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Immunoadsorption as maintenance therapy for refractory neuromyelitis optica spectrum disorder

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a rare relapsing autoimmune disease of the central nervous system, affecting mainly optic nerves and spinal cord. NMOSD pathophysiology is associated with anti-aquaporin-4 (AQP4) immunoglobulin G (IgG) autoantibodies. Rapid extracorporeal elimination of autoantibodies with apheresis techniques, such as immunoadsorption (IA), was proven to be an effective treatment of NMOSD attacks. Data on the long-term use of IA to prevent attacks or progression of NMOSD are lacking.

Objectives: The aim of this study was to evaluate efficacy and safety of maintenance IA for preventing recurrence of NMOSD attacks in patients refractory to other immunotherapies.

Design: Case study.

Methods: Retrospective analysis of two female patients with severe NMOSD refractory to conventional immunotherapies was performed. Both patients had responded to tryptophan IA (Tr-IA) as attack therapy and subsequently were treated with biweekly maintenance Tr-IA.

Results: *Patient 1* (AQP4-IgG seropositive, age 42 years) had 1.38 attacks of optic neuritis per year within 10.1 years before commencing regular Tr-IA. With maintenance Tr-IA for 3.1 years, one mild attack occurred, which was responsive to steroid pulse therapy. Expanded Disability Status Scale (EDSS) was stable at 5.0. Visual function score of the last eye improved from 3 to 1. *Patient 2* (AQP4-IgG seronegative, age 43 years) experienced 1.7 attacks per year, mainly acute myelitis and optic neuritis, during the period of 10.0 years before the start of Tr-IA. During regular Tr-IA treatment, no further NMOSD attack occurred. The patient was clinically stable without any additional immunosuppressive treatment for 5.3 years. EDSS improved from 6.0 to 5.0, and the ambulation score from 7 to 1. Tolerability of Tr-IA was good in both patients. No serious adverse events occurred during long-term clinical trajectories.

Conclusion: Tr-IA was well tolerated as maintenance treatment and resulted in clinical stabilization of two patients with highly active NMOSD, who were refractory to standard drug therapy.

Keywords: apheresis, aquaporin-4, case report, immunotherapy, neuromyelitis optica spectrum disorder

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune-mediated disorder of the central nervous system with female predominance. Originally considered as a subtype of multiple sclerosis (MS), NMOSD has been recognized

as a distinct disease entity. NMOSD occurs much less frequently compared to MS with a prevalence of 1–4 per 100,000 cases.[1]

NMOSD is characterized by inflammatory lesions in the optic nerves, spinal cord, and central parts of the brain, and an autoimmune-mediated process directed against aquaporin-4 (AQP4), an astrocytic water channel protein. Most patients have AQP4-immunoglobulin G (IgG) autoantibodies, which are highly specific and pathogenic for NMOSD. However, up to 20% of patients meeting the diagnostic criteria for NMOSD are AQP4-IgG seronegative.[2] A proportion of these patients have IgG antibodies against myelin oligodendrocyte glycoprotein (MOG). MOG-IgG-associated disorder (MOGAD) was recognized as a separate entity in recent years.[3] Due to clinical overlap, MOGAD should always be considered in AQP4-IgG-seronegative NMOSD.[4] The group of patients who have neither AQP4- nor MOG-IgG represents a diagnostic challenge.

NMOSD typically has a relapsing course. The standard care for treatment of acute attacks is high-dose intravenous corticosteroids and as add-on escalation therapy plasma exchange (PE) or immunoadsorption (IA).[5–7] Prompt initiation of apheresis is a strong predictor of beneficial outcome in severe attacks.[8] Apheresis as initial treatment for NMOSD attacks is recommended and especially effective when previous attacks have responded well to apheresis therapies but not to high-dose corticosteroids, particularly in patients with myelitis.[7,9] The use of apheresis therapy in parallel with high-dose corticosteroids was reported to be more effective in achieving remission from NMOSD attacks than high-dose corticosteroids alone[10–12] and is recommended for severe cases in current guidelines.[7] In general, a series of five to six procedures of PE or IA is performed for acute attacks or relapses. If neurological symptoms do not improve sufficiently, a second treatment series with apheresis should follow immediately.[7]

As the disease worsens by incomplete recovery with each attack, attack prevention is crucial in NMOSD. Standard immunosuppressive medications, such as oral steroids, azathioprine, mycophenolate mofetil, rituximab and tocilizumab (*all off-label use*), were widely used, before the recent approval of eculizumab, satralizumab, and inebilizumab for AQP4-IgG-seropositive NMOSD.[13–16] Evidence on the efficacy of therapeutic apheresis as maintenance treatment for severe therapy-refractory NMOSD is limited. Retrospective studies have shown that PE may be beneficial as a chronic treatment for the prevention of NMOSD attacks in select patients.[17–21]

Data on the long-term use of IA to prevent attack or progression of NMOSD are lacking. We present the clinical course of two patients with therapy-refractory NMOSD who were successfully treated with tryptophan IA (Tr-IA) maintenance therapy.

Methods

A retrospective analysis of two NMOSD patients treated with long-term Tr-IA was performed. Written informed consent was obtained from both patients for publication.

Patients were diagnosed according to current NMOSD diagnostic criteria.[2] AQP4-IgG- and MOG-IgG-serostatus were tested by cell-based assays at certified laboratories. The clinical course before and with regular Tr-IA was analyzed including original patient records and review of original radiological imaging. Patient information was pseudonymized before data entry. The clinical course during Tr-IA treatment was analyzed from the time of commencing treatment until the end of data collection in April 2022.

The frequency of NMOSD attacks before and after commencement of regular Tr-IA treatment was analyzed. NMOSD attacks were defined as follows: any clinical event with objective neurological deterioration as revealed by clinical examination, lasting for at least 24 h and in the absence of fever or alternative explanations. Further objectives were visual acuity (VA) and clinical progression determined by clinical examination, grade of disability assessed by the functional system scores (FSS) visual function and ambulation, the expanded disability status scale (EDSS), and subclinical disease activity assessed by magnetic resonance imaging (MRI).

Tr-IA treatments were performed using the membrane plasma separator Plasmaflo OP-05W or OP-08W in combination with the single-use tryptophan immunoadsorber column TR-350 (all Asahi Kasei Medical, Tokyo, Japan) and the tubing system PA-420 (Effe Emme, Cigliano, Italy)

together with the Octo Nova Technology (DIAMED, Cologne, Germany). The treated plasma volume per IA was between 2000 and 3000 ml. Unfractionated heparin was used for anticoagulation. It was ascertained that the patients had not taken an angiotensin-converting inhibitor in the last 5 days before Tr-IA treatment. Peripheral veins were used for vascular access. In general, a series of six single Tr-IA treatments within 14 days was performed for steroid-refractory attacks. The protocol for outpatient maintenance Tr-IA consisted of one treatment every 14 days. The time point when regular Tr-IA treatment was started was an individual decision of the treating physician considering the entire clinical course of the patient.

Results

Patients' characteristics and main symptoms are summarized in Table 1. A timeline with patients' individual clinical trajectories regarding relevant clinical events, MRI findings, and interventions before and with regular Tr-IA is depicted in Figure 1.

Case 1

Shortly after the birth of her first child, a 22-year-old woman had suffered a complete and since then persistent loss of vision in the left eye (nulla lux, amaurosis) due to optic neuritis (ON). She was diagnosed with MS at another hospital 11 years later (EDSS of 5.0). No MS-specific drug therapy was initiated. The patient was clinically stable, without disease progression or relapses for the following 10 years.

At the age of 42 years (Figure 1(a), start of observation period), the patient had an ON attack in the right eye. After two high-dose steroid treatments (5x 1000 mg, followed by 5x 2000 mg), VA improved. However, 2 months later, the patient experienced another severe ON attack in the right eye with rapid deterioration of VA to 0.05 and visual field defects. The patient was treated with Tr-IA (six treatments within 14 days). VA improved to 0.50 immediately after the last treatment.

A single infusion of mitoxantrone (12 mg/m^2 i.v.) was followed by severe infections of the larynx, paranasal sinuses, and appendix and substantial deterioration of the general health condition. In the following year, another ON occurred. MRI of the brain and spinal cord demonstrated lesions in the cervical spinal cord at C1/C2 and in the optic nerve. AQP4-IgG (titer 1:1000, immunofluorescence test) was detected in the serum. Diagnosis of MS was revised and replaced by the diagnosis of NMOSD.

Intravenous immunoglobulin (IVIg) infusions (20 g, 1x/month) were started, and the patient was stable for 2.5 years, until there was another ON attack in the right eye and sensory deficits of both legs. MRI of the brain demonstrated longitudinally extensive gadolinium enhancement in the right optic nerve. In the following years, disease activity could not be reduced despite two courses of rituximab (500 mg i.v.), leading to a long-lasting and complete CD19$^+$ B cell depletion, and an occasional IVIg infusion. Nevertheless, the patient experienced eight further attacks of ON and sensory deficits in both legs, accompanied by thoracic and lower limb dysesthesia and bladder dysfunction. MRI demonstrated two new inflammatory lesions in the cervical spinal cord at C2 and C3/4. Steroid-refractory attacks were successfully treated with Tr-IA (six treatments within 14 days) as escalation therapy. Due to the increasing frequency of attacks and the detection of another inflammatory lesion in the thoracic spinal cord at T6 (Figure 2(a)), continued Tr-IA was considered to stabilize the disease course and to prevent further attacks. Before start of Tr-IA, a total of 14 attacks occurred in 10 years. For 2 years with regular outpatient Tr-IA once every 14 days, the patient was clinically stable without disease progression or attacks. VA of the right eye improved from 0.2 to 0.85. The FSS visual function improved from 3 to 1 accordingly. EDSS was 5.0 consistently due to blindness of the left eye since the age of 22 years (Figure 1(a)).

She was vaccinated three times against Covid-19 with the Pfizer-Biontech vaccine. After the first vaccination, she had mild flu symptoms, which rapidly regressed. Approximately 2 weeks after her second vaccination, the patient experienced a mild ON in the right eye with deterioration of VA (cerebral and spinal MRI with stable findings, Figure 2(b)) and mild sensory deficits in the right leg. Symptoms were fully responsive to steroid pulse therapy (3x 2 g i.v.). The patient reported a mild recurrence of disease symptoms 2 weeks after her third vaccination that did not require steroid pulse therapy and regressed within 3 weeks.

Table 1. Demographic and clinical characteristics.

	Case 1	Case 2
Gender	Female	Female
Age and manifestation at disease onset	22 years; optic neuritis left eye with residual amaurosis	43 years; optic neuritis left eye
Age at the start of observation period; initial diagnosis	42 years; MS	43 years; MS
Age at NMOSD diagnosis	44 years	49 years
AQP4-IgG serostatus	Positive (titer 1:1000)	Negative
MOG-IgG serostatus	Negative	Negative
Clinical manifestation		
Optic nerve	Unilateral ON left and right eye	Unilateral ON left and right eye
Brain	–	Supra- and infratentorial lesions with residual homonymous hemianopsia to right side
Spinal cord	TM with sensory and mild motor deficits, bladder dysfunction	LETM and TM with sensory and moderate motor deficits, persistent bowel and bladder dysfunction
MRI presentation	TM (C1/C2, C3/4, T6), longitudinally extensive gadolinium enhancement in the optic nerve	Lesions in occipital lobes, mesencephalon, pons, cerebellar peduncle; TM (T4, T5/6); LETM (C1-5, C7-T4, T2-4, T1-5)
Drug therapy before start of regular Tr-IA	High-dose steroid pulses for acute attacks (Σ11 pulses with 5x 1000 mg; Σ3 pulses with 5x 2000 mg); Mitoxantrone (12 mg/m^2 once); IVIg (20 mg i.v. monthly for 3.7 years); Rituximab (2x 500 mg i.v.)	High-dose steroid pulses for acute attacks (Σ10 pulses with 5x 1000 mg); Glatiramer acetate (20 mg s.c. daily for 2.7 years); Rituximab (2x 500 mg i.v.) IVIg (20 mg i.v. monthly; for 10 months); Tocilizumab (480 mg i.v. monthly for 4 months); Mitoxantrone (total dose 75 mg within 9 months)
Number of attacks before start of regular Tr-IA	14	17
Observation period *before* start of maintenance Tr-IA	10.1 years	10.0 years
Annual attack rate *before* maintenance Tr-IA	1.38	1.70
Observation period *with* maintenance Tr-IA	3.1 years	5.3 years
Annual attack rate *with* maintenance Tr-IA (total number of attacks)	0.32 (1)	0 (0)
Concomitant therapy since beginning with maintenance Tr-IA	High-dose steroid pulse therapy for acute attack (1 pulse with 3x 2000 mg)	Levetiracetam Vitamin D

AQP4-IgG, IgG antibodies to aquaporin-4; C, cervical; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; maintenance Tr-IA, one treatment every 14 days; MS, multiple sclerosis; MOG-IgG, IgG antibodies to myelin oligodendrocyte glycoprotein; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; T, thoracal; TM, transverse myelitis; Tr-IA, tryptophan immunoadsorption.

At the end of the observation period with Tr-IA as maintenance therapy, the patient was in remission with a VA of 0.85–0.90 in the right eye and a stable EDSS at 5.0. She was still seropositive for AQP4-IgG (titer 1:1000, immunofluorescence test), MOG-IgG in the serum was negative. The patient was informed about the emerging therapy options with eculizumab and satralizumab for

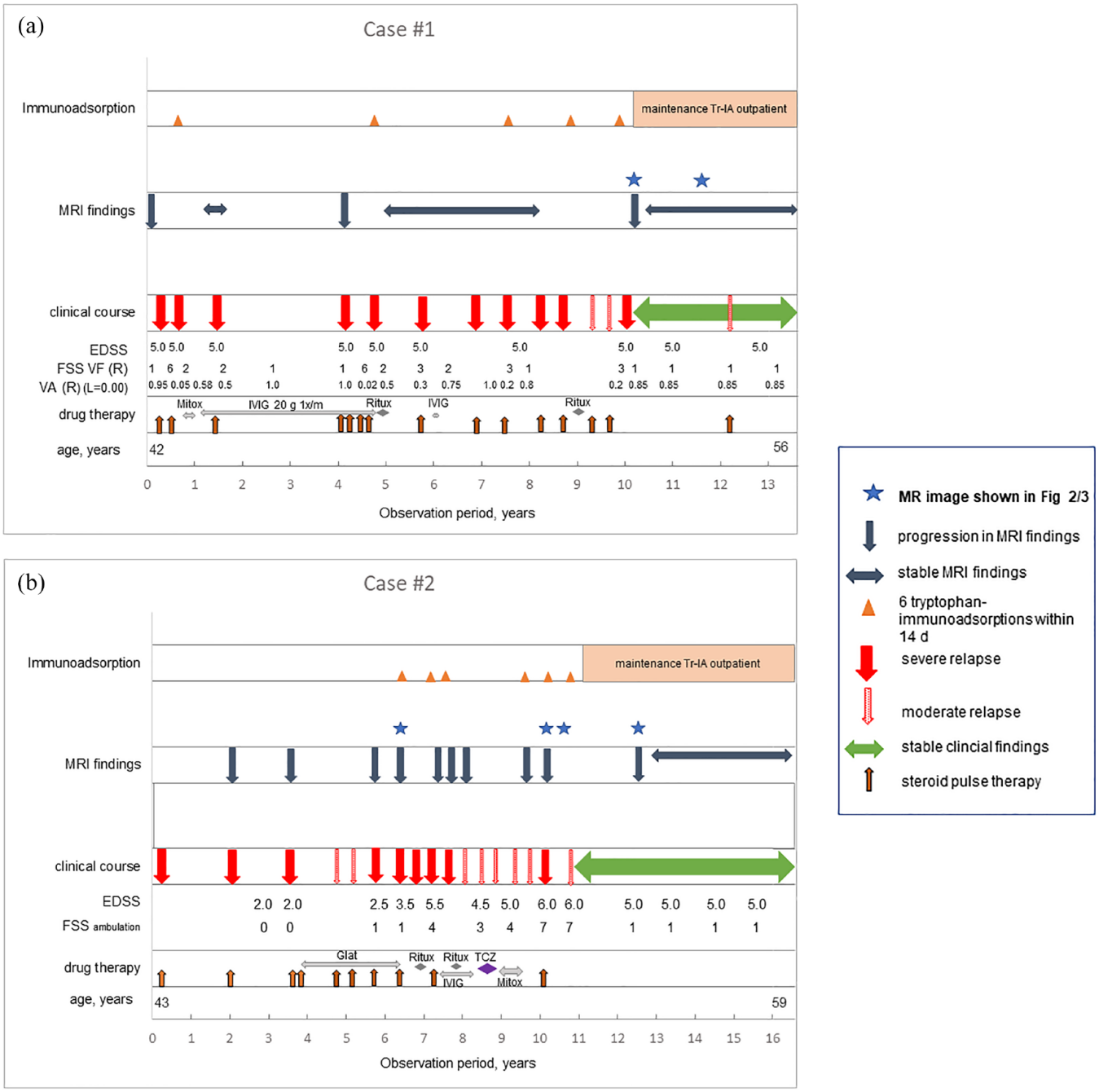

Figure 1. Timeline with relevant data of events and interventions before and with maintenance tryptophan immunoadsorption (Tr-IA) in two cases with severe NMOSD.
EDSS, expanded disability status scale; FSS, functional system score; Glat, glatirameracetate; IVIG, intravenous immunoglobulin; Mitox, mitoxantron; R, right eye; Ritux, rituximab; TCZ, Tocilizumab; Tr-IA, tryptophan immunoadsorption; VA, visual acuity; VF, visual function.

AQP4-IgG-seropositive NMOSD. However, due to her satisfaction with Tr-IA therapy, she explicitly wanted to retain the current treatment regimen without change.

Case 2

At the age of 43 years, a female, otherwise healthy, patient experienced her first attack of ON (Figure 1(b), start of observation period), which was fully

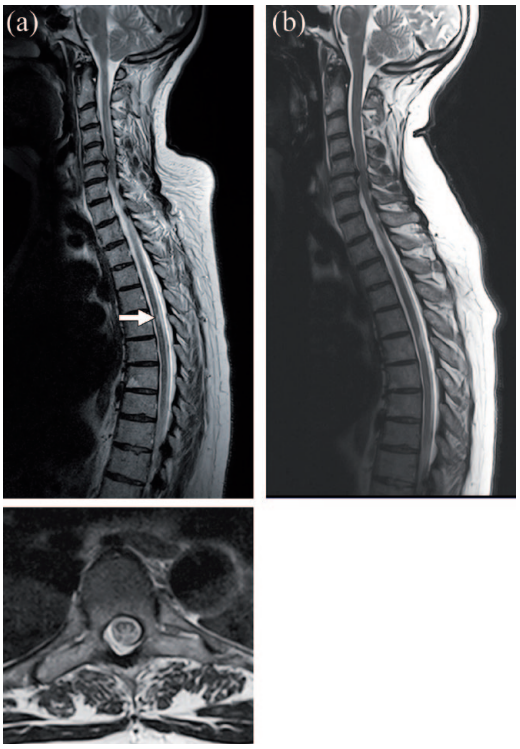

Figure 2. MRI imaging of a 52-year-old female patient with AQP4-IgG-seropositive NMOSD (case 1): (a) T2-weighted sagittal and axial spinal cord imaging revealing a new lesion at Th6 (arrow) before start of Tr-IA maintenance therapy and (b) after 2.5 years of Tr-IA therapy stable disease without new spinal lesion.

responsive to high-dose steroids. However, 2 years later, an acute urinary retention and paresthesia of both legs occurred, with partial remission on high-dose steroids. MRI of the brain and spinal cord demonstrated several short lesions in pons and thoracic spinal cord with gadolinium enhancement at T4 and T5/6. No oligoclonal bands or other abnormalities were detected in cerebrospinal fluid (CSF). In the following year, there was another attack with sensory deficits at the right hand and arm and a new pontine MRI lesion. AQP4-IgG was negative, and the diagnosis of relapsing–remitting multiple sclerosis (RRMS) was made. Therapy with glatiramer acetate (20 mg s.c. daily) was started and given for 2.7 years. During glatiramer acetate therapy, a total of four relapses occurred. Six years after onset of disease at the age of 49 years, MRI showed for the first time longitudinally extensive transverse myelitis (LETM) from T2 to T4 (Figure 3(a)). Sensory deficits from this attack were only partially responsive to high-dose steroids and symptoms deteriorated again. Bilateral sensory deficits below T5, gait ataxia, and a mild paresis of both legs evolved. Repeated MRI showed enlargement of the lesion, now extending from T1 to T5, with gadolinium enhancement at the rim. Since the clinical symptoms were refractory to repeated high-dose steroid treatment (5x 1000 mg), escalation therapy with a total of six Tr-IA treatments was performed, resulting in a partial improvement of neurological deficits. The patient was again seronegative for AQP4-IgG; CSF testing revealed normal cell counts, no intrathecal IgG production, and identical oligoclonal bands in serum and CSF. Laboratory investigations revealed a monoclonal gammopathy of undetermined significance (MGUS). Bone marrow biopsy was unsuspicious. Visual evoked potentials were delayed bilaterally. Diagnosis of MS was according to the diagnostic criteria revised to seronegative NMOSD at that time, strongly supported by the typical MRI lesion pattern and clinical course.[22] Glatiramer acetate therapy was discontinued due to the known lack of efficacy for NMOSD.[23] During further course of the disease, AQP4-IgG and MOG-IgG were investigated several times with cell-based assays, both during attacks and during remission, but test results remained negative.

After a further thoracic myelitis with paraparesis and streaky gadolinium enhancement (C7–T4) on MRI, rituximab treatment (500 mg i.v.) was initiated, but not continued after the second infusion due to insufficient efficacy with clinical deterioration and new cerebral gadolinium-enhancing lesions. Add-on treatment with IVIg (IVIg, 20 g, 1x/month) started 2 months after the last rituximab infusion for 10 months, but did not prevent the occurrence of further attacks and progression of the disease. The walking distance deteriorated to 300 m. Several courses of high-dose steroids and Tr-IA were given within 1 year. Subsequent therapy with tocilizumab (480 mg i.v. monthly for 4 months) was started, but was unsuccessful regarding clinical and radiological disease activity. Also, under treatment with mitoxantrone (12 mg/m^2, duration 9 months, total dosage 75 mg/m^2), another myelitis occurred. MRI showed lesions in almost the complete spinal cord, with patchy gadolinium enhancement at several positions (Figure 3(b)). From this time, the patient refused any further treatment with immunosuppressive medication. During the course of the disease (Figure 1(b), observation

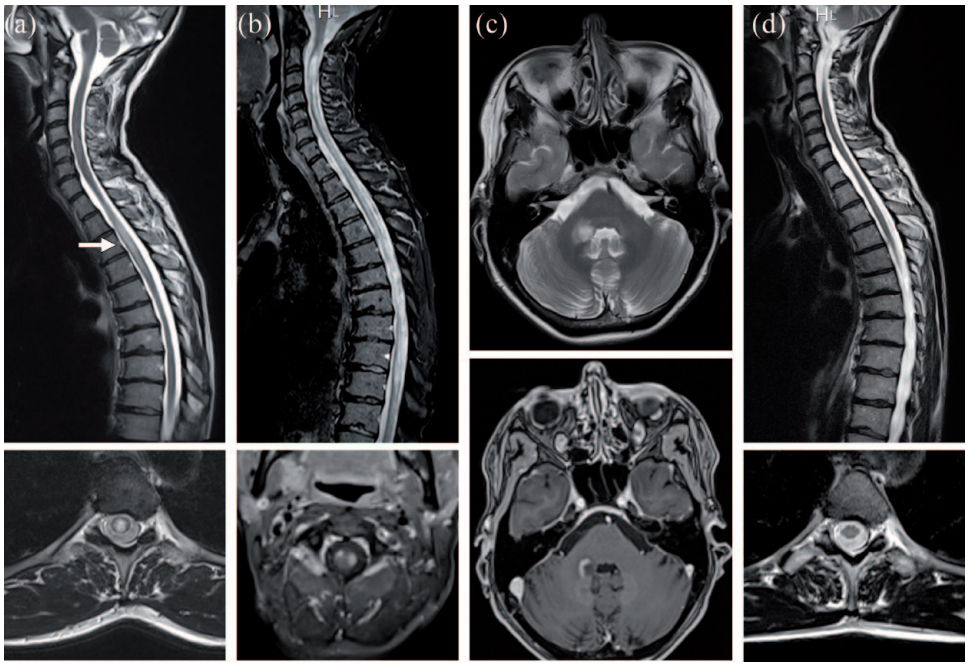

Figure 3. MRI imaging of a 49-year-old woman with AQP4-IgG-seronegative NMOSD (case 2). (a) T2-weighted sagittal and axial spinal cord imaging revealing an LETM extending from T2 to T4 (arrow), associated with acute myelitis, 6 years after onset of disease. (b) Sagittal STIR- and axial T1-gadolinium-enhanced images 10 years after disease onset showing acute cervical myelitis and widespread lesions in the entire spinal cord. (c) Axial T2-weighted and T1-gadolinium-enhanced images 11 years after disease onset and before start of Tr-IA maintenance therapy. (d) After 2 years of maintenance therapy with Tr-IA, almost complete regression of spinal lesion load on T-weighted sagittal and axial images is seen.

period year 0–10), multiple high-dose steroid pulse therapies were performed to treat acute exacerbations, partly with good response, especially for episodes of ON. In case of steroid refractory attacks, escalation therapy with Tr-IA was performed, which was always effective to induce at least partial remission. Over a period of 4.4 years, Tr-IA treatment (six Tr-IA within 14 days, in hospital) was occasionally performed, after the end of mitoxantrone approximately every 3 months. Each treatment series led to a clinical improvement or at least temporary stabilization of the symptoms. However, approximately 8 weeks after Tr-IA treatments, there was a worsening of clinical symptoms, partly associated with a progression of MRI findings, revealing new lesions and gadolinium-positive lesions (Figure 3(c)). With the objective to stabilize the disease in the long term, the frequency of Tr-IA treatments was increased to one treatment every 14 days in an outpatient setting. After 1 year of maintenance Tr-IA treatment, spinal cord MRI showed almost complete regression of T2-W hyperintense lesions. However, cerebral MRI 20 months after start of maintenance Tr-IA therapy showed one new gadolinium-enhancing lesion in the mesencephalon, without new clinical symptoms. The frequency of Tr-IA treatments was continued at every 14 days and the patient received concomitant physiotherapy. During the remaining observation period of 4 years, no new disease attacks or MRI lesions (Figure 3(d)), based on yearly investigations occurred. Walking ability improved from about 30 m with wheeled walker at the start of regular Tr-IA treatment to 4 km without assistance after 3 years of treatment. She was able to start hiking again. The EDSS improved from 6.0 to 5.0, the FSS ambulation improved from 7 to 1 (Figure 1(b)). As a residuum of previous disease attacks, the patient had persistent homonymous hemianopsia to right side and bowel and bladder dysfunction, requiring intermittent self-catheterization. Due to a new-onset symptomatic epilepsy, levetiracetam was added. Nevertheless, the patient was very satisfied with her current disease-related quality of

life. The patient was fully vaccinated against Covid-19 (Moderna vaccine) without clinical or MRI signs of disease activity.

IA tolerability

In total, 308 Tr-IA treatments were performed in both patients without any major complication. Assessment of tolerability by nurses and physicians was considered *very good* to *good* in 98% of treatments. Patient 1 developed headache and nausea (3x, 2.8% of her treatments) during Tr-IA treatment. In Patient 2, transient hypotension occurred (2x, 1.0% of her treatments), which could be managed by infusion of NaCl 0.9% solution. The rate of infections did not increase in particular not including any severe infections or Covid-19.

Discussion

Disability in NMOSD is an accumulating process due to persistent damage from attacks. Therefore, both treatment and prevention of attacks are essential for long-term outcome. For the first time, the role of long-term Tr-IA as final treatment escalation in NMOSD was analyzed in patients with a fulminant clinical course, refractory to standard disease-modifying therapies. So far, data on the long-term use of therapeutic apheresis to prevent attacks or clinical progression of NMOSD were limited to PE.[17–21] Therapeutic apheresis is often part of multimodal or escalating treatment strategies for autoimmune neurologic disorders. Immediate antibody elimination, pulsed induction of antibody redistribution, and immunomodulation are the three major mechanisms of action for PE and IA in this context.[24] During PE, patient's plasma is discarded, including valuable proteins, such as coagulation factors. During IA, patient's plasma is reinfused after the removal of antibodies and immune complexes. For selected indications, IA is increasingly replacing PE due to its superior safety profile, lower number of adverse events, and avoiding substitution with alloproteins.[25,26] Protein replacement fluids bear the risk of allergic reactions, and a small but clinically relevant risk of virus transmission.[27,28] IA has been used successfully in various autoimmune neurological disorders, particularly for the treatment of acute symptoms in MS[29–31] and NMOSD[12,32–37] and is recommended by national and international guidelines.[6,7,38]

Efficacy of long-term maintenance treatment with Tr-IA to prevent disease exacerbation and progression has been reported in patients with refractory generalized myasthenia gravis and chronic inflammatory demyelinating polyneuropathy.[39,40] The rationale for the regular use of Tr-IA in our patients was the good response of acute NMOSD attacks to Tr-IA treatment, whereas previous other disease-modifying interventions had either severe side effects or inadequate treatment response. With the objective to stabilize the disease in the long term, the frequency of Tr-IA treatments was increased to one treatment every 14 days in an outpatient setting. Frequency of therapeutic apheresis is an important issue for the acute and maintenance treatment. Not much systematic research has been conducted in this field, but substantial experience is providing guidance for routine care. Weekly to monthly intervals have been successfully applied with Tr-IA and seemed to establish an effective reduction of autoantibody concentration below pathophysiologically active thresholds. Due to IgG half-life of approximately 21 days, weekly treatments may result in a certain decrease in overall IgG concentration. Aspects of minimizing the treatment burden for patients, economical restraints, and organizational matters must also be taken in consideration. With regular Tr-IA therapy, the clinical course of the patients could be stabilized in the long term. Moreover, both patients showed sustained improvement in disability while on maintenance Tr-IA therapy, without other disease-modifying drug therapy. The incidence of acute NMOSD exacerbations was significantly reduced in both patients compared to the period before starting maintenance Tr-IA. Tolerability of Tr-IA was good and no significant side effects, particularly those associated with vascular access, occurred. In both patients, peripheral venous access could be used, providing a substantial safety advantage compared to the use of central venous lines or the surgical establishment of an arteriovenous shunt with their increased risk profile for associated infections, especially for long-term outpatient treatment.[41] The use of peripheral access for therapeutic apheresis requires sound experience and, unfortunately, is still a less common approach. In patients with difficult vascular conditions, the use of ultrasound guidance for the placement of peripheral access needles can reduce the need for central venous lines and the risk associated therein.[42]

There was a lag of 6 and 22 years, respectively, between first symptoms and diagnosis of NMOSD in our patients. Both patients had initially been diagnosed with MS. Revised diagnostic criteria that have become available in the meantime facilitate NMOSD diagnosis earlier and more accurately by identifying individuals who would have been diagnosed with idiopathic TM, idiopathic ON, or atypical MS.[2] This is important because treatment strategies for attack prevention in NMOSD and MS are different.[23,43] In NMOSD, autoantibodies against AQP4 are pathogenic. Immunoglobulins, mainly of IgG1 of IgG3 subclasses, binding to AQP4 lead to complement-dependent cytotoxicity, cytokine release, leukocyte infiltration, and blood–brain barrier disruption, resulting in oligodendrocyte death, myelin loss, and neuron death.[1] With therapeutic apheresis, pathogenic AQP4-IgG can be effectively eliminated from the patient's plasma, which is one rationale for the use of PE and IA in NMOSD.[12,35,44] However, IA and PE improved attack-related disability not only in AQP4-IgG-seropositive but also in -seronegative patients, suggesting additional mechanisms of action, for example, elimination of other types of autoantibodies, complement factors, or cytokines.[8,10,32,34,45–47] Our patients were heterogeneous with regard to autoantibodies against AQP4. Patient 2 was seronegative for AQP4-IgG and MOG-IgG, supporting an additional mechanism of action of Tr-IA besides elimination of autoantibodies including removal of immune complexes, complement, proinflammatory cytokines, and subsequent immunomodulation.[24,45–47] A prospective, randomized controlled study revealed in parallel to clinical improvement significant reduction of proinflammatory cytokines (Il-12, Il-17, Il-6, INF-gamma, TNF-alpha) with Tr-IA treatment in patients with autoimmune neurological disorders, including NMOSD.[48] Recently, significant reduction of B cell subsets following Tr-IA treatment in correlation with clinical improvement was demonstrated in MS patients with steroid-refractory relapses indicating that modulation of B cells potentially represents a major mechanism of action of Tr-IA treatment.[49]

A correlation of autoantibody decreases (AQP4-IgG, MOG-IgG) and clinical improvement up to 6 months after Tr-IA was described with a new fluorescent radiometric assay, a method to detect even slight variation in antibody titer.[50] Fluctuating AQP4-IgG levels have been reported in NMOSD patients; previously seropositive patients were seronegative during recurrent exacerbations but responded to therapy with IA in both situations.[33,36] For these reasons, apheresis therapies could also be considered in AQP4-IgG-seronegative NMOSD patients.[8,9] AQP4-IgG-seronegative NMOSD patients should receive individualized therapy, guided by severity and remission of attacks and the clinical course.[5,7,16] It cannot be completely excluded that a yet unidentified autoantibody plays a role in the disease process in these patients.

Limitations of this analysis are the observational and retrospective nature, different pre-Tr-IA therapies, and in particular, the small number of two cases. Given the putatively low incidence of such cases, a registry could be an appropriate approach.

In conclusion, our patients with severe therapy-refractory NMOSD were successfully treated with maintenance Tr-IA to prevent cumulative disability from progressive disease. With long-term Tr-IA, the frequency of NMOSD attacks and progression of impairment was significantly reduced in both high-risk patients with severe NMOSD that previous therapies had failed to terminate. Regular Tr-IA was found to be safe and well tolerated. Our results suggest that response to previous therapy is an important aspect of individualized NMOSD maintenance therapy. Select patients with NMOSD who had a high attack rate despite adequate immunotherapy and responded well to previous apheresis therapies are candidates for maintenance Tr-IA treatment. Further studies with a larger number of patients are needed.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patients gave written informed consent to publication of medical information.

Author contributions

Franz Heigl: Conceptualization; Data curation; Investigation; Supervision; Validation; Writing – original draft; Writing – review & editing.

Reinhard Hettich: Writing – review & editing.

Cordula Fassbender: Conceptualization; Data curation; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Reinhard Klingel: Writing – review & editing.

Erich Mauch: Investigation; Writing – review & editing.

Joachim Durner: Investigation; Writing – review & editing.

Rolf Kern: Investigation; Writing – review & editing.

Ingo Kleiter: Conceptualization; Data curation; Investigation; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests
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Availability of data and materials
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