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MRI activity and extended interval of Natalizumab dosing regimen: a multicentre Italian study

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ABSTRACT

Background: To minimize the risk of Progressive Multifocal Leukoencephalopathy and rebound in JCV-positive multiple sclerosis (MS) patients after 24 natalizumab doses, it has been proposed to extend the administrations interval. The objective is to evaluate the EID efficacy on MRI activity compared with the standard interval dosing (SID).

Methods: Observational, multicentre, retrospective cohort study, starting from the 24th natalizumab infusion to the loss of follow-up or 2 years after baseline. Three hundred and sixteen patients were enrolled. The median dose interval (MDI) following the 24th infusion was 5 weeks, with a bimodal distribution (modes at 4 and 6 weeks). Patients were grouped into 2 categories according to the mean number of weeks between doses: <5 weeks, SID; ≥ 5 weeks, EID.

Results: One hundred and eighty-seven patients were in the SID group (MDI = 4.5 weeks) and 129 in the EID group (MDI 6.1 weeks). The risk to develop active lesions on MRI is similar in SID and EID groups during the 6 and 12 months after the 24th natalizumab infusion, respectively 4.27% (95% CI:0.84–7.70) vs 4.71% (95% CI:0.16–9.25%) [p = 0.89] and 8.50% (95% CI:4.05–12.95) vs 6.55% (95% CI:2.11–11.00%) [p = 0.56]. The EID regimen does not appear to increase the occurrence of MRI activity during follow-up.

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Conclusion: There is no evidence of the reduced efficacy of natalizumab in an EID setting regarding the MRI activity. This observation supports the need for a bigger randomized study to assess the need to change the standard of the natalizumab dosing schedule, to better manage JCV-positive patients.

1. Introduction

Natalizumab is a high efficacy second-line treatment for highly active relapsing multiple sclerosis (R-MS) [1]. Its most serious side effect is the development of progressive multifocal leukoencephalopathy (PML), a rare and potentially lethal infection caused by the hPyJCV [2,3], whose risk is higher after 24 monthly consecutive natalizumab administration. According to Food and Drug Association (FDA)-approved package insert, Natalizumab is administered with a fixed dose of 300 mg intravenously every 4 weeks [4]. A recent cohort study [5] revealed that most natalizumab treated patients maintain high drug serum concentrations at the time of redosing; MS reactivation or the rebound effect peak at around 10–12 weeks following drug withdrawal [6]. To minimize the risk of both PML and rebound in JCV-positive MS patients following 24 consecutive monthly doses it has been proposed to extend the interval between administrations. Two retrospective analyses [6,7] suggested that dosing intervals ranging from 6 to 8 weeks do not reduce the efficacy of natalizumab.

Our study group recently published the data of an observational, multicenter, retrospective cohort study [8] aimed to evaluate the impact on the efficacy of an extended interval dosing (EID) after the 24th natalizumab dose in patients with R-MS with a PML risk due to JCV seropositivity and number of natalizumab administrations received. Consistent with predecessor studies [6,7], our results showed that there is no evidence of reduced efficacy of natalizumab in an EID setting [8]. We decided to evaluate in the same patients' population the radiological MS activity evaluated by MRI in patients with an EID regimen as compared with patients treated at the standard interval dosing (SID).

2. Methods

This study is a spontaneous, observational, multicentre cohort study with retrospective analysis of information collected in standard clinical practice. A total of 360 adult patients with clinically definite R-MS, according to revised Mc Donald's criteria [9], who received at least 24 consecutive natalizumab doses and decided to continue natalizumab, were enrolled from 14 Italian MS centres between March 2007 and March 2018. All patients within one month after the 24th natalizumab administration underwent brain MRI to exclude PML signs and to detect MS brain activity, thereafter patients underwent brain MRI according to Good Clinical Practice or in case of neurological signs or symptoms onset. MRI sequences used were T-1 weighted with and without gadolinium, T-2 weighted and FLAIR sequences. No central reading or homogeneous scanning protocols were pre-planned due to the retrospective design of the study. MRI MS activity was defined as any new or enlarging T2-weighted lesion compared with lesions in the previous MR images or any gadolinium-enhancing lesion.

Patients were assigned to the SID arm if the mean interval between doses was <5 weeks and to the EID arm if the mean interval between doses was ≥ 5 weeks. The 5-week cut-off was defined as a priori since it is the mid-point between the theoretical SID (4 weeks) and the EID (6 weeks). The follow-up period started at the 24-month infusion (baseline) and ended at loss to follow-up or 2 years after baseline, whichever occurs first. The primary outcome of the study was the probability of active MRI at 6, 12, and 24 months of follow-up after 24th Natalizumab administration while the secondary outcome was the time to first active MRI in the first 2 years from 24th Natalizumab administration.

3. Statistical analyses

The baseline was set at the completion of 24th Natalizumab infusion.

Two different analyses were performed: the effect of EID vs SID was evaluated comparing the 2 groups according to the definition of SID and EID obtained in the first 6 months after baseline (intention-to-treat (ITT)). A per-protocol (PP) analysis was run, where the definition of SID and EID was obtained from all follow-up using mean intervals from baseline to the end of follow-up (2 years or lost to follow-up) or the first active MRI, whichever occurred first. The probability of MRI activity during follow-up was calculated using a logistic model with MRI activity (yes/no) as the dependent variable.

All clinical characteristics as Center of treatment, age, edss at baseline, edss change during Natalizumab, relapse-rate during first 24 months of Natalizumab and in the 2 years before, disease duration, number of previous treatments, JCV+ at 24th infusion and active lesions at the baseline were assessed in a univariable model.

A multivariable model was performed including independent variable dose intervals (EID vs SID) and adjusting for clinical characteristics found to be significantly different between groups at univariable analysis. The length of follow-up on the log-scale for each patient was included as an offset in the logistic model. The cumulative probability of active MRI was calculated by the mean of the Kaplan-Meier method and the log-rank test was used to compare the two groups.

Table 1
Patients' demographic and baseline clinical characteristics according to interval dose groups.

	All sample (n = 316)	Intention to treat (ITT)			Per protocol (PP)		
		SID (n = 187)	EID (n = 129)	P-value	SID (n = 150)	EID (n = 166)	P-value
Age at 24 months Tysabri, mean (SD)	34.7 (10.3)	34.9 (10.7)	34.4 (9.8)	0.66	34.7 (10.7)	34.8 (10.0)	0.93
EDSS Pre-Tysabri, median (IQR)	2.5 (2–4)	2.5 (1.5–3.5)	3 (2–4.5)	0.003	2.5 (1.5–4)	3 (2–4)	0.020
Disease duration (years), median (IQR)	4.7 (1.3–9.2)	4.6 (1.0–9.4)	5.4 (1.8–9.2)	0.32	4.0 (0.8–7.8)	5.4 (1.6–9.8)	0.050
Delta EDSS 24 months Tysabri, mean (SD)	−0.33 (0.99)	−0.14 (0.90)	−0.42 (0.85)	0.005	−0.07 (0.84)	−0.43 (0.90)	0.001
ARR during 24 months Tysabri, mean (SD)	0.081 (0.20)	0.075 (0.20)	0.089 (0.22)	0.46	0.067 (0.20)	0.094 (0.21)	0.17
ARR 2y pre Tysabri, mean (SD)	1.09 (0.64)	0.99 (0.60)	1.22 (0.68)	0.002	0.93 (0.57)	1.23 (0.68)	<0.001
JCV status at baseline, n(%)	132/311 (42.4)	66/182 (36.3)	66/129 (51.2)	0.009	46/146 (31.5)	86/165 (52.1)	0.010
Active lesions at baseline, n/N (%)	44/309 (14.2)	39/182 (21.4)	5/127 (3.9)	<0.001	40/149 (26.9)	4/160 (2.5)	<0.001
Number of previous treatments, median (IQR);range	1 (1–2); 0–7	1 (1–2); 0–5	1 (1–2); 0–7	0.004	1 (1–2); 0–5	1 (1–2); 0–7	0.002
MRI assessment, n(%)							
6 months	229 (72.5)	127 (67.9)	102 (79.1)	0.030	101 (67.3)	128 (77.1)	0.059
12 months	281 (88.9)	160 (85.6)	121 (93.8)	0.028	126 (84.0)	155 (93.4)	0.011
24 months	316 (100)						
Dose interval first 6 months, median (IQR)	4.8 (4.3–6.0)	4.3 (4.1–4.6)	6.2 (5.6–6.8)		4.3 (4.1–4.7)	5.8 (4.8–6.5)	
Dose interval whole follow-up, median (IQR)	5.1 (4.3–6.1)	4.5 (4.2–5.2)	6.1 (5.4–6.5)		4.3 (4.1–4.6)	6.0 (5.6–6.4)	

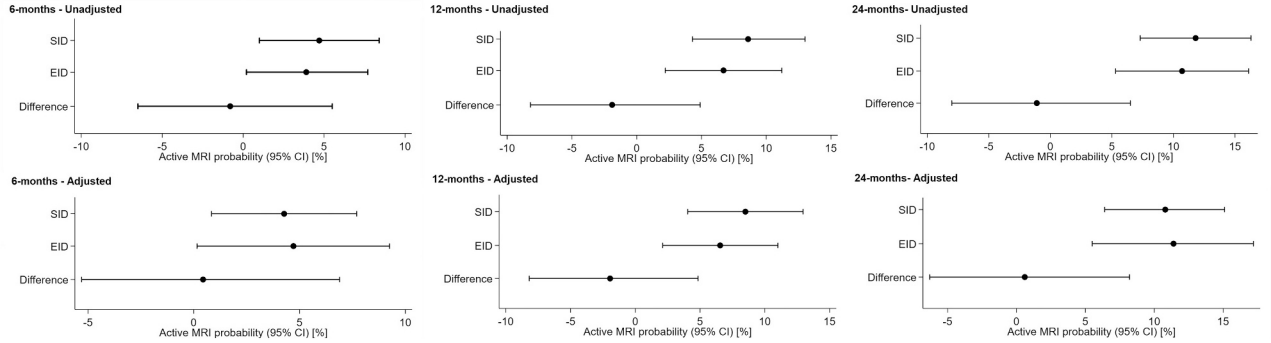

Fig. 1. Adjusted risk to develop active lesions on MRI in the ITT analysis.

A sensitivity analysis was performed using a multiple imputation approach with 10 replications to replace missing values for MRI activity at 6 and 12 months. Age, relapse-rate during first 24 months of Natalizumab and in the 2 years before and EDSS at baseline were used as covariates in the logit regression model for multiple imputation.

Stata (v.14; StataCorp) was used for the computation.

4. Results

In total, 360 patients were enrolled; for 316 patients (88%) MRI data were available during follow-up. Patients were followed for a median of 2.3 years (range 0.11–8.8). At the time of the analysis, 193 (61.1%) patients had at least 2 years of follow-up. At least one MRI assessment was available for 229 patients (72.5%) in the first 6 months and for 281 (89%) in the first year. A higher frequency of MRI assessment available was observed in the EID group both at 6 (n = 102; 79.1% in EID vs n = 127; 67.9% in SID) and 12 months (n = 121; 93.8% in EID vs 160 (85.6%) in SID).

Patients' demographic and baseline clinical characteristics were reported in Table 1.

The mean interval between doses in the 6 months following the month 24 infusion was 5.3 weeks (median 4.8 weeks, IQR 4.3–6.0), with a clear bimodal distribution (modes at 4 and 6 weeks) associated with individual centres strategies (the median was 4.4 weeks in 194 patients from 12 centres and 6.1 in 118 patients from 2 centres). The mean interval between doses was 5.3 weeks (median: 5.1; IQR 4.3–6.1) over the whole follow-up. In the ITT analysis, 187 patients were in the SID (median dose interval: first 6 months = 4.3 weeks [IQR: 4.1–4.6]; whole follow-up = 4.5 [IQR:4.2–5.2]) and 129 in the EID group (MDS: first 6 months = 6.2 weeks [IQR:5.6–6.8]; whole follow-up = 6.1 [IQR: 5.4–6.5]).

Only presence of active lesions at 24-months was significantly associated to MRI activity during the 6 months after the 24th natalizumab infusion (OR = 5.53; 95% CI: 1.45,21.06; p = 0.012) while a trend was observed for ARR in the 2 years pre-Tysabri (OR = 1.92; 95% CI: 0.90,4.12; p = 0.086). Relapse rate in the 2 years pre-Tysabri (OR = 1.81; 95% CI: 1.03,3.18; p = 0.04) and during Tysabri (OR = 2.64; 95% CI: 1.24,5.61; p = 0.012) were associated to MRI activity during the 12 months while only active lesions at 24-months were significantly associated to MRI activity over the longer 2 years of follow-up (OR = 2.62; 95% CI: 1.12,6.15; p = 0.027) with a trend for ARR in the 2 years pre-Tysabri (OR = 1.54; 95% CI: 0.95,2.49; p = 0.079).

In the ITT scenario, the adjusted risk to develop active lesions on MRI is similar in SID and EID groups during the 6 and 12 months after the 24th natalizumab infusion (Fig. 1), respectively 4.27% (95% CI: 0.84,7.70) vs 4.71% (95% CI: 0.16,9.25%) [$\Delta_{\text{EID vs SID}} = 0.44\%$, 95% CI: −5.30,6.89%; $\text{OR}_{\text{EID vs SID}} = 1.11$, 95% CI: 0.26,5.06); p = 0.89] and 8.50% (95% CI: 4.05,12.95) vs 6.55% (95% CI: 2.11,11.00%) [$\Delta_{\text{EID vs SID}} = -1.95$, 95% CI: −8.19,4.84; $\text{OR}_{\text{EID vs SID}} = 0.78$; 95% CI: 0.40,1.80; p = 0.56]. Further, no differences were identified over the longer 2 years of follow-up (Fig. 1). Similar results were observed also in the per-protocol analysis: the adjusted risk to develop active lesions on MRI at 12 months in SID and EID was, respectively, 10.8% (95% CI:4.8,16.7) and 5.5% (95% CI:1.9,9.0) with a $\Delta_{\text{EID vs SID}}$ of −5.3, 95% CI: −11.7,1.5 and an $\text{OR}_{\text{EID vs SID}}$ of 0.54 (95% CI: 0.24,1.30; p = 0.20) (Fig. 2). Fig. 3 shows the time to first active MRI for the ITT and PP cohorts was reported. The cumulative probability of active MRI was similar for SID and EID.

The sensitivity analysis confirmed the previous results. In particular, in the ITT analysis the adjusted risk to develop active lesions on MRI was 5.10% (95% CI: 1.17,9.02) vs 3.59% (95% CI: 0.16,7.02%) after 6 months and 9.15% (95% CI: 4.70,13.59) vs 6.23 (95% CI: 2.11–10.36).

5. Discussion

Many studies have been carried out to detect the best strategy to minimize both PML and rebound risk [10]. The purpose of this study was to compare a Natalizumab EID regimen versus the 4-week SID schedule on radiological outcomes. The results show no evidence of reduced efficacy of natalizumab in an EID setting, from a median of 4.3 to a median

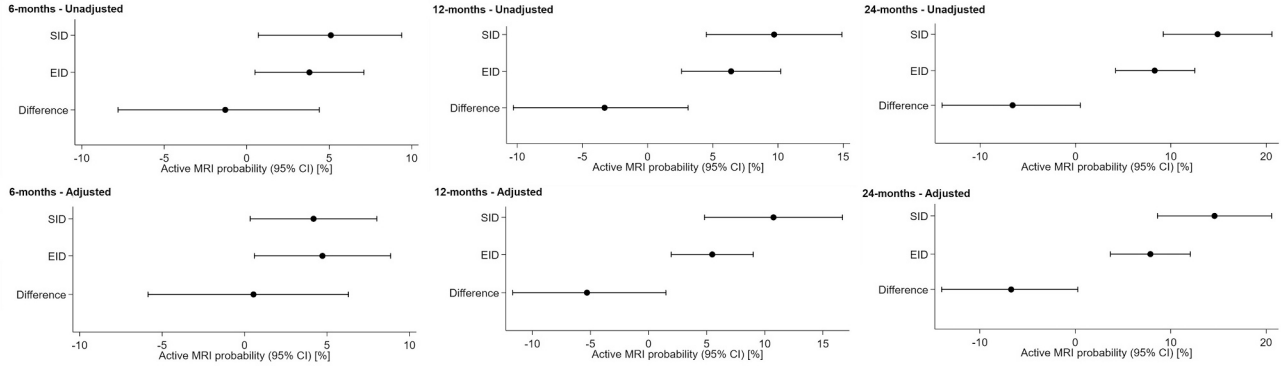

Fig. 2. Adjusted risk to develop active lesions on MRI in the PP analysis.

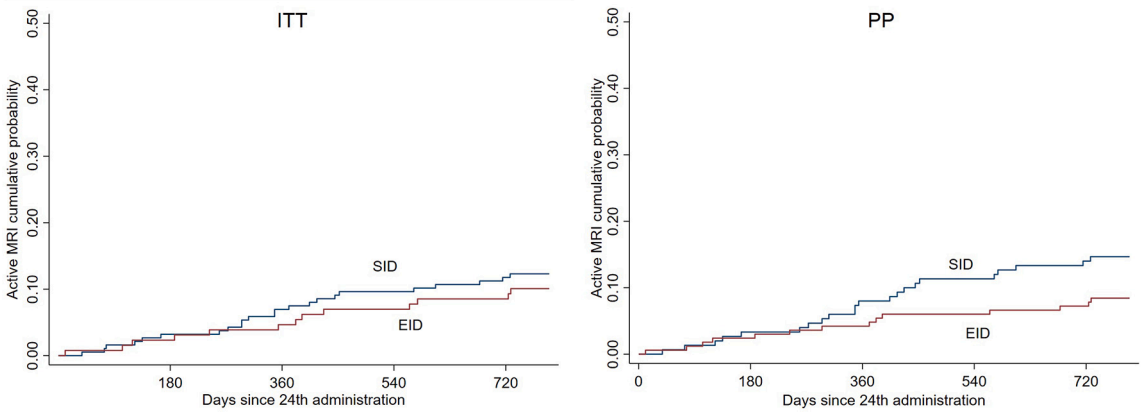

Fig. 3. Time to first active MRI.

of 6.2 weeks, with comparable results seen across the measured outcomes. This study is limited by the retrospective design that leads to the lack of a systematic MRI assessment, which is performed with different timing in each center.

No severe adverse events nor PML have been identified among our cohorts across the participating Italian Centres. Nevertheless, our investigation was not adequately powered to detect a difference in PML incident rates, especially given that the average incidence in those receiving SID is approximately 1:250; with a range of 1:89 to 1:1,000 treated patients; risk which is also intensified in those who have received antecedent immunosuppression or chemotherapy. Our observations, in conjunction with those from previous studies [6,8] suggest that natalizumab extended interval dosing does not reduce its clinical nor paraclinical measures of treatment efficacy. Particularly, in a recent prospective multicenter single-arm trial [11], where 84% of included RRMS patients extended the interval from 4-weeks to a 5–7 interval, no GD-enhancing lesions or new/enlarging T2 lesions were observed during subsequent 2 years (one-year of follow-up and one of extension phase). This study supported the conclusion that a personalized extended interval dosing not induced recurrence of MS disease activity.

Our study has a number of limitations which preclude us from making specific and definitive prosciptions with respect to the application of EID treatment regimens for natalizumab in MS. Specifically, the retrospective design (e.g. devoid of any randomization assignment to either remain on SID vs transitioning to EID treatment regimens), along with the heterogeneity of dosing intervals (broader in the EID vs the SID cohorts), the non-uniform criteria relating to decision-making with respect to requesting MRI surveillance, the lack of an homogenous scanning protocol or of a central reading and the fundamental basis for the patient's managing neurologist to recommend continuation of standard natalizumab dosing vs an extended interval dosing regimen, comprise considerable confounders. Further, neurologist was aware of the interval dosing of each patients and, also if the classification in SID and EID was done retrospectively, this could represent a potential bias. As such, our investigation provides Class III evidence that EID vs SID treatment regimens of natalizumab for relapsing MS, appears to provide similar efficacy upon MRI measures of MS disease activity. We cannot exclude a difference as high as 5% in the absolute risk or a as high as 1.8 times greater relative risk of MRI activity between the two groups.

6. Conclusion

Our study corroborates data from previous investigations [6,7,11], that EID of intravenous natalizumab is not necessarily associated with reduced efficacy on either clinical or paraclinical measures of MS disease activity.

Ultimately, an adequately powered, prospective, randomized controlled trial will be necessary in order to confirm the non-inferiority of the efficacy of EID regimens of natalizumab in MS, but most crucially that with an increased latency between doses is associated with a significantly reduced risk of PML.

Obviously, an accurate pharmacological data collection starting at baseline of the first natalizumab dose in an EID setting compared with any prior dosing of NTZ would be the only protocol to clearly show the natalizumab clinical effect in patients in the EID regimen. Biogen, the drug agency producing Natalizumab, evaluates continuously the efficacy, safety and tolerability of natalizumab EID through the prospective NOVA trial (NCT03689972) [12].

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