Efficacy of the anti–IL-6 receptor antibody tocilizumab in neuromyelitis optica

A pilot study

OPEN

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ABSTRACT

Objective: To evaluate the safety and efficacy of a humanized anti–interleukin-6 receptor antibody, tocilizumab (TCZ), in patients with neuromyelitis optica (NMO).

Methods: Seven patients with anti–aquaporin-4 antibody (AQP4-Ab)-positive NMO or NMO spectrum disorders were recruited on the basis of their limited responsiveness to their current treatment. They were given a monthly injection of TCZ (8 mg/kg) with their current therapy for a year. We evaluated the annualized relapse rate, the Expanded Disability Status Scale score, and numerical rating scales for neurogenic pain and fatigue. Serum levels of anti-AQP4-Ab were measured with AQP4-transfected cells.

Results: Six females and one male with NMO were enrolled. After a year of TCZ treatment, the annualized relapse rate decreased from 2.9 ± 1.1 to 0.4 ± 0.8 ($p < 0.005$). The Expanded Disability Status Scale score, neuropathic pain, and general fatigue also declined significantly. The ameliorating effects on intractable pain exceeded expectations.

Conclusion: Interleukin-6 receptor blockade is a promising therapeutic option for NMO.

Classification of evidence: This study provides Class IV evidence that in patients with NMO, TCZ reduces relapse rate, neuropathic pain, and fatigue. *Neurology*® 2014;82:1302–1306

GLOSSARY

Ab = antibody; **AQP4** = aquaporin-4; **AZA** = azathioprine; **EDSS** = Expanded Disability Status Scale; **IL** = interleukin; **IL-6R** = interleukin-6 receptor; **NMO** = neuromyelitis optica; **PB** = plasmablasts; **PSL** = prednisolone; **TCZ** = tocilizumab.

Neuromyelitis optica (NMO) is a relatively rare autoimmune disease that predominantly affects the spinal cord and optic nerve. Anti–aquaporin-4 antibody (AQP4-Ab), which is a disease marker of NMO, has an important role in causing the destruction of astrocytes that express AQP4.[1] Empirically, the use of disease-modifying drugs for multiple sclerosis, including interferon β, is not recommended for NMO,[2] which is consistent with the distinct pathogenesis of NMO and multiple sclerosis. We have recently described that plasmablasts (PB), which are a subpopulation of B cells, increased in the peripheral blood of patients with NMO and that PB are a major source of anti-AQP4-Ab among peripheral blood B cells.[3] In addition, we observed that exogenous interleukin (IL)-6 promotes the survival of PB and their production of anti-AQP4-Ab in vitro. Given the increased levels of IL-6 in the serum and CSF during relapses of NMO,[1,3] we postulated that blocking IL-6 receptor (IL-6R) pathways might reduce the disease activity of NMO by inactivating the effector functions of PB. A humanized anti–IL-6R monoclonal antibody, tocilizumab (TCZ) (Actemra/RoActemra), has been approved in more than 100 countries for use in the treatment of rheumatoid arthritis.[4] Herein, we describe our clinical study that aimed to explore the efficacy of TCZ in NMO.

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Table Demographics of the patients

	Patient						
	1	2	3	4	5	6	7
Age, y/sex	37/F	38/F	26/F	31/M	55/F	62/F	23/F
Age at onset, y	23	27	21	12	38	60	21
Anti-AQP4-Ab	+	+	+	+	+	+	+
Myelitis	+	+	+	+	+	+	–
Optic neuritis	+	+	+	+	+	+	+
EDSS score	3.5	6.5	3.5	6.0	6.5	6.5	3.0
Total no. of relapses	20	9	6	16	20	3	7
ARR before TCZ	3	2	2	2	3	3	5
Immunotherapies for exacerbations	IVMP, PLEX	IVMP, PLEX	IVMP, PLEX	IVMP, OBP, PLEX	IVMP, PLEX	IVMP, PLEX	IVMP, PLEX
Past immunotherapies	IFNβ, IVIg	IFNβ	—	IFNβ, MITX	IFNβ, AZA	—	AZA
Present immunotherapies	PSL, AZA	AZA	PSL	PSL, AZA	PSL, CyA	PSL, CyA	PSL, tacrolimus
Neuropathic pain (e.g., girdle pain), NRS	4	4	2	4	4	3	0
General fatigue, NRS	5	8	6	7	5	3	9
Pain and antispasticity medication	GBP, CZP, NTP, NSAID	CZP, mexiletine, NTP, tizanidine, NSAID	—	CBZ, baclofen, NSAID	CBZ	PGB	—

Abbreviations: AQP4-Ab = aquaporin-4 antibody; ARR = annualized relapse rate; AZA = azathioprine; CBZ = carbamazepine; CZP = clonazepam; CyA = cyclosporine; EDSS = Expanded Disability Status Scale; GBP = gabapentin; IFNβ = interferon β; IVIg = IV immunoglobulin; IVMP = IV methylprednisolone; MITX = mitoxantrone; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; NTP = Neurotropin (an extract from the inflamed skin of vaccinia virus–inoculated rabbits); OBP = oral betamethasone pulse therapy; PGB = pregabalin; PLEX = plasma exchange; PSL = prednisolone; TCZ = tocilizumab.

METHODS

Level of evidence. The aim of this Class IV evidence study was to evaluate the effect and safety of a monthly injection of TCZ (8 mg/kg) with their current therapy in patients with NMO. We evaluated the adverse events based on Common Terminology Criteria for Adverse Events, version 4.0.

Standard protocol approvals, registrations, and patient consents. All patients gave written informed consent before the first treatment with TCZ. The institutional ethical standards committee on human experimentation approved this clinical study. The study is registered with University Hospital Medical Information Network Clinical Trials Registry, numbers UMIN000005889 and UMIN000007866.

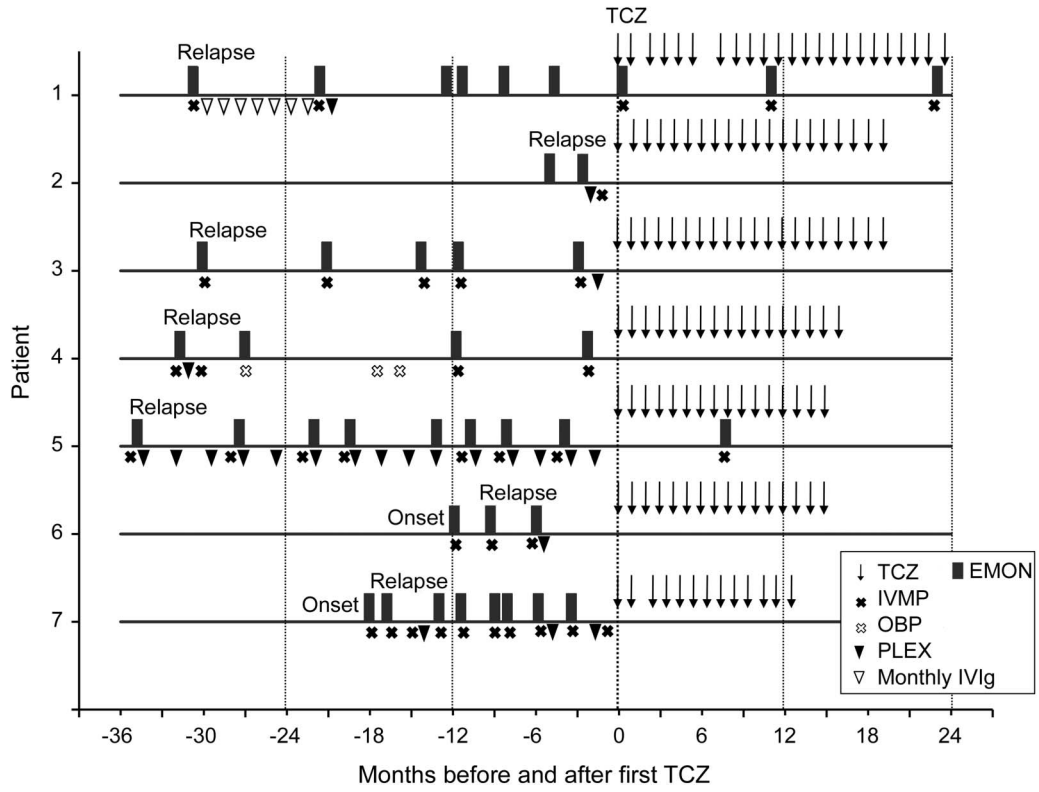
Patients and treatment. Seven patients who met the diagnostic criteria of NMO in 2006 were enrolled after providing informed consent (table). Results of chest x-rays, interferon γ release assays, and plasma 1,3-β-D-glucan measurement excluded latent tuberculosis and fungal infection. All of the patients had been treated with combinations of oral prednisolone (PSL) and immunosuppressants, including azathioprine (AZA). Nevertheless, they had at least 2 relapses during the year before enrollment (figure 1). Among their past immunomodulatory medications, interferon β had been prescribed in 4 patients before the anti-AQP4-Ab assay became available. Although symptomatic treatments had been provided, the patients experienced general fatigue and intractable pain in their trunk and limbs. There were no abnormalities in their routine laboratory blood tests. Neither pleocytosis nor increased levels of IL-6 were observed in the CSF. MRI revealed high-intensity signals in the optic nerves and longitudinally extensive lesions in the spinal cord. All patients except one had scattered brain lesions. A monthly dose (8 mg/kg) of TCZ was added to the patients' oral corticosteroid and immunosuppressive drug regimen.

Clinical and laboratory assessment. As clinical outcome measures, we evaluated alterations in the number of relapses, Expanded Disability Status Scale (EDSS) scores, and pain and fatigue severity scores (numerical rating scales). A relapse was defined as an objective exacerbation in neurologic findings that lasted for longer than 24 hours with an increase in the EDSS score of more than 0.5. Brain and spinal cord MRI scans were examined every 4 or 6 months. CSF examinations, sensory-evoked potentials, and visual-evoked potentials were also evaluated at the time of entry into the study and 12 months later. We measured serum anti-AQP4-Ab levels by evaluating the binding of serum immunoglobulin G to AQP4 transfectants, as previously described.[5] All outcome measures were analyzed with nonparametric Wilcoxon rank-sum tests, with the use of 2-tailed statistical tests at a significance level of 0.05.

RESULTS

After starting TCZ treatment, the total number of annual relapses in the patients significantly reduced (figures 1 and 2). Notably, 5 of the 7 patients were relapse-free after starting TCZ. The relapses observed in patients 1 and 5 were mild and their symptoms recovered after IV methylprednisolone. On average, the annualized relapse rate reduced from 2.9 ± 1.1 (range, 2–5) during the year before study to 0.4 ± 0.8 (range, 0–2) during the year after

Figure 1 Clinical course of the patients before and after tocilizumab treatment



The zero on the x-axis represents the first administration of tocilizumab (TCZ). Dark gray bars: exacerbations of myelitis or optic neuritis (EMON); downward arrow: TCZ treatment; black X: IV methylprednisolone (IVMP); white X: oral betamethasone pulse (OBP) therapy; black triangle: plasma exchange (PLEX); white triangle: IV immunoglobulin (IVIg). After receiving 12 injections, all patients continued treatment with TCZ by entering an extension study that evaluates the long-term safety and efficacy of TCZ. We showed the clinical status after completion of the 1-year study to indicate the continuation of remission.

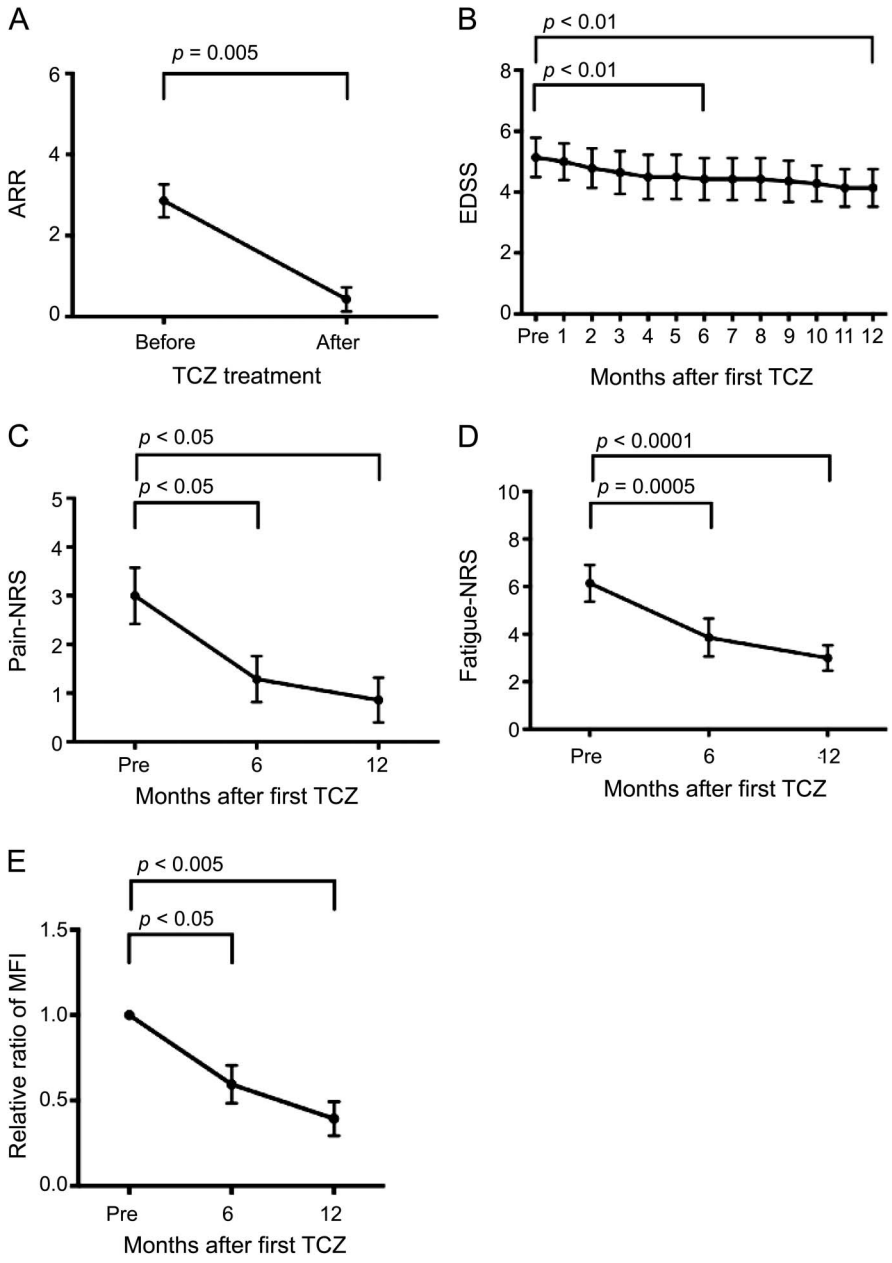
starting TCZ (figure 2). The EDSS score decreased modestly but significantly from 5.1 ± 1.7 (range, 3.0–6.5) to 4.1 ± 1.6 (range, 2.0–6.0) at 12 months. The chronic neurogenic pain in their trunk and extremities, which is characteristic of NMO[6,7] (table), gradually lessened after the patients started TCZ. Consequently, the numerical rating scale for pain reduced from 3.0 ± 1.5 upon study entry to 1.3 ± 1.3 after 6 months and 0.9 ± 1.2 after 12 months. General fatigue also improved from 6.1 ± 2.0 to 3.9 ± 2.1 at 6 months and 3.0 ± 1.4 at 12 months. The MRI scans, sensory- and visual-evoked potentials, and CSF observations did not show any interval changes. Serum anti-AQP4-Ab levels represented by the relative mean fluorescence intensity were significantly reduced (figure 2E).

Adverse events included upper respiratory infections (patients 1 and 7), acute enterocolitis (patients 1 and 4), acute pyelonephritis (patient 1), leukocytopenia and/or lymphocytopenia (patients 1, 4, and 7), anemia (patients 3 and 7), and a slight decline in systolic blood pressure (patient 1). However, none of the events was severe. Oral PSL and AZA were tapered in patients 1, 3, 4, and 7, resulting in a reduction of the mean doses (PSL from 19.5 ± 7.6 to 8.8 ± 5.6 mg/d [average of patients 1, 3, 4, and 7], AZA from 37.5 to 5.4 mg/d [average of patients 1 and 4]).

DISCUSSION Pain management is a difficult problem in patients with NMO. In fact, a retrospective study of 29 patients with NMO who experienced pain has documented that 22 of the 29 patients were taking pain medications, but none of them rated their current pain as 0 out of 10 on a 10-point scale.[6] In the present study, the intractable pain reduced gradually after the patients started TCZ treatment. After 6 or 12 months of therapy, 3 of the 6 patients with pain were completely free of pain. These results suggested a role of IL-6 in NMO pain and the possible merits of the use of TCZ in clinical practice as a pain reliever.

The pathophysiology of neurogenic pain is now understood in the context of interactions between the immune and nervous systems,[8] which involve proinflammatory cytokines such as IL-6 as well as immune cells, activated glia cells, and neurons. Supportive for the role of IL-6 in pain, recent work in

Figure 2 Effects of tocilizumab on clinical and immunologic parameters



(A) Annualized relapse rate (ARR) before and after tocilizumab (TCZ) treatment. (B) Expanded Disability Status Scale (EDSS) score during the 1-year study period. Pain severity (numerical rating scale [NRS]) (C) and fatigue severity (D) scores before, 6 months after, and 12 months after the start of TCZ treatment. The dots and I bars indicate means ± SEM. We analyzed only data obtained during the first year of TCZ treatment. (E) The alterations in the serum anti–aquaporin-4 antibody (AQP4-Ab) were evaluated by the relative ratio of the mean fluorescence intensity (MFI), which was based on the MFI before TCZ treatment. Serum anti-AQP4-Ab detection assay was performed as described previously[3,5] with minor modifications. In brief, optimally diluted serum was added to human AQP4-expressing Chinese hamster ovary (CHO) cells. CHO cell-bound anti-AQP4-Ab was detected using fluorescein isothiocyanate–anti-human immunoglobulin G antibody by flow cytometry. For comparison, the MFI of each sample was divided by the MFI of the sample before the start of TCZ treatment.

rodents showed that gp130 expressed by nociceptive neurons might have a key role in pathologic pain.[9] Although expression of membrane-bound IL-6R is restricted to hepatocytes, neutrophils, and subsets of T cells, the gp130, ubiquitously expressed in cellular membranes, can transduce IL-6R signaling via binding to the IL-6/soluble IL-6R complex.[4] This indicates that IL-6 trans-signaling via the soluble IL-6R could be pivotal in causing pain in NMO, although alternative possibilities cannot be excluded.

TCZ treatment recently showed efficacy for patients with aggressive NMO who were refractory to the anti-CD20 antibody rituximab.[10] The efficacy of TCZ could result from its effect on IL-6–dependent inflammatory

processes, involving CD20-negative PB, pathogenic T cells, and regulatory T cells. This work, however, does not restrict the use of TCZ in serious NMO. Although the need for monitoring latent infection and adverse events is obvious, we propose that the use of TCZ may be considered at an early stage of NMO before disability or a lower quality of life becomes evident.

AUTHOR CONTRIBUTIONS

T.Y., S.M., S.K., M.M., and M.A.: design and conceptualization of the study. M.A., K.M., T.O., and T.Y.: analysis and internalization of the data. T.M. and T.A.: flow cytometry analysis and anti-AQP4-Ab assay. M.A. and T.Y.: drafting and revising of the manuscript. T.Y.: supervising the entire project.

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