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Tocilizumab treatment in severe recurrent anti-MOG associated optic neuritis

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Patients presenting with a clinical phenotype indicative of neuromyelitis optica spectrum disease (NMOSD) including its limited variants such as recurrent optic neuritis (ON) or longitudinally extensive transverse myelitis (LETM) negative for AQP-4-antibodies, may test positive for IgG antibodies against myelin oligodendrocyte glycoprotein (MOG), a transmembrane protein expressed on oligodendrocytes and the outer layers of the myelin sheath. MOG antibody associated autoimmunity has gained increasing attention over recent years due to its clinical overlap with NMOSD, despite the latter being considered an autoimmune astrocytopathy. Anti-MOG-antibody positive patients show a relapsing disease course that can lead to substantial visual loss and spinal cord involvement.¹⁻³ Data on therapy in MOG-antibody associated disease as of yet is limited, but similar to NMOSD, it appears critical to start an efficacious treatment early in order to prevent severe functional sequelae including blindness. Tocilizumab (TCZ), a humanized antibody targeting the Interleukin 6 (IL6) receptor, has shown promise in patients with breakthrough disease and highly active forms of AQP-4-antibody positive NMOSD.^{4, 5} Prolonged treatment with TCZ has been reported both efficacious and safe⁵ and leading to a reduction of AQP-4 antibody titers^{4, 5}.

Here we present a case of an anti-MOG seropositive patient, who is stable on TCZ for more than 4.5 years after having failed various immunotherapies including the anti-CD20 antibody rituximab and cyclophosphamide.

Case report

A 59-year old male Caucasian patient was admitted to our hospital due to gait ataxia, urinary retention, constipation, nystagmus and double vision. The initial MRI showed multiple, non-longitudinally extensive T2 hyperintense lesions in the cervical, thoracic and lumbar spinal cord, as well as lesions in both thalami and the pons (figure 1). Short-term MRI follow-up indicated progressive hyperintense lesions in the cervical cord with Gadolinium (Gd) enhancement. CSF analysis revealed 15 mononuclear cells per μ l and an elevated protein of 906 mg/l, whereas oligoclonal bands were negative. The patient was tested negative for anti-AQP-4-antibody twice. Extensive bacteriological and virology screenings remained unremarkable, and the patient improved upon high dose steroids. Three months later he developed ON of the right eye followed by 6 relapses over the following 19 months while the left eye was affected once. Every relapse was treated with high dose steroids followed by plasmapheresis once with only partial recovery leading to a residual visual acuity (VA) below 20/400 (Snellen chart) on the right. Initially, treatment with the anti-VLA4 monoclonal antibody natalizumab had been initiated (3 administrations in total) followed by rituximab (2x 1g in 2 weeks) due to disease breakthrough (see figure). Due to further relapses the patient was switched to cyclophosphamide (in total 12 administrations). Following further clinical- and MRI breakthrough activity (relapsing ON) and suspected seronegative NMO, monthly TCZ (8mg/kg bodyweight) was initiated for 12 months and then tapered to applications every 6 weeks. Meanwhile the patient was tested positive for anti-MOG-antibodies (titer 1:320). Currently, a 2-monthly TCZ regime is installed. No further relapses occurred, MRI remained stable throughout, new lesions were not detected.

Discussion

MOG antibody-associated disease can present with relapsing disease leading to severe functional deficits including amblyopia and severe spinal cord syndrome.^{1, 2} Efficacious immune treatment should therefore be installed early. Currently, no treatment consensus exists for this relatively novel entity. We observed natalizumab not only failing to control but worsen disease activity, which has similarly been reported for AQP-4-antibody positive cases.⁶ We suggest that, similar to AQP4-antibody positive NMOSD, the administration of TCZ in MOG antibody associated autoimmunity should be evaluated early as well as in cases of treatment failure to anti-CD20 therapy (rituximab).⁷ Our single case report without controls provides class

IV evidence on the efficacy of the IL-6 antibody TCZ in MOG-antibody associated autoimmunity.

Appendix 1. Authors

Name	Location	Role	Contribution
Helen Hayward-Koennecke, MD	University Hospital Zurich, Switzerland	Author	Drafted the manuscript for intellectual content
Markus Reindl, PhD	Medical University of Innsbruck, Innsbruck, Austria	Author	Revised the manuscript for intellectual content
Roland Martin, MD	University Hospital Zurich, Switzerland	Author	Revised the manuscript for intellectual content
Sven Schippling, MD	University Hospital Zurich, Switzerland	Author	Revised the manuscript for intellectual content

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Figure 1. MRI findings, treatment history and relapse timeline.

Figure legend: (A) MRI scans: left: T2-hyperintense bilateral thalamic and extensive longitudinal lumbar spinal cord lesion; right: follow-up scan 8 months later without T2-hyperintense lesions. (B) Timeline of treatment interventions: ON: optic neuritis.