Natalizumab Therapy for Highly Active Pediatric Multiple Sclerosis

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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 disease-modifying therapy. The mean (SD) age at initiation of natalizumab therapy was 16.7 (1.1) years, and the mean (SD) pretreatment period was 18 (10) months.

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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Patients after the discontinuation of natalizumab therapy. We further report on the clinical outcome of 9 patients who are younger than 18 years of age is not indicated, limited data show that this drug may also be effective against active pediatric relapsing-remitting MS.17-20 Data on the frequency of neutralizing antibodies against natalizumab and the JCV-antibody status in pediatric patients with MS treated with natalizumab are not yet available. We further report on the clinical outcome of 9 patients after the discontinuation of natalizumab therapy.

### METHODS

**Participants**

We performed a retrospective analysis of 20 pediatric patients with MS who started treatment with natalizumab prior to 18 years of age.21 The demographic and clinical data (ie, sex, age at onset of MS, age at initiation of natalizumab therapy, number of relapses, Expanded Disability Status Scale [EDSS] scores,22 and types of DMT) before, during, and after natalizumab therapy were analyzed in detail. Relapses were defined as new or recurrent symptoms not associated with fever or infection and lasting for a minimum of 24 hours after a stable period of at least 30 days.23 Patients underwent magnetic resonance imaging (MRI) as clinically indicated. Data from the first available MRI scan, from the scan from the MRI performed before initiation of natalizumab therapy, and from the last available MRI scan during natalizumab therapy were collected. All the MRI scans were analyzed twice by 2 experienced radiologists (R.I.M. and D.P.), who analyzed them independently from each other.

### RESULTS

#### 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, the mean (SD) number of months before and during NA therapy was 11 (7) and 25 (16), respectively. For analysis of the number of gadolinium-enhancing lesions using MRI for 13 patients, the mean (SD) number of months before and during NA therapy was 16.0 (9.6) and 21.0 (14.5), respectively. The horizontal line in each box indicates the median, whereas the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box extend to the most extreme data point, which is no more than 1.5 times the interquartile range from the box. The open diamonds are the outliers beyond 1.5 times the interquartile range.

**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.
Duration of various treatments

No. of Months After Discontinuation of NA Therapy

Patient No.

Duration without specific treatment apart from corticosteroids

No. of Months During NA Therapy

Figure 3. Clinical course of pediatric patients with multiple sclerosis after discontinuation of natalizumab (NA) therapy. Patient numbers are given on the left side of the panel. Please note that patients 1, 9, and 14 restarted NA therapy. *Patient 14 missed her infusion 3 and 5 months after restarting NA therapy. GA indicates glatiramer acetate.

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 discontinuation 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,13,20 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.6 However, the high frequency of pediatric patients with MS who have an inadequate treatment response to first-line agents8 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

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In summary, in addition to former reports on the use of natalizumab so far, there is no evidence 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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