Disease Amelioration With Tocilizumab in a Treatment-Resistant Patient With Neuromyelitis Optica

Implication for Cellular Immune Responses

Bernd C. Kieseier, MD; Olaf Stüve, MD, PhD; Thomas Dehmel, PhD; Norbert Goebels, MD; Verena I. Leussink, MD; Anne K. Mausberg, PhD; Marius Ringelstein, MD; Bernd Turowski, MD; Orhan Aktas, MD; Gerald Antoch, MD; Hans-Peter Hartung, MD

Background: Neuromyelitis optica (NMO) is an autoimmune disease of the central nervous system in which aberrant antibody responses to the astrocytic water channel aquaporin 4 have been described. Experimental evidence is emerging that NMO is partly driven by the proinflammatory cytokine interleukin 6 (IL-6), which propagates the survival of disease-specific B cell subclasses, and deviates CD4+ T helper cell differentiation toward IL-17-producing T helper 17 cells. Tocilizumab is a recombinant humanized monoclonal antibody against the IL-6 receptor approved for treatment of rheumatoid arthritis.

Objectives: To study clinical and paraclinical effects of tocilizumab in a patient with NMO.

Design: Case report.

Setting: Academic neurology department.

Patient: A patient with highly active aquaporin 4-seropositive NMO who failed numerous immunosuppressive interventions, including high-dose corticosteroids, mitoxantrone, plasma exchange (PE), rituximab (anti-CD20), and alemtuzumab (anti-CD52), before receiving tocilizumab.

Main Outcome Measures: Clinical disability, magnetic resonance imaging, cytokines and transcription factors levels in the cerebrospinal fluid, and peripheral blood mononuclear cells.

Results: A patient who continued to accumulate neurological disability and magnetic resonance activity while receiving numerous immunosuppressive therapies stabilized, and eventually improved clinically and on magnetic resonance metrics after treatment initiation with tocilizumab. Treatment and clinical response correlated with a significant reduction of IL-6 levels in the CSF as well as a diminished expression of signal transducer and activator of transcription 3.

Conclusions: Tocilizumab might be effective in NMO, here in a patient not responding to leukocyte depletion. Our findings further support data that implicate IL-6 as a critical molecule in the immunopathogenesis of NMO, and a critical role for T cells in the pathogenesis of this disorder.


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therapy in patients with NMO otherwise unresponsive to established treatment approaches.

REPORT OF A CASE

A 34-year-old female was diagnosed with NMO according to established criteria including the presence of anti-aquaporin-4 IgG antibodies. The disease initially manifested with recurrent optic neuritis. Subsequently, she experienced a relapse with incomplete tetraplegia 24 months ago (Expanded Disability Status Scale [EDSS] score, 6.5), caused by contiguous extensive spinal cord lesions (C1-C5, T2-T6). High-dose methylprednisolone therapy was ineffective, whereas plasma exchange (PE) resulted in an incomplete clinical remission (EDSS score, 4.0). She then received a course of intravenous (IV) rituximab, 2 doses of 1000 mg, 14 days apart. Six weeks later, she presented with another severe relapse, which resulted in worsening of her tetraparesis (EDSS score, 6.5), and an increased lesion burden on spinal magnetic resonance imaging (MRI) with the presence of gadolinium (Gd)-enhancing T1 lesions. Plasma exchange again led to some clinical improvement (EDSS score, 4.0), and was followed up by therapy with mitoxantrone, IV 12 mg/m². Eight weeks later, a new relapse occurred that caused paraplegia and severe paresis of both upper extremities (EDSS score, 9.0). Plasma exchange was reinitiated and the patient’s condition slowly improved. Magnetic resonance imaging still revealed Gd-enhancement in the spinal cord. No CD19⁺ B lymphocytes were detected in the peripheral venous blood or CSF. At this point, anti-CD52-mediated immunosuppression with alemtuzumab was started, IV 12 mg/d over 5 days. This resulted in a complete depletion of CD52⁺ cells in the peripheral blood. Immunophenotyping revealed absence of CD3⁺, CD4⁺, CD8⁺, CD19⁺, and CD20⁺ cells in CSF and peripheral blood. Six weeks later, she suffered from yet another exacerbation characterized by tetraparesis with paraplegia (EDSS score, 8.0). On MRI the extensive cervical cord lesion continued to exhibit unchanged Gd-enhancement and edema. Corticosteroids were given intrathecally, and the patient showed some improvement (EDSS score, 6.0).

At this juncture, it was decided to initiate treatment with tocilizumab at a dose of 8 mg/kg body weight IV every 4 weeks. The patient recovered clinically within the following weeks and has remained fully and unrestrictedly ambulatory (current EDSS score, 2.5) (Figure 1). In addition, the MRI has remained free of Gd activity (Figure 2). Intrathecal IL-6 levels, which had been elevated prior to administration of tocilizumab, decreased under this treatment. Furthermore, peripheral blood mononuclear cells (PBMCs) exhibited a substantial reduction in signal transducer and activator of transcription 3 (STAT3) messenger RNA expression, which was maintained over time (Figure 3).

COMMENT

To our knowledge, we report the first case of a patient with highly active NMO whose condition continued to deteriorate despite intensive immunotherapy, which included high-dose corticosteroids, PE, mitoxantrone, rituximab, and alemtuzumab. Despite complete depletion of CD19⁺ and CD52⁺ lymphocytes and elimination of humoral factors by PE, the patient continued to exhibit clinical disease activity, and revealed Gd enhancement of spinal cord lesions on MRI. This observation suggests that potentially a CNS-intrinsic inflammatory cascade may drive disease activity rather than the cellular and humoral immune responses in the systemic immune compartment. The concept of using tocilizumab in this setting was based on the observation of IL-6-dependent B cell subtypes in patients with NMO as well as the previously reported involvement of IL-6 in NMO. Our clinical and para-
clinical observations support the view that IL-6 might have a crucial role in the immunopathogenesis of this autoimmune disorder and represents an interesting potential therapeutic target. However, our findings argue against a central humoral response in the pathogenesis of NMO: (1) although CD19+ B lymphocytes were fully depleted for more than 4 months after treatment with rituximab, the disease was still active, both clinically and on MRI (Figure 2A). A humoral response should wane at least to some extent 3 months after B cell depletion by anti-CD20 plus anti-CD52 antibodies, which was not the case; (2) a clinical response after the first dose of tocilizumab became apparent already 4 weeks later (Figure 2D). This would be too fast for an impact on immunoglobulin-mediated effects. Interleukin 6 has been shown to promote polarization of T helper 17 cells, which have been reported to be highly activated in patients with NMO. In our patient, the drop in IL-6 protein levels in the CSF after treatment initiation with tocilizumab corresponded well with clinical and paraclinical improvement, and at the same time with a decrease in the expression of PBMCs of STAT-3 messenger RNA, an IL-6 dependent transcription factor driving the development of T helper 17 cells. Our finding may support the concept that NMO is mediated, at least in part, by a relevant T-cell response. Because lymphocytes were depleted with the anti-CD52 antibody, the overall cell count in the CSF was too low to assess lymphocyte subclasses by fluorescence-activated cell sorting prior to treatment initiation with tocilizumab. Thus, we cannot provide cell numbers, but only indirect evidence. However, one has to consider that therapeutic inhibition of T- and B-cell migration into the CNS was not beneficial in a subset of patients with NMO. Alternative immunopathogenic pathways of IL-6 in the NMO lesion can not be excluded. Nevertheless, with continuous treatment with tocilizumab for 16 months, the clinical and MRI effects are still maintained, and as such additive effects from previous alternative immunosuppressive strategies may be excluded by now. So far, no safety signals have occurred.

In summary, our findings represent a single case report only and, therefore, any generalization should be avoided. Nevertheless, this observation suggests it may be worthwhile to explore the safety and efficacy of tocilizumab in NMO in a controlled clinical trial.

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Figure 2. Six magnetic resonance images performed sequentially revealing cervical cord lesion; gadolinium enhancement (arrow) was still detectable after treatment initiation with rituximab (A) and alemtuzumab (B and C); after application of tocilizumab gadolinium enhancement diminished rapidly (D and E) and fully disappeared. Cranial magnetic resonance imaging revealed no lesions outside the spinal cord (C and F).

Figure 3. Interleukin-6 levels were assessed in the CSF by enzyme-linked immunosorbent assay and found at high levels prior to treatment initiation with tocilizumab. A, Therapeutic blockade of the interleukin 6 receptor resulted in a profound reduction of interleukin-6 levels already within 1 week, an effect that was maintained in the following weeks. B, The RNA expression of signal transducer and activator of transcription 3 in peripheral blood mononuclear cells (PBMCs) was reduced during treatment with tocilizumab as well. RNA levels declined within 1 week and remained low thereafter. CSF indicates cerebrospinal fluid.
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