Failure of Natalizumab to Prevent Relapses in Neuromyelitis Optica

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Objective: To describe first experiences with the integrin inhibitor natalizumab, given to patients with suspected relapsing-remitting multiple sclerosis (MS) who were later diagnosed with aquaporin 4–positive neuromyelitis optica (NMO).

Design: Retrospective case series.

Setting: Neurology departments at tertiary referral centers in Germany.

Patients: Patients with NMO who tested positive for antibodies to aquaporin 4.

Intervention: Treatment with natalizumab.

Main Outcome Measures: Relapses and accumulation of disability.

Results: We identified 5 patients (4 female; median age, 45 years) who were initially diagnosed with MS and treated with natalizumab before diagnosis of NMO was established. Natalizumab was given as escalation therapy after failure of first- or second-line immunomodulatory therapies for MS. During natalizumab therapy (median duration, 8 infusions; range, 2-11 infusions), all 5 patients displayed persisting disease activity; a total of 9 relapses occurred (median duration to relapse, 120 days; range, 45-230 days) after the start of treatment. Four patients had an accumulation of disability and 1 patient died 2 months after cessation of natalizumab treatment.

Conclusions: Our results suggest that natalizumab fails to control disease activity in patients with NMO. Neuromyelitis optica should be considered as a differential diagnosis in patients with suspected MS who are unresponsive to natalizumab therapy.

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lapses during natalizumab therapy.

METHODS

PATIENTS

To identify patients with NMO who were treated with natalizumab, we used the network of the German Neuromyelitis Optica Study Group (http://www.nemos-net.de). This network is a nationwide open association of neurological centers interested in NMO/NMO spectrum disorders. It collects clinical features of such patients in a retrospective and prospective fashion approved by the institutional review boards of the participating academic centers and in accordance with the German data protection law. At the time of analysis, 133 patients with NMO or NMO spectrum disorders according to the revised 2006 criteria by Wingerchuk et al23 had been captured. In the present retrospective approach, we included all patients with confirmed NMO and IgG antibodies to AQP4 (AQP4-Abs) who had a history of treatment with natalizumab. We identified 5 patients at 4 university medical centers (Ruhr University Bochum, Ludwig-Maximilians-University Munich, Technische Universität München, Munich, and University Medical Center Regensburg). All patients had initially been diagnosed with relapsing-remitting MS, according to the McDonald criteria revised in 2005,26 before receiving natalizumab as an escalation therapy after failure of first- or second-line MS therapies.

Medical records were retrospectively assessed for disease duration, previous treatments, total number of relapses, exacerbations before, during, and after cessation of natalizumab, disability scored by the Expanded Disability Status Scale,21 duration until NMO diagnosis, and anti-AQP4 antibody titers. Brain and spinal cord magnetic resonance imaging (MRI) findings during and after therapy with natalizumab were reevaluated for MS- or NMO-typical lesions in the brain and spinal cord, in particular for longitudinally extensive spinal cord lesions extending over 3 vertebral segments. Furthermore, detailed clinical information was obtained with regard to the period of natalizumab treatment, cessation of natalizumab, and diagnosis of NMO. Clinical, radiological, and histopathological features of patient 5 have been described elsewhere in detail.25

AQP4 SEROLOGY

A recently described cell-based flow cytometry assay was used for quantification of serum AQP4-Abs by detection of the difference in median fluorescence intensity (ΔMFI).5

RESULTS

DEMOGRAPHICS AND CLINICAL FEATURES PRIOR TO NATALIZUMAB THERAPY

We identified 5 patients (4 female, 1 male) who had initially been treated with natalizumab for suspected relapsing-remitting MS but were subsequently diagnosed with AQP4-Abs–positive NMO (Table). The median disease duration at initiation of natalizumab was 9 years (range, 4-31 years) and the median age was 45 years (range, 35-56 years). All patients had experienced pronounced disease activity (median, 12 relapses; range, 6-40 relapses) prior to receiving natalizumab. Recurrent op-
relapses were generally severe, with paraparesis or hemiparesis due to myelitis in 4 patients and marked visual deterioration in 2. There was no apparent change in the pattern or severity of relapses compared with disease phases prior to natalizumab therapy. Furthermore, MRI showed new or gadolinium-positive active lesions during relapse in all 5 patients. Four patients had new spinal cord lesions; additionally, patients 1 and 5 showed atypical necrotic cerebral lesions. During natalizumab therapy, clinical disability as measured by the Expanded Disability Status Scale was stable in 1 patient and progressed in 4 patients by 1.0 to 4.5 points. The median Expanded Disability Status Scale score was 4.0 at the start of natalizumab therapy and 7.0 at the end. Patient 3 presented with an allergic reaction (and tested positive for anti-natalizumab-neutralizing antibodies) after the second infusion, and natalizumab therapy was discontinued. Natalizumab therapy was suspended in the other 4 patients because of persisting disease activity, as displayed by relapses and concomitant MRI alterations.
After natalizumab cessation, NMO was immediately confirmed in most patients (2-5) according to clinical, radiological, and serological criteria and 9 months later in patient 1. This patient had an atypical presentation with extensive bilateral white matter lesions and new cystic cortical lesions. The latter initially were suspected to be due to natalizumab-associated progressive multifocal leukoencephalopathy or other opportunistic viral infections, but repeated CSF and polymerase chain reaction examinations for a variety of viral, fungal, and parasitic pathogens including John Cunningham virus remained negative.

All patients tested positive for AQP4 (patients 2-5 during relapse), with a mean serum titer of 1978 MFI (range, 850-4023 MFI), which was about twice as high as the mean ΔMFI (1013 ΔMFI; range, 67-5604) from a recently published cohort of 52 patients with NMO or NMO spectrum disorders. The highest value was measured in patient 2, who was tested during natalizumab therapy, whereas patient 1 had the lowest value, obtained during remission 9 months after discontinuation of natalizumab therapy.

Simultaneously with cessation of natalizumab, 4 of 5 patients required plasma exchange because of only minor improvement in relapse-associated symptoms achieved with high-dose intravenous steroids. However, all of the 4 patients had further disease activity in the months following plasma exchange and experienced a clinically unfavorable course before NMO-specific immunotherapy was started. Both patients 1 and 5 had severe bilateral optic neuritis leading to blindness, and patient 5 had brainstem involvement and finally died after 2 months because of pneumonia. The 4 surviving patients subsequently received azathioprine (patient 1) or rituximab (patients 2, 3, and 4); 2 of them remained relapse-free thereafter (patients 1 and 3), and patient 4 stabilized. The mean annual relapse rate decreased from 3.2 (range, 3-4) in the year prior to natalizumab therapy and 3.0 (range, 2.4-6.0) during natalizumab therapy to 1.5 (range, 0-3) in the first year after natalizumab therapy. Patient 2 had further relapses despite therapy with rituximab, cyclophosphamide, and alemtuzumab. The Expanded Disability Status Scale at the last visit (median, 18 months after the end of natalizumab) decreased in patient 1, was stable in patients 3 and 4, and increased in patients 2 and 5.

In this study, we retrospectively analyzed the responses of 5 patients with NMO to natalizumab and found that this therapy, established for treatment of breakthrough disease in MS, did not show the anticipated beneficial effect. Our data indicate that relapse frequency was unchanged during natalizumab therapy, and most patients experienced severe exacerbations during and shortly after natalizumab treatment.

Neuromyelitis optica is a relapsing, often disabling disorder with a high mortality rate. Treatment of NMO mainly relies on immunosuppressive therapies such as azathioprine, methotrexate, mycophenolate mofetil, or mitoxantrone, as well as B-cell depletion with rituximab. Interferon beta, an immunomodulatory drug used as first-line therapy for relapsing-remitting MS, has been shown to be ineffective, even harmful in some cases. Natalizumab is an effective therapy for relapsing-remitting MS, which reduced the annual relapse rate by 69% in the pivotal placebo-controlled study. Recently published subgroup analyses of this phase 3 trial showed that 37% of patients treated with natalizumab, but only 7% of patients with placebo, were free of any detectable disease activity over 2 years, defined by the absence of relapses, sustained disability progression, gadolinium-enhancing lesions, and new or enlarging T2-hyperintense lesions on cranial MRI. Importantly, natalizumab was also effective in patients with highly active MS, defined as at least 2 relapses in the year before study entry and at least 2 gadolinium-enhancing lesions at study entry. In contrast, no reduction in relapse activity was found in our cohort of patients with NMO who were treated with natalizumab for suggested MS. Exacerbations of NMO during natalizumab treatment were severe, and all patients had further relapses shortly after cessation or removal of natalizumab therapy.

Natalizumab inhibits the migration of T and B cells to the CNS and causes a redistribution of lymphocyte subsets in the periphery. Whereas in the CSF the number of CD19+ B cells and CD138+ plasma cells is reduced for at least 6 months after infusion, the absolute number of mature CD19+ B cells is increased in the periphery by approximately 3-fold from month 1 of natalizumab treatment. Furthermore, levels of CD138+ plasma cells and, in particular, immature CD19+ CD10+ pre-B cells are elevated in the blood of natalizumab-treated patients. Total peripheral lymphocyte counts are increased as well, but only the relative frequencies of B cells increase, whereas frequencies of CD4+ T cells, CD8+ T cells, and CD16+CD56+ natural killer cells remain unaltered.

In recent years it has become clear that NMO is an antibody-mediated disease characterized by the occurrence of pathogenic AQP4- Abs, perivascular deposition of complement and immunoglobulin, and a subsequent...
The activity with the number of B cells only. Similarly, a marked damage can occur. Our data suggest that, even in the patient 1, cystic brain lesions indicating irreversible tissue damage can occur. Similar to an associate with an increase in AQP4-Abs, whereas another investigation showed a correlation of disease activity with the number of peripheral CD19+B cells, and breakthrough disease in patients with NMO who were treated with rituximab was found in a patient with NMO who was treated with interferon beta. However, owing to the retrospective design of our study, neither AQP4-Abs titers nor the number of B cells in the peripheral blood were measured before natalizumab therapy.

Alternative immunological mechanisms, which may contribute to therapy failure, include increased B-cell costimulation by activated T cells and enhanced recruitment of eosinophils. Natalizumab was shown to increase the frequency of T cells secreting proinflammatory cytokines such as tumor necrosis factor, interferon gamma, and interleukin 17, presumably by sequestration of these cells in the peripheral blood. In particular, the enhanced secretion of interleukin 6 might drive relapses, since the interleukin 6 level is increased in the blood and CSF of patients with NMO during exacerbations and promotes CD19+/CD27+/CD38+/CD180− plasmablasts to produce AQP4-Abs. Moreover, natalizumab increases the frequency of peripheral eosinophils, which were implicated in NMO pathogenesis.

Although the patients presented a clinical disease course compatible with NMO, they were initially diagnosed with relapsing-remitting MS, mainly because of the presence of brain lesions. Recently, the traditional concept of NMO as a disease affecting only the optic nerves and the spinal cord was revised, since histopathological and MRI findings demonstrated cerebral involvement in a high proportion of patients. Brain MRI lesions in NMO are usually asymptomatic, show a distribution pattern not compatible with the Barkhof/Tintore criteria, and sometimes present as tumefactive lesions. The existence of periventricular and callosal lesions does not exclude NMO, but extensive symmetric brain parenchymal lesions as seen in patient 1 are more frequent in NMO than in MS, and cloud-like enhancement seems to be a distinctive feature of NMO brain lesions. Similar to patient 1, cystic brain lesions indicating irreversible tissue damage can occur. Our data suggest that, even in the presence of white matter brain lesions, a diagnosis of NMO should be considered, particularly in cases with severe optic neuritis, absence of CSF oligoclonal bands, suspicious lesion distribution pattern, and lack of response to otherwise efficient MS therapies. As a cautionary note, our study was not able to exclude the possibility that some patients with NMO similarly misdiagnosed with MS experience a therapeutic benefit from natalizumab. Further studies with a different design will be required to address this issue.

In summary, we present the first evidence that natalizumab is not beneficial in NMO and might even exacerbate disease during or shortly after therapy. Our study emphasizes the distinct pathophysiology of MS and NMO and has clinical implications. Obviously, not all therapeutic approaches used for breakthrough disease in MS such as autologous hematopoietic stem cell transplantation or, in our observation, natalizumab may be beneficial for NMO. Thus, prior to therapy with natalizumab, the diagnosis of MS should be carefully reconfirmed, at least in patients with a primary opticospinal manifestation and unusual brain lesions. We propose testing for AQP4-Abs prior to initiation of natalizumab in all ambiguous cases, although AQP4-Abs might be undetectable in 20% to 30% of patients with NMO. If a patient with MS experiences relapses despite natalizumab therapy, one should consider not only inefficacy of the drug, neutralizing antibodies, or progressive multifocal leukoencephalopathy but also NMO.
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REFERENCES


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