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Long-Term Treatment With Interleukin-6 Receptor Inhibitor Tocilizumab in Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease

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Abstract

Background and Objectives

Data about efficacy and safety of disease-modifying therapeutic options in myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) are scarce. Interleukin-6 signaling has been suggested to be involved in the pathogenesis of MOGAD. The aim of this study was to evaluate the effectiveness and safety of the interleukin-6 receptor inhibitor tocilizumab (TCZ) in MOGAD.

Methods

In this longitudinal, retrospective study, we included patients diagnosed with MOGAD at a single tertiary referral center who received treatment with TCZ for at least 6 months. The annualized relapse rate (ARR), the Expanded Disability Status Scale (EDSS) scores, imaging findings, autoantibody titers, and adverse events were evaluated before and after initiation of TCZ. The assessment of side effects, such as dyslipidemia, impaired liver function, and infectious complications, was based on anamnestic, clinical, and laboratory data.

Results

Sixteen patients (mean age 49.4 years, range 28–71; 43.8% female) with a median observation period of 2.5 years on TCZ treatment (range 0.5–10.0) were enrolled. The median ARR significantly decreased from 0.75 (interquartile range [IQR] 0.5–1.0) at 24 months before TCZ initiation to 0 (IQR 0-0) at 12 months after TCZ initiation (95% CI 0.4–1.0, $p = 0.005$). The EDSS score improved from 2.8 (IQR 2.0–3.5) at baseline to 2.3 (IQR 1.1–3.0) at 12 months after starting TCZ (95% CI 0.0–1.5, $p = 0.046$). The median visual acuity improved significantly from 0.5 (IQR 0.3–0.9) before initiation of TCZ to 0.9 (IQR 0.5–1.0; $p = 0.0003$) at the last follow-up. In the first year after starting TCZ treatment, MOG-IgG titers decreased in 10 of 13 patients (76.9%). No patient showed radiologic progression under TCZ. Infectious adverse events requiring medical treatment occurred in 4 of 16 patients (25%). Side effects such as dyslipidemia and impaired liver function were frequent but rarely required the interruption of TCZ. In 5 patients (31.3%), the route of administration of TCZ was switched to subcutaneous injections over the disease course.

Discussion

TCZ shows promise as a potentially effective treatment in MOGAD, and its subcutaneous administration may improve long-term therapy adherence. However, the retrospective design and small cohort size limit generalizability. Future prospective randomized trials are needed to determine its definitive efficacy.

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Glossary

ARR = annualized relapse rate; **EDSS** = Expanded Disability Status Scale; **GGT** = α-glutamyl transferase; **GOT** = glutamate oxaloacetate transaminase; **GPT** = glutamate pyruvate transaminase; **IL-6** = interleukin-6; **IQR** = interquartile range; **LDL** = low-density lipoprotein; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disease; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **TCZ** = tocilizumab.

Classification of Evidence

This study provides Class IV evidence that treatment with TCZ reduces ARR and improves disability and visual acuity compared with pretreatment in patients with MOGAD.

Introduction

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) is an autoimmune demyelinating disease of the CNS characterized by a relapsing-remitting course. Approximately half of untreated patients experience relapses in the first 10 years after disease onset.[1] Because the number of relapses correlates with a higher disability score,[2] there is an urgent need to find effective disease-modifying therapies to prevent accumulating disability over time.

Since identifying MOGAD as a distinct disease entity from neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS), defining the best treatment strategy to prevent further relapses has proven challenging.[3,4] Moreover, the first diagnostic criteria for MOGAD, proposed in 2023,[5] highlighted the heterogeneity of patients included in previously published studies. While no approved medication for MOGAD is available, several agents have been used off-label as first-line maintenance therapy in clinical practice, mostly azathioprine, mycophenolate mofetil, rituximab, or IV immunoglobulin.[6-9]

Efficacy in MOGAD was shown for some of these treatments,[7,8] although they were not always as effective as in NMOSD cohorts.[9] In a meta-analysis including 238 patients with MOGAD, only 55% of the participants were relapse-free while being on treatment with rituximab,[10] which is insufficient considering that a relevant percentage of patients do not completely recover after a relapse.[11-13]

MOG-IgG is believed to cause demyelination through activation of different pathways of the innate and, to a larger extent, the adaptive immune system. Their binding to the MOG protein on the surface of oligodendrocytes results in inflammation, involving the release of different cytokines, particularly interleukin-6 (IL-6). IL-6 is increased in serum and CSF of patients with MOGAD, especially during relapses.[14]

Tocilizumab (TCZ) is a humanized anti–IL-6 receptor monoclonal antibody. Previous studies in NMOSD showed an effect of TCZ on the regulation of B-cell differentiation and the inhibition of T-cell activation,[15] resulting in approximately 90% successful relapse reduction.[16,17] Considering the similar pathophysiologic features of NMOSD and MOGAD,[18,19] several case reports have been published showing clinical stabilization of patients with MOGAD on TCZ therapy after experiencing relapses under other therapy regimens.[20,21] Similar findings have been observed in a retrospective study, which evaluated maintenance TCZ in adult patients with MOGAD[22] over a period of 1.5 years. However, in recent clinical practice data regarding immunotherapy choices for MOGAD, TCZ remains notably underrepresented, reflecting the limited experience with its use in this patient population.[23,24] Furthermore, potential side effects—both infectious and noninfectious such as dyslipidemia and impaired liver function—as well as long-term tolerability of TCZ in patients with MOGAD remain insufficiently understood.

The aim of this study was to evaluate the effectiveness of TCZ in reducing relapse activity and disability and its long-term tolerability in patients with MOGAD.

Methods

Study Design and Participants

In this monocentric, observational, retrospective study, we obtained demographic and clinical information through review of regular medical records at the Neuroimmunology Outpatient Clinic at the University Hospital Zurich. We had access to the regular laboratory tests and to the cerebral and spinal MRI scans performed for clinical purposes.

Patients were identified by screening our clinical database using the keywords "MOG," "Actemra," and "tocilizumab." Only patients aged 18 years or older and who fulfilled the Banwell 2023 diagnostic criteria[5] were included. Patients were excluded from the analysis if they were treated with TCZ for less than 6 months to avoid possible overestimation of the relapse-free proportion in the TCZ group. Patients were also excluded if their medical records were incomplete.

MOG-IgG antibodies were measured in-house using a fixed cell-based assay. Follow-up measurements were performed in-

house using the same fixed cell-based assay. In all 10 cases in which serum samples were further sent to our external reference laboratory, the positive results were confirmed using a live cell-based assay. In 1 case with a borderline elevated MOG-IgG titer reported by our reference laboratory, the sample was sent to a third laboratory, where the positive result was finally confirmed. Owing to the retrospective nature of this study, the number and time point of MOG-IgG measurements varied, depending on the clinical course of the disease. To improve comparability, we limited our analysis to measurements taken from 1 year before up to 1 year after initiation of TCZ treatment.

The assessment of side effects including infectious complications was based on anamnestic, clinical, and laboratory data. We defined hypercholesterinemia as total cholesterol >200 mg/dL (>5.0 mmol/L) or low-density lipoprotein (LDL) >120 mg/dL (>3.0 mmol/L), and triglyceridemia as triglycerides > 180 mg/dL (2.0 mmol/L). We considered the diagnosis of new-onset dyslipidemia if the values exceeded the cutoff in 2 consecutive measurements. Increased liver function tests were defined as glutamate oxaloacetate transaminase (GOT) or glutamate pyruvate transaminase (GPT) >35 U/L and/or α-glutamyl transferase (GGT) >40 U/L. In addition, in this case, we considered new-onset increase in liver function tests if the values exceeded the cutoff in 2 consecutive measurements.

Statistical Analysis

The cohort was described using absolute and relative frequencies, along with the mean or median and appropriate measures of variability such as SD, interquartile range (IQR), and range (minimum, maximum). Assuming that our data are not normally distributed, only nonparametric tests were used. The annualized relapse rate (ARR) before and after initiation of TCZ treatment was calculated as the ratio of the number of demyelinating attacks per year. A relapse was defined as a new neurologic deficit or an acute, objective worsening of a preexisting neurologic deficit without an alternative explanation (e.g., concomitant infection) lasting at least 24 hours. The disability was measured using the Expanded Disability Status Scale (EDSS). The visual acuity of affected eyes was assessed using standardized testing (ETDRS or logMAR charts) before starting TCZ and at the last follow-up. To compare the median ARR, median EDSS scores, and median visual acuity before and after starting TCZ, the Wilcoxon signed-rank test was used. The difference between data before and after TCZ treatment initiation was considered as statistically significant if $p < 0.05$. The statistical analysis was performed with Prism version 10.3.1 (GraphPad, Boston, MA). Figures were crafted with Affinity Designer 2 (Serif).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Ethics Board of the Canton of Zurich (KEK-ZH-Nr. 2024-00239). All patients provided written informed consent for data collection.

Data Availability

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

Results

Demographics and Clinical Presentation

Among 75 patients with MOGAD in our database, 16 patients met the inclusion criteria (Figure 1). Seven patients were female (7/16, 43.8%) (Table 1). The median age at disease onset was 49.4 years (range 28–71 years), and the median body mass index was 27.2 kg/m^2 (range 18.7–34.1). The most common clinical manifestation was optic neuritis (13/16 patients, 81.3%), with bilateral optic nerve involvement in 8 of these patients (61.5%). Seven patients had myelitis (7/16, 43.8%) while 4 patients developed both ocular nerve and spinal involvement over the course of the disease (4/16, 25%).

TCZ Initiation, Previous Therapies, and Concurrent Treatments

All patients received TCZ as monotherapy, with a median interval of 9.5 months (range 1–98) between disease onset and treatment initiation. In 6 patients, TCZ was started after the first MOGAD manifestation (6/16, 37.5%), whereas the remaining 10 patients received it after 2 or more attacks (10/16, 62.5%).

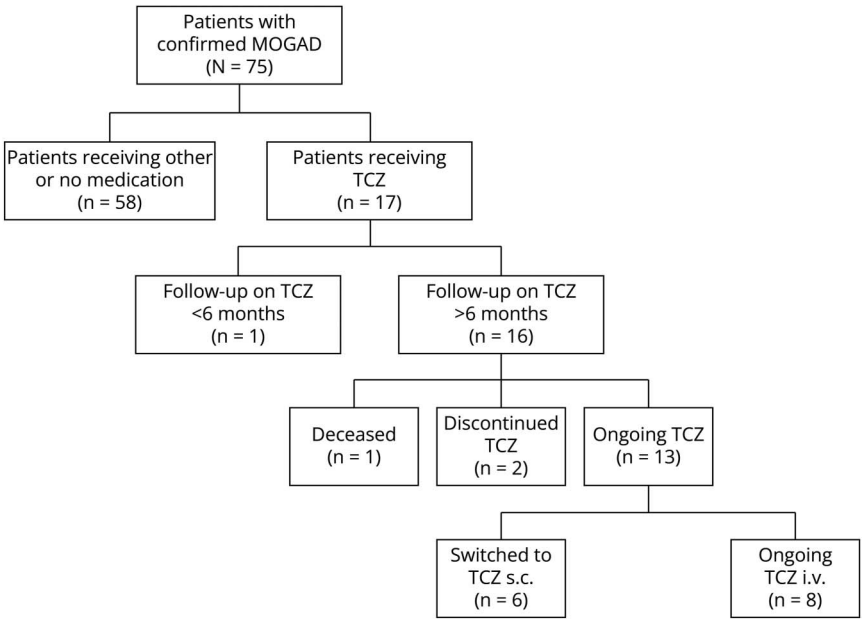
All patients received high-dose corticosteroid pulse therapy during their initial attack and for any subsequent acute relapses, including the 2 patients who experienced relapses while on TCZ treatment. Tapering protocols varied between patients (2–4 months, 10 months in 1 case). None of the patients received long-term corticosteroids at a stable maintenance dose.

In most of the patients (62.5%), TCZ was used as the first-line disease-modifying therapy, while the remaining patients (37.5%) had previously received other steroid-sparing immunomodulatory treatments. All 6 had been treated with rituximab; among them, 2 had previously received cyclophosphamide, 1 received a single dose of natalizumab, and 1 had been previously treated with mycophenolate mofetil and azathioprine (Figure 2). The switch to TCZ was prompted by persistent disease activity in 2 patients (12.5%), while in the remaining 4 cases, the change was due to other factors such as incomplete B-cell depletion or an increased risk of infectious complications in older patients receiving rituximab.

Effectiveness of TCZ

The median observation period on TCZ treatment was 29.5 months (range 6–126). Most relapses occurred before the initiation of TCZ. Only 2 patients (2/16 cases, 12.5%), both men, experienced a relapse while on TCZ treatment. The median ARR before the start of TCZ was 2.8 (range 0.1–12.0) when the whole patient history was considered, and 0.75 (range 0–3.5) when considering the last 24 months before TCZ initiation. The median ARR in the 12 months after

Figure 1 Flowchart Illustrating the Inclusion of Patients With MOGAD



Seventy-five patients with confirmed MOGAD were screened in our local database, 17 of whom received TCZ over the course of the disease. Among them, 16 were treated with TCZ for at least 6 months and were included in the analysis. At the time of data collection, 13 patients were still on TCZ, 8 patients were still on IV TCZ, and 5 patients had switched to subcutaneous administration. MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; TCZ = tocilizumab.

TCZ initiation significantly decreased to 0 (range 0.0–1.9) (p = 0.005, 95% CI 0.4–1.0) (Figure 3A). Likewise, the median EDSS score improved from 2.8 (range 0.0–4.0) at baseline to 2.3 (range 0.0–4.0) 1 year after starting TCZ (p = 0.046, 95% CI 0.0–1.5) (Figure 3B). The median visual acuity improved significantly from 0.5 (IQR 0.3–0.9) before initiation of TCZ to 0.9 (IQR 0.5–1.0; p = 0.0003) at the last follow-up. The proportion of patients (4/16) who had a visual acuity below 0.1 (decimal) in at least 1 eye at the final follow-up after initiation of TCZ remained unchanged compared with the period before treatment initiation.

Effect of TCZ on MOG-IgG Titers

Longitudinal assessment of MOG-IgG titers was available in 13 of 16 patients. In the first year after starting TCZ, the MOG-IgG titer decreased in 10 of 13 patients (10/13, 76.9%). In 2 patients, the titer remained stable (2/13 cases, 15.3%), and in 1 patient, the titer slightly increased (1/13, 7.6%; Figure 4). One patient had initially been diagnosed with MOGAD based on a positive MOG-IgG result from an external laboratory (live cell-based assay) 1.5 years before their first presentation at our center. During subsequent follow-up at our institution after therapy initiation, MOG-IgG testing was persistently negative, consistent with seroconversion. Both patients who experienced MOGAD relapses while on TCZ therapy still showed a reduction in MOG-IgG titers in the subsequent measurement compared with the value immediately preceding the relapse.

MRI Findings During Treatment With TCZ

All patients underwent a cerebral and spinal MRI scan before starting TCZ. Follow-up MRI data were available for the brain in 15 patients and for the spinal cord in 14 patients. The median radiologic follow-up time was 32 months. In clinically stable patients, cerebral MRI was performed annually and spinal MRI every 12–24 months. If new symptoms emerged, contrast-enhanced MRI was performed based on clinical judgment.

At treatment initiation, cerebral MRI abnormalities consistent with MOGAD were present in 11 of 15 patients (73.3%) and spinal cord lesions were observed in 5 of 14 patients (35.7%). At the last follow-up (range: 7.0–145.0 months), no new cerebral or spinal lesions were detected. Among the 11 patients with initial cerebral lesions, 8 (72.7%) showed either a reduction in lesion number/size or complete resolution (5 reduction, 3 complete resolution). All patients (100%) with initial spinal cord abnormalities demonstrated a decrease in lesion burden. Of note, the 2 patients experiencing relapses during TCZ treatment had stable MRI findings because the relapses consisted of MR-negative optic neuritis. In both cases, the diagnosis of optic neuritis was based on the presence of ocular pain, reduced visual acuity, a relative afferent pupillary defect, and deterioration on optical coherence tomography, according to diagnostic criteria suggested by Petzold et al.[25]

Tolerability and Safety of Tocilizumab

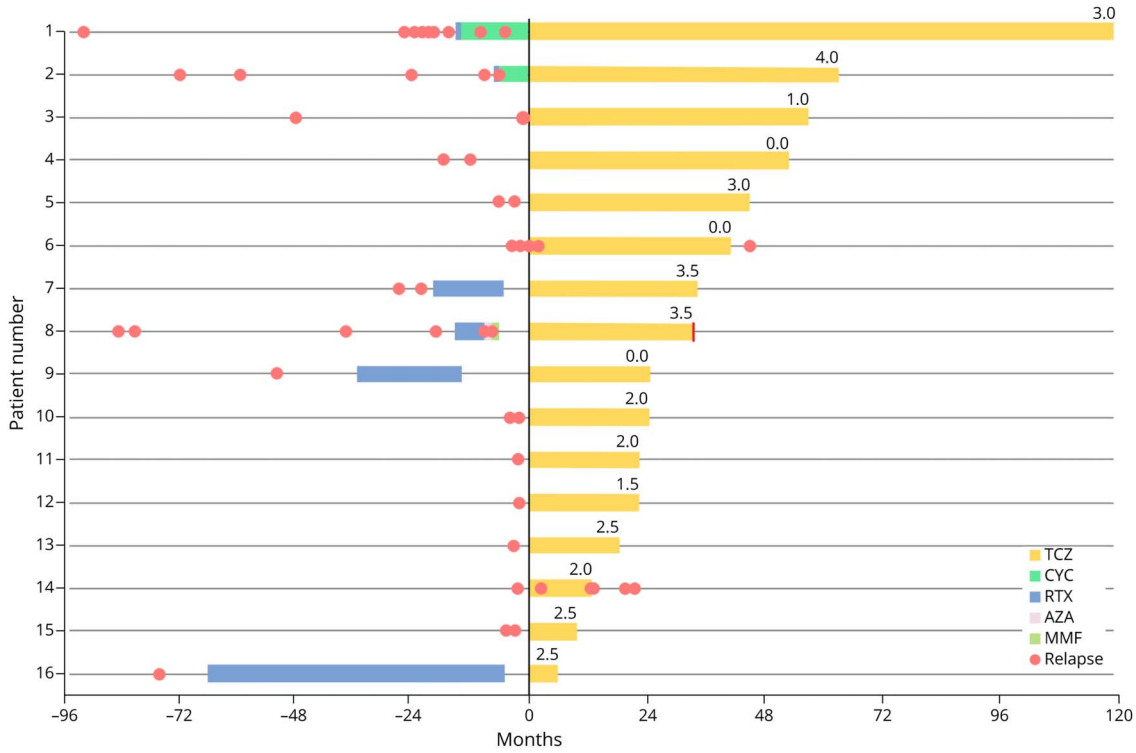
More than 80% of patients with MOGAD were still on TCZ at the time of the data collection (13/16, 81.3%) while 3 patients had stopped the treatment. In the first patient, the therapy was switched from TCZ to rituximab because of new clinical disease activity. In the second patient, TCZ was discontinued because the patient requested a therapy pause due

Table 1 Demographics and Patient Characteristics

Demographics	MOGAD (n = 16)
Sex, n: female/male (% female)	7/9 (43.8)
Age at disease onset, y: mean (SD)	49.4 (13.1)
Clinical presentation	
Optic neuritis, n (%)	13/16 (81.3)
Myelitis, n (%)	7/16 (43.8)
Multifocal, n (%)	4/16 (25)
Disease duration before TCZ, mo: median (IQR)	9.5 (2.3–76.8)
Number of attacks before TCZ	
1 attack	6/16 (37.5)
≥ 2 attacks	10/16 (62.5)
Age at TCZ start, y: mean (SD)	52.1 (14.1)
Duration of TCZ therapy, mo: median (IQR)	29.5 (20.0–52.8)
ARR before TCZ, n: median (IQR)	2.8 (1.1–6)
ARR in last 2 y before TCZ, n: median (IQR)	0.8 (0.5–1.0)
ARR under TCZ, n: median (IQR)	0 (0)
EDSS score before TCZ, median (IQR)	2.8 (2.0–3.5)
EDSS score on TCZ, median (IQR)	2.3 (1.3–3.0)
Visual acuity before TCZ, decimal: median (IQR)	0.5 (0.3–0.9)
Visual acuity at last follow-up, decimal: median (IQR)	0.9 (0.5–1)
Brain MRI on TCZ, n (%)	
Pathologic brain MRI	11/15 (73.3)
Lesion burden increased compared with baseline	0/15 (0)
Lesion burden decreased compared with baseline	8/11 (72.7)
Lesions resolved completely	3/11 (27.2)
Spinal MRI on TCZ, n (%)	
Pathologic spinal MRI	5/14 (35.7)
Lesion burden increased compared with baseline	0/14 (0)
Lesion burden decreased compared with baseline	4/5 (80)
Lesions resolved completely	1/5 (20)
Dyslipidemia before TCZ, n: total (%)	8/16 (50)
Increased total cholesterol before TCZ, n: total (%)	8/16 (50)
Increased LDL cholesterol before TCZ, n: total (%)	6/16 (37.5)
Increased triglycerides before TCZ, n: total (%)	3/16 (18.8)
Impaired liver function before TCZ, n: total (%)	4/16 (25)
Increased transaminases before TCZ, n: total (%)	2/16 (12.5)
Increased GGT before TCZ, n: total (%)	3/16 (18.8)

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; GGT = α-glutamyl transferase; IQR = interquartile range; LDL = low-density lipoprotein; n = number; TCZ = tocilizumab.

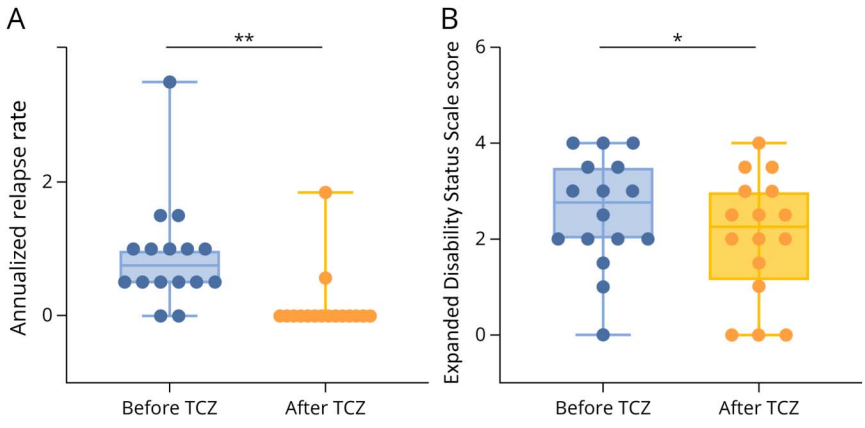
Figure 2 Relapse Activity of Patients With MOGAD Before and After Initiation of TCZ



Each horizontal line corresponds to 1 patient (TCZ1 to TCZ16), listed in decreasing order according to the duration of the TCZ therapy. Initiation of TCZ was set as month zero (vertical black line). On the left from the black line is the time before initiation of TCZ (negative months) and on the right the time after starting TCZ (positive months). Red circles represent relapses. The orange bars show the duration of TCZ treatment, and other color bars indicate previous treatments. Treatment with steroids and a single dose of natalizumab is not shown. Italicized numbers above the bars indicate the EDSS score at the last follow-up while the patient was receiving TCZ. The red vertical line marks the time point of the patient's death. AZA = azathioprine; CYC = cyclophosphamide; MMF = mycophenolate mofetil; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; RTX = rituximab; TCZ = tocilizumab.

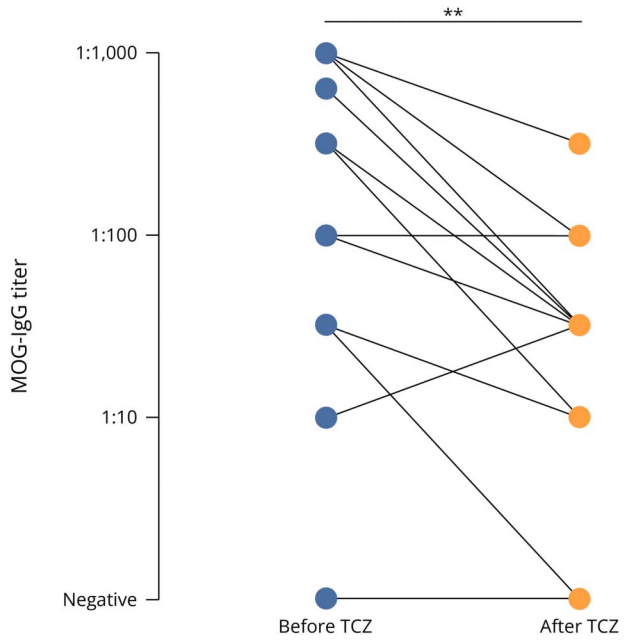
to back pain and headaches, which were considered possibly related to TCZ. Both patients who discontinued TCZ experienced further MOGAD relapses, 5 and 6 months, respectively, after discontinuation. In the last patient, the treatment was interrupted due to death from a severe infection (mentioned further). In all patients, TCZ was initially administered intravenously. The route of administration was switched from IV to subcutaneous injections over the course of treatment in 5 patients (5/16, 31.3%) for different reasons. In 1 patient, the reason was to enable administration of the drug at home during the COVID-19 pandemic. Another patient switched to subcutaneous TCZ because of poor venous

Figure 3 ARR and EDSS Scores Before and After Starting TCZ Treatment in Patients With MOGAD



Box-and-whisker plots illustrating the median, IQR, and range ARR (A) and EDSS score (B) 24 months before and 12 months after starting TCZ treatment (Wilcoxon signed-rank test, respectively, $p = 0.0084$ in (A) and $p = 0.0338$ in (B)). Each dot represents a single patient (n = 16). ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; TCZ = tocilizumab.

Figure 4 Longitudinal Course of MOG-IgG Titers Before and Under TCZ Treatment



Individual courses of MOG-IgG titers (assessed by cell-based assays) in patients with MOGAD (n = 13) within 12 months before starting TCZ (blue points) and 1 year after therapy initiation (orange points); $p = 0.0029$. Titers below 1:10 were considered as negative. MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; TCZ = tocilizumab.

access. In another patient, the change was made because the patient had to undergo 2 surgical procedures in a short time frame. The last 2 patients desired to reduce the number of hospital visits. All patients who switched to subcutaneous treatment have remained relapse-free so far (Figure 2).

Infections

Relevant infections occurred in 4 patients (4/16, 25%) treated with TCZ. One patient had to be treated for a local genital fungal infection (Table 2). Three patients were hospitalized and treated with IV antibiotics: 1 patient for erysipelas and 2 for bilateral pneumonia, 1 of whom died. The patient who died was 77 years old and had previously been treated with azathioprine, mycophenolate mofetil, and rituximab. Owing to ongoing relapse activity (specifically a seventh episode of optic neuritis), treatment was switched to TCZ after a risk-benefit assessment, with the goal of preventing further severe visual deterioration. She was hospitalized for fever and dyspnea 11 days after the last TCZ administration. She quickly developed distributive shock, acute-on-chronic kidney failure, and delirium. The shock did not respond to volume, vasoactive medications, and steroids, and the clinical condition deteriorated despite escalation of antibiotic therapy. PCR testing for adenovirus was positive, but no additional pathogens were isolated from the various samples. According to the patient's will, supportive treatment was discontinued 1 week after hospitalization and the patient died (Table 2).

Table 2 Safety Profile of TCZ in Patients With MOGAD

Adverse events	Patients (n = 16)
Infectious diseases, n total (%)	4/16 (25)
Bacterial infection, n (%)	3/16 (18.8)
Pneumonia, n (%)	2/16 (12.5)
Erysipelas, n (%)	1/16 (6.3)
Fungal infection, n (%)	1/16 (6.3)
Hospitalization needed, n (%)	3/16 (18.8)
Death, n (%)	1/16 (6.3)
New-onset dyslipidemia, n: total (%)	6/8 (75)
New increased total cholesterol, n (%)	4/8 (50)
New increased LDL cholesterol, n (%)	4/8 (50)
New increased triglycerides, n (%)	5/8 (62.5)
Worsening of known dyslipidemia, n (%)	2/8 (25)
Necessity to start statin treatment, n (%)	3/8 (18.8)
New-onset liver function impairment, n total (%)	3/12 (25)
New-onset transaminase increase, n (%)	3/12 (25)
New-onset GGT increase, n (%)	0/12 (0)
Other side effects	
Tiredness, headaches, back pain, n (%)	1/16 (6.3)

Abbreviations: GGT = α-glutamyl transferase; LDL = low-density lipoprotein; n = number.

Laboratory Findings

Eight patients (8/16, 50%) had dyslipidemia before starting TCZ. More precisely, 8 patients had increased total cholesterol (8/16, 50%), 6 had increased LDL values (6/16, 37.5%), and 3 had hypertriglyceridemia (3/16, 18.8%). Among these patients, 2 started statin therapy after TCZ initiation (2/8, 25%). Considering the 8 patients without preexisting dyslipidemia, 6 developed it after starting TCZ (6/8, 75%) (Table 2). In patients with new-onset hypercholesterolemia, LDL-cholesterol levels were only mildly elevated (<4.1 mmol/L) in all cases. Statin therapy was initiated in 1 patient because of the presence of concomitant cardiovascular risk factors.

Four patients had abnormal liver function tests before starting TCZ (4/16, 25%). Transaminases (GPT and/or GOT) were elevated in 2 of 16 patients (12.5%), and GGT was elevated in 3 patients (3/16, 18.8%). Of the 12 patients without preexisting impairment of liver function tests, an elevation of GPT and/or GOT was found in 3 patients (3/12, 25%). Liver enzyme levels either stabilized or regressed spontaneously over the course of several weeks, and no further investigation was deemed necessary. No patient showed an increase in GGT after starting TCZ.

Other Side Effects

Relevant headache, which is described as a frequent side effect of TCZ, was a rare event in our cohort. Only 1 patient (1/16, 6.3%) experienced headaches, which promptly disappeared few weeks after the last TCZ infusion. Neutropenia was not observed in any patient.

Discussion

Owing to the lack of clinical data and randomized trials, MOGAD is treated heterogeneously across different regions and countries and there is no consensus on which therapy to use to prevent relapses. In this retrospective longitudinal study, we report long-term experience with TCZ treatment in patients with MOGAD for up to 10 years.

In line with previously reported case series and reports,[20-22] our long-term single-center experience treating MOGAD with TCZ suggests notable therapeutic effectiveness, as reflected by a marked and sustained decrease in ARR for up to 10 years after treatment initiation. Previously, in a retrospective study of 14 patients with MOGAD, Ringelstein et al. suggested that TCZ was associated with high effectiveness and a good safety profile[22] for a median observational time of 16 months. Moreover, we report a significant improvement in clinical end points, including EDSS scores and visual acuity. Paraclinical measures also stabilized or improved: in all but 3 patients, the MOG-IgG titer declined within the first year after TCZ initiation, and no patient showed radiologic progression under TCZ. These findings support the need for a more comprehensive evaluation of IL-6 receptor inhibition in patients with MOGAD through prospective clinical trials.

Although MOGAD can have a monophasic course,[5] most patients included in our study experienced at least 2 relapses before starting TCZ. Therefore, it seems unlikely that the possible self-limiting natural course of the disease had a significant influence on ARR reduction. Concomitant prednisolone treatment may be another potential confounding factor in assessing the effectiveness of TCZ.[26] While all patients in our cohort received high-dose corticosteroid pulse therapy for acute attacks, followed by tapering, none remained on long-term corticosteroids at a stable maintenance dose. Therefore, we consider it unlikely that corticosteroid use fully explains the long-term stabilization of disease activity observed in our cohort.[27]

Our data suggest reasonable tolerability of long-term treatment with TCZ, as heralded by the fact that only one of 16 patients had to change treatment because of side effects, which indeed regressed after discontinuation of TCZ. There were no new safety concerns of TCZ over the observational period. The patient who died due to complications from pneumonia was the oldest patient in our cohort and had significant comorbidities (hypertensive hearth disease, liver cirrhosis, chronic kidney failure, peripheral artery disease, obstructive lung disease), so that her death may not have been related to TCZ. Moreover, a carry-over effect from previous immunosuppressive treatments may have contributed to an increased risk of infection in this case. The most commonly reported infectious side effects of TCZ in previous studies for other indications included upper respiratory tract infections, urinary tract infections, and pneumonia. Serious infections, though less frequent, such as opportunistic infections, sepsis, and reactivation of latent infections, have also been reported.[28] In addition, patients receiving TCZ may present with atypical signs of infection due to suppression of C-reactive protein, which can complicate timely diagnosis and management. Overall, while TCZ is generally well tolerated, vigilance for infectious complications, especially in older multimorbid patients with MOGAD, remains critical throughout therapy to mitigate these risks.

Dyslipidemia, which has been described as a common side effect of TCZ, occurred in three-quarters of the patients who did not have dyslipidemia before TCZ initiation, but medical treatment was instituted in only 1 patient. Nevertheless, a relatively high preexisting body mass index in our MOGAD cohort, as also observed in previous studies comparing patients with MOGAD with multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) populations,[29] could have an influence on these data. A mild, asymptomatic increase in liver enzymes was observed in one-quarter of patients without previous known liver dysfunction and remained stable or returned to baseline over time. Neutropenia was not observed, which might be partly explained by the use of TCZ as monotherapy in this patient population in contrast to previous reports.[30]

So far, all patients who switched to subcutaneous TCZ administration remained relapse-free since changing the route of administration. This could be a promising approach to further improve treatment adherence and lower therapy costs, as the injections can be performed at the patients' home after appropriate instruction to ensure correct application. However, more clinical experience is needed to confirm the noninferiority of the subcutaneous dosing route.

Notably, there is a lack of published head-to-head comparison studies evaluating rituximab vs TCZ as first-line therapy in MOGAD. However, several retrospective studies have suggested that rituximab may be less effective in this patient population.[9] The present findings highlight the potential role of IL-6 inhibition both early in the disease course and as a second-line option in refractory cases.

Our study has several limitations. Owing to the small size of the study population, the lack of head-to-head comparisons with other off-label medications, and the retrospective nature of this study, one must be cautious when generalizing these findings and drawing definitive conclusions about long-term effectiveness and safety of TCZ as a treatment option in MOGAD. Because the study was restricted to adult patients

(>18 years old), the results may not be applicable to the pediatric population, which should be examined separately. Our study was also underpowered to analyze possible gender differences of efficacy and tolerability of the TCZ treatment. Prospective studies are warranted to further assess the potential of TCZ for long-term treatment in MOGAD. A phase III placebo-controlled trial with the anti–IL-6 receptor monoclonal antibody satralizumab, which has been approved for treatment of aquaporin-4-seropositive NMOSD,[31] is ongoing (NCT05271409, WN43194, 2023-507196-22-00), highlighting the raising interest in the IL-6 inhibition as a therapeutic option for patients with MOGAD.

Overall, this study provides important long-term data on effectiveness and tolerability of TCZ in relapsing MOGAD and suggests the subcutaneous administration of TCZ as a potential strategy to achieve long-term therapy adherence. In line with previous reports, TCZ shows promise as a potentially effective treatment option for MOGAD. Future prospective randomized trials are needed to determine its definitive efficacy.

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Author Contributions

F. Capecchi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Graure: analysis or interpretation of data. S. Yasaroglu: major role in the acquisition of data; analysis or interpretation of data. S Schubert: major role in the acquisition of data. N. Nierobisch: analysis or interpretation of data. V. Kana: drafting/revision of the manuscript for content, including medical writing for content. M. Weller: drafting/revision of the manuscript for content, including medical writing for content. P. Roth: drafting/revision of the manuscript for content, including medical writing for content. M. Herwerth: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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