Natalizumab Therapy for Highly Active Pediatric Multiple Sclerosis

Barbara Kornek, MD; Fahmy Aboul-Enein, MD; Kevin Rostasy, MD; Ruxandra-Julia Milos, MD; Irene Steiner, MSc; Johann Penzien, MD; Kerstin Hellwig, MD; Kalliopi Pitarokoili, MD; Karin Storm van’s Gravesande, MD; Michael Karenfort, MD; Astrid Blaschek, MD; Andreas Meyer, MD; Rainer Seidl, MD; Diana Debelic, MD; Karl Vass, MD; Daniela Prayer, MD; Wolfgang Kristoferitsch, MD; Antonios Bayas, MD.

Importance: Given the high frequency of failure of first-line therapies, there is an urgent need for second-line treatment strategies for pediatric patients with multiple sclerosis (MS).

Objective: To report the use of natalizumab in pediatric MS. Natalizumab, a humanized monoclonal antibody targeting α4 integrin, is effective against active relapsing-remitting MS in adults.

Design: Retrospective study.

Setting: Eleven centers for neurology and pediatric neurology in Germany and Austria.

Participants: A total of 20 pediatric patients with MS who started treatment with natalizumab prior to 18 years of age. These patients underwent magnetic resonance imaging as clinically indicated, despite the fact that 19 of these 20 patients were undergoing first-line therapies, there is an urgent need for second-line treatment strategies for pediatric patients with multiple sclerosis (MS).

Intervention: Natalizumab, 300 mg every 4 weeks.

Main Outcome Measures: Annualized relapse rates, Expanded Disability Status Scale scores, number of new T2/fluid-attenuated inversion recovery lesions and contrast-enhancing lesions on magnetic resonance imaging, number of adverse events, the prevalence of neutralizing antibodies against natalizumab, and serum JC virus–antibody status.

Results: Treatment with natalizumab was associated with reductions in mean annualized relapse rates (3.7 without treatment vs 0.4 with treatment; \( P < .001 \)), median Expanded Disability Status Scale scores (2 without treatment vs 1 with treatment; \( P < .02 \)), and mean number of new T2/fluid-attenuated inversion recovery lesions per year (7.8 without treatment vs 0.5 with treatment; \( P < .001 \)). Two patients developed high-titer neutralizing antibodies against natalizumab and had to stop therapy. Adverse events included headaches, asthenia, infections, and hypersensitivity. Abnormal laboratory results were found for 8 patients. JC virus antibodies were found in 5 of 13 patients. After the discontinuation of natalizumab therapy, relapse activity occurred in 6 of 8 patients within 6 months.

Conclusions and Relevance: Our data indicate that natalizumab may be safe and effective against MS in pediatric patients with breakthrough disease.


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Results of blood analysis were collected and screened for elevation of liver enzymes and the presence of hyperbilirubinemia, anemia, leukocytosis, lymphocytosis, monocytosis, and/or eosinophilia. Laboratory abnormalities were graded using the Common Terminology Criteria for Adverse Events, Version 4.0. Furthermore, the presence of neutralizing natalizumab antibodies and seropositivity against JCV as measured by the STRATIFY JCV (Unilabs; http://www.stratifyjcv.com) were recorded.13,14

Our study was approved by the local ethics committee. Informed consent was obtained from all parents (and patients) before treatment onset.

TABLE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of MS, mean (SD), y</td>
<td>15.2 (1.3)</td>
</tr>
<tr>
<td>Female patients, No. (%)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>White patients, No. (%)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Age at initiation of NA therapy, mean (SD), y</td>
<td>16.7 (1.1)</td>
</tr>
<tr>
<td>Disease duration before NA therapy, mean (SD), mo</td>
<td>18 (10)</td>
</tr>
<tr>
<td>MS attacks before NA therapy, mean (SD), No.</td>
<td>4.3 (1.1)</td>
</tr>
<tr>
<td>MS attacks in the year before NA therapy, mean (SD), No.</td>
<td>3.1 (1.2)</td>
</tr>
<tr>
<td>EDSS score before NA therapy, median (Q1, Q3)</td>
<td>2 (1.5, 3.0)</td>
</tr>
<tr>
<td>Duration of NA therapy, mean (SD), mo</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Type of DMT received before NA therapy, No. (%) of patients</td>
<td>20 (100)</td>
</tr>
<tr>
<td>No DMT</td>
<td>1 (5)</td>
</tr>
<tr>
<td>1 type of DMT</td>
<td>15 (75)</td>
</tr>
<tr>
<td>2 types of DMT</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Patients requiring plasma exchange for a severe protracted relapse before NA therapy, No (%)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>T2/FLAIR brain lesions before NA therapy, mean (SD), No.</td>
<td>30 (17)</td>
</tr>
<tr>
<td>Gd-enhancing brain lesions before NA therapy, mean (SD), No.</td>
<td>2 (3.5)</td>
</tr>
</tbody>
</table>

Abbreviations: DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium; MRI, Magnetic Resonance Imaging; MS, multiple sclerosis; NA, natalizumab; Q1, lower quartile; Q3, upper quartile.

STATISTICS

Statistical analysis was performed by an independent analyst (I.S.). The end points of our study were the annualized relapse rate, the EDSS score, the number of gadolinium-enhancing lesions, and the number of new T2 lesions per year. The annualized relapse rates were calculated by dividing the total number of relapses by the total number of person-years at risk. The annualized relapse rates before and after natalizumab therapy were calculated irrespective of the use of first-line DMT.

Differences between observation periods (before, during, and after natalizumab therapy) were analyzed by paired t tests or Wilcoxon signed rank tests. The distribution of data was checked by histograms. We adjusted for multiple testing by Bonferroni correction (with the number of hypotheses being 4).

Descriptive statistics are reported as the mean (standard deviation) for normally distributed data, as the median, the lower quartile (Q1), and the upper quartile (Q3) for nonnormally distributed data, and as absolute frequencies (percentages) for categorical data.

Statistical analyses were conducted with the statistics program SAS, version 9.3.3 (SAS Institute Inc), and R, version 2.14.0 (R Foundation for Statistical Computing). For all analyses, the significance level was set at $\alpha = 0.05$.

PATIENT CHARACTERISTICS

The demographic and clinical data for the 20 patients are summarized in our Table. Of the 20 patients, 19 received at least 1 first-line DMT before initiation of natalizumab therapy (13 patients received 22 or 44 μg of interferon beta-1a subcutaneously 3 times a week, 4 patients received 6 million IU [MIU] of interferon beta-1a intramuscularly once a week, 3 patients received 8 MIU of interferon beta-1b subcutaneously every other day, and 3 patients received 20 mg of glatiramer acetate subcutaneously daily). None of the patients received immunosuppressants before initiation of natalizumab therapy.

RESPONSE TO NATALIZUMAB THERAPY

Clinical and MRI findings before and during natalizumab treatment are summarized in Figure 1. The documented relapses of the 20 patients before and during natalizumab therapy are shown in Figure 2.

Of the 20 patients, 14 (70.0%) remained relapse free during the mean (SD) treatment period of 20 (13) months. Ten of 15 patients (66.7%) with a treatment duration of 1 year or more and 4 of 7 patients (57.1%) with a treatment duration of 2 or more years remained relapse free.
For 18 patients, the annualized relapse rate was significantly lower during therapy than before therapy (mean difference, −3.44 [95% CI, −4.27 to −2.62]; unadjusted *P* < .001 and adjusted *P* < .001). Significant improvement during therapy was also observed for the EDSS score of 20 patients (median difference [Q1, Q3], 0.25 [−1.25, 0.00]; unadjusted *P* = .006 and adjusted *P* = .02 determined by use of the Wilcoxon signed rank test), for the number of gadolinium-enhancing lesions in 13 patients (median difference [Q1, Q3], −1 [−2, 0]; unadjusted *P* = .02 and adjusted *P* = .06 determined by use of the Wilcoxon signed rank test), and for the number of new T2 lesions per year using magnetic resonance imaging (MRI) for 10 patients (mean difference, 8.00 [95% CI, −11.16 to 4.84]; unadjusted *P* = .001 and adjusted *P* = .001). After Bonferroni correction (with the number of hypotheses being 4), the *P* values for the annualized relapse rate, the EDSS score, and the number of new T2 lesions per year remained significant.

**COMBINED CLINICAL AND MRI DATA**

Overall, 6 of 13 patients (46.2%) with clinical and MRI data available for analysis remained free of disease activity in terms of reoccurrence of relapses, progression of disability, or the development of new and/or contrast-enhancing lesions on MRI scans during a mean (SD) treatment period of 21.0 (14.5) months. Of the 10 patients with an observation period of 1 year or more, 4 (40.0%) remained free of disease activity (mean [SD] treatment period, 28 [8] months).

**ADVERSE EVENTS**

Adverse events were reported for 10 of 20 patients (50.0%): headache (4 patients), mild asthenia (3 patients), severe asthenia (1 patient), pruritus (1 patient), infections of the upper respiratory tract (2 patients), urinary tract infection (1 patient), orchitis (1 patient), phlegmon of the cheek (1 patient), laryngeal edema (1 patient), and anaphylaxis (1 patient). It has to be noted, however, that reported infections occurred in only 2 patients: one patient (a boy) experienced, consecutively, tonsillitis, 3 urinary tract infections, orchitis, and phlegmon of the face (diffuse facial inflammation after a minor trauma) during therapy, and the other patient experienced recurrent sinusitis. All infections resolved completely after systemic antibiotic treatment. The patient with laryngeal edema, which we considered a hypersensitivity reaction not related to neutralizing antibodies, responded well to steroid therapy.

**ABNORMAL LABORATORY RESULTS**

Abnormal laboratory results were found for 8 of 20 patients (40.0%). Mild anemia occurred in 4 of 20 patients.
(20.0%), transient elevation of liver enzymes was found in 2 of 20 patients (10.0%), and hyperbilirubinemia was found in 2 of 16 patients (12.5%). Of 19 patients, 3 (15.8%) developed mild leukocytosis. The differential white blood cell count was available for 16 patients, showing relative lymphocytosis in 4 patients (25.0%), relative monocytosis in 4 patients (25.0%), and eosinophilia in 1 patient (6.3%). Atypical lymphocytes, polychromasia, and anisocytosis were noted in 2 patients (12.5%). Of the 22 laboratory abnormalities reported, 13 (59.1%) occurred within the first 3 months, 3 (13.6%) within the first year, and 6 (27.3%) 1 year or more after initiation of treatment. Four abnormalities (18.2%) persisted until the last visit. All laboratory abnormalities were classified as mild.24

NEUTRALIZING ANTIBODIES AGAINST NATALIZUMAB

Of 16 patients, 2 (12.5%) developed high-titer neutralizing antibodies (patients 8 and 15). One of them experienced an anaphylactic reaction during the second infusion, requiring symptomatic treatment; the other patient developed a severe relapse 4 months after initiation of treatment (2 positive test results separated by 6 weeks). Both patients stopped therapy. The remaining 14 patients tested negative (6 patients after a single test and 8 patients after 2-6 tests).

JCV-ANTIBODY STATUS

Of 13 patients, 5 (38.5%) were found to be seropositive for JCV antibodies (using STRATIFY JCV).13,14 In all but 1 patient, the test was performed after initiation of treatment. Because of his highly active disease course, one patient (patient 16) started therapy irrespective of the presence of JCV antibodies. For 3 patients from 1 center, JCV polymerase chain reaction was performed on cerebrospinal fluid samples before initiation of natalizumab therapy, and the results were negative in all 3 cases. Three patients discontinued therapy after 3.5, 1.8, and 3.5 years of continuous natalizumab therapy owing to the test results (patients 5, 12, and 20, respectively).

DISCONTINUATION OF NATALIZUMAB THERAPY

On the last follow-up, 12 patients were still receiving natalizumab therapy. Four patients had their therapy interrupted (1 owing to pregnancy,26 1 owing to noncompliance, and 2 owing to fear of PML), but they restarted after 2, 5, 6, and 29 months, respectively, owing to recurrence of relapse activity. Eight patients discontinued therapy until the last visit. Reasons for discontinuation were as follows: anaphylactic reaction associated with high-titer neutralizing antibodies (1 patient), a severe relapse and high-titer neutralizing antibodies (1 patient), the presence of JCV antibodies (3 patients), severe asthenia (1 patient stopped 1 year after initiation of therapy), and discontinueation against physicians advice despite stable disease (2 patients).

Two patients were lost to follow-up after the end of natalizumab therapy. The patient who discontinued natalizumab because she was pregnant was not included in this analysis. The relapse activity of the remaining 9 patients is illustrated in Figure 3. Of 8 patients, 6 experienced 1 or more relapses within 6 months. For 9 patients, the annualized relapse rate after therapy was slightly higher than during therapy, but this difference failed to
In our retrospective study, we provide data on the safety, tolerability, and efficacy of natalizumab in 20 children with highly active relapsing-remitting MS. Disease activity in our cohort was reflected by the high frequency and severity of relapses within a relatively short period, by the increase in the number of T2-fluid-attenuated inversion recovery lesions on MRI scans, and by the presence of gadolinium-enhancing lesions in 7 of 13 patients before initiation of natalizumab therapy. Of our 20 patients, 19 showed ongoing clinically detected and MRI-detected disease activity (despite receiving DMT), and therefore they fulfilled the recently proposed criteria for treatment failure of first-line therapies in children.4,5

As demonstrated in other pediatric patients with MS,17-20 disease activity was also strongly suppressed in our cohort after a mean follow-up of 20 months. We observed reductions in annualized relapse rates, in EDSS scores, and in the numbers of new T2 lesions during natalizumab therapy. Data on improvement in EDSS scores, however, have to be interpreted with caution because an EDSS score obtained during stable disease was not available in all cases owing to the high relapse rate. Overall, 46% of patients remained free of clinically detected and MRI-detected disease activity during the treatment period.

Our results, however, differ from the results presented by Ghezzi et al,19 who prospectively followed 19 pediatric patients with MS receiving natalizumab therapy. Although the annualized relapse rate decreased significantly, 6 of our 20 patients (30.0%) continued to experience MS attacks, and there was evidence for MRI-detected disease activity in 7 of 13 patients (53.8%). Compared with the cohort in Ghezzi et al,19 our patients were slightly older at initiation of natalizumab therapy (16.7 vs 14.6 years), our observation period was longer (20 vs 15 months), and the reoccurrence of a severe relapse associated with neutralizing antibodies was not described in the Ghezzi et al19 cohort. Our results are therefore more in line with efficacy data observed in adults, with 37% of patients remaining free of disease activity within 2 years.9 However, given the higher relapse rate in pediatric-onset vs adult-onset MS, irrespective of the use of DMT,3 our patients showed a significant and sustained treatment response to natalizumab.

So far, the only report on the outcome after discontinuation of natalizumab in children showed that the reoccurrence of relapse activity in a 12-year-old girl occurred within 5 months.20 After discontinuation of natalizumab in our study, a new attack occurred in 6 of 8 patients within 6 months. This is in line with the results from adult studies27,28 showing that clinically detected and MRI-detected disease activity may return after cessation of natalizumab therapy.

Adverse effects were found in 50% of our patients. Infections of the respiratory and urinary tracts occurred that required antibiotic medication. Both types of infections are also common in otherwise healthy individuals. However, the frequent number of infections, as well as the severe facial phlegmon in one patient, may point toward an impaired immune defense system. Whether these infections were ultimately related to natalizumab therapy remains an open question.

Neutralizing antibodies against natalizumab were found in 2 of 16 patients. In both cases, the therapy was stopped because of either a severe relapse or anaphylaxis.

Our study has several limitations. They include the retrospective design, with clinical, laboratory, and radiological evaluation at nonuniform times; the use of nonuniform protocols; and the small number of patients studied. Furthermore, treatment duration varied significantly, with 5 patients being treated for less than 1 year. Because all our patients were older than 12 years of age at initiation of natalizumab therapy, we cannot comment on its use in patients younger than 12 years of age.

The use of natalizumab is limited by the risk of PML, which occurs in 2 per 1000 patients.12 The risk of PML increases with prior use of immunosuppressants, longer treatment duration, and the presence of anti-JCV antibodies.12,15,16 Assessment of the JCV-antibody status may help for risk stratification of patients treated with natalizumab.16 A sensitive test was developed recently13,14 that showed JCV antibodies in about 55% of adult patients with MS.13,20 Anti-JCV antibodies were detected less frequently in patients younger than 20 years of age (48.9%),20 but so far specific infection rates are unknown in the pediatric MS population. In our cohort, only 5 of 13 patients (38.5%) were found to be seropositive for JCV antibodies as measured by the STRATIFY JCV.13,14

Experience with second-line agents for pediatric patients with MS is limited, and therefore specific treatment recommendations are not yet available.13 However, the high frequency of pediatric patients with MS who have an inadequate treatment response to first-line agents6 underscores the importance of further treatment options.

According to the recently published consensus statement of the International Pediatric Multiple Sclerosis Study Group,5 such treatment options may include natalizumab or cyclophosphamide. Cyclophosphamide may induce infections, amenorrhea, bladder cancer, and secondary malignant tumors.30 Fingolimod has been recently approved for adult MS,31 but there are no data available on its use in pediatric patients with MS. However, its unknown effect on thymic T-cell maturation and egress,32 as well as its assumed immunosuppressive properties, which may increase the risk of PML with subsequent natalizumab use, may limit its use in children at the current state of knowledge. Daclizumab, a humanized monoclonal antibody specific for the IL-2Ra chain, has been shown to be only partially effective in 7 pediatric patients with MS with breakthrough disease.33 Mitoxantrone hydrochloride, which is approved for adults with highly active relapsing-remitting MS, is not recommended for children owing to its cardiotoxicity and the risk of secondary leukemia.5

Given the increasing experience with natalizumab in pediatric MS, to which our study may contribute, a risk-benefit analysis may favor natalizumab for pediatric breakthrough disease. First, natalizumab appears to be highly effective in treating highly active relapsing-remitting pediatric MS, to which our study may contribute, a risk-benefit analysis may favor natalizumab for pediatric breakthrough disease. First, natalizumab appears to be highly effective in treating highly active relapsing-remitting pediatric MS.
effective and well tolerated in pediatric MS. Second, although specific infection rates are unknown in the pediatric MS population, JCV seropositivity seems to be lower in younger people, which may reduce the risk of JCV-induced PML in this age group. Third, if data derived from adult studies are applied to children, the primary use of immunosuppressants may limit a subsequent use of natalizumab owing to an increased risk of PML.13,14 Immunosuppressive treatment may further cause secondary malignant tumors, a risk that has not been described for natalizumab so far. At present, there is no indication that natalizumab may have a negative effect on maturing organ systems, including the immune system in a growing child, but so far long-term data are lacking. In summary, in addition to former reports on the use of natalizumab for pediatric MS, our study underlines the need for controlled studies on the use natalizumab and other second-line agents for children and adolescents with breakthrough disease.

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Author Affiliations: Departments of Neurology (Drs Kornek and Vass) and Radiology (Drs Milos and Prayer), Center for Medical Statistics, Informatics, and Intelligent Systems, Section for Medical Statistics (Ms Steiner), and Department of Pediatrics and Adolescent Medicine, Division of Pneumology, Allergology, and Endocrinology (Dr Seidl), Medical University of Vienna, Department of Neurology, Sozialmedizinisches Zentrum—Öst Donauphita (Dr Aboul-Enein), Gottfried von Payer Children Hospital (Dr Storm van’s Gravesande), and Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders (Dr Kristoferitsch), Vienna, Department of Pediatrics IV, Division of Pediatric Neurology, Innsbruck Medical University (Dr Rostasy), and Department of Neurology, Klinikum Mistelbach-Gänserndorf, Mistelbach (Dr Debelic), Austria; and Children’s Hospital Klinikum Augsburg (Dr Penzien) and Department of Neurology, Klinikum Augsburg (Dr Bayas), Department of Neurology, St Josef Hospital, Ruhr University Bochum (Drs Hellwig and Pitarokoili), Department of Neuropediatrics and Muscular Disorders, University Medical Center, Freiburg (Dr Storm van’s Gravesande), Department of General Pediatrics and Neonatology, University Children’s Hospital, Heinrich Heine University Düsseldorf (Dr Karenfort), Department of Pediatric Neurology and Developmental Medicine, Dr von Hauner’s Children’s Hospital, Ludwig-Maximilians University, Munich (Dr Blaschek), and Department of Neurology Weissenau, Zentrum für Psychiatrie Südwestrheinisch, Ravensburg (Dr Meyer), Germany.

Correspondence: Barbara Kornek, MD, Department of Neurology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria (barbara.bajer-kornek@meduniwien.ac.at).

Author Contributions: Study concept and design: Kornek, Aboul-Enein, and Vass. Acquisition of data: Kornek, Aboul-Enein, Rostasy, Penzien, Hellwig, Pitarokoili, Storm van’s Gravesande, Karenfort, Blaschek, Meyer, Seidl, Debelic, and Bayas. Analysis and interpretation of data: Kornek, Aboul-Enein, Milos, Steiner, Vass, Prayer, Kristoferitsch, and Bayas. Drafting of the manuscript: Kornek, Aboul-Enein, and Bayas. Critical revision of the manuscript for important intellectual content: Kornek, Aboul-Enein, Rostasy, Milos, Steiner, Penzien, Hellwig, Pitarokoili, Storm van’s Gravesande, Karenfort, Blaschek, Meyer, Seidl, Debelic, Vass, Prayer, Kristoferitsch, and Bayas. Statistical analysis: Steiner and Vass. Administrative, technical, and material support: Aboul-Enein, Rostasy, Milos, Steiner, Pitarokoili, Karenfort, Blaschek, Debelic, Vass, Prayer, and Bayas.

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