Effective Prevention with Maintenance Treatment of Tocilizumab in Pediatric MOG-IgG Associated Disorder (MOGAD) Relapse

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Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a demyelinating disorder of the central nervous system with distinct clinical, demographic, and radiological features that differentiate it from aquaporin-4 (AQP4) autoantibody-associated neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis. Unlike NMOSD, where AQP4-immunoglobulin G (IgG) primarily targets astrocytes, MOGAD is characterized by macrophage infiltration, microglial activation, and the upregulation of inflammatory mediators like interleukin-6 (IL-6). IL-6 plays a central role in the induction and relapses of MOGAD by promoting the differentiation of T helper 17 (Th17) lymphocytes, leading to direct demyelination and creating a feedback loop for IL-6 production [1].

The immunotherapy options for MOGAD include the anti-CD20 monoclonal antibody rituximab (RTX), azathioprine, mycophenolate mofetil, and intravenous immunoglobulin (IVIG). Despite RTX therapy, some MOGAD patients may experience clinical relapses and new brain demyelinating lesions. Recent findings indicate that tocilizumab (TCZ), an IL-6 receptor antibody, has demonstrated efficacy and safety in a few reports involving adult patients with MOGAD and NMOSD that are intractable to RTX [2]. A recent report described two pediatric MOGAD patients who had malignant cerebral edema with early brain herniation. Remarkably, these patients experienced significant neurological recovery following treatment with TCZ [3]. However, there are few reports on the long-term effects and side effects of using TCZ in pediatric patients with MOGAD [3,4].

We report a pediatric patient diagnosed with relapsing MOGAD, who initially presented with visual disturbance and hemiparesis, successfully treated with TCZ. We also review the current immunopathological and clinical evidence regarding the potential efficacy of IL-6 inhibition as an alternative immunotherapeutic approach to reduce steroid dependence for this condition.

A previously healthy 11-year-old girl presented with dysarthria, uvular deviation, facial asymmetry with drooling, and decreased sensation on the right side of her face and blurred vision that began 1 week prior. She had been diagnosed with coronavirus disease 2019 (COVID-19) 2 months earlier. A complete blood count showed no significant abnormalities, and C-reactive protein was negative. Lumbar puncture revealed mildly elevated protein without pleocytosis (protein 49 mg/dL,
white blood cell 2 cells/mm³). Contrast-enhanced brain magnetic resonance imaging (MRI) demonstrated multiple rim-enhancing nodular lesions in the bilateral cerebral hemisphere, more prominent in the left hemisphere. (Fig. 1A). In an ophthalmic examination, marginal blurring of the optic disc and vessel engorgement were detected (Fig. 2A). The patient received methylprednisolone (mPD) pulse therapy at 1,000 mg/day for 5 days (April 10, 2022, to April 14, 2022) and IVIG at 0.4 g/kg/dose for 5 days (April 15, 2022, to April 19, 2022), resulting in improvement of all symptoms. She was then discharged with a tapering dose of oral prednisolone (60 mg from April 15, 2022, to April 21, 2022; 50 mg from April 22, 2022, to April 28, 2022; and 40 mg from April 29, 2022, to May 3, 2022) and scheduled for a myelin oligodendrocyte glycoprotein (MOG) antibody test.

Two weeks after discharge, the patient was re-admitted due to the recurrence of dysarthria, left-sided weakness, drowsiness, and decreased visual acuity during the prednisolone tapering process. The left-sided weakness, including foot drop and a decrease in left upper motor strength to grade 3, progressively worsened within a day. Similar marginal blurring of the optic disc was observed (Fig. 2B). Contrastbrain MRI showed increased areas of demyelinating lesions in the occipital white matter and both centra semiovalia compared to the first attack (Fig. 1B). Serum MOG-IgG was positive (0.597%, reference 0.141% to 0.254%; April 11, 2022), while serum AQP4-IgG was negative.

On the day of the second admission, immediate treatment with a second round of IVIG at 0.4 g/kg/dose for 5 days (May 2, 2022, to May 6, 2022) was initiated. However, left-sided weakness and visual disturbance progressed rapidly. Visual acuity dropped from 0.5 to 0.1, and the patient was unable to raise their hand or foot. Despite administering RTX (600 mg, May 3, 2022) and a second course of mPD pulse therapy (1,000 mg/day for 5 days, May 4, 2022, to May 8, 2022), there was no improvement, and the visual impairment worsened progressively. Consequently, TCZ at 8 mg/kg/dose was administered intravenously (May 6, 2022), leading to gradual improvement in left-sided weakness. However, there was no clear improvement in visual acuity. Therefore, therapeutic plasma exchange was initiated, and the blurred vision gradually improved. Five sessions of plasmapheresis were conducted (May 10, 13, 16, 18, 23, 2022).

She has been undergoing treatment with monthly IVIG at a dosage of 1 g/kg and maintenance therapy with TCZ at a dosage of 8 mg/kg every 2 months without experiencing any relapses. A recent brain MRI revealed a residual demyelinating lesion that is smaller than before and mild brain atrophy (Fig. 1C). Her optic disc appeared clear (Fig. 2C). Serum MOG-IgG was positive during the initial attack (April 11, 2022), borderline during relapse.
(May 3, 2022) while tapering prednisolone, and negative thereafter (May 30, 2022, August 18, 2022, and March 16, 2023). As a result, a low dose of oral prednisolone (10 mg/day) and oral azathioprine were maintained. She complained of transient hand tremors and intermittent exotropia, which gradually resolved over time. After 24 months of TCZ and monthly IVIG maintenance therapy, the patient, now a middle school student, is performing well academically with no functional limitations.

TCZ, a humanized monoclonal antibody, selectively binds to the IL-6 receptor. IL-6 is a proinflammatory cytokine that triggers its signaling cascade following complement deposition. This cascade compromises the blood-brain barrier, facilitates leukocyte migration, stimulates the production of various cytokines and chemokines, and facilitates B-cell activation. This process potentially fosters the production of MOG-IgG and facilitates the entry of activated MOG-reactive cells and circulating MOG-IgG antibodies [1].

Autopsies and brain biopsies have shown that demyelinating lesions in MOGAD exhibit significant amounts of complement and immunoglobulin depositions, suggesting substantial humoral immune mechanisms similar to those observed in AQP4+NMOSD [5]. The presence of abundant MOG-laden macrophages and MOG-dominant demyelinating debris in MOGAD suggests the pathogenicity of the MOG antigen itself. These findings differ significantly from the marked reduction in oligodendrocytes and the loss of myelin-associated glycoprotein observed in AQP4+NMOSD [5]. Preliminary investigations into cytokine and chemokine profiles in MOGAD suggest that IL-6 signaling pathways play a pivotal pathobiological role in this condition [4,6,7].

Previous case reports provide evidence for the safety and efficacy of TCZ in adult patients with MOGAD resistant to RTX or other treatments. In a study examining the efficacy and long-term safety of TCZ in 14 adults with MOGAD over a 24-month period, 79% did not experience relapses while on TCZ treatment [8]. Only two patients experienced adverse events related to TCZ therapy, which included a dental infection and TCZ-induced hypertriglyceridemia requiring a statin prescription. No therapy-related adverse events were observed in our patient.

Our findings, along with supporting evidence from other studies, strengthen the hypothesis that IL-6-mediated mechanisms may play a crucial role in driving MOGAD disease activity. TCZ appears to be a promising therapeutic option for relapsing MOGAD in children and adolescents who are resistant to other forms of immunotherapy.

This case report represents the first demonstration that long-term maintenance therapy with TCZ and IVIG is safe and effective in preventing relapse in pediatric MOGAD. TCZ and IVIG dual therapy has shown safety and effectiveness in a pediatric MOGAD patient with no adverse effects. Although few cases of TCZ use in pediatric patients have been documented, no specific side effects have been reported. An 11-year-old girl with MOGAD received TCZ treatment with no side effects other than hyperlipidemia [4]. A 7-year-old boy and a 15-year-old boy, both diagnosed with MOGAD, received TCZ treatment without experiencing any side effects [3]. Therefore, considering our case in the context of previous case reports, the long-term use of TCZ in relapsing pediatric patients appears to be safe, without significant adverse effects.

This study received approval from the Research Ethics Committee of Seoul Metropolitan Government Seoul National University Borame Medical Center (approval number: 20-2023-92). Due to the retrospective nature of the study, the requirement for written informed consent was waived.
Conflicts of interest

Jieun Choi is an associate editor of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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References