Natalizumab Treatment in a Patient With Chronic Inflammatory Demyelinating Polyneuropathy

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Objective: To study clinical and paraclinical effects of natalizumab in a patient with chronic inflammatory demyelinating polyneuropathy (CIDP).

Design: Case report.

Setting: Department of Neurology, Heinrich-Heine University, Düsseldorf, Germany.

Patient: A patient with highly active CIDP who did not respond to standard therapies.

Intervention: Standard therapy then treatment with natalizumab (300 mg).

Main Outcome Measures: Clinical disability, magnetic resonance imaging, and saturation of the $\alpha_4$ integrin on T lymphocytes.

Results: T cells expressing the $\alpha_4$ integrin were found in the inflamed peripheral nerve. Natalizumab bound with high affinity to the $\alpha_4$ integrin on T lymphocytes in our patient. However, the patient’s clinical condition deteriorated and as seen on magnetic resonance imaging without any measurable effect after treatment with this antibody.

Conclusions: Although experimental evidence suggests that natalizumab could theoretically be effective in immune-mediated disorders of the peripheral nervous system, our patient with CIDP did not benefit from this therapeutic approach. Natalizumab cannot be recommended in CIDP at present and should only be explored in controlled clinical trials.


Natalizumab is a humanized monoclonal antibody against the $\alpha_4$ integrin approved for treating relapsing forms of multiple sclerosis. Experimental evidence in an animal model suggests that targeting $\alpha_4$ integrins in the inflamed peripheral nervous system may translate into clinical efficacy. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated disease in which an aberrant immune response, often T cell driven, is mounted against a yet unknown target antigen within the peripheral nerve. A number of immunomodulatory and suppressive treatment strategies, though generally not approved by regulatory authorities, are currently used for treating CIDP. However, clinical efficacy of these therapeutic approaches varies in the clinical subtypes of this disease, requiring different strategies, including individualized regimens of drug administration. Theoretically, there is a good rationale that natalizumab should be clinically effective in CIDP as well, yet clinical experience has not been reported so far.

REPORT OF A CASE

We report on the case of a 61-year-old woman with CIDP diagnosed 28 months before presentation. Clinical and paraclinical evidence for a paraneoplastic disorder was not given; a monoclonal gammopathy was excluded. The patient failed to respond to established treatment strategies, including steroids, azathioprine (discontinued after 8 months because of loss of hair), intravenous immunoglobulins, mycophenolate mofetil, and cyclophosphamide (Figure 1). Plasma exchange (PE) was the only therapeutic approach that resulted in transient clinical improvement. After a course of 5 cycles of PE within 10 consecutive days, mild tetraparesis remained. However, within 3 weeks the patient's condition deteriorated dramatically clinically and paraclinically (Table 1 and Table 2). She became paraplegic and required a new course of PE; she recovered with the remaining sequelae just described. The patient was referred to our center to explore alternative treatment options.

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Given the need for PE at high frequency and the lack of established alternative treatment choices, we considered natalizumab to be a therapeutic option. After discussing the experimental nature of this treatment and its potential adverse effects, informed consent was obtained and the patient was given a new course of PE followed by 300 mg of natalizumab intravenously. We were anticipating to stabilize the clinical course of the disease and to prolong the time to the next PE required. However, she did not respond clinically to natalizumab and showed measurable disease progression on the Inflammatory Neuropathy Cause and Treatment scale6 3 weeks after the infusion, requiring a new course of PE. Our clinical observation was shown on magnetic resonance imaging (Figure 2), where strong gadolinium enhancement of the roots was visible prior to PE, reduced enhancement was visible after PE and prior to the infusion of natalizumab, and reappearance of strong gadolinium uptake of the roots was visible 3 weeks after natalizumab. The patient progressed clinically and currently requires weekly PE.

**COMMENT**

We describe a case of highly active CIDP that further deteriorated despite initiation of anti-α4 integrin therapy with natalizumab. By labeling natalizumab with biotin and applying this antibody for immunohistochemistry on a sural nerve biopsy from a patient with CIDP, we were able to stain the α4 integrin on invading T cells (arrows). Green indicates anti-CD3-PE, phycoerythrin; red, natalizumab; and blue, 4,6-diamidino-2-phenylindol.

Table 1. Electrophysiological Assessments in a Patient With Chronic Inflammatory Demyelinating Polyneuropathy

<table>
<thead>
<tr>
<th>Date</th>
<th>Nerve</th>
<th>Conduction Velocity, m/s</th>
<th>Amplitude, mV</th>
<th>Distal Motor Latency, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2008</td>
<td>Right tibial nerve</td>
<td>8.8</td>
<td>0.4</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>Right median nerve</td>
<td>16.8</td>
<td>3.1</td>
<td>35.4</td>
</tr>
<tr>
<td>September 2008</td>
<td>Right tibial nerve</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Right median nerve</td>
<td>19.3</td>
<td>3.1</td>
<td>22.7</td>
</tr>
<tr>
<td>October 2008</td>
<td>Right tibial nerve</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Right median nerve</td>
<td>21.2</td>
<td>2.1</td>
<td>26.4</td>
</tr>
</tbody>
</table>

Table 2. Analysis of Cerebrospinal Fluid in a Patient With Chronic Inflammatory Demyelinating Polyneuropathy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF WBC count, /µL</td>
<td>2</td>
</tr>
<tr>
<td>CSF total protein, g/dL</td>
<td>23.4</td>
</tr>
<tr>
<td>CSF glucose, mg/dL</td>
<td>49</td>
</tr>
<tr>
<td>CSF lactate, mg/dL</td>
<td>10.5</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviation: NR, no response.

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; lactate to millimoles per liter, multiply by 0.111; protein to grams per liter, multiply by 10.0; and WBCs to \(^{10^9}/\text{L}\), multiply by 0.001.
ied the saturation of the α4 integrin on peripheral venous T lymphocytes from our patient before and after treatment with natalizumab by flow cytometry analysis (Figure 4) as described before. This analysis revealed clear evidence that natalizumab sufficiently binds to its target antigen on T cells and as such could have been effective in blocking inflammatory egress out of the blood vessels into the peripheral nervous system.

The role of α4 integrin in the inflamed peripheral nerve is not fully understood. Experimental studies in an animal model suggest that blocking this molecule translates into clinical disease amelioration and induction of apoptosis in invading T lymphocytes within the peripheral nervous system. Our patient, however, did not show any clinical or paraclinical indications that natalizumab was effective. The antibody has a high affinity to its target antigen and already a single infusion translates into measurable efficacy, as seen on magnetic resonance imaging in patients with multiple sclerosis. Thus, despite the short treatment we could probably have expected some degree of effectiveness of the drug already after a single infusion. In addition, long-term therapy with natalizumab obviously exerts some long-lasting immunomodulatory changes that clearly exceed the immediate effects on transmigration over a short period.

Given the clinical and immunopathologic heterogeneity of CIDP, this case report clearly does not exclude natalizumab from being effective in patients with another subform of this immune-mediated disease. At present, however, given its safety profile, the application of natalizumab cannot be recommended in CIDP and should only be explored in controlled clinical trials.

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REFERENCES