Original Investigation

Treatment of Relapsing-Remitting Multiple Sclerosis After 24 Doses of Natalizumab

Evidence From an Italian Spontaneous, Prospective, and Observational Study (the TY-STOP Study)

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IMPORTANCE The evaluation of therapeutic choices is needed after 24 doses of natalizumab in patients with multiple sclerosis (MS).

OBJECTIVE To evaluate the effect of therapeutic choices on the mean annualized relapse rate and on magnetic resonance imaging MS activity after 24 doses of natalizumab in patients with relapsing-remitting MS.

DESIGN, SETTING, AND PARTICIPANTS The TY-STOP study, which recruited participants between October 22, 2010, and October 22, 2012, at 8 Italian MS centers (secondary care outpatient clinics) among 124 adult patients who demonstrated no clinical or magnetic resonance imaging MS activity after 24 doses of natalizumab.

INTERVENTIONS Natalizumab, no treatment, interferon beta, glatiramer acetate, or fingolimod.

MAIN OUTCOMES AND MEASURES The primary end point was the mean annualized relapse rate. Statistical analyses were performed in 124 patients with complete follow-up data among 130 patients who were recruited and stratified into study groups. In the intent-to-treat group, the decision was made to continue or interrupt natalizumab after 24 doses. In the as-treated group, natalizumab continuers received natalizumab, natalizumab switchers changed to different therapies, and natalizumab quitters discontinued natalizumab during the study year.

RESULTS No significant differences in demographic or baseline clinical characteristics were found among the study participants. In the intent-to-treat group (n = 124), clinical (P = .004) and radiologic (P = .02) MS activity was significantly lower in patients continuing natalizumab (n = 43) than in patients interrupting natalizumab (n = 81), with a protective effect of natalizumab continuation on both outcomes (odds ratio [OR], 0.33; 95% CI, 0.15-0.70 for clinical activity and OR, 0.35; 95% CI, 0.15-0.79 for radiologic activity). In the as-treated group (n = 124), clinical (P = .003) and radiologic (P = .03) MS activity was significantly lower in natalizumab continuers than in natalizumab switchers or quitters, confirming a protective effect of natalizumab on the risk of relapse in natalizumab continuers compared with natalizumab quitters (OR, 4.40; 95% CI, 1.72-11.23) and natalizumab switchers (OR, 3.28; 95% CI, 0.99-10.79). No disease rebound was observed in natalizumab quitters. After natalizumab discontinuation, 1 patient developed progressive multifocal leukoencephalopathy during the observation period, with complete recovery.

CONCLUSIONS AND RELEVANCE This study provides class III evidence of an increased risk of MS activity resumption after natalizumab discontinuation. Therapy discontinuation after 24 doses in natalizumab-responding patients should be considered only if the risk of progressive multifocal leukoencephalopathy is high and outweighs the benefits of continuing the drug.

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Editorial

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Natalizumab, a humanized anti-α4 integrin monoclonal antibody, is a highly effective treatment approved for relapsing-remitting multiple sclerosis (RR-MS).[1-3] Although natalizumab therapy is well tolerated, it can be associated with a rare serious and potentially fatal opportunistic infection of the central nervous system caused by the John Cunningham virus (JCV) known as progressive multifocal leukoencephalopathy (PML).[4-6] The first episodes of this adverse effect had an effect on the evaluation of the safety profile of natalizumab and led to the implementation of tools to stratify patients according to their risk to ensure better therapeutic management. The increased frequency of PML cases over time created serious concern in the medical community and among patients with MS and led the European Medicines Agency (EMA) to establish a meticulous risk management plan.[7] According to this plan, patients are asked to provide consent to continue natalizumab treatment after 24 doses and to resign a standardized informed consent. Alternatively, patients may consider switching to any other treatment for MS or quitting all therapies.

Few studies[8-15] have attempted to evaluate the course of clinical and radiologic (ie, magnetic resonance [MR] imaging) MS activity after natalizumab discontinuation and to compare this activity with that in patients continuing natalizumab. Herein, we describe the results of a spontaneous, prospective, multicenter, observational study aimed at evaluating MS clinical activity, determined by the mean annualized relapse rate (ARR) and by disease progression measured on the Expanded Disability Status Scale (EDSS) by Kurtzke,[16] as well as by MR imaging MS activity, in patients with RR-MS stratified according to therapeutic choices after 24 doses of natalizumab.

Methods

Ethical committees of each participating hospital or university approved the study protocol. The study was registered with the Osservatorio Nazionale Sulla Sperimentazione Clinica dei Medicinali (No. 131/2010). All participating patients provided written informed consent.

The TY-STOP study is a spontaneous, observational, prospective multicenter trial. A total of 130 patients 18 years or older with clinically definite RR-MS who received 24 doses of natalizumab, had clinical and MR imaging MS stability, and had at least 1 MR image within 10 days after 24 doses of natalizumab were recruited from 8 Italian MS centers (secondary care outpatient clinics) between October 22, 2010, and October 22, 2012, and were followed up for 1 year.

Clinical MS stability was defined as the absence of documented relapses and the absence of EDSS progression during the preceding 6 months. Magnetic resonance imaging MS stability was defined as the absence of new or enlarging T2-weighted lesions compared with MR imaging acquired 1 year before study entry and the absence of gadolinium-enhancing lesions on baseline MR imaging.

Exclusion criteria were pregnancy, severe depression, alcohol or drug addiction, and any clinical condition in addition to MS. Data for each patient were collected by the evaluating neurologist (M.C., S.F.D.M., R.L., A.G., S.R., F.V., P.C., and D.P.) in an electronic case report form located on the server of the coordinating center (Division of Neurology, Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga University Hospital, Orbassano, Italy).

After 24 doses of natalizumab, treatment was rediscussed with individual patients in accord with EMA recommendations.[7] The treatment options offered to patients were (1) continuing intravenous natalizumab (300 mg) every 28 days, (2) switching to another disease-modifying therapy (DMT), (3) discontinuing all treatment, or (4) beginning intravenous mitoxantrone hydrochloride (12 mg/m^2 every month or every 3 months). Alternative DMTs were (1) interferon beta-1a (intramuscular 30 µg once weekly or subcutaneous 22 or 44 µg 3 times weekly) or subcutaneous interferon beta-1b (250 µg every other day), (2) glatiramer acetate (subcutaneous 20 mg every day), or (3) oral fingolimod (0.50 mg every day).

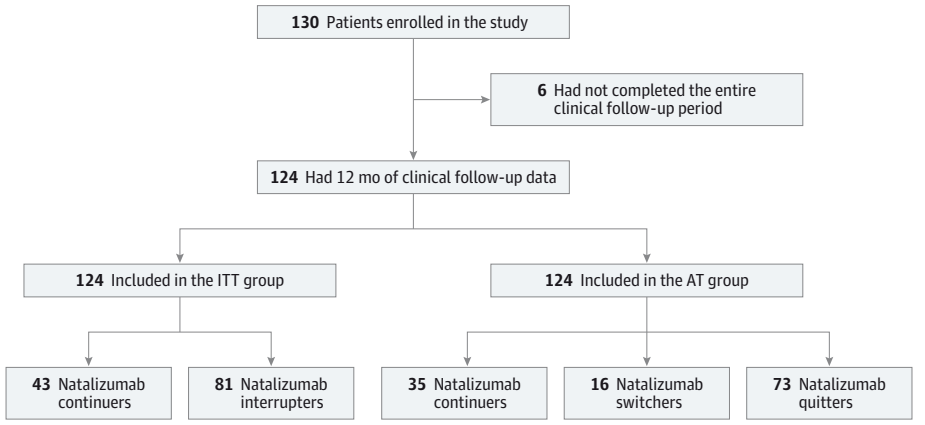
Interferon beta was not considered an option for patients with known positivity for serum anti–interferon beta neutralizing antibodies. The chosen treatment was begun immediately after natalizumab discontinuation, except for fingolimod, which requires a 3-month washout period according to the manufacturer's recommendations.

Patients were examined after 24 doses of natalizumab and every 3 months thereafter. Assessments included a physical examination and a neurologic examination with the evaluation of the EDSS. All evaluating neurologists at the Italian MS centers participating in this study were trained to use the EDSS scale to measure disability. Safety assessments, performed at each visit, included vital signs, concomitant medication use, and collection of information on any adverse effect. Patients also underwent hematologic and biochemical tests, including tests of liver and kidney function, every 3 months.

Proton density T2-weighted and pre-post gadolinium-enhanced T1-weighted MR images were obtained at months 0, 3, 6, and 12 after 24 doses of natalizumab. The MR imaging was scheduled at 3-month intervals to detect possible disease reactivation in patients discontinuing natalizumab and to monitor for the occurrence of PML in patients continuing treatment with the monoclonal antibody. Repositioning was achieved using internal anatomical landmarks located on T1-weighted axial, coronal, and sagittal scouts. The MR images were evaluated for radiologic MS activity during the observation year (annual MR imaging MS activity). Magnetic resonance imaging MS activity in the follow-up year was defined as any new or enlarging T2-weighted lesion compared with lesions in the previous MR images or any gadolinium-enhancing lesion.

In the event of exacerbations or adverse effects during the follow-up period, patients were asked to contact the referral MS center, and exacerbations were treated with high-dose intravenous methylprednisolone sodium succinate if needed. An exacerbation was defined as the occurrence of a new neurologic symptom or a worsening of an old one, with an objective change of at least 1 point on the EDSS, which lasted at least 24 hours in the absence of fever and followed a period of clinical stability or improvement of at least 30 days.

Figure. Enrollment of Patients in the Study



Patients are shown according to the intent-to-treat (ITT) group and the as-treated (AT) group. Among natalizumab switchers after 24 doses, 8 patients continued to receive natalizumab for 1 or more doses, stopping it thereafter, and the other 8 patients stopped natalizumab use after the initial course of 24 doses and began it later again.

The primary outcome of the study was the mean ARR. Annual MR imaging MS activity and the 3-month confirmed mean EDSS at 1 year were the secondary outcomes.

For the statistical analysis, patients were divided into study groups according to the following 2 criteria: (1) the decision about whether to continue or interrupt natalizumab treatment after 24 doses (intent-to-treat [ITT] group) and (2) the treatment patients actually received during the follow-up year (some patients reverted to taking natalizumab after having decided to stop it) (as-treated [AT] group). Patients in the latter group were further divided into the following 3 subgroups based on when and for how long they received natalizumab during the 1-year follow-up period: (1) patients continuing natalizumab during the entire observation year (natalizumab continuers); (2) patients switching to different DMTs, including natalizumab (natalizumab switchers); and (3) patients discontinuing natalizumab during the entire observation year (although they could have received another DMT) (natalizumab quitters).

Normality of continuous variables was evaluated by an analysis of the histograms and was confirmed by the Kolmogorov-Smirnov test. Demographic and disease characteristics at baseline were summarized as numbers (percentages), means (SDs), and medians (ranges). Any relationship between treatment group and age (at baseline and age at onset) was assessed by linear regression analysis. Treatment group differences in EDSS score, body mass index, disease duration, and ARR before the study were evaluated with the nonparametric Mann-Whitney test or Kruskal-Wallis test. χ^2 Test or Fisher exact test was performed to compare categorical variables and particularly to evaluate any association between treatment group and types of therapy used before natalizumab treatment. Any association between treatment group and ARR at the end of the study was assessed by negative binomial regression analysis.[17] Binary logistic regression was used to verify whether treatment group was a statistically significant predictor of MR imaging MS activity. Data are expressed as odds ratios (ORs) with 95% CIs.

Statistical analyses were performed using commercially available software (SPSS version 20; IBM). All statistical tests were 2-sided, and the significance level (α error) was set at .05.

Results

In total, 130 patients with clinically and MR imaging stable MS were enrolled in the study, and 124 (95.4%) of them had completed the entire clinical follow-up period at the time of the analysis (**Figure**). **Table 1** summarizes their demographic and baseline clinical characteristics (EDSS score, disease duration, ARR, MR imaging MS activity, and therapy before natalizumab). Following EMA recommendations,[7] natalizumab therapy was rediscussed after 24 doses, considering the increased risk of PML[6,18,19] and the risk of clinical or radiologic reactivation of MS.[8,9,11] At study baseline (ie, after receiving 24 doses of natalizumab), 81 patients (65.3%) decided to interrupt natalizumab therapy, while 43 patients (34.7%) decided to continue it and signed a second informed consent form. Their JCV antibody status and prior immunosuppressive therapy had no role in this decision because these had not been characterized as risk factors for the occurrence of PML at the time of study recruitment.[6] No significant differences were observed between these 2 groups of patients. In addition, no significant differences were observed in demographic and baseline clinical characteristics between the 6 patients who did not complete the entire follow-up period and the 124 patients who completed it (data not shown). Therefore, all efficacy analyses were performed among 124 patients who completed the follow-up period.

Table 2 summarizes the results of the comparison of patients who decided to continue natalizumab compared with those who decided to interrupt natalizumab therapy (ITT group). During the 1-year observation period, the mean ARR (OR, 0.33; 95% CI, 0.15-0.70; P = .004) and MR imaging MS activity (OR, 0.35; 95% CI, 0.15-0.79; P = .02) were lower for patients continuing natalizumab compared with patients interrupting natalizumab.

Among natalizumab switchers (Figure), only 2 patients were treated with fingolimod because the drug was registered in Italy during the last months of the recruitment period.[20] All natalizumab switchers who began natalizumab again after a temporary discontinuation did so because of MS

Table 1. Demographic and Baseline Characteristics of the Patients

Variable	Total (N = 124)	Natalizumab Continuers (n = 43)	Natalizumab Interrupters (n = 81)	*P* Value[a]
Age, y				.22
Mean (SD)	38.71 (9.69)	37.36 (9.46)	39.52 (9.79)	
Median (range)	38.00 (18.00-63.00)	37.00 (19.00-60.00)	39.00 (18.00-63.00)	
Body mass index[b]				.22
Mean (SD)	23.62 (3.80)	22.99 (2.75)	23.97 (4.25)	
Median (range)	23.40 (17.40-37.30)	22.90 (17.60-30.70)	23.70 (17.40-37.30)	
Age at MS onset, y				.80
Mean (SD)	26.60 (8.58)	26.85 (9.46)	26.45 (8.09)	
Median (range)	26.00 (11.00-56.00)	25.00 (12.00-56.00)	26.00 (11.00-49.00)	
Female sex, No. (%)	**88** (71.0)	32 (74.4)	56 (69.1)	.94
Disease duration, y				.10
Mean (SD)	11.35 (6.87)	9.96 (5.85)	12.19 (7.32)	
Median (range)	10.00 (0.00-31.00)	9.00 (2.00-24.00)	10.50 (0.00-31.00)	
EDSS score				.67
Mean (SD)	3.38 (1.69)	3.31 (1.65)	3.42 (1.73)	
Median (range)	3.50 (0.00-7.00)	3.50 (1.00-7.00)	3.50 (0.00-6.50)	
Annualized relapse rate before natalizumab therapy				.12
Mean (SD)	2.00 (1.32)	2.29 (1.53)	1.84 (1.17)	
Median (range)	2.00 (0.00-7.00)	2.00 (0.00-7.00)	2.00 (0.00-6.00)	
MR imaging MS activity before natalizumab therapy, No. (%)	73 (58.9)	29 (67.4)	44 (54.3)	.27
Previous therapy, No. (%)				.38
Other	**7** (5.6)	2 (4.7)	5 (6.2)	
Glatiramer acetate	**20** (16.1)	11 (25.6)	9 (11.1)	
Intramuscular interferon beta-1a	**17** (13.7)	3 (7.0)	14 (17.3)	
Interferon beta-1b	**23** (18.5)	7 (16.3)	16 (19.8)	
Subcutaneous interferon beta-1a, 22 µg	**13** (10.5)	3 (7.0)	10 (12.3)	
Subcutaneous interferon beta-1a, 44 µg	**28** (22.6)	9 (20.9)	19 (23.5)	
None	**16** (12.9)	8 (18.6)	8 (9.9)	

Abbreviations: EDSS, Expanded Disability Status Scale; MR, magnetic resonance; MS, multiple sclerosis.

[a] Statistically significant at $P < .05$.

[b] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Analysis of the ITT Group

Variable	Natalizumab Continuers (n = 43)	Natalizumab Interrupters (n = 81)	*P* Value
Discontinuations, No. (%)	8 (18.6)	8 (9.9)	NA
EDSS score			.23
Mean (SD)	3.36 (1.69)	3.80 (1.83)	
Median (range)	3.50 (0.00-6.50)	3.50 (0.00-7.00)	
Annualized relapse rate			.004[a]
Mean (SD)	0.24 (0.48)	0.73 (0.85)	
Median (range)	0.00 (0.00-2.00)	1.00 (0.00-4.00)	
OR (95% CI)	0.33 (0.15-0.70)	1 [Reference]	
MR imaging MS activity in the observation year			.02[a]
No. (%)	11 (25.6)	39 (48.1)	
OR (95% CI)	0.35 (0.15-0.79)	1 [Reference]	

Abbreviations: EDSS, Expanded Disability Status Scale; ITT, intent-to-treat; MR, magnetic resonance; MS, multiple sclerosis; NA, not applicable; OR, odds ratio.

[a] Statistically significant at $P < .05$.

activity resumption. The results from the AT group (n = 124) are summarized in **Table 3**. During the 1-year follow-up period, the mean ARR was about 3 times higher in natalizumab switchers (OR, 3.28; 95% CI, 0.99-10.79; $P = .05$) and more than 4 times higher in natalizumab quitters (OR, 4.40; 95% CI, 1.72-11.23; $P = .002$) compared with natalizumab continuers.

With regard to annual MR imaging MS activity, significant differences were observed between natalizumab con-

Table 3. Analysis of the AT Group

Variable	Total (N = 124)	Natalizumab Continuers (n = 35)	Natalizumab Quitters (n = 73)	Natalizumab Switchers (n = 16)	*P* Value
EDSS score					.14
Mean (SD)	3.59 (1.77)	3.16 (1.69)	3.79 (1.82)	4.03 (1.76)	
Median (range)	3.5 (0.0-7.0)	2.50 (0.00-6.00)	3.50 (0.00-7.00)	4.00 (1.00-6.50)	
Annualized relapse rate					.003[a]
Mean (SD)	0.56 (0.78)	0.17 (0.38)	0.75 (0.86)	0.56 (0.73)	
Median (range)	0.00 (0.0-4.0)	0.00 (0.00-1.00)	1.00 (0.00-4.00)	0.00 (0.00-2.00)	
Relative risk (95% CI)	NA	1 [Reference]	4.40 (1.72-11.23)	3.28 (0.99-10.79)	
MR imaging MS activity in the observation year					.03[a]
No. (%)	**50** (40.3)	10 (28.6)	36 (49.3)	4 (25.0)	
OR (95% CI)	NA	1 [Reference]	2.81 (1.17-6.74)	1.00 (0.25-3.94)	

Abbreviations: AT, as-treated; EDSS, Expanded Disability Status Scale; MR, magnetic resonance; MS, multiple sclerosis; NA, not applicable; OR, odds ratio.

[a] Statistically significant at $P < .05$.

tinuers (n = 35) and natalizumab quitters (n = 73). The latter had a higher probability of MR imaging MS activity compared with the former (OR, 2.81; 95% CI, 1.17-6.74; $P = .03$).

At the end of the study, a decreasing trend in EDSS scores was observed among the 3 groups of patients: natalizumab switchers had the highest mean (SD) EDSS score (4.03 [1.76]), whereas natalizumab continuers had the lowest mean (SD) EDSS score (3.16 [1.69]). The differences were not statistically significant ($P = .14$).

During the year before beginning natalizumab and during the year after stopping natalizumab, no significant clinical or radiologic rebound phenomena were observed among natalizumab quitters. In particular, the ARR was significantly lower ($P < .001$) at the end of the study period than before the group began natalizumab. We observed no significant difference in annual MR imaging MS activity before vs after natalizumab use among natalizumab quitters.

In the subgroup of patients who began interferon beta, 52.7% developed a flulike syndrome, 54.2% manifested biohumoral alterations, and 72.8% had injection site reactions. Seventy-five percent of the participants who began glatiramer acetate developed injection site reactions. Among the patients who began fingolimod, leukopenia and a significant increase in liver enzyme levels were found in 3.5% and 12.9% of cases, respectively.

One case of pyelonephritis was documented in the group of patients continuing natalizumab. In addition, one myocardial infarction occurred in this group of patients.

Three months after natalizumab discontinuation, one patient had a generalized epileptic seizure associated with expressive aphasia. The MR imaging was consistent with PML, and polymerase chain reaction testing for JCV DNA in the cerebrospinal fluid was positive. The patient was treated with plasmapheresis and mirtazapine, achieving complete remission of neurologic deficits (remission of aphasia and cessation of seizures). This patient's EDSS score was 1.00 at baseline and at 5 months after stopping natalizumab. The patient then began treatment with glatiramer acetate. However, 10 months after interrupting natalizumab and when receiving glatiramer acetate therapy, the patient had a clinical relapse that caused a 1.00-point worsening of the EDSS score, despite the administration of high-dose corticosteroids.

Discussion

Our spontaneous, prospective, observational multicenter clinical and MR imaging study allowed us to evaluate the efficacy of treatment options after 24 doses of natalizumab in patients with RR-MS. The results show that patients who continued natalizumab for the entire follow-up period fared significantly better than those who completely stopped natalizumab (despite receiving other DMTs) or those who began natalizumab again for some months during the 1-year observation period.

Natalizumab is the most effective drug for RR-MS.[1] However, treatment with natalizumab may be associated with PML.[4,5] As of February 4, 2014, a total of 439 confirmed cases of natalizumab-associated PML had been reported,[21] and it was shown that the risk of PML increases after 24 doses of natalizumab. Based on these data, the EMA implemented a risk mitigation plan requiring neurologists to reevaluate natalizumab treatment after 24 doses, and patients opting to continue receiving this drug for longer periods must sign a second informed consent form.[7]

Data about the risk of clinical reactivation of MS after natalizumab discontinuation have been inconsistent.[8,9,11] Some studies[8,11] showed disease activity recurring approximately 5 to 6 months following natalizumab discontinuation. The largest cohort was analyzed in an 8-month retrospective study[11] of clinical and MR imaging MS activity among 1866 patients who had received at least 1 dose of natalizumab before discontinuing it. Recurrent disease peaked at 4 to 7 months after natalizumab interruption, regardless of the administration of alternative DMTs for MS.

The evaluation of the efficacy of alternative therapeutic strategies for patients discontinuing natalizumab has been the goal of other studies, and the results have been controversial. In 2 small prospective studies, 9 patients[22] and 13 patients[12] switched from natalizumab to a first-line DMT (interferon beta or glatiramer acetate): most of the patients treated with interferon beta remained free of clinical relapses, while the patients treated with glatiramer acetate showed a return of disease activity. Better results with glatiramer acetate used after natalizumab interruption were shown in a 12-month study[23]

prospectively following up 40 patients treated with glatiramer acetate after 12 to 18 months of natalizumab use. Approximately 60% of patients remained relapse free during the observation period. Other studies[13,24] evaluated the efficacy of switching from natalizumab to fingolimod. In these studies, clinical or radiologic disease activity recurred in 40% to 50% of patients switching to fingolimod. However, the cohorts in both studies were small (range, 22-36 patients), and the length of time between discontinuing natalizumab and beginning fingolimod could have affected the return of disease activity, as suggested by other study[15] findings.

In our observational, prospective study, the decision to continue or discontinue natalizumab after 24 doses was based only on the EMA recommendation to exercise care in prescribing natalizumab beyond 24 months.[7] The EMA statement that 24 months of treatment represent the crucial time when treatment should be rediscussed is probably arbitrary because PML can occur much earlier than 2 years and thereafter.[6,18,19] In any case, following the EMA recommendation meant that the distribution of our patients into the various therapy subgroups was not biased by JCV antibody status or prior immunosuppressive therapy.

In our cohort of patients with RR-MS who had reached clinical and MR imaging stability of MS after 24 doses of natalizumab, the risk of relapsing was about 3 times higher in natalizumab switchers (P = .05) and more than 4 times higher in natalizumab quitters (P = .002) compared with natalizumab continuers. Annual MR imaging MS activity was also significantly lower in natalizumab continuers than in natalizumab quitters (P = .03). Although EDSS scores did not differ between the groups of patients at the beginning of the observation period, 1 year later the mean EDSS score was lowest in natalizumab continuers, likely suggesting a protective effect of natalizumab continuation on disease progression. The difference in scores was not statistically significant, and a longer follow-up period is necessary for a significant effect to be manifested.

The phenomenon of rebound MS was not observed in our study. Among natalizumab quitters, we observed a significantly lower relapse rate after natalizumab discontinuation compared with clinical activity before starting natalizumab (data not shown). Therefore, our prospective study in this large patient group does not confirm the occurrence of rebound MS after stopping natalizumab that had been found in previous retrospective or small cohort investigations[8] but confirms the results of prospective or larger studies.[9,11]

In our study, the incidence of adverse effects was comparable to that known for the various RR-MS treatments.[25-27] The one case of pyelonephritis and the one instance of myocardial infarction were probably unrelated to natalizumab treatment. Progressive multifocal leukoencephalopathy occurred in one patient at 3 months after natalizumab discontinuation: the patient subsequently achieved complete remission of neurologic deficits following treatment with plasmapheresis and mirtazapine.

Conclusions

Our study shows that clinical and MR imaging MS reactivation occurs more frequently in patients stopping natalizumab than in those continuing treatment after 24 doses. The results from a large, prospective multicenter study such as this one can better translate into clinical practice than the results from small, single-center studies, particularly relative to a high-prevalence disease such as MS.[28] According to our results, continuing natalizumab seems to be the most efficacious therapeutic strategy in patients who have already received 24 doses of the drug, although it may be associated with a risk of developing PML in patients previously exposed to JCV. Therefore, any decision about the therapeutic management of JCV-positive patients after 24 doses of natalizumab should take into account the risk of disease reactivation associated with natalizumab discontinuation and the risk of PML potentially associated with prolonged natalizumab treatment. Careful individual evaluation of PML risk based on the risk factors is needed,[18,19] and natalizumab discontinuation can be reasonably advised for patients whose risk is considered too high. In all other cases, natalizumab should be continued, with meticulous monitoring of MR imaging to detect the occurrence of possible PML at a subclinical stage.[29,30]

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Study supervision: Sormani, Durelli.

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