Pharmacokinetics and pharmacodynamics of natalizumab in pediatric patients with RRMS

Angelo Ghezzi, MD, Giancarlo Comi, MD, Luigi Maria Grimaldi, MD, Lucia Moiola, MD, Carlo Pozzilli, MD, Simone Fantaccini, MD, and Paolo Gallo, MD

Correspondence
Dr. Ghezzi
angelo.ghezzi@asst-valleolona.it

Abstract

Objective

This phase I study investigated pharmacokinetic (PK) and pharmacodynamic (PD) profiles of natalizumab in pediatric patients with relapsing-remitting MS (RRMS).

Methods

Pediatric patients with RRMS who were prescribed natalizumab 300 mg IV every 4 weeks were enrolled. Blood samples were collected on days 1, 2, 8, 15, and 22 and at weeks 4, 8, 12, and 16 to estimate PK parameters; PD properties were evaluated by measuring α4-integrin saturation and lymphocyte counts over time. Natalizumab's safety profile was also evaluated.

Results

PK parameters were similar to those reported in adult patients; natalizumab concentrations peaked approximately 1 day after infusion in most of the participants (Cmax 142.9 μg/mL, AUClast 47389.4 hr*μg/mL), followed by a biphasic decline with a rapid distribution phase and a slow elimination phase, with a terminal half-life of 215.1 hours. In terms of PD, both time course and magnitude of α4-integrin saturation and increase in lymphocyte counts were similar to those observed in adults. During the 16-week study follow-up, 3 adverse events attributed to natalizumab were observed; no unexpected safety events occurred.

Conclusions

PK profile, α4-integrin saturation, lymphocyte counts, and safety observed in these pediatric patients are comparable to those reported in adults.

Classification of evidence

This study provides Class I evidence that natalizumab PK/PD parameters and safety profile are similar in adults and pediatric patients in the short term. Longer studies, also including a larger number of younger subjects (aged 10–12 years), are required to further inform about long-term PK and PD parameters in pediatric patients with MS.

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→ **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
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From the Multiple Sclerosis Study Center (A.G.), ASST Valle Olona, Gallarate Hospital (VA); Department of Neurology (G.C., L.M.), Institute of Experimental Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan; Department of Neurology (L.M.G.), Fondazione Istituto G. Giglio, Cefalù; Department of Neurology (C.P.), "La Sapienza" University, Rome; Biogen Italia (S.F.), Milan; and Department of Neuroscience DNS, Multiple Sclerosis Centre (P.G.), Università degli Studi di Padova, Italy.

Glossary

Natalizumab (Tysabri; Biogen, Cambridge, MA), a recombinant humanized anti-α4-integrin antibody, has proven to be efficacious for the reduction of clinical progression in adult patients with relapsing-remitting MS (RRMS).[1–3] Following the results of pivotal trials, natalizumab 300 mg IV every 4 weeks has been approved in Europe for the treatment of RRMS in adult patients.[4] This molecule is not indicated for patients aged <18 years; pediatric usage is off label, almost exclusively as second line,[5–9] primarily because of safety concerns.[10–12] However, in Italy, natalizumab use is allowed in adolescents aged 12–18 years with active MS and for whom no other alternative treatments are available (according to the Italian Law 648/96[13]).

The adult dose (300 mg IV every 4 weeks) seems to be well tolerated and effective in reported case series of pediatric patients,[8,11,14–23] and based on postmarketing safety reporting, including 2 retrospective studies on 29 pediatric patients and 2 registries comprising 133 participants, the adverse event (AE) profile appears to be similar between the pediatric and the adult population.[19–22] Moreover, no apparent pharmacokinetic (PK) differences have been reported between adult and pediatric patients with Crohn disease treated with comparable natalizumab doses, thus suggesting that disposition of natalizumab is not likely to change with age.[23] Last, global data from observational studies[7,9,24] and national registries[21,22] suggest that natalizumab 300 mg IV every 4 weeks is effective and well tolerated in pediatric patients with MS (majority aged ≥10 years).

Although information on the safety of natalizumab in pediatric patients seems to be in line with that of adult patients,[19–22] evidence on the PK and pharmacodynamic (PD) profile of natalizumab in this specific patient population is still scant and would be necessary to further extend the use of this molecule to pediatric patients.

Moreover, these studies would provide important information on the use of new medications in the pediatric MS population.[22,25–27] This phase I study was designed to determine the PK and PD profile of natalizumab in pediatric patients with RRMS.

Methods

Study setting and design

This was an open-label, multiple-dose, multicenter prospective study to evaluate the PK/PD profile, safety, and tolerability of natalizumab 300 mg every 4 weeks administered IV to male and female pediatric patients (aged 10–18 years at the time of informed consent) with RRMS.

Figure 1 summarizes the study design. Participants attended clinic visits on days 1, 2, 8, 15, and 22 and at weeks 4, 8, 12, and 16 to complete assessments. A follow-up contact by telephone at 12 weeks (±2 weeks) after the last infusion of study treatment was required for patients who received ≥1 infusion of study treatment and who did not continue treatment with natalizumab in the Italian National Registry (see below).
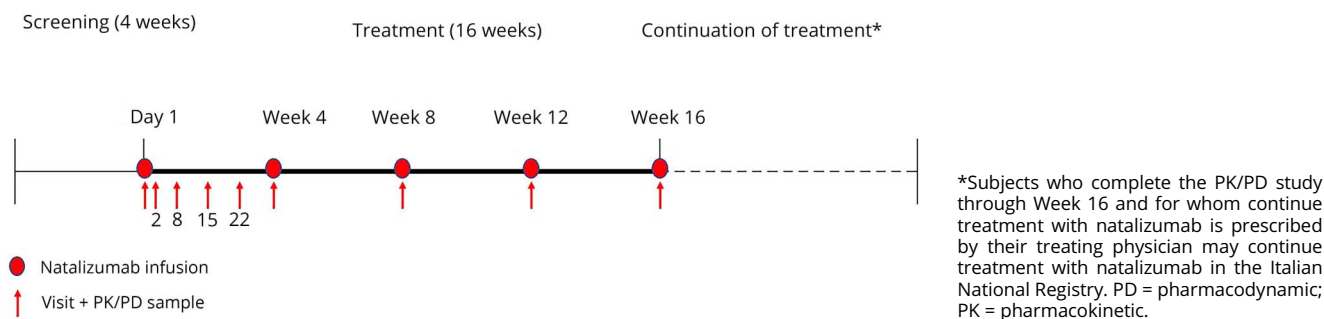
Standard protocol approvals, registrations, and patient consents

Patients were included in the study after they and their parents signed the informed consent. The study has been approved by the ethics committee of the coordinating center and by all the sites that participated to the study. Trial registration number: 101MS328.

Patients

Patients were eligible to participate in the study if they met the following criteria: (1) age 10–18 years; (2) diagnosis of rapidly evolving severe RRMS (defined by 2 or more disabling

Figure 1 Study design

Screening (4 weeks)   Treatment (16 weeks)   Continuation of treatment*

Day 1   Week 4   Week 8   Week 12   Week 16

2 8 15 22

● Natalizumab infusion

↑ Visit + PK/PD sample

*Subjects who complete the PK/PD study through Week 16 and for whom continue treatment with natalizumab is prescribed by their treating physician may continue treatment with natalizumab in the Italian National Registry. PD = pharmacodynamic; PK = pharmacokinetic.

relapses in 1 year) and 1 or more gadolinium (Gd)-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI; (3) natalizumab treatment deemed appropriate by the treating physician; and (4) agree to the use of contraceptives if the participant is sexually active.

Exclusion criteria were as follows: (1) any potential differential diagnosis other than pediatric-onset RRMS; (2) any major infection (HIV, Hepatitis C virus, and Hepatitis B virus); (3) any major illness (progressive multifocal leukoencephalopathy [PML]), inflammatory disorders, metabolic neurogenetic leukodystrophies, toxic leukoencephalopathies, vascular conditions, malignancies, neurologic/psychiatric conditions, and severe allergic or anaphylactic reactions); (4) known drug hypersensitivity; (5) MS relapse within 30 days before enrollment; (6) abnormal laboratory values, absolute lymphocyte count, hemoglobin, platelet count, serum creatinine, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, bilirubin, or any abnormal laboratory values indicative of significant medical, neurologic—other than MS—or psychiatric disorders); (7) previous treatment with natalizumab, lymphoid irradiation, cladribine, mitoxantrone, fingolimod, teriflunomide, T cell or T-cell receptor vaccination, cyclophosphamide, cyclosporine, azathioprine, methotrexate, mycophenolate, mofetil, or any therapeutic monoclonal antibody or immunoglobulins, corticosteroids or immunosuppressive/immunomodulatory therapy, plasmapheresis, or cytapheresis within 12 months before the first infusion of study treatment; and (8) participation in any other investigational study. The following concomitant treatments were also disallowed and could lead to patient's exclusion if administered during the course of the study: alternative immunotherapy or immunosuppressant therapy, any investigational product, any systemic steroids (apart from short courses of high-dose corticosteroids for exacerbation of MS disease), total lymphoid irradiation, cladribine, T cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, IV immunoglobulin (IVIg), plasmapheresis, or cytapheresis.

Treatment and assessments
Eligible patients who entered the study received natalizumab 300 mg IV every 4 weeks for 16 weeks for a total of 5 doses. Blood samples were collected on days 1, 2, 8, 15, and 22 and at Weeks 4, 8, 12, and 16 to estimate PK parameters from natalizumab concentrations. At least 12 patients, including at least 5 females, were planned to be enrolled.

Blood samples to determine natalizumab concentrations were collected from day 1 through the week 16 visit (for detailed timeline, see figure 1) to measure the following: maximum observed concentration (Cmax); minimum observed concentration (Cmin); predose (trough) serum concentration (Cpredose); time to reach maximum observed concentration (Tmax); area under the concentration-time curve from time zero to infinity (AUCinf); area under the concentration-time

curve to the last measurable concentration as measured by the trapezoidal rule (AUClast); clearance; volume of distribution; and elimination half-life (t½).

The following tests were performed to assess the PD properties of natalizumab: (1) α4-integrin saturation and (2) lymphocyte counts.

The following clinical assessments were performed to assess the safety profile of natalizumab: AE and severe AE (SAE), according to the common terminology criteria for AEs, version 4.0; physical and neurologic examinations; vital sign measurements; weight and height; and concomitant therapy and procedures. Complete laboratory assessments were also performed. Last, immunogenicity assessments (anti-natalizumab antibody status) were performed to assess the safety of natalizumab at baseline and at the time of last infusion. All data were analyzed by descriptive statistics, using Microsoft Excel software.

Italian National Registry
Patients who completed the PK/PD study were expected to enroll in the Italian National Registry. This was limited to adolescents aged between 12 and 18 years who fall in the characteristics of "group B" of the Italian National Registry (patients with rapidly evolving severe RRMS as defined above). Patients who enrolled in the Italian National Registry received commercial natalizumab in accordance with any related pharmacovigilance recommendations as described in the prescribing information.

Data availability
Study protocol and anonymized individual participant data collected during the trial are available by request via the Biogen Clinical Data Request Portal (biogenclinicaldatarequest.com). Data access will be available upon approval for qualified scientific researchers who provide a methodologically sound research proposal. To gain access, data requestors will need to sign a data-sharing agreement.

Results
Patients
A total of 13 pediatric patients with RRMS were enrolled, and all of them completed the study; no participant withdrew before dosing, and no one discontinued natalizumab treatment or withdrew from the study for any reason. All 13 patients entered the Italian National Registry at the end of the study.

Patients' baseline characteristics are shown in table 1. Median age was 16 years (range, 11–17 years). The majority of the participants (n = 9) were older than 13 years. Ten patients (77%) were female. Mean weight and height were 59.1 kg (±12.7 kg) and 162.4 cm (±7.8 cm), respectively. Mean body mass index was 22.2 kg/m^2 (±3.710 kg/m^2).

Table 1 Patient and disease characteristics

	Patients enrolled (n = 13)
Sex [n (%)]	
Male	3 (23%)
Female	10 (77%)
Age [mean (range)]	16 (11–17) y
Ethnicity [n (%)]	
White	13 (100%)
Weight (kg)	
Mean ± SD	59.1 ± 12.7
Median (range)	58.0 (42, 84)
Height (cm)	
Mean ± SD	162.4 ± 7.8
Median (range)	160.0 (155, 183)
BMI (kg/m^2)	
Mean ± SD	22.2 ± 3.71
Median (range)	22.31 (16.8, 28.9)
Anti-JCV antibody	
Positive	7 (54%)
Negative	6 (46%)
MS diagnosis, mean (range)	
Time from onset	1.0 (0–5) y
Age at onset	14.0 (10–17) y
Time from diagnosis	1.0 (0–5) y
Age at diagnosis	14.2 (10–17) y
Relapses, mean (range)	
No. relapses—past 12 months	1.9 (1–3)
No. relapses—past 2 years	2.5 (1–5)
Time since last relapse	3.0 (1–6) mo
MRI at inclusion	
Gd+ administration in the last mo [n (%)]	3 (23%)
Gd+ lesions (mean ± SD)	1.8 ± 2.3
0	1 (8%)
1–5	11 (85%)
6–10	1 (8%)
New or enlarging T2 lesions (mean ± SD)	10.7 ± 8.9
≤1	2/10 (20%)
>1–5	1/10 (10%)
>5–10	2/10 (20%)
>10–15	3/10 (30%)

Table 1 Patient and disease characteristics (continued)

	Patients enrolled (n = 13)
>15–20	0
>20–25	2/10 (20%)
Medical history [n (%)]	
Neurologic	13 (100%)
Allergy	2 (15%)
Heent	2 (15%)
Dermatologic	1 (8%)
Gastrointestinal	1 (8%)
Genitourinary	1 (8%)
Endocrine/metabolic	1 (8%)
Musculoskeletal	1 (8%)
Infectious disease	1 (8%)
Previous treatment, n (%)	
≥1 treatment	7 (54%)
IFN β-1a	5 (48%)
GA	1 (8%)
IVIg + IFN β-1b	1 (8%)
Treatment discontinuation	
Lack of efficacy	6 (48%)
Intolerability	1 (8%)

Abbreviations: BMI = body mass index; GA = glatiramer acetate; Gd = gadolinium; Heent = head, eyes, ears, nose, and throat, IFN = interferon; IVIg = IV immunoglobulin; JCV = JC virus.

Table 1 also summarizes participant's disease characteristics. The median time since the onset of first MS symptoms was 1.0 years (range, 0–5 years), and the median time since the diagnosis of MS was 1.0 years (range, 0–5 years). The mean age at the onset of MS symptoms was 14.0 years (±2.6 years), and the mean age at the diagnosis of MS was 14.2 years (±2.6 years). All participants had experienced at least 1 relapse in the past 12 months before enrollment. The mean number of Gd-enhancing lesions observed in MRI for study inclusion was 1.8 (±2.3), with the majority (85%) of the patients having between 1 and 5 Gd-enhancing lesions.

Seven patients had received at least 1 previous treatment for MS; most patients had received interferon β-1a (IFN β-1a), 1 patient had received glatiramer acetate, and 1 patient had received IVIg and IFN β-1b. Six of the 7 patients had stopped their previous treatment because of efficacy reasons, and 1 patient had stopped the previous treatment because of intolerability (table 1).

Figure 2 Natalizumab concentration-time profile following a single dose

A. Linear: Linear

B. Log: Linear

(A) Linear-linear concentration-time profile. (B) Log-linear concentration-time profile.
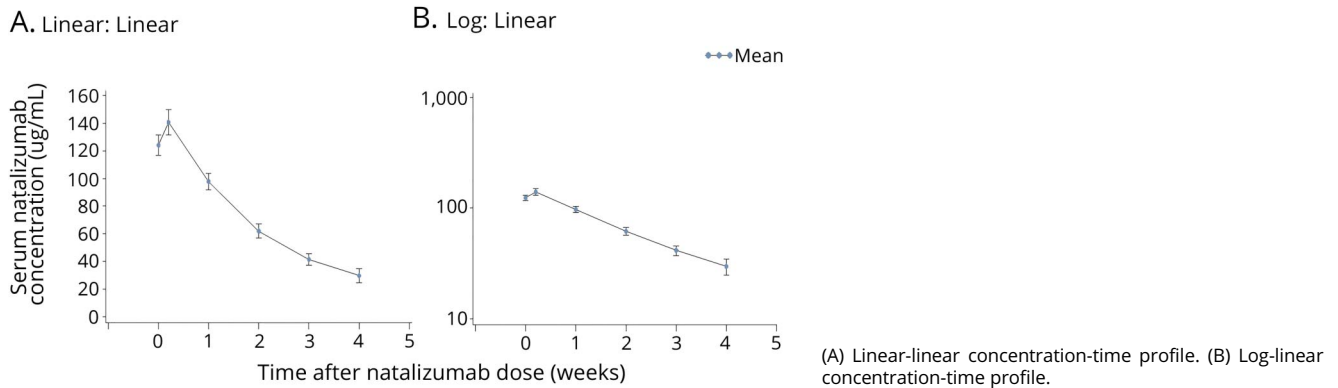
Exposure to study treatment

No participant missed a scheduled dose of natalizumab, and all patients received the full 300 mg dose. The median time between infusions was 28 days (range, 24–33 days), and the median time on study was 16.1 weeks (range, 16.1–17.0 weeks). There were no major protocol deviations that concerned the administration of a dose to a patient.

PK assessment

A mean number of 13 samples were measured for natalizumab concentrations at each time points. A summary of serum natalizumab concentrations is presented in table e-1 (links. lww.com/NXI/A125), and a summary of serum natalizumab concentrations by age group is presented in table e-2.

Following administration of the first natalizumab dose, the median Tmax was 24.7 hours (range, 1.1–29.0 hours). The maximum serum natalizumab concentration was observed to occur in most of the patients (8/13) approximately 1 day

postinfusion and in 5 patients at the end of infusion (within 15 minutes of the end of the infusion). The percentage difference in concentrations measured 24 hours postinfusion, compared with the end of infusion, ranged between 4% and 123%.

The geometric mean exposure to natalizumab as estimated by Cmax was 142.9 μg/mL and by AUClast was 47389.4 hr*μg/mL. Variability in exposure, as measured by Cmax and AUClast, was low to moderate for natalizumab, with coefficients of variance of 18.49% and 26.88%, respectively.

The natalizumab concentration-time profile after peak concentration exhibited a biphasic decline with a rapid distribution phase and a slow elimination phase. The inflection between the 2 phases occurred at approximately 8–15 days postdose (figure 2). Natalizumab was eliminated with a geometric mean terminal half-life (t½) of 215.1 hours. Half-life could not be estimated in 4 of 13 participants, as the terminal elimination phase could not be adequately characterized.

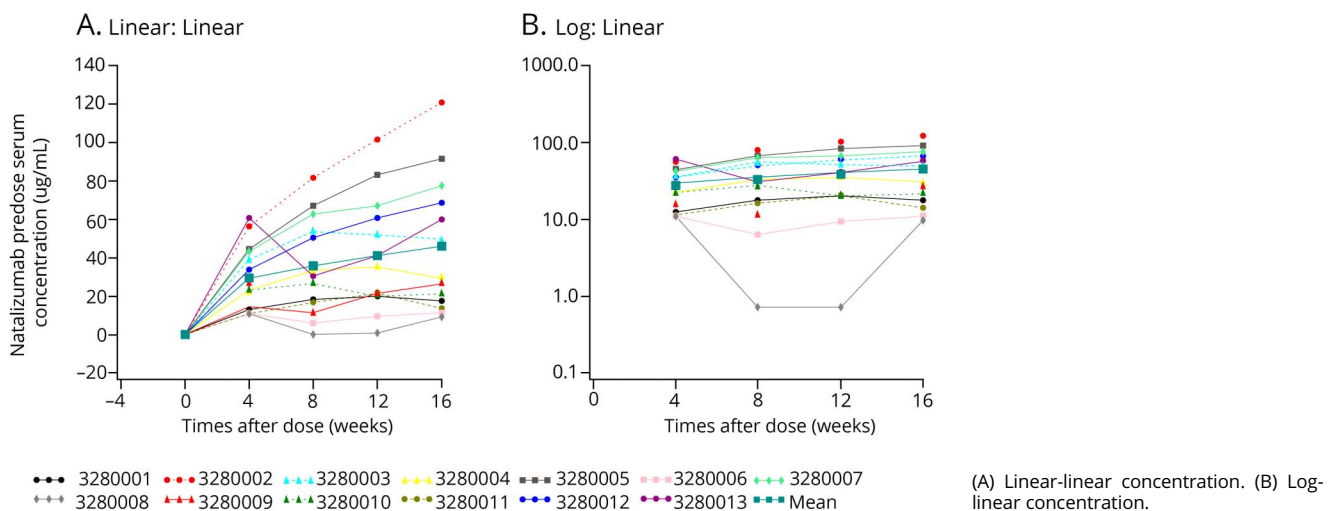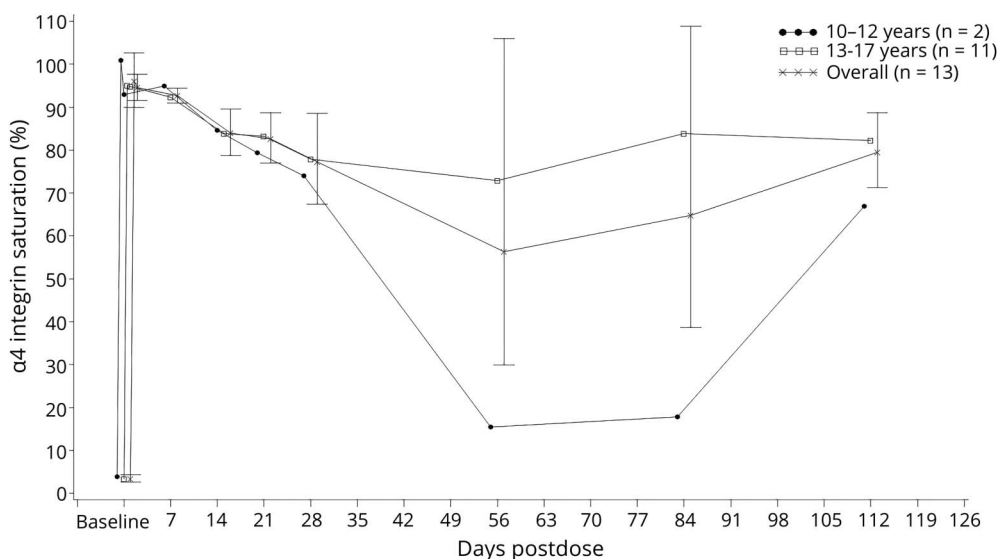**Figure 3** Mean trough (preinfusion) serum natalizumab concentrations

A. Linear: Linear

B. Log: Linear

| 3280001 | 3280002 | 3280003 | 3280004 | 3280005 | 3280006 | 3280007 |
| 3280008 | 3280009 | 3280010 | 3280011 | 3280012 | 3280013 | Mean |

(A) Linear-linear concentration. (B) Log-linear concentration.

Figure 4 Geometric mean of α4-integrin saturation over time

Legend: 10–12 years (n = 2); 13-17 years (n = 11); Overall (n = 13). X-axis: Days postdose. Y-axis: α4 integrin saturation (%).

Qualitative inspection of mean trough (preinfusion) serum natalizumab concentrations suggests that steady-state concentrations were not reached by week 16 (figure 3).

PD assessment

Figure 4 depicts the geometric mean of α4-integrin saturation over time. Peak α4-integrin saturation occurred within 15 minutes following the first infusion (week 1) of natalizumab. Saturation remained elevated with mean Cmin values at or above 72.1% through week 16.

Lymphocyte counts increased over time, sharply increasing from a mean baseline value of 1.86×10^9 cells/L to 3.48×10^9 cells/L by week 4 and rising more slowly to 4.03×10^9 cells/L by week 16. Overall, this elevation was greater than 110% increase over baseline counts.

Safety assessments

Table 2 summarizes the overall incidence of AEs. Of the 13 patients who received at least 1 dose of study treatment, 10 (77%) experienced at least 1 AE. Three patients (23%) experienced an AE that was assessed as related to natalizumab treatment; these AEs were in detail: upper respiratory tract infection (n = 1), asthenia (n = 1), and headache and nausea (n = 1). None of the patients experienced increase in liver enzyme, acute infusion-related hypersensitivity reactions, or development of PML. Of note, table e-3 (links.lww.com/NXI/A125) summarizes mean lymphocyte counts by age group throughout the study.

Two patients (15%) experienced an AE of moderate intensity. No SAE was observed. Only 1 patient (8%) experienced a serious AE; this patient was hospitalized for evaluation of dizziness, but no cause was identified. This SAE was assessed as not related to natalizumab treatment by the investigator,

and the patient's symptoms resolved within 2 days. Anti-natalizumab antibodies were not observed at any of the sampled time points for immunogenicity.

Table 2 Incidence of AEs

	Patients, n (%)
AEs	10 (77%)
Infection and infestation	5 (38%)
Psychiatric disorders	2 (15%)
Nervous system disorders	6 (46%)
Cardiac disorders	1 (8%)
Gastrointestinal disorders	2 (15%)
Musculoskeletal and connective tissue disorders	3 (23%)
General disorders and administration site conditions	2 (15%)
Injury, poisoning, and procedural complications	1 (8%)
Adverse drug reactions	3 (23%)
Infection and infestation	1 (8%)
Nervous system disorders	1 (8%)
Gastrointestinal disorders	1 (8%)
General disorders and administration site conditions	1 (8%)
Serious AEs	1 (8%)
Premature discontinuations	0

Abbreviation: AE = adverse event.

Discussion

The present study has provided useful information on the PK/PD profile of natalizumab administered to RRMS children and adolescents. PK parameters (AUC and Cmax) following the administration of the first natalizumab dose and of trough concentrations (Cmin) at week 12 in pediatric patients were similar to those reported in studies with adult patients (Study 101MS102 [NCT00559702], Study C-1801 [NCT00027300], and Study C-1802 [NCT00030966]) indicating an overlap of PK parameters between the 2 populations. Although the number of evaluated patients was low, at each time point, there were no major differences in natalizumab concentrations between the 2 pediatric patients aged 10–12 years and the 11 patients aged 13–17 years. The similarity in natalizumab PK profile between pediatric and adult patients is further confirmed by the fact that steady state was not reached by week 16 in the pediatric population; similarly, in adult patients, the predicted time to steady state was approximately 36 weeks.[28] Moreover, similarly to adults, this pediatric population showed an interindividual variability in natalizumab concentrations. We acknowledge that the number of patients included in the study was small (especially for younger subjects, as only 2 patients aged between 10 and 12 years were included) and that the CIs recorded were wide. The concentration of serum natalizumab observed in this study has several deviations both above and below the therapeutic range predicted for adult patients: based on the Emax model, natalizumab serum concentrations of approximately 2.5–3 µg/mL would be required to maintain a minimum α4-integrin saturation of 80%.[29] As expected from studies with adult patients with MS,[30,31] peak α4-integrin saturation occurred shortly (≤15 minutes) after the first infusion of natalizumab, and saturation remained elevated during the study. A decrease of α4-integrin saturation was observed at the time of the 3rd and 4th administration in the 2 subjects with less than 12 years. Further studies may clarify whether this pattern is specifically related to the younger age or reflects the normal variability observed in adults and the relationship between lower concentrations of natalizumab and α4-integrin saturation.

Mean lymphocyte counts increased over time, especially from baseline to week 4 and subsequently at a lower rate between week 4 and week 16. Overall, the time course and magnitude of α4-integrin saturation and the change in lymphocyte counts in these pediatric patients with MS were consistent with the results seen in studies with adult patients.

In terms of safety, natalizumab administration proved to be safe in pediatric patients, and all AEs observed were consistent to the known safety profile of the drug, with the most common AEs occurring in the System Organ Classes of nervous system disorders, infections and infestations, and musculoskeletal and connective tissue disorders. The frequency and severity of AEs were similar to those seen in adult patients; only 1 patient reported a serious AE (dizziness) that occurred 24 days after the previous infusion of natalizumab and was assessed by the investigator as mild in severity and not related to natalizumab treatment. There were no discontinuations of treatment, withdrawals due to AEs, and no acute infusion-related hypersensitivity reactions reported in the study. Moreover, the immunogenicity assessment showed no production of anti-natalizumab antibodies at week 16 for all the treated patients. Of note, the safety profile of natalizumab was not adversely affected by the slight increased exposure, in terms of serum concentrations of natalizumab, observed during the study.

Although larger studies are necessary to confirm the above-reported findings, based on the results of this study, the administration of natalizumab 300 mg IV every 4 weeks can be considered safe in pediatric patients with RRMS. Importantly, the PK profile, the α4-integrin saturation, and the increase in lymphocyte counts in this population are comparable to those reported in adult patients.

Disclosure

A. Ghezzi received fees for consultant and speaking activities from Merck, Novartis, Biogen, Genzyme, Teva, Roche, Almirall, and Mylan. Dr. Ghezzi has served on scientific advisory boards of Merck Serono, Sanofi-Genzyme, Novartis, Mylan, Biogen, and Teva and has received speaker honoraria from Merck Serono, Teva, Biogen Idec, Sanofi-Genzyme, Novartis, Serono Symposia International, and Almirall. G. Comi has received personal compensation for consulting and speaking activities from Biogen and Excemed. L.M. Grimaldi 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 institutional research support from Biogen Idec and Serono Foundation. L. Moiola has received compensation for speaking or for participation to advisory board from Novartis, Roche, Sanofi-Genzyme, Biogen, Serono, and Teva. C. Pozzilli reports no disclosures. S. Frantaccini was an employee of Biogen Italia at the time of the study. P. Gallo reports no disclosures. Go to Neurology.org/NN for full disclosures.

Appendix Authors

Name	Location	Role	Contributions
Angelo Ghezzi, MD	Gallarate Hospital (VA), Italy	Author	Designed the study, coordinated the conduction of the study, recruited patients, collected and analyzed data, and wrote and revised the manuscript
Giancarlo Comi, MD	San Raffaele Scientific Institute, Milan, Italy	Author	Was one of the investigators, enrolled patients, revised data, was involved in revision of this manuscript, and approved the submitted version
Luigi Maria Grimaldi, MD	Fondazione Istituto San Raffaele G. Giglio, Cefalù, Italy	Author	Was one of the investigators, enrolled patients, revised data, was involved in revision of this manuscript, and approved the submitted version
Lucia Moiola, MD	San Raffaele Scientific Institute, Milan, Italy	Author	Was one of the investigators, enrolled patients, revised data, was involved in revision of this manuscript, and approved the submitted version
Carlo Pozzilli, MD	La Sapienza University, Rome, Italy	Author	Was one of the investigators, enrolled patients, revised data, was involved in revision of this manuscript, and approved the submitted version
Simone Fantaccini, MD	Biogen Italia, Milan, Italy	Author	Was one of the investigators, enrolled patients, revised data, was involved in revision of this manuscript, and approved the submitted version
Paolo Gallo, MD	Università degli Studi di Padova, Padova, Italy	Author	Was one of the investigators, enrolled patients, revised data, was involved in revision of this manuscript, and approved the submitted version

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