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ORIGINAL COMMUNICATION

Natalizumab wearing-off symptoms: effect of extend interval dosing during Sars-CoV-2 pandemic

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Abstract

Background Many patients treated with Natalizumab experience wearing-off symptoms (WoS) towards the end of the administration cycle. During the pandemic we advised and asked patients undergoing treatment with Natalizumab if they wanted to be shifted from a standard interval dosing (StID of 4 weeks) to an extended interval dosing (ExID of 5–6 weeks), regardless of their JCV index. Our main objective was to study prevalence and incidence of WoS when ExID was adopted.

Methods We enrolled 86 patients, from May 2020 to January 2021, evaluated at baseline and during a 6 months follow-up with a survey focused on WoS, Fatigue Severity Scale (FSS), Expanded Disability Status Scale (EDSS) and MRI.

Results Among the 86 patients, 32 (37.2%) reported WoS. Most common one was fatigue (93.7%). Mean EDSS was higher in the group reporting WoS (3.8 WoS vs 3.1 non-WoS, $p < 0.05$). *Sphincterial function* was the EDSS item that significantly differed between the WoS group and the non-WoS group (1.4 WoS vs 0.6 non-WoS, $p < 0.001$). WoS correlate with the FSS scale ($p < 0.001$).

Conclusion Adopting an extended interval dosing does not result in significantly different occurrence of WoS between the ExID and the StID populations, in our cohort of patients. Interestingly, there is a strong correlation between WoS and a higher EDSS and FSS. Safety and efficacy of Natalizumab with ExID are relatively preserved in our study.

Keywords Fatigue · Multiple sclerosis · Natalizumab wearing-off symptoms (WoS) · End of dosing interval symptoms (EDIs) · Extended interval dosing (ExID)

Introduction

Natalizumab (NTZ) is a humanized monoclonal antibody that acts as an antagonist of α4 integrin, which is on the surface of mononuclear cells. This way it reduces migration of lymphocytes into the central nervous system (CNS) [1]. This leads to reduction of inflammation in the CNS in relapsing remitting multiple sclerosis (MS) and reduction of radiological and clinical disease activity [2]. Main adverse effect is the development of progressive multifocal leukoencephalopathy (PML), which is a rare and severe infection caused by the John Cunningham (JC) virus resulting from reduced immune-surveillance in the CNS [2]. The recommended fixed dose for NTZ is 300 mg intravenously every 4 weeks, the standard interval dosing (StID), which ensures maximal α4 integrin receptor saturation [3]. A saturation lower than 50% occurs more than 8 weeks after drug administration [4]. Different approaches were proposed to minimize PML risk, especially in the JCV positive population, and to do so, many neurologists adopted an extended interval dosing (ExID) between NTZ administrations. Some retrospective studies are beginning to show that ExID schedules (ranging from 6 to 8 weeks) do not reduce efficacy of NTZ, although randomized trials are needed to evaluate safety, efficacy and PML risk reduction [5–7]. Many patients treated with NTZ experience wearing-off symptoms (WoS) towards the end of the administration cycle [8, 9]. During the Sars-CoV-2

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pandemic, to reduce patients access to the hospital and minimize viral exposure, we advised and asked patients undergoing treatment with NTZ if they wanted to be shifted from a StID of 4 weeks to an ExID of 5–6 weeks, regardless of their JCV index. Some studies reported a higher prevalence of WoS in the StID group [10], considering the variable prevalence of WoS among previous studies, we studied the prevalence and incidence of WoS in our cohort of patients treated with NTZ, during the pandemic, along with efficacy and safety of an ExID and its consequences on WoS.

Materials and methods

During the pandemic, from May 2020 to January 2021, we enrolled 86 patients treated with NTZ in our MS center. All patients treated with NTZ for more than a year in our MS center, were asked to shift from a StID of 4 weeks to an ExID of 5 or 6 weeks regardless of their JCV index. Patients who had started NTZ within a year were excluded from the study. Enrolled subjects were classified in three groups (StID, ExID of 5 weeks and ExID of 6 weeks) according to the protocol of NTZ administration adopted. The following data have been collected for each patient at baseline: age, sex, body mass index (BMI), age at onset and time on treatment with NTZ. At the beginning of the study and after 6 months all patients had a complete evaluation comprehensive of: clinical neurological examination performed by dedicated trained and expert neurologists, evaluation of the Expanded Disability Status Scale (EDSS) and brain and spine MRI with and without contrast. After 6 months follow-up, before the next drug infusion, we asked all patients to answer a survey of three questions: "Have you experienced any worsening of your symptoms around the time of the next administration? And if yes, this happened always or only when the interval was shifted? How would you describe the worsening of your symptoms?". Patients were considered to be affected by WoS whenever they answered positively to the survey. Patients who answered "yes" to the first question were asked to specify if his/her symptoms matched any of the following: fatigue, cognitive difficulties, headache, walking difficulties, paresthesia, craving for the drug. This list was obtained from previous studies [8, 9]. After completing the survey, they were given the Fatigue Severity Scale (FSS) [11]. To monitor the risk of PML, all patients performed MRI follow-up at 6 months (or less) as suggested by the good clinical practice and the MAGNIMS study group [12] and ECTRIMS [13] recommendations. EDSS analysis was performed considering total score and each item (pyramidal, cerebellar, brainstem, sensory, sphincterial function, visual function, cerebral functions). For outcome analysis, we classified the patients in two groups according to the presence or absence of WoS. Moreover, analysis of data comparing the subjects adopting StID and ExID protocol and between the subjects on 4-, 5- or 6-weeks interval of NTZ administration was performed. Data are expressed as mean ± standard deviation for continuous variables and counts and percentages for categorical variables. For group comparisons, we used the two-tailed unpaired *t* test or 1-way analysis of variance for continuous variables with Bonferroni multiple testing correction and Pearson χ^2 test or Fisher's exact test for categorical variables, as appropriate. All analyses were performed using SPSS statistical software (version 25; IBM-SPSS), with p value < 0.05 considered as statistically significant. The study was conducted at University Magna Graecia of Catanzaro. All participants provided written informed consent and the study was approved by the local institutional ethics committee.

Results

Table 1 shows demographic characteristics of the population. Among the total of 86 patients enrolled in the study, 47 patients were shifted to an ExID of 6 weeks, 23 to an ExID

Table 1 Demographic and clinical characteristics of enrolled subjects

	Total sample	NTZ treatment interval			
		4 weeks	5 weeks	6 weeks	*p* value
N (%)	86	16 (18.6%)	23 (26.7%)	47 (54.6%)	
Mean (SD) age (years)	40.3 (10.1)	37.2 (12.5)	41.7 (9.3)	40.7 (9.7)	*0.371*
Sex F/M (%)	62/24 (71.2/28.8)	12/4 (75.0/25.0)	17/6 (73.9/26.1)	33/14 (68.7/31.3)	
Mean (SD) BMI	25.5 (5.2)	25.8 (5.8)	24.2 (3.5)	26.1 (5.6)	*0.355*
Mean (SD) disease duration (months)	183.0 (94.1)	124.5 (78.7)	207.4 (115.0)	190.2 (83.5)	***<0.001***
Mean (SD) treatment duration with NTZ (months)	80.5 (40.2)	31.4 (9.4)	84.1 (43.1)	95.4 (31.6)	***0.036***
Mean EDSS	3.3 (1.5)	2.8 (1.2)	3.5 (1.7)	3.5 (1.6)	*0.303*

NTZ natalizumab, *BMI* body mass index, *EDSS* Expanded Disability Status Scale

Bolditalics for significant values, italics for non significant *p* values

of 5 weeks, and 16 refused ExID and remained on a StID of 4 weeks (7 of them already exhibited WoS, the remaining ones (9) had personal/logistic reasons). Mean treatment duration with NTZ of patients treated every 4 weeks was significantly lower than those treated every 5 and 6 weeks ($p < 0.001$), whereas mean disease duration was significantly lower in patients treated every 4 weeks respect to those treated every 5 weeks ($p = 0.044$). Among the 86 patients, 32 (37.2%) reported WoS at the 6-months follow-up (Table 2). Prevalence of WoS, considering the total of 86 patients, was 23.2% at baseline and it increased to 37.2% at the 6-month follow-up. Occurrence of WoS was not significantly statistically different between the patients that remained on StID vs those on ExID ($\chi^2 = 0.360$; $p = 0.372$). Moreover, no difference in WoS occurrence was found considering the time of interval of NTZ dose (i.e. 4-, 5- or 6-weeks; $\chi^2 = 4.332$; $p = 0.115$; Table 3). The most common WoS was fatigue, reported by 30 out of 32 patients with WoS (93.7%); other symptoms included a feeling of craving for the drug and headache (reported in a percentage of less than 6%). Of note, WoS of new onset were reported only by patients on ExID (12 out of 70, 17.1%), however no statistically significant difference was found between the StID and ExID group ($\chi^2 = 3.188$; $p = 0.070$) and in all these patients the new symptom was "fatigue": 3 of them were on a ExID of 5 weeks and 9 of them were on a ExID of 6 weeks.

Mean EDSS was higher in the group reporting WoS (3.8 WoS vs 3.1 non-WoS, $p < 0.05$). Considering the single EDSS items, sphincterial function was the one that differed the most and with statistical significance between the WoS group and the non-WoS group (1.4 WoS vs 0.6 non-WoS, $p < 0.001$). No other statistically significant differences were found in the other EDSS items between the two groups. Patients with WoS had a higher FSS score (46.5 WoS vs 32.9 non-WoS) with statistically significant difference ($p < 0.001$). BMI was similar in the WoS group (26.1 kg/m^2) and the non-WoS group (25.1 kg/m^2), as difference was not statistically significant (Table 3). The WoS group and the non-WoS group did not significantly differ for disease duration or treatment duration (Table 3). Considering exclusively the subjects on ExID, subjects with WoS showed a statistically higher mean EDSS and FSS

Table 2 Occurrence of WoS according to the length of the interval of NTZ administration

WoS	NTZ administration interval			
	4 weeks StID	5-week ExID	6-week ExID	Total
No (%)	9 (16.6%)	11 (20.3%)	34 (63%)	54 (62.8%)
Yes (%)	7 (21.9%)	12 (37.5%)	13 (40.6%)	32 (37.2%)
Fatigue	7 (23.3%)	11 (36.7%)	12 (40%)	30 (93.7%)
Craving	–	–	1 (100%)	1 (3.1%)
Headache	–	1 (100%)	–	1 (3.1%)

WoS wearing-off symptoms, *NTZ* natalizumab, *StID* standard interval dosing, *ExID* extended interval dosing

Table 3 Characteristics of patients with and without wearing-off symptoms (WoS)

Patients characteristics	Wearing off symptoms (WoS)								
	Total sample (*n*: 86)			StID (*n*: 16)			ExID (*n*: 70)		
	Yes	No	*p* value	Yes	No	*p*	Yes	No	*p* value
N (%)	32 (37.2%)	54 (62.8%)	–	7 (43.7%)	9 (26.3%)	–	25 (35.7%)	45 (64.3%)	–
Mean (SD) age (years)	41.4 (8.9)	39.7 (10.8)	*0.446*	36.3 (9.0)	37.9 (15.3)	*0.810*	42.8 (8.5)	40.0 (9.9)	*0.237*
Sex F/M (*n*)	27/5	35/19	***0.042***	6/1	6/3	*0.392*	21/4	29/16	*0.070*
Mean (SD) BMI	26.1 (6.3%)	25.1 (4.5%)	*0.339*	27.1 (8.5)	24.8 (2.7)	*0.453*	25.9 (5.7)	25.2 (7.7)	*0.607*
Mean (SD) disease duration (mos)	201.1 (98.4)	171.8 (98.4)	*0.189*	144.3 (103.8)	107.0 (51.3)	*0.411*	215.8 (93.7)	183.2 (91.5)	*0.182*
Mean (SD) treatment duration with NTZ (mos)	87.0 (43.1)	76.6 (38.3)	*0.294*	35.7 (11.4)	28.0 (6.2)	*0.105*	101.4 (37.2)	86.3 (34.4)	*0.092*
StID/ExID	7/25	9/45	*0.372*	–	–	–	–	–	–
4-/5-/6-week ID	7/12/13	9/11/34	*0.115*	7/–/–	9/–/–	*0.127*	–/12/13	–/11/34[a]	***0.041***
Mean (SD) EDSS	3.8 (1.5)	3.1 (1.6)	***0.025***	3.1 (1.2)	2.2 (1.2)	*0.153*	3.8 (1.8)	2.9 (1.8)	***0.048***
Sphincterial function	1.4 (1.1)	0.6 (0.8)	***< 0.001***	1.3 (1.1)	0.2 (0.4)	***0.020***	1.4 (1.1)	0.6 (0.8)	***0.002***
Mean (SD) FSS	46.5 (14.4)	32.9 (15.3)	***< 0.001***	48.1 (9.4)	25.4 (14.4)	***0.003***	46.0 (15.6)	34.4 (15.2)	***0.004***

WoS wearing-off symptoms, *StID* standard interval dosing, *ExID* extended interval dosing, *NTZ* Natalizumab, *ID* interval dose, *EDSS* Expanded Disability Status Scale, *FSS* Fatigue Severity Scale

[a]Analysis was performed considering only 5- and 6-week groups

Bolditalics for significant values, italics for non significant *p* values

score compared to those not complaining of WoS (3.8 vs 2.9, $p=0.048$; 46.0 vs 34.4, $p=0.004$, respectively). Patients on 6-week ExID showed less occurrence of WoS compared to patients on 5-week ExID, although with slightly statistical significance ($\chi^2=4.042$; $p=0.048$, Table 3). No other differences were evident (Table 3). At the 6 months MRI follow-up since adopting the ExID, 5 patients showed new small non enhancing lesions: none of them had a clinical relapse. Four of them were on a 6 weeks ExID, one was on a StID. No patient developed any adverse event during follow-up after adopting ExID. We did not observe significant EDSS change over time during the follow-up period in our cohort of patients after adopting the ExID. No patient developed major depression or behavior disorders of any kind that required symptomatic treatment during follow-up.

Discussion

During the Sars-CoV-2 pandemic, to reduce patients access to the hospital and minimize viral exposure, we advised and asked patients undergoing treatment with NTZ if they wanted to be shifted from a StID to and ExID, regardless of their JCV index. Our main objective was to study the prevalence of WoS in our cohort of patients, comparing its occurrence in patients in StID and ExID. Wearing-off at the end of NTZ dosing intervals and subsequent WoS have been described in previous studies [8, 14], and some showed that after adopting the ExID efficacy is still preserved [5, 15]. Moreover, ExID carries the advantages of reducing the risk of NTZ-associated PML in patients with MS [16]. ExID proved to be safe and effective up to an interval of 8 weeks in other studies [6, 7]. Our study shows a high prevalence (37.2%) of WoS in MS patients treated with NTZ. Wearing-off effect in our cohort did not statistically differ between the StID and ExID population. When considering exclusively new WoS onset, a similar incidence was found in the StID vs the ExID, and in the longer ExID group of 6 weeks vs the 5 weeks ExID group. A previous study on wearing-off symptoms conducted during Covid pandemic by Bringeland et al. reported a similar prevalence of WoS to our cohort, but an increase of WoS after ExID [17]. This last result varies among different studies: some showing a higher prevalence of WoS in the StID group instead [18]. Comparison between these studies is hard, as studies design is different. The most common WoS in our cohort was fatigue, reported by 93.7% of patients complaining of WoS, whilst other symptoms such as headache and a feeling of craving for the treatment were less common and were reported in a percentage of less than 6%. This result is in accordance with previous studies, as it is the prevalence of fatigue in NTZ treated MS patients [8, 10, 14, 17–19]. Of note, mean EDSS was significantly higher in the group reporting WoS (Table 3). EDSS had never been positively correlated with fatigue in previous studies adopting ExID [8, 10, 14, 17–19]. Fatigue and EDSS are intertwined, as shown in different works [20, 21]. Although the group in which this phenomenon occurs may have been treated for a longer time and can thus be assumed to have a longer disease duration and/or a worse disease course which brings more complaints by itself. More studies are needed to evaluate the contribution of EDSS on fatigue when ExID is adopted.

Interestingly the subgroup analysis of EDSS items, revealed a higher impairment of sphincterial functions in the WoS group, as already shown. EDSS correlates with sphincterial functions and with a lower quality of life in MS patients with more compromised sphincterial functions [22]. This is the first study to evaluate EDSS items in patients with fatigue after adoption of ExID. Patients with WoS had also a higher FSS (46.5 WoS vs 32.9 non-WOS, $p<0.01$), thus showing how our survey on fatigue was in accordance with the FSS score. Few studies have investigated the phenomenon of wearing-off and symptoms recrudescence at the end of the dosing cycle. There are at least three possible explanations of WoS: one involves cytokines [8], the other involves cell-mediated inflammatory response [23] and a lower receptor occupancy of NTZ (especially in the higher BMI population) [14]. The association between high BMI and lower receptor occupancy (RO) has led some to suggest that the dose of NTZ should be adjusted for body weight [24–26]. Lower NTZ RO at the end of the dosing interval could increase migratory capacity of cytokine-producing leukocytes into CNS, especially in the higher BMI population, thus reducing the risk of PML. In our population mean BMI differences were not statistically significant between the WoS and non-WoS group. Of note, fatigue in MS patients has been intensively studied in relation to clinical variables such as treatment duration and disability in previous studies, but no clear statistical difference was found between the WoS and non-WoS group regarding these two variables [23, 27–29]. Our data also do not show any statistically significant difference. Our study shows that when ExID was adopted efficacy was relatively preserved, as only 4 patients showed some evidence of minimal radiological disease activity (new small non-enhancing lesions) despite no worsening or new onset of their symptoms, this is in accordance with previous studies [5, 15], but more studies are needed to confirm this result. Limitations of our study include the small sample size, no evaluation of possible anxiety disorders associated, especially since it was conducted during COVID-19 pandemic, although no patients developed behavior disorders that needed symptomatic treatment. Another important limitation is recall bias, since patients were asked about WoS in retrospect and selection bias, as this was not a randomized study, since patients with more severe disease may be less inclined to switch from StID to

ExID. Moreover, the study is mainly based on patients interpretation of their symptoms, which brings a high risk of bias. Selection bias was kept relatively low as 81.4% of patients agreed upon extending the dosing interval, but not as low as in previous studies [17]. We need more studies to better understand the pathogenesis of fatigue related symptoms in MS patients undergoing treatment with NTZ. It could be interesting in the future to evaluate also possible influences of cognitive aspects such as anxiety and depression on WoS. Our study demonstrates that adoption of ExID does not increase the occurrence of WoS in patients treated with NTZ. With this study we confirm that fatigue is the most prevalent symptom among WoS in both the StID and the ExID. In our cohort, WoS correlates with a higher EDSS (especially with sphincterial function impairment) and with the FSS scale. ExID did not compromise safety and efficacy of NTZ in our patients. Based on our results, we suggest to adopt a fatigue scale, such as FSS, besides EDSS score in the routine evaluation of MS patients; moreover, we suggest to evaluate WoS to adopt possible strategies to ameliorate quality of life in MS patients with rehabilitation and treatments targeting fatigue.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards All participants gave their informed consent prior to their inclusion in the study. All participants provided written informed consent and the study was approved by the local institutional ethics committee.

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