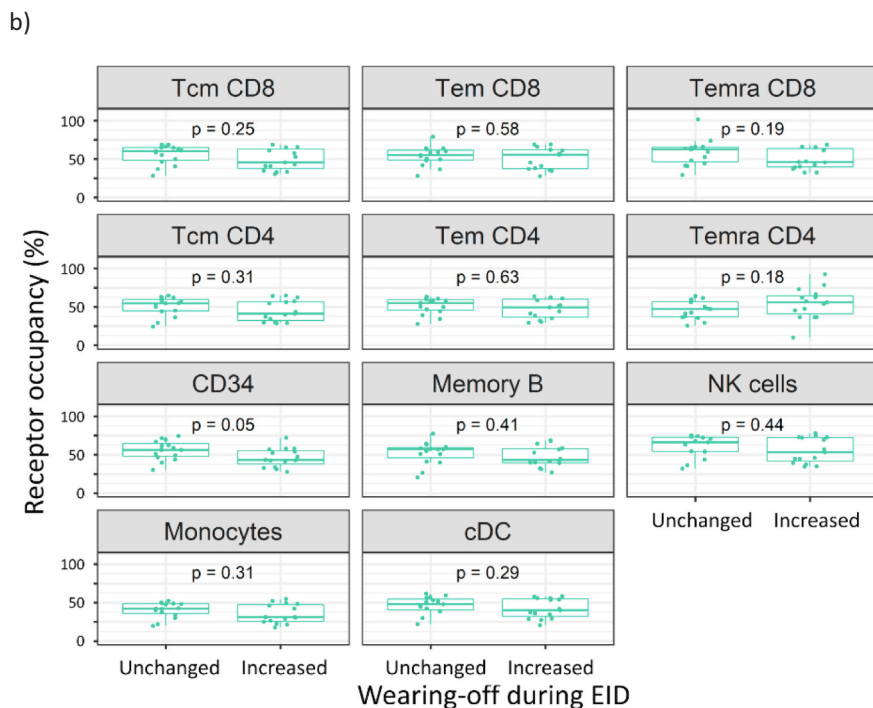


Fig. 1. Natalizumab RO measured by mass cytometry at the end of a standard dosing interval in 11 leukocyte subtypes: CD8+ central memory (T_{CM}), effector memory (T_{EM}), and effector memory RA (T_{EMRA}) T cells; CD4+ T_{EM} , T_{CM} , and T_{EMRA} cells; CD34+ cells; memory B cells; natural killer (NK) cells; monocytes; and conventional dendritic cells (cDCs).

a) Spider plot of median natalizumab receptor occupancy (RO) in patients with increased (blue) and unchanged (red) wearing-off symptoms during extended interval dosing (EID).

b) Box plot comparing RO in patients with increased ($n = 15$) versus unchanged ($n = 15$) symptoms during EID, together with corresponding p-values (Kruskal-Wallis test).



journal was assessed for signs and symptoms of clinical relapse during or 6 months after starting treatment with EID.

2.3. Statistical analysis

A Fisher's exact test was used to evaluate whether there was an association between pre-existing wearing-off symptoms during SID and changes in symptoms during EID. Median natalizumab RO at SID was compared between patients with increased *versus* unchanged symptoms during EID using a Kruskal-Wallis test. Statistical differences with $p < 0.05$ were considered significant using a two-sided comparison.

3. Results

At the outbreak of COVID-19, a total of 31 patients were receiving natalizumab at our department, and all were advised to extend dosing intervals from 4 to 6 weeks. One refused due to fear of deterioration of pre-existing wearing-off symptoms and was excluded from further analyses. The remaining 30 (97%) received EID for two or more treatment cycles. Out of these, 15 (50%) reported unchanged symptoms and 15 (50%) had new or increased wearing-off symptoms. None had decreased symptoms. Symptom increase during EID was more frequent in patients with pre-existing wearing-off symptoms during SID [$p = 0.0005$] (Table 1). None had signs or symptoms of clinical relapse during or 6 months after starting treatment with EID.

Median natalizumab RO at SID was lower in 9 of 11 leukocyte subtypes in patients who later reported symptom increase during EID compared to patients with unchanged symptoms during EID, but the difference was not statistically significant (Fig. 1).

4. Discussion

The effect of EID on wearing-off symptoms in natalizumab therapy has not been evaluated in randomized controlled trials (RCTs). Here, we found that EID increased wearing-off symptoms, especially in patients with pre-existing wearing-off. One previous observational study where patients could contribute to the choice of dosing interval reported more frequent wearing-off in the SID than the EID group [3]. As also pointed out by the authors of the study, such non-randomized study design implies risk of selection bias because patients with wearing-off may be less motivated to choose EID. Although our study was not randomized, selection bias was avoided as 97% of our patients temporarily switched to EID due to extraordinary circumstances. Symptom increase during EID was considerably more frequent in patients with pre-existing wearing-off symptoms. This indicates that the effect of EID on wearing-off may be underestimated in a non-randomized study if patients with pre-existing wearing-off are reluctant to extend dosing intervals.

Although common, the wearing-off phenomenon is poorly understood. We and others have reported more severe fatigue and cognitive impairment in patients with wearing-off, but no increased short term risk of disease activity [2,8]. Some argue that the cause of wearing-off symptoms is psychological [3], whereas we have suggested low natalizumab RO as a contributing factor [4]. EID generally reduces RO [6,7]. Here, we found lower median natalizumab RO at the end of a standard dosing interval in patients who would later report increased wearing-off during EID, but this was not statistically significant. However, this trend could represent a possible mechanism for the individual variation: patients with low RO at the end of standard dosing intervals may be more vulnerable to wearing-off when RO is further reduced by EID.

The small patient cohort in our study could limit its ability to reveal

possible differences and the absence of disease activity was not confirmed by MRI. Another limitation is that we only measured natalizumab RO during SID (due to routine laboratory restrictions in blood sample collection during the COVID-19 outbreak). Although EID generally reduces natalizumab RO, the individual change in RO may vary between patients. Further, we had no control group and cannot rule out that our findings can be explained by fluctuating wearing-off symptoms over time independent of changes in dosing intervals or by psychological factors. Negative expectations to EID may be more pronounced in patients already experiencing wearing-off symptoms and cause a placebo effect. Blinding of dosing intervals is required to clarify whether psychological factors contribute to wearing-off symptoms.

The results from our small cohort need further investigation of possible associations between wearing-off, natalizumab RO and dosing intervals in RCTs of different dosing regimens to elucidate the cause of the wearing-off phenomenon and possibly provide further tools to individualize natalizumab therapy.

Declaration of Competing Interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: N. B., C.A.V., and S.G. have nothing to disclose. G.H.B. has received research support from Novartis. K.M.M. has received unrestricted grants and personal fees from Biogen and Novartis and personal fees from Genzyme, Roche, and Merck.

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