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ORIGINAL COMMUNICATION

Radiologic MS disease activity during natalizumab treatment interruption: findings from RESTORE

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Abstract The objective of this study is to characterize the timing and extent of radiologic MS disease recurrence during the 24-week natalizumab treatment interruption period in RESTORE. RESTORE was a randomized, partially placebo-controlled exploratory study. Natalizumab-treated patients with no gadolinium-enhancing (Gd+) lesions at screening ($n = 175$) were randomized 1:1:2 to continue natalizumab ($n = 45$), switch to placebo ($n = 42$), or switch to other therapies ($n = 88$) for 24 weeks. MRI assessments were performed every 4 weeks. Predictors of increased numbers of Gd+ lesions during natalizumab treatment interruption were evaluated. The numbers of Gd+ lesions were compared with retrospectively collected pre-natalizumab MRI reports and data from placebo-treated patients from two historical randomized clinical trials. Gd+ lesions were detected in 0 % (0/45) of natalizumab patients, 61 % (25/41) of placebo patients, and 48 % (39/81) of other-therapies patients during the randomized treatment period. Gd+ lesions were detected starting at week 12; most were observed at week 16 or later. Thirteen percent (14/107) of patients had >5 Gd+ lesions on ≥1 (of 6) scans during the randomized treatment period versus 7 % (7/107) of patients pre-natalizumab (based on medical record of a single scan). Younger patients and those with more Gd+ lesions pre-natalizumab were more likely to have increased MRI activity. Distribution of total and persistent Gd+ lesions in RESTORE patients was similar to placebo-treated historical control patients. In most patients, recurring radiological

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disease activity during natalizumab interruption did not exceed pre-natalizumab levels or levels seen in historical control patients.

Keywords Multiple sclerosis · Natalizumab · MRI · Treatment interruption · Gadolinium-enhancing lesions

Introduction

Natalizumab (Tysabri®, Biogen Idec Inc., Cambridge, MA, USA) is effective in previously untreated multiple sclerosis (MS) patients, in patients switching from other MS treatments, and in patients who have high disease activity [1–4]. Longer natalizumab treatment duration, particularly >2 years, is associated with increased risk of progressive multifocal leukoencephalopathy (PML) in patients who are anti-JC virus (JCV) antibody positive [5]. In an effort to reduce the risk of PML, some patients and clinicians may choose to interrupt or discontinue natalizumab treatment [6].

Discontinuation of natalizumab is associated with return of MS disease activity [7–20]. Some reports suggest disease activity after natalizumab cessation exceeds baseline levels [11, 13, 16, 18, 19, 21–23], while other studies do not [12, 14, 17, 24].

RESTORE was a randomized, partially placebo-controlled study of natalizumab treatment interruption [25]. To better characterize the timing and extent of radiological disease after natalizumab cessation, we performed post hoc analyses of RESTORE using retrospectively collected pre-natalizumab MRI data. In addition, we used data from placebo-treated patients from two phase II randomized trials in which patients underwent monthly MRI scans to approximate expected MRI activity, albeit in natalizumab-naive patients.

Methods

Patients and study design

RESTORE was a randomized, partially placebo-controlled, multicenter trial that enrolled patients who had been treated with natalizumab for ≥1 year, had no relapses within 12 months prior to randomization, and had no Gd+ lesions on screening MRI. Patients were randomized 1:1:2 to continue natalizumab, to switch to placebo, or to switch to other therapies: intramuscular interferon beta-1a (IM IFNβ-1a), glatiramer acetate (GA), or methylprednisolone (MP). All analyses were performed on patients included in the efficacy population [25].

Patients in the placebo and other-therapies groups received their last infusion of natalizumab at week 0. In the other-therapies group, IM IFNβ-1a or GA was started on day 0 following natalizumab infusion, and MP was started at week 12. Placebo infusions began (placebo group) or natalizumab infusions continued (natalizumab group) at week 4. The randomized treatment period extended from week 0 to 28. At week 28, patients discontinued placebo or other therapies and restarted open-label natalizumab. The follow-up visit occurred at week 52. MRI scans were performed at the screening visit (week −4) and at weeks 0, 4, 8, 12, 16, 20, 24, 28, and 52 and were read by the Central MRI Reading Center (NeuroRx Research, Montreal, Canada).

If a patient experienced protocol-defined evidence of MS disease recurrence during the randomized treatment period, the investigator had the option of administering high-dose corticosteroid treatment as per local standard of care and/or restarting open-label natalizumab infusions (placebo or other-therapies groups). Disease recurrence criteria were (1) one Gd+ lesion of >0.8 cm^3 in volume, (2) two or more Gd+ lesions of any size, as reported by the Central MRI Reading Center, or (3) a relapse meeting specific criteria, including changes in Expanded Disability Status Scale (EDSS) score, as previously described [25].

Patients who restarted natalizumab early (prior to week 28) entered the follow-up period immediately and were followed on open-label natalizumab for 24 weeks. Full RESTORE study details are described in a separate report [25].

Each site's institutional review board reviewed and approved the study protocol and amendments, and all participants provided written informed consent. The RESTORE study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guideline on Good Clinical Practice and is registered with ClinicalTrials.gov, number NCT01071083.

Pre-RESTORE MRI data

For patients with natalizumab interruption in RESTORE, pre-natalizumab data on the number of total Gd+ lesions were collected retrospectively from medical records of a single scan. Pre-natalizumab scans were obtained a median of 2.5 months (range 0–27 months) prior to the start of natalizumab and a median of 2.8 years (range 4.3–1.1 years) prior to the baseline visit. One hundred and

seven of 122 placebo and other-therapies patients had pre-natalizumab MRI readings available.

Placebo-treated historical cohorts

Patients with relapsing-remitting MS randomized to placebo in one of two phase II trials were included in the analyses. In one trial, patients with MS naive to natalizumab were randomized to receive placebo or natalizumab infusions for 24 weeks; MRI scans (manual reads) were performed at weeks −4 (screening), 0, 4, 8, 12, 16, 20, 24, and 36 and 52 (follow-up) [26]. In the other trial, patients with relapsing-remitting MS were randomized to receive placebo or dimethyl fumarate for 24 weeks. Brain MRI scans (automated reads) were performed at baseline and at weeks 4, 8, 12, 16, 20, and 24 [27]. Data were compared across common time points (weeks 4, 8, 12, 16, 20, and 24).

Statistical analysis

Summary statistics were performed for most analyses. McNemar test was used to compare the proportion of RESTORE patients with >5 Gd+ lesions as reported on the pre-natalizumab scan versus the proportion with at least one scan showing >5 Gd+ lesions during natalizumab treatment interruption in RESTORE.

Odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated from a multivariate proportional odds model to identify the factors associated with high Gd+ lesion counts following natalizumab interruption during RESTORE. Three categories were used for the outcome variable: no lesions across all time points, 1–5 (noncumulative) lesions at ≥1 time point, or >5 (noncumulative) lesions at ≥1 time point following natalizumab interruption. Models were run for (noncumulative) total Gd+ lesion counts and for (noncumulative) new Gd+ and persistent Gd+ lesion counts. Covariates considered in the models were age, gender, disease duration, number of relapses in the year prior to natalizumab, number of Gd+ lesions prior to natalizumab, treatment group, and number of infusions prior to randomization. Data were compared by treatment group (GA, IM IFNβ-1a, MP, or placebo), and patients without pre-natalizumab data were excluded from the odds ratio analyses.

Results

Patient demographics and disease characteristics

A total of 175 patients enrolled in RESTORE: 45 patients (26 %) were randomized to natalizumab, 42 patients (24 %) were randomized to placebo, and 88 patients (50 %) were randomized to other therapies; 167 patients were evaluable for efficacy. Baseline demographics and disease characteristics were similar across the three groups [25].

Number of Gd+ lesions: total, new, and persistent

As specified by the protocol, no patient had Gd+ lesions on screening brain MRI. During the randomized treatment period, no patients in the natalizumab group developed Gd+ lesions. In contrast, in the placebo and other-therapies groups, Gd+ lesions were detected starting at week 12, with most Gd+ lesions observed starting at week 16 or later (Fig. 1).

Prior to originally starting natalizumab, 7 of 107 patients (7 %) with data available in the placebo and other-therapies groups had >5 Gd+ lesions reported on the most recent MRI, with the highest count being 25 lesions. During the randomized treatment period of RESTORE, 14 of the 107 patients (13 %) in the placebo and other-therapies groups had >5 Gd+ lesions (noncumulative) on ≥1 scan, and the highest count was 34 lesions. The percentage of patients with >5 Gd+ lesions was not statistically significantly different between the pre-natalizumab period and the treatment interruption period ($p = 0.0707$).

Cumulative Gd+ lesion counts (over 28 weeks) for individual RESTORE patients in treatment interruption groups are shown in Fig. 2. Baseline characteristics and clinical outcomes in patients with the highest cumulative number of Gd+ lesions (>30) during RESTORE are listed in Table 1. At the 52-week follow-up visit, EDSS scores in these patients were the same as those at baseline. None of the natalizumab-treated RESTORE patients with MRI data at 52 weeks ($n = 41$) had new T2 lesions (Table 2). Two natalizumab patients discontinued in the randomized period due to relapse, and two had missing data at 52 weeks.

During the randomized treatment period, 31 of 40 patients (78 %) who met MRI criteria for disease recurrence without experiencing a clinical relapse restarted natalizumab, per protocol; an additional 2 patients were treated with corticosteroids only.

Predictors of Gd+ lesions

Predictors of higher numbers of (noncumulative) total (new and persistent) Gd+ lesions after natalizumab discontinuation were evaluated using data segregated into patients with no Gd+ lesions at any time point ($n = 58$; 48 %), 1–5 total Gd+ lesions at ≥1 time point ($n = 48$; 39 %), or >5 total Gd+ lesions at ≥1 time point ($n = 16$; 13 %) following natalizumab interruption.

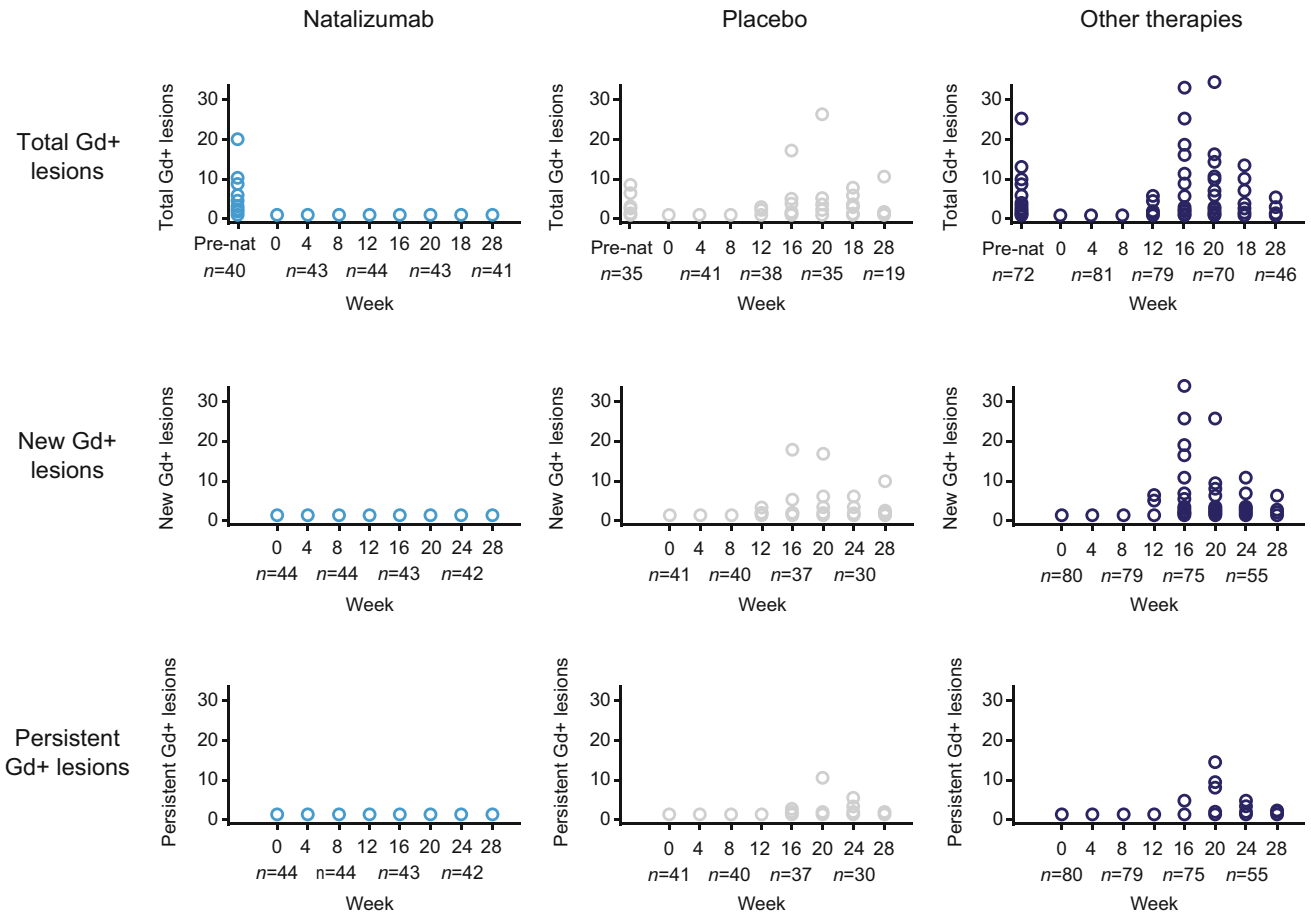

Fig. 1 Total, new, and persistent Gd+ lesions (noncumulative) in RESTORE. Each *dot* represents an individual patient; patients with duplicate values appear as a *single dot*. Total lesions were defined as all Gd+ lesions detected by MRI. New Gd+ lesions were defined as Gd+ lesions not present in a prior scan. Persistent Gd+ lesions were defined as Gd+ lesions present at one MRI image time point and remaining Gd enhancing at the subsequent MRI 4 weeks later. *Gd+* gadolinium enhancing, *pre-nat* pre-natalizumab

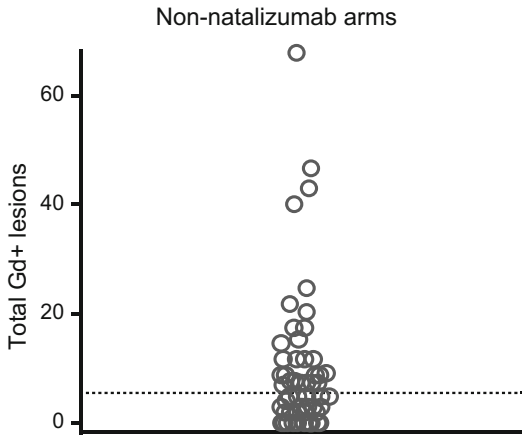

Fig. 2 Cumulative number of Gd+ lesions during RESTORE in patients interrupting natalizumab. Total Gd+ lesions include new Gd+ lesions and persistent Gd+ lesions (Gd+ lesions present at one MRI image time point and remaining Gd enhancing at the subsequent MRI 4 weeks later). *Symbols above the dashed horizontal line* represent patients with >5 Gd+ lesions (cumulative) during RESTORE. *Gd+* gadolinium enhancing

The odds of developing higher numbers (>1 vs 0, or >5 vs ≤5) of total Gd+ lesions were 3.8-fold greater in patients <40 years than in patients ≥40 years of age [OR (95 % CI) = 3.83 (1.71–8.56); $p = 0.0011$], 2.7-fold greater in patients with 1–5 total Gd+ lesions as reported on a single MRI scan prior to natalizumab therapy than in patients with no Gd+ lesions prior to natalizumab therapy [OR (95 % CI) = 2.71 (1.18–6.23); $p = 0.0193$], and 6.2-fold greater in patients with >5 total Gd+ lesions prior to natalizumab therapy than in patients with no Gd + lesions prior to natalizumab therapy [OR (95 % CI) = 6.23 (1.31–29.69); $p = 0.0217$]. In addition, the odds were 0.2-fold less in patients switching to IM IFNβ-1a than in patients receiving placebo [OR (95 % CI) = 0.20 (0.04–0.95); $p = 0.0435$] or switching to MP [OR (95 % CI) = 0.21 (0.05–0.95); $p = 0.0426$]. The odds did not differ significantly between placebo-treated patients and patients who switched to GA [OR (95 % CI) = 0.83 (0.23–2.93); $p = 0.7725$] or MP [OR (95 % CI) = 0.97 (0.40–2.32); $p = 0.9378$], nor between patients switching

Table 1 Baseline characteristics and study outcomes in patients with >30 total Gd+ lesions (cumulative) during RESTORE

Baseline characteristics					Gd+ lesions during RESTORE				Approximate time of confirmed relapse[c]	Time of natalizumab restart (approximate)[d]	EDSS score		
Age (years), race, gender	Years since start of MS symptoms/ MS diagnosis	High disease activity[a]	No. of Gd+ lesions in pre-natalizumab MRI scan	Treatment group during RESTORE	RESTORE week[b]	Total Gd+ lesions	New Gd+ lesions	Persistent Gd+ lesions			Day 0	Natalizumab restart	Week 52
36, white, female	14/11	Yes	0	GA	16	16	16	0	Week 26	Week 28	1.0	3.0	1.0
					20	34	25	9					
					24	13	10	3					
					28	5	5	0					
41, white, female	12/4	No	Missing	MP	16	33	33	0	N/A	Week 20	2.5	2.5	2.5
					20	14	0	14					
30, white, female	9/4	No	0	Placebo	16	17	17	0	N/A	Week 20	1.0	1.0	1.0
					20	26	16	10					
31, white, female	9/7	No	2	MP	16	25	25	0	N/A	Week 24	4.0	4.0	4.0
					20	15	7	8					
					24	0	0	0					

EDSS Expanded Disability Status Scale, *GA* glatiramer acetate, *Gd+* gadolinium enhancing, *MP* methylprednisolone, *N/A* not applicable (as patient did not have a confirmed relapse)

[a] High disease activity was defined as ≥2 relapses in the year prior to starting natalizumab

[b] No Gd+ lesions were detected in these patients prior to week 12

[c] Confirmed relapse was defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 h, and associated with any of the following: an increase of ≥1 grade in ≥2 functional scales of the EDSS; an increase of ≥2 grades in 1 functional scale of the EDSS; an increase of ≥1.0 in EDSS score if the previous EDSS score was 0.0–5.5; or an increase of ≥0.5 if the previous EDSS score was >5.5

[d] Patients restarting natalizumab prior to week 28 proceeded directly to the open-label natalizumab 24-week follow-up period

Table 2 T2 lesion counts at week 52 in RESTORE patients who entered the follow-up period

T2 lesion count	Natalizumab ($n = 41$)	Placebo ($n = 35$)	IM IFNβ-1a ($n = 12$)	GA ($n = 14$)	MP ($n = 45$)
Mean ± SD (95 % CI)	0 ± 0 (0–0)	2.2 ± 10.0 (0–5.1)	0.1 ± 0.3 (0–0.2)	0.4 ± 0.6 (0.1–0.7)	0.6 ± 1.1 (0.3–0.9)
Median (range)	0 (0–0)	0 (0–59)	0 (0–1)	0 (0–2)	0 (0–5)

The T2 lesion count at week 52 is counted with reference to counts at week 28

CI confidence interval, *GA* glatiramer acetate, *IM IFNβ-1a* intramuscular interferon beta-1a, *MP* methylprednisolone, *SD* standard deviation

Table 3 Baseline demographics and disease characteristics

	RESTORE (placebo patients) $n = 41$	RESTORE (other-therapies patients) $n = 81$	Natalizumab phase II (placebo patients) $n = 45$	Dimethyl fumarate phase II (placebo patients) $n = 65$
Age (years), mean ± SD	40 ± 10.5	42 ± 9.9	40 ± 8.8	36 ± 8.2
Female patients, %	73 %	75 %	71 %	55 %
Race, white, %	93 %	95 %	82 %	98 %
Time since symptom onset, years, median (IQR; range)	9 (6–7; 3–31)	10 (6–16; 2–41)	5 (3–10; 1–25)	6 (4–11; 0–28)
Baseline EDSS score, mean ± SD[a]	2.9 ± 1.6, $n = 16$	3.4 ± 1.7, $n = 41$	3.7 ± 1.4	2.7 ± 1.2
Number of relapses in the prior year, mean ± SD[a]	1.5 ± 1.2	1.4 ± 1.3	1.5 ± 0.8[b]	1.4 ± 0.7
Baseline number of Gd + lesions, median (IQR; range)[a]	0 (0–1; 0–8) $n = 35$	0 (0–2; 0–25) $n = 72$	0 (0–1; 0–45)	0 (0–2; 0–53)

EDSS Expanded Disability Status Scale, *Gd+* gadolinium enhancing, *IQR* interquartile range, *SD* standard deviation

[a] For RESTORE, data are from start of natalizumab

[b] Number of relapses in past 2 years divided by 2

to IM IFNβ-1a versus GA [OR (95 % CI) = 0.25 (0.04–1.39); $p = 0.1125$]. Similarly, the odds did not differ significantly between patients who switched to GA or MP. The total number of Gd+ lesions (noncumulative, categories 0, 1–5, >5) observed during natalizumab treatment interruption did not significantly differ based on prior natalizumab exposure (cut at >18 or >24 months).

The initial analyses assessed the odds of higher numbers (>1 vs 0, or >5 vs ≤5) of total (new and persistent) Gd+ lesions. When the model was used to evaluate the odds of developing higher numbers of new Gd+ lesions (excluding persistent lesions) during RESTORE, similar results were seen. The odds of developing higher numbers of new Gd+ lesions were 4.2 times greater in patients <40 years than in patients ≥40 years of age [OR (95 % CI) = 4.17 (1.89–9.22); $p = 0.0004$]; 2.5 times greater in patients with 1–5 total prior Gd+ lesions than in patients with no prior Gd+ lesions [OR (95 % CI) = 2.45 (1.08–5.53); $p = 0.0318$], and 5.2 times greater in patients with >5 total prior Gd+ lesions than in patients with no prior Gd+ lesions [OR (95 % CI) = 5.16 (1.10–24.25); $p = 0.0379$]. Lastly, the odds of developing higher numbers of persistent Gd+ lesions were 2.6 times greater for patients with <10 years' disease duration than for patients with ≥10 years' disease duration [OR (95 % CI) = 2.61 (1.18–5.78); $p = 0.0180$].

Extent of radiological disease

In the assessment of radiologic disease recurrence, the RESTORE placebo group data are not confounded by the use of alternate therapies. MRI disease in RESTORE placebo patients and in historical, placebo-treated control patients was compared to assess the relative severity of disease activity during RESTORE. Characteristics of the three patient groups are shown in Table 3. MRI disease activity was generally similar across the groups (Table 4; Figs. 3, 4). More than five cumulative Gd+ lesions were seen in 24 % of the RESTORE placebo patients and in 38 % of both the natalizumab and dimethyl fumarate phase II placebo groups (Fig. 3a).

Table 4 Total and persistent Gd+ lesions (cumulative) in postbaseline assessments

	RESTORE placebo	Natalizumab phase II placebo	Dimethyl fumarate phase II placebo
Total Gd+ lesions			
n	41	45	53
Mean ± SD	3.8 ± 7.2	16.1 ± 40.4	10.4 ± 22.0
Median (IQR)	2 (0–5)	3 (0–13)	4 (1–10)
Range	0–43	0–246	0–145
Persistent Gd+ lesions as a proportion of total Gd+ lesions[a]			
n[b]	22	33	40
Mean ± SD	0.16 ± 0.17	0.32 ± 0.25	0.21 ± 0.25
Median (IQR)	0.13 (0–0.25)	0.29 (0.15–0.50)	0.17 (0–0.42)
Range	0–0.57	0–1.0	0–1.0

Persistent Gd+ lesions were defined as Gd+ lesions present at one MRI image time point and remaining Gd enhancing at the subsequent MRI 4 weeks later

Weeks 4–24

Gd+ gadolinium enhancing, *IQR* interquartile range, *SD* standard deviation

[a] The proportion for each patient was calculated as follows: cumulative number of persistent Gd+ lesions (sum weeks 4–24)/cumulative number of total Gd+ lesions (sum weeks 4–24). Summary statistics for each cohort were calculated using the individual patient results

[b] Patients with >0 total Gd+ lesions in postbaseline assessments

Persistent Gd+ lesions

The proportion of RESTORE placebo patients with persistent Gd+ lesions was less than that of placebo patients in the other groups (Fig. 3b). The mean percentage of persistent Gd+ lesions (out of all Gd+ lesions) was 16 % for RESTORE placebo patients, 32 % for natalizumab phase II trial placebo patients, and 21 % for dimethyl fumarate placebo patients (Table 4). Placebo-treated patients with persistent Gd+ lesions during RESTORE were more likely to restart natalizumab early than patients without persistent Gd+ lesions.

Timing of Gd+ lesion appearance

In RESTORE, Gd+ lesion activity returned to pre-natalizumab levels around 16 weeks after the last natalizumab dose. There was a similar distribution of total Gd + lesions observed in individual MRIs over time in RESTORE patients at weeks 16–24 as in historical placebo control patients at weeks 0–24 (Fig. 4).

Discussion

RESTORE, the largest randomized, prospective study of natalizumab interruption to date, showed that radiological MS disease activity appeared approximately 12–16 weeks after the last dose of natalizumab. As in other reports [8, 16, 17], younger patients and those with more pretreatment Gd+ activity were more likely to have return of Gd+ activity during treatment interruption in RESTORE. High Gd+ lesion counts during treatment interruption did not appear to be associated with changes in disability, as measured by EDSS, over 1 year of follow-up.

In the majority of RESTORE patients, recurring radiological disease activity during natalizumab interruption did not exceed pre-natalizumab levels, nor did it exceed levels seen in natalizumab-naive patients treated with placebo in historical control patients.

Some reports have suggested that an increased level of MS disease activity (radiological disease or relapse) may occur following natalizumab cessation, even after switching to other therapies, including GA and fingolimod [13, 19, 28]; however, in some cases this was attributed to an initial high level of disease activity and/or few doses of natalizumab prior to interruption [11, 16, 18, 29]. Importantly, these studies did not use monthly MRI scans to monitor subclinical disease activity. RESTORE was designed to include radiographic criteria of disease recurrence (1 Gd+ lesion $\geq$8 cm^3 or $\geq$2 Gd+ lesions of any size) as measured by monthly MRI. The observation that >75 % of patients with MRI disease recurrence, but without clinical relapse, restarted natalizumab suggests that investigators used MRI evidence of disease activity for clinical treatment decisions.

There are several potential limitations to these analyses. Pre-natalizumab MRI data were retrospectively collected from medical records, not by review of MRI images, which may have inaccurately characterized and underestimated pretreatment MRI disease activity. Each patient had only one pre-natalizumab MRI scan but had multiple scans during RESTORE, which increased the likelihood of detecting MRI activity during RESTORE as compared with disease activity prestudy and prior to natalizumab. Also, because some patients restarted natalizumab prior to week 28 due to clinical or MRI disease activity, the study may not have fully captured the effects of longer treatment interruption in patients with active disease. Finally, unlike patients in the comparator phase II studies who received placebo, most RESTORE patients with recurring disease restarted natalizumab, which may explain the lower number of Gd+ lesions in RESTORE patients versus the historical control patients.

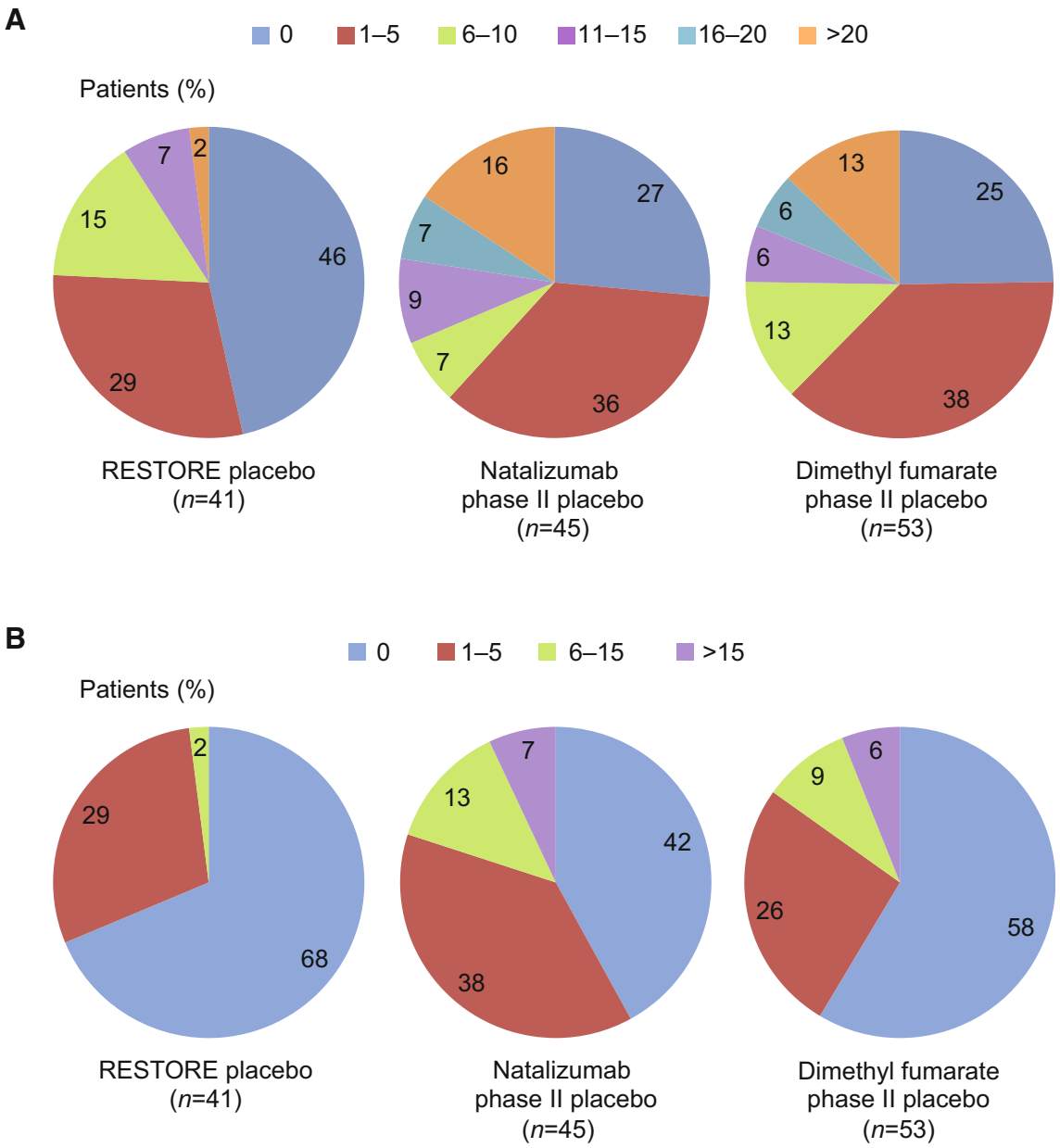

Fig. 3 Percentage of patients with Gd+ lesions in postbaseline assessments: **a** total Gd+ lesions and **b** persistent Gd+ lesions. Total Gd+ lesions include the cumulative number of new Gd+ lesions and persistent Gd+ lesions. Persistent Gd+ lesions were defined as Gd+ lesions present at one MRI image time point and remaining Gd enhancing at the subsequent MRI 4 weeks later. *Gd+* gadolinium enhancing

In this randomized prospective study, there was no evidence of MRI disease activity in patients who were clinically and radiographically stable on natalizumab at entry and who stayed on natalizumab. Further, MS disease activity after cessation of natalizumab did not appear to exceed pretreatment levels. However, given the variability in disease course among individual patients, practitioners must remain alert to signs of recurring MS disease activity in patients discontinuing or switching immunomodulatory therapies, particularly younger patients and those with a history of Gd+ lesions prior to the initiation of natalizumab. The fact that no natalizumab-treated RESTORE patient developed new T2 lesions through 52 weeks of follow-up suggests that any new T2 lesion in an otherwise stable natalizumab-treated patient warrants

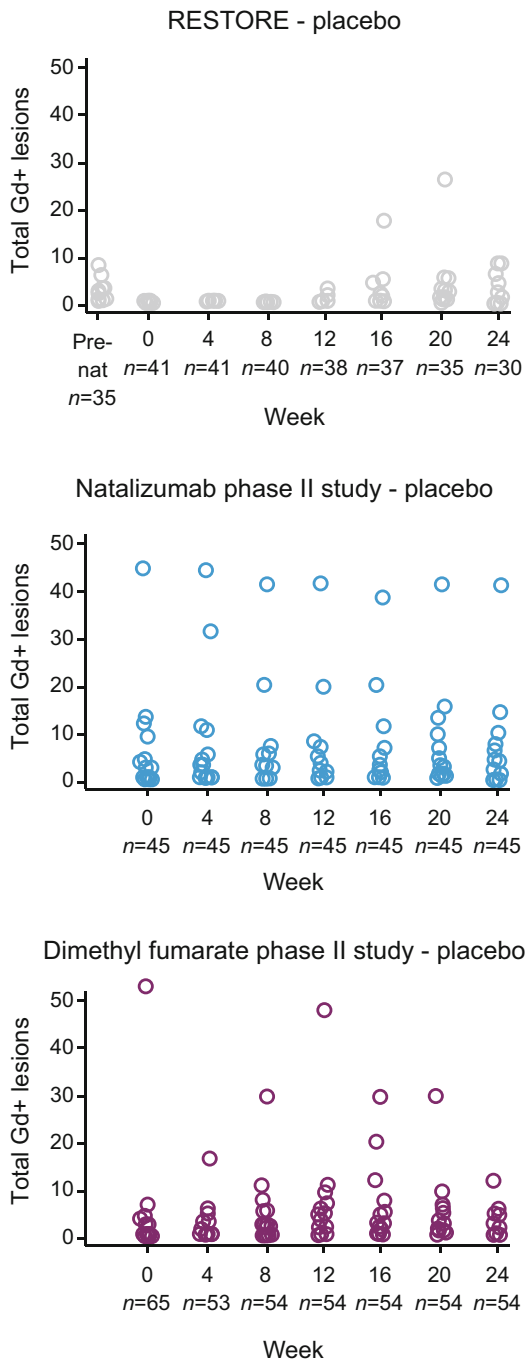

Fig. 4 Number of total Gd+ lesions over time (noncumulative) across placebo groups. Total lesions were defined as all Gd+ lesions detected by MRI. The number of Gd+ lesions detected on individual MRIs at different time points are shown. *Gd+* gadolinium enhancing, *pre-nat* pre-natalizumab

full evaluation, including testing for anti-natalizumab antibodies and the possibility of asymptomatic PML [30–32].

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Ethical standard Each site's institutional review board reviewed and approved the study protocol and amendments, and all participants provided written informed consent. The RESTORE study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guideline on Good Clinical Practice.

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