



Original Article

Treatment modifiers across different regimens of natalizumab treatment in MS: An Italian real-world experience

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ABSTRACT

Despite its widespread use in clinical practice, the effectiveness of natalizumab extended interval dosing (EID) adopted from treatment start across different treatment intervals and individual modifiers (body mass index - BMI) is still under-investigated. Here, seven-hundred and forty-five multiple sclerosis (MS) patients, exposed to natalizumab for 3.30 ± 1.34 years, were retrospectively enrolled in an observational multicenter study. After stratifying patients in EID or standard interval dosing (SID), we assessed differences in time to relapse, MRI activity and Expanded Disability Status Scale (EDSS) progression. The primary analysis was conducted on patients exposed to EID interval from 5 weeks and 1 day to 7 weeks, while a secondary analysis included also EID periods up to 8 weeks. An additional analysis explored the impact of BMI. No differences in time to first relapse, time to radiological activity, time to EDSS progression or time to EDA (evidence of disease activity) were detected between SID and EID group (EID interval from 5 weeks to 1 day to 7 weeks). When including EID periods from 7 weeks and 1 day to 8 weeks, the EID group showed a trend towards higher risk of experience clinical relapses than the SID group. A higher EDA risk was also identified in EID patients with BMI above median. In conclusion, a higher risk of relapses seems to occur for EID above 7 weeks. Independently from the EID scheme adopted, higher BMI increases the risk of EDA in these patients.

Introduction

Natalizumab usage in highly active patients with Multiple Sclerosis (MS) has been largely established during the last 10 years in both clinical trials and real world practice [1].

Despite the high level of efficacy in reducing both clinical and radiological activity in MS [2], natalizumab use has been limited by

potential risk of progressive multifocal leukoencephalopathy (PML), an infrequent but possibly fatal opportunistic brain infection caused by the John Cunningham virus (JCV) reactivation.

To date, the strategy to minimize the risk of PML occurrence is based on an established algorithm embedding the duration of natalizumab treatment, the former use of immunosuppressants and anti-JC virus antibody status [3]. Over the years, several studies have suggested an

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approach to minimize PML risk based on the switch from the standard-interval dosing (SID) of 28 (\pm 7) days to an extended-interval dosing (EID) of 35 days or longer. Recently, a large cohort study has shown positive results for EID in terms of lowering PML risk in anti-JCV antibody positive treated subjects [4]. The concept of EID is supported by both pharmacodynamic and clinical evidence. From a pharmacodynamic perspective, a partial saturation of α 4-integrin might preserve immune surveillance in the central nervous system, preventing JC virus reactivation and therefore reducing the risk of PML. Indeed, it has been demonstrated that patients on EID (defined as having received \leq 15 infusions in the previous 18 months of treatment) maintain natalizumab concentration above the threshold of 2.0 μ g/mL and α 4-integrin saturation higher than 50%, both considered therapeutical cut-off for natalizumab efficacy [5]. Several real-world studies have provided data supporting EID effectiveness in controlling disease activity in terms of clinical relapses [6–8], magnetic resonance activity [9,10] or both [11, 12], while fewer studies have included disability worsening among the explored outcomes [8,11,13].

Only recently two prospective clinical trials investigated the efficacy of EID. A single-arm trial found that extending the drug administration schedule did not result in any disease reactivation [14]. However, the only randomized controlled trial comparing SID and EID showed a numerical difference in the mean number of new or newly enlarging T2 hyperintense lesions at week 72 between the once every 6 weeks and once every 4 weeks groups [15] with no significant differences in clinical endpoints at week 72 between the two therapeutic regimens. No Evidence of Disease Activity (NEDA)-3 status, a secondary outcome, was achieved at the end of follow-up with the same probability by both groups [15].

The somehow surprising findings from NOVA study [15] in relation to MR disease activity spur further debate in the scientific community [16–18] and represented the *primum movens* for the conceptualization of the current work.

Indeed, despite this growing body of evidence, some aspects related to the effectiveness of different natalizumab dosing still need to be addressed. First, in clinical practice (and also in the NOVA study) patients are usually switched to EID after an initial period on SID. More data are needed about the effectiveness of the two regimes adopted from treatment start. Second, despite its widespread use in clinical practice, no consensus exists on the definition of EID, which ranged, in previous works, from an interval dosing of 4 weeks and 3 days [12] to 8 weeks [7, 11,12]. Apart from indirect comparison of these studies results, no data are available on natalizumab effectiveness at different EID. Third, while the therapeutic aim in clinical practice has moved towards the concept of NEDA, the focus in terms of outcome measures in previous studies exploring natalizumab EID effectiveness has been on disease activity, partly in consideration of their follow-up duration, mostly covering a 2-years observation period [6–8,10–12]. Finally, individual factors that may affect EID efficacy are under investigated. Apart from dosing interval, body mass index (BMI) is the main variable found to influence the pharmacology of natalizumab [19]. Although a recent model-based simulation suggested that every-5-week or every-6-week dosing is likely to keep the efficacy of natalizumab, mostly at body weights $<$ 80 kg [20], observational data on the effect of EID at different BMIs is lacking.

To shed further light on the effectiveness of natalizumab EID, the aims of this multicenter real-world observational study were: (i) to assess NEDA-3 in a large population of patients with MS treated, from treatment start, with SID vs different EID intervals adopted in clinical practice; (ii) to explore the impact of EID vs SID across BMIs.

Methods

Study design and participants

This is an independent, multi-center, real world, retrospective study. Clinical and MRI data from patients with a diagnosis of MS according to

revised McDonald's criteria [21] and treated with natalizumab, from 2007 to 2018, at 8 MS Italian Centers, were collected. To be included in the study patients had to meet the following inclusion criteria: a) age $>$ 18 years at treatment start; b) at least one-year treatment with natalizumab; c) availability of clinical and MRI evaluation performed at least yearly; d) date of each infusion along course of natalizumab identifiable. After identifying eligible patients, data were collected up to latest natalizumab infusion or natalizumab treatment stop/switch. The following parameters were recorded and collected in a specific electronic case report form built for this project and detained from the coordinator center: age, gender, disease duration, previous therapies, reason for switching to natalizumab, MS phenotype, date of natalizumab initiation, date of each infusion, date of last natalizumab infusion, reason for natalizumab discontinuation if occurred, BMI. For each subject, clinical variables as number of relapses during the two years prior to natalizumab start, relapses occurred during the observational period (date), Expanded Disability Status Scale (EDSS) [22] score at treatment start and every year during natalizumab treatment were collected. Brain MRI scans were evaluated within 3 months from natalizumab start and yearly over the follow-up. The MRI acquisition protocol needed to adhere to minimum requirements as suggested by MAGNIMS guidelines for MS treatment monitoring [23]. All images were rated by the local neuroradiologist. We centrally computed the number of days occurring between each infusion of natalizumab to define groups by mean interval between dose per year as follows: 1) SID: mean interval dosing between 4 and 5 weeks; 2) EID: mean interval dosing above 5 weeks (ranging from 5 weeks and 1 day to 8 weeks). Across all centers, the most used EID mean interval ranged from 5 weeks and 1 day to 7 weeks, while only in a minority of treatment periods EID mean interval exceeded 7 weeks. Each patient was considered belonging to the exposure group as observed during the first year of treatment. If a patient changed exposure group during the follow-up, he/she was censored at that time. In order to fulfill our first aim, we conducted a primary analysis focused on EID interval from 5 weeks and 1 day to 7 weeks (whose results reflect the impact of commonly adopted strategies in clinical practice). In this analysis, EID intervals $>$ 49 days were censored. A secondary analysis was then performed including EID interval ranging from 7 weeks and 1 day to 8 weeks (to verify whether exposure to longer EID interval would affect effectiveness outcomes). To fulfill our second aim, we stratified the population according to median BMI, to verify whether EID effectiveness could be confirmed across BMI groups.

Outcome measures

As effectiveness outcomes, we considered NEDA-3 status and its components. NEDA-3 is a combined measure defined as the contemporary absence of clinical relapses, confirmed disability worsening and MRI activity. A relapse was defined as any new neurologic symptom in the absence of fever or infection lasting for at least 24 h, corroborated by new neurologic signs and confirmed by the treating neurologist [21]. Disability worsening was considered as 1.5-point increase (if baseline EDSS score was 0), 1.0-point increase (if baseline EDSS score was $<$ 5.5), or 0.5-point increase (if baseline EDSS score was \geq 5.5) confirmed 6 months apart [24]. MRI activity was defined as the occurrence of gadolinium-enhancing (GD+) lesions on T1-weighted images or new hyperintense lesions on T2-weighted images (compared to the baseline scan) on brain scans. We did not consider the enlarging T2-hyperintense lesions because a previous study demonstrated a poor inter-rater agreement for this metric during routine clinical practice [25].

Statistical analysis

Baseline clinical patients' characteristics are reported as mean and standard deviation (or median and range, as appropriate) or as frequencies and percentage for continuous and categorical variables, respectively. The time-to-EDSS progression was defined as the time between enrollment and EDSS progression. For subjects who did not

experience the endpoint, time-to-EDSS progression was censored at the time of the last available follow-up visit. The time-to-first-relapse was defined as the time between enrollment and first relapse. For subjects who did not experience the endpoint, time-to-first-relapse was censored at the time of the last available follow-up visit. The time-to-radiological-activity was defined as the time between enrollment and first radiological-activity. For subjects who did not experience the endpoint, time-to-radiological-activity was censored at the time of the last available follow-up visit. EDA endpoint was defined as the first occurred of the three endpoints defined above. The time-to-EDA was defined as the time between enrollment and EDA. For subjects who did not experience the endpoint, time-to-EDA was censored at the time of the last available follow-up visit. Each patient was considered belonging to the exposure group as observed at baseline. If a patient changed exposure group during the follow-up, he/she was censored at that time. We run three types of analyses: i) Crude (not adjusted) Cox regression model; ii) Cox regression model adjusted for age at enrollment, gender, disease duration, previous treatment (yes/no), number of relapses in the 2 years before enrollment, active MRI at baseline (yes/no), baseline EDSS; iii) inverse probability treatment weighted (IPTW) Cox regression using the same covariates as in ii). A further exploratory analysis according to body mass index (BMI) was also conducted, investigating i) the treatment effectiveness (EID vs. SID) in two subgroups, according to the median BMI cut-off (23.74 kg/m²) and ii) if a treatment (EID vs. SID) by BMI (as continuous variable) interaction could modulate the study endpoints. All statistical analyses were performed using SAS Software Release 9.4 (SAS Institute, Cary, NC) and the computing environment R (R Development Core Team, version 3.3.2).

Ethics statement

The present study was conducted in accordance with specific national laws and the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Given its retrospective design, this study did not interfere in the care received by patients. In addition, specific ethical approval was not required owing to the retrospective design, and since all clinical assessments were part of the clinical practice in a university- or hospital-based specialized center setting. However, as per Italian regulations (<https://www.gazzettaufficiale.it/eli/id/2008/03/31/08A02109/sg>) the principal investigator of each site notified the local ethic committee about this retrospective study. Patients provided their informed consent to collect data for clinical purposes.

Results

Study population

We retrospectively enrolled 745 patients (flowchart in Fig. 1), whose baseline demographic and clinical characteristics are reported in Table 1. Mean follow-up (exposure period to natalizumab) was 3.30 ± 1.34 years.

Natalizumab effectiveness according to EID regimen

Outcomes for EID between 5 and 7 weeks

Baseline demographic and clinical characteristics of the study population, according to treatment arm, are shown in Table 1. Patients in the SID group showed higher number of relapses in the two years prior to study enrollment than patients in the EID group. No other difference was identified at baseline between the two groups. No differences in time to first relapse, time to radiological activity, time to EDSS progression or time to EDA were detected between SID and EID group (Table 2, Supplementary Table 1 and Fig. 2).

Outcomes when including EID interval above 7 weeks

Baseline demographic and clinical characteristics of the study population are the same shown in Table 1, but the mean average time between treatments in EID cohort was equal to 42.00 ± 6.99 days. While no differences were detected between SID and EID groups in terms of time to radiological activity, time to EDSS progression or time to EDA, the EID group showed a trend towards higher risk of experience clinical relapses than the SID group (Table 3).

Natalizumab effectiveness according to BMI

An exploratory analysis according to BMI was conducted in a subset of patients, whose demographic and clinical characteristics are shown in Table 4. At baseline patients in the EID group were more likely naïve than patients in the SID group. The two exposure groups were well balanced

Table 1

Baseline demographic and clinical characteristics of the study population.

	Overall	SID	EID	P
N	745	627	118	
Age (years, mean (SD))	35.24 (9.45)	35.21 (9.27)	35.40 (10.40)	0.845
Sex = M (%)	245 (32.9)	214 (34.1)	31 (26.3)	0.119
Disease duration years, mean (SD)	8.50 (6.75)	8.55 (6.73)	8.23 (6.86)	0.635
Previous treatment (yes, %)	655 (87.9)	558 (89.0)	97 (82.2)	0.054
EDSS baseline (median [min, max])	2.50 [0.00, 8.00]	2.50 [0.00, 7.50]	2.00 (8.00)	0.597
Positive MRI baseline (yes, %)	568 (76.2)	474 (75.6)	94 (79.7)	0.405
Relapse 1yPrior (median [min, max])	1.00 [0.00, 6.00]	1.00 [0.00, 6.00]	0.00 [0.00, 4.00]	<0.001
Relapse 2yPrior (median [min, max])	1.00 [0.00, 7.00]	1.00 [0.00, 7.00]	1.00 [0.00, 5.00]	<0.001
Average time between treatment, mean (SD)	35.71 (7.03)	31.33 (1.78)	40.16 (3.72)	<0.001

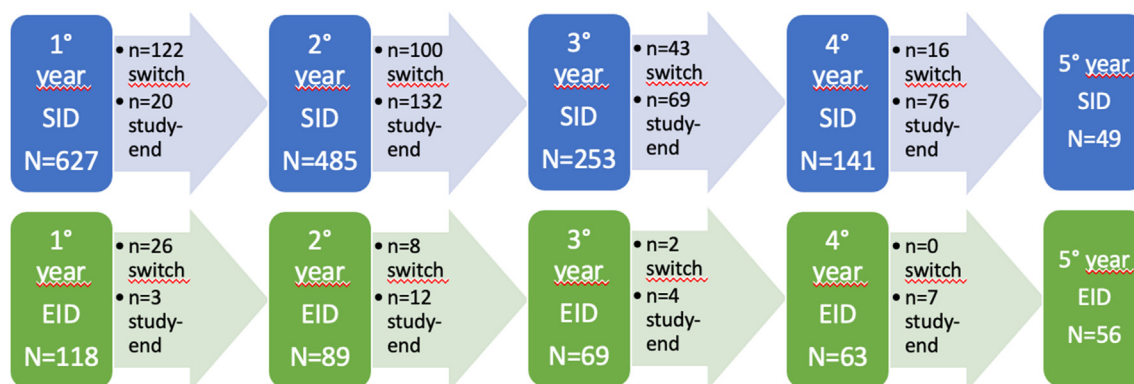


Fig. 1. Study flow chart: raw data and percentage of patients switching along the follow-up.

Table 4

Baseline demographic and clinical patients' characteristics according to treatment regimen in the BMI-available subset.

	SID	EID	P
N	352	63	
Age (mean (SD))	33.92 (9.17)	36.14 (10.66)	0.086
Sex = M (%)	118 (33.5)	13 (20.6)	0.06
BMI (mean (SD))	23.87 (3.38)	23.22 (3.72)	0.166
BMI above the median (≥ 23.74) (%)	179 (50.9)	28 (44.4)	0.424
BMI categories (%)			0.054
<18.5	9 (2.6)	6 (9.5)	
18.5–24.9	247 (70.2)	40 (63.5)	
25–29.9	82 (23.3)	14 (22.2)	
≥ 30	14 (4.0)	3 (4.8)	
Disease duration (mean (SD))	7.73 (6.22)	8.55 (7.37)	0.348
Previous treatment (%)	312 (88.6)	49 (77.8)	0.031
EDSS baseline (mean (SD))	2.62 (1.56)	2.55 (1.60)	0.753
Active MRI baseline (%)	288 (81.8)	54 (85.7)	0.57
Relapse 1yPrior (mean (SD))	0.92 (0.92)	0.79 (0.97)	0.319
Relapse 2yPrior (mean (SD))	1.30 (1.16)	1.13 (1.18)	0.275
Average time between treatment, (mean (SD))	34.55 (4.30)	38.92 (3.46)	<0.001

Table 5

P-values of the interaction term from Cox regression model including treatment regimen, BMI and their interaction term.

Endpoint	BMI	Interaction term's p-value
Relapse	Continuous	0.320
Relapse	Binary (above vs below 23.74 kg/m ²)	0.158
RMN worsening	Continuous	0.014
RMN worsening	Binary (above vs below 23.74 kg/m ²)	0.158
EDSS worsening	Continuous	0.028
EDSS worsening	Binary (above vs below 23.74 kg/m ²)	0.944
EDA	Continuous	0.016
EDA	Binary (above vs below 23.74 kg/m ²)	0.026

BMI was considered both as a continuous variable and a dichotomous variable (above and below median value).

differences between our findings and previous observations [7,12]. More in detail, Zhovtis Ryerson et al. [12] compared the effectiveness of different extended interval dosing regimens to SID and documented that EID for up to 8 weeks and 5 days did not reduce the effectiveness of natalizumab compared to SID. Furthermore, no differences were observed among the various EID regimens, except for a reduction in the annualized relapse rate in patients with a dosing interval greater than 7 weeks. These contrasts with what was shown in our study may be the result of a selection bias for patients with lower prior disease activity. Additionally, patients with the longest dosing intervals had a lower mean BMI than the other subgroups [12]. Therefore, we may hypothesize that

Table 6

Subgroup analysis according to BMI.

BMI subgroup	Sample size	Model	Endpoint	HR (EID vs. SID)	95% CI	p-value	p-value heterogeneity
<23.74 kg/m ²	N = 208 (37 events)	Un-adjusted	EDA	0.46	0.16	1.32	0.148
≥ 23.74 kg/m ²	N = 207 (63 events)	Un-adjusted	EDA	1.88	0.98	3.61	0.059
<23.74 kg/m ²	N = 208 (37 events)	Adjusted ^a	EDA	0.43	0.15	1.28	0.129
≥ 23.74 kg/m ²	N = 207 (63 events)	Adjusted ^a	EDA	1.90	0.97	3.73	0.061
<23.74 kg/m ²	N = 208 (37 events)	IPTW	EDA	0.74	0.22	2.44	0.62
≥ 23.74 kg/m ²	N = 207 (63 events)	IPTW	EDA	1.59	0.72	3.50	0.247

^a Adjusted for sex, age at recruitment, disease duration, previous treatment (yes/no), baseline EDSS, active MRI at baseline, number of relapses in the 2 years before.

BMI influenced the risk of disease activation in this case. Indeed, in addition to the dosing interval, our results support the role of BMI as treatment effect modifier, with higher BMI values being predictive of a higher risk of EDA in EID. Although this is the first study comparing the effectiveness of EID and SID in reaching NEDA-3 status in MS patients with different BMI, our findings appear in line with previous reports of an association between BMI and higher rate of relapses [26]. These data suggest a connection between natalizumab dosage and BMI, as the interval regimen alone (SID vs EID) does not appear sufficient to modify the EDA risk in these subgroups. Indeed, it has long been known that body weight is related to the degree of $\alpha 4$ -integrin saturation. Weight-based natalizumab treatment has been proposed but has never been studied in clinical trials [27]. The model described by Chang et al. [20], indicates that the efficacy of natalizumab decreases with increasing dosing interval and body weight. According to this model, efficacy is maintained, particularly for patients weighing less than 80 kg, who switch to a 5- or 6-week dosing interval after a period of stability on SID.

EID has been shown to reduce nadir serum natalizumab levels and $\alpha 4$ -integrin receptor occupancy, while increasing $\alpha 4$ -integrin cell surface expression. While these effects are known to improve JCV immune surveillance and prevent PML, it is possible that in some patients the drug concentration reaches, at the nadir, inadequate levels to maintain efficacy. Although many different thresholds have been proposed, the exact level of $\alpha 4$ -integrin receptor occupancy by natalizumab required for clinical efficacy is still unknown. Pharmacokinetic studies have shown that natalizumab concentration and receptor occupancy levels are significantly affected by body weight, BMI and dosing regimen, with EID patients with the highest BMI showing the lowest levels [19,28].

Few other studies have evaluated the impact of BMI on various aspects of natalizumab therapy. The well-known wearing-off effect, particularly evident in the use of an EID, is influenced by BMI [29,30]. Other authors have hypothesized that a lower alpha integrin saturation in subjects with higher BMI could underlie the reduction in the efficacy of therapy [5]. This is supported by pharmacokinetic studies and experimental models hypothesizing a reduced efficacy of EID in subjects with body weight <80 kg [19,20,28].

Our study is not without limitations. First, patients included in the SID group showed a higher disease activity at baseline and were less likely naive compared to EID patients. Although our analysis accounted for disease activity in the 2 years before natalizumab start, a selection bias toward less aggressive disease phenotypes for patients in EID may have influenced our findings. In addition to limitations intrinsic to the retrospective nature of the study, the limited amount of periods during which MS patients were exposed to EID >7 weeks prevented us from conducting a direct comparison of different EID schemes. Caution should therefore be adopted when indirectly assessing the outcomes of our primary vs secondary analysis. Additionally, our findings related to BMI were not confirmed in the inverse probability treatment weighted analysis, and this suggest the need to confirm our hypothesis in a larger sample, were the potential of this technique might be fully exploited. Finally, although we covered a longer observation period in comparison with previous reports, this is still quite limited, and future studies should be planned to confirm natalizumab EID effectiveness over time. In conclusion, we confirm previous findings on natalizumab EID effectiveness over a longer

observation period and including as main outcome the therapeutic goal of NEDA. A treatment regimen of EID with interval between 5 and 7 weeks from treatment start seems to grant the same effectiveness than SID, with known advantages in terms of safety. This approach could therefore be considered when opting for high efficacy treatment with natalizumab in naïve patients. Although further confirmatory studies are needed, extending the interval dosing above 7 weeks might increase the risk of relapses occurrence. Finally, as BMI seems to play a differential role in affecting disease activity across treatment regimens, this factor should be considered in the perspective of therapy tailoring.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Carlo Pozzilli reports financial support was provided by Biogen. Many authors (see manuscript) reports a relationship with Teva, Janssen, Merck, Biogen, Novartis, Eisai, Intercept, Bayer, Sanofi, Genzyme, Bristol, Almirall, GW, Roche, Mitsubishi, Celgene, Actelion, Serono Foundation, CSL, Behring, Ultragenix, Horizon, HEALTH&LIFE, AIM Education, FARECOMUNICAZIONE E20 that includes: board membership, consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurot.2024.e00338>.

References

- [1] Butzkueven H, Kappos L, Wiendl H, Trojano M, Spelman T, Chang I, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). *J Neurol Neurosurg Psychiatry* 2020;91:660–8.
- [2] Lucchetta RC, Tonin FS, Borba HHL, Leonart LP, Ferreira VL, Bonetti AF, et al. Disease-modifying therapies for relapsing–remitting multiple sclerosis: a network meta-analysis. *CNS Drugs* 2018;32(9):813–26.
- [3] Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012;366:1870–80.
- [4] Ryerson LZ, Foley J, Chang I, Kister I, Cutter G. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology* 2019;93:e1452–62.
- [5] Ryerson LZ, Li X, Goldberg JD, Hoyt T, Christensen A. Pharmacodynamics of natalizumab extended interval dosing in MS. *Neurol - Neuroimmunol Neuroinflammation*. 2020;7:e672.
- [6] Clerico M, Mercanti SF De, Signori A, Iudicello M, Cordioli C, Signoriello E, et al. Extending the interval of natalizumab dosing: is efficacy preserved. *Neurotherapeutics* 2020;17:200–7.
- [7] Bompreszi R, Pawate S. Extended interval dosing of natalizumab: a two-center, 7-year experience. *Ther Adv Neurol Disord* 2014;7(5):227–31.
- [8] Chisari CG, Grimaldi LM, Salemi G, Ragonese P, Iaffaldano P, Bonavita S, et al. Clinical effectiveness of different natalizumab interval dosing schedules in a large Italian population of patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2020;91(12):1297–303.
- [9] Grimaldi LM, Prosperini L, Vitello G, Borriello G, Fubelli F, Pozzilli C. Multiple sclerosis journal. *Mult Scler J* 2012;18(9):1337–9.
- [10] De Mercanti SF, Signori A, Cordioli C, Signoriello E, Lus G, Bonavita S, et al. Journal of the Neurological Sciences MRI activity and extended interval of Natalizumab dosing regimen: a multicentre Italian study. *J Neurol Sci* 2021;424:117385.
- [11] Yamout BI, Sahraian MA, Ayoubi N El, Tamim H, Nicolas J. Efficacy and safety of natalizumab extended interval dosing. *Mult Scler Relat Disord* 2018;24:113–6.
- [12] Ryerson LZ, Frohman TC, Foley J, Kister I, Tornatore C, Pandey K, et al. Extended interval dosing of natalizumab in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2016;87(8):885–9.
- [13] Riancho J, Setien S, Sanchez de la Torre JR, Torres-barquin M, Misiego M, Perez JL, et al. Does extended interval dosing natalizumab preserve effectiveness in multiple sclerosis? A 7 Year- retrospective observational study. *Front Immunol* 2021;12:614715.
- [14] van Kempen ZLE, Hoogervorst ELJ, Wattjes MP, Kalkers NF, Mostert JP, Lissenberg-witte BI, et al. Personalized extended interval dosing of natalizumab in MS A prospective multicenter trial. *Neurology* 2020;95:e745–54.
- [15] Foley JF, Defer G, Ryerson LZ, Cohen JA, Arnold DL, Butzkueven H, et al. Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. *Lancet Neurol* 2022;21:608–19.
- [16] Hellwig K. Natalizumab for multiple sclerosis: the dilemma of NOVA. *Lancet Neurol* 2022;21:579–81.
- [17] Stuve O, Tugemann B. Extended-interval dosing of natalizumab in NOVA. *Lancet Neurol* 2023;22:199–200.
- [18] Foley JF, Campbell N, Kong G. Authors' reply. *Lancet Neurol* 2023;22(3):200–1.
- [19] López-Matencio JMS, García YP, Meca-lallana V, Vries A De, Rispens T, Muñoz-calleja C. Evaluation of natalizumab pharmacokinetics and pharmacodynamics: toward individualized doses. *Front Neurol* 2021;12:716548.
- [20] Chang I, Muralidharan KK, Campbell N, Ho P. Modeling the efficacy of natalizumab in multiple sclerosis patients who switch from every-4-week dosing to extended-interval dosing. *J Clin Pharmacol* 2021;63(3):339–48.
- [21] Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018 Feb;17(2):162–73.
- [22] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52.
- [23] Wattjes MP, Rovira À, Miller D, Youssry TA, Sormani MP, De Stefano N, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis - establishing disease prognosis and monitoring patients. *Nat Rev Neurol* 2015;11(10):597–606.
- [24] Rio J, Nos C, Tintore M, Te N, Gala I, Comabella M, et al. Defining the response to interferon- β in relapsing-remitting multiple sclerosis patients. *Ann Neurol* 2006;59:344–52.
- [25] Altay EE, Fisher E, Jones SE, Hara-Cleaver C, Lee J-C, Rudick RA. Reliability of classifying multiple sclerosis disease activity using magnetic resonance imaging in a multiple sclerosis clinic. *JAMA Neurol* 2013;70(3):338–44.
- [26] Escobar JM, Cortese M, Edan G, Freedman MS, Hartung H, Montalbán X, et al. Body mass index as a predictor of MS activity and progression among participants in BENEFIT. *Mult Scler J* 2022;28(8):1277–85.
- [27] Tanaka M, Kinoshita M, Foley JF, Tanaka K, Kira J, Carroll WM, et al. Body weight-based natalizumab treatment in adult patients with multiple sclerosis. *J Neurol* 2015;262(3):781–2.
- [28] Foley JF, Goelz S, Hoyt T, Christensen A, Metzger RR, Mountain R, et al. Evaluation of natalizumab pharmacokinetics and pharmacodynamics with standard and extended interval dosing. *Mult Scler Relat Disord* 2019;31:65–71.
- [29] Bringeland GH, Blaser N, Myhr K. Wearing-off at the end of natalizumab dosing intervals is associated with low receptor occupancy. *Neurol - Neuroimmunol Neuroinflammation*. 2020;7:e678.
- [30] Magro G, Barone S, Tosto F, Martino A De, Santange D, Manzo L, et al. Natalizumab wearing-off symptoms: effect of extend interval dosing during Sars-CoV-2 pandemic. *J Neurol* 2023;270(2):595–600.