Long-term Therapy With Interleukin 6 Receptor Blockade in Highly Active Neuromyelitis Optica Spectrum Disorder

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IMPORTANCE Neuromyelitis optica (NMO) is characterized by disabling relapses of optic neuritis and myelitis and the presence of aquaporin 4 antibodies (AQP4-abs). Interleukin 6, which is significantly elevated in serum and cerebrospinal fluid of patients with NMO, induces AQP4-ab production by plasmablasts and represents a novel therapeutic target.

OBJECTIVE To evaluate the long-term safety and efficacy of tocilizumab, a humanized antibody targeting the interleukin 6 receptor, in NMO and NMO spectrum disorder.

DESIGN, SETTING, AND PARTICIPANTS Retrospective observational study with 10 to 51 months of follow-up between December 2010 and February 2015, in neurology departments at tertiary referral centers. Participants were 8 female patients of white race/ethnicity with highly active AQP4-ab-seropositive NMO (n = 6) and NMO spectrum disorder (n = 2) whose disease had been resistant to previous medications, including B-cell depletion, and who switched to tocilizumab (6-8 mg/kg of body weight per dose).

MAIN OUTCOMES AND MEASURES Annualized relapse rate, Expanded Disability Status Scale score, spinal cord and brain magnetic resonance imaging, AQP4-ab titers, pain levels (numerical rating scale), and adverse effects.

RESULTS Patients were followed up for a mean (SD) of 30.9 (15.9) months after switching to tocilizumab. Two of eight patients received add-on therapy with monthly corticosteroid pulses (temporary) or azathioprine, respectively. During tocilizumab treatment, the median annualized relapse rate significantly decreased from 4.0 (interquartile range, 3.0-5.0) in the year before tocilizumab therapy to 0.4 (interquartile range, 0.0-0.8) (P = .008), and the median Expanded Disability Status Scale score significantly decreased from 7.3 (interquartile range, 5.4-8.4) to 5.5 (interquartile range, 2.6-6.5) (P = .03). Active magnetic resonance imaging lesions were seen in 6 of 8 patients at tocilizumab initiation and in 1 of 8 patients at the last magnetic resonance imaging. Three patients remained relapse free during tocilizumab treatment. In 5 patients, a total of 8 relapses occurred, 4 within the first 2½ months of therapy. Five attacks were associated with delayed tocilizumab administration (>40 days), and 6 attacks were associated with reduced tocilizumab dosage (6 vs 8 mg/kg). The AQP4-ab titers (P = .02) and pain levels (P = .02) dropped significantly during tocilizumab treatment. Adverse effects included moderate cholesterol elevation in 6 of 8 patients, infections in 4 of 8 patients, and deep venous thrombosis and neutropenia in one patient each.

CONCLUSIONS AND RELEVANCE Prolonged tocilizumab therapy may be safe and effective from early treatment phases onward for otherwise therapy-resistant highly active NMO and NMO spectrum disorder. Relapse patterns indicate that adherence to a regular therapeutic regimen with monthly infusions of tocilizumab (8 mg/kg) may increase efficacy.
IL-6 Receptor Blockade in Highly Active Neuromyelitis Optica Spectrum Disorder

Original Investigation Research

Euromyelitis optica (NMO) is a severe inflammatory disease of the central nervous system characterized by relapsing optic neuritis and longitudinally extensive transverse myelitis, with frequently poor recovery.1,2 Acute NMO attacks are usually treated with high-dose corticosteroids or require escalation therapy with plasma exchange.3 However, relapse prevention remains a challenging issue in NMO because established multiple sclerosis therapies such as interferons, natalizumab, and fingolimod have been reported to show little efficacy or even to be detrimental.4-6 According to smaller case series or retrospective cohort studies, long-term immunosuppression with azathioprine7 or mycophenolate mofetil8 is recommended for mild NMO cases, with methotrexate being an alternative treatment option.9 In patients with more severe NMO courses, rituximab10 and mitoxantrone hydrochloride11 have been reported to diminish the relapse frequency. However, in these retrospective case series, some patients with NMO manifested persistent disease activity or experienced major adverse effects, rendering additional potent and well-tolerable medicaments desirable.

The autoantibody against aquaporin 4 (AQP4-ab), highly specific for NMO and its spectrum disorder (NMOSD),12-13 has been suggested to contribute to the pathogenesis of the disease, and the related B-cell–mediated immune processes were considered a potential target for future therapeutic interventions. Increased interleukin 6 (IL-6) levels were detected in serum and cerebrospinal fluid (CSF) of patients with NMO, particularly during relapses.14 Interleukin 6 promotes AQP4-ab production and secretion from B-cell–derived plasmablasts, whereas the blockade of IL-6 receptor signaling by an anti–IL-6 receptor antibody reduces the survival of plasmablasts in vitro.15 Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor approved for treatment of rheumatoid arthritis,16 recently showed beneficial clinical and paraclinical effects in single patients with NMO and in one prospective cohort for treatment periods of 12 to 24 months.17-22

The aim of this retrospective multicenter study was to evaluate the long-term safety and efficacy of tocilizumab in patients with highly active NMO. The patients had not adequately responded to previous first-line and second-line treatments.

Methods

Patients and Treatment

Eight female patients of white race/ethnicity with AQP4-ab seropositive NMO (n = 6) and NMOSD (n = 2) diagnosed according to current criteria22,23 were retrospectively analyzed at the German departments of neurology at Heinrich Heine University Düsseldorf, St Josef Hospital at Ruhr University Bochum, German Diagnostic Clinic in Wiesbaden, and Clinic Osnabrück. All 6 patients with NMO had experienced 1 or more previous episodes of longitudinally extensive transverse myelitis and optic neuritis. In the 2 patients with NMOSD, no episodes of optic neuritis were reported, but recurrent longitudinally extensive transverse myelitis, 2 cerebellar attacks, and one brainstem attack had occurred. Before beginning tocilizumab therapy, all patients had been pretreated with immunomodulatory or immunosuppressant medications, including interferon beta-1b (n = 3), interferon beta-1a (n = 2), azathioprine (n = 2), mitoxantrone (n = 2), mycophenolate mofetil (n = 1), natalizumab (n = 1), glatiramer acetate (n = 1), alemtuzumab (n = 1), and monthly intravenous corticosteroids (250 mg/mo) (n = 1). Rituximab had been administered at least once to every patient before tocilizumab therapy, with a range of 1 to 3 therapeutic cycles comprising 1 to 2 infusions per cycle. Patient 1 received 1 cycle of 1500 mg, followed by 2 cycles of 1000 mg in yearly intervals (Table). Patients 2 and 4 received 1 cycle of 1500 mg. Patients 3, 5, and 6 received 1 cycle of 1000 mg. Patients 7 and 8 received 2 cycles of 1000 mg with a 2-week interval. Tocilizumab was initiated in 4 of 8 patients at a reduced dosage of 6 mg/kg of body weight in 4-week intervals and was switched to 8 mg/kg in 2 of 4 patients after relapses had occurred. The reduced dosage was chosen by the treating physicians for safety reasons. In the other 4 patients, tocilizumab was continuously administered from the beginning of treatment at a higher dosage of 8 mg/kg at regular 4-week intervals. On some occasions, intervals between tocilizumab administration were prolonged (eg, due to holidays, missed appointments, or patient request). Among 8 patients, 5 had been previously reported in single case studies or smaller series on the effect of short-term tocilizumab intervention of 12 to 24 months: these included patients 1, 2, and 4 in a 2013 study,18 patient 3 in another 2013 study,17 and patient 5 in a 2014 study.23 This study was approved by the local ethics committees in Düsseldorf and Bochum as part of an observational study examining the treatment and disease course of NMO. All participants gave written informed consent.

Study Design

This was a retrospective observational study with 10 to 51 months of follow-up between December 2010 and February 2015 in neurology departments at tertiary referral centers. All clinical and paraclinical data were analyzed retrospectively by medical record review. Since beginning rituximab therapy, all patients had been treated continuously at one of the participating tertiary referral centers, all specialized in multiple sclerosis care, ensuring the regular assessment of clinical data (attacks and Expanded Disability Status Scale [EDSS] score)24 and paraclinical data (magnetic resonance [MR] imaging, AQP4-ab titers, and other laboratory tests). The primary outcome was the annualized relapse rate (ARR), calculated as the total number of attacks per patient, divided by the total observation time in years. An acute attack was defined as a new neurological worsening lasting for at least 24 hours and occurring more than 30 days after the previous attack. Laboratory tests, performed at regular intervals of 4 to 6 weeks during the first 6 months and quarterly thereafter, included complete blood cell count, electrolytes, kidney values, liver enzymes, C-reactive protein, coagulation status, and lipid values, including total cholesterol and high-density and low-density cholesterol levels. The AQP4-ab titers were tested by a cell-based assay35 before tocilizumab initiation (n = 6) or within the first year of tocilizumab treatment (n = 2) and were retested during the last 3 tocilizumab treatment months. Pain levels were measured with a numerical rating scale, ranging from 0 (no pain) to 10.
Table. Cohort of Patients With Neuromyelitis Optica (NMO) or Neuromyelitis Optica Spectrum Disorder (NMOSD) Receiving Tocilizumab Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>NMO</td>
<td>NMO</td>
<td>NMO</td>
<td>NMO</td>
<td>NMOSD</td>
<td>NMO</td>
<td>NMO</td>
<td>NMOSD</td>
</tr>
<tr>
<td>Age at tocilizumab initiation, y (date of first dose)</td>
<td>43 (December 2010)</td>
<td>27 (April 2011)</td>
<td>36 (July 2011)</td>
<td>39 (January 2012)</td>
<td>31 (October 2012)</td>
<td>48 (October 2013)</td>
<td>25 (December 2013)</td>
<td>49 (April 2014)</td>
</tr>
<tr>
<td>Disease duration before tocilizumab initiation, y</td>
<td>12.1</td>
<td>8.8</td>
<td>5.5</td>
<td>2.8</td>
<td>8.9</td>
<td>24.0</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Immunomodulatory or immunosuppressant therapy before tocilizumab initiation</td>
<td>Interferon beta-1b, mitoxantrone hydrochloride, rituximab</td>
<td>Interferon beta-1b, interferon beta-1a, glatiramer acetate, interferon beta-1a, rituximab</td>
<td>Interferon beta-1b, interferon beta-1a, mitoxantrone hydrochloride, alemtuzumab, trimcinolone</td>
<td>Mycophenolate mofetil, rituximab</td>
<td>Azathioprine, rituximab</td>
<td>Natalizumab, rituximab</td>
<td>Azathioprine, interferon beta-1b, interferon beta-1a, methylprednisolone, rituximab</td>
<td>Rituximab</td>
</tr>
<tr>
<td>No. of tocilizumab cycles (treatment time until the last follow-up)</td>
<td>46 (51.0 mo)</td>
<td>38 (46.9 mo)</td>
<td>46 (43.4 mo)</td>
<td>32 (37.1 mo)</td>
<td>31 (28.1 mo)</td>
<td>18 (16.6 mo)</td>
<td>14 (14.4 mo)</td>
<td>10 (10.0 mo)</td>
</tr>
<tr>
<td>Tocilizumab dosage, mg/kg</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>8</td>
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<td>Treatment intervals, wk</td>
<td>4-5</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>No. of attacks before tocilizumab initiation</td>
<td>19 (6 ON, 13 myelitis)</td>
<td>18 (2 ON, 16 myelitis)</td>
<td>14 (4 ON, 10 myelitis)</td>
<td>5 (2 ON, 3 myelitis)</td>
<td>11 (8 Myelitis, 1 cerebellar, 2 brainstem)</td>
<td>17 (8 ON, 8 myelitis, 1 cerebral)</td>
<td>5 (1 ON, 4 myelitis)</td>
<td>age 3 Myelitis</td>
</tr>
<tr>
<td>No. of attacks during tocilizumab therapy (time after tocilizumab initiation)</td>
<td>2 (1½ and 23 mo)</td>
<td>1 (33 mo)</td>
<td>0</td>
<td>2 (2½ and 8 mo)</td>
<td>0</td>
<td>0</td>
<td>1 (2 mo)</td>
<td>2 (2 and 8½ mo)</td>
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<td>ARR before tocilizumab initiation during entire disease duration</td>
<td>1.6</td>
<td>2.1</td>
<td>2.5</td>
<td>2.5</td>
<td>1.2</td>
<td>1.2</td>
<td>0.7</td>
<td>5.5</td>
</tr>
<tr>
<td>ARR before tocilizumab initiation during last 12 mo</td>
<td>3.0</td>
<td>3.0</td>
<td>7.0</td>
<td>1.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0*</td>
</tr>
<tr>
<td>ARR during tocilizumab therapy</td>
<td>0.5</td>
<td>0.3</td>
<td>0.0</td>
<td>0.6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.8</td>
<td>2.4</td>
</tr>
<tr>
<td>MR imaging at tocilizumab initiation</td>
<td>No active spinal and brain lesions</td>
<td>Active spinal lesion, no active brain lesions</td>
<td>Active spinal lesion, normal brain MR imaging</td>
<td>No active spinal and brain lesions</td>
<td>Active spinal lesion, no active brain lesions</td>
<td>Active spinal lesion, normal brain MR imaging</td>
<td>Active spinal lesion, normal brain MR imaging</td>
<td>Active spinal lesion, normal brain MR imaging</td>
</tr>
<tr>
<td>Findings on last MR imaging (time after tocilizumab initiation)</td>
<td>No new or active spinal lesions (47 mo)</td>
<td>No new or active spinal lesions (33 mo)</td>
<td>No new or active spinal lesions (41 mo), normal brain MR imaging (29 mo)</td>
<td>No new or active spinal lesions (34 mo)</td>
<td>No new or active spinal lesions (14 mo)</td>
<td>No new or active spinal lesions (12 mo)</td>
<td>No new or active spinal lesions, normal brain MR imaging (3 mo)</td>
<td>No new or active spinal lesions, normal brain MR imaging (3 mo)</td>
</tr>
<tr>
<td>Tocilizumab adverse effects</td>
<td>Transient diarrhea, deep venous thrombosis</td>
<td>Recurrent UTI during self-catheterization</td>
<td>None</td>
<td>Headache, fatigue</td>
<td>None</td>
<td>Transient mild fatigue</td>
<td>Mild postinfusion nausea, transient gastritis, recurrent UTI</td>
<td>Recurrent UTI</td>
</tr>
<tr>
<td>Laboratory abnormalities during tocilizumab therapy</td>
<td>Recurrent C-reactive protein, cholesterol</td>
<td>Mild cholesterol</td>
<td>Cholesterol</td>
<td>Mild liver enzyme, mild cholesterol</td>
<td>Mild lipase</td>
<td>Cholesterol, leukopenia</td>
<td>Transient transaminitase, cholesterol</td>
<td>Leukopenia, neutropenia during azathioprine comedication</td>
</tr>
</tbody>
</table>

Abbreviations: ARR, annualized relapse rate; MR, magnetic resonance; ON, optic neuritis; UTI, urinary tract infection; ↑, increasing. * The disease duration before tocilizumab initiation of patients 7 and 8 was less than 1 year.
Results

We identified 8 AQP4-ab–seropositive female patients of white race/ethnicity with NMO (n = 6) or NMOSD (n = 2). Mean ages were 29.4 (9.9) years at disease onset and 37.3 (9.1) years at first tocilizumab administration, with a mean disease duration of 7.9 (7.7) years (Table). The mean number of attacks before tocilizumab treatment was 11.5 (6.5). All patients had high disease activity and had failed to respond to previous therapies, including B-cell depletion with rituximab (Figure 1).

At the time of treatment initiation with tocilizumab, B-cell numbers were still reduced in 7 patients (mean, 1.4% [1.3%] relative amount of CD19+ B cells) but had normalized in 3 of 5 patients tested again after 4.6 (3.0-15.5) months. Spinal cord MR imaging revealed longitudinally extensive transverse myelitis in all patients, with gadolinium-enhancing lesions in 6 of 8 patients. Brain MR imaging was unremarkable in 3 of 8 patients and showed nonspecific nonactive white matter lesions in 5 of 8 patients.

A mean of 29.4 (14.0) tocilizumab infusions during a mean follow-up time of 30.9 (15.9 months) was administered at a dosage of 6 or 8 mg/kg. Patient 3 received the first 8 tocilizumab infusions in combination with intravenous prednisolone sodium succinate (1 g) because of persisting spinal cord MR imaging activity with gadolinium-enhancing lesions, and patient 8 was treated with add-on azathioprine (100 mg) following a relapse after the second tocilizumab infusion. No other additional immunomodulatory or immunosuppressant medications were administered.

The median ARR over the entire disease duration before tocilizumab initiation was 2.0 (1.3-4.8), which increased in the year before tocilizumab initiation to 4.0 (3.0-5.0). During tocilizumab treatment, the ARR dropped significantly to 0.4 (0.0-0.8) (P = .008) (Figure 2). Three patients remained relapse free during tocilizumab treatment. In 5 patients, a total of 8 relapses occurred. Four of eight relapses occurred during the first 2½ months after tocilizumab initiation (40, 54, 58, and 74 days after tocilizumab initiation). These 4 relapses occurred at a dosage of 6 mg/kg in 3 patients (one each with optic neuritis, mild sensorimotor hemiparesis, and myelitis) and at a dosage of 8 mg/kg in one patient (with myelitis at 54 days after infusion). Three relapses (all in patients receiving 6 mg/kg of tocilizumab) manifesting as hemisensory syndrome in 2 patients and severe myelitis in one patient occurred 8, 23, and 33 months after the first tocilizumab infusion. Another relapse (worsen-
ing of paraparesis) occurred after a 55-day interval due to leukopenia and neutropenia in a patient concomitantly treated with azathioprine. Therefore, 6 of 8 relapses occurred when receiving a reduced tocilizumab dosage of 6 mg/kg, and 5 of 8 attacks occurred after prolongation of the infusion interval to 40 days or longer. However, there were 31 additional prolongations of the infusion interval to 40 days or longer in 4 other patients that did not result in further attacks.

All 8 relapses were initially treated with high-dose intravenous methylprednisolone hydrogensuccinate (1000 mg for 2-5 days). This was followed by rescue therapy in 5 patients, including plasma exchange or immunoadsorption using tryptophan as an adsorber (TR-350; Diamed Medizintechnik GmbH) in 4 attacks, an additional corticosteroid pulse with 4 cycles of 2000 mg in 2 attacks, and intrathecal application of corticosteroids in one attack. This treatment led to complete remission of 7 attacks and to persisting deficits after a severe case of myelitis in patient 2.

Disability measured by the EDSS score improved from 7.3 (5.4-8.4) at tocilizumab initiation to 5.5 (2.6-6.5) at the last follow-up ($P = .03$) (Figure 3). Six patients had a lower EDSS score, and no patient’s condition deteriorated. In patients 4 and 5, the EDSS score had improved 16 and 21 months after the last relapse, respectively.

The median, interquartile range, and range are shown. The median annualized relapse rate significantly decreased from 4.0 (interquartile range, 3.0-5.0) in the year before tocilizumab therapy to 0.4 (interquartile range, 0.0-0.8) during tocilizumab therapy ($P = .008$).

### Figure 2. Annualized Relapse Rate Before and During Tocilizumab Therapy

The annualized relapse rate was significantly lower during tocilizumab therapy compared to the year before therapy ($P = .008$).

### Figure 3. Features of Disease Activity Before and During Tocilizumab Therapy

**A** Expanded Disability Status Scale (EDSS) scores. **B**, Alterations of aquaporin 4 antibody (AQP4-ab) titers. **C**, Alterations of pain severity assessed by a numerical rating scale. **D**, Alterations of EDSS scores between tocilizumab initiation and the last follow-up.
Pain was mainly reported as neuropathic pain. Pain levels decreased significantly from a median of 6.5 (5.0–7.0) at tocilizumab therapy initiation to 2.5 (0.3–4.5) at the last follow-up (P = .02) (Figure 3). Seven of eight patients had less pain at the last follow-up, with 2 of them completely pain free. Four patients received continuous pain medication with carbamazepine (n = 1); amitriptyline hydrochloride (n = 1); combinations of nalozone hydrochloride, oxycodone hydrochloride, and tetrahydrocannabinol (n = 1); or combinations of amitriptyline, pregabalin, tidilidin hydrochloride, and nalozone (n = 1). Two other patients were treated by request with gabapentin or acetysalicilic acid and paracetamol, respectively, and 2 patients were taking no pain medication at the last visit. During tocilizumab treatment, AQP4-ab titers dropped significantly from a median of 1:1000 to 1:66 (P = .02).

Active MR imaging lesions were seen in 6 of 8 patients at tocilizumab initiation and in 1 of 8 patients at the last MR imaging. Follow-up MR imaging revealed no active T1-weighted or new T2-weighted lesions in 6 patients with spinal cord MR imaging and 3 patients with cranium MR imaging available in the last year of tocilizumab therapy. Exceptions were persisting active spinal cord lesions in patient 3 during the initial treatment period and an active spinal lesion in patient 6 at 14 months after tocilizumab initiation.

During tocilizumab therapy, mild postinfusion nausea (n = 1), transient gastritis (n = 1), transient diarrhea (n = 1), headache (n = 1), fatigue (n = 2), and recurrent urinary tract infections (n = 3) were reported by the patients. Patient 1 had deep venous thrombosis of the right leg 3 years after tocilizumab initiation. However, no severe infections or other tocilizumab-related major adverse effects occurred. No further laboratory abnormalities were observed except for transient mild liver enzyme increase in 3 patients, recurrent C-reactive protein elevation in one patient (due to NMO attacks twice, venous catheter-associated infection once, and deep venous thrombosis once), leukopenia or neutropenia in 2 patients (in one patient during azathioprine comedication), and elevation of cholesterol levels in 6 patients.

Discussion

Neuromyelitis optica attacks are often disabling and result in a poor recovery. While therapeutic interventions with immunosuppressive drugs can reduce the frequency of NMO relapses,3,7-11 individual patients in most studies did not respond sufficiently to treatment or experienced major adverse effects. Therefore, better preventive NMO therapies are desirable. Herein, we present data demonstrating successful long-term treatment with the anti-IL-6 receptor antibody tocilizumab in 8 female patients with NMO or NOMSD who had failed to improve with several previous medications, including the B-cell-depleting antibody rituximab.

Tocilizumab is approved for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. In both diseases, increased serum IL-6 levels have been shown to promote synovitis and induce progressive bone resorption and cartilage degeneration.40 Interleukin 6 also mediates inflammation, demyelination, and astrogliosis in the central nervous system.26 It is secreted primarily by activated astrocytes in the setting of infection, stroke, or inflammation.26 In patients with transverse myelitis, IL-6 levels are elevated in the CSF and directly correlate with total nitrite oxide production, spinal cord tissue injury, and long-term clinical disability.27 In patients with NMO, increased levels of IL-6 were detected in the CSF and serum, particularly in AQP4-ab-seropositive patients with severe disease activity.14 Using an ex vivo spinal cord organotypic section model, NMO IgG-mediated AQP4 loss and demyelination in the presence of IL-6 were markedly increased.28 Finally, IL-6 enhances survival and AQP4-ab synthesis of the CD19 (intermediate), CD27 (high), CD38 (high), and CD180 (negative) phenotype plasmablasts, which were shown to circulate at increased levels in the peripheral blood of patients with NMO.15 Therapeutic inhibition of the IL-6–IL-6 receptor axis with tocilizumab reduced the level of AQP4-ab in the serum of patients with NMO.19-21 Several case reports17-19,21 (6 patients) and one recent prospective pilot study20 (7 patients) demonstrated that tocilizumab administered for 12 to 24 months also reduced clinical and MR imaging disease activity of NMO.

Our longitudinal cohort extends these observations to a treatment time of up to 51 months (a total of 235 tocilizumab infusions) and to divergent treatment schedules. Most important, we confirmed several previous findings,17-21 particularly a significant reduction in the median ARR during tocilizumab long-term therapy from 4.0 to 0.4. The extent of ARR reduction in our cohort of white race/ethnicity is similar to that reported in a Japanese study,20 indicating that tocilizumab suppresses NMO disease activity across different racial/ethnic populations. In contrast to the Japanese cohort, all of our patients (but none of their patients) had been pretreated at least once with rituximab and had a higher EDSS score (mean, 6.7 vs 5.1) and more relapses in the prior year (mean ARR, 4.0 vs 2.9) at tocilizumab initiation. Except for 2 patients with monthly high-dose corticosteroid infusions (temporary) and add-on azathioprine, respectively, our patients received no concomitant immunosuppressive medication during tocilizumab therapy. However, we cannot rule out that long-lasting biological effects of preceding immunotherapies such as rituximab overlapped with the subsequent tocilizumab therapy. In the Japanese cohort, all 7 patients received continuous comedication, including azathioprine, prednisolone, tacrolimus, and cyclosporine A.20 Nevertheless, relapse activity was equally reduced in our cohort, demonstrating that tocilizumab can reduce the frequency of attacks in NMO without concomitant immunosuppression, even in patients with high disease activity. In addition, we observed a paraclinical improvement in MR imaging–detectable disease activity, illustrated by a reduction in gadolinium-enhancing MR imaging lesions from 6 of 8 patients at tocilizumab initiation to 1 of 8 patients at the last follow-up.

In line with previous case reports19-21 and a pilot study by Araki et al,20 we also observed a decrease in the EDSS score and the AQP4-ab titers in most patients during tocilizumab treatment. Considering that disability in NMO is due to insufficient remission of attacks and that secondary progression is
uncommon, it is remarkable that 6 of 8 patients experienced an improvement in the EDSS score over 1 to 4 years, 2 of them dramatically (by 5.0 and 5.5 points, respectively). Because tocilizumab was initiated in all patients shortly after an NMO attack, enhanced remission from this attack is the most likely explanation. Disability improved in 2 patients long after the last relapse. Therefore, it may be hypothesized that the tocilizumab-mediated reduction in AQP4- Abs, which has been shown to be pathogenic in experimental models29 and is associated with disease activity,30 facilitates tissue recovery. However, the precise underlying mechanisms remain to be clarified.

Despite good overall efficacy, 8 attacks occurred in 5 patients after tocilizumab therapy initiation. Except for one severe case of myelitis in patient 2, all attacks were mild to moderate, with complete recovery on the receipt of relapse therapy. Reasons for persisting disease activity in some patients remain elusive. Regarding a possible pattern, we found that 4 of 8 attacks occurred during the first 2½ treatment months (1 of 4 attacks in the study by Araki et al30 was in the same period). Five relapses were related to delayed tocilizumab administration (intervals of ≥40 days), and 6 of 8 attacks were related to a lower tocilizumab dosage (6 vs 8 mg/kg). In contrast, no further attacks occurred after additional 31 prolonged infusion intervals (≥40 days). However, these data indicate that adherence to strict dosing regimens might improve the therapeutic efficacy of tocilizumab.

Chronic pain is a common symptom of NMO and is difficult to treat.31,32 Pathological mechanisms are not well characterized, but the release of potentially pronociceptive cytokines (including tumor necrosis factor, IL-1β, IL-17, and IL-6) might be important for the development of intractable pain in patients with NMO.33-34 Inhibition of the IL-6 receptor with tocilizumab was thought to alleviate chronic pain in Japanese patients with NMO.30 We found a similar decrease in pain as assessed with a numerical rating scale in our patients. It is possible that the effect of tocilizumab on pain is at least partly independent of effects on the immune system because epidural administration of tocilizumab was shown to reduce radicular pain in patients with lumbar spinal stenosis.35

Regarding adverse effects of tocilizumab, a slightly elevated risk of infections has been reported in patients with rheumatoid arthritis.36 These mainly included upper respiratory tract infections and reactivation of latent tuberculosis, along with increased concentrations of hepatic aminotransferases and plasma lipids and decreased absolute neutrophil counts and C-reactive protein levels. In our study, no major adverse effects or laboratory abnormalities were detected except for elevation of cholesterol levels in 6 patients and neutropenia in 1 patient.

Conclusions
Long-term tocilizumab therapy without concomitant immunosuppression in patients of white race/ethnicity with highly active NMO or NMOSD appears to be safe and effective in reducing relapses in otherwise treatment-resistant patients, particularly in rituximab nonresponders. A reduced dosage of tocilizumab (6 mg/kg) and a prolonged tocilizumab administration interval (≥40 days) seem to increase the risk of relapses, especially during the first 2 to 3 months of treatment. In the absence of a randomized clinical trial for tocilizumab, our study findings suggest a dense therapeutic regimen with infusions every 28 days at a dosage of 8 mg/kg to achieve optimal response to tocilizumab therapy. Subcutaneous IL-6 receptor blockade formulations are being prospectively studied in NMO and have shown beneficial effects in patients with rheumatoid arthritis.37
patients and receiving travel, accommodation, and meeting expenses from Novartis, Bayer, and Merck Serono with permission by the rectory of Heinrich Heine University Düsseldorf). Dr Kleiter reported receiving honoraria for consultancy or speaking and travel reimbursement from Bayer, Biogen Idec, Chugai, and Novartis and reported receiving research grants from the Mercator Foundation, Bayer, Biogen Idec, Novartis, and Teva.

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**REFERENCES**


