CASE REPORT

Clinical improvement in a patient with neuromyelitis optica following therapy with the anti-IL-6 receptor monoclonal antibody tocilizumab

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Abstract Neuromyelitis optica (NMO) is a disabling autoimmune disease associated with an elevation of anti-aquaporin 4 (AQP4) autoantibodies. Here, we present a case with NMO who responded to monthly administration of the anti-IL-6 receptor antibody tocilizumab. The treatment rapidly reduced the elevated numbers of plasmablasts and anti-AQP4 autoantibodies in the patient. Furthermore, neuropathic pain and disability scores gradually improved. Tocilizumab may be considered as a therapeutic option for NMO.

Keywords Interleukin-6 · Neuromyelitis optica · Plasmablast · Tocilizumab

Introduction

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system (CNS) characterized by recurrent episodes of destructive inflammation that target mainly the optic nerves and spinal cord. Patients with NMO often suffer from persistent neurological complications, including blindness, neuropathic pain, or difficulty walking. Previously, the identity of NMO was controversial because of its resemblance to multiple sclerosis (MS), but there is now international consensus that NMO is a distinct disease associated with elevated pathogenic autoantibodies specific for aquaporin 4 (AQP4) water channel protein [1, 2]. Whereas multiple sclerosis (MS) is classified as a CNS demyelinating disease, the hallmarks of NMO pathology are a loss of AQP4 in astrocytes, perivascular deposits of immunoglobulins with complements, and severe necrosis with macrophage and granulocyte infiltration [3]. There is an increasing amount of evidence to support the notion that anti-AQP4 antibodies are involved in the immune-mediated injury to astrocytes which occurs in NMO. In fact, in vivo injection of anti-AQP4 antibody causes the complement-dependent destruction of astrocytes [4] and enhances the manifestations of rodent experimental autoimmune encephalomyelitis (EAE) [5].

Acute exacerbations of NMO usually respond to intravenous methylprednisolone (IVMP). However, plasmapheresis may be given to cases with NMO who are refractory to IVMP. This is a reasonable therapy for NMO, considering the pathogenic role of anti-AQP4 antibodies [6]. In contrast, the effects of disease-modifying drugs prescribed for MS, including interferon β (IFNβ) [6, 7], natalizumab [8], and fingolimod [9], are unpredictable and could even exacerbate the disease activity of NMO. Therefore, oral corticosteroid and an immunosuppressant such as azathioprine (AZA) are broadly used to prevent relapses of NMO. More recently, B-cell-depleting anti-CD20 antibody, rituximab, has shown some therapeutic efficacy in NMO [10]. An interpretation by the authors is that targeting anti-AQP4 antibody-producing cells might be an attractive therapeutic option for NMO.

We recently reported that plasmablasts (PB), a sub-population of B cells, are the main producers of anti-AQP4 antibody, and that PB are increased in number in the

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peripheral blood of patients with NMO [11]. We also found that exogenous IL-6 promotes the production of anti-AQP4 antibody from PB in vitro, whereas serum IL-6 level is elevated in active NMO in vivo [11]. Overall, these results suggest that IL-6 receptor (IL-6R) signaling pathways are involved in the pathogenesis of NMO.

IL-6, originally identified as a differentiation-inducing factor of B cells [12], is now known to play a variety of roles in autoimmunity and chronic inflammation. In fact, the anti-IL-6 receptor antibody tocilizumab (TCZ), humanized anti-IL6R monoclonal antibody, proved to be efficacious in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and Castleman disease (CD) [13]. Of note, anti-IL-6R antibody may inhibit the survival of anti-AQP4 antibody-producing PB in vitro [11]. Therefore, we set up a clinical study to explore the efficacy of TCZ in vivo in the treatment of NMO ["The safety and efficacy of

tocilizumab in patients with neuromyelitis optica" (SET-NMO); UMIN000005889]. Here, we describe alterations in immunological parameters and clinical manifestations in the first registered patient with NMO [14].

Case report

A 36-year-old female patient first complained of back pain and numbness on her trunk and lower extremities in May 1998. Because of T2-weighted MRI scans showing a high-intensity lesion on the thoracic spine (Th10-11) and an episode of clinical relapse, she was tentatively diagnosed with MS, and IFNβ-1b treatment was started in combination with low-dose oral prednisolone (PSL) in May 2002. After measurement of anti-AQP4 antibody confirmed the diagnosis of NMO, IFNβ was stopped and switched to a
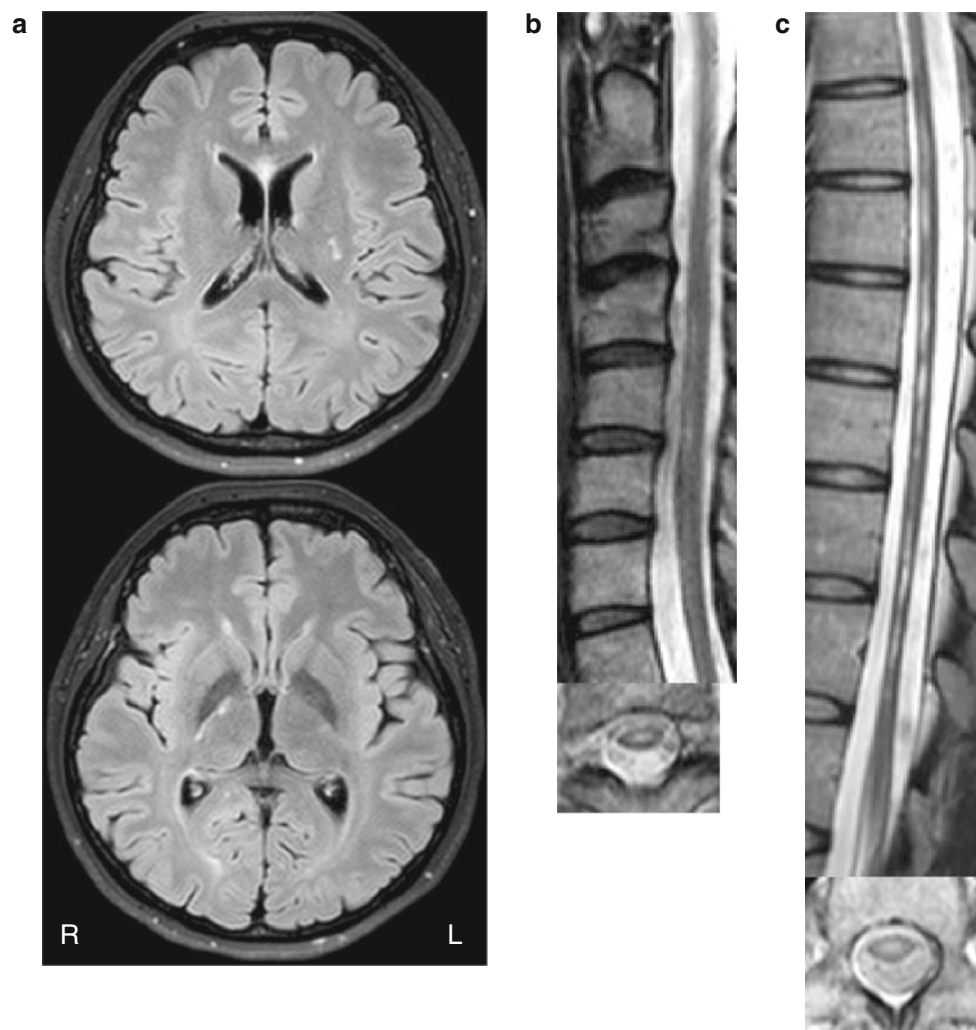
Fig. 1 MRI before TCZ administration. **a** MRI showed multiple high-intensity lesions in the corpus callosum, left putamen, and right posterior limb of the internal capsule on T2-weighted images. **b, c** T2-weighted cervical and thoracic MRI demonstrates extensive scattered high-intensity lesions involving central gray matter

combination of PSL and AZA in January 2008. However, she had six relapses in 2010 and two relapses in the first half of 2011. She consented to participate in the SET-NMO study and was admitted in October 2011 for first administration of TCZ.

On admission, she had left ptosis, hypoesthesia in distal limbs, truncal and plantar paresthesia, and hyperreflexia in all extremities. The Expanded Disability Status Scale of Kurtzke (EDSS) [15] was 3.5. Her gait was spastic and she complained of pain on walking, with a score of 4 judged on the numeric rating scale (NRS) [16]. A blood test was unremarkable except for increased levels of total cholesterol [275 mg/dl; reference range 128–219], LDL cholesterol [159 mg/dl; 70–139], and triglyceride [262 mg/dl; 30–149]. Serum IL-6 was normal 1.6 pg/dl (reference < 4.1), and antinuclear antibody, anti-SS-A and SS-B antibodies were negative. A cerebrospinal fluid (CSF) test was also unremarkable [IgG index 0.46, negative oligoclonal IgG bands, and IL-6 1.6 pg/dl]. No gadolinium-enhanced lesion was detected on brain MRI (Fig. 1a). T2-weighted spinal cord MRI showed high-intensity lesions consistent with longitudinally extensive transverse myelitis (LETM), a hallmark of NMO (Fig. 1b, c). Central conduction times of sensory evoked potentials on upper and lower extremities were within the normal limits. Visual evoked potential and auditory brainstem response were also normal.

Intravenous TCZ of 8 mg/kg was given monthly to the patient for six months until April 2012. As clinical outcome measures, we evaluated the number of relapses and changes in EDSS and NRS. Serum levels of IL-6, PB, and anti-AQP4 antibody were also examined. The PB frequency (CD19$^+$CD27^{high}CD38^{high}CD180$^-$ cells) was measured by flow cytometry (FACS Canto II, BD Biosciences), as described previously [11]. Serum anti-AQP4 antibody titers were estimated by measuring the binding of IgG in the serum to AQP4 transfectants, as previously described (with minor modifications) [11]. Median fluorescence intensity (MFI) values were obtained from indirect FITC-anti-human antibody staining. The MFI values were measured for serially diluted serum from the patient. The cut-off value for the MFI was determined by calculating the average of the values for six healthy subjects $+ 3 \times$ SEM.

Four days after the first administration of TCZ, she developed a minor relapse with truncal paresthesia and gait disturbance. However, she experienced no relapse afterwards and the sensory disturbances and pain in her extremities and trunk gradually improved. The NRS score decreased from four to zero within four administrations (Fig. 2a). She could walk for more than 1 h without any assistance and her EDSS improved to 2.0 (Fig. 2a).

Oral PSL was tapered from 13 mg to 6 mg daily during the six courses of TCZ. AZA was also reduced in six months from 50 mg every second day to 50 mg weekly (Fig. 2b). The serum IL-6 level immediately increased after the TCZ treatment, and the high IL-6 value persisted until the second administration of TCZ (Fig. 3a). In contrast, the frequency of PB as well as the anti-AQP4 antibody titer reduced within the first month (Fig. 3a, b). The frequency of PB increased to 34 % at six months (before the sixth administration). We assume that this increase in

Fig. 2 Clinical course after TCZ administration. a Follow-up for EDSS and NRS. b Dosages of concomitant drugs given to the patient (AZA and PSL). Numbers from 1–6 show the timing of each TCZ administration. URI upper respiratory infection
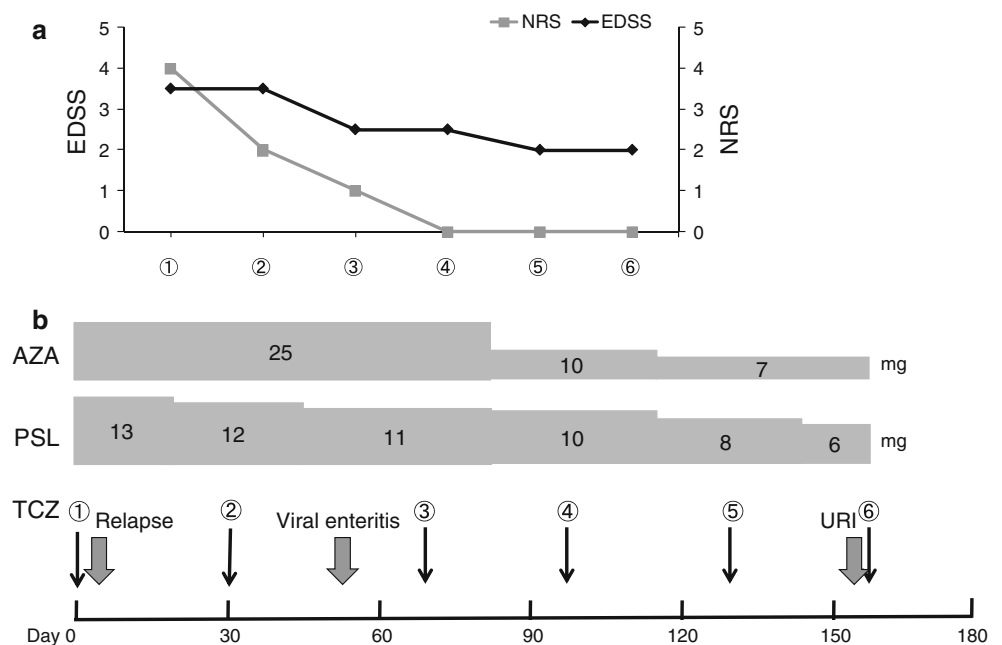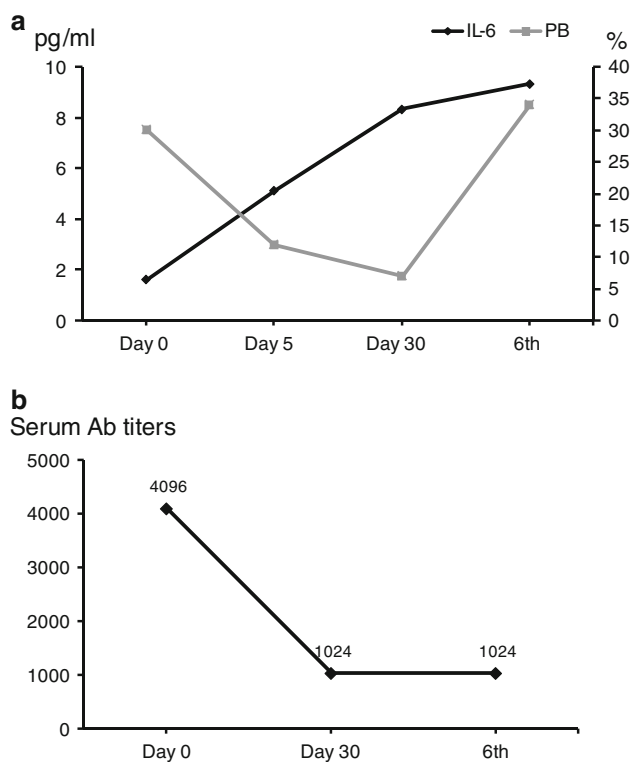
Fig. 3 a Alterations in serum IL-6 and PB frequency (%) after injection of TCZ. *Black dots* and *line* represent the concentration of serum IL-6 (reference range: <4 pg/ml); *gray dots* and *line* represent the frequency of PB (%) among all B cells. *Day 0* shortly before the first injection of TCZ, *Day 5* five days after the first TCZ injection, *Day 30* shortly before the second injection of TCZ, *6th* shortly before the sixth TCZ injection. **b** Changes in the anti-AQP4 antibody titer

PB could have resulted from the preceding upper respiratory infection. In fact, our preliminary data indicate that PB numbers in healthy individuals increase after minor infection (unpublished). In addition, we evaluated the proportions (%) of CD19$^+$ cells among PBMCs. Although it appeared that the CD19$^+$ cell frequency reduced from 3.98 to 2.49 % in the first five days after the first TCZ injection, this reduction did not appear to persist, considering the frequency measured on day 30 (4.03 %). Brain and spinal MRI findings showed no significant changes in the number and size of lesions (data not shown), which is consistent with an absence of major relapses and clinical improvement.

Adverse events following TCZ were a decline in systolic blood pressure by 20 mmHg after the first injection and lymphocytopenia of 438/μl on day 14 after the second administration. Two months after starting TCZ, she developed enteritis caused by a norovirus. She also experienced an upper respiratory infection of unknown origin. Neither infections were serious, and they were improved by intravenous fluid replacement.

Discussion

In the present case, significant effects of TCZ were observed in clinical as well as immunological parameters. Overall, TCZ therapy was considered to be safe and satisfactory, as stable remission without side effects was maintained during the six-month period of the SET-NMO study. Moreover, her neuropathic pain and paresthesia improved greatly, such that her clinical condition as assessed by EDSS and NRS was greatly improved six months after starting TCZ. We assume that the clinical improvement resulted from the anti-inflammatory effect of TCZ on the CNS inflammatory response. However, as others have speculated that IL-6 may cause the neuropathic pain directly [17], these effects of TCZ may have been due to the blockade of the IL-6R pathway leading to neuropathic pain. If this was indeed the case, the application of TCZ appears to be a promising approach for treating this pain syndrome.

On the other hand, the effects of TCZ effects on immunological parameters were obvious in terms of the number of PB, the serum IL-6 level, and the anti-AQP4 antibody titer. A decrease in PB was apparent 5 and 30 days after the first administration of TCZ. Moreover, serum titers of anti-AQP4 antibody started to decline. Inhibition of IL-6 signaling induced a reduction in PB in vitro [11]. The present results validate the notion that PB survival depends on IL-6R signals, and that TCZ may be efficacious in cases with NMO because it targets PB, which secrete anti-AQP4 antibody. Furthermore, we suggest that PB could serve as a biomarker for monitoring the effects of TCZ in vivo.

In contrast, serum IL-6 levels increased after TCZ was started (Fig. 3a). Because an increase in serum IL-6 after starting TCZ has also been reported in patients with RA and CD [18], the increased IL-6 levels can be attributed to the inhibition of IL-6 consumption due to the blocking of IL-6R signaling in the presence of TCZ. Further in vivo study is required to prove the link between IL-6 and PB in NMO.

Conflict of interest None.

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