Allergic and Nonallergic Delayed Infusion Reactions During Natalizumab Therapy

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Background: The monoclonal antibody natalizumab is a novel therapeutic option in the treatment of relapsing forms of multiple sclerosis. In general, therapy with natalizumab is well tolerated. Allergic reactions and acute infusion reactions typically occur during or shortly after infusion, with a peak at the second infusion. Delayed infusion reactions resembling serum sickness–type reactions (type III reaction) are commonly reported in other monoclonal antibody therapies (eg, infliximab and rituximab), but are not described yet for natalizumab.

Results: Delayed infusion reactions occurred in 4 of 40 relapse-remitting multiple sclerosis patients treated with natalizumab.

Conclusions: Clinicians need to consider the occurrence of infusion reactions, with especially delayed reactions occurring more frequently than previously assumed. Our cases illustrate that some of these infusion reactions may be treated effectively with steroids and reduction of the infusion rate. In cases of antibody-mediated reactions, treatment should be stopped immediately.

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MONTHLY INFUSIONS OF 300 mg of the monoclonal α4 integrin antibody natalizumab reduces the relapse rate, lesion number, and progression of disability in patients with relapsing-remitting multiple sclerosis (RRMS).1 This therapy is generally well tolerated, with fatigue and headaches as the most common adverse events. Acute hypersensitivity reactions occur in about 4% of the patients, while severe anaphylactic reactions were reported in approximately 1%. Occurrence of persistent serum anti-natalizumab antibodies appeared in up to 6% of patients in the pivotal clinical trial, and is closely related to an increase in infusion-related adverse events and an almost complete loss of effectiveness.2 Generally, acute infusion reactions (type I reactions) occur during, or within a short interval after, the infusion. The onset is typically during or after the second natalizumab infusion.3 If acute hypersensitivity and antibody-mediated reactions occur in natalizumab-treated patients, the treatment should be discontinued. Delayed infusion reactions, such as serum sickness–type reactions (type III reactions), are more common in other monoclonal antibody therapies, such as infliximab and rituximab.3-6 In the case of natalizumab, type III reaction has been reported only in 1 patient.7,8 No data are available regarding the handling of severe, recurrent infusion reactions in natalizumab-treated RRMS patients who do not develop anti-natalizumab antibodies. There is some evidence from other monoclonal antibody or intravenous immunoglobulin therapies that prior steroid application or reduction of the infusion rate decrease the rate and severity of infusion reactions.9,10 Here we report our experience with natalizumab treatment in the first year of open-label treatment, with a specific focus on the types and frequency of severe acute and delayed infusion reactions.

METHODS

Anti-natalizumab antibodies were evaluated by standard sandwich enzyme-linked immunosorbent assay in our certificated clinical laboratory, as reported.1 We treated 40 RRMS patients (32 women, 8 men; mean [SD] age, 36.1 [8.1] years; mean [SD] duration of MS 8.6 [5.9] years; mean [SD] disability score [by Expanded Disability Status Scale], 3.7 [1.1]; mean [SD] number of infusions, 5.1 [1.6]) with natalizumab since July 2006. They received the...
standard dose of 300 mg of natalizumab dissolved in 100 mL of isotonic solution as an infusion for 1 hour. Every patient was observed for another hour following the infusion, which was repeated every 4 weeks. The onset of significant acute and delayed infusion reactions in 4 of 40 natalizumab-treated RRMS patients prompted this report.

CASE 1
A 38-year-old white female RRMS patient started natalizumab treatment after cessation of interferon beta, because of the adverse effects and ineffectiveness of intravenous immunoglobulin therapy. Her Expanded Disability Status Scale score increased from 3.5 to 4.5 owing to 2 relapses of residual brainstem symptoms during the preceding 8-month interval. Following the first natalizumab infusion that was tolerated without any complications, the patient developed arthralgia, followed by neck stiffness, fever up to 40°C, and general malaise later during the night. Tremor appeared, and vertigo increased within the next days. No clinical or serological signs of general viral infection or systemic autoimmune reaction were found. The symptoms almost disappeared within the next weeks. Later, the patient came in for the second natalizumab application. She reported residual symptoms (ie, fatigue and headache). With some delay, we hospitalized the patient to perform the second natalizumab infusion at a slower rate (100 mL/2 h) in combination with 250 mg of methylprednisolone administered intravenously on the days before and after the infusion. In addition, intravenous antihistaminic H1-blocker and histamine2-blocker therapy was administered. The natalizumab infusion was better tolerated; again the patient reported headache and fever (up to 38°C) in the night following the infusion, but these symptoms disappeared within a few days. Further natalizumab infusions were combined with a decreasing dosage of steroids and antihistaminic compounds, and the adverse effects were reduced each time. After the fifth natalizumab treatment with 125 mg of methylprednisolone, the patient remained free of symptoms. Antibodies against natalizumab were never found, despite repeated testing after each infusion. Since starting the treatment with natalizumab, the patient did not experience any relapses of MS.

CASE 2
The 43-year-old white female RRMS patient received natalizumab because of a high relapse rate during preceding interferon beta and glatiramer acetate treatment. Four days after the first infusion, she developed a fever of up to 38°C, a headache, and arthralgia lasting for 3 days. Thorough medical examination revealed no other underlying disease or signs of infection. When she came in 3 weeks later for the second natalizumab infusion, severe headache and neck pain occurred the day after the infusion. She then developed a fever of up to 40°C and severe pain in her knees and shoulders. No serological signs of infection or autoimmune reaction were found in a clinical screening. Symptoms lasted for about 4 weeks. Because we assumed there was a delayed infusion reaction, we administered a similar regimen as in case 1 with the third natalizumab infusion. The patient developed fewer pronounced clinical symptoms, with a fever (body temperature of up to 38.6°C), fatigue, eyelid edema, and headache lasting up to 3 days. All of these symptoms completely disappeared within the next fortnight. No antibody synthesis against natalizumab was found on repeated analyses. The next natalizumab infusion, 4 weeks later, was again combined with methylprednisolone treatment; at that time the patient’s temperature went up to 39°C, and joint stiffness and headache appeared for a period of only 2 days. Similar to our first case, this patient did not have any relapse since starting the treatment with natalizumab.

CASE 3
The 27-year-old white female RRMS patient was started on natalizumab because of a high relapse rate of 2 per year under therapy with interferon beta or glatiramer acetate, and a related high lesion load in the spinal cord. The first 4 natalizumab infusions were well tolerated and she only reported a mild migraine-like headache. No antibodies against natalizumab were detected after the fourth infusion. She described an increased frequency and severity of headaches during the 4 weeks following the fourth natalizumab infusion. The fifth natalizumab administration was accompanied by an acute anaphylactic reaction, with rash, dyspnea, and orthostatic syndrome. She then received a 250-mg intravenous methylprednisolone and antihistaminic treatment. Her main symptoms subsequently disappeared, but she still reported a feeling of tightness of the chest thereafter. We therefore hospitalized her for 1 day. Test results were positive for antibodies against natalizumab after the fifth infusion; the results were confirmed 2 months later. Natalizumab treatment was stopped after the fifth infusion.

COMMENT
Natalizumab, the first antibody approved in the treatment of RRMS, represents a dramatic improvement in our ability to treat RRMS patients affected by active disease. However, we observed in 10% of our patients significant and delayed infusion reactions, clinically resembling a serum sickness (type III) reaction, characterized by symptoms such as fever, headache, arthralgia, edema, and lymphadenopathy, progressing for several days, that have not yet been described in natalizumab-treated patients in this frequency and in detail. Importantly, the symptoms in antibody-positive and antibody-negative infusion reactions were clinically indistinguishable. Only 2 patients developed anti-natalizumab antibodies. In the other patients, adverse effects considerably decreased with concomitant steroid treatment that was tapered off during further natalizumab infusions. Such steroid administration generally improves the monoclonal antibody tolerability in combination with reduction of the infusion rate, but has not been described for natalizumab to
These patients remained clinically stable, and their adverse effects finally faded. In cases of antibody-mediated reactions, treatment should be stopped immediately.

The mode of action of the infusion reactions remains unclear. In analogy to polyclonal immunoglobulin infusion, this kind of reaction may be mediated by Fc receptor signaling and release of tumor necrosis factor α. Prior interferon beta therapy may also contribute to an increased prevalence of anti-natalizumab antibodies by supporting humoral immune responses. Therefore, we suggest screening for anti-natalizumab antibodies earlier or more frequently in patients with previous or current interferon beta exposure than in treatment-naive patients.

With the marked increase in the use of natalizumab, we expect an increasing number of patients with delayed infusion reactions. Therefore, it is important that neurologists associate the symptoms with natalizumab treatment. Our cases indicate that repeated measurement of antibodies against natalizumab can help to differentiate infusion reactions during natalizumab treatment. Of note, in none of the 4 patients were severe life-threatening reactions observed. Our cases may promote differential handling of natalizumab-associated infusion reactions among other clinicians. Antibody-negative patients’ delayed infusion reactions can be treated effectively with steroids and reduction of the infusion rate.

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REFERENCES