

# Interleukin-6 Receptor Blockade in Treatment-Refractory MOG-IgG–Associated Disease and Neuromyelitis Optica Spectrum Disorders

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*Neurol Neuroimmunol Neuroinflamm* 2022;9:e1100. doi:10.1212/NXI.0000000000001100

## Abstract

### Background and Objectives

To evaluate the long-term safety and efficacy of tocilizumab (TCZ), a humanized anti-interleukin-6 receptor antibody in myelin oligodendrocyte glycoprotein–IgG–associated disease (MOGAD) and neuromyelitis optica spectrum disorders (NMOSD).

### Methods

Annualized relapse rate (ARR), Expanded Disability Status Scale score, MRI, autoantibody titers, pain, and adverse events were retrospectively evaluated in 57 patients with MOGAD (n = 14), aquaporin-4 (AQP4)-IgG seropositive (n = 36), and seronegative NMOSD (n = 7; 12%), switched to TCZ from previous immunotherapies, particularly rituximab.

### Results

Patients received TCZ for 23.8 months (median; interquartile range 13.0–51.1 months), with an IV dose of 8.0 mg/kg (median; range 6–12 mg/kg) every 31.6 days (mean; range 26–44

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Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by Heinrich Heine University Düsseldorf, Germany.

Neuromyelitis Optica Study Group (NEMOS) coinvestigators are listed in the appendix at the end of the article.

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## Glossary

**ADEM** = acute disseminated encephalomyelitis; **AQP4** = aquaporin-4; **ARR** = annualized relapse rate; **AZA** = azathioprine; **EDSS** = Expanded Disability Status Scale; **HDS** = high-dose steroid; **IL-6** = interleukin-6; **IQR** = interquartile range; **IVIG** = IV immunoglobulin; **LDS** = low-dose steroid; **MMF** = mycophenolate mofetil; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = myelin oligodendrocyte glycoprotein–IgG–associated disease; **MTX** = methotrexate; **NMOSD** = neuromyelitis optica spectrum disorder; **ON** = optic neuritis; **RTX** = rituximab; **SLE** = systemic lupus erythematosus; **TCZ** = tocilizumab; **UTI** = urinary tract infection.

days). For MOGAD, the median ARR decreased from 1.75 (range 0.5–5) to 0 (range 0–0.9;  $p = 0.0011$ ) under TCZ. A similar effect was seen for AQP4-IgG+ (ARR reduction from 1.5 [range 0–5] to 0 [range 0–4.2];  $p < 0.001$ ) and for seronegative NMOSD (from 3.0 [range 1.0–3.0] to 0.2 [range 0–2.0];  $p = 0.031$ ). During TCZ, 60% of all patients were relapse free (79% for MOGAD, 56% for AQP4-IgG+, and 43% for seronegative NMOSD). Disability follow-up indicated stabilization. MRI inflammatory activity decreased in MOGAD ( $p = 0.04$ ; for the brain) and in AQP4-IgG+ NMOSD ( $p < 0.001$ ; for the spinal cord). Chronic pain was unchanged. Regarding only patients treated with TCZ for at least 12 months ( $n = 44$ ), ARR reductions were confirmed, including the subgroups of MOGAD ( $n = 11$ ) and AQP4-IgG+ patients ( $n = 28$ ). Similarly, in the group of patients treated with TCZ for at least 12 months, 59% of them were relapse free, with 73% for MOGAD, 57% for AQP4-IgG+, and 40% for patients with seronegative NMOSD. No severe or unexpected safety signals were observed. Add-on therapy showed no advantage compared with TCZ monotherapy.

## Discussion

This study provides Class III evidence that long-term TCZ therapy is safe and reduces relapse probability in MOGAD and AQP4-IgG+ NMOSD.

Myelin oligodendrocyte glycoprotein (MOG)-IgG–associated disease (MOGAD) and neuromyelitis optica spectrum disorder (NMOSD) with or without anti-aquaporin-4 (AQP4)-IgG are antibody-mediated, chronic inflammatory CNS conditions in most cases.<sup>1–4</sup> Although the clinical presentation with unilateral or bilateral optic neuritis (ON), longitudinally extensive transverse myelitis, or brain stem syndromes may be similar in MOGAD and NMOSD, demographic, clinical, imaging, and pathophysiologic findings strongly suggest the presence of 2 distinct disease entities.<sup>4–8</sup> As MOGAD, excluding acute disseminated encephalomyelitis (ADEM), and NMOSD typically follow a relapsing course in adults,<sup>3,9</sup> attack prevention is key to avoid disability accumulation. Recently, a variety of therapeutic strategies such as CD19/20-mediated B-cell depletion,<sup>10,11</sup> complement inhibition,<sup>12</sup> and interleukin-6 (IL-6) receptor blockade<sup>13,14</sup> were successfully investigated in pivotal NMOSD trials, particularly in AQP4-IgG+ patients. Yet, insights concerning the effectiveness and safety of such agents in MOGAD are scarce.

IL-6 plays an important role in the pathophysiology of NMOSD.<sup>15</sup> Increased levels were detected in the serum and CSF, particularly during attacks.<sup>16</sup> IL-6 promotes the differentiation of inflammatory Th17 cells<sup>17</sup> and the production of AQP4-IgG by B cell–derived plasmablasts in NMOSD<sup>18</sup> and increases the permeability of the blood-brain barrier,<sup>19</sup> facilitating CNS inflammation. The efficacy of IL-6 receptor blockade in AQP4-IgG+ NMOSD was suggested by studies using tocilizumab (TCZ) in adults and children<sup>20–26</sup> and demonstrated by 2 pivotal trials of satralizumab,

whereas the effect in AQP4-IgG–seronegative patients was less evident.<sup>13,14</sup> As AQP4-IgG+ NMOSD and MOGAD both display antibody- and complement-mediated CNS injury and similar inflammatory CSF profiles (with elevated IL-6),<sup>27,28</sup> IL6-blockade may also be beneficial in MOGAD, supported by recent case reports.<sup>23,25,26,29–33</sup> This retrospective multicenter study explored the safety and efficacy of TCZ in patients with MOGAD and is able to connect these findings with the effects of TCZ in classical (i.e., AQP4-IgG+) or double-seronegative NMOSD.

## Patients and Previous Treatments

Fifty-seven patients with relapsing MOGAD ( $n = 14$ ),<sup>34</sup> excluding ADEM, classical AQP4-IgG+ NMOSD ( $n = 36$ ), or double-seronegative NMOSD ( $n = 7$ ), mainly of Caucasian descent ( $n = 50$ ; Table 1), from neurologic departments of 23 tertiary referral centers in Germany ( $n = 13$ , all members of the German Neuromyelitis Optica Study Group [NEMOS]), France ( $n = 5$ , all members of the NOMADMUS cohort), Austria (1), Italy (1), Switzerland (1), United Kingdom (1), and United States of America (1) were retrospectively analyzed. The evaluated TCZ treatment period ranged from December 2010 until November 2019. Regarding demographic parameters (Table 1), the mean age at disease manifestation was comparable for patients with MOGAD or AQP4-IgG+ NMOSD (35.5 or 36.1 years, respectively;  $p = 0.89$ ), as well as the age when TCZ was started (38.4 or 42.8 years,  $p = 0.35$ ). Five patients were younger than 18 years at disease manifestation, and 3 of them younger than 18 years at initiation of TCZ. Of note, patients with AQP4-IgG+

NMOSD were predominantly female, in contrast to patients with MOGAD (91% vs 35% female, respectively). Patients with AQP4-IgG+ NMOSD tended to have a longer history of disease (median 5.5 years) and were more severely affected at TCZ start (median Expanded Disability Status Scale [EDSS] score 6.25) than patients with MOGAD (median disease duration 2.2 years,  $p = 0.13$ ; median EDSS score 2.75,  $p < 0.01$ ). In the MOGAD group, 7 patients (50%) fulfilled the 2015 revised international consensus diagnostic criteria for NMOSD.<sup>35</sup> Before TCZ therapy, patients with MOGAD had had a median of 6 attacks (range 1–12 attacks) with 4.5 ON (median; range 1–10 ON) and 2.0 myelitis events (median; range 1–5 myelitis events). In the NMOSD group, 5/7 double-seronegative (71%) and 27/36 AQP4-IgG+ (75%) patients fulfilled the 2006 NMO diagnostic criteria,<sup>36</sup> whereas all AQP4-IgG+ and double-seronegative patients fulfilled the 2015 NMOSD diagnostic criteria.<sup>35</sup> Of note, 47/57 (83%) patients were tested for both antibodies, and none was double positive. Ten AQP4-IgG+ patients were not tested for MOG-IgG. Before TCZ, all patients had been treated with different immunotherapies following established recommendations, and, remarkably, all had received rituximab (RTX) (Table 1; Figures 1 and 2 for seropositive patients). Within the last 24, 12, and 6 months before TCZ switch, 53/57 (93%), 44/57 (77%), and 31/57 (54%) of the patients were treated with RTX, respectively. B-cell counts, collected briefly before the start of TCZ (median interval 0.9 months; interquartile range [IQR] 0.4–1.9 months), were available for 33/57 (58%) patients (25/36 [69%] AQP4-IgG+ NMOSD, 6/14 [43%] MOGAD, and 2/7 [29%] double-seronegative patients). Of these 33 patients, 28 (85%) patients (21/25 [84%] AQP4-IgG+ NMOSD, 5/6 [83%] MOGAD, and 2/2 [100%] double-seronegative patients) showed markedly reduced or depleted B cells. During the total pre-TCZ treatment phase (median duration of 2.9 years), patients had 6.0 attacks (median; range 1–30 attacks). Considering the last 2 years before TCZ start, 3.0 attacks (median; range 0–10 attacks) were recorded (Table 1).

## Methods

All clinical and paraclinical data were analyzed retrospectively by chart review. Patients were continuously treated at the contributing centers, specialized in clinical neuroimmunology, with regular assessment of clinical (attacks, EDSS score, and pain levels) and paraclinical (MRI, AQP4- and MOG-IgG, and other laboratory tests) data. AQP4-IgG and MOG-IgG antibodies were exclusively measured by cell-based assays. The primary outcome was the annualized relapse rate (ARR). An attack was defined as definitely new neurologic symptom or clear acute worsening of previous neurologic deficits with objective clinical signs, lasting for at least 24 hours and attributed to an inflammatory CNS event, confirmed by the treating physician. Safety aspects comprised infusion-related reactions, infections, tumors, cardiovascular events, and standard laboratory tests. AQP4-IgG titers, EDSS score, and chronic pain (occurrence and intensity, classified as mild = 1, moderate = 2, or severe = 3) were

assessed at TCZ start and, if available, at last follow-up during TCZ. MRI of the cervicothoracic spinal cord and the brain, evaluated at TCZ onset and last available follow-up, was classified as nonactive or active, indicated by the presence of new T2 or contrast-enhancing lesions.

## Statistical Analysis

In general, the ARR was calculated by dividing the number of attacks within the last 2 years before TCZ switch or during TCZ treatment time by 2. However, for 19 patients, who had a TCZ pretreatment phase of <2 years (median 1.1 years), we categorically divided the total number of attacks by 2, and for 13 patients with a follow-up period of <1 year (median 0.5 years) during TCZ treatment, we divided the number of attacks by the concrete treatment duration and thus extrapolated this measure to 1 year. To avoid possible overestimation of the relapse-free proportion in the latter group, we excluded those 13 patients with TCZ treatment durations of <12 months for subgroup analyses.

In the descriptive analysis, values are given as mean or median, with the appropriate measures of dispersion (i.e., range, SD, or IQR). In all cases, the assumption of normal distribution could not be affirmed. Therefore, only nonparametrical tests were used. To test for statistically significant differences between 2 related samples like ARR before TCZ switch and ARR under TCZ therapy, the Wilcoxon signed-rank test was used. In case of paired categorical data with a dichotomous trait, the exact binomial test was used. For count data-like relapses, we also applied an unconditional Poisson regression. Statistical results are presented as  $p$  values and 95% confidence intervals.  $p$  Values <0.05 were considered to indicate statistically significant results. Because of the exploratory nature of the study, no adjustment for multiple comparisons was made. Version 3.6.3 of the R statistics package was used for statistical analysis.

## Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was obtained from the Institutional Review Board of the Heinrich Heine University Düsseldorf (#3419) and from each participating center by their local institutional review boards according to ICH/GCP. All patients provided written informed consent.

## Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

## Results

### TCZ Reduced ARR

Forty-five of 57 (79%) patients switched to TCZ due to ongoing disease activity, 5/57 (9%) due side effects of prior immunotherapies (including allergic reactions on RTX in 3 patients), and 6/57 (10%) because of concomitant disease activity and adverse events. In 1 patient, the detection of

**Table 1** Demographics and Disease Characteristics of Patients With MOGAD and NMOSD

Cohort	MOGAD (n = 14)	AQP4-IgG+ NMOSD (n = 36)	Double seronegatives (n = 7)	Total (N = 57)
<b>Ethnicity, n (%)</b>				
Caucasian	13 (93)	30 (83)	7 (100)	50 (88)
African	—	3 (8)	—	3 (5)
Arabian	1 (7)	2 (6)	—	3 (5)
Latin American	—	1 (3)	—	1 (2)
Sex, n: female/male (% female)	5/9 (35)	33/3 (91)	6/1 (85)	44/13 (77)
AQP4 serostatus, n: pos/neg (% positive)	0/14 (0)	36/36 (100)	0/7 (0)	36/21 (63)
MOG serostatus, n: pos/neg/NA <sup>a</sup> (% positive)	14/0/0 (100)	0/26/10 (0)	0/7/0 (0)	14/33/10 (25)
NMO based on 2006 criteria, n: yes/no (% yes)	4/10 (28)	27/9 (75)	5/2 (71)	36/21 (63)
NMO based on 2015 criteria, n: yes/no (% yes)	7/7 (50)	36/0 (100)	7/0 (100)	50/7 (87)
Age at disease manifestation, y: mean (SD)	35.5 (14.7)	36.1 (15.2)	42.7 (11.5)	36.8 (14.6)
Disease duration before TCZ, y: median (IQR)	2.2 (1.2–3.4)	5.5 (1.2–9.0)	2.4 (2.3–5.1)	2.9 (1.3–8.2)
Relapses under last immunotherapy, n: median (IQR)	1.5 (1.0–2.0)	1.0 (1.0–2.0)	3.0 (1.5–3)	1.0 (1.0–2.0)
Relapses during last 2 y before TCZ, n: median (IQR)	3.5 (2.2–5.0)	3.0 (2.0–5.0)	6.0 (2.5–6.0)	3.0 (2.0–5.0)
Age at TCZ start, y: mean (SD)	38.4 (15.0)	42.8 (14.6)	46.5 (10.8)	42.2 (14.3)
Number of TCZ infusions, n: mean (SD)	26.9 (21.7)	37.6 (31.1)	28.4 (21.9)	34.0 (28.2)
TCZ intervals, d: mean (SD)	30.8 (4.6)	32.1 (4.6)	30.4 (0.8)	31.6 (4.3)
TCZ treatment duration, mo: median (IQR)	16.3 (14.2–44.6)	27.9 (12.9–53.2)	30.4 (10.3–38.1)	23.8 (13.0–51.1)
Relapses before TCZ, n: median (IQR)	6.0 (4.2–8.0)	5.0 (3.0–10.2)	6.0 (5.5–8.5)	6.0 (3.0–9.0)
Relapses under TCZ, n: median (IQR)	0 (0–0)	0 (0–1.0)	1.0 (0–2.0)	0 (0–1.0)
EDSS score before TCZ: median (IQR)	2.75 (2.0–3.5)	6.25 (3.0–7.6)	5.0 (4.5–5.8)	4.5 (3.0–7.0)
EDSS score under TCZ: median (IQR)	2.0 (1.2–2.9)	4.25 (2.5–7.0)	5.0 (3.5–6.8)	3.5 (2.0–6.5)
<b>Immunotherapies before TCZ, n (%):</b>				
Rituximab	14 (100)	36 (100)	7 (100)	57 (100)
Azathioprine	3 (21)	13 (36)	2 (29)	18 (32)
Mycophenolate mofetil	3 (21)	7 (19)	1 (14)	11 (19)
Low-dose steroid monotherapy	4 (29)	7 (19)	0 (0)	11 (19)
Methotrexate	1 (7)	7 (19)	3 (43)	11 (19)
Cyclophosphamide	2 (14)	8 (22)	1 (14)	11 (19)
IVIg	3 (21)	4 (11)	0 (0)	7 (12)
Interferon-beta	0 (0)	5 (14)	1 (14)	6 (11)
Mitoxantrone	0 (0)	5 (14)	0 (0)	5 (9)
Glatiramer acetate	0 (0)	2 (6)	1 (14)	3 (5)
Natalizumab	0 (0)	1 (3)	1 (14)	2 (4)
Long-term plasma exchange	1 (7)	1 (3)	0 (0)	2 (4)
Alemtuzumab	0 (0)	1 (3)	0 (0)	1 (2)
Fingolimod	0 (0)	1 (3)	0 (0)	1 (2)
Cyclosporin A	0 (0)	1 (3)	0 (0)	1 (2)

Continued

**Table 1** Demographics and Disease Characteristics of Patients With MOGAD and NMOSD (continued)

Cohort	MOGAD (n = 14)	AQP4-IgG+ NMOSD (n = 36)	Double seronegatives (n = 7)	Total (N = 57)
Belimumab	1 (7)	0 (0)	0 (0)	1 (2)
Etanercept	0 (0)	1 (3)	0 (0)	1 (2)

Abbreviations: AQP4 = aquaporin-4; EDSS = Expanded Disability Status Scale; MOG = myelin oligodendrocyte glycoprotein; MOGAD = MOG-IgG-associated disorder; NMOSD = neuromyelitis optica spectrum disorder; TCZ = tocilizumab. <sup>a</sup> MOG-IgG ab not tested.

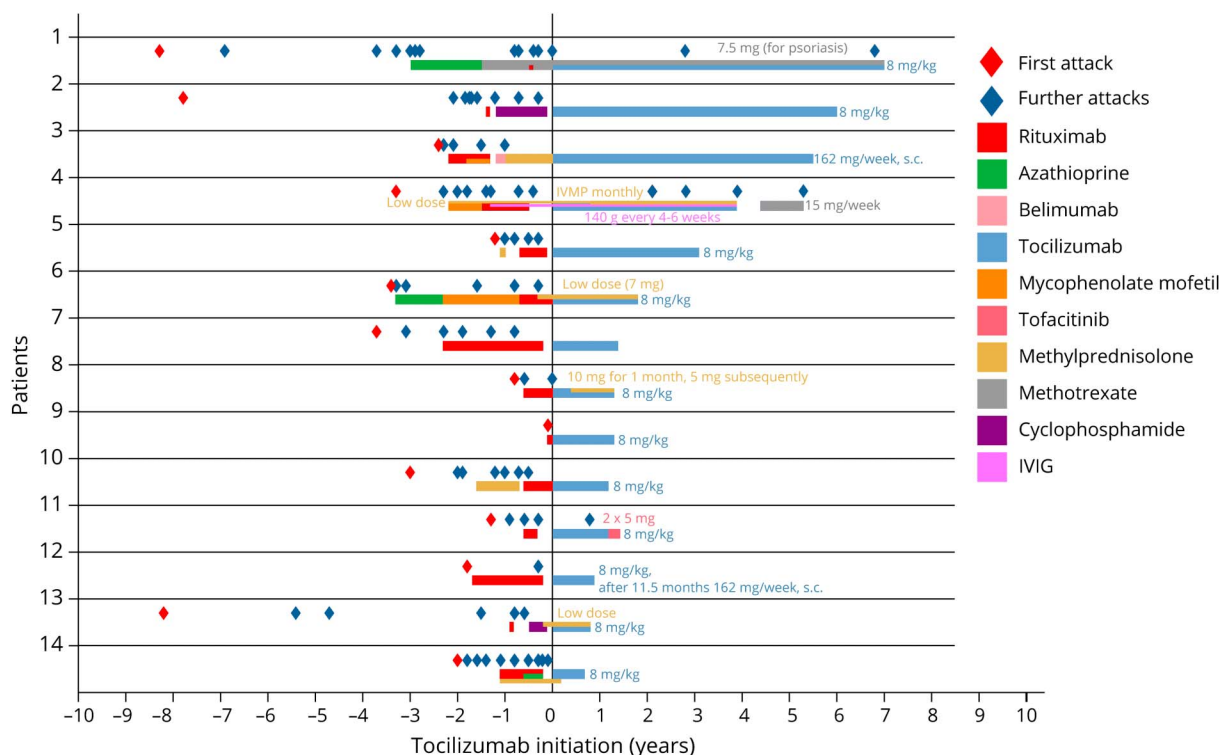
neutralizing antibodies against RTX was the reason for treatment switch. TCZ was administered IV (mean 34 infusions, range 3–109) in 56 patients (98%) at a mean interval of 31.6 days (range 26.1–44.2 days) and with a median dose of 8.0 mg/kg body weight (range 6.0–12.0 mg/kg body weight; Table 1) and subcutaneously in 1 patient (2%) with weekly injections of 162 mg. The interval from last relapse to initiation of TCZ was similar for all groups, i.e., 2.2 months (median, IQR 1.1–5.1 months) for patients with AQP4-IgG+ NMOSD, 3.2 months (1.5–4.8 months) for the MOGAD subgroup, and 2.4 months (1.7–6.2 months) for double seronegatives.

The median treatment duration was 23.8 months (IQR 13.0–51.1 months), with patients with AQP4-IgG+ NMOSD

showing the longest TCZ exposure (27.1 months), compared with MOGAD (16.3 months) and double-seronegative (30.4 months) patients. In one-third of patients (20/57), TCZ was given as an add-on treatment; in 2 of them due to comorbidities (psoriasis cotreated with methotrexate [MTX]; chronic polyarthritis with oral low-dose steroids [LDSs]). Additional medications included LDS (n = 10), MTX (n = 4), mycophenolate mofetil (MMF; n = 2), azathioprine (AZA; n = 1), IV immunoglobulins (IVIG; n = 1), RTX (n = 1), and monthly high-dose steroids (HDS; n = 1), administered for <6 months in 3 patients and >6 months in 17 patients during TCZ treatment.

Initiation of TCZ was followed by a decrease of the median ARR in patients with AQP4-IgG+ NMOSD from 1.5 to 0 ( $p < 0.001$ , 95% CI 0–0.2) compared with the last 2

**Figure 1** Disease Courses and Individual Maintenance Immune Therapies of Patients With MOGAD



First attacks are indicated as red diamonds and further attacks as blue diamonds. IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; MOG = myelin oligodendrocyte glycoprotein; MOGAD = MOG-IgG-associated disease.

years before TCZ start. Of note, patients with MOGAD showed a similar median ARR reduction from 1.75 to 0 ( $p = 0.0011$ , 95% CI 1.3–2.6). For patients with double-seronegative NMOSD, median ARR reduction was less prominent but still significant (from 3.0 to 0.2 [ $p < 0.032$ , 95% CI 0.3–2.8]). For the total cohort, the median ARR decreased from 1.5 to 0 ( $p < 0.001$ , 95% CI 1.1–1.8; Figure 3). Of note, ARR reductions were also detectable when analysis was confined to those patients treated with TCZ for at least 12 months, including MOGAD and AQP4-IgG+ NMOSD, but not double-seronegative patients (Figure 3).

Regarding individual patients, 3/14 (21.4%) patients with MOGAD (Figure 1) and 14/36 (39%) patients with AQP4-IgG+ NMOSD (Figure 2) had at least 1 attack during TCZ treatment, and 2/14 (14.3%) patients with MOGAD and 2/36 (5.6%) patients with AQP4-IgG+ NMOSD showed 2 or more attacks. Sixty percent of all patients were relapse free (79% for MOGAD, 56% for AQP4-IgG+ NMOSD, and 43% for double-seronegative NMOSD). When analyzing only patients treated with TCZ for at least 12 months, 26/44 (59%) of all patients, 8/11 (73%) MOGAD, 16/28 (57%) AQP4-IgG+, and 2/5 (40%) double-seronegative patients, remained relapse free.

The median time to first relapse was 9 months (range 0.5–47 months) for the whole group, 9.4 months for MOGAD (range 9–15 months), 4.4 months for AQP4-IgG+ NMOSD (range 0.5–47 months), and 12.2 months for double-seronegative NMOSD (range 2.6–18.9 months). An unconditional Poisson regression analysis showed an average increase in relapses by 16% per year under TCZ therapy, indicating that a relapse is not expected until after 5 years under TCZ in the total cohort ( $p < 0.03$ ). Moreover, double-seronegative patients had average 2.6 times the relapse counts compared with patients with AQP4-IgG+ NMOSD ( $p < 0.03$ ), and in the MOGAD subgroup, relapses occurred 8% less than in AQP4-IgG+ NMOSD, which was not significant ( $p = 0.86$ ).

When comparing patients treated with TCZ plus add-on treatment (20/57) with those on TCZ monotherapy (37/57), the ARR in the add-on group was higher in the 2 years before TCZ initiation (median 2.0 [IQR 1–3] vs 1.5 [IQR 1–2.5]) as well as during TCZ treatment (0.2 [IQR 0–0.8] vs 0 [IQR 0–0]). In line, freedom from relapses was achieved in 40% of patients in the add-on group and in 78% in the monotherapy group.

By comparing the 2 groups of patients who switched to TCZ due to ongoing disease activity or side effects, the median ARR in the first group was 2.0 (IQR 1.0–2.5) during the 2 years prior TCZ and was 0 (IQR 0–0.2) during TCZ treatment, whereas the median ARRs were 1.0 (IQR 0.5–1.0) and 0 (IQR 0–0), respectively, for both intervals in the second subgroup.

## Relapsing vs Nonrelapsing Patients During TCZ Treatment

When comparing patients who relapsed vs those who did not relapse during TCZ treatment (across the different subgroups), relapsing patients with AQP4-IgG+ NMOSD were younger at disease manifestation than nonrelapsing patients (years, median, relapsing vs nonrelapsing, 31.4 vs 36.4, respectively). At TCZ start, MOGAD and double-seronegative patients who later relapsed were older than nonrelapsing patients, whereas relapsing and nonrelapsing AQP4-IgG+ patients had comparable age (years, median, relapsing vs nonrelapsing, AQP4-IgG+ 43.7 vs 43.6, MOGAD 48.5 vs 41.2, double seronegatives 50.7 vs 37.8, respectively). Relapsing patients had a longer disease duration than nonrelapsing in the AQP4-IgG+ and MOGAD groups (years, median, AQP4-IgG+ NMOSD 8.76 vs 2.93, MOGAD 3.33 vs 2.11, respectively). Sex had no effect on relapses in all subgroups. Under TCZ therapy, most of the myelitis and ON attacks occurred in AQP4-IgG+ NMOSD and double-seronegative patients (AQP4-IgG+ NMOSD: myelitis [14], ON [4]; MOGAD: myelitis [2], ON + myelitis [1]; double seronegatives: myelitis [4]).

## TCZ Discontinuation

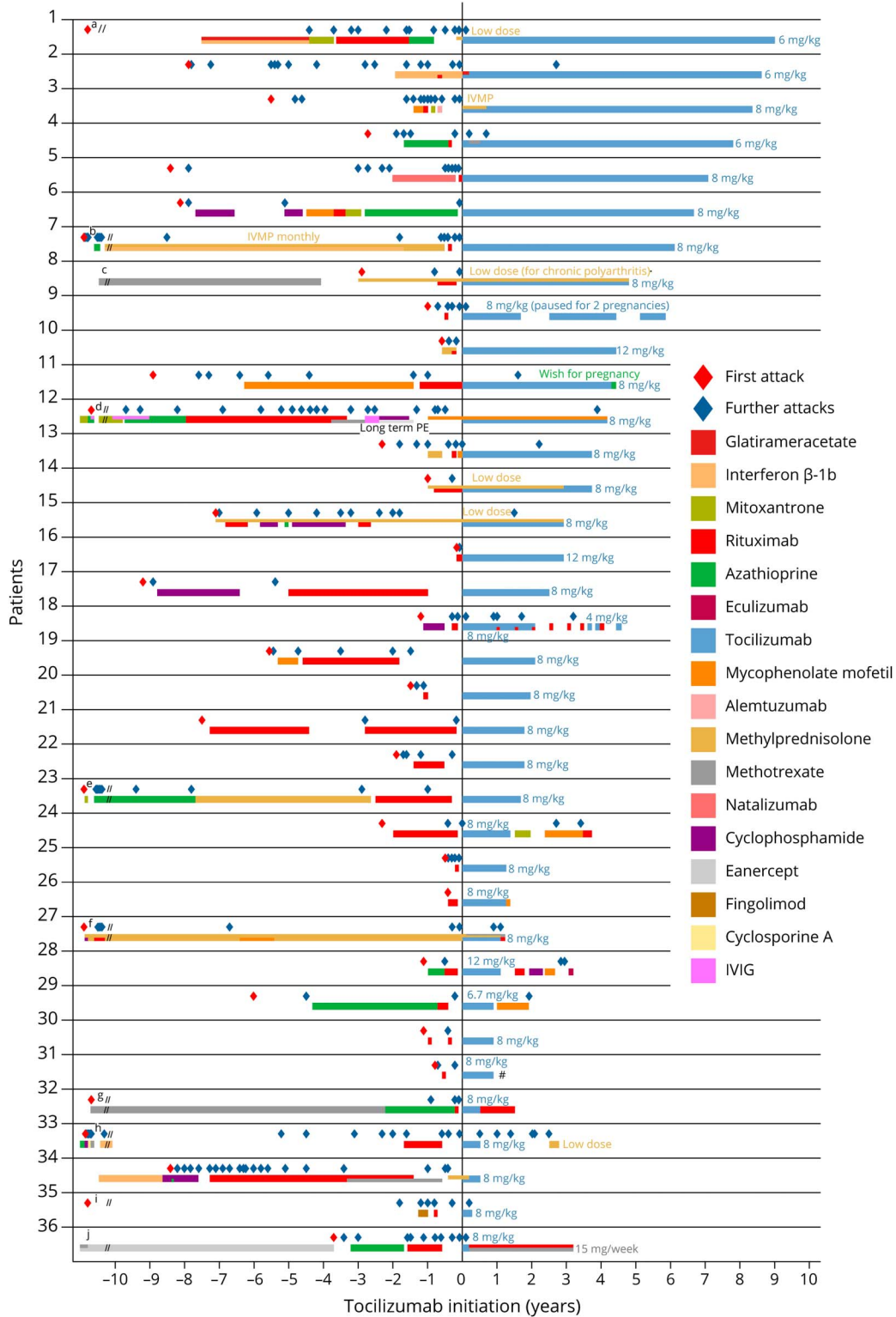
TCZ therapy was discontinued in 20/57 patients (35.1%; 15/36 [41.7%] AQP4-IgG+, 2/14 [14%] MOGAD, and 3/7 [42.9%] double-seronegative patients) after 14.5 treatment months (median; range 2.9–53.9 treatment months). Of note, 45% (9/20) of them stopped TCZ for general reasons such as pregnancy, plans for pregnancy, and patient's preference (e.g., for oral medications), and 2 patients were lost to follow-up. However, 6 of the 20 patients (2 AQP4-IgG+, 3 double seronegative, and 1 MOGAD) presented ongoing MRI activity or attacks, and 5/20 patients (all AQP4-IgG+) discontinued due to suspected side effects such as ileus ( $n = 1$ ), nephritis and urticaria in the context of systemic lupus erythematosus (SLE;  $n = 1$ ), psoriasis exacerbation ( $n = 1$ ), and upper respiratory tract infections ( $n = 3$ ). Two patients who stopped TCZ restarted it after completion of pregnancy and ileus treatment. Of the 11 patients with disease activity or suspected side effects, 6 patients (55%) received TCZ as add-on therapy, and 5 patients (45%) showed relapse activity, which occurred 256 days (median, IQR 73–329 days) after TCZ initiation, indicating that delayed onset of efficacy may have contributed to early discontinuation.

## Disability

The median EDSS score significantly decreased in both seropositive groups, in MOGAD from 2.75 to 2.0 ( $p < 0.031$ ) and in AQP4-IgG+ NMOSD from 6.25 to 4.25 ( $p < 0.003$ ). The median EDSS score remained stable on 5.0 in 7/7 double-seronegative patients ( $p < 0.77$ ; Table 1; Figure 4).

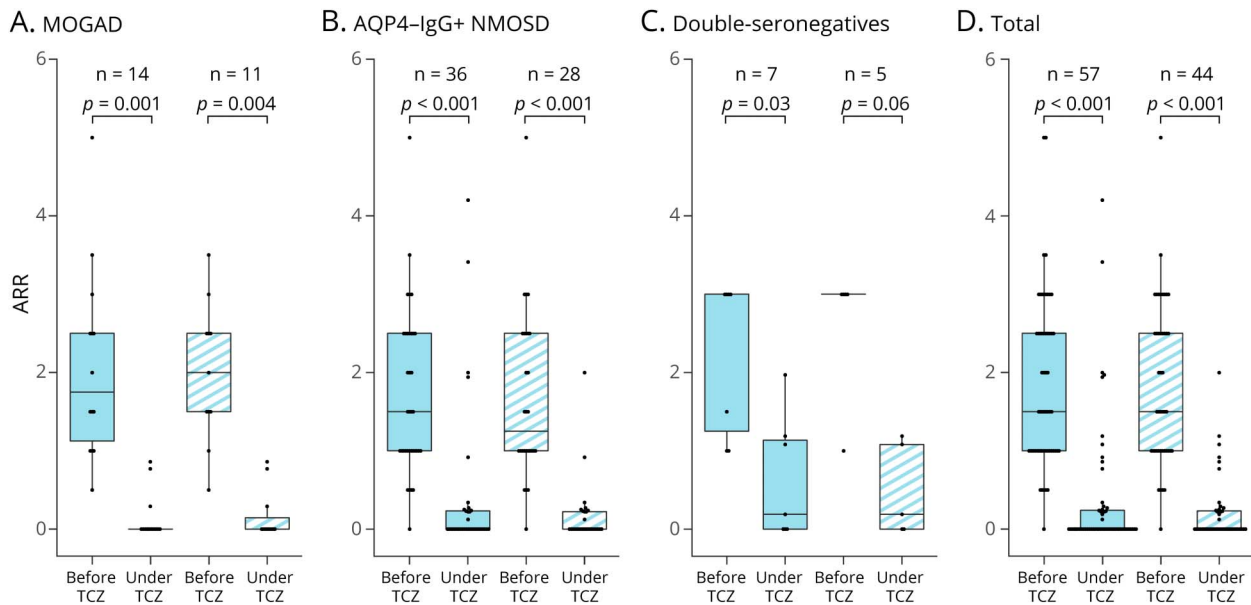
When including patients with TCZ treatment duration >12 months only, the EDSS score improvement was still significant for AQP4-IgG+ NMOSD and the whole cohort (Figure 4). The EDSS score worsened in only 5/57 (9%)

**Figure 2** Disease Courses and Individual Maintenance Immune Therapies of Patients With AQP4-IgG–Seropositive NMOSD



First attacks are indicated as red diamonds and further attacks as blue diamonds. AQP4 = aquaporin-4; IVIG = IV immunoglobulin; NMOSD = neuromyelitis optica spectrum disorder; IVMP = IV methylprednisolone; PE = plasma exchange; SLE = systemic lupus erythematosus. (a) Twelve years before tocilizumab (TCZ) initiation. (b) Twenty-four years before TCZ initiation. (c) Therapy of chronic polyarthritis 2 and a half years before TCZ initiation. (d) Fifteen years before TCZ initiation. (e and f) Sixteen years before TCZ initiation. (g) Ten and a half years before TCZ initiation. (h) Twenty-two years before TCZ initiation. (i) Eleven and a half years before TCZ initiation. (j) Psoriasis therapy; psoriasis flare-up finally remitted completely under rituximab; #loss to follow-up.

**Figure 3** ARR Before and During TCZ Treatment



Box-and-whisker plots showing the median, IQR, and range of the annualized relapse rate 2 years before and during TCZ treatment for the MOGAD (A), the AQP4-IgG+ NMOSD (B) and the double seronegative (C) subgroups of patients, as well as for the total cohort (D). Each dot indicates 1 single patient. Hatched bars represent those patients who had been treated with TCZ for at least 12 months. AQP4 = aquaporin-4; ARR = annualized relapse rate; IQR = interquartile range; MOGAD = MOG-IgG-associated disease; NMOSD = neuromyelitis optica spectrum disorder; TCZ = tocilizumab.

patients of the entire cohort, i.e., none of patients with MOGAD, 3/36 (8%) patients with AQP4-IgG+ NMOSD, and 2/7 (29%) double-seronegative patients.

### Pain

Initial disease-related chronic pain was reported in 28/51 patients (55%), with a median pain intensity of 2.0 (IQR 1–3; data from 27 patients). Presence and intensity of pain were not modulated during TCZ treatment, as 25/52 patients (48%) still had ongoing chronic pain with a median intensity of 2.0 (IQR 1–3; data available from 24 patients) at last follow-up, regardless of the AQP4-IgG/MOG-IgG serostatus.

### Antibody Titers

Regarding AQP4-IgG immunoreactivity, most patients (12/16) showed decreased or stable titers after initiation of TCZ (Figure 5 for individual courses). Longitudinally assessed MOG-IgG antibody titers were available in only 2 of 14 patients and showed a similar pattern as seen in AQP4-IgG+ NMOSD, i.e., a decrease from 1:320 to 1:32 and from 1:1,280 to 1:10, respectively.

### Magnetic Resonance Imaging

For brain MRI, the proportion of patients with active scans (presence of new T2 or contrast-enhancing lesions) significantly decreased from 43.5% at TCZ baseline (20/46 patients with available longitudinal data at TCZ onset and follow-up) to 15.2% (7/46 patients;  $p = 0.007$ ) at last available scan, within 31.6 months (mean; range 4.2–95.8 months). This reduction was detectable for MOGAD (change from 7/13 [53.8%] to 1/13 patients [7.7%] with active scans;  $p = 0.031$ ),

but not for AQP4-IgG+ (9/26 [34.6%] to 3/26 [11.5%];  $p = 0.146$ ) or seronegative (4/7 [57.1%] to 3/7 [42.9%];  $p = 1$ ) subgroups.

For spinal cord MRI, the proportion of patients with active scans decreased from 71.4% (25/35 patients) to 28.6% (10/35;  $p = 0.00006$ ) during TCZ (mean interval 40.5 months; range 3.7–111.3). This effect was mainly driven by the AQP4-IgG+ group with a decrease from 74.1% (20/27) to 25.9% (7/27) of patients during TCZ ( $p = 0.0002$ ). For double-seronegative NMOSD and MOGAD, the proportion of patients with active scans was low and stable during TCZ.

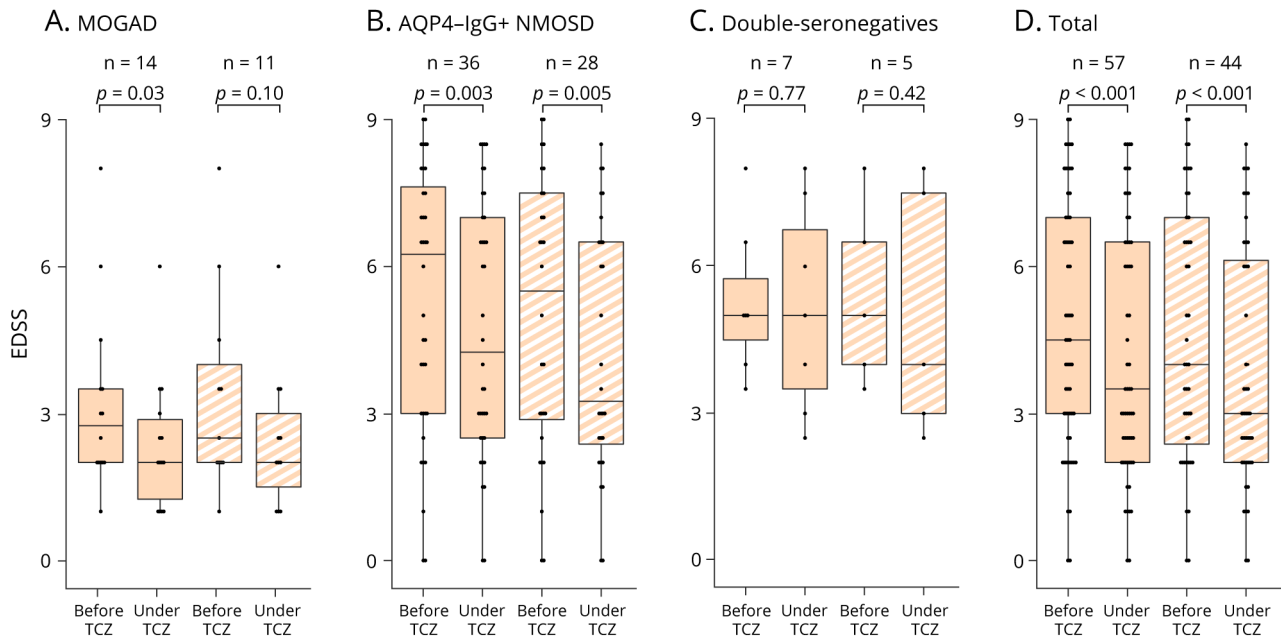
### Safety Data

#### Clinical Events

Infusion-related reactions occurred in 7/57 (12.3%) patients and included headache, abdominal pain, vertigo, nausea, fatigue, leg edema, rash, mild bruising, and bloating (Table 2). Infections comprised recurrent urinary tract infections (UTI, in 16% of patients), upper respiratory tract infections, common cold, bronchitis and pneumonia (in 16%), oral or lip infections (in 7%; including herpes simplex virus, ulcers, and candidiasis), erysipelas and skin lesions compatible with SLE (in 5%), and (pyelo)nephritis (in 3.5%). In 19/57 (33%) patients, 23 chronic underlying inflammatory diseases were reported, including Hashimoto thyroiditis (N = 7), SLE (5), psoriasis (4), Sjogren syndrome (2), and vitiligo, polyarthritis, immune thrombocytopenic purpura, myasthenia gravis, and Crohn disease (1 each). Exacerbation of SLE and psoriasis



**Figure 4** Level of Disability Measured as EDSS Score Before and During TCZ Treatment



Box-and-whisker plots showing the median, IQR, and range of the EDSS score 2 years before and during TCZ treatment for the MOGAD (A), the AQP4-IgG+ NMOSD (B) and the double seronegative (C) subgroups of patients, as well as for the total cohort (D). Each dot indicates 1 single patient. Hatched bars represent those patients who had been treated with TCZ for at least 12 months. AQP4 = aquaporin-4; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MOGAD = MOG-IgG-associated disease; NMOSD = neuromyelitis optica spectrum disorder; TCZ = tocilizumab.

during TCZ occurred in 4 patients (2 from each) and led to TCZ discontinuation in 2 of these 19 (11%) patients (both AQP-IgG+ NMOSD). No new cancer occurred. One case of type 1 focal nodular hyperplasia of the liver was diagnosed during TCZ. Cardiovascular events occurred in 3 patients, including a non-ST elevation myocardial infarction after the initial infusion, a deep vein thrombosis, and a slight increase in blood pressure. One death due to recurrent pneumonia occurred 2 months after discontinuation of a 6-month TCZ treatment period, but this was not regarded as treatment related by the treating physician, as the 58-year-old patient had a history of severe AQP4-IgG+ NMOSD with concomitant SLE and uterus carcinoma, including surgery and radiation.

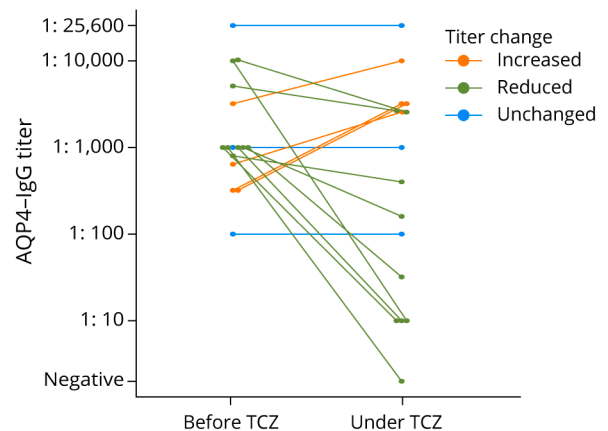
TCZ-treated patients with additional immunotherapies suffered more frequently from pneumonia compared with the monotherapy group (18% vs 6%); other side effects like reactivation of chronic latent infections (5% vs 6%) were equally distributed in both groups.

### Laboratory Changes

Neutropenia during TCZ treatment, with a maximum cell count reduction of 61% below the lower reference level, occurred in 10/57 (18%) patients, with 3 patients on a concomitant immunotherapy (MTX, RTX, and LDS; Table 2). However, these 10 patients had no higher frequency of common neutropenia-related conditions such as UTI, pneumonia, and other (unspecific) infections. Transient and mild to moderate increases of liver enzymes and lipase (2- to 3-fold above the upper reference level) were reported in 20/57

(35.1%) patients. In particular, alanine aminotransferase was elevated at least once in 17/57 (29.8%) patients during TCZ and increased from 28.2 U/L (mean; range 8–90 U/L; at TCZ start) to 75.6 U/L (range 21–179 U/L;  $p < 0.001$ ). Mean total cholesterol levels increased slightly during TCZ treatment from 195.3 mg/dL ( $n = 37/57$ ; range

**Figure 5** Longitudinal Aquaporin-4-IgG Titers Before and During TCZ Treatment



Individual longitudinal courses of AQP4-IgG titers (assessed by cell-based assays) for patients with AQP4-IgG-seropositive NMOSD ( $n = 16$ ) are shown. Most patients (12/16) showed decreased or stable titers on initiation of TCZ; in 4/16 patients, the AQP4-IgG titer increased. AQP4 = aquaporin-4; NMOSD = neuromyelitis optica spectrum disorder; TCZ = tocilizumab.

**Table 2** Safety Profile of Tocilizumab in Patients With MOGAD and NMOSD

Cohort	MOGAD (n = 14)	AQP4-IgG+ NMOSD (n = 36)	Double seronegatives (n = 7)	Total (N = 57)
Infusion-related reactions, n (%)	1 (7%)	6 (17%)	0 (0%)	7 (12%)
<b>Infections</b>				
Recurrent urinary tract infections	1 (7%)	7 (19%)	1 (14%)	9 (16%)
Viral upper respiratory tract infections/common cold/bronchitis/pneumonia	2 (14%)	5 (14%)	2 (29%)	9 (16%)
Oral or lip infections	0 (0%)	4 (11%)	0 (0%)	4 (7%)
Erysipelas and skin lesions compatible with SLE	0 (0%)	3 (8%)	0 (0%)	3 (5%)
(Pyelo)nephritis	1 (7%)	1 (3%)	0 (0%)	2 (4%)
Reactivation of chronic latent infection, n (%)	0 (0%)	3 (8%)	0 (0%)	3 (5%)
Tumor, n (%)	0 (0%)	1 <sup>a</sup> (3%)	0 (0%)	1 <sup>a</sup> (2%)
Cardiovascular events, n (%)	0 (0%)	3 (8%)	1 (14%)	4 (7%)
Neutropenia, n (%)	2 (14%)	8 (22%)	0 (0%)	10 (17%)
Any liver enzyme changes, n (%)	2 (14%)	12 (33%)	6 (86%)	20 (35%)
Cholesterol before TCZ, mg/dL: mean (SD)	195.8 (42.2)	190.5 (65.0)	220.3 (66.8)	195.3 (58.5)
Cholesterol under TCZ, mg/dL: mean (SD)	199.6 (66.3)	199.9 (46.2)	235.2 (80.4)	203.8 (56.6)
LDL before TCZ, mg/dL: mean (SD)	126.9 (50.0)	114.0 (47.4)	140.7 (54.5)	121.0 (48.0)
LDL under TCZ, mg/dL: mean (SD)	129.8 (44.9)	119.2 (43.3)	166.3 (49.5)	126.4 (44.9)
HDL before TCZ, mg/dL: mean (SD)	60.6 (21.4)	59.4 (22.7)	66.3 (35.7)	60.5 (22.8)
HDL under TCZ, mg/dL: mean (SD)	70.7 (40.3)	69.8 (41.9)	57.8 (38.5)	68.9 (40.2)

Abbreviations: AQP4 = aquaporin-4; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MOG = myelin oligodendrocyte glycoprotein; MOGAD = MOG-IgG-associated disorder; NMOSD = neuromyelitis optica spectrum disorder; SLE = systemic lupus erythematosus; TCZ = tocilizumab.

SI conversion factors: to convert cholesterol, LDL and HDL to mmol/L, multiply values by 0.0259.

<sup>a</sup> FNH (focal nodular hyperplasia).

59–311 mg/dL) to 203.8 mg/dL (n = 44/57; range 85–372 mg/dL;  $p = 0.5554$ ), with no changes within the subgroups as well. Similarly, low- and high-density lipoprotein (LDL/HDL) cholesterol levels were stable during TCZ (Table 2).

## Discussion

Our study designed as a multicenter real-world approach confirms and extends existing evidence, as it shows that in MOG- or AQP4-IgG-mediated inflammatory demyelinating syndromes, IL-6 blockade offers a therapeutic perspective, even if patients were exposed to standard immunotherapies before, including targeted B-cell depletion by RTX. Importantly, our data provide insights into therapeutic long-term management of these diseases, with a follow-up far beyond the observation periods in existing pivotal trials.

MOGAD in adults and NMOSD in general almost exclusively follow a relapsing disease course,<sup>3,9</sup> emphasizing the relevance of attack prevention for disease prognosis.

Considering the long-term course, MOGAD was assumed to have a less severe prognosis than NMOSD.<sup>37,38</sup> However, recent studies indicate that retinal neuroaxonal damage and visual impairment after ON are similar in both diseases, suggesting that a higher attack rate in MOGAD, compared with fewer, but more severe ON episodes in AQP4-IgG+ NMOSD, results in comparable tissue damage.<sup>39</sup>

Previous case series in NMOSD reported that IL-6R blockade with TCZ confers beneficial effects for attack prevention in retrospective and 1 prospective case series in NMOSD.<sup>20,24,40,41</sup> Moreover, the recent TANGO trial showed that TCZ (n = 56 patients) better prevents NMOSD attacks than azathioprine (n = 52 patients).<sup>42</sup> Finally, 2 recent pivotal trials compared satralizumab with placebo, either as a monotherapy (SakuraStar)<sup>14</sup> or as an add-on therapy (SakuraSky)<sup>13</sup> and revealed that satralizumab reduces the relapse rate, particularly in AQP4-IgG+ NMOSD. However, follow-up in these trials was rather short with a range of 60–90 weeks<sup>42</sup> and a median treatment duration in the double-blind period of 107.4

and 92.3 weeks, respectively.<sup>13,14</sup> Moreover, real-world NMOSD patient cohorts on TCZ covered a limited number of patients (ranging from 3 to 19)<sup>20,24,40,41</sup> and did not investigate the effects of IL-6R blockade in MOGAD. Of note, 12/36 patients with AQP4-IgG+ NMOSD from this work were previously reported in 4 TCZ-specific studies.<sup>21,22,25,26</sup>

In our study on 57 patients including 14 individuals with MOGAD and 36 individuals with AQP4-IgG+ NMOSD, we provide real-world data with a mean and maximum treatment duration of nearly 3 and 9 years, respectively, with 65% of patients receiving TCZ as monotherapy. The mean ARR, as a primary outcome measure, significantly decreased during TCZ treatment by 80% in the total cohort and by 76% in the AQP4-IgG+ subgroup. Of note, our main results—ARR reductions in MOGAD and AQP4-IgG+ NMOSD subgroups and the whole cohort—remained stable when the analysis was restricted to patients receiving TCZ for at least 12 months. Our findings confirm the recent pivotal trials on the beneficial effects of IL-6 blockade by satralizumab in NMOSD, particularly for AQP4-IgG-seropositive patients. We also observed clinical stabilization and reduced spinal cord MRI activity in AQP4-IgG+ patients, along with decreased or stable AQP4-IgG titers in most of them, whereas pain remained constant during TCZ. The decrease of the EDSS score, spinal cord MRI activity, and AQP4-IgG titers could at least in part be explained by fact that baseline values were ascertained during the acute phase and follow-up measures mainly during remission phase while TCZ treatment. Beyond that, the AQP4-IgG titer decrease/stabilization may also be an indirect effect of the IL-6 blockade by TCZ, as IL-6 signaling promotes the autoantibody production from plasmablasts in NMOSD.<sup>18</sup> Our clinical and imaging findings are in line with those in smaller retrospective case series and the TANGO trial.<sup>22,23,41,42</sup> The effect on pain remains ambiguous, as it was reported in smaller case series,<sup>20,22</sup> but was not confirmed in our study or the satralizumab SakuraSky trial.<sup>13</sup>

Regarding the patients with double-seronegative NMOSD, we observed a significant ARR reduction, when considering all 7 patients, independently of the treatment duration, which was not reported in the pivotal trials for satralizumab and could be explained by the heterogeneity of this less-defined patient group, hampering direct comparisons.<sup>13,14</sup>

In line with the satralizumab studies, no effect on EDSS score, pain, and, furthermore, on MRI activity, was detectable in AQP4-IgG+ NMOSD in this study.

For MOGAD, treatment recommendations are scarce, and approaches well established for AQP4-IgG+ NMOSD such as CD20-mediated B-cell depletion have shown limited efficacy in MOGAD.<sup>43-45</sup> Another MOGAD treatment study showed that under azathioprine therapy, 14 of 17

MOG-IgG+ patients (82%) had at least 1 attack, particularly during the first 6 months and in patients without concomitant steroid therapy.<sup>3</sup> Reports on IVIG or MTX treatment in MOGAD are so far rather anecdotal<sup>3,46</sup>; however, recent data revealed the lowest ARR being associated with an IVIG maintenance therapy (n = 10 patients), compared with RTX, MMF, and AZA.<sup>45</sup> Of note, recent findings in a Chinese MOGAD cohort indicate that MMF may prevent relapses, particularly with concomitant oral prednisolone.<sup>47</sup> Compared with untreated adult patients with MOGAD, AZA, MMF, and RTX, but not MTX, mitoxantrone, and cyclophosphamide, significantly reduced the risk of new relapses and the ARR in a cohort of 125 patients.<sup>48</sup> So far, only 14 different MOGAD patients, treated IV and/or subcutaneously with TCZ, were reported in 7 small case reports/series<sup>23,26,29-33</sup>; 6 of these 14 patients were included in the present cohort.

Here, in our series of 14 patients with MOGAD, the ARR decreased by 93%, the median EDSS score was reduced from 2.75 to 2.0 over a mean TCZ treatment duration of 31 months, and an anti-inflammatory effect was obvious also on brain MRI. Notably, the ARR reduction persisted when considering only those patients who were treated for more than 12 months. Again, the effect on EDSS score and MRI activity was mainly driven by the fact of high disease activity at baseline and remission phase at follow-up assessment. Most patients with MOGAD (79% and 73% for the patients treated for >12 months, respectively) remained relapse free, and in 57% of them, TCZ was used as monotherapy. The remaining 6 patients were cotreated with LDS (n = 4), monthly HDS plus IVIG (n = 1), or MTX (due to psoriasis, n = 1). No effects were found on pain, which is a common symptom in MOGAD,<sup>49</sup> and spinal cord MRI activity. A single attack during TCZ treatment occurred in 21% of patients with MOGAD, 2 or 4 attacks in 14% and 7% of patients, respectively. Our findings are in line with those of a recent study, which showed that TCZ therapy was associated with clinical and radiographic relapse freedom, resolution of eye pain, and ability to discontinue corticosteroids in a cohort of 10 patients with MOGAD over an average treatment duration of 28.6 months.<sup>33</sup> Overall, when considering disease activity, including ARR, as well as suspected side effects during TCZ therapy, we did not observe a clear advantage of add-on treatments, supporting the use of TCZ as monotherapy.

Considering safety, adverse events occurred within the expected range based on the established use of TCZ in clinical practice. Infusion-related reactions appeared in 12% of all patients, and infections of the urinary or respiratory tract were reported with similar frequency. Of note, (re)activation or worsening of chronic latent inflammatory diseases was observed in patients with already established SLE (n = 2) and psoriasis (n = 2), indicating that these patients should be particularly monitored. Laboratory changes included mild to

moderate neutropenia in 18% and liver enzyme changes in 35% of patients. Total cholesterol, as well as HDL and LDL cholesterol levels, did not change during TCZ treatment, as expected.<sup>22</sup>

An obvious limitation of this study is the retrospective multicenter design resulting in heterogeneity of TCZ treatment regimens and MRI protocols, as well as missing data, e.g., the lack of MOG-IgG testing in 10/36 (28%) AQP4-IgG+ patients. However, the latter issue may not be a serious limitation as co-occurrence of AQP4- and MOG-IgG at significant titers is extremely rare.<sup>50</sup> Another constraint is the relatively small sample size, which is justifiable by the rarity of NMOSD and MOGAD on a concomitant rare and off-label treatment with TCZ. Nevertheless, we attempted to enroll all of these seldom patients from 2 of the largest cohorts in Europe, NEMOS in Germany and NOMADMUS in France, and additional patients from other countries. Moreover, because of the lack of a control cohort and the timing of the switch to TCZ (i.e., during a phase of active disease), we have to consider regression to the mean as an important limitation of our study design, as mean disease activity could decrease spontaneously even without treatment.

Despite these limitations, this largest real-world study supports the long-term safety and therapeutic relevance of the IL-6 pathway in RTX-refractory AQP4-IgG+ NMOSD for up to 9 years. Moreover, our findings suggest a similar role for MOGAD, pointing toward the need for randomized controlled trials to evaluate the efficacy of IL-6 blockade in patients with MOGAD. This study provides Class III evidence that TCZ decreases the probability of relapses in patients with refractory MOGAD and NMOSD.

### Acknowledgment

The authors thank all patients and their families for contributing to our study. Contributing members of the Neuromyelitis Optica Study Group are listed in Appendix 2. MR, IA, GL, IK, and OA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

### Study Funding

The Neuromyelitis Optica Study Group (NEMOS) is partially funded by the German Ministry for Education and Research (BMBF) as part of the German Competence Network Multiple Sclerosis (KKNMS; for NEMOS NationNMO FKZ 01GI1602).

### Disclosure

M. Ringelstein received speaker honoraria from Novartis, Bayer Vital GmbH, Roche, Alexion, and Ipsen and travel reimbursement from Bayer Schering, Biogen Idec, Merz, Genzyme, Teva, Roche, and Merck. I. Ayzenberg received personal fees from Roche, Alexion, and Merck and received research support from Diamed, none related to this study.

G. Lindenblatt received travel reimbursement from Bayer HealthCare, not related to this study. K. Fischer, A. Gahlen, and G. Novi report no disclosures relevant to the manuscript. H. Hayward-Könnecke received compensation for advice, lecturing, or travel support from Biogen, Genzyme, Merck, Novartis, and Teva. S. Schippling received consulting and speaker fees and travel grants from Biogen Idec, Bayer, Merck, Sanofi Genzyme/Sanofi Aventis, Novartis, and Teva and research grants from Bayer, Biogen Idec, Merck Serono, Sanofi Genzyme/Sanofi Aventis, and Novartis. He is currently an employee at Roche Pharmaceutical Research and Development Neuroscience and Rare Diseases. P. Rommer received speaker or consultancy honoraria from AbbVie, Alexion, Almirall, Biogen, Daiichi Sankyo, Merck, Novartis, Sanofi Genzyme, Sandoz, and Roche and research funding from Biogen, Merck, Roche, and Austrian Science Funds (KLI 837-8), none related to this study. B. Kornek received speaker honoraria from Bayer, Biogen, Celgene-BMS, Merck, Novartis, Roche, Sanofi Genzyme, and Teva and participated in advisory boards from Celgene-BMS, Merck, Novartis, Sanofi Genzyme, and Roche. No COIs related to this study. T. Zrzavy has participated in meetings sponsored by or received travel funding from Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva. D. Biotti reports no disclosures relevant to the manuscript. J. Ciron received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Novartis, Merck, Genzyme, and Roche, none related to this study. B. Audoin reports no disclosures relevant to the manuscript. A. Berthele has received speaker and consulting honoraria from Alexion, Biogen, Bayer HealthCare, Celgene, Merck, Novartis Pharma, and Roche, all outside the submitted work. K. Gighlhuber reports no disclosures relevant to the manuscript. H. Zéphir reports speaker honoraria, travel reimbursement, and consulting fees from Biogen Idec, Merck, Novartis, Roche, Teva, Genzyme, and Bayer Pharma and research grants from Roche, Teva, ARSEP, and LFSEP, not relevant to the manuscript. T. Kümpfel has received speaker honoraria and/or personal fees for advisory boards from Bayer HealthCare, Teva Pharma, Merck, Novartis Pharma, Sanofi Aventis/Genzyme, Roche Pharma, and Biogen and grant support from Novartis and Chugai Pharma in the past. R. Berger reports no disclosures relevant to the manuscript. J. Röther received speaker honoraria from Bayer Vital GmbH, Bristol Myers Squibb, Pfizer, AstraZeneca, Portola, Daiichi Sankyo, and Servier, none related to this study. V. Häußler reports no disclosures relevant to the manuscript. J.-P. Stellmann received research grants and speaker honoraria from Biogen, Genzyme, and Alexion. D. Whittam and A. Jacob report no disclosures relevant to the manuscript. M. Krämer received honoraria for teaching and scientific activities from Chugai Pharma, Janssen-Cilag, and Roche Pharma. A. Gueguen served as an editorial board member of Biogen Idec, Novartis, and Teva and received consulting fees from Biogen Idec, Novartis, and Teva; he received funding for

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## Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* February 8, 2021. Accepted in final form August 25, 2021.

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## Appendix 1 (continued)

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Continued

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*Neurol Neuroimmunol Neuroinflamm* 2022;9;

DOI 10.1212/NXI.0000000000001100

**This information is current as of November 16, 2021**

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