EClinicalMedicine 16 (2019) 98–106

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Safety and efficacy of immunoadsorption versus plasma exchange in steroid-refractory relapse of multiple sclerosis and clinically isolated syndrome: A randomised, parallel-group, controlled trial

Johannes Dorst[a,*], Tanja Fangerau[a], Daniela Taranu[a], Pia Eichele[a], Jens Dreyhaupt[b], Sebastian Michels[a], Joachim Schuster[a], Albert C Ludolph[a], Makbule Senel[a], Hayrettin Tumani[a]

[a] Department of Neurology, University of Ulm, Oberer Eselsberg 45, D-89081 Ulm, Germany
[b] Institute for Epidemiology und Medical Biometry, University of Ulm, Germany

ARTICLE INFO

Article History:
Received 7 October 2019
Revised 21 October 2019
Accepted 28 October 2019
Available online 14 November 2019

Keywords:
Multiple sclerosis
Therapeutic plasma exchange
Immunoadsorption
Relapse

SUMMARY

Background: Plasma exchange (PE) constitutes the standard therapy for steroid-refractory relapse in multiple sclerosis and clinically isolated syndrome. Immunoadsorption (IA) is an alternative method of apheresis which selectively removes immunoglobulines (Ig) while preserving other plasma proteins. Although IA is regarded as a well-tolerated, low-risk procedure, high-level evidence for its efficacy is lacking. Therefore, we sought to investigate whether IA is superior to PE in patients with acute relapse of multiple sclerosis or clinically isolated syndrome who had insufficiently responded to high-dose intravenous methylprednisolone (MP).

Methods: Patients with acute relapse of multiple sclerosis or clinically isolated syndrome and without complete clinical remission of symptoms after at least one cycle of high-dose intravenous MP therapy were enrolled to our randomised, controlled, parallel-group, monocentric trial. Eligible patients were aged at least 12 years and had no clinical or laboratory signs of systemic infection. Eligible patients were randomly assigned (1:1) to receive either IA or PE. Patients in both groups received 5 treatments on 5 consecutive days. In the IA group, the 2.0-fold individual total plasma volume was processed on day 1, and the 2.5-fold on days 2–5. In the PE group, 2 liters of plasma (corresponding to the 0.69 ± 0.12-fold individual total plasma volume) were removed each day and substituted by 5% human albumin solution. Patients were followed up directly after last apheresis as well as 2 and 4 weeks after last treatment. The primary endpoint was change of the Multiple Sclerosis Functional Composite (MSFC) after 4 weeks compared to baseline. Analyses of primary outcome and safety measures were done in all patients who received at least one treatment (intention-to-treat-population). The trial is registered with ClinicalTrials.gov, number NCT02671682.

Findings: Between January 21, 2016, and October 26, 2018, 63 patients were screened for eligibility, and 61 patients were randomly assigned to receive IA ($n = 31$) or PE ($n = 30$). All randomised patients were included in the intention-to-treat-analysis. For the primary outcome, the median improvement of MSFC after 4 weeks compared to baseline was 0.385 (IQR 0.200–0.675; $p < 0.001$) in the IA group and 0.265 (IQR 0.100–0.408; $p < 0.001$) in the PE group. Improvement in the IA group was significantly larger ($p = 0.034$) compared to PE. Response rates after 4 weeks were 86.7% in the IA group and 76.7% in the PE group. One deep venous thrombosis occurred in each group.

Interpretation: Both IA and PE were safe in patients with steroid-refractory relapse and resulted in significant improvements of the primary outcome MSFC after 4 weeks compared to baseline. IA patients showed significantly larger improvements of MSFC compared to PE patients after 4 weeks. The results indicate a potential superiority of IA compared to PE in treatment of steroid-refractory relapse in multiple sclerosis and clinically isolated syndrome, which has to be confirmed by future studies.

Funding: Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany

* Corresponding author.
E-mail address: johannes.dorst@uni-ulm.de (J. Dorst).

https://doi.org/10.1016/j.eclinm.2019.10.017

Panel: Research in Context

Evidence before this study

We systematically searched MEDLINE (since January 1966), Cochrane Central / Cochrane Neuromuscular Disease Group Specialized Register, Cochrane Library, EMBASE (since January 1980), AMED (since January 1985), CINAHL plus (since January 1938), LILACS (since January 1982), OVID HealthSTAR (since January 1975), clinicaltrials.gov (since January 1997), and International Clinical Trials Search Portal (since November 2004) for all clinical trials, observational studies, and reviews published between Jan 1, 1963, and February 1, 2019, in English, Spanish, Italian, German, and French. Search terms were "multiple sclerosis", "MS", "clinically isolated syndrome", "CIS", "immunoadsorption", "IA", "therapeutic plasma exchange", "TPE", "plasma exchange", "PE", "plasmapheresis", and "relapse". Overall we found 12 review articles, 32 observational studies (26 retrospective, 6 prospective), and one randomised placebo-controlled trial regarding the use of immunoadsorption or plasma exchange in steroid-refractory relapse in multiple sclerosis or clinically isolated syndrome.

Added value of the study

This prospective, randomised, controlled trial assessed the safety and efficacy of immunoadsorption in patients with steroid-refractory relapse of multiple sclerosis or clinically isolated syndrome compared to plasma exchange, which is regarded as standard escalation therapy of steroid-refractory relapse. The intention-to-treat analysis revealed a significant beneficial therapeutic effect for both treatment arms, but primary endpoint analysis (change of Multiple Sclerosis Functional Composite after 4 weeks) showed a larger beneficial effect for immunoadsorption.

Implications of all the available evidence

The intention-to-treat analysis showed a larger improvement of Multiple Sclerosis Functional Composite after 4 weeks in patients who received immunoadsorption compared to patients who received plasma exchange, indicating a potential superiority compared to the current standard escalation therapy of steroid-refractory relapse in multiple sclerosis and clinically isolated syndrome.

1. Introduction

Multiple sclerosis is the most frequent disabling disease of young adults and is therefore of large medical and socioeconomic significance. It is an autoimmune-mediated, chronic inflammatory disease of the central nervous system leading to demyelination and axonal damage. More than 80% of patients primarily show a relapsing remitting course of disease. Relapses tend to improve after intravenous high-dose methylprednisolone (MP) therapy [1]. A single relapse without fulfillment of the diagnostic criteria for multiple sclerosis defines the term of a clinically isolated syndrome which is treated analogous to a relapse in multiple sclerosis.

Although over the last years various drugs have been discovered which significantly reduce relapse rates in relapsing remitting multiple sclerosis, only few therapy options are available for treatment of an acute relapse itself. In case of insufficient response to high-dose ($3-5 \times 500-1000$ mg) intravenous MP, some guidelines recommend a second, ultra-high-dose ($3-5 \times 2$ g) intravenous MP cycle based on the finding that clinical response might be dose-dependent [2], although direct evidence is missing in this regard.

So far, plasma exchange (PE) has been regarded as the standard escalation therapy in case of MP-refractory relapse, based on one randomised, sham-controlled study in 22 patients which showed a response rate of 42.1% [3] as well as several case series which found response rates between 44% and 70% [4-6]. During PE, the patient's plasma including all plasma proteins is removed and substituted by human albumin solution or fresh frozen plasma. The mode of action of PE in autoimmune diseases is based on the removal of pro-inflammatory plasma components from the blood. However, the procedure is unspecific, and the loss of coagulation factors and other plasma constituents may cause complications, including thrombosis, bleeding, hypotension (due to volume-shift), and sepsis [7,8]. Furthermore, the need of a volume replacement solution carries the risk of severe allergic reactions [7]. Life-threatening complications have been reported in 0.12% of patients [8], and a higher risk of adverse events in patients with neurological diseases has been described [7].

In recent years, immunoadsorption (IA) is increasingly recognized as an alternative approach of apheresis with the potential to replace PE in a variety of autoimmune neurological disorders. During IA, plasma components are separated by adsorber systems, which are designed to selectively bind immunoglobulins (Igs) while largely preserving other plasma proteins, allowing higher plasma volumes to be processed. The processed plasma is returned to the patient, therefore no volume replacement solution is needed. IA has repeatedly been described as a safe and well-tolerated procedure [9–11]. Furthermore, studies investigating other auto-immune neurological indications like myasthenia gravis suggest that side effects might be significantly reduced in IA compared to PE [12,13]. Life-threatening complications have not been described for IA so far. Since other pro-inflammatory proteins are spared, IA is primarily considered a therapeutic option in diseases which are based on Ig-mediated pathomechanisms.

The importance of Igs (and especially IgG) in the pathogenesis of multiple sclerosis has been firmly established. Evidence of intrathecal Ig production, oligoclonal IgG bands and a positive MRZ (Measles, Rubella, Varicella-Zoster) reaction contribute to diagnosis, and B-cell depleting agents like rituximab [14] and ocrelizumab [15] are used in therapy of multiple sclerosis. Furthermore, different types of specific autoantibodies against myelin have been identified in subgroups of patients with multiple sclerosis, such as anti-myelin basic protein (anti-MBP) and anti-myelin oligo-dendrocyte glycoprotein (anti-MOG [16]). Antibody-producing B-cells play a pathogenetic key-role as they constantly travel between CNS, blood, and peripheral lymphatic organs, interacting with other immune cells and thus sustaining the inflammation process [17]. Clonally expanded B-cells can be found in the meninges, brain, and cerebrospinal fluid of patients with multiple sclerosis [18,19], and histopathologic analysis of meninges show lymphoid structures containing aggregated B-cells and plasma cells [20]. Accordingly, it has been hypothesized that apheresis is most effective in MS patients with the immunopathological pattern II, which is characterized by Ig and complement deposits [21].

In accordance with the pathophysiological aspects outlined above, several case series showed promising results for the use of IA in steroid-refractory relapse of multiple sclerosis, reporting response rates between 71% and 88% [22-26]. Retrospective studies suggest about equal efficacy and tolerability of PE and IA in this indication [27]. However, high-level evidence in terms of a randomised controlled trial (RCT) is missing. Therefore, we did an investigator-initiated RCT to compare efficacy and tolerability of IA compared to PE in patients with multiple sclerosis or clinically isolated syndrome suffering from acute relapse with insufficient response to high-dose MP therapy.

2. Methods

2.1. Study design and participants

This study was an RCT of IA compared to PE in patients with steroid-refractory relapse of multiple sclerosis or clinically isolated syndrome at the University Clinic of Ulm in Germany. The study was done in

accordance with the Declaration of Helsinki, International Conference on Harmonisation Guideline for Good Clinical Practice, and the applicable regulations. The Competent Ethics Committee of the University of Ulm, Germany, approved the study protocol (approval number 298/15). The trial protocol can be accessed online. The study was conducted in adherence to standard guidelines (CONSORT).

Patients with diagnosis of multiple sclerosis or clinically isolated syndrome were considered for enrolment into the study. Included patients were aged at least 12 years and had an acute relapse without complete remission after at least one cycle of high dose MP therapy (at least $3-5 \times 500-1000$ mg). Exclusion criteria were clinical or laboratory signs of infection, or intake of an angiotensin converting enzyme inhibitor within 1 week prior to first treatment. All patients gave written informed consent.

2.2. Randomisation

At the randomisation visit, each eligible patient was randomly assigned (1:1) to one of the two treatment groups, and received the next consecutive randomisation number. The randomisation list was generated by the Institute of Epidemiology and Medical Biometry, University of Ulm, Germany, by use of a validated system, which involves a pseudorandom number generator to ensure that the resulting treatment sequence will be both reproducible and non-predictable.

The trial was not blinded due to the extensive differences regarding required equipment, procedures, and concomitant treatment for each group. Therefore, neither patients nor site personnel were masked to treatment allocation. However, evaluators for primary and secondary endpoints were otherwise not involved in the patients' treatment, i.e., not responsible for any medical decisions regarding indication or execution of IA or PE.

There was no placebo group, since PE has already been established as the standard escalation therapy for steroid-refractory relapse in multiple sclerosis. Hence it would have been ethically unacceptable to do a sham apheresis.

2.3. Procedures

Before randomisation, a systemic infection was excluded by analyses of blood (leukocytes and CRP) and urine. Study participants received five treatments of either IA or PE on five consecutive days. Venous access was established by a central venous catheter (Shaldon catheter) which was placed in the right jugular vein. Daily blood analysis included blood count, electrolytes, total protein, coagulation parameters including fibrinogen, and inflammation parameters. All patients underwent continuous monitoring of vital signs (heart rate, blood pressure, and oxygen saturation) during apheresis.

IA was performed using an adsorber system (ADAsorb, medicap clinic GmbH, Ulrichstein, Germany) with regenerating protein A adsorber columns (Immunosorba, Fresenius Medical Care, Bad Homburg, Germany) after separating cells and plasma with a plasma separator (ART Universal, Fresenius Medical Care, Bad Homburg, Germany). Protein A is a cell wall protein from staphylococcus aureus which selectively binds human immunoglobulins. Compared to single-use tryptophan adsorbers as used in most previous studies, protein A adsorbers offer the advantage of a more selective removal of immunoglobulins as well as a regenerating mechanism which allows multiple uses of each column, resulting in larger blood volumes which can be processed in a given time frame. The individual total plasma volume for each patient was calculated using the formula published by Sprenger et al. [28]. The 2.0-fold total plasma volume was processed on day 1, and the 2.5-fold total plasma volume was processed on day 2–5. Heparin and citrate were used as anticoagulants. Serum calcium levels were continuously monitored, and calcium was substituted when necessary.

In PE patients, 2 liters of plasma were removed each day using the cell separator COM.TEC (Fresenius Kabi AG, Bad Homburg, Germany) and substituted by 5% human albumin solution. Citrate was used as anticoagulant.

Since there is no universally accepted standard, the amount of treated plasma volumes for both procedures as defined by the study protocol was chosen based on local experience and controlled by the reduction rates of immunoglobulines.

Enrolled patients underwent a screening phase, which lasted up to 4 days, and a 5-day treatment phase. Clinical and physical examinations (outcome measures) and blood sampling were recorded at on-site visits directly after last treatment (V1) as well as 2 weeks (V2) and 4 weeks (V3) after last treatment. Quality of life was additionally recorded 12 weeks (V4) after last treatment via telephone. Neuropsychological testing was done at V0 and V3. The investigators observed patients for adverse events and instructed patients to report any events.

2.4. Outcomes

The primary outcome was change of Multiple Sclerosis Functional Composite (MSFC) score after 4 weeks (V3) compared to baseline (V0). Secondary efficacy outcomes were change of Expanded Disability Status Scale at V1–V3, change of Quality of Life (visual analogous scale) at V1–V4, change of vision (defined as percentage of normal vision as measured by EDSS standardized visual testing; only affected eyes in patients with optic neuritis were considered) at V1–V3, change of Symbol Digit Modalities Test (SDMT) score at V3, change of Verbaler Lern- und Merkfähigkeitstest (VLMT) score at V3, change of MSFC at V1+V2, and response rate (defined as an improvement of at least 10% in MSFC score) at V1–V3. In all cases, change was defined as the difference from baseline (i.e. V0). Safety endpoints included the terms and frequency of reported adverse events and serious adverse events, safety laboratory parameters (clinical chemistry and hematology), and vital signs. Values for safety laboratory parameters were compared with both the appropriate normal ranges and ranges of potential clinical concern as defined by the treating study physician. Reduction rates of Immunoglobulines were calculated by comparing respective serum values at baseline and directly after the last treatment.

2.5. Statistical analysis

We calculated the sample size based on the following assumptions, taking into account feasibility: type I error 0.05 (two-sided), power 0.80, effect size of Cohen's $d = 0.74$ (medium effect size). Under the assumption of equal numbers of patients in each group, this scenario required 30 patients in each group.

All continuous data are given as median and interquartile range (IQR) or mean and standard deviation as appropriate. Categorical data are presented as frequencies and percentages. Changes in continuous data were investigated with the Wilcoxon signed rank test. Group comparisons for continuous data were performed using the Mann–Whitney-U-test or two-sample *t*-test as appropriate. Group comparisons for categorical data were carried out with the chi-square test or Fisher's exact test as appropriate. No adjustment for multiple testing was done. Results from secondary endpoints have to be interpreted as hypothesis generating rather than proof of efficacy.

We analysed the study population according to the intention-to-treat principle. All patients randomly assigned to study groups who received at least one treatment were analysed for safety and efficacy. To estimate the treatment effect, we calculated the median difference in the primary endpoint, including a two-sided 95% confidence interval. Adverse events were analysed descriptively.

Statistical analyses were done using SAS, version 9.4, and GraphPad Prism, version 7.05. The trial is registered with ClinicalTrials.gov, number NCT02671682.

2.6. Role of the funding source

This study is an investigator-initiated trial of the University of Ulm, with institutional support from Fresenius Medical Care Deutschland GmbH. Fresenius Medical Care Deutschland GmbH had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author has full access to all the data in the study and has final responsibility for the decision to submit for publication.

3. Results

3.1. Trial profile

Between January 21, 2016, and October 26, 2018, 63 patients with multiple sclerosis or clinically isolated syndrome were screened (Fig. 1). 61 patients were enrolled, and randomly assigned to receive either IA ($n = 31$) or PE ($n = 30$). All 61 patients received 5 treatments of PE or IA as intended by study protocol and were included in the intention-to-treat analysis. The study cutoff date (i.e., the last patient's visit) was January 25, 2019.

3.2. Baseline characteristics

Baseline characteristics of both study groups were similar (Table 1); both groups of patients were of similar age and functional status as measured by EDSS. The distribution of sexes and diagnoses (multiple sclerosis and clinically isolated syndrome) was equal. The latencies between onset of relapse and high-dose MP therapy as well as between onset of relapse and apheresis were similar in both groups. There was also no difference with regard to number of MP cycles and total MP dosage.

3.3. Primary outcome

The primary efficacy endpoint at the end of the study showed a significantly larger improvement of MSFC ($p = 0.034$) in the IA group (0.385 [0.200–0.675]) compared to PE (0.265 [0.100–0.408]; Fig. 2).

Table 1
Patient characteristics at baseline (intention-to-treat population).

	Immunoadsorption ($n = 31$)	Plasma exchange ($n = 30$)
Age, years	40.1 (33.7–50.8)	37.5 (30.1–41.0)
Sex		
- female	23 (74.2%)	18 (60.0%)
- male	8 (25.8%)	12 (40.0%)
EDSS	3.0 (2.0–4.0)	3.0 (2.0–3.5)
Diagnosis		
- multiple sclerosis	21 (67.7%)	20 (66.7%)
- clinically isolated syndrome	10 (32.3%)	10 (33.3%)
Symptoms		
- motor	8 (25.8%)	8 (26.7%)
- sensory	18 (58.1%)	11 (36.7%)
- visual	13 (41.9%)	16 (53.3%)
- cerebellar	1 (3.2%)	4 (13.3%)
- brainstem	1 (3.2%)	2 (6.7%)
Latency between relapse and apheresis, days	43.0 (31.0–70.0)	40.0 (32.0–54.8)
Latency between high-dose MP therapy and apheresis, days	33.0 (22.0–55.0)	29.5 (18.8–42.3)
Number of high-dose MP cycles		
- 1 cycle	15/31 (48.4%)	17/30 (56.7%)
- 2 cycles	13/31 (41.9%)	13/30 (43.3%)
- >2 cycles	3/31 (9.7%)	0/30 (0.0%)
Total dosage MP, gram	9.5 ± 4.6	8.3 ± 4.4
Treated plasma volume per treatment	2.5 fold (day 1) 2.0 fold (day 2–5)	0.69 ± 0.12 fold (day 1–5)

Data are median (interquartile range), mean ± SD, or n (%). EDSS=Expanded Disability Status Scale. MP=methyl-prednisolone.

The median difference in the primary endpoint between IA and PE was 0.160 [0.020–0.310].

The median MSFC in the IA group increased from 0.09 [IQR −0.19–0.39] at baseline to 0.63 [IQR 0.21–0.90] after 4 weeks. The median MSFC in the PE group increased from 0.22 [IQR −0.27–0.55] at baseline to 0.57 [IQR 0.15–0.82] after 4 weeks (Fig. 3, Table 2). Improvement in MSFC score occurred later in the IA group compared to the PE group, i.e. the MSFC score directly after apheresis (V1) already showed a significant improvement in the PE group, but not in the IA group (Fig. 3, Table 2). Response rates directly after intervention (V1)

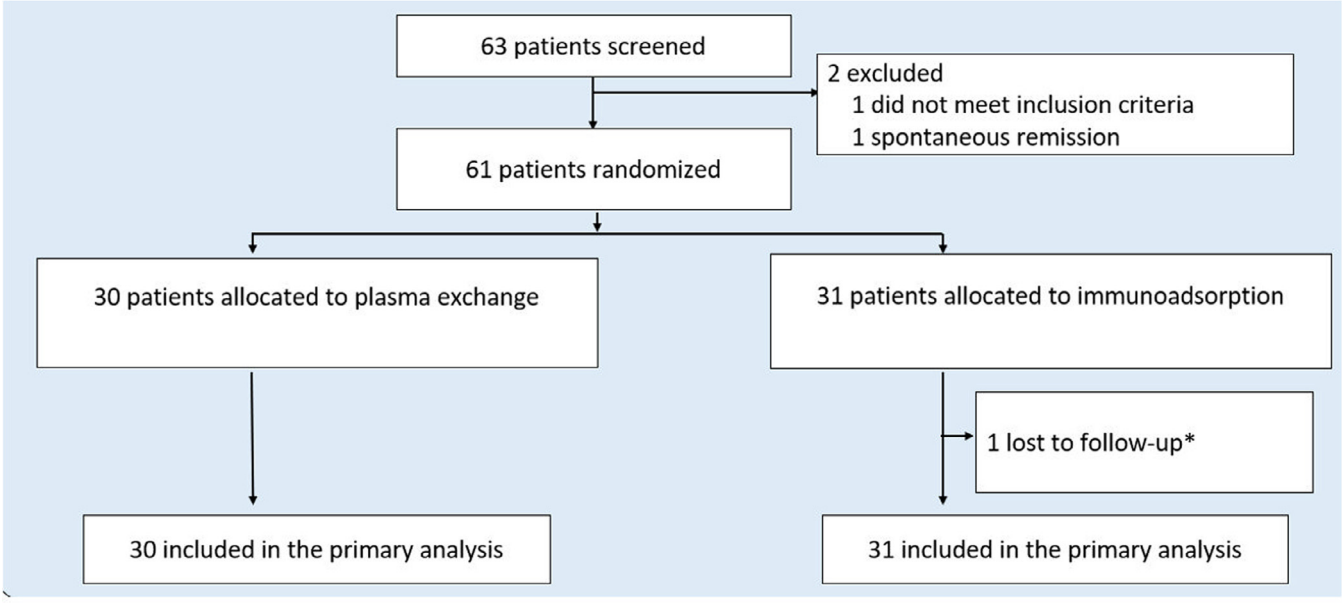

Fig. 1. Trial profile.
* One patient was lost to follow-up; this patient was included in ITT analysis, but one more patient was recruited for this treatment arm in order to obtain the required number of patients according to power calculation for primary endpoint analysis.

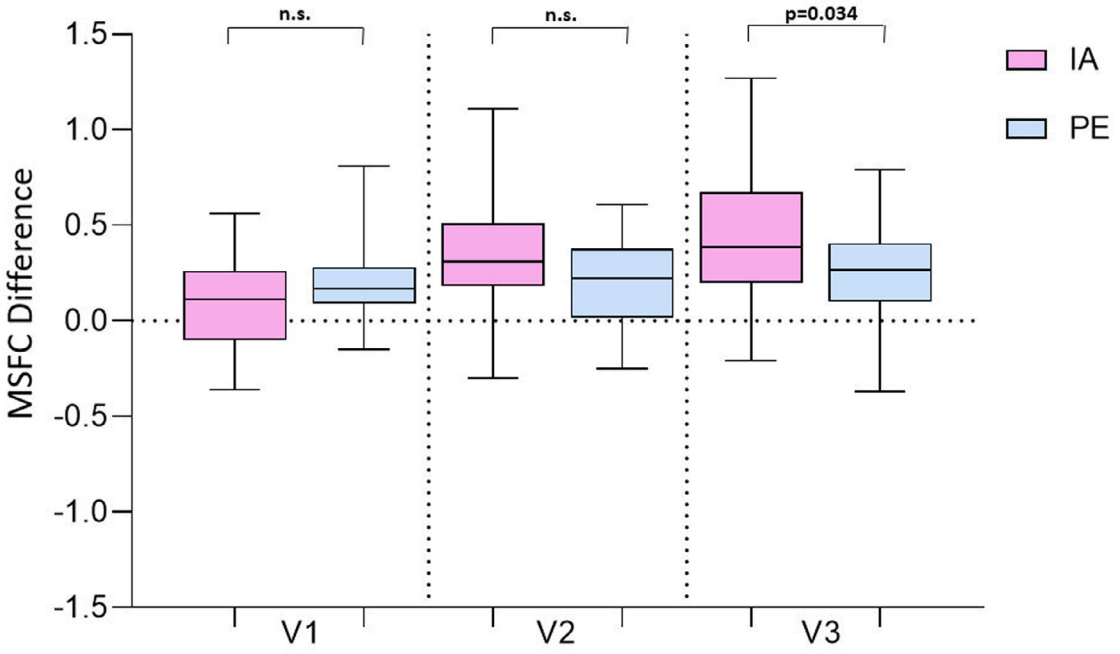

Fig. 2. MSFC difference to baseline in intention-to-treat population.
IA=immunoadsorption. PE=plasma exchange. V1=directly after apheresis. V2=2 weeks after apheresis. V3=4 weeks after apheresis. MSFC=Multiple Sclerosis Functional Composite.

were 61.3% in the IA group and 86.7% in the PE group, which was significantly different ($p = 0.024$; Fig. 3, Table 2). However, IA patients showed further improvement up to 4 weeks after intervention, while PE patients did not. Moreover, 4 patients in the PE group had a secondary worsening of symptoms between V1 and V3, but none of the IA-treated patients. Response rates 4 weeks after intervention (V3) were 86.7% in the IA group and 76.7% in the PE group (Fig. 3, Table 2).

3.4. Secondary outcomes

Similar to the primary endpoint, secondary efficacy endpoints also generally showed earlier improvements in the PE group, but more sustainable and larger long-term improvements in the IA group. In the PE group, significant improvements compared to baseline were present for EDSS and quality of life at all visits, no significant improvements were found for vision, SDMT, and VLMT. In the IA group, significant improvements compared to baseline were present for EDSS, quality of life, vision, and SDMT after 2 and 4 weeks (V2 +V3), no significant improvement was found for VLMT. As opposed to PE, there was no significant improvement for any secondary endpoint in the IA group directly after intervention (V1). Improvements in the IA group compared to PE after 4 weeks were significantly larger for SDMT. Improvements in other secondary endpoints after 4 weeks were generally larger in the IA group as well, but not statistically significant (Table 2).

3.5. Target engagement

Immunoglobulins were significantly reduced in both treatment arms as measured by serum analysis directly after the last treatment compared to baseline (Fig. 4). In the PE group, reduction rates were 85.0% [IQR 81.9–87.4] for IgG, 83.1% [IQR 80.2–85.2] for IgA, and 80.8% [IQR 67.2–86.0] for IgM. In the IA group, reduction rates were 96.0% [IQR 95.0–96.9] for IgG, 61.6% [IQR

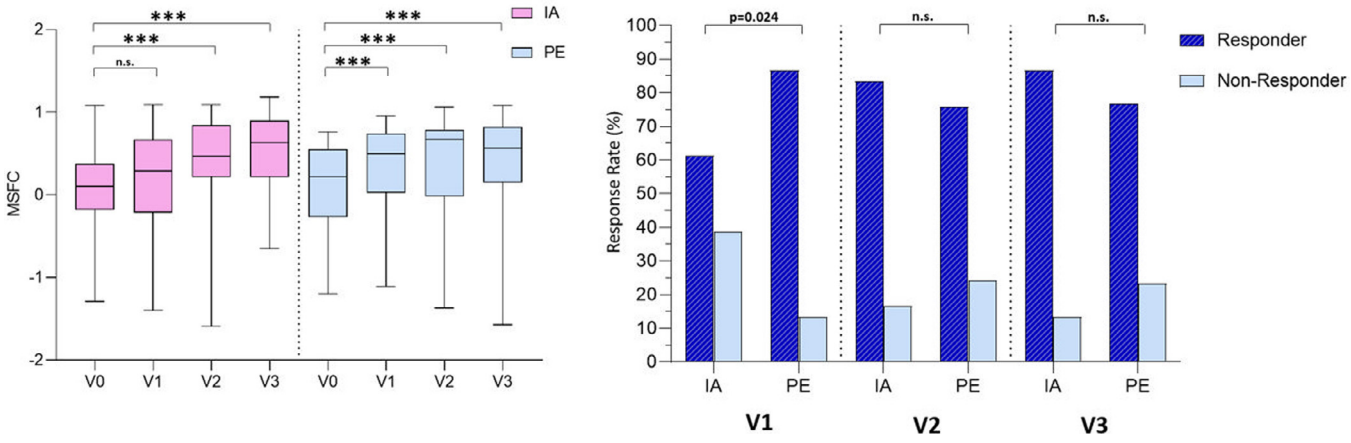

Fig. 3. Development of MSFC (left) and response rates (right) in intention-to-treat population.
IA=immunoadsorption. PE=plasma exchange. V0=baseline. V1=directly after apheresis. V2=2 weeks after apheresis. V3=4 weeks after apheresis. $p < 0.001$. n.s.=not significant.

Table 2
Primary and secondary outcomes.

	Immunoadsorption				Plasma exchange				p value (IA vs. PE, change from V0 to V3)
	V0	V1	V2	V3	V0	V1	V2	V3	
Primary outcome									
MSFC	0.09 [−0.19−0.39]			0.63 [0.21−0.90] ***p* < 0.001**	0.22 [−0.27−0.55]			0.57 [0.15−0.82] ***p* < 0.001**	**0.034**
Secondary outcomes									
MSFC	0.09 [−0.19−0.39]	0.29 [−0.22−0.67] *p* = 0.071	0.47 [0.22−0.84] ***p* < 0.001**		0.22 [−0.27−0.55]	0.50 [0.02−0.74] ***p* < 0.001**	0.67 [−0.02−0.79] ***p* < 0.001**		
25FTW	−0.44 [−0.48−0.36]	−0.41 [−0.45−0.33] *p* = 0.17	−0.41 [−0.45−0.35] *p* = 0.46	−0.43 [−0.46−0.37] *p* = 0.56	−0.41 [−0.48−0.31]	−0.43 [−0.49−0.35] *p* = 0.34	−0.44 [−0.48−0.40] *p* = 0.91	−0.41 [−0.48−0.36] *p* > 0.99	0.279
9HPT	0.56 [−0.16−1.04]	0.57 [−0.08−0.94] *p* = 0.90	0.88 [0.28−1.29] ***p* = 0.01**	0.73 [0.16−1.08] *p* = 0.12	0.37 [−0.13−0.86]	0.62 [−0.22−1.17] ***p* = 0.04**	0.57 [−0.26−1.28] ***p* < 0.001**	0.50 [0.14−0.98] ***p* = 0.008**	0.808
PASAT	−0.50 [−1.07−0.25]	0.16 [−1.08−0.83] ***p* = 0.02**	0.61 [−0.373−1.09] ***p* < 0.001**	0.74 [0.00−1.18] ***p* < 0.001**	0.00 [−0.79−0.51]	0.58 [−0.09−0.91] ***p* < 0.001**	0.58 [0.04−1.16] ***p* < 0.001**	0.78 [0.00−1.07] ***p* < 0.001**	**0.029**
Response rate (%)		61.3	83.3	86.7		86.7	75.9	76.7	0.317
EDSS	3.0 [2.0−4.0]	3.0 [2.0−4.0] *p* = 0.250	2.0 [1.4−3.1] ***p* < 0.001**	2.0 [1.0−3.1] ***p* < 0.001**	3.0 [2.0−3.5]	3.0 [1.5−3.5] ***p* = 0.031**	2.0 [1.3−3.5] ***p* = 0.002**	2.0 [1.0−3.5] ***p* < 0.001**	0.814
Vision (%, number of affected eyes)	45 [10−90] *n* = 18	55 [18−83] *p* = 0.625	80 [35−93] ***p* = 0.027**	83 [53−96] ***p* = 0.008**	60 [20−85] *n* = 19	80 [20−90] *p* = 0.094	75 [23−90] *p* = 0.225	80 [30−95] *p* = 0.155	0.344
Vision (%, affected eyes)	45 [10−90] *n* = 14	55 18−83] *p* = 0.625	80 [35−93] ***p* = 0.027**	85 [45−98] ***p* = 0.010**	60 [20−85] *n* = 19	80 [20−90] *p* = 0.094	75 [23−90] *p* = 0.241	80 [30−95] *p* = 0.164	0.344
Quality of Life	65.0 [50.0−80.0]	70.0 [50.0−80.0] *p* = 0.502	80.0 [58.8−86.3] ***p* = 0.025**	80.0 [57.5−90.0] ***p* = 0.003**	63.5 [49.8−80.0]	70.0 [50.0−82.8] ***p* = 0.013**	70.0 [46.5−85.0] ***p* = 0.019**	71.0 [60.0−85.0] ***p* < 0.001**	0.701
SDMT	49.5 [45.5−57.8]			57.5 [48.8−67.0] ***p* < 0.001**	52.0 [38.0−60.5]			52.0 [43.8−65.3] *p* = 0.154	**0.019**
VLMT	55.0 [49.0−63.0]			59.0 [50.8−65.3]	52.0 [44.5−57.5]			57.5 [45.5−62.3]	*p* > 0.05
- Dg 1−5	11.0 [9.0−13.0]			11.0 [10.0−13.5]	10.0 [8.0−12.3] 11.0			11.0 [7.8−14.0] 11.5	
- Dg 6	13.0 [10.0−14.0]			12.5 [11.0−15.0]	[8.0−13.0] 14.0			[8.0−14.0] 13.0	
- Dg 7	14.0 [13.0−15.0]			14.0 [13.0−15.0]	[11.0−15.0]			[11.8−15.0] *p* > 0.05	
- W-F				*p* > 0.05					

Data are median (IQR). IA=immunoadsorption. PE=plasma exchange. V0=baseline. V1=directly after last apheresis. V2=2 weeks after apheresis. V3=4 weeks after apheresis. MSFC=Multiple Sclerosis Functional Composite. EDSS=Expanded Disability Status Scale. 25FTW=25-Foot Walk. 9HPT=9-Hole Peg Test. PASAT= Paced Auditory Serial-Addition Task. SDMT=Symbol Digit Modalities Test. VLMT=Verbaler Lern- und Merkfähigkeitstest. P-values in right column refer to PE vs. IA (changes to baseline at V3). Other p-values refer to change to baseline for respective treatment and visit.

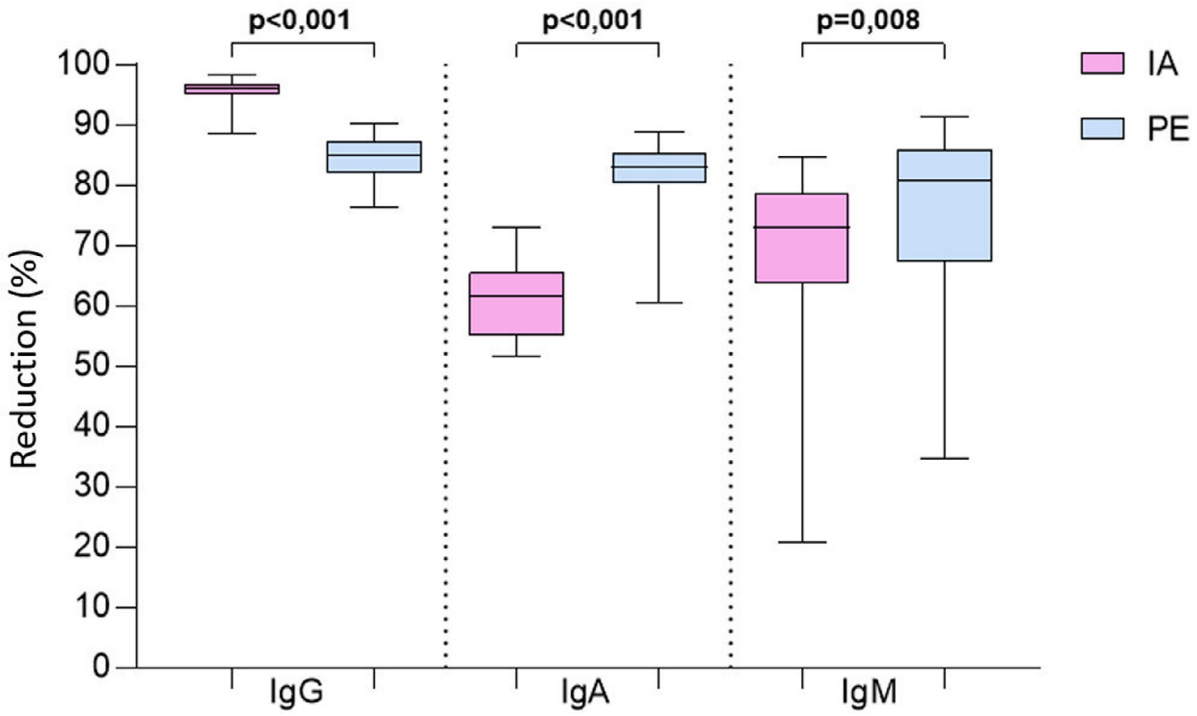

Fig. 4. Reduction rates of immunoglobulins.
IA=immunoadsorption. PE=plasma exchange. Ig=immunoglobulin.

55.0–65.6] for IgA, and 73.0% [IQR 63.7–78.6] for IgM. Therefore, reduction rates were about equal for each subclass in PE, while in IA reduction of IgG was considerably larger than reduction of IgA and IgM. Comparing both treatments, PE patients showed a significantly larger reduction of IgA ($p < 0.001$) and IgM ($p = 0.008$) compared to IA, while IA patients showed a significantly larger reduction of IgG ($p < 0.001$).

3.6. Tolerability

Both treatments were generally well tolerated (Table 3). One deep venous thrombosis occurred in each group with uncomplicated recovery under oral anticoagulation. There were 5 mild infections in the PE group, and none in the IA group. On the other hand, 4 mild allergic reactions in terms of skin reactions were observed in the IA group, and none in the PE group. Other adverse events in both groups were unspecific and clinically not relevant. Laboratory analysis revealed anemia, thrombocytopenia, and hypoproteinemia as the most common side effects (Table 3). Anemia was more frequent in PE (50.0% vs. 25.8%) while thrombocytopenia was more frequent in IA (35.5% vs. 3.3%). Thrombocytopenia was mild in most cases (>100.000/μl), and pronounced in 3 cases (94.000/μl, 76.000/ μl, 70.000/ μl). Anemia and thrombocytopenia were asymptomatic in all cases. Frequency of hypoproteinemia was similar in PE and IA (63.3% vs. 61.1%). Although PE was performed on a daily basis, daily safety analysis of coagulation factors did not necessitate the substitution with FFPs or coagulation factors.

Table 3
Adverse events and laboratory changes.

	IA	PE	Total
Deep venous thrombosis	1 (3%)	1 (3%)	2 (3%)
Mild systemic infections	0	5 (17%)	5 (8%)
Vegetative symptoms (changes of blood pressure or heart rate)	3 (10%)	0	3 (5%)
gastrointestinal symptoms	4 (13%)	0	4 (7%)
Allergic skin reactions	4 (13%)	0	4 (7%)
Anemia	8 (26%)	15 (50%)	23 (38%)
Erythropenia	9 (29%)	12 (40%)	21 (34%)
Leukopenia	1 (3%)	3 (10%)	4 (7%)
Thrombocytopenia	11 (36%)	1 (3%)	12 (20%)
Hypokalemia	4 (13%)	1 (3%)	5 (8%)

Data are n (%). Table presents all adverse events that occurred in 3 (5%) or more patients (across both treatment groups) in the intention-to-treat population during the whole study.

4. Discussion

IA was hypothesized to be superior to PE in treatment of steroid-refractory relapses of multiple sclerosis and clinically isolated syndrome as it is a specific method which effectively and instantly removes immunoglobulins as a key element in pathogenesis of multiple sclerosis. Furthermore, IA was hypothesized to induce fewer side effects than PE since other plasma proteins are largely preserved, and no volume replacement solution is needed.

Analysis of the primary endpoint (change of MSFC after 4 weeks compared to baseline) revealed that both treatments induced a significant improvement of symptoms without any major complications, strongly suggesting that apheresis should be applied when impairing symptoms persist after intravenous high-dose MP therapy. The question whether an ultra-high-dose steroid therapy with increased dosage should be interpolated was outside the scope of this study.

Improvement of MSFC after 4 weeks (primary endpoint) was significantly larger in IA patients compared to PE. Furthermore, the IA group showed a higher response rate after 4 weeks (86.7% vs. 76.7%), no secondary worsening of symptoms (0 vs. 3 patients), and generally larger improvements of secondary efficacy endpoints. Moreover, a significant improvement of vision in patients with optic neuritis was present in the IA group, but not in the PE group. However, since it has been shown previously that patients with optic neuritis benefit from PE [29], the number of patients with optic neuritis in this study might be too small in order to demonstrate a significant effect in the PE group.

Of note, IA patients (but not PE patients) showed a significant improvement of the SDMT, a neuropsychological test which mainly relies on attention and concentration, as well as the PASAT, the neuropsychological subscore of the MSFC. Since training effects should be present in both groups, the difference may reflect an improvement of subclinical cognitive deficits in the IA group.

Interestingly, although the final outcome was better in IA, the onset of improvement was delayed as (opposed to PE) significant beneficial effects (measured by primary and secondary efficacy parameters) were not present directly after therapy (V1), but only at later visits (2 and 4 weeks after last treatment, V2+V3). Still, considering the stronger long-term effects, our results suggest a superior efficacy of IA compared to PE, which may be attributed to the higher reduction rate of IgG, but possibly also to the preservation of anti-inflammatory plasma proteins. Furthermore, secondary immune-modulating effects of IA like up- and downregulation of anti- and pro-inflammatory interleukins [30] have been described. Comparable data from other studies are missing, since this was the first study to directly compare both apheresis methods. Previously, retrospective case series had found similar response rates for PE and IA [25,31]. The delayed effect of IA compared to PE highlighted in this trial is a new finding, and the underlying immunological mechanisms need to be clarified in future studies.

Both methods were safe; only one serious event (deep venous thrombosis) without any long-term consequences occurred in each group. Importantly, other severe adverse events as described before [7,8] did not occur in PE. Five mild infections occurred in the PE group compared to none in the IA group which possibly reflects a more pronounced impairment of the immune system due to an unspecific removal of plasma constituents. On the other hand, IA patients more frequently showed mild allergic reactions ($n = 4$) and thrombocytopenia ($n = 11$), warranting clarification of etiology such as heparin application or protein A reinfusion. Importantly, all laboratory alterations were transient and clinically inapparent in all cases. Overall, both procedures showed about equal results in terms of tolerability.

Although reduction rates of IgG (and therefore possibly efficacy) in PE could be increased by removing higher plasma volumes as in this study, the incidence of side effects would most likely rise as well due to the increased loss of coagulation factors and other plasma proteins with the need to use fresh frozen plasma instead of human albumin as volume replacement solution and to prolong breaks between treatments.

As a limitation of this study the lack of blinding has to be mentioned. Furthermore, the number of subjects might be too small in order to detect potential differences in secondary outcome parameters. Therefore, the results should be confirmed by further studies. Furthermore, it has to be noted that we used two standard treatment schemes for IA and PE which reflect the advantages and disadvantages for both methods in clinical practice, i.e., larger amounts of blood plasma can be processed with IA in the same period of time. However, different schemes regarding frequency of treatment and amount of processed plasma volumes can be applied for both procedures and should be evaluated in future studies. Lastly, a potential learning effect in the MSFC cannot be ruled out, but this should affect both groups and does therefore not explain the observed differences.

In summary, both treatments showed high efficacy and good tolerability. Considering the superior efficacy of IA in this study, the results indicate that IA may possibly offer a better risk to benefit relation compared to PE in the treatment of steroid-refractory relapse in multiple sclerosis and clinically isolated syndrome.

Since non-medicamentous procedures and devices can be approved without evidence from RCTs in most countries, non-effective or even harmful treatments may have entered clinical practice. The results of this study highlight the importance to do RCTs not only for drugs, but also for non-medicamentous therapies.

Declaration of Competing Interest

JDo reports personal fees and research grants from Fresenius Medical Care GmbH, Fresenius Medical Care Deutschland GmbH and Miltenyi Biotec GmbH.

MS has received consulting or speaker honoraria as well as travel reimbursements from Bayer, Biogen, Celgene, Roche, Sanofi Genzyme and TEVA and research funding from the Hertha-Nathorff-Program and University of Ulm, none related to this study.

HT reports personal fees and/or research grants from Fresenius Medical Care GmbH and Fresenius Medical Care Deutschland GmbH, Bayer, Biogen, Merck, Mylan, Novartis, Roche, Sanofi-Genzyme, Teva, DMSG, and BMBF.

DT has received speaker honoraria from Sanofi-Genzyme and Novartis, as well as travel and accommodation reimbursements from Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, and TEVA, none related to this study.

TF, PE, JDr, SM, JS, and ACL report no conflicts of interest.

CRediT authorship contribution statement

Johannes Dorst: Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Tanja Fangerau:** Investigation, Data curation, Writing - review & editing. **Daniela Taranu:** Investigation, Data curation, Writing - review & editing. **Pia Eichele:** Formal analysis, Data curation, Writing - review & editing. **Jens Dreyhaupt:** Data curation, Writing - review & editing. **Sebastian Michels:** Data curation, Writing - review & editing. **Joachim Schuster:** Data curation, Writing - review & editing. **Albert C Ludolph:** Data curation, Writing - review & editing. **Makbule Senel:** Data curation, Writing - review & editing. **Hayrettin Tumani:** Data curation, Writing - review & editing.

Acknowledgments

We thank the study patients for their willingness to participate in the study and all participating staff for their excellent work. The study was financed by Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany.

Data sharing

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, and figures), as well as the study protocol will be available. Data will be available beginning 3 months and ending 5 years following article publication. Data will be shared with researchers who provide a methodologically sound proposal. Data will be shared for analyses to achieve the aims in the approved proposal. Proposals should be directed to johannes.dorst@uni-ulm.de; to gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at https://www.uniklinik-ulm.de/neurologie.html.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2019.10.017.

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