Interleukin 6 Receptor Blockade in Patients With Neuromyelitis Optica Nonresponsive to Anti-CD20 Therapy

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Objective: To report first experiences with interleukin 6 receptor inhibition in therapy-resistant neuromyelitis optica (NMO).

Design: Retrospective case series.

Setting: Neurology department at a tertiary referral center.

Patients: Patients with an aggressive course of NMO switched to tocilizumab after failure of anti-CD20 therapy.

Main Outcome Measures: Annualized relapse rate and disability progression measured by the Expanded Disability Status Scale.

Results: We report 3 female patients with a median age of 39 years (range, 26-40 years) and aquaporin 4-positive NMO. All patients had been treated with different immunosuppressive and immunomodulating agents, followed by 1 to 3 cycles of rituximab. Despite complete CD20-cell depletion during rituximab therapy, the median annualized relapse rate was 3.0 (range, 2.3-3.0) and the median Expanded Disability Status Scale score increased from 5.0 (range, 4.5-7.0) to 6.5 (range, 5.0-7.0). After the switch to tocilizumab (median duration of therapy, 18 months), the median annualized relapse rate decreased to 0.6 (range, 0.1-3.3). A total of 2 relapses occurred; however, they were mild and there were no changes in clinical disability.

Conclusions: Interleukin 6 receptor–blocking therapy can be effective in therapy-resistant cases of NMO. Larger controlled studies are needed to confirm the efficacy of tocilizumab.


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EUROMYELITIS OPTICA (NMO) is a rare, severely disabling autoimmune disease, preferentially affecting optic nerves and the spinal cord, structures highly expressing the target antigen aquaporin 4 (AQP4). Because of the severity of NMO attacks, prophylactic therapy must be started as soon as possible. Therapy response in NMO differs from that in multiple sclerosis; immunomodulatory medications (interferon beta and glatiramer acetate) seem to be not effective and natalizumab appears to even exacerbate disease activity. Several small studies and case report series demonstrated moderate efficacy of a number of immunosuppressive agents. More promising results have been shown for B cell–depleting therapy, yet approximately 20% of patients experience relapses despite the complete depletion of B cells.

Recently, specific AQP4-secreting plasmablasts exhibiting a CD19hi/CD77hi/CD38hi/CD180− phenotype have been described in NMO. Secretion of AQP4 antibodies by these cells is dependent on interleukin 6 (IL-6), a cytokine also known to be increased in NMO relapses. To evaluate if the IL-6 receptor–blocking antibody tocilizumab (ACTEMRA) could be a new therapeutic option for NMO, we analyzed the clinical course of 3 patients who were switched to tocilizumab after ongoing aggressive disease despite rituximab therapy.

METHODS

PATIENTS

Patients were identified from a cohort of 18 patients with confirmed NMO treated at a tertiary referral center. We searched for patients with aggressive disease who did not respond to rituximab therapy and had been switched to tocilizumab thereafter. Annual relapse rate and progression of disability, scored by the Expanded Disability Status Scale (EDSS), before
and during rituximab and tocilizumab treatment were analyzed. Routine brain and spinal cord magnetic resonance imaging was evaluated for contrast-enhancing new or enlarged lesions before and during both therapies.

**ETHICAL STATEMENT**

The presented 3 patients were treated on an individual basis according to internal recommendations. All data were analyzed retrospectively from patient files. All patients gave written informed consent for publication.

**RESULTS**

**DEMOGRAPHIC AND CLINICAL FEATURES**

Three female patients were diagnosed with AQP4 antibody–positive NMO (Table). All patients had longitudinal spinal cord lesions (>3 segments) and a history of optic neuritis and transverse myelitis. No intrathecal immunoglobulin synthesis or oligoclonal bands were in the cerebrospinal fluid of any of the 3 patients. No patient had concomitant autoimmune diseases. Previous long-term therapies included interferon beta-1a and 1b (n=2), glatiramer acetate (n=1), and mitoxantrone hydrochloride (n=1). All patients had experienced pronounced disease activity (median, 13 relapses; range, 4-16; median annualized relapse rate, 2.6; range, 1.7-2.7; median EDSS score, 5.0; range, 4.5-7.0) prior to receiving rituximab. The median disease duration at initiation of rituximab was 8.2 years (range, 2.5-9.4 years) and the median age was 39 years (range, 26-40 years).

**TREATMENT RESPONSE TO RITUXIMAB**

Rituximab was administered at a dose of 2000 mg/cycle (1000 mg + 1000 mg, patient 1) or 1500 mg/cycle (500 mg + 1000 mg, patients 2 and 3), with a 2-week interval between infusions. Patients 1 to 3 received rituximab for 32 (3 cycles), 8 (1 cycle), and 4 (1 cycle) months, respectively. Despite complete CD20-cell depletion, patients continued to experience relapses (median, 2; range, 1-4).

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### Table. Patients’ Baseline Characteristics and Clinical Course During Rituximab and Tocilizumab Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics at start of RTX treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Age, y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>Disease duration, y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.4</td>
<td>8.2</td>
<td>2.5</td>
</tr>
<tr>
<td>AQP4 Abs Positive</td>
<td>IFN beta-1b (2003-2006/10); mitoxantrone hydrochloride, 52 mg/㎡ (2006-2007/3)</td>
<td>IFN beta-1b (2004-2005/3); IFN beta-1a (2005-2006/1); glatiramer acetate (2006/3); IFN beta-1a (2006-2009/9)</td>
<td>No therapy (2009-2010/2); azathioprine (2010-2011/2)</td>
</tr>
<tr>
<td><strong>Total No. of previous relapses/estimated ARR&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>13/2.6</td>
<td>16/2.7</td>
<td>4/1.7</td>
</tr>
<tr>
<td><strong>RTX therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, mo</td>
<td>32</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>No. of CD19 cells during the first relapse, /μL</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No. of relapses/estimated ARR</td>
<td>6/2.3</td>
<td>2/3.0</td>
<td>1/3.0</td>
</tr>
<tr>
<td>Time from first application to the first relapse, d</td>
<td>18</td>
<td>137</td>
<td>40</td>
</tr>
<tr>
<td>EDSS score at start of RTX treatment</td>
<td>5.0</td>
<td>4.5</td>
<td>7.0</td>
</tr>
<tr>
<td>EDSS score at end of RTX treatment</td>
<td>6.5</td>
<td>5.0</td>
<td>7.0</td>
</tr>
<tr>
<td>MRI findings</td>
<td>Enlargement of spinal cord lesions with contrast enhancement</td>
<td>ND</td>
<td>Enlargement of spinal cord lesions with contrast enhancement</td>
</tr>
<tr>
<td><strong>TCZ therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, mo</td>
<td>21</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>No. of CD19 cells at start of TCZ treatment, /μL</td>
<td>44</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>No. of relapses/estimated ARR</td>
<td>1/0.6</td>
<td>0</td>
<td>1/1.3</td>
</tr>
<tr>
<td>EDSS score at start of TCZ treatment</td>
<td>6.5</td>
<td>5.0</td>
<td>7.0</td>
</tr>
<tr>
<td>EDSS score at the last visit</td>
<td>6.5</td>
<td>4.0</td>
<td>7.0</td>
</tr>
<tr>
<td>MRI/time since start of TCZ treatment, mo</td>
<td>No new lesions, no contrast enhancement/12</td>
<td>No new lesions, no contrast enhancement/9</td>
<td>No new lesions, no contrast enhancement/7</td>
</tr>
</tbody>
</table>

Abbreviations: Abs, anti–AQP4 antibodies; AQP4, aquaporin 4; ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; IFN, interferon; MRI, magnetic resonance imaging; ND, not determined; RTX, rituximab; TCZ, tocilizumab.

<sup>a</sup>Relative to start of RTX treatment.

<sup>b</sup>Treatments appear in chronological order.
1-6), with at least 1 severe relapse, defined by an EDSS score progression of 1.0 or more; the median annualized relapse rate was 3.0 (range, 2.3-3.0) (Table and Figure). Interestingly, in 2 patients, relapses occurred shortly after the first application of rituximab (after 18 and 40 days). Magnetic resonance imaging confirmed acute gadolinium-enhancing spinal lesions in patients 1 and 3. The clinical disability progressed in patients 1 and 2 by 1.5 and 0.5 points, respectively, and remained unchanged, with an EDSS score of 7.0, in patient 3.

**TREATMENT RESPONSE TO TOCILIZUMAB**

Because of ongoing disease activity, patients were further switched to the anti–IL-6 receptor antibody tocilizumab. Tocilizumab was administered at a dose of 6 mg/kg every 6 weeks in patients 1 and 2 and every 4 weeks in patient 3. Duration of tocilizumab therapy was 21, 18, and 9 months in patients 1 to 3, respectively. Patient 2 was relapse-free and demonstrated improvement of her gait and EDSS score from 5.0 to 4.0 (Table and Figure). Two patients experienced a mild relapse without EDSS score progression, clinically presenting as isolated optic neuritis in patient 1 and moderate progression of the pre-existing motor deficit in patient 3. The relapses occurred 3 and 4 months after tocilizumab treatment initiation, respectively. In both cases, deficits were reversible after receiving steroid pulse therapy. After the therapy regimen in patient 1 had been changed from every 6 to every 4 weeks, she was stable for the next 18 months. Compared with rituximab therapy, the median annualized relapse rate decreased from 3.0 (range, 2.3-3.0) to 0.6 (range, 0-1.3). Tocilizumab therapy was ongoing in all 3 patients.

Tocilizumab was well tolerated. There was no serious infection, malignancy, hypersensitivity reaction, or elevation of transaminase levels. Patient 3 experienced urinary tract infection in the fourth month and mild oral mucositis in the seventh month of therapy. Cholesterol levels had been elevated in patients 1 and 3 prior to tocilizumab therapy and demonstrated no significant increase after therapy initiation.

In this case series, we demonstrated the efficacy of the anti–IL-6 receptor antibody tocilizumab in rituximab-refractory, aggressive cases of NMO. The exact mechanism of action of rituximab in NMO remains unknown. Despite complete depletion of CD20+ B cells, it spares CD20-negative plasma cells and has only moderate and probably indirect effects on antibody production.5,6 Other rituximab effects include monocyte activation and increased synthesis of B-cell activating factor, a key molecule supporting differentiation and survival of B cells as well as immunoglobulin production.5,6 In line with this, an early transient increase of AQP4 antibodies after rituximab application has been reported.10 Notably, in 2 of our patients, relapses occurred early after rituximab initiation.

Inhibition of CD20-negative plasmablasts, which produce pathogenic AQP4 antibodies, might be an alternative treatment strategy. In the presented cases, a switch to tocilizumab led to definite clinical improvement. Recently, another patient successfully treated with tocilizumab was reported by Araki et al.11 They demonstrated a substantial reduction of the frequency of CD19intCD27highCD38highCD18− plasmablasts and titer of anti–AQP4 antibodies within 1 month after tocilizumab initiation. Similarly, tocilizumab decreased the frequency of CD27highCD38highIgD− plasmablasts and the titer of anti–double-stranded DNA antibodies in systemic lupus erythematosus as well as titers of rheumatoid factor in patients with rheumatoid arthritis.12

Despite overall clinical stabilization, mild relapses occurred in 2 of our patients as well as in the Araki et al case.11 In patient 1, we reduced the application intervals from every 6 to 4 weeks and the patient was relapse-free afterward. Accordingly, an escalation study demonstrated further clinical improvement in rheumatoid arthritis after dose escalation from 4 to 8 mg/kg.13

As demonstrated in rheumatoid arthritis, tocilizumab has a good safety and tolerability profile. Infections are the most common adverse events; however, rates of serious infections remain low at least for 5 years, demonstrating safety of continuous tocilizumab therapy.13 Possible tuberculosis reactivation and opportunistic infections make careful observations essential. Importantly, C-reactive protein is directly downregulated by tocilizumab and cannot be used as a sensitive diagnostic marker. In our patients, no serious adverse events were observed. Reported urinary tract infection and mild oral mucositis have been treated on an ambulatory basis without any complications.

We propose that IL-6 receptor blockade with tocilizumab is a promising therapeutic option for aggressive, therapy-resistant cases of NMO. Larger controlled studies with longer follow-up periods are needed to confirm the efficacy, safety, and optimal responders for tocilizumab in NMO.
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Drafting of the manuscript: Ayzenberg and Kleiter. Critical revision of the manuscript for important intellectual content: Ayzenberg, Kleiter, Schröder, Hellwig, Chan, Yamamura, and Gold. Administrative, technical, and material support: Hellwig, Chan, and Gold. Study supervision: Kleiter and Gold.

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REFERENCES


