Neurochemistry International 130 (2019) 104315

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Blockade of IL-6 signaling in neuromyelitis optica

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ARTICLE INFO

Keywords:
Aquaporin 4
Anti-IL-6 receptor monoclonal antibody
Tocilizumab
Neuromyelitis optica spectrum disorders

ABSTRACT

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD) are autoimmune diseases associated with a disease-specific autoantibody directed against the water channel protein aquaporin-4. Standard immunotherapy, immunosuppressive agents, and corticosteroids can prevent acute attacks and maintain remission in most patients with NMOSD. However, there is a strong need for additional options for patients who are refractory to standard treatments. Emerging therapies targeting specific molecules related to the pathogenicity of NMOSD are currently being developed. The review focuses on improving preventive treatments for NMOSD, including ongoing randomized clinical trials using biological drugs targeting CD19 and CD20 on B cells, interleukin-6, and complement protein C5. The anti-IL-6 receptor monoclonal antibody tocilizumab (TCZ), which can block IL-6 signaling, was shown to be highly effective for refractory patients with NMOSD. Notably, TCZ has marked effects on chronic neuropathic pain and general fatigue in patients refractory to standard medications. TCZ is a promising drug for preventing acute attacks in patients with NMOSD.

1. Introduction

Neuromyelitis optica (NMO) is an autoimmune inflammatory disease of the central nervous system (CNS), which is associated with disease-specific autoantibodies directed against the water channel protein aquaporin-4. Eugène Devic et al. first reported a transient syndrome characterized by bilateral optic neuritis and transverse myelitis at the end of the 19th century, which is now recognized as Devic's disease. Thereafter, a recurrent type of the disease was also reported, and the diagnostic criteria of NMO was proposed in 1999 (1) (Wingerchuk et al., 1999). NMO was characterized as a longitudinally extensive transverse myelitis (LETM) by magnetic resonance imaging (MRI) and as a rare disorder in Europe and North America, distinct from multiple sclerosis (MS). In Asian countries including Japan, many patients with MS are predominantly affected in the optic nerves and by spinal cord lesions, and they were categorized as having optic-spinal MS, as compared to patients with the conventional type of MS with cerebral white matter lesions that are more common in Caucasians.

A major turning point in elucidating the pathogenesis of NMO was the discovery of disease-specific NMO-immunoglobulin G (IgG) autoantibodies (2) (Lennon et al., 2004). Specific autoantibodies were identified in the patient's sera and in the following year, it was found that the target antigen was aquaporin 4 (AQP-4), which constitutes a water channel (3) (Lennon et al., 2005). Because of this discovery, elucidation of the related immunopathogenesis progressed and diagnostic criteria including anti-AQP4 antibody measurement were proposed (4) (Wingerchuk et al., 2006). Based on this diagnostic criterion, a history of optic neuritis and myelitis was regarded as an indispensable item for diagnosis of definite NMO. Even if the anti-AQP4 antibody status is negative, diagnosis of definite NMO can be made based on characteristic MRI images, such as LETM. Thereafter, the analysis of positive cases of anti-AQP4 antibodies revealed that some patients showed a limited disease type involving only optic neuritis or myelitis, symptomatic brain lesions, or comorbid other autoimmune diseases. NMO spectrum disorder (NMOSD) was proposed as a disease spectrum related to anti-AQP4 antibodies, and new diagnostic criteria were subsequently provided in 2015 (5) (Wingerchuk et al., 2015), resulting in the suggestion that the disease nomenclature should be unified to

Abbreviations: NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; TCZ, tocilizumab; CNS, central nervous system; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; IgG, immunoglobulin G; AQP-4, aquaporin 4; BBB, blood-brain barrier; Ab, antibody; IL, interleukin; PB, plasmablast; BAFF, B-cell activating factor; APRIL, proliferation-inducing ligand; IL-6R, IL-6 receptor; TGF, transforming growth factor; iTreg, TGF-β−induced regulatory T cell; IVMP, intravenous methylprednisolone; PLEX, plasma exchange; IAPP, immunoadsorption plasmapheresis; DFPP, double-filtration plasmapheresis; DMD, disease-modifying drug; IFN-β, interferon-β; RTX, rituximab; ECU, eculizumab; EDSS, expanded disability status scale; ARR, annualized relapse rate; SLE, systemic lupus erythematosus

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https://doi.org/10.1016/j.neuint.2018.10.012
Received 23 July 2018; Received in revised form 4 October 2018; Accepted 17 October 2018
Available online 17 October 2018
0197-0186/

NMOSD. Diagnostic criteria were established based on anti-AQP4 antibody production, major clinical symptoms (core clinical characteristics), and characteristic MRI findings. The nomenclature of NMOSD remains controversial even among MS/NMO specialists; the pathogenesis of seronegative NMOSD is still heterogeneous, because it possibly includes the patients with anti-MOG antibody. However, in this review, I will use the unified nomenclature of NMOSD.

2. Immunopathogenesis in NMOSD

AQP4, which is a target of autoantibodies, is abundantly distributed in the foot processes of astrocytes existing near the blood-brain barrier (BBB) (6) (Rash et al., 2004). NMOSD is pathologically characterized by loss of AQP4 and glial fibrillary acidic protein, which is a specific marker of astrocytes in the lesions, IgG and IgM, complement deposition surrounding the blood vessels, and infiltration of macrophages and granulocytes, accompanied highly necrotic changes (7) (Lucchinetti et al., 2002). However, the expression of myelin basic protein, which is the target for inflammatory demyelination in MS pathology, is relatively stable. NMOSD pathogenesis is mainly based on astrocytic damage (astrocytopathic disease) (8) (Fujihara et al., 2012). In addition, serum anti-AQP4 antibody (AQP4-Ab) levels correlate with clinical disease activity (9) (Jarius et al., 2008). The roles of anti-AQP4 antibodies include BBB breakdown and induced hyperpermeability (10, 11) (Vincent et al., 2008; Takeshita et al., 2016); astrocytic damage with loss of AQP4 (12) (Misu et al., 2007); and activation of neutrophils, eosinophils, and complement (13) (Hinson et al., 2007). Finally, excitotoxicity of neurons and oligodendrocytes via the sodium-dependent excitatory amino acid transporter (Na^+-dependent excitatory amino acid transporter 2, EAAT2) results in neuronal cell and oligodendrocyte death (14, 15) (Matute et al., 2001; Hinson et al., 2008). The immunological mechanism of NMOSD is much different from that of MS. MS is thought to be a T cell-mediated disease, given that a genome-wide association study identified many genetic loci associated with T cells (16) (International Multiple Sclerosis Genetics Consortium et al., 2011). In contrast, NMOSD is considered associated with humoral immunity involving B cells. Th17 cytokines including interleukin (IL)-6 and IL-17, and Th2 cytokines including IL-5 and IL-13 are elevated in the serum and cerebrospinal fluid of the patients with NMOSD (17) (Uzawa et al., 2014). Plasmablasts (PBs, $CD19^+CD27^{high}CD38^{high}CD180^-$), which are a subpopulation of B cells, are capable of producing autoantibodies, including AQP4-Ab (18) (Chihara et al., 2011). The survival of PBs and the production of AQP4-Ab are both promoted by IL-6, but not B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL). Moreover, increased levels of IL-6 in the serum and cerebrospinal fluid of patients with NMOSD have been reported (19, 17, 20) (Uzawa et al., 2010, 2014; Sato et al., 2014). IL-6 was originally cloned as B-cell stimulatory factor-2 (21) (Hirano et al., 1986). IL-6 activates a receptor complex consisting of the IL-6 receptor (IL-6R) and the signal-transducing receptor subunit gp130. IL-6 can bind to both a transmembrane form and a soluble form of IL-6R, which can interact with gp130 to trigger downstream signal transduction and gene expression. IL-6 exerts pleiotropic effects on immune cells, bone marrow cells, and hepatocytes. In the event of infection or tissue injury, IL-6 is promptly synthesized, induces acute-phase proteins such as C-reactive protein, thereby contributing to host defense and inflammatory immune responses (22) (Tanaka et al., 2014). In contrast, IL-6 also plays an important role in immune regulation (23) (Kimura and Kishimoto, 2010). Th17 cells can be differentiated from naïve T cells by IL-6 and transforming growth factor (TGF)-β, whereas IL-6 inhibits the differentiation into TGF-β−induced regulatory T cells (iTregs). IL-6 dysregulation is involved in the development of autoimmune diseases. Based on these characteristics, IL-6 signal-blockade therapy is a promising option to decrease disease activity in autoimmune diseases, including NMOSD.

3. Standard and emerging therapy for NMOSD

In general, the treatment of acute attacks in NMOSD is similar to MS treatment. Administering high-dose corticosteroids, in particular intravenous methylprednisolone (IVMP), is a first-line therapy (24, 25) (Araki and Yamamura, 2017; Kleiter and Gold, 2016). When IVMP is ineffective, plasma exchange (PLEX) or plasmapheresis (immunoadsorption plasmapheresis: IAPP, double-filtration plasmapheresis: DFPP) is chosen as an escalation therapy. More severe and faster deterioration is commonly observed in the acute phase of NMOSD, compared to that in MS. The inflammatory responses involve autoantibody, complement, and granulocyte activation, followed by demyelination as well as astrocytic and neuronal damage. It should be noted that the prompt decision to shift to PLEX/IAPP/DFPP therapy is important when patients are refractory to IVMP.

To prevent acute attacks in NMOSD, administering disease-modifying drugs (DMDs) for MS is not recommended, including interferon-β (IFN-β), fingolimod (S1P receptor antagonist), natalizumab (anti-VLA monoclonal antibody), or dimethyl fumarate. Heavy relapses occurred after the initiation of those DMDs in patients who had been diagnosed with MS (26, 27) (Shimizu et al., 2010; Jacob et al., 2013), and most patients were later found to be positive for anti-AQP4 antibodies. Instead, oral immunosuppressant drugs and corticosteroids are widely adopted as a first-line therapy to prevent acute NMOSD exacerbations (24, 28) (Araki and Yamamura, 2017; Trebst et al., 2014). Monotherapy or combination of prednisolone, azathioprine, mycophenolate mofetil, methotrexate, are generally recommended. Rituximab (RTX) is indicated as a second-line or first-line therapy for patients with high disease activity. Although these drugs reduce the number of relapses in many patients with NMOSD, they represent a very poor alternative treatment option when disease activity is very high or when first-line medications must be discontinued due to ineffectiveness or side effects. In such cases, intravenous cyclophosphamide, periodic PLEX or plasmapheresis, and mitoxantrone are selected as second-line therapy, although long-term treatment with these therapies it is often problematic due to severe side effects.

Alternative therapeutic approaches for patients who are resistant to standard immunotherapies are still needed. The development of emerging therapies, including molecularly targeted drugs, i.e., biological drugs (monoclonal antibodies), has been supported by the insights into NMOSD pathogenesis (24) (Araki and Yamamura, 2017). The phase III clinical trials of four monoclonal antibodies are currently underway in Japan. IL-6 receptor-blockade therapy (humanized anti-IL-6 receptor monoclonal IgG1 antibody satralizumab, formerly known as SA237), B cell-depletion therapy (chimeric murine–human anti-CD20 monoclonal IgG1 antibody RTX, and humanized anti-CD19 monoclonal IgG1 antibody inebilizumab, formerly known as MEDI-551), complement depletion therapy (anti-C5 monoclonal IgG2/4 antibody eculizumab [ECU]). The results from several clinical studies have already been reported, indicating that anti-CD20 monoclonal antibody RTX showed efficacy in preventing attack in patients with NMOSD (29, 30) (Cree et al., 2005; Kim et al., 2013). However, refractory cases to RTX have been often reported (31, 32) (Lindsey et al., 2012; Kim et al., 2015). The reasons for refractoriness are as follows; CD20 is not expressed on PBs which produce anti-AQP 4 antibodies, increased production of BAFF (33) (Nakashima et al., 2011), and genetic polymorphisms in the Fc receptor gene *FCGR3A* (32) (Kim et al., 2015). With respect to the anti-CD19 monoclonal antibody inebilizumab, the target antigen CD19 is widely expressed on B-cell lineages, including AQP4-Ab-producing PBs. Inebilizumab mediates the antibody-dependent and cell-mediated toxicity of B cells, which results in B cell depletion and the suppression of disease activity. As an anti-complement therapy, complement activation and accumulation in NMO lesions have been shown to be involved in NMOSD pathogenesis (34, 35) (Roemer et al., 2007; Jones et al., 2014). ECU is a humanized anti-C5 monoclonal IgG2/4 antibody that inhibits the terminal complement cascade.

Hemolysis and thrombogenesis are attributed to activation of the classical complement pathway, suggesting that inhibition of the pathway can regulate hemolytic diseases. Furthermore, the complement pathway induces cleavage of the C5 protein into C5a and C5b, which initiates the assembly of the cytolytic terminal C5b-9 membrane attack complex. Both C5a and C5b-9 can act in immune cells and inflammatory states; thus, C5 cleavage inhibition may be a promising therapeutic target. ECU was already approved for treating paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and myasthenia gravis (36) (Howard et al., 2013). In a pivotal pilot study for NMOSD, 14 patients with refractory NMOSD received ECU for 12 months. After 12 months of ECU treatment, 12 of 14 patients were relapse-free, and the expanded disability status scale (EDSS) values improved from 4.3 to 3.5 during the treatment period (37) (Pittock et al., 2013). A phase III randomized controlled trial for NMOSD is currently in progress (NCT01892345).

4. IL-6 signal blockade therapy in NMOSD

A humanized IL-6R monoclonal IgG1 antibody, tocilizumab (TCZ), was approved for treating rheumatoid arthritis, juvenile arthritis, and Castleman's disease. A multicenter pilot study of TCZ for treating refractory NMOSD was performed (UMIN000005889, UMIN000007866). Refractory patients with NMOSD were defined as the patients with repeated acute exacerbations although the standard immunotherapies such as corticosteroid and/or immunosuppressants had been sufficiently administered. The single case report (38) (Araki et al., 2013) and seven case series (39) (Araki et al., 2014) have been published. Seven patients with refractory NMOSD received monthly intravenous administration of TCZ (8 mg/kg) for 12 months and showed a significant reduction of the annualized relapse rate (ARR; decreasing from 2.9 ± 1.1 to 0.4 ± 0.8, $p < 0.005$) and improvement of EDSS values (from 5.1 ± 1.7 to 4.1 ± 1.6, $p < 0.01$). Interestingly, chronic neuropathic pain and general fatigue were gradually mitigated after the initiation of TCZ administration. Immunological analysis showed that AQP4-Ab was reduced after TCZ therapy, which was accompanied by clinical improvement. A German group also demonstrated that TCZ was highly effective against refractory NMOSD (40, 41) (Ayzenberg et al., 2013; Ringelstein et al., 2015). Eight patients who were refractory to RTX had markedly reduced ARRs, from 4.0 before treatment to 0.4 after treatment, and improved EDSS values, decreasing from 7.3 to 5.5. The authors also reported a reduction in chronic pain following TCZ therapy.

Thereafter, data from our clinical study continued to confirm the long-term efficacy and safety of TCZ, and 19 patients received monthly infusion of TCZ (maximum 6 years and 8 months). The median age at onset of NMOSD was 27 years old (10–60 years old), and the median age at the first dose of TCZ was 40 years old (21–66 years old). The median total relapse numbers before TCZ treatment and for 1 year before TCZ treatment were 8 (3–25) and 2 times (1–5), respectively. Regarding the history of previous immunotherapy, IFN-β was used in 4 cases before the anti-AQP4 antibody positivity was identified, but IFN-β was ineffective, resulting in its discontinuation. Corticosteroids and/or immunosuppressants were continued as concomitant drugs after TCZ treatment was initiated. Fig. 1 shows the clinical courses of 19 patients before and after TCZ treatment. In all cases, the number of relapses decreased under TCZ treatment, and 10 patients did not relapse. Five patients relapsed under TCS treatment, but they were mild compared to the severe relapses they had experienced in the past. The acute exacerbations improved promptly with one or two courses of IVMP. Among 15 patients who received TCZ for more than a year, the ARR in the first year after treatment decreased markedly from 2.2 ± 1.1 to 0.3 ± 0.7 ($p < 0.001$, Fig. 2), and the ARR after treatment decreased by 86% compared to before treatment. The EDSS significantly improved from 4.5 ± 1.8 to 3.8 ± 1.4 ($p < 0.05$, Fig. 2). Chronic neuropathic pain and general fatigue also improved significantly from 3.2 ± 2.2 to 1.7 ± 2.6 ($p < 0.001$, Fig. 2) and 4.4 ± 2.9 to 2.3 ± 1.8 ($p < 0.0005$, Fig. 2), respectively, as determined using a numerical rating scale. For concomitant medications, oral corticosteroids and immunosuppressants could be reduced in all cases, and three patients sustained remission under TCZ monotherapy. Of the 5 patients who experienced relapses after initiating TCZ treatment, two patients (Patients 1 and 5) had a history of systemic lupus erythematosus (SLE) or a comorbid SLE. Both patients discontinued tacrolimus and cyclosporine after starting TCZ; however, it was necessary to resume tacrolimus and cyclosporine because of their repeated acute exacerbations. For patient 1, combination therapy with TCZ, prednisolone (5 mg/day), and tacrolimus (2 mg/day) maintained remission for almost 2 years. Regarding patient 12 with comorbid SLE, no relapse of NMOSD was observed under TCZ treatment, and severe neuropathic pain also disappeared. However, exacerbation of SLE dermatitis was observed after 1 and half years of TCZ treatment, and topical tacrolimus was initiated. An open label clinical trial of TCZ for patients with SLE revealed that disease activity including arthritis had been significantly decreased (42) (Illei et al., 2010). With regards to patients with NMOSD comorbid with SLE, they tended to have high disease activity, and combination therapy with steroids and immunosuppressive drugs was more recommended over TCZ monotherapy as well as rheumatoid arthritis and SLE (43) (Maeshima et al., 2012).

More severe and intractable neuropathic pain is a characteristic clinical symptom of NMOSD, when compared to MS (44, 45) (Zhao et al., 2014; Bradl et al., 2014). Neuropathic pain is associated with the inflammatory cytokines IL-6, IL-1β, and tumor necrosis factor-α probably produced by activated microglial cells (46) (Vallejo et al., 2010), suggesting that microglia and inflammatory cytokines are targets for treating neuropathic pain (47) (Wen et al., 2011). In a rodent model, blockade of the inflammatory cytokine IL-6 mitigated neuropathic pain, including allodynia (48) (Arruda et al., 2000). Pain relief after TCZ treatment implies that IL-6 could be associated with the pathogenicity of chronic neuropathic pain in NMOSD. The therapeutic effect of TCZ in this study indicates that TCZ may be a good indication for refractory neuropathic pain, based on NMOSD and other disease etiologies. Regarding the ability of TCZ to improve general fatigue, a similar report was published for patients with rheumatoid arthritis (49) (Strand et al., 2012), suggesting an association between general fatigue in immunological diseases and IL-6 (50) (Srirangan and Choy, 2010).

Infections, leukocytopenia, anemia, and hypercholesterolemia are the most common adverse events of TCZ in patients with NMOSD (38). Severe infections have not been reported in pilot studies on NMOSD, whereas serious pneumonia and bowel perforation under TCZ treatment have been reported in patients with rheumatoid arthritis. There is concern that IL-6 signal-blockade therapy may underestimate severe infection by mitigating the appearance of symptoms, including low-grade fever or afebrile pneumonia and painless acute enterocolitis. Furthermore, TCZ can cause a downregulation of infection biomarkers, such as elevation of the white blood cell count, C-reactive protein, and the erythrocyte-sedimentation rate. Patients with long-lasting infectious symptoms should be carefully monitored by X-ray and computed tomography to prevent severe infections. Of interest, the progression of iron-deficiency anemia occurred in 4 patients with NMOSD in our pilot study, although anemia associated with rheumatoid arthritis is generally improved by TCZ. The development of inflammatory anemia in patients with rheumatoid arthritis is thought to be caused by IL-6-dependent hepcidin production (51) (Ganz, 2003). Hepcidin regulates iron metabolism by preventing iron transport and the release of iron from macrophages (51) (Ganz, 2003). The anemia associated with chronic inflammation is improved by IL-6 signal-blockade therapy. In patients with NMOSD, possible hemorrhagic gastric ulcers or gastritis due to concomitant corticosteroids was considered, but the patients had neither gastrointestinal symptoms nor blood in their stools. Moreover, the bleeding source could not be identified in anemic patients who underwent upper gastrointestinal endoscopy. AQP4 is expressed in the

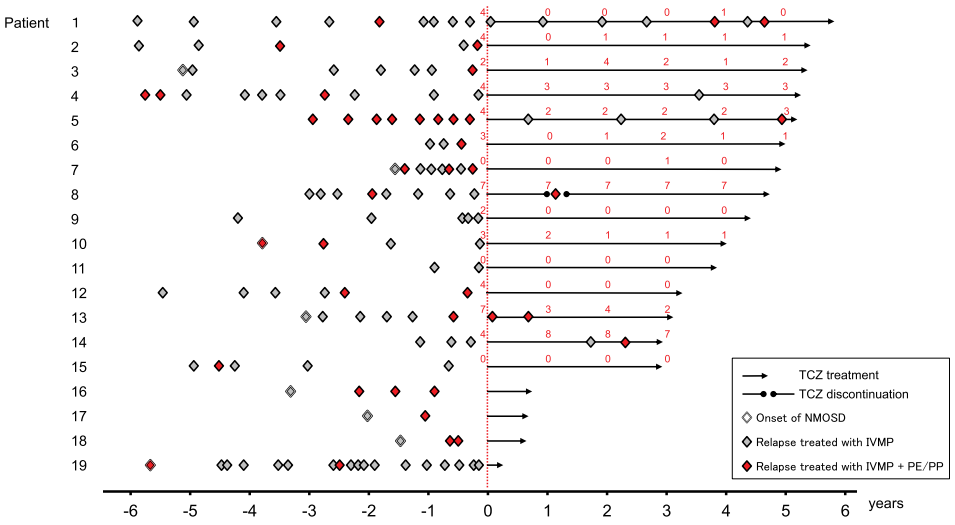

Fig. 1. Clinical course before and after TCZ treatment in 19 patients with NMOSD. On the X axis, 0 represents the first dose of TCZ. ▶ refers to the last visit. Numerical rating scales each patient are depicted at pretreatment and annual evaluations. TCZ treatment is ongoing for all patients. Abbreviations. IVMP, intravenous methylprednisolone; PE, plasma exchange; PP, plasmapheresis; TCZ, tocilizumab.

stomach and kidney in addition to the brain and spinal cord, so there is a possibility that unknown mechanisms of anemia may exist.

During the analysis of immunological parameters, PBs frequency decreased with TCZ treatment and the anti-AQP4 antibody titer also decreased in all patients compared to pre-treatment levels. In addition, TCZ treatment increased the production of regulatory immune cells such as $CD56^{high}$ natural killer cells and activated Tregs in the blood, and regulated granulocytes involved in CNS inflammation (Matsuoka et al., manuscript in preparation). Moreover, TCZ, which is detected in trace amounts in the CNS, can potentially act in the CNS, based on the

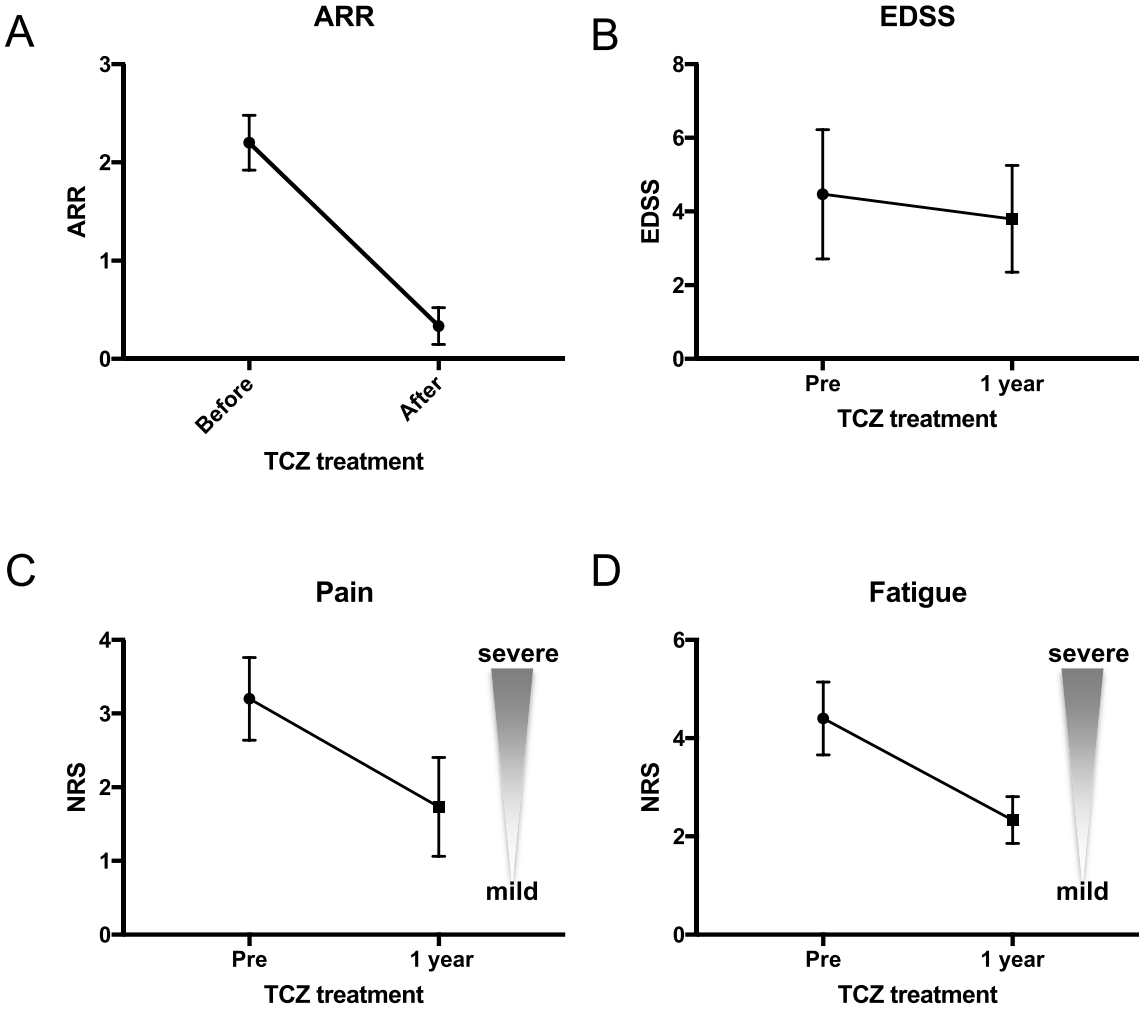

Fig. 2. Effects of TCZ on clinical and immunological parameters.
The annualized relapse rate (ARR) before and after TCZ (**A**). The expanded disability status scale (EDSS) during the 1-year study period (**B**). Pain severity scale (**C**) and fatigue severity scale (**D**) before and 1-year after the start of TCZ treatment. The dots and I bars indicate means ± standard error of the mean (SEM).

following considerations: activated PBs in the periphery enter into the CNS and may produce anti-AQP4 antibodies (52) (Chihara et al., 2013); anti-AQP4 antibodies are detected in both patient sera and cerebrospinal fluid; IL-6 levels were also increased in the cerebrospinal fluid of patients with acute exacerbation (52) (Chihara et al., 2013).

5. Conclusions

Many basic and clinical studies have revealed that NMOSD is an autoimmune disease associated with pathogenic autoantibodies directed against AQP4, which are distributed in the foot process of astrocytes. The pathology of NMOSD greatly differs from that of MS, which is a representative demyelinating disease of the CNS. Immunosuppressive agents and corticosteroids with off-target immunosuppression and toxicity are still the mainstay of treatment for both acute attacks and prevention in NMOSD. In addition, therapeutic agents targeting specific molecules associated with NMOSD pathogenesis are currently being developed. Several randomized clinical trials using monoclonal antibodies targeting B cells, inflammatory cytokines (including IL-6), and the complement pathway are currently underway for the prevention of acute attacks in NMOSD. Among them, IL-6 signal-blockade therapy was shown to be highly effective for refractory patients with NMOSD. Of note, TCZ has an obvious effect on chronic neuropathic pain and general fatigue that are refractory to medications. Some problems remain to be solved, but TCZ is a promising drug for preventing attack in NMOSD.

Standard protocol approvals and patient consents

With regards to the multicenter pilot study using TCZ for refractory NMOSD (UMIN000005889, UMIN000007866), the Ethics Committee of the NCNP on human experimentation approved the study (approved number: A2014-082), and written informed consent for the publication of patient information was obtained from all participants.

Funding

Supported by the Health and Labour Sciences Research Grants on Intractable Diseases (Neuroimmunological Diseases) and on Promotion of Drug Development from the Ministry of Health, Labour and Welfare of Japan, and Chugai Pharmaceutical Co. Ltd.

Role of the funding

Tocilizumab was given from Chugai Pharmaceutical Co. Ltd.

Acknowledgments

I thank Dr. Takashi Yamamura for conducting the multicenter pilot study using TCZ for refractory NMOSD (UMIN000005889, UMIN000007866) as the principal investigator. I also thank Dr. Katsuichi Miyamoto for providing medical information on the pilot study, and Dr. Yuji Takahashi for providing administrative support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2018.10.012.

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