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RESEARCH ARTICLE

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Immunoadsorption and plasma exchange—Efficient treatment options for neurological autoimmune diseases

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Abstract

Background: Therapeutic plasma exchange (TPE) and immunoadsorption (IA) are first or second line treatment options in patients with neurological autoimmune diseases, including multiple sclerosis, neuromyelitis optica spectrum disorders (NMSOD), chronic inflammatory demyelinating polyneuropathy, acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome), and autoimmune encephalitis.

Methods: In this prospective randomized controlled monocentric study, we assessed safety and efficacy of therapy with IA or TPE in patients with neurological autoimmune diseases. Treatment response was assessed using various neurological scores as well by measuring immunoglobulin and cytokine concentrations. Clinical outcome was evaluated by application of specific scores for the underlying diseases.

Results: A total of 32 patients were analyzed. Among these, 19 patients were treated with TPE and 13 patients with IA. IA and TPE therapy showed a comparable significant treatment response. In patients with MS and NMOSD, mean EDSS before and after treatment showed a significant reduction after treatment with IA. We observed a significant reduction of the pro-inflammatory cytokines IL-12, lL-17, IL-6, INF-γ, and tumor necrosis factor alpha during IA treatment, whereas this reduction was not seen in patients treated with TPE.

Conclusions: In summary, both IA and TPE were effective and safe procedures for treating neurological autoimmune diseases. However, there was a trend towards longer therapy response in patients treated with IA compared to TPE, possibly related to a reduction in plasma levels of pro-inflammatory cytokines seen only in the IA-treated group.

Abbreviations: AQP-4 abs, aquaporin-4 autoantibodies; CIDP, chronic inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid; EEG, electroencephalography; GBS, Guillain-Barré syndrome; IA, immunoadsorption; MRI, magnet resonance imaging; MS, multiple sclerosis; NMDAR, anti-*N*-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorder; PE, plasma exchange.

KEYWORDS
cytokine, immunoadsorption, immunoglobulin, neurological autoimmune diseases, plasma exchange

1 | INTRODUCTION

Therapeutic apheresis represents an established therapeutic option for the treatment of autoimmune diseases in multiple medical disciplines. The therapeutic effect is mainly based on the rapid extracorporeal elimination of autoantibodies, or in the case of therapeutic plasma exchange (TPE) inflammatory, cytokines, or other plasmatic pathogens. Therefore, therapeutic apheresis is particularly used if an immediate response to therapy is required.[1] TPE has the disadvantage of discarding the entire plasma, including valuable proteins, coagulation factors, or hormones. Substitution of human fresh frozen plasma or albumin is necessary, which is associated with a relevant risk of allergic reactions or transmitting infectious diseases.[2–4] In contrast, selective methods of therapeutic apheresis like immunoadsorption (IA) offer the advantage of eliminating immunoglobulins and immune complexes without the necessity of human plasma product substitution.[5] The American Society for Apheresis (ASFA) has been updating and categorizing the indications of interdisciplinary use of therapeutic apheresis through publishing guidelines since 1986, which received worldwide attention. The eighth edition of the ASFA guidelines issued in 2019 included recommendations for the use of TPE or IA in several autoimmune-mediated neurological diseases, for example, multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome (GBS), and autoimmune encephalitis.[5] Guidelines of the German Society of Neurology and the German Society for Nephrology are largely concordant with the ASFA guidelines regarding the above-mentioned neurological diseases.[5]

1.1 | Pathophysiological relevance of autoantibodies in neurological autoimmune diseases

MS is an autoimmune-mediated neuroinflammatory disease of the central nervous system (CNS). It is associated with focal demyelination and progressive neurodegeneration caused by the interplay of genetic and environmental factors. Although the precise underlying pathomechanisms still remain unclear, focal lesions are thought to be caused by the infiltration of immune cells including T cells, B cells, and myeloid cells into the CNS parenchyma with associated neuronal injury. However, no specific autoantibody target has been identified so far.[6,7] Lesions associated with immunoglobulin and complement deposition along myelin sheaths suggest an antibody and complement-mediated mechanism of action.[8] In contrast to MS, NMOSD show a strong association with immunoglobulin G (IgG) antibodies directed against aquaporin-4 (AQP-4 abs), a water channel expressed by CNS astrocytes.[9,10]

Polyneuropathies are common neurological disorders that can be caused by immune responses against autoantigens of the peripheral nervous system. These immune-mediated neuropathies can be subdivided into disorders with an acute onset (eg, GBS) and chronic diseases (eg, CIDP).[11] In GBS, specific autoantibodies against gangliosides can be detected in only few patients,[12] whereas antibodies against GQ1b (a subtype of gangliosides) are common in patients with Miller-Fisher syndrome, a GBS-related disorder, in which the cranial nerves are predominantly affected. In recent years, a set of autoantibodies against proteins located at the node of Ranvier has been identified in some patients with CIDP. These antibodies target neurofascin, contactin1, or contactin-associated protein 1, and CIDP patients with these antibodies were proposed as seropositive.[13,14]

Autoimmune-mediated encephalitides comprise a group of inflammatory brain disorders that are often characterized by prominent neuropsychiatric symptoms. Many of these are associated with IgG antibodies against neuronal cell-surface proteins, ion channels, or receptors such as *N*-methyl-D-aspartate receptors (NMDAR, resulting in NMDAR-encephalitis).[15]

It is well known that treatment with apheresis is a safe and effective therapy for neurological autoimmune diseases. In a prospective randomized controlled trial the effect and safety of therapy with IA or TPE in patients with above-mentioned neurological autoimmune diseases was now investigated. This was assessed on the one hand by the clinical response of the patients and on the other hand, the efficacy of the treatment was measured by changes in immunoglobulins and cytokines concentrations.

2 | METHODS

Patients with an autoimmune-mediated neurological disease, who were refractory to first line standard treatment and therefore received either tryptophan IA or TPE, were

enrolled in a prospective randomized controlled monocentric study between 2016 and 2019. This study was approved by the ethics committee of the University Medical Centre Mainz, Germany and the medical associations Rhineland Palatinate and conformed to the standards of the Declaration of Helsinki of the World Medical Association (Approval No 2018-13039). Written consent was obtained from all participating patients at the beginning of the study.

After study inclusion, 1:1 randomization was performed. However, because of current ACE inhibitor medication, therapy with TPE had to be performed in four cases, since the use of an ACE inhibitor is contraindicated in IA. One study group arm received treatment with TPE, the other group arm received treatment with IA. The goal was for all patients to receive a total of five IA sessions or five TPE sessions (days 1, 2, 3, 5, and 7).

For vascular access, double-lumen central venous catheters were used in all patients. IA treatments were performed using the single-use tryptophan adsorber TR-350 in combination with the OP-0.5 W plasma separator (Asahi Kasei Medical, Tokyo, Japan) and the tubing system PA-420 (combination of AV-210 and PA-220) together with the Octo Nova Technology (DIAMED, Cologne, Germany). The treated plasma volume per IA was 2000 mL. TPE treatments were performed using Plasmaflow OP 0.5 W (L) and the tubing system AV-210 and FS-250 together with the Octo Nova Technology (DIAMED). The treated plasma volume exchange per TPE was 3000 mL (in first PE: with 3000 mL 4% human albumin solution, PE Nr. 2-5: with 1500 mL FFPs and 1500 mL 4% human albumin solution). Anticoagulation in IA or TPE was performed either with unfractionated heparin (bolus injection of 2500 IU of sodium heparin) and/or citrate dextrose, formula A (ACD-A; Baxter, Munich, Germany). To evaluate efficiency of TPE/IA procedures, IgM, IgG levels, and IgG subclasses were determined immediately before and after each TPE/IA treatment.

The main outcome parameter for efficacy was change of acute (relapse-related) disability. Clinical evaluation was performed before the first and after the last treatment of the treatment series and 90 days after the last apheresis treatment. As patients with various neurological autoimmune diseases were included in the study, the overall treatment response was reported descriptively.

Additionally, disability was assessed with the EDSS in MS and NMOSD patients.[16] Moderate improvement represented a definite change of the neurologic deficit (decrease in EDSS by 0.5 steps in patients with initial EDSS 1-3.5) Marked improvement was defined as clinically significant improvement in function (decrease in EDSS by ≥1 step in patients with an initial score 1-3.5; decrease in EDSS by 0.5 steps in patients with an initial score 4-10). No change in EDSS represented any change in neurologic function whereas deterioration in neurologic function was defined by an increase in EDSS.

Also, we used the Hughes functional grading scale (HFGS) for GBS patients and the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score for CIDP patients for the assessment of neurological symptoms at the beginning of therapy, after apheresis treatment, and 90 days after therapy.[17,18] In order to approximate the overall treatment response in our rather heterogeneous cohort, we also assessed disability using the modified Rankin-Scale (mRS) in al studied patients.[19] Because the mRS is a relatively general measure of neurological impairment, the scale can be used with regard to the neurological symptoms of the neurological diseases that were included in the study. An improvement in mRS of one point was considered as treatment response.

In addition, serum was collected before and after each IA/TPE. Freshly drawn blood samples were collected, centrifuged, divided into aliquots, and stored at −80°C before batch analysis.

We measured human cytokine levels in serum using a human Duoset ELISA kit (IL-12, IL-17, IL-18, CSF-1, IL-34, IL-6, tumor necrosis factor alpha [TNF-α], IL-28) according to the manufacturer's instructions (R&D Systems; McKinley Place, MN). Samples were thawed and spun down and the supernatant fraction was used for the ELISA. All measurements were made in duplicate. The laboratory personnel was blinded to clinical data (ClinicalTrials.gov NCT04687332).

3 | STATISTICS

Data represent the means ± SEM prepared using GraphPad Prism software, version 7.0. We used the nonparametric Mann-Whitney *U* test to evaluate *P* values. For correlation analysis, we used the Spearman correlation calculation. Multiple comparisons were analyzed using the Kruskal-Wallis test.

4 | RESULTS

A total of 32 patients were included in this study. The neurological underlying diseases were MS in 11 patients (according to the revision of the McDonald criteria),[20] NMOSD in six patients according to 2015 NMOSD criteria[21] (two of these were anti-AQP4-IgG positive, all were negatively tested for anti-MOG antibodies), six suffered from CIDP, six from GBS and three had autoimmune encephalitis. The mean age of patients during treatment was 43 (SD 17.2) and median duration of disease before treatment was 3.2 years (SD 6.6). The

majority of patients (n = 21) was presented with a first episode of neurological symptoms at time point of study enrollment. In one patient, who was included in the study with suspected neuromyelitis optica, Leber's optic atrophy (LHON) was confirmed by molecular genetics in the further course of the study, so that this patient was excluded from the results. Patient characteristics are summarized in Table 1.

All patients were treated with either TPE or IA between June 2016 and September 2019. In total, 13 patients were treated with IA and 19 patients with TPE. Altogether, 63 cycles of IA and 93 cycles of TPE were performed. IA patients received an average of 4.9 treatments and TPE patients received 4.7 treatments (see Table 2). All patients received their treatment series within 5 to 7 days.

In 24 of the 31 treated patients, the extracorporeal procedure was used due to a refractory disease to therapy or a severe relapse of the disease despite immunosuppressive therapy. Sixteen patients received IA or TPE because of a steroid refractory disease or relapse. The steroid pulse therapy was done with a median cumulative dose of 4 g (see Table 2; see Table 1 of the supplement). Furthermore, a patient with neuromyelitis optica under azathioprine had a relapse event and a patient with CIDP under treatment with rituximab. In addition, 6 patients received immunoglobulins before the indication for IA/TPE was given. These included three patients with CIDP, one patient with a cerebellar syndrome with anti-GAD-abs. and two patients with GBS. In seven patients, the therapy with IA/TPE was applied as first-line therapy.

4.1 | Immunological effects of IA and TPE

In 19 of the 31 patients, IgG, IgM levels, and IgA subclasses were measured to evaluate efficiency of IA/TPE

TABLE 1 Patient characteristics

Diagnosis	IA	TPE	total
MS	6	5	11
Neuromyelitis optica (antibody negative)	0	4 (−1)	4 (−1)
AQP4-IgG pos. NMOSD	1	1	2
GBS	2	4	6
CIDP	2	4	6
Autoimmune encephalitis (limbic encephalitis, anti-NMDA-receptor encephalitis, cerebellar syndrome with anti-GAD-antibodies)	2	1	3
= in total	***13***	***18***	***32 (−1)***
Age at treatment			
Mean age	38	46	43
Mean age—SD	15.8	17.8	17.2
Mean age—range	17-67	24-72	17-72

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; IA, immunoadsorption; NMDAR, anti-*N*-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorders; TPE, therapeutic plasma exchange.

TABLE 2 Treatment characteristics

	IA	TPE	total
Number of treatments	63	93	156
Number of treatments per patients	4.9	4.7	4.9
Plasma volume per treatment mL, mean (SD)	2000	3000	—
Initial treatment with steroids			
Yes	7	10	17
No	6	9	15
Cumulative dose g/mean, SD)	4.1 (1.2)	3.7 (1.5)	4 (1.3)

Abbreviations: IA, immunoadsorption; TPE, therapeutic plasma exchange.

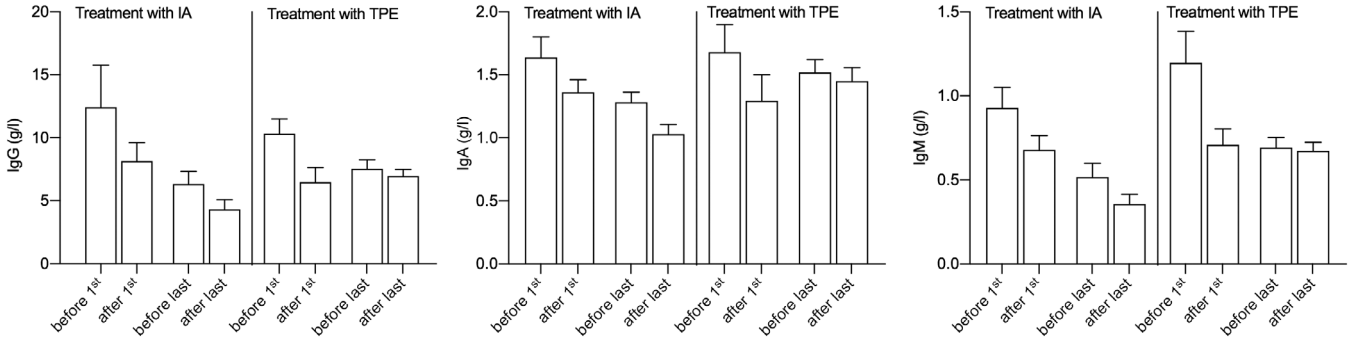

FIGURE 1 Immunoglobulin concentration before and after treatment with immunoadsorption (IA)/therapeutic plasma exchange (TPE)

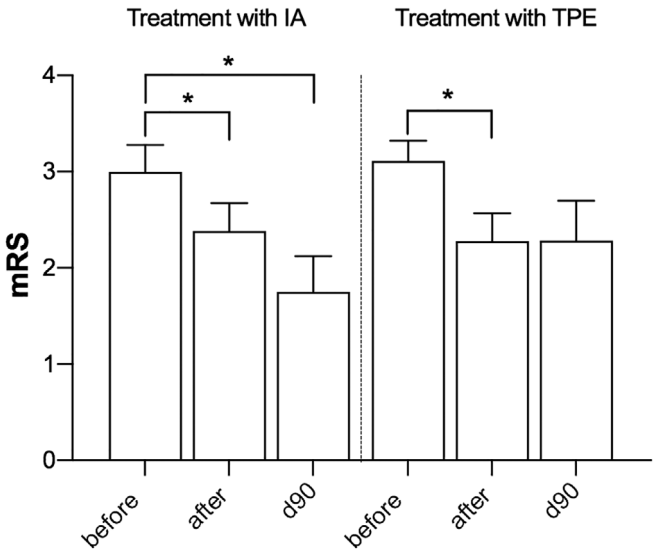

FIGURE 2 Treatment response measured with modified Rankin-Scale (mRS) before and after treatment with therapeutic plasma exchange (TPE)/immunoadsorption (IA), as well as after 90 days

procedures. A continuous decrease of immunoglobulin concentration was observed during the series of five IA treatments. As expected, the reduction of IgG was the most efficient, followed by IgM and IgA (Figure 1). Exact concentrations can be found in Table 2 of the supplement. With regard to TPE, there was a clear drop in all immunoglobulin classes after the first treatment, which then, however, stabilized.

4.2 | Clinical efficacy of IA and TPE

A total of 32 of the heterogeneous patient collective reported descriptively a reduction in symptoms during treatment. In addition, 16 of the 31 patients received a steroid pulse therapy, according to the guideline recommendations for the particular disease, before treatment with an extracorporeal procedure. The detailed clinical manifestations of the individual patients can be seen in Table 1 of the supplement. To objectivize the response to therapy, the mRS was recorded in the entire patient collective, as already mentioned. In this context, it should be noted, that we were able to show a correlation between the EDSS and the mRS in the subgroup analysis of MS and NMOSD patients. Based on our internal validation, we assume that we can assess treatment response using the mRS in MS and NMOSD patients. Based on the small number of patients, a correlation between the HFGS and INCAT with mRS was not possible.

Both treatment groups (IA and TPE) showed a comparable significant response ($P = .05$) to therapy immediately after treatment with IA/TPE (see Figure 2). After 90 days, the TPE study group showed stable symptoms. However, patients treated with IA showed a further improvement after 90 days, but which was not significant compared to the mRS values after treatment with IA ($P = .11$).

In a subgroup analysis, we further collected the corresponding scores for each of the studied disorders to improve the characterization of neurological outcomes (see Figure 3). Here, a response to therapy is shown in the different patient collectives when the individual courses are considered. As shown in Figure 3, the amelioration of neurological symptoms was reflected by all scores. However, due to the small sample sizes of the subgroups, it was not possible to compare treatment responses using a statistical test.

This subgroup analysis of MS and NMOSD patients showed that the clinical benefit of treatment with IA was particularly encouraging. The evaluation of the EDSS before and after treatment (see Figure 3A) showed that four patients demonstrated no change in EDSS, four patients showed a moderate response to therapy, and nine patients improved noticeably.

When considering separately the response to therapy in patients who were treated with TPE, a mean reduction from 3.6 to 2.7 could be shown ($P = .06$). In patients

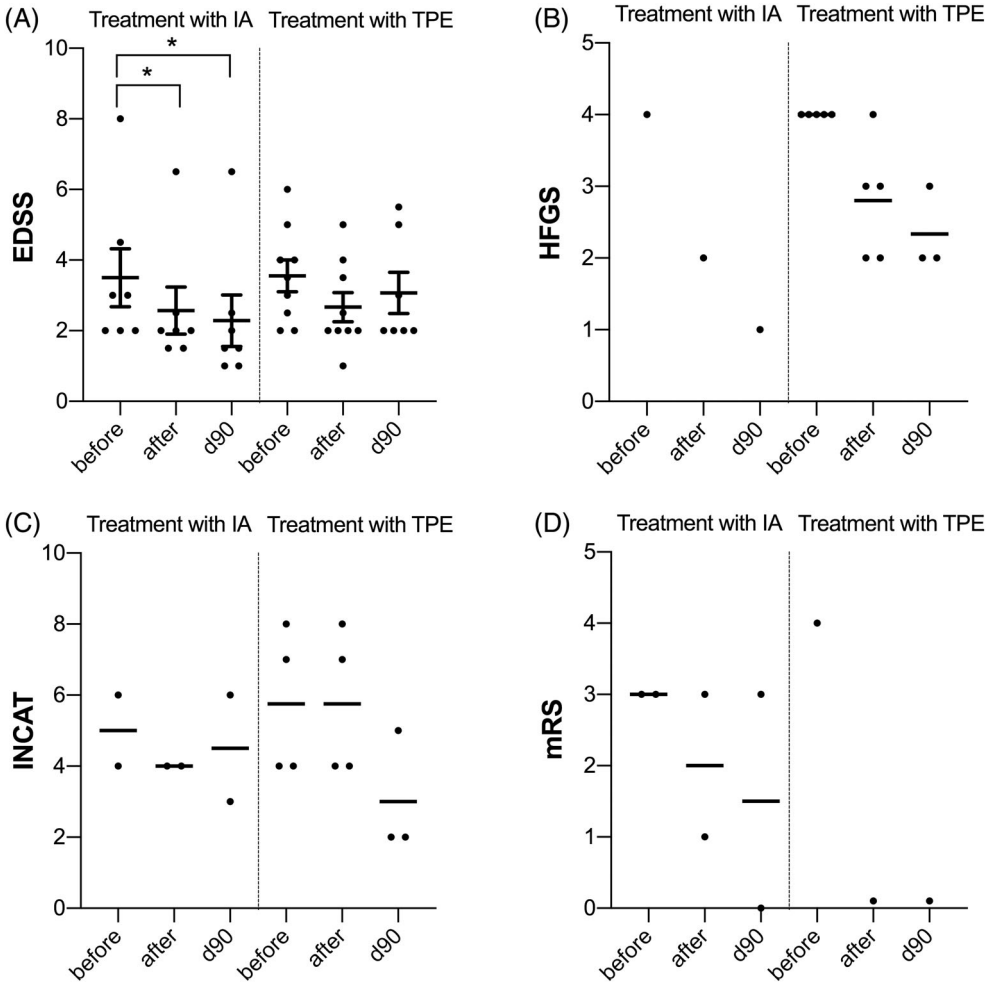

FIGURE 3 Characterization of neurological outcomes before, after and d90 after treatment (immunoadsorption (IA)/ therapeutic plasma exchange (TPE)): (A) EDSS for multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) patients, (B) Hughes functional grading scale (HFGS) for Guillain-Barré syndrome (GBS) patients, (C) Inflammatory Neuropathy Cause and Treatment (INCAT) disability score for chronic inflammatory demyelinating polyneuropathy (CIDP) patients, and (D) modified Rankin-Scale (mRS) for autoimmune encephalitis patients

treated with IA, a mean EDSS score of 3.6 could be assessed, which decreased to 2.6 after treatment (*$P < .05$). Accordingly, there was a significant reduction of −1 (see Figure 3). After 90 days, there was again an increase in the EDSS of 0.2 points in the group treated with TPE. In addition, the EDSS score in the patients who received IA treatment remained stable after 90 days (−0.3 points) compared to EDSS after treatment with IA.

A detailed description of the symptoms in MS and NMOSD patients before and after treatment is given in Table 3.

4.3 | Changes of circulating inflammatory cytokines related to TPE or IA treatment

Measurement of cytokines before and after the first and last apheresis treatment was performed to further evaluate possible underlying mechanisms of IA and TPE treatment additional to reduction of pathogenic autoantibodies (Figure 4). IL-12, lL-17, IL-6, IL-10, TNF-α, and interferon-gamma (INF-γ) were measured. In the course of treatment with IA, the majority of these evaluated cytokines showed a significant decrease from baseline. Especially, the cytokines IL-17 and IL-6 showed the most significant reduction. Surprisingly, these results were not found in patients treated with TPE. Even a slight increase from baseline levels was observed. Only IL-10 was neither affected by IA nor TPE.

4.4 | Safety of IA and PE

In total, 63 cycles of IA and 93 cycles of TPE were performed in 31 patients with a mean of 4.9 IA treatments and 4.7 TPE treatments, respectively, per patient. The overall tolerability was good. One patient experienced an allergic reaction to fresh frozen plasma during the first TPE. The patient switched to IA for the following treatments without any tolerability issue. Furthermore, two patients developed symptomatic hypocalcaemia during the citrate anticoagulation (one patient on TPE, one patient on IA). This was treated by increased calcium

TABLE 3 Characteristics of patients with MS (patients 1-11), and NMOSD (patients 12-16)

Patient	Duration of disease (y)	Disease specific medication prior to or with initiation of apheresis	Treatment	Steroid pulse	Clinical manifestation	EDSS before apheresis treatment	EDSS after apheresis treatment	EDSS after 90 d	Therapy response before and immediately after apheresis (no response = 0 moderate improvement = 1 marked improvement = 2)
1	15	Mitoxantron and Fingolimod 2011/2013; Fingolimod since May 16	TPE	2 g	Diplopia, dizziness, paresis of the right leg	4.0	4.0	3.0	0
2	7	Interferon-1-β 2011 over 6 mo; natalizumab 2013-2015; Finglomod since January 16	TPE	3 g	Gait ataxia	3.5	2.5	5.5	2
3	30	Glatiramer acetate and Interferon-1-β; Fingolimod since July 13	IA	3 g	Ataxia, reduced visual acuity	4.5	2.5	2.5	2
4	2.5	Immunotherapy + dimethyl fumarate (November 3, 2017)	IA	5 g	ON	2.0	1.5	1.5	1
5	18	Interferon-1-β approximately 2014-August 2017; renewed start since January 18	IA	Acute liver failure, no steroids	Vigilance reduction and dysphagia	8.0	6.5	6.5	2
6	Initial diagnosis	No premedication	TPE	3 g	Sensomotory hemiparesis of the left side	6.0	3.5	Missing	2
7	9	Interferon-beta—2009 to 2010; natalizumab—2010 to 2012; fumarate till September 18	TPE	5 g	Recurrent central scotoma	2.0	2.0	2.0	0

TABLE 3 (Continued)

Patient	Duration of disease (y)	Disease specific medication prior to or with initiation of apheresis	Treatment	Steroid pulse	Clinical manifestation	EDSS before apheresis treatment	EDSS after apheresis treatment	EDSS after 90 d	Therapy response before and immediately after apheresis (no response = 0 moderate improvement = 1 marked improvement = 2)
8	Initial diagnosis	No premedication	IA	5 g	ON left eye	3.0	2.0	1.0	2
9	Initial diagnosis	No premedication	TPE	5 g	Incomplete hemianopsia to the left, left corporal hypesthesia below Th4	2.5	2	2.0	1
10	3	Interferon-1-β and glatiramer acetate 2016	IA	5 g	ON left eye	3.0	2.0	2.0	2
11	1.5	Secukinumab 150 mg s.c. 4 wk and repeated glatiramer acetate 40 mg s.c. 3x/wk	IA	5 g	ON right eye	2.0	1.5	1.5	1
12	3	Azathioprine	TPE	No steroids	ON left eye	3	2	2	2
13	Initial diagnosis	No premedication	TPE	3 g	ON left eye	2	1	—	2
14	Initial diagnosis	No premedication	TPE	3 g	ON left eye	4	2	2	2
15	Initial diagnosis	No premedication	IA	3 g	Headache	2	2	1	1
16	9	MMF since 2018	TPE	3 g	ON both eyes	5	5	5	0

Abbreviations: IA, immunoadsorption; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; TPE, therapeutic plasma exchange.

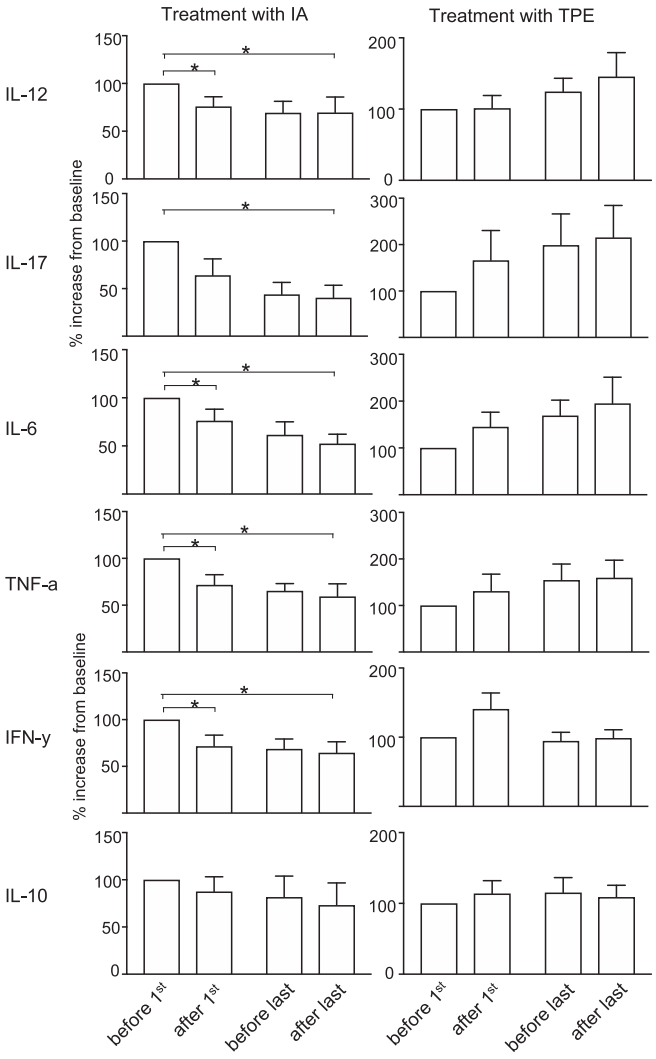

FIGURE 4 Cytokine expression following first and last immunoadsorption (IA) (before and after) vs therapeutic plasma exchange (TPE) (before and after) treatment

substitution, so that the symptoms quickly subsided. One patient experienced a light decrease of blood pressure that resolved upon infusion of 1 L of saline solution.

Catheter associated complications occurred in three patients. A catheter-associated thrombosis in the jugular vein was discovered as an incidental finding in the computed tomography (CT), which took place due to their neurological diagnostic work-up. The patients were anticoagulated for 3 months.

5 | DISCUSSION

The prospective investigation of 32 patients with autoimmune neurological diseases demonstrated efficacy and safety of IA and TPE as essential parts of treatment or escalating treatment regimens. Clinical efficacy of TPE and IA was essentially identical for treated diseases. However, our study demonstrated a significant reduction of the pro-inflammatory cytokines IL-12, lL-17, IL-6, INF-γ, and TNF-α during IA treatment, which could not be observed during the treatment with TPE.

Only a few studies have investigated differential effects of the treatment with IA vs TPE in neurological autoimmune diseases. In 2019, a two-center retrospective study investigating the efficacy and safety of treatment with IA vs TPE of MS and NMO in steroid-refractory relapses reported a significantly increased improvement with regard to clinical symptoms in MS patients treated with IA compared to TPE. The MS functional composite index, a quantitative survey of findings that applies the 7.6 m walk distance, the so-called nine-hole pegboard test, and the PASAT3 test, a neurocognitive test, to assess the functionality of MS patients, was used to evaluate the response to therapy (MSFC IA: 0.385 vs PE: 0.265). The higher efficacy in IA-treated patients was explained by a more significant reduction of IgG by IA than by TPE.[22] The results of our study also point to a trend that MS patients treated with IA may benefit more and we, too, were able to clearly demonstrate a more clearer reduction of IgG in our IA-treated patient collective over the entire treatment period. In addition, this was also demonstrated for IgM and IgA in our work. However, it must be stated that in our case, foreign immunoglobulins were substituted through the addition of FFPs to the exchange volume during therapy with TPE. A relation to the effectiveness of the treatment with TPE with regard to the reduction of immunoglobulins is therefore difficult to examine. Furthermore, it should be noted that the reduction of immunoglobulins during the first treatment with IA or TPE was comparable. In this first treatment, as explained in Section 2, plasma exchange took place exclusively with human albumin, so that no foreign immunoglobulins were substituted here.

In a further study by Dorst et al., a prolonged response to therapy in MS patients treated with IA compared to treatment with TPE was shown.[23] This trend for a longer-lasting effect can also be seen in our entire patient collective. Patients who had received therapy with IA showed a further decrease in the mRS after 90 days.

On the other hand, in a few retrospective studies, no significant difference of the efficacy of TPE and IA treatment was observed in patients with MS, for example, in the recently published study by Lipphardt et al.[22,24,25] However, a slight reduction of side effects in IA could be shown in the study by Faissner et al. with comparable efficacy.[24] In the other studies mentioned, there was no difference in terms of side effects.

In studies comparing IA vs TPE for other neurological autoimmune diseases (myasthenia and CIDP), no significant difference were seen either.[3,26,27] In the case of the study comparing IA with TPE in CIDP, however, a

tendency was found which, in contrast, showed a higher efficiency of IA treatment.[26]

A remarkable observation of our study is the significant reduction of the pro-inflammatory cytokines IL-12, lL-17, IL-6, INF-γ, and TNF-α during IA treatment. This is in contrast to the tendency of an increase of IL-12, lL-17, IL-6, and TNF-α under therapy with TPE. By changes of the cytokine serum concentration, IA and TPE might influence the cellular immunity. However, only little data on immune modulation under treatment with IA or TPE is currently available.

To the best of our knowledge, Baggi et al. conducted the first and only study to date, which investigated the effect of IA on serum cytokines.[28] This was done on patients with myasthenia gravis (N = 6) and Lambert-Eaton myasthenic syndrome (N = 3). In their study, a reduction of the serum levels of IL-18, IL-17, and TGF-β was reported. In contrast, they measured an increase in IL-10 under IA treatment. The authors of that study speculated that the probably linked IgG resynthesis process might underlie the observed increase of IL-10 under IA therapy.[28] In contrast, we observed no significant changes in Il-10 concentrations upon IA treatment. The connection between the resynthesis of IgG and IL-10 therefore also offers a possible explanation that in our data IL-10 does not decrease as significantly as the pro-inflammatory cytokines. On the other hand, IL-10 is the most important anti-inflammatory cytokine, which suppresses the pro-inflammatory autoimmune response in the context of autoimmunity. The change in ratio between IL-10 and pro-inflammatory cytokines may favor the clinical response to IA treatment.

In another study, elevated levels of pro-inflammatory cytokines (IL-6, IL-8, and IL-1ra) were measured compared to baseline after treatment with TPE in patients with ANCA-positive vasculitis. This observation was related to an activation of cytokine synthesis through the contact of blood with the synthetic membrane.[29] However, this cannot be an explanation with regard to our results, since there was a significant decrease in pro-inflammatory cytokines in patients treated with IA compared to treatment with TPE, showing an increase. Moreover, IA-treated patients received the same filter (plasma flow OP 0.5 W) to separate the plasma from the cellular blood components as TPE-treated patients in the first step of treatment. A possible explanation for the lack of reduction in cytokines during treatment with TPE could be a possible activation of cytokine production by the foreign fresh frozen plasma or albumin. In vitro, Patlán et al. could demonstrate that exposure to FFPs leads to an increased cytokine production by monocyte activation.[30] This activation of cytokine production could thus lead to an activation of the immune system by the application of foreign FFPs, which may explain why the clinical response to treatment may favor IA over TPE and, in this context, also indicates a longer response to therapy. Thus, if this hypothesis were to be confirmed, IA would be given preference to TPE as a therapeutic method for the treatment of neurological autoimmune diseases.

Our study is not without limitations. We acknowledge that the heterogeneity of patient groups enrolled in this study might threaten generalizability of our findings. Furthermore, the lack of validated scores across disease entities makes interpretation of clinical outcomes challenging. Therefore, larger studies addressing these limitations are needed to confirm our hypothesis.

With regard to the side effects, a severe allergic reaction to FFP during treatment with TPE was observed during the course of the study. There was no serious side effect with IA therapy. Furthermore, only mild side effects were found with no difference seen between the treatments IA or TPE. Thus, IA might be the treatment option with a reduction in possible side effects, since no substitution of fresh frozen plasma or albumin with the risk of allergic reactions is necessary.

Another side effect of the therapy was, as already mentioned, the catheter associated thrombosis. In relation to current data, this rate of catheter associated complications of about 10% seems comparatively low. Rather, in a review after evaluation of 25 studies, the prevalence of catheter-associated symptomatic thromboses was detected in 41% of patients.[31] However, it should be noted that not all patients received a CT and all patients received thromboprophylaxis during treatment.

In conclusion, both IA and TPE treatments are highly effective and well tolerated. However, there was a tendency for patients treated with IA to benefit longer after treatment, and their clinical condition may continue to improve after treatment. However, in our study treatment with IA in patients with MS seems slightly superior to treatment with TPE. A possible explanation could be an apparent immune activation by the substitution of FFPs or albumin during treatment with TPE with subsequent secretion of pro-inflammatory cytokines. However, in order to strengthen this hypothesis, further studies with a significantly higher number of patients are necessary.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Schneider-Gold C, Krenzer M, Klinker E, et al. Immunoadsorption vs plasma exchange vs combination for treatment of myasthenic deterioration. *Ther Adv Neurol Disord*. 2016;9(4):297-303.
2. Hewitt PE, Ijaz S, Brailsford SR, et al. Hepatitis e virus in blood components: a prevalence and transmission study in Southeast England. *Lancet*. 2014;384(9956):1766-1773.
3. Köhler W, Bucka C, Klingel R. A randomized and controlled study comparing immunoadsorption and plasma exchange in myasthenic crisis. *J Clin Apher*. 2011;26(6):347-355.
4. Álvarez M, Luis-Hidalgo M, Bracho MA, et al. Transmission of human immunodeficiency virus Type-1 by fresh-frozen plasma treated with methylene blue and light. *Transfusion*. 2016;56(4):831-836.
5. Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. *J Clin Apher*. 2019;34(3):171-354.
6. Goodin DS. The epidemiology of multiple sclerosis. Insights to disease pathogenesis. *Handbook of Clinical Neurology*. Vol 122; Amsterdam, The Netherlands: Elsevier B.V.; 2014:231-266.
7. Nylander A, Hafler DA. Multiple sclerosis. *J Clin Invest.* 2012;122(4):1180-1188.
8. Stork L, Ellenberger D, Beißbarth T, et al. Differences in the responses to apheresis therapy of patients with 3 histopathologically classified immunopathological patterns of multiple sclerosis. *JAMA Neurol*. 2018;75(4):428-435.
9. Aungsumart S, Apiwattanakul M. Clinical outcomes and predictive factors related to good outcomes in plasma exchange in severe attack of NMOSD and long extensive transverse myelitis: case series and review of the literature. *Mult Scler Relat Disord*. 2017;13:93-97.
10. Cañellas AR, Gols AR, Izquierdo JR, Subirana MT, Gairin XM. Idiopathic inflammatory-demyelinating diseases of the central nervous system. *Neuroradiology*. 2007;49(5):393-409.
11. Van Den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, Van Doorn PA. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. *Nat Rev Neurol*. 2014;10(8):469-482.
12. Cutillo G, Saariaho AH, Meri S. Physiology of gangliosides and the role of antiganglioside antibodies in human diseases. *Cell Mol Immunol*. 2020;17:313-322.
13. Querol L, Siles AM, Alba-Rovira R, et al. Antibodies against peripheral nerve antigens in chronic inflammatory demyelinating polyradiculoneuropathy. *Sci Rep*. 2017;7(1):14411.
14. Vural A, Doppler K, Meinl E. Autoantibodies against the node of ranvier in seropositive chronic inflammatory demyelinating polyneuropathy: diagnostic, pathogenic, and therapeutic relevance. *Front Immunol*. 2018;9:1029.
15. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med*. 2018;378(9):840-851.
16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452.
17. Hughes R, Newsom-Davis J, Perkin G, et al. Controlled trail of prednisolone in acute polyneuropathy. *Lancet*. 1978;2(8093):750-753.
18. Merkies J et al. Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry*. 2002;72(5):596-601.
19. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten H, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607.
20. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet*. 2018;17(2):162-173.
21. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.
22. Lipphardt M, Mühlhausen J, Kitze B, et al. Immunoadsorption or plasma exchange in steroid-refractory multiple sclerosis and neuromyelitis optica. *J Clin Apher*. 2019;34(4):381-391.
23. Dorst J, Fangerau T, Taranu D, et al. Safety and efficacy of immunoadsorption vs plasma exchange in steroid-refractory relapse of multiple sclerosis and clinically isolated syndrome: a randomised, parallel-group, controlled trial. *EClinicalMedicine*. 2019;16:98-106.
24. Faissner S, Nikolayczik J, Chan A, et al. Plasmapheresis and immunoadsorption in patients with steroid refractory multiple sclerosis relapses. *J Neurol*. 2016;263(6):1092-1098.
25. Mühlhausen J, Kitze B, Huppke P, Müller GA, Koziolek MJ. Apheresis in treatment of acute inflammatory demyelinating disorders. *Atheroscler Suppl*. 2015;18:251-256.
26. Lieker I, Slowinski T, Harms L, Hahn K, Klehmet J. A prospective study comparing tryptophan immunoadsorption with therapeutic plasma exchange for the treatment of chronic inflammatory demyelinating polyneuropathy. *J Clin Apher*. 2017;32(6):486-493.
27. Yeh JH, Chiu HC. Comparison between double-filtration plasmapheresis and immunoadsorption plasmapheresis in the treatment of patients with myasthenia gravis. *J Neurol*. 2000;247(7):510-513.
28. Baggi F, Ubiali F, Nava S, et al. Effect of IgG immunoadsorption on serum cytokines in MG and LEMS patients. *J Neuroimmunol*. 2008;201-202:104-110.
29. Tesař V, Jelínková E, Mašek Z, et al. Influence of plasma exchange on serum levels of cytokines and adhesion molecules in ANCA-positive renal vasculitis. *Blood Purif*. 1998;16(2):72-80.
30. Patlán M, Sánchez-Muñoz F, Amezcua-Guerra LM, et al. Effect of fresh frozen plasma on the in vitro activation of U937

monocytes: a potential role for the age of blood donors and their underlying cytokine profile. *Biol Res*. 2017;50:42.

31. Geerts W. Central venous catheter-related thrombosis. *Hematology*. 2014;2014(1):306-311.

SUPPORTING INFORMATION

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