Dramatic Response to Anti-IL-6 Receptor Therapy in Children With Life-Threatening Myelin Oligodendrocyte Glycoprotein-Associated Disease

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Abstract

Objectives
Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an immune-mediated neuroinflammatory disorder leading to demyelination of the CNS. Interleukin (IL)-6 receptor blockade is under study in relapsing MOGAD as a preventative strategy, but little is known about the role of such treatment for acute MOGAD attacks.

Methods
We discuss the cases of a 7-year-old boy and a 15-year-old adolescent boy with severe acute CNS demyelination and malignant cerebral edema with early brain herniation associated with clearly positive serum titers of MOG-IgG, whose symptoms were incompletely responsive to standard acute therapies (high-dose steroids, IV immunoglobulins (IVIGs), and therapeutic plasma exchange).

Results
Both boys improved quickly with IL-6 receptor inhibition, administered as tocilizumab. Both patients have experienced remarkable neurologic recovery.

Discussion
We propose that IL-6 receptor therapies might also be considered in acute severe life-threatening presentations of MOGAD.
Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a monophasic or relapsing inflammatory demyelinating disorder, with international consensus criteria recently published. The most common clinical presentations include acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis, although cortical encephalitis with malignant cerebral edema has also been described. Patients with severe ADEM (defined by encephalopathy and polyfocal neurologic deficits) may also have seizures and extensive cortical involvement that overlap with features seen in the cortical encephalitis phenotype. Attacks are typically responsive to corticosteroid therapy, IV immunoglobulin (IVIG), and/or therapeutic plasma exchange (PLEX).

We present 2 patients with severe, acute manifestations of MOGAD, whose marked cerebral inflammation and edema stabilized with aggressive intracranial pressure monitoring, although with ongoing intermittent spikes in cerebral pressure. Severe neurologic deficits failed to respond to acute therapies but did dramatically improve within 24 hours of administration of IL-6 receptor inhibition. Both patients have experienced remarkable neurologic recovery.

Case Presentation

Patient 1

A 7-year-old Hispanic boy presented with headache, vomiting, obtundation, and a generalized convulsive seizure. Lumbar puncture (LP) revealed markedly elevated opening pressure and CSF with lymphocytic predominant pleocytosis (WBC 68 cells/mm³), as demonstrated in Figure 1.

Contrasted MRI demonstrated multifocal areas of restricted diffusion, cortical and subcortical T2/FLAIR hyperintensities, and mild leptomeningeal enhancement (Figure 2A and B). He deteriorated over 48 hours to a Glasgow Coma Scale (GCS) of 8. Head CT revealed diffuse cerebral edema with impending herniation (Figure 2C). He was transferred to our tertiary pediatric intensive care unit (PICU).

An intraparenchymal intracranial pressure (ICP) monitoring catheter recorded pressures between 10 and 36 mm Hg, which improved, albeit with intermittent pressure spikes despite supportive strategies: hyperosmolar therapy, sedation and analgesia, pentobarbital coma, and hyperventilation (see also case report). Serum MOG-IgG was clearly positive (titer 1:1,000, live cell-based assay, Mayo Laboratories).

Despite 4 days of methylprednisolone 1,000 mg IV daily (7 days total) and 3 sessions of PLEX (6 sessions total), ICP elevations continued. One tocilizumab 8 mg/kg/dose IV was given on day 13. Within 12 hours, his GCS improved to 12. His episodes of intracranial hypertension resolved. Over the next 72 hours, he became fully alert and followed simple commands. He received a second dose of tocilizumab on day 19 and was transferred from PICU on day 22. He received inpatient rehabilitation for 5 weeks.

Nine months after onset, neurologic examination normalized. However, he has ongoing impulsivity and mild behavioral issues. Brain MRI with and without contrast showed evolving FLAIR hyperintensities and developing encephalomalacia (Figure 2D). His course has been monophasic to date.

Patient 2

A 15-year-old White adolescent boy presented with headache, somnolence, and emesis. LP was performed and revealed an elevated opening pressure of 60 mm Hg. CSF analysis showed lymphocytic predominant pleocytosis (WBC 149 cells/mm³), normal protein, and normal glucose level. He became progressively encephalopathic and was admitted to a local PICU.

On day 9, his mental status worsened and he seized. Contrasted brain MRI showed multifocal areas of T2/FLAIR hyperintensity with diffuse leptomeningeal enhancement (Figure 2E). On day 11, his right pupil was dilated and poorly reactive. CT demonstrated diffuse cerebral edema with impending tonsillar herniation (Figure 2F). After ICP monitor placement, hyperosmolar therapy with hypertonic saline and IV mannitol was administered. He was transferred to our PICU; there his GCS was 8, with minimal withdrawal to noxious stimulation, brisk reflexes, and a right-sided extensor response. He had multiple episodes of ICP crisis (range: 30–40 mm Hg) despite supportive strategies (Figure 1). He received methylprednisolone 1,000 mg IV daily for 7 days and IVIG 2 g/kg divided over 2 days. An external ventricular drain and meningeal and brain parenchymal biopsy were performed. Pathology demonstrated neutrophilic predominant inflammation with microglial activation and scattered CD3⁺ lymphocytic inflammation (Figure 3). Serum MOG-IgG was clearly positive (titer 1:1,000, live cell-based assay, Mayo Laboratories).

Owing to ongoing, severe cerebral edema despite symptomatic therapies, tocilizumab 8 mg/kg/dose IV was given for 2 doses 3 days apart (days 19 and 22). Within 24 hours of the first dose of tocilizumab, ICPs normalized. By 48 hours, he was awake (GCS of 14) and identified family members. After completion of 7 sessions of PLEX (started on day 20), he received 2g/kg of IVIG divided over 3 days. He was transferred to a local rehabilitation unit on day 40. Five months after onset, he had a normal neurologic examination and mild memory/cognitive impairment. MRI showed improvement in T2/FLAIR hyperintensity (Figure 2G), and serum MOG-IgG was negative.

Seven months after onset, he presented with recurrent seizures, positive serum MOG-IgG (1:40), and elevated serum IL 6 (246 pg/mL). Given concern for MOGAD relapse, monthly IVIG was started. He returned to school with no further relapses or seizures.
Discussion

Malignant cerebral edema secondary to MOGAD is life-threatening and may not respond quickly to corticosteroids, PLEX, or IVIG. We report 2 children who experienced rapid resolution of raised ICP and cerebral edema after treatment with the IL-6 receptor blocker, tocilizumab.

Our decision to administer IL-6 receptor blockade was based on studies demonstrating elevated cytokine concentrations, particularly IL-6, in MOGAD. In a study of CSF and serum obtained from 29 untreated patients (15 children) with MOGAD, CSF IL-6 concentrations were elevated compared with patients with multiple sclerosis (n = 20) and were comparable with levels measured in patients with AQP4 antibody–positive neuromyelitis optica spectrum disorder (NMOSD) (n = 20). Phase III studies of anti-IL-6 receptor therapies in NMOSD clearly demonstrated suppression of relapses, and these therapies are approved for this condition. Case reports describe tocilizumab treatment in relapsing patients with MOGAD who have failed treatment with other therapies with prolonged periods of disease suppression. Clinical trials of IL-6 receptor blockade for relapsing patients with MOGAD are now enrolling.
Patient 1: (A) MRI performed on day 2 (at outside hospital) demonstrating multifocal areas of restricted diffusion weighted imaging on the left with apparent diffusion coefficient correlate on the right. (B) MRI multifocal areas of T2/FLAIR hyperintensity in cortical and subcortical matter, basal ganglia, and brainstem and mild leptomeningeal enhancement (not pictured). (C) Head computed tomography performed on day 5 showing diffuse cerebral edema with effacement of sulci. (D) MRI on day 39: interval evolution of the multiple extensive cortical and subcortical lesions of both cerebral hemispheres and in the brainstem as detailed. This includes developing encephalomalacia in many of the previously involved regions. The cerebrum has overall, mildly decreased in volume. Patient 2: (E) Brain MRI with T2/FLAIR hyperintensity in the frontotemporal and occipital lobes and bilateral cerebellar peduncles with diffuse leptomeningeal enhancement (not pictured). (F) Head CT obtained on day 11 on arrival to CHOP showing diffuse cerebral edema in supratentorial and infratentorial parenchyma with effacement of sulci, fissures, basal cistern, and cerebellar tonsillar descent. (G) Brain MRI showing partial improvement in T2/FLAIR hyperintensity of lesions involving both cerebral hemispheres, diencephalon, and brainstem. MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease.
IL-6 is known to promote CD4+ T-cell differentiation into a Th17 phenotype and is capable of activating plasmablasts and B cells (potentially promoting MOG-IgG production). Murine models of experimental autoimmune encephalitis (EAE), which are induced by MOG immunization, require both MOG antibody production and MOG-reactive T cells for clinical disease. IL-6 in the brain increases permeability of the blood-brain barrier (BBB), leading to increased ingress of activated MOG-reactive cells and circulating MOG-IgG antibodies.

BBB disruption is an important consideration for the use of anti-IL-6 receptor therapies, which bind the soluble and fixed IL-6 receptor leading to increased levels of circulating IL-6. Tocilizumab is not believed to cross the BBB, would not be able to mitigate IL-6 binding in the CNS, and, conceptually, could worsen cerebral symptoms in MOGAD. As an analogous example, patients with chimeric antigen receptor T-cell toxicity have increased circulating IL-6 levels in both peripheral cytokine release syndrome (CRS) and in CNS immune effector cell–associated neurotoxicity syndrome (ICANS). Tocilizumab is effective only in CRS and is not advised in ICANS because of concerns of further elevation of IL-6 without the ability of tocilizumab to effectively cross the BBB to mitigate this effect. In AQP4-NMOSD and MOGAD, however, AQP4- or MOG antibodies increase BBB permeability through reduced expression of endothelial tight junction proteins. This BBB disruption leads not only to entry of plasmablasts and T cells but also to entry of therapeutic antibodies. In cell-based modeling, satralizumab was shown to cross through BBB endothelia in the presence of serum-containing AQP4-IgG, potentially explaining why IL-6 receptor blockade with tocilizumab or satralizumab might be both efficacious and safe in NMOSD and possibly MOGAD, as in our patients. Siltuximab, a direct IL-6 inhibitor, which reduces IL-6 concentrations, would be an interesting consideration for future trials.

We propose that IL-6 receptor therapies might also be considered in acute severe life-threatening presentations of MOGAD.

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