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Efficacy and safety of tocilizumab treatment in refractory MOG-IgG related optic neuritis

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Abstract

Background: Myelin oligodendrocyte glycoprotein (MOG) IgG related optic neuritis (ON) which manifests as recurrent episodes and severe visual impairment remains a challenging issue in relapse prevention. Tocilizumab (TCZ), a human monoclonal antibody against IL-6R, may be an alternative treatment for the prevention of relapse in refractory MOG-ON patients.

Objectives: To investigate the efficacy and safety of Tocilizumab (TCZ) in patients with recurrent myelin oligodendrocyte glycoprotein IgG related optic neuritis (MOG-ON).

Design: We conducted an open-label, single-arm, nonrandomized, uncontrolled clinical trial at a tertiary neuro-ophthalmology center between April 1, 2021, and April 1, 2022.

Methods: Participants with relapsed MOG-ON, whose disease had been resistant to previous immunotherapies, received tocilizumab as monotherapy or as an add-on therapy and were followed up for at least 12 months. Annual recurrence rate (ARR), best corrected visual acuity (BCVA), and adverse events were recorded for analyses.

Result: Ten patients (7 females and 3 males) with relapsed MOG-ON were included with a mean (SD) ages of 28.6 (20.5) years old at disease onset and 30.9 (19.7) years at first TCZ administration, with a mean disease duration of 26.6 (11.3) months. Seven (70%) patients remained relapse-free, and the median (range) ARR dropped significantly from 1.9 (0.4–3.5) to 0.0 (0–4.0) during TCZ treatment ($p = 0.006$). Three patients experienced a relapse of ON at 2, 3, and 7 months after TCZ therapy. The median BCVA improved from 2.7 (2.0–3.0) logMAR at the nadir to 0.2 (0–2.0) logMAR at the last follow-up. Adverse effects included transient diarrhea ($n = 1$) and upper respiratory infection ($n = 1$).

Conclusion: This study supports that Tocilizumab therapy, with or without concomitant immunosuppression, is safe and effective in reducing relapses in MOG-ON patients who have failed immunosuppressive therapy or targeted B-cell therapy.

Trial registration: This trial is registered with the Chinese Clinical Trial Registry, number ChiCTR2100045273. (URL: https://www.chictr.org.cn/showproj.html?proj=124810)

Keywords: adverse effects, annual recurrence rate, MOG-ON, tocilizumab

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Introduction

Myelin oligodendrocyte glycoprotein associated disease (MOGAD) has been recognized as a distinct disease entity due to the immunopathology mediated by MOG-IgG. Optic neuritis (ON) is one of the most frequent clinical manifestations of MOGAD.[1,2] MOG-ON often manifests as recurrent episodes and severe visual impairment (even blindness), with optic disc swelling and extensive optic nerve lesions.[3,4] Relapse prevention remains a challenging issue in MOG-ON because maintenance therapy treatment to reduce recurrence including oral low-dose corticosteroids, mycophenolate mofetil (MMF), azathioprine (AZA), methotrexate, intravenous immunoglobulin (IVIG), and CD20-mediated B cell-depleting

monoclonal antibody rituximab (RTX), have been to show no efficacy in a small proportion of patients,[5–7] and currently, no treatment consensus exists for patients with relapsed MOG-ON.

Tocilizumab (TCZ) is the first human monoclonal antibody against interleukin-6 receptor (IL-6R) and is primarily used in the treatment of rheumatoid arthritis. There is now sufficient evidence that tocilizumab significantly reduces the risk of neuromyelitis optica spectrum disorder (NMOSD) recurrence, and it is also effective in patients with aggressive manifestations that are refractory to rituximab or other immunosuppressants.[8–16] Although the immunopathogenic mechanisms of MOGAD differ from those of AQP4-IgG positive NMOSD, studies have demonstrated that the elevated concentration of cerebrospinal fluid (CSF) IL-6 in MOGAD is comparable to levels measured in patients with AQP4-IgG positive NMOSD.[17] Case reports have shown that TCZ stabilizes the disease for at least 4.5 years in patients with refractory MOG-ON, along with improvements in clinical symptoms and imaging manifestations.[18,19]

Based on this evidence, TCZ may be an alternative drug of choice for the prevention of relapse in patients with refractory MOG-ON. Therefore, we designed a small sample-size clinical trial to investigate the safety and efficacy of TCZ in patients with recurrent MOG-ON.

Methods

Participants

Patients were recruited into an open-label trial at the department of neuro-ophthalmology in the Chinese People's Liberation Army General Hospital between April 1, 2021, and April 1, 2022. Several inclusion and exclusion criteria were used:

Inclusion criteria:

- Diagnosis of optic neuritis, as defined by Optic Neuritis Treatment Trial criteria[20]
- Seropositivity for IgG specific to MOG, identified by Cytometric Bead Array (CBA)
- Patients with two or more relapses ON in the previous 12 months (with at least one relapse in the preceding 6 months) with the treatment of immunotherapies
- Aged ⩾ 12 years
- Willing to comply with this test protocol, and voluntarily sign the informed consent

The trial protocol and supporting documentation were approved by the PLA review board. Patients provided written informed consent at enrollment.

Exclusion criteria

- Pregnancy, breast feeding, or plans to conceive during the course of the study (applicable to women only)
- Allergy to any component of the experimental drug
- Patients with severe cardiovascular, liver, kidney, or hematopoietic diseases, diabetes mellitus, or blood pressure ⩾ 140/90 mmHg
- Participation in other clinical trials within the last 3 months

Procedures

An attack was defined as a new worsening of visual function or neurological symptoms lasting for more than 24 h and not attributable to an identifiable cause, such as intercurrent infection. Each relapse was treated with 500–1000 mg of intravenous methylprednisolone (IVMP) for 3 days, followed by a tapering dose of oral prednisone starting at 1 mg/kg/day, with variable durations (at least 3 months). Patients who were previously on add-on immunosuppressants, including azathioprine (AZA) at a dose of 2.5–3.0 mg/kg/day or mycophenolate mofetil (MMF) at a dose of 750 mg/kg/day, continued their treatment with oral methylprednisolone at a dose of 4–6 mg/day simultaneously. Monthly tocilizumab at a dose of 8 mg/kg was initiated for 12 months, after which the frequency was tapered to every 2 months.

During treatment, patients returned to the clinic at 1, 3, 6, and 12 months after the initial TCZ treatment. At each visit, a complete neuro-ophthalmology examination was conducted, including funduscopic examination, Humphry visual field test, orbital MRI (when relapse occurred), optical coherence tomography imaging (measuring peripapillary retinal nerve fiber layer (pRNFL) thickness and macular ganglion cell—inner plexiform layer (mGCL-IPL) thickness). Serum was obtained before the initiation of TCZ and at the screening visit, as well as at 1, 3, 6, 12, and

24 months. Serum MOG-IgG titers were measured using the CBA.

The primary endpoints were efficacy, measured by the annual recurrence rate (ARR), and safety, which was assessed through an adverse event questionnaire completed by the study coordinator. Secondary endpoints included the best-corrected visual acuity (BCVA) at the last follow-up. The BCVA was recorded using decimal acuity and then converted to a logarithm of the minimum angle of resolution (logMAR) for statistical analysis. The mean BCVA was calculated for patients with bilateral visual loss.

Statistical analysis

In general, the ARR was calculated by dividing the number of attacks that occurred before switching to TCZ or during the TCZ treatment period by the corresponding treatment duration. However, for two patients with a follow-up period of <12 months during TCZ treatment, we divided the total number of attacks by the specific treatment duration to extrapolate this measure to 1 year. To avoid possible overestimation of the ARR in the latter group, we excluded those two patients with TCZ treatment durations of <12 months for subgroup analyses.

Values are reported as the mean (SD) when normally distributed, and otherwise as the median (range). Paired comparisons of continuous outcomes of interest between any two time points were conducted using the Wilcoxon signed rank test due to the small sample size. All tests were two-sided, and p-values of <0.05 were considered significant. Statistical analyses were performed using a software package (Prism 9; GraphPad, La Jolla, CA).

Standard protocol approvals and registrations

This trial is registered with the Chinese Clinical Trial Registry, number ChiCTR2100045273.

The study protocol and statistical analysis plan are available in eSAP 1.

Result

TCZ reduced ARR

We included 10 MOG-IgG seropositive patients (18 affected eyes) with ON, including 7 females and 3 males. Mean ages were 28.6 (20.5) years old at disease onset and 30.9 (19.7) years at first TCZ administration, with a mean disease duration of 26.6 (11.3) months. The mean number of disease attacks before TCZ treatment was 4.1 (1.4; Table 1). All patients had relapsing course due to failure to respond to previous therapies, including methylprednisolone, immunosuppressant (MMF and cyclophosphamide), or B-cell depletion with rituximab (Figure 1).

A mean of 9.9 (4.8) TCZ infusions was administered during a mean follow-up time of 16.0 (7.6) months at a dosage of 8 mg/kg. In 9 out of 10 patients (90%), TCZ was given as an add-on treatment. Additional medications included mycophenolate mofetil (MMF; $n=3$), IV immunoglobulins (IVIG; $n=1$), and oral low-dose steroids ($n=8$). Patient 4, who had been given add-on MMF (0.5 g) for recurrent myelitis, continued to receive MMF during treatment with TCZ until the end of the follow-up. (Figure 1). Patient 7, a child, has been receiving continuous monthly infusions of IVIG (1 g/kg) to prevent recurrence due to the side effects of methylprednisolone. Patient 10 discontinued treatment after 4 doses of TCZ; however, there was no recurrence within 1 year of follow-up. Besides, three patients (Patients 4, 6, and 9) received the first TCZ infusion in combination with intravenous prednisolone sodium succinate due to persistent optic nerve MR imaging activity with T1 gadolinium-enhancing lesions. One patient (Patient 10) was treated with intravenous immunoglobulin infusion following a relapse. Another patient (Patient 5) underwent plasma exchange due to severe visual loss during the relapsed acute stage.

The median ARR over the entire disease duration before TCZ initiation was 1.9 (0.4–3.5). During TCZ treatment, the ARR dropped significantly to 0.0 (0–4.0) ($p=0.006$) (Figure 2(b)). The median time to first relapse was 5 months (range 3–7 months) for the whole group. Seven out of ten patients (70%) remained relapse-free during TCZ treatment. Three patients (Patients 6, 7, and 9) experienced a confirmed relapse due to nonresponse to TCZ therapy. In three patients, a total of four relapses occurred. After two cycles of TCZ, Patient 6 relapsed with optic neuritis and mild numbness in both upper extremities following a prolongation of the infusion interval to 8 weeks. The relapse of the other two patients presented as optic neuritis. Patient 7 had the first

Table 1. Cohort of patients with relapsed MOG-IgG related optic neuritis receiving tocilizumab therapy.

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age at disease onset, year (date of first attack)										
	58 (January 2019)	37 (July 2020)	16 (August 2017)	10 (December 2019)	12 (July 2019)	30 (October 2020)	10 (July 2019)	69 (July 2021)	20(May 2018)	24 (February 2018)
Unilateral or bilateral ON										
	Bilateral	Bilateral	Unilateral	Bilateral	Bilateral	Unilateral	Bilateral	Bilateral	Bilateral	Bilateral
Sex, female/male										
	Female	Female	Male	Female	Female	Female	Male	Female	Male	Female
Age at tocilizumab initiation, year (date of first dose)										
	59 (April 2021)	38 (May 2021)	20 (June 2021)	12 (December 2021)	15 (March 2022)	31 (March 2022)	13 (November 2021)	70 (July 2022)	23 (May 2021)	28 (April 2021)
Disease duration before tocilizumab, month										
	28	10	46	24	32	17	27	12	36	38
Immunomodulatory or immunosuppressant therapy before tocilizumab										
	MP	MP	MP, MMF	MP, MMF	MP, MMF, CTX, RTX	MP, MMF, RTX	MP, MMF, RTX	MP	MP, MMF, RTX	MP, MMF, RTX
Number of tocilizumab cycles, *n* (treatment time until the last follow-up/treatment time until the first relapsed attack)										
	15 (25 mo)	14 (25 mo)	11 (24 mo)	12 (18 mo)	14 (15 mo)	2 (3 mo)	14 (19 mo)	8 (12 mo)	5 (7 mo)	4 (12 mo)
Tocilizumab dosage, mg/kg										
	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
Tocilizumab treatment intervals, week										
	4–8	4–8	4–8	5–6	4	4	4–6	4–6	4–6	4
Relapses before tocilizumab initiation, *n*										
	4	2	4	4	5	5	4	2	7	4
Relapses during tocilizumab therapy, *n* (time after tocilizumab initiation)										
	0	0	0	0	0	1(3 mo)	2(3 mo/11 mo)	0	1(7 mo)	0
BCVA at nadir, LogMAR										
	3.0	2.3	3.0	2.0	3.0	2.3	2.0	3.0	2.3	3.0

(Continued)

Table 1. (Continued)

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
BCVA before Tocilizumab treatment, LogMAR										
	0.1	0.0	0.2	0.2	0.9	0.0	1.3	0.1	2.0	1.5
BCVA at the last follow-up, LogMAR										
	0.0	0.2	0.2	0.0	0.2	0.0	0.2	0.1	0.3	2.0
ARR before tocilizumab initiation during the entire disease duration										
	1.8	2.4	1.0	2.0	1.9	3.5	1.8	2.0	2.6	1.3
ARR during tocilizumab therapy										
	0.0	0.0	0.0	0.0	0.0	4.0	1.5	0.0	1.7	0.0
Tocilizumab adverse effects										
	None	None	None	None	None	None	None	None	None	None
Laboratory abnormalities during tocilizumab therapy										
	neutropenia, interleukin-6↑	Cholesterol↑	neutropenia	leukocytosis	None	LDL-Cholesterol↑	neutropenia, lymphocythemia	leukocytosis, lymphocytopenia	neutropenia, lymphocythemia	leukocytosis, lymphocytopenia, interleukin-6↑

ARR, annual recurrence rate; BCVA, best-corrected visual acuity; CTX, Cyclophosphamide; mo, month; MP, Methylprednisolone; MMF, mycophenolate mofetil; MOG, myelin oligodendrocyte glycoprotein; RTX: Rituximab.

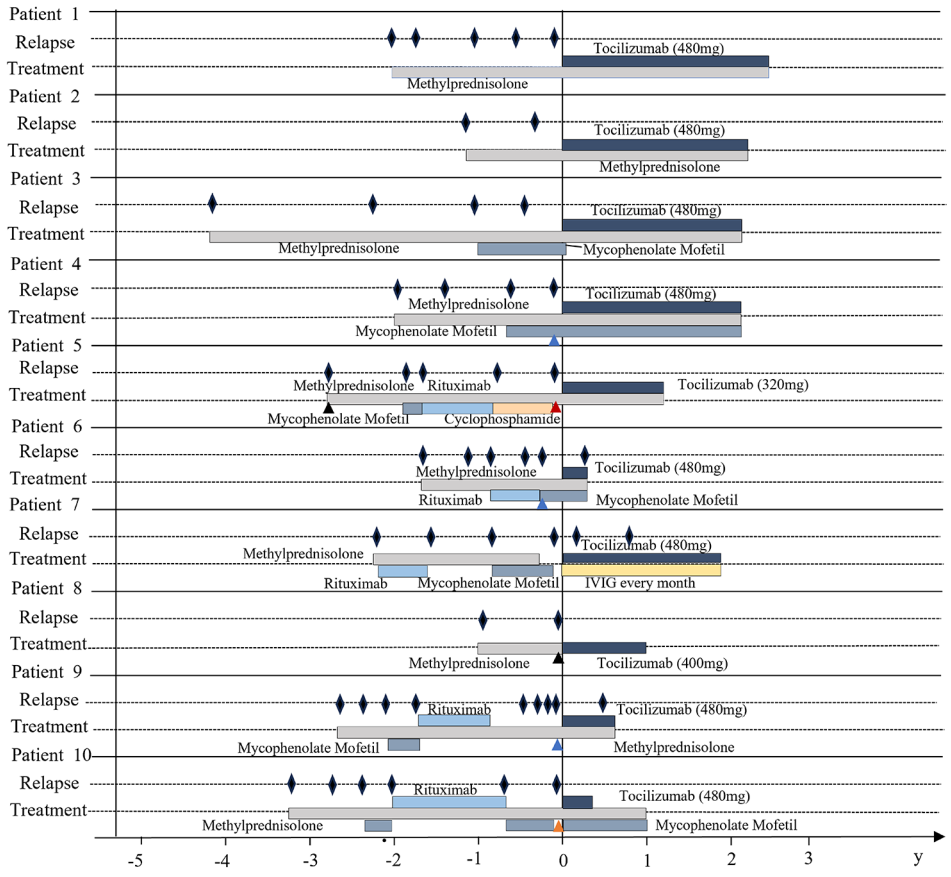

Figure 1. Disease course and immunomodulatory or immunosuppressant therapies of MOG-IgG related optic neuritis. Clinical relapses (black diamonds) and treatments are shown. IVMP (blue triangle): intravenous methylprednisone. IVIG (orange triangle): intravenous immune globulin. PE (red triangle): plasm exchange.
IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MOG, myelin oligodendrocyte glycoprotein

attack within the first 3 months after TCZ initiation and then experienced a second relapse at 11 months follow-up. Patient 9 relapsed after 5 cycles of TCZ treatment, during the 7 months follow-up period. When analyzing patients treated with TCZ for at least 12 months, 7 out of 8 (87.5%) remained relapse-free. In the group of patients treated with TCZ plus add-on treatment (9 patients), TCZ was effective in suppressing relapse in 6 out of 9 (66.7%). Furthermore, 4 out of 7 patients (57.1%) (Patients 4, 5, 9, and 10) have remained stable on TCZ for more than a year despite having previously failed various immunotherapies, including mycophenolate mofetil (MMF), azathioprine (AZA), rituximab, and cyclophosphamide.

Visual function

The median visual acuity improved from 2.7 (2.0–3.0) logMAR at its nadir to 0.2 (0–2.0) logMAR at the last follow-up. Compared to the visual acuity before TCZ treatment, which was 0.2 (0–2.0) logMAR, there was no significant difference during the TCZ treatment period ($p = 0.2$; Figure 2(a)).

Antibody titers

After TCZ treatment, the median MOG-IgG titers dropped from 1:66 to 1:32 ($p = 0.65$) in the entire cohort. MOG-IgG titers in 4 out of 10 patients (40%) decreased compared to the initiation of TCZ treatment. Among these four

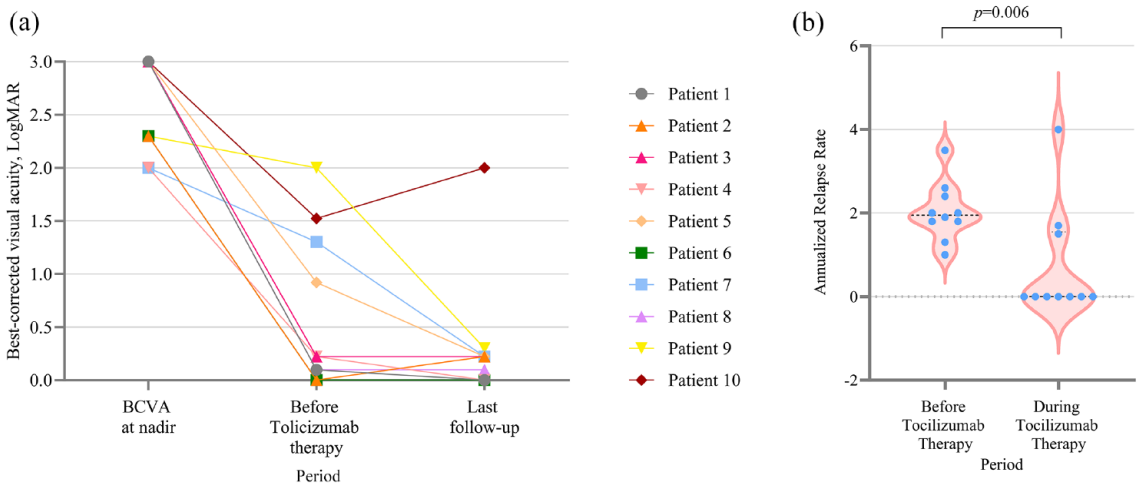

Figure 2. Best-corrected visual acuity of each patient and annualized relapse rate before and during tocilizumab therapy. (a) Alterations of best-corrected visual acuity of each patient before and during Tocilizumab therapy. (b) The median annualized relapse rate significantly decreased from 1.9 (range: 0.4–3.5) before tocilizumab therapy to 0.0 (range: 0–4.0) during tocilizumab therapy ($p = 0.006$).

patients, two remained free from relapses after TCZ treatment, while the other two experienced one attack during the treatment period (Figure 3(a)). However, MOG-IgG negative seroconversion was observed in one patient who relapsed during the follow-up.

Safety data

During TCZ therapy, transient diarrhea ($n = 1$) and upper respiratory infection ($n = 1$) were reported. No severe infections or other major adverse effects related to TCZ occurred. Laboratory abnormalities were observed, including mild elevation of cholesterol levels in 4 out of 10 patients (40%), neutropenia in 4 patients (40%), leukocytosis in 3 patients (30%), and lymphocytosis or lymphocytopenia in 4 patients (40%). However, there was no statistical difference before TCZ treatment and at the last follow-up (Figure 3(c)–(f)). Additionally, mild elevation of serum IL-6 levels was observed in 6 out of 10 patients (60%) at the last follow-up compared to that before TCZ treatment ($p = 0.02$) (Figure 3(b)). The supplementary results compare lymphocyte and IL-6 levels before and after relapse in three patients treated with tocilizumab. The median lymphocyte counts before and after relapse were 0.237 and 0.211 ($p = 0.7$) 10^9/L, respectively, and the median IL-6 values were 2.01 and 1.96 ($p > 0.9$) pg/ml, respectively.

Discussion

MOGAD patients, especially children, may experience a monophasic course, while others tend to run a highly relapsing course, potentially resulting in long-lasting neurologic disability, akin to those with NMOSD, emphasizing the relevance of attack prevention for disease prognosis. However, the optimal treatment strategy for MOGAD remains unclear, especially for patients experiencing a relapsing course with optic neuritis. TCZ, a humanized IL-6 receptor inhibitor, has emerged as a promising therapeutic option for NMOSD following evidence from several case series and a prospective, multicenter, randomized, open-label phase II study, which demonstrated its efficacy in reducing the relapse risk.[11,12,16] Herein, we present data demonstrating successful treatment with the anti-IL-6 receptor antibody TCZ in 10 patients with MOG-ON who had previously failed standard immunotherapies, including targeted B-cell depletion by RTX.

Our longitudinal cohort study extends these observations to a treatment duration of up to 27 months, comprising a total of 103 TCZ infusions. Importantly, we confirmed a significant reduction in the median ARR during TCZ therapy, from 1.9 to 0.0, in patients who had failed several previous immunosuppressive therapy or targeted B-cell therapy. On the other hand, the BCVA of each patient remained stable after TCZ

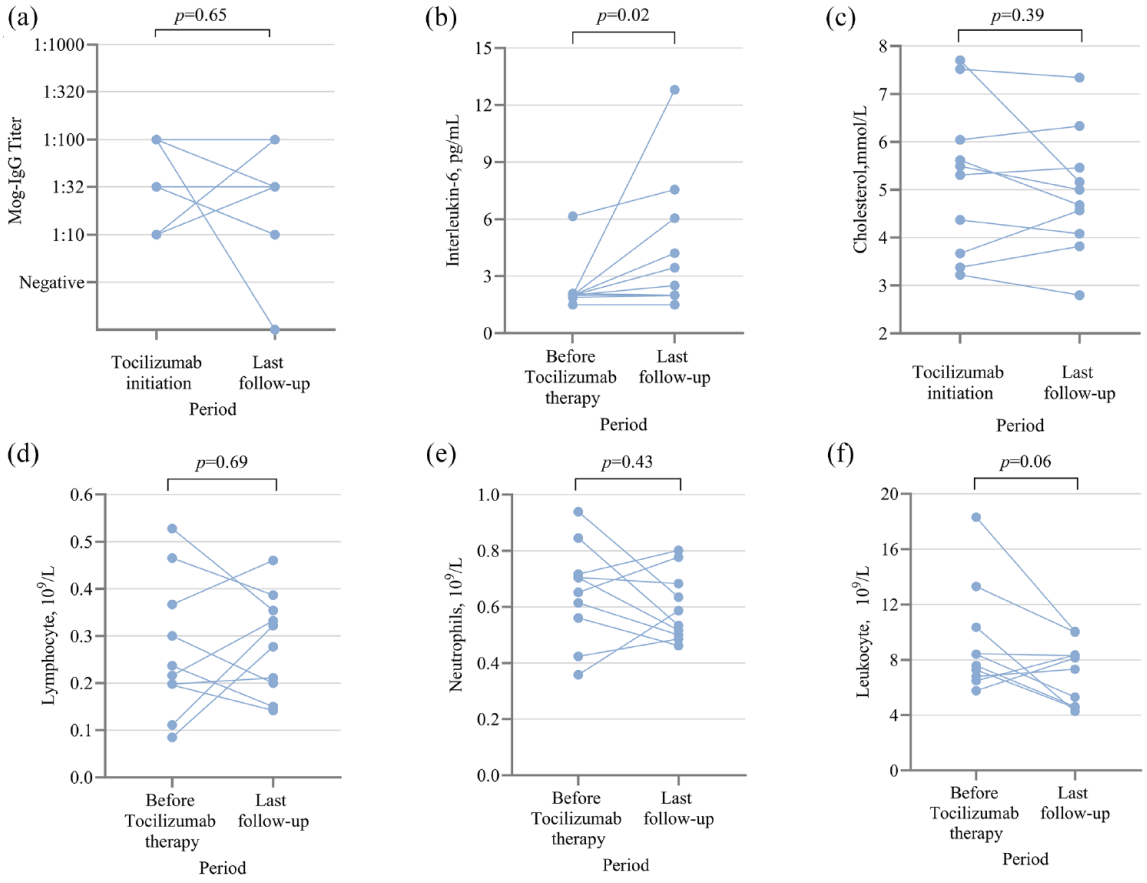

Figure 3. Features of disease activity before and during tocilizumab therapy. (a) Alterations of MOG-IgG titers. (b) Alterations of interleukin-6 levels. (c) Alterations of cholesterol levels. (d) Alterations of lymphocyte levels. (e) Alterations of neutrophils levels. (f) Alterations of leukocyte levels.
MOG, myelin oligodendrocyte glycoprotein.

therapy. A previous study demonstrated that two cases involving a 7-year-old boy and a 15-year-old adolescent with severe acute central nervous system demyelination and malignant cerebral edema, including early brain herniation, which were incompletely responsive to standard acute therapies, showed rapid improvement with IL-6 receptor inhibition administered as TCZ.[19] A recent study demonstrated that the ARR decreased by 93% in a retrospective series of 14 patients with MOGAD. The median EDSS score was reduced from 2.75 to 2.0 over a mean treatment duration of 31 months with TCZ, and an anti-inflammatory effect was also evident on brain MRI scans.[21] However, the patients in this study differ from our cohort of ON patients with a relapsing course, all of whom had previously failed immunosuppressive therapy or targeted B-cell therapy. For this patient group, 70% remained relapse-free, leading us to view the research results as very optimistic.

Despite the overall good efficacy, four attacks occurred in three patients after the initiation of TCZ therapy. One attack occurred during the first 2½ treatment months, and two relapses were related to prolongation of the infusion interval to 8 weeks, the same attacks had been reported by a previous study.[11] In other words, these data suggest that adherence to strict dosing regimens may improve the therapeutic efficacy of TCZ.

It is worth mentioning that TCZ did not reduce the titer of MOG-IgG in the patients' serum. This is consistent with the recent data suggesting that the correlation between MOG-IgG titers and recurrence remains controversial. Patients might remain seropositive for many years without

relapsing, and even those who become seronegative could still experience relapses.[5,22] More interestingly, we found that IL-6 levels were elevated. We hypothesize that increased IL-6 in the brain enhances the permeability of the blood–brain barrier (BBB), allowing TCZ to cross the disrupted BBB and bind to both soluble and fixed IL-6 receptors, leading to increased levels of circulating IL-6.[23] Investigating the predictive role of lymphocyte and IL-6 levels could provide clues for treating MOGAD patients with anti-IL6Rs. Due to the small sample size, we are unable to perform additional statistical analyses to assess the correlation between lymphocyte or IL-6 levels and relapse. Subsequent studies with larger sample sizes are needed.

Regarding the adverse effects of TCZ, they primarily included upper respiratory tract infections and reactivation of latent tuberculosis, along with increased concentrations of hepatic aminotransferases and plasma lipids, as well as decreased absolute neutrophil counts and C-reactive protein levels.[11,18,21] In our study, no major adverse effects or significant laboratory abnormalities were detected, except for mild elevations in cholesterol levels and variations in granulocyte counts. Due to the small sample size in our study, we were unable to comprehensively discuss the safety profile of tocilizumab. Therefore, we analyzed the safety data of tocilizumab from other studies. In a real-world study involving 65 patients with NMOSD treated with tocilizumab, 43% experienced mild-to-moderate elevations in serum alanine aminotransferase levels, 27.7% developed infections, and 7.7% had infusion-related reactions, including rash (2 cases), lower extremity edema (2 cases), headache (1 case), dizziness (1 case), and hypotension (1 case). Another study, which included both NMOSD and MOGAD patients, reported that 7 out of 57 (12.3%) experienced infusion-related reactions, 7%–16% developed various degrees of infection, and 35% had mild-to-moderate elevations in liver enzyme levels. Overall, the safety profile of tocilizumab is favorable, with adverse event rates within the expected range.

Recently, biopsy and autopsy data have demonstrated that lesions in MOGAD often contain significant complement and immunoglobulin deposition, indicating a substantial humoral immune component similar to that of AQP4-IgG positive NMOSD.[24] Consistent with these findings, cytokine and chemokine profile studies in MOGAD have confirmed consistently elevated levels of the proinflammatory cytokine IL-6 in CSF.[25,26] Taken together, these data may explain the profound mechanism of anti-IL-6 receptor antibodies in MOG-ON.

An obvious limitation of this study is its small sample size, which is justifiable due to the rarity of MOG-ON and the concurrent off-label treatment with TCZ. In this study, we enrolled a total of 10 patients, but only 8 completed at least 1 year of follow-up. The two patients who did not complete the follow-up discontinued Tocilizumab after relapse and switched to other immunosuppressants, making it impossible to continue monitoring them. Another constraint is that we treated these patients with continuous immunotherapies that overlapped with TCZ therapy due to their higher relapsing course. It is also worth noting that there are no patients with other mixed phenotypes (ADEM-ON, etc.) in our study. ADEM-ON and other phenotypes predominantly occur in children and are treated within the pediatric department. Since our department only conducts ophthalmological examinations, we have excluded patients with other mixed phenotypes. Despite these limitations, this study supports the notion that adding TCZ to patients who have not responded to other immunosuppressive drugs or targeted B-cell therapy can result in a significant decrease in ARR. This finding confirms the effectiveness of TCZ in refractory MOG-ON. Moreover, it is absolutely necessary to evaluate the efficacy of IL-6 blockade in patients with MOGAD through randomized controlled trials. What makes us excited is that a randomized controlled trial with satralizumab (METEOROID, CT: WN43194) is currently underway. This phase III clinical trial is investigating the efficacy, safety, and pharmacokinetics of satralizumab in MOGAD. Perhaps we will obtain more results in the near future.

Conclusion

Our study supports that Tocilizumab therapy with or without concomitant immunosuppression appears to be safe and effective in reducing relapses in MOG-ON patients who have failed immunosuppressive therapy or targeted B-cell therapy. Future studies with higher levels of

evidence-based are needed to validate the effectiveness and safety of IL-6R antagonists in treating MOGAD.

Declarations

Ethics approval and consent to participate

Ethical approval (S2021-130-01) was obtained from the PLA Hospital Review Board. All patients provided written informed consent.

Consent for publication

Not applicable.

Author contributions

Xintong Xu: Data curation; Formal analysis; Writing – original draft.

Yuhang Wang: Data curation; Resources.

Mingming Sun: Methodology; Writing – review & editing.

Yuyu Li: Formal analysis; Software.

Biyue Chen: Investigation; Writing – review & editing.

Xiyun Chen: Data curation; Resources.

Quangang Xu: Project administration; Writing – review & editing.

Shihui Wei: Project administration; Writing – review & editing.

Huanfen Zhou: Methodology; Project administration; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Anonymized data sets for defined study outcomes will be made available on reasonable request by a suitably qualified individual.

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References

1. Hennes EM, Baumann M, Lechner C, et al. MOG Spectrum disorders and role of MOG-antibodies in clinical practice. *Neuropediatrics* 2018; 49(1): 3–11.
2. Marignier R, Hacohen Y, Cobo-Calvo A, et al. Myelin-oligodendrocyte glycoprotein antibody-associated disease. *Lancet Neurol* 2021; 20: 762–772.
3. Yao Y, Li X, Xu Y, et al. The difference of the retinal structural and microvascular characteristics in patients with MOGAD-ON and AQP4-ON. *BMC Neurol* 2022; 22: 323.
4. Toosy AT, Mason DF and Miller DH. Optic neuritis. *Lancet Neurol* 2014; 13: 83–99.
5. Armangue T, Olivé-Cirera G, Martínez-Hernandez E, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. *Lancet Neurol* 2020; 19: 234–246.
6. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J Neuroinfl* 2016; 13: 280.
7. Durozard P, Rico A, Boutiere C, et al. Comparison of the response to rituximab between myelin oligodendrocyte glycoprotein and aquaporin-4 antibody diseases. *Ann Neurol* 2020; 87: 256–266.
8. Araki M. Blockade of IL-6 signaling in neuromyelitis optica. *Neurochem Int* 2019; 130: 104315.
9. Wallach AI, Tremblay M and Kister I. Advances in the treatment of neuromyelitis optica spectrum disorder. *Neurol Clin* 2021; 39: 35–49.

10. Takeshita Y, Fujikawa S, Serizawa K, et al. New BBB model reveals That IL-6 blockade suppressed the BBB disorder, preventing onset of NMOSD. *Neurol Neuroimmunol Neuroinflamm* 2021; 8: e1076.

11. Ringelstein M, Ayzenberg I, Harmel J, et al. Long-term therapy with interleukin 6 receptor blockade in highly active neuromyelitis optica spectrum disorder. *JAMA Neurol* 2015; 72: 756–763.

12. Yang S, Zhang C, Zhang T-X, et al. A real-world study of interleukin-6 receptor blockade in patients with neuromyelitis optica spectrum disorder. *J Neurol* 2023; 270(1): 348–356.

13. Pittock SJ, Lennon VA, McKeon A, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. *Lancet Neurol* 2013; 12: 554–562.

14. Funakoshi K and Suzuki K. A safe change from eculizumab to satralizumab in a patient with neuromyelitis optica spectrum disorder. *Neurol Sci* 2023; 44: 1097–1098.

15. Xue T, Yang Y, Lu Q, et al. Efficacy and safety of monoclonal antibody therapy in neuromyelitis optica spectrum disorders: evidence from randomized controlled trials. *Mult Scler Relat Disord* 2020; 43: 102166.

16. Lotan I, McGowan R and Levy M. Anti-IL-6 Therapies for neuromyelitis optica spectrum disorders: a systematic review of safety and efficacy. *Curr Neuropharmacol* 2021; 19: 220–232.

17. Kaneko K, Sato DK, Nakashima I, et al. CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications. *J Neurol Neurosurg Psychiatry* 2018; 89: 927–936.

18. Rigal J, Pugnet G, Ciron J, et al. Off-label use of tocilizumab in neuromyelitis optica spectrum disorders and MOG-antibody-associated diseases: a case-series. *Mult Scler Relat Disord* 2020; 46: 102483.

19. McLendon LA, Gambrah-lyles C, Viaene A, et al. Dramatic response to anti-IL-6 receptor therapy in children with life-threatening myelin oligodendrocyte glycoprotein-associated disease. *Neurol Neuroimmunol Neuroinflamm* 2023; 10: e200150.

20. The clinical profile of optic neuritis. Experience of the Optic Neurit is Treatment Trial. Optic Neuritis Study Group. *Arch Ophthalmol* 1991; 109: 1673–1678.

21. Ringelstein M, Ayzenberg I, Lindenblatt G, et al. Interleukin-6 receptor blockade in treatment-refractory mog-igg-associated disease and neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm* 2022; 9: e1100.

22. Waters P, Fadda G, Woodhall M, et al. Serial anti–myelin oligodendrocyte glycoprotein antibody analyses and outcomes in children with demyelinating syndromes. *JAMA Neurol* 2020; 77: 82–93.

23. Fujihara K, Bennett JL, De Seze J, et al. Interleukin-6 in neuromyelitis optica spectrum disorder pathophysiology. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e841.

24. Takai Y, Misu T, Kaneko K, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. *Brain* 2020; 143: 1431–1436.

25. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology* 2014; 82: 474–481.

26. Kwon YN, Kim B, Ahn S, et al. Serum level of IL-1β in patients with inflammatory demyelinating disease: marked upregulation in the early acute phase of MOG antibody associated disease (MOGAD). *J Neuroimmunol* 2020; 348: 577361.