Original Article

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

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## ARTICLE INFO

## 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 ( ± 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 α4-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 ≤15 infusions in the previous 18 months of treatment) maintain natalizumab concentration above the threshold of 2.0 μg/mL and α4-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 natalizuamb 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 ≥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 ($23.74 \text{ kg/m}^2$) 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 $3.30 \pm 1.34$ 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 $42.00 \pm 6.99$ 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 |
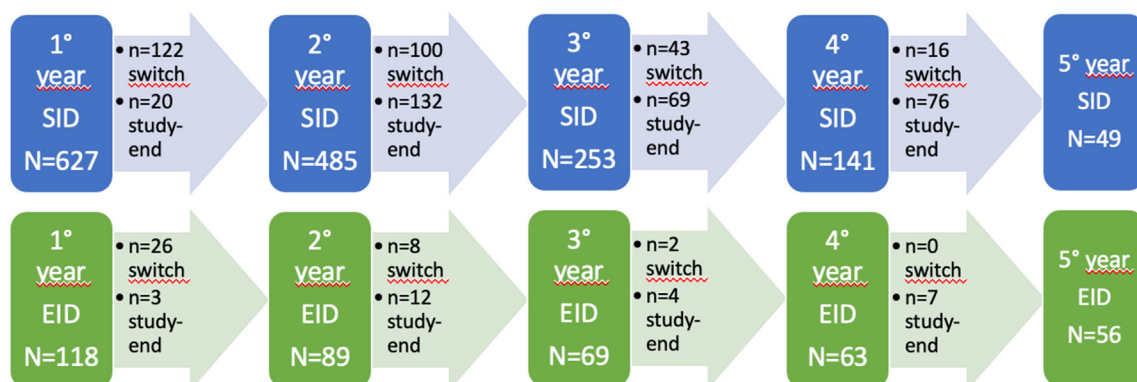


**Fig. 1.** Study flow chart: raw data and percentage of patients switching along the follow-up.

**Table 2**
Unadjusted, adjusted and inverse probability treatment weighted (IPTW) proportional hazard Cox models.

| Model | Endpoint | HR (EID vs. SID) | 95% CI | | p-value |
|---|---|---|---|---|---|
| Un-adjusted | Relapse | 1.34 | 0.82 | 2.17 | 0.239 |
| Adjusted[a] | Relapse | 1.52 | 0.92 | 2.52 | 0.097 |
| IPTW | Relapse | 1.33 | 0.76 | 2.33 | 0.310 |
| Un-adjusted | MRI activity | 1.21 | 0.75 | 1.93 | 0.433 |
| Adjusted[a] | MRI activity | 1.26 | 0.78 | 2.05 | 0.346 |
| IPTW | MRI activity | 1.21 | 0.71 | 2.07 | 0.476 |
| Un-adjusted | EDSS worsening | 0.61 | 0.34 | 1.14 | 0.122 |
| Adjusted[a] | EDSS worsening | 0.71 | 0.38 | 1.33 | 0.287 |
| IPTW | EDSS worsening | 0.67 | 0.33 | 1.36 | 0.262 |
| Un-adjusted | EDA | 1.02 | 0.73 | 1.45 | 0.889 |
| Adjusted[a] | EDA | 1.12 | 0.78 | 1.6 | 0.531 |
| IPTW | EDA | 0.98 | 0.65 | 1.46 | 0.907 |

[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.

for all other features, including BMI and BMI categories. The Cox regression models including treatment arm, BMI (continuous and binary) and their interaction term indicated that BMI could be considered a treatment effect modifier (Table 5).

The exploratory subgroup analysis investigating the treatment effectiveness (EID vs. SID) in patients classified according to the population median BMI value (23.74 kg/m$^2$) suggested a higher EDA risk in EID patients with BMI $\geq$23.74 kg/m$^2$ with respect to SID patients in the same BMI class. (Table 6).

## Discussion

In this multi-center, real-world, retrospective study we analyzed clinical and MRI data from a large population of MS patients treated with different natalizumab regimens. We identified no differences in the risk of losing NEDA-3 status among patients treated with EID (every 5–7

weeks) in comparison with SID (<5 weeks) over a mean follow-up of 3 years. These results confirm, over a longer follow-up period, the findings at 72 weeks of the randomized controlled trial NOVA, that, comparing the efficacy of natalizumab 6-week vs 4-week dosing, identified no differences in the proportions of participants who reached the exploratory endpoint of NEDA [15]. Additionally, our results extend this finding to patients exposed to EID from treatment start (rather than switching to EID after initial SID). In line with previous real-world observations including similar EID regimens followed up to 2 years, no differences emerged even when analyzing the three sub-components of NEDA-3 independently [6,8,10]. However, when including in the analysis interval dosing >7 weeks, EID was associated with a trend towards a higher risk of experiencing a clinical relapses, compared to SID. Few studies have analyzed EID intervals longer than 7 weeks [7,12], reporting no differences in relapse rate between EID and SID. The shorter follow-up and minimum exposure to natalizumab might account for the

**Table 3**
Unadjusted, adjusted and inverse probability treatment weighted (IPTW) proportional hazard Cox models.

| Model | Endpoint | HR (EID vs. SID) | 95% CI | | p-value |
|---|---|---|---|---|---|
| Un-adjusted | Relapse | 1.31 | 0.81 | 2.13 | 0.271 |
| Adjusted[a] | Relapse | 1.50 | 0.91 | 2.48 | 0.109 |
| IPTW | Relapse | 1.74 | 0.99 | 3.02 | 0.054 |
| Un-adjusted | MRI activity | 1.21 | 0.76 | 1.94 | 0.420 |
| Adjusted[a] | MRI activity | 1.27 | 0.79 | 2.07 | 0.327 |
| IPTW | MRI activity | 1.20 | 0.70 | 2.05 | 0.507 |
| Un-adjusted | EDSS worsening | 0.61 | 0.33 | 1.12 | 0.111 |
| Adjusted[a] | EDSS worsening | 0.71 | 0.38 | 1.32 | 0.274 |
| IPTW | EDSS worsening | 0.64 | 0.32 | 1.32 | 0.230 |
| Un-adjusted | EDA | 1.01 | 0.71 | 1.43 | 0.959 |
| Adjusted[a] | EDA | 1.11 | 0.77 | 1.58 | 0.577 |
| IPTW | EDA | 1.25 | 0.85 | 1.85 | 0.252 |

[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.
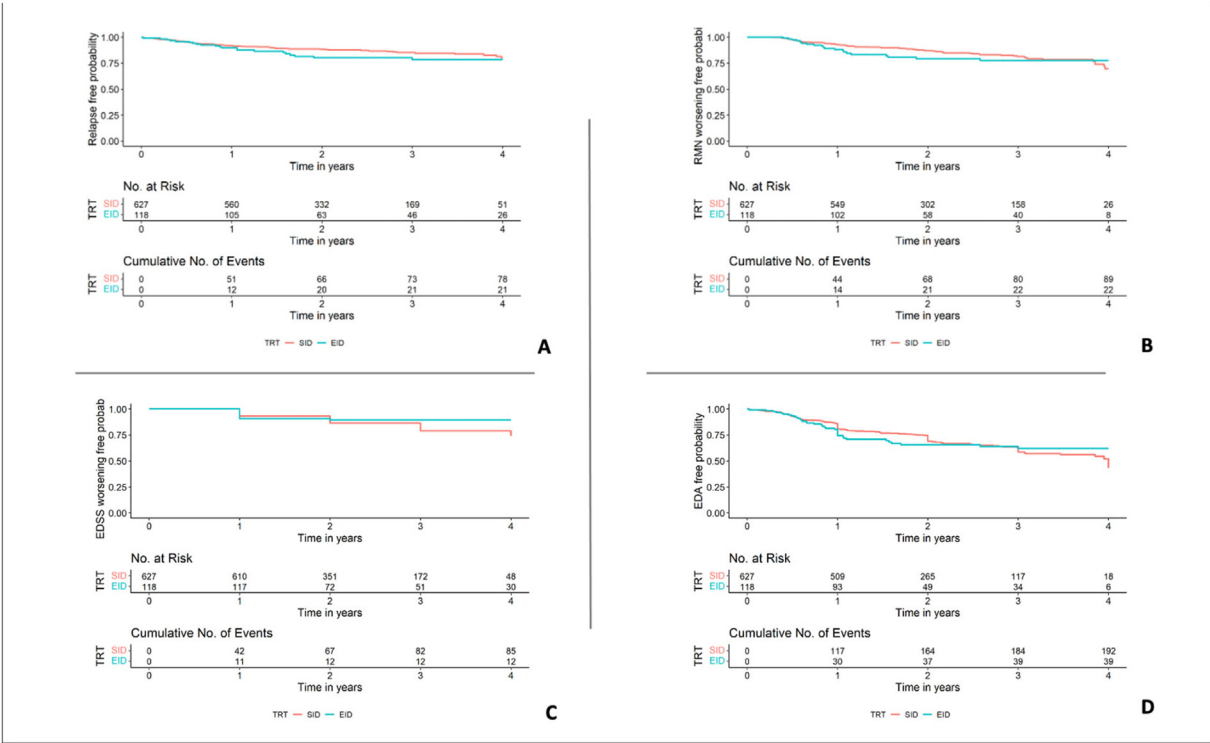


**Fig. 2.** Kaplan-Meier estimated curve of relapse free probability (A), radiological activity free probability (B), EDSS worsening free probability (C) and EDA free probability (D) during the follow-up according to treatment exposure.

**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

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 α4-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 α4-integrin receptor occupancy, while increasing α4-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 α4-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 if 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

**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 | 0.0261 |
| ≥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 | 0.0334 |
| ≥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 | 0.313 |
| ≥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.

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.

## Funding

## Disclosures

**Ruggieri S** has received fee as speaking honoraria from Teva, Merck Serono, Biogen; travel grant from Biogen, Merck Serono; fee as advisory board consultant from Merck Serono and Novartis. **De Giglio L** received speaking onoraria from Genzyme and Novartis, travel grant from Biogen, Merk, Teva, consulting fee from Genzyme, Merk and Novartis. **Altieri M** received payment for travel, accommodations, or meeting expenses from Merck Serono, Teva, Novartis, Bayer Schering, Sanofi- Aventis, and Biogen Idec. **Centonze D** is an Advisory Board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Teva. His preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi- Genzyme e Teva. **Copetti M** received consulting fees from Biogen, Eisai, Intercept and Teva. **Cortese A** received speaker honoraria from Biogen, Teva; travel grants from Biogen, Merck, Sanofi Genzyme, Teva; advisory boards member honoraria from Biogen, Merck, Novartis, Teva. **Fantozzi R** received honoraria for speaking or consultation fees from Almirall, Merck Serono, Novartis, Sanofi, Teva, and Biogen; advisory board membership for Teva, Biogen, Merck Serono, and Novartis. **Tortorella C received** has served on advisory boards and/or has received travel grants and/or speaker honoraria from Biogen, Merck-Serono, Teva, Almirall, Sanofi-Aventis, Novartis, Genzyme, Alexion. **Gasperini C** has served on advisory boards and/or has received travel grants and/or speaker honoraria from Merck Serono, Roche, Teva Italia, Biogen, Almirall, Novartis, Sanofi-Genzyme. **Grimaldi LME** has received funding for travel to attend scientific events or speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd., Roche, Novartis and Bayer Schering Pharma; and receives institutional research support from Biogen Idec and Serono Foundation. **Landi D** received travel funding from Biogen, Merck Serono, Sanofi-Genzyme and Teva, honoraria for speaking from Sanofi-Genzyme and Teva, and consultation fees from Merck Serono and Teva. She is subinvestigator in clinical trials being conducted for Biogen, Merck Serono, Novartis, Roche and Teva. **Marfia GA** is an Advisory Board member of Biogen Idec, Genzyme, Merck-Serono, Novartis, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen Idec, Merck Serono, Sanofi-Genzyme, Teva. She is the principal investigator in clinical trials for Actelion, Biogen Idec, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Teva. **Mirabella M** scientific advisory board membership for Bayer Schering, Biogen, Sanofi-Genzyme, Merck Serono, Novartis, and Teva; consulting and/or speaking fees, research support, or travel grants from Almirall, Bayer Schering, Biogen, CSL Behring, Sanofi- Genzyme, Merck Serono, Novartis, Teva, and Ultragenix; principal investigator in clinical trials for Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva, and Ultra-genix. **Nociti V** received honoraria for speaking, advisory board, consulting from Teva, Genzyme, Almirall, Biogen, Bayer Schering, Merck, and Novartis. **Oddo O** has nothing to disclose **Romano S** has received fees as a speaker from Biogen, Merck and Novartis. **Salemi G** received personal fees for speaking activities from Bayer Biogen, Merck, Novartis, and Teva. **Salvetti M** consulting fees and/or honoraria for speaking and/or research grants from Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva. **Pozzilli C** scientific advisory boards for Actelion, Biogen, Genzyme, Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi, and Teva; con-sulting and/or speaking fees, research support, and travel grants from Allergan, Almirall, Biogen, Genzyme, Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi, and Teva. **Petracca M** discloses travel/meeting expenses from Novartis, Janssen, Roche and Merck; speaking honoraria from HEALTH-&LIFE S. r.l., AIM Education S. r.l., Biogen, Novartis and FARE-COMUNICAZIONE E20; honoraria for consulting services and advisory board participation from Biogen and research grants from Baroni Foundation.

## Author contributions (Credit author statement)

**Serena Ruggieri:** conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing – original draft, writing – review and editing, visualization, supervision. **Antonio Ianniello:** investigation, resources, data curation, writing – original draft, visualization. **Massimiliano Copetti:** methodology, software, formal analysis, data curation. **Marta Altieri:** investigation, resources, supervision. **Maria Chiara Buscarinu:** investigation, resources, visualization. **Diego Centonze:** investigation, resources, supervision. **Antonio Cortese:** investigation, resources, visualization. **Laura De Giglio:** investigation, resources, visualization. **Roberta Fantozzi:** investigation, resources, supervision. **Carla Tortorella:** investigation, resources, visualization. **Claudio Gasperini:** investigation, resources, supervision. **Luigi ME Grimaldi:** investigation, resources, supervision. **Doriana Landi:** investigation, resources, visualization. **Girolama A Marfia:** investigation, resources, supervision. **Massimiliano Mirabella:** investigation, resources, supervision. **Riccardo Nistri:** investigation, resources, data curation, writing – original draft, visualization. **Viviana Nociti:** investigation, resources, visualization. **Oscar Oddo:** investigation, resources, visualization. **Silvia Romano:** investigation, resources, visualization. **Giuseppe Salemi:** investigation, resources, supervision. **Carlo Pozzilli:** conceptualization, methodology, writing – original draft, visualization, supervision, funding acquisition. **Maria Petracca:** conceptualization, methodology, software, validation, formal analysis, writing – original draft, writing – review and editing, visualization.

## 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.

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