Background: Natalizumab, a humanized monoclonal antibody raised against $\alpha_4$ integrins, is approved for treatment of active relapsing-remitting multiple sclerosis (RRMS) in adult patients.

Objective: To determine the safety, effectiveness, and tolerability of natalizumab use in pediatric patients with MS.

Design: Case report.

Setting: Center for MS in childhood and adolescents, Göttingen, Germany.

Patients: Three pediatric patients with RRMS having a poor response to other immunomodulatory therapies or having intolerable adverse effects.

Interventions: Natalizumab given every 4 weeks at a dosage of 3 to 5 mg/kg of body weight.

Main Outcome Measures: Cranial magnetic resonance (MR) imaging before treatment and every 6 months thereafter.

Results: During 24, 16, and 15 months of treatment, no further relapses occurred in the 3 pediatric patients; all reported significant improvement in their quality of life. Follow-up MR imaging showed no new T2-weighted lesions or gadolinium-enhancing lesions. No adverse events were seen when dosage was adjusted to body weight.

Conclusions: Natalizumab treatment was effective and well tolerated in our pediatric patients with RRMS who did not respond to initial immunomodulatory treatments. Therefore, it is a promising second-line therapy for pediatric patients with RRMS.

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Diagnosis of MS was based on McDonald criteria. Informed consent was obtained from the parents. Figure 1 shows the clinical course of the 3 patients described. Figure 2 shows the cranial magnetic resonance imaging before and 6 months after starting natalizumab therapy.

CASE 1

Patient 1 received the diagnosis of her condition at age 12 years. She had experienced 17 relapses. Her first attack manifested as gait ataxia, followed 1 week later by weakness of the left hand and reduced sensation in the right thumb. Findings from cerebrospinal fluid (CSF) analysis revealed mild lymphocytic pleocytosis and oligoclonal IgG. Magnetic resonance imaging demonstrated 71 supratentorial and infratentorial lesions, as well as several spinal hyperintense T2-weighted lesions, with most of them showing gadolinium enhancement. Following a relapse 1 month later with weakness in the right foot and paresthesia in the left lower leg, therapy with interferon beta-1a was started at a dosage of 22 µg 3 times a week. During the next 4 years, 10 relapses occurred, and the dosage of interferon beta-1a was increased to 44 µg. During the next 4 years, 10 relapses were documented. Development of antibodies against interferon beta-1a was excluded. Following a cluster of relapses, interferon beta-1a was discontinued, and glatiramer acetate once daily was started. Nevertheless, 4 further relapses ensued within 3 months. Therapy with glatiramer acetate was discontinued, and treatment with natalizumab (300 mg [5 mg/kg of body weight]) every 4 weeks was started at age 17 years. Two years after commencement of therapy, no further relapses or disease progression was observed on MR imaging. Initially, viral disease–like symptoms and herpes labialis were experienced on the days following natalizumab infusions, as well as frequent upper airway and urinary tract infections. After reducing the natalizumab dosage to 3 mg/kg, no further adverse effects occurred.

CASE 2

Patient 2 had an initial manifestation of disease at age 7 years with left-sided facial paralysis, double vision, and bilateral hemianopsia. Findings from CSF analysis showed mild pleocytosis and oligoclonal IgG. Cranial and spinal MR imaging showed 24 lesions (5 with gadolinium enhancement). Her symptoms resolved without therapy. A week later, she was seen again with paralysis of the left leg and new lesions on MR imaging. Methylprednisolone was administered, and the symptoms disappeared. A fourth admission followed 1 month later because of double vision, intermittent headache, and paresthesia affecting both feet. Azathioprine therapy was commenced, and prednisolone therapy was added after a further episode. During the following 9 months, she had 4 relapses. Azathioprine and prednisolone treatments were discontinued, and interferon beta-1a (22 µg twice a week) was initiated. After a symptom-free period of 8 months, she experienced 4 further relapses within 1 year. The interferon beta-1a dosage was increased to 22 µg 3 times a week. During the next 2½ years, 7 further relapses occurred, with paresthesia of the hands and feet as residual symptoms. Between attacks, she reported frontal headaches, temperature spikes, concentration deficits, and tiredness, which were worse on the days following interferon beta-1a administration. As a result of this, she was unable to attend school for longer than 2 hours daily. At age 12 years, interferon therapy was discontinued, and natalizumab therapy was started at a dosage of 3 mg/kg every 4 weeks. It was well tolerated, and her general well-being improved significantly. She was able to attend school with success and to accomplish normal
daily activities. Her residual neurologic symptoms resolved. After 10 months of treatment, she had a short episode of seeing fine lines with both eyes, without other symptoms. Results of ophthalmologic examination, visual-evoked potentials, and cranial MR images were normal. JC (John Cunningham) virus infection was excluded by CSF polymerase chain reaction because the symptoms were not typical for optic neuritis.

CASE 3

Patient 3 was seen at age 13 years with headache, dizziness, and right-sided facial paralysis. Findings from CSF analysis were normal with no evidence of oligoclonal banding, but cranial MR imaging showed 31 hyperintense T2-weighted lesions, with gadolinium enhancement in 2 lesions. She received a treatment course of oral prednisolone, and her symptoms resolved. Three weeks later, she was seen again with headache, vomiting, nystagmus, and right-sided hemiplegia. Magnetic resonance imaging showed 5 new lesions, all with gadolinium enhancement. At 6 and 12 months of follow-up, she was clinically asymptomatic except for mild sensory disturbance affecting the right hand and the right leg. Because MR imaging showed multiple new hyperintense T2-weighted lesions, some with gadolinium enhancement, immunomodulatory therapy with interferon beta-1a (44 µg 3 times a week) was started. During the following 2 years, she reported several episodes (<24 hours) of blurred vision or paresthesia in the left hand or the right leg but no definite relapses. However, MR imaging continued to show disease activity. She reported multiple adverse effects related to therapy, including frontal headaches, tiredness, poor concentration, nausea, dizziness, abdominal pain, and depressive mood swings. Subsequently, her school performance declined. Because of ongoing disease activity seen on MR imaging and intolerable adverse effects, treatment with interferon beta-1a was discontinued. Because she refused treatment with glatiramer acetate, an intravenous regimen of natalizumab (300 mg [5 mg/kg]) every 4 weeks was begun. Within 3 months, the patient reported marked improvement in her physical and mental health. At 6 and 12 months of follow-up, she showed no signs of relapse or disease progression on MR imaging.

COMMENT

The patients described herein did not respond adequately to interferon beta or glatiramer therapy and had severe adverse effects. All patients had in common a very high lesion load at first attack and continuous signs of disease progression.
activity on MR imaging. Patients 1 and 2 had high relapse rates, indicating risk of developing a secondary progressive form of MS. Because natalizumab therapy has been found to be efficient as second-line therapy in adult RRMS, we decided to start off-label treatment. In patients 1, 2, and 3, the durations of treatment with natalizumab have been 24, 16, and 15 months, respectively. During this time, there was no clinical disease progression. Compared with MR images that had shown continuous signs of disease activity before treatment with natalizumab, no new hyperintense T2-weighted lesions or contrast-enhancing lesions were seen. All patients reported significantly improved quality of life and school performance. They were also relieved that they did not have to receive regular subcutaneous injections. Because poor compliance is a common problem in pediatric patients with MS, this point should be emphasized. Patient 1 was initially treated with the adult dosage of 300 mg but regularly experienced infections on the days following interferon beta-1a infusions. Therefore, we reduced the dosage, and the symptoms disappeared, indicating that the dosage of natalizumab needs to be adjusted to body weight in pediatric patients with MS. Patients 2 and 3, who initially received a dosage that was adjusted to their body weight, did not experience any adverse effects. Borriello et al recently described a 12-year-old girl who was treated for 12 months with natalizumab and had a similar favorable outcome. The question of the duration of natalizumab treatment remains open and will depend on future long-term safety and efficacy, as well as new treatment strategies. In patients who are clinically and radiologically stable for a defined period, further treatment regimens could possibly include reduction of natalizumab dosage or reverting to approved basic treatment such as interferons or glatiramer.

Natalizumab therapy has not been approved for use in patients younger than 18 years. However, the positive effect and the lack of adverse effects of natalizumab use in our pediatric patients and in the patient described by Borriello et al indicate that it is a promising drug not only for adults with MS but also for pediatric patients with MS. Furthermore, children and adolescents with MS are affected at an age that is critical to their physical, psychological, and social development. To prevent permanent damage, we need alternative drugs for those patients who do not respond to immunomodulatory therapies. Our limited experience with natalizumab therapy during 2 years indicates that it might be such a drug.

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