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Clinical short communication

Wearing-off at the end of natalizumab dosing interval and risk of MS disease activity: A prospective 1-year follow-up study

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ABSTRACT

Natalizumab effectively prevents disease activity in relapsing-remitting multiple sclerosis by binding α4 integrin and inhibiting leukocyte migration to the central nervous system. We recently reported an association between low natalizumab receptor occupancy and subjective wearing-off symptoms at the end of the 4-week dosing interval. Here, we aimed to evaluate the short-term risk of disease activity in a 1-year prospective follow-up of the same patient cohort (n = 40). We found that all patients available for follow-up after one year (n = 35) fulfilled the criteria for no evidence of disease activity (NEDA). Thus, wearing-off symptoms were not associated with increased short-term risk of disease activity. Longer follow-up in a larger patient cohort is required to establish whether therapeutic efficacy is maintained in patients with wearing-off symptoms.

1. Introduction

Natalizumab (Tysabri®, Biogen) administered intravenously at a standard dose of 300 mg every 4 weeks efficiently reduces disease activity in relapsing-remitting multiple sclerosis (RRMS) [1]. By blocking α4 integrin on leukocytes, natalizumab inhibits leukocyte adhesion to and migration over the blood-brain barrier. Natalizumab receptor occupancy (RO) refers to the proportion of α4 integrins occupied by natalizumab on single cells, and has been suggested as a biomarker to monitor therapeutic efficacy and possibly patient-tailor therapy [2]. Neurofilament light chain (NF-L) is another emerging biomarker for disease activity and neuroaxonal damage in RRMS, and is reported to return to levels of healthy individuals following initiation of natalizumab therapy [3].

Approximately 50% of patients treated with natalizumab report a feeling of the effect "wearing off" towards the end of the 4-week dosing interval, and that subjective symptoms, most commonly fatigue, increase during the last week of the dosing interval and improve shortly after receiving the next infusion [4–6]. The underlying mechanisms of this phenomenon are unknown, but we recently found that patients who regularly reported wearing-off symptoms at the end of dosing intervals had lower natalizumab RO than those reporting such symptoms occasionally or never [6]. Here, we aimed to investigate if the patients who regularly reported wearing-off symptoms had increased risk of disease activity during a 1-year follow-up.

2. Methods

2.1. Subjects

We invited all patients with a diagnosis of RRMS over 18 years of age who had received a minimum of six natalizumab infusions at the Department of Neurology, Haukeland University Hospital (n = 45) to participate, of whom 40 (88.9%) participated after written informed consent. The study was approved by the Regional Ethics Committee (REK 2016/579).

2.2. Evaluation at inclusion and after one year

At inclusion, we obtained baseline demographic and clinical data including MRI lesion activity and clinical relapses in the last year prior to inclusion from the patient's medical journal. Each patient filled in questionnaires on fatigue (Fatigue Severity Scale; FSS) [7], and on working status, smoking habits, weight, height, and whether they had wearing-off symptoms regularly (at the end of every dosing interval), sometimes (at the end of some dosing intervals), or never. A trained

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; RO, receptor occupancy; NF-L, neurofilament light chain; FSS, Fatigue Severity Scale; EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; NEDA, no evidence of disease activity

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neurologist evaluated disability levels by the Expanded Disability Status Scale (EDSS) and cognitive function was assessed by the Symbol Digit Modalities Test (SDMT) [8] at inclusion and after one year. In addition, the first registered SDMT score, assessed when each patient received their first natalizumab infusion at our department, was obtained from the medical journal. MRI was conducted at inclusion and after one year and clinical relapses were registered during the 1-year prospective follow-up. No evidence of disease activity (NEDA) was defined as freedom of relapses and EDSS worsening, and lack of new or enlarged T2 lesions on MRI. Serum collected at inclusion and after one year was stored at −80 °C and NF-L was quantified with a single-molecule array (Simoa) assay (Quanterix).

2.3. Statistical analysis

For statistical analysis, patients were separated into two groups based on whether they reported wearing-off symptoms regularly (at the end of every dosing interval) or not (only sometimes or never). Patient characteristics, clinical and radiological signs of disease activity, and NF-L levels at baseline and after a 1-year follow-up were compared between the groups using a Kruskal-Wallis test. Statistical differences with $p < .05$ were considered significant using a two-sided comparison. Holm's method was used to adjust for multiple comparisons.

3. Results

Table 1 shows patient characteristics at inclusion and after a 1-year follow-up. After one year, five of the 40 included patients no longer received natalizumab therapy at our hospital; one had moved to another region and four had switched to other therapies due to antibodies against JC virus ($n = 2$), side effects of natalizumab ($n = 1$), or planned pregnancy (n = 1). None of these five patients had reported wearing-off symptoms regularly at inclusion.

None of the 35 remaining patients experienced clinical relapses, new or enlarged T2 lesions on MRI or EDSS score changes of > 1 point during the 1-year follow-up period. Thus, all remaining patients fulfilled the criteria for NEDA.

At inclusion, patients reporting regular wearing-off symptoms had higher BMI and higher frequency of sick-leave than patients with wearing-off symptoms only sometimes or never [6]. None of the patients had experienced clinical relapses or new or enlarged MRI lesions in the year prior to inclusion in the study. Median EDSS was similar between the wearing-off groups both at baseline and after one year. Patients reporting wearing-off regularly had poorer median FSS (higher score) and SDMT (lower score) than patients reporting symptoms only sometimes or never both at inclusion and after one year, and these differences became statistically significant after 1-year follow-up. However, none of the differences were statistically significant after adjusting for multiple comparisons. SDMT scores from the time of the first natalizumab infusion at our department (at initiation of natalizumab therapy for all but two patients) was similar between wearing-off groups. NF-L levels in serum were similar between the groups at inclusion and after 1-year follow-up.

Table 1
Patient characteristics at inclusion and after a 1-year follow-up.

	Total	Wearing-off symptoms		p	p_{adj}
		Regularly	Not regularly		
RRMS patients, n (%)					
Baseline	40 (100)	8 (20)	32 (80)		
After 1 year	35 (87,5%)	8 (23)	27 (77)		
Patient characteristics at inclusion					
Age, y	43.0 (34.0–49.3)	43 (37–43.75)	44 (33.5–51)	0.531	1.000
Sex, females, n (%)	25 (62.5)	7 (87.5)	18 (51)	0.107	1.000
BMI	25.3 (22.6–27.2)	27.8 (26.5–31.2)	24.30 (22.34–26.11)	0.008	0.136
Current smoker, n (%)	7 (17.5)	1 (12.5)	6 (18.8)	0.681	1.000
Sick-leave, n (%)	9 (22.5)	4 (50.0)	5 (15.6)	0.040	0.600
Disease duration, y	13.0 (8.0–17.0)	12.5 (8.8–16.0)	13 (8–17.25)	0.747	1.000
Treatment duration, y	4.0 (3.0–7.3)	4.5 (2.0–8.0)	4 (3–7.25)	0.959	1.000
Dose number	56.5 (39.0–102.3)	63.5 (33.5–111.8)	56.5 (39–95.5)	0.933	1.000
Days since last dose	28.0 (28.0–28.0)	28.00 (27.0–28.0)	28 (28–28)	0.382	1.000
Markers of disease activity					
New or enlarged MRI T2 lesions					
Last year prior to inclusion	0	0	0	–	–
During 1-year follow-up	0	0	0	–	–
Clinical relapses					
Last year prior to inclusion	0	0	0	–	–
During 1-year follow-up	0	0	0	–	–
EDSS					
At inclusion	2 (1.375–3.5)	2 (1.5–2.75)	2 (1–3.5)	0.681	1.000
After 1 year	2 (1.5–3.5)	2 (1.88–2.38)	2 (1–3.5)	1.000	1.000
FSS					
At inclusion	4.78 (3.33–5.67)	5.33 (4.83–5.78)	4.44 (3.25–5.67)	0.119	1.000
After 1 year	4.89 (3.56–5.72)	5.89 (5.31–6.31)	4.11 (3.39–5.39)	0.005	0.090
SDMT					
At first natalizumab dose	53 (44.5–60.25)	51 (39.5–60.5)	53 (46.5–59.5)	0.672	1.000
At inclusion	57 (50–67.25)	48.5 (45.5–56)	58 (52.75–68.25)	0.052	0.728
After 1 year	59 (50.5–69)	48.5 (47–55.75)	62 (56–70)	0.023	0.368
S-NF-L pg/ml					
At inclusion	7.09 (5.27–9.38)	5.19 (5.03–6.09)	7.12 (5.55–9.64)	0.098	1.000
After 1 year	7.71 (5.57–10.82)	6.46 (5.89–7.89)	8.02 (5.45–11.59)	0.610	1.000

Patients reporting wearing-off symptoms at the end of natalizumab dosing intervals regularly (every dosing interval) or not (only sometimes or never). RRMS = relapsing-remitting multiple sclerosis, EDSS = Expanded Disability Status Scale, FSS = Fatigue Severity Scale, SDMT = Symbol Digit Modalities Test. S-NF-L = serum neurofilament light chain. *P* values of independent samples *t*-test. P_{adj} values are adjusted for multiple comparisons using Holm's test.

4. Discussion

Subjective wearing-off symptoms at the end of the 4-week dosing interval are frequent among patients receiving natalizumab infusions, but the phenomenon remains poorly understood. Recently, we reported lower natalizumab RO in patients experiencing wearing-off symptoms regularly, possibly caused by high BMI [6]. In this study, we aimed to evaluate the risk of disease activity in a 1-year prospective follow-up of the same patient cohort.

We found that all patients available for follow-up after one year fulfilled the criteria for NEDA, and that subjective wearing-off symptoms were not associated with increased short-term risk of clinical or radiological signs of disease activity. The similar baseline and 1-year serum NF-L levels between the patient groups further supported this. Nevertheless, the small patient cohort and short follow-up in our study could limit its ability to reveal possible differences in therapeutic effect. Our patient cohort had a median disease duration of 13 years and had received natalizumab therapy for median 4 years, which could indicate that they were a selected group of stable patients. The risk of disease activity may differ in patients with shorter disease and therapy duration. Wearing-off symptoms were not associated with cessation of natalizumab therapy.

Patients reporting wearing-off regularly had more severe fatigue and cognitive impairment than patients with symptoms only sometimes or never. MS-related fatigue and cognitive impairment are common and affect quality of life independently of physical disability, and the current criteria for NEDA have been criticized for not emphasizing fatigue and cognitive function in the evaluation of therapeutic efficacy [9]. Natalizumab has positive effects on fatigue and cognitive function [10] and more severe symptoms in the patient group with wearing-off regularly could thus represent a sub-optimal therapeutic effect. However, the differences in FSS and SDMT were small and need to be confirmed in larger populations. SDMT scores were similar between the two groups at initiation of natalizumab therapy. We have no pre-treatment FSS scores and can therefore not exclude that differences in fatigue existed already before initiation of natalizumab therapy.

In conclusion, although regular subjective wearing-off symptoms are associated with lower natalizumab RO [6], they were not associated with increased short-term risk of breakthrough disease. Patients with wearing-off symptoms regularly had more severe fatigue and cognitive impairment in the 1-year follow-up. The results provide some reassurance that the presence of the wearing-off phenomenon is not associated with reduced efficacy of the drug. However, longer prospective follow-up of a larger patient cohort is necessary to determine whether the therapeutic efficacy of natalizumab is maintained over time in patients reporting wearing-off symptoms regularly. The characteristics and clinical significance of the wearing-off phenomenon should be evaluated in future randomized studies of natalizumab using different dosing intervals.

Declaration of Competing Interest

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References

[1] C.H. Polman, P.W. O'Connor, E. Havrdova, et al., A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis, N. Engl. J. Med. 354 (2006) 899–910 2006/03/03 https://doi.org/10.1056/NEJMoa044397.

[2] J. Punet-Ortiz, J.V. Hervas-Garcia, A. Teniente-Serra, et al., Monitoring CD49d receptor occupancy: A method to optimize and personalize natalizumab therapy in multiple sclerosis patients, Cytometry B Clin. Cytom. (2017), https://doi.org/10.1002/cyto.b.21527 2017/04/06.

[3] M. Gunnarsson, C. Malmestrom, M. Axelsson, et al., Axonal damage in relapsing multiple sclerosis is markedly reduced by natalizumab, Ann. Neurol. 69 (2011) 83–89 2011/02/01 https://doi.org/10.1002/ana.22247.

[4] J.N. Ratchford, R. Brock-Simmons, A. Augsburger, et al., Multiple sclerosis symptom recrudescence at the end of the natalizumab dosing cycle, Int. J. MS Care 16 (2014) 92–98 2014/07/26 https://doi.org/10.7224/1537-2073.2013-017.

[5] Z.L.E. van Kempen, D. Doesburg, I. Dekker, et al., The natalizumab wearing-off effect: End of natalizumab cycle; recurrence of MS symptoms, Neurology (2019), https://doi.org/10.1212/WNL.0000000000008357 2019/09/26.

[6] G.H. Bringeland, N. Blaser, K.M. Myhr, et al., Wearing-off at the end of natalizumab dosing intervals is associated with low receptor occupancy, Neurol. Neuroimmunol. Neuroinflamm. 7 (2020), https://doi.org/10.1212/NXI.0000000000000678 2020/02/06.

[7] L.B. Krupp, LaRocca NG, J. Muir-Nash, et al., The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus, Arch. Neurol. 46 (1989) 1121–1123 1989/10/01 https://doi.org/10.1001/archneur.1989.00520460115022.

[8] A. Smith, Symbol digit modalities test: Manual, Los Angeles, CA, Western Psychological Services, 1982.

[9] M. Stangel, I.K. Penner, B.A. Kallmann, et al., Towards the implementation of 'no evidence of disease activity' in multiple sclerosis treatment: the multiple sclerosis decision model, Ther. Adv. Neurol. Disord. 8 (2015) 3–13 2015/01/15 https://doi.org/10.1177/1756285614560733.

[10] P. Iaffaldano, R.G. Viterbo, D. Paolicelli, et al., Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study, PLoS One 7 (2012) e358432012/05/05 https://doi.org/10.1371/journal.pone.0035843.