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Immunoadsorption with Regenerating Columns in Treatment of Steroid-Refractory Relapse in Multiple Sclerosis and Optic Neuritis

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Abstract

Objective: Immunoadsorption (IA) is increasingly recognized as a promising and low-risk therapy option in a variety of autoimmune neurologic disorders. Along with plasma exchange (PE) it is considered as a second line therapy in multiple sclerosis (MS) and optic neuritis (ON) and usually regarded as a therapy option in case of steroid-refractory relapse in most guidelines. However, systematic prospective data is missing, especially regarding modern efficient adsorber systems with regenerating columns. The aim of this study was to provide efficacy and tolerability data in patients with steroid-refractory multiple sclerosis and optic neuritis.

Methods: We prospectively investigated the clinical course of 25 patients with steroid-refractory relapse of MS or ON who were treated with IA using regenerating protein A columns. IA was performed on 5 consecutive days, and 2- to 2.5-fold plasma volumes were processed each day. As objective outcome parameters, Expanded Disability Status Scale (EDSS) and visual acuity measurement were conducted before as well as on day 5 of IA and 14 days after treatment. Additionally, adverse events and laboratory data were collected.

Results: After 14 days, mean EDSS improved from 3.4 ± 2.0 to 2.3 ± 2.0 (p=0.001), and visual acuity improved from 0.39 ± 0.33 to 0.66 ± 0.36 (p=0.01). Response rate was 64%. No relevant adverse events were observed. IA was effective even in patients with long latency since relapse, defined as a time of >6 weeks between first symptoms and treatment.

Interpretation: Our data provide preliminary evidence that immunoadsorption with regenerating columns is an effective and well-tolerated treatment option for steroid-refractory MS and ON and might even be considered for patients with long latency since relapse. However, our results have to be confirmed by a randomized controlled trial with a higher number of subjects, and additional studies are needed to compare efficacy of IA and PE.

Keywords: Multiple sclerosis; Optic neuritis; Immunoadsorption; Plasma exchange; Efficacy; Tolerability; EDSS

Introduction

Extracorporal apheresis procedures like plasma exchange (PE) and immunoadsorption (IA) are increasingly recognized as useful therapeutic options for a variety of acute and chronic auto-immunologic disorders like multiple sclerosis (MS), Guillain-Barré, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, or autoimmune encephalitis. Postulated mechanisms of action include direct removal of auto-antibodies, induction of antibody redistribution, and immunomodulatory changes [1].

In PE, which is still the most common method, plasma is separated from corpuscular blood components and replaced by a substitution fluid; therefore removal of plasma proteins is unspecific. In IA, plasma components are separated by adsorber systems, which are designed to selectively bind immunoglobulins, although studies have shown that other substrates like complement factors or fibrinogen are removed as well to a lesser extent [2-4]. However, preservation of plasma proteins like albumin or coagulation factors as well as lower shift of blood volumes during the procedure are generally regarded as advantages of IA over PE. Accordingly, IA is generally described as a well-tolerated therapy with little adverse events. Moreover, due to preservation of plasma proteins, IA can usually be performed with higher frequency, and larger blood volumes can be processed, leading to highly effective removal of immunoglobulins.

Several different adsorbers like tryptophan, protein A, or polyclonal sheep antibodies can be used for IA. Most existing data refers to single use tryptophan adsorbers which are less selective for immunoglobulins and limited by their adsorbing capacity. Adsorbers with protein A or sheep antibodies offer the advantage of more selective removal of immunoglobulins as well as a regenerating mechanisms which allow multiple uses of each column, resulting in larger blood volumes which can be processed. Modern systems contain 2 of those columns which undergo alternating loading and regeneration cycles, therefore saving time for even larger blood volumes to be processed (Figure 1).

While in most existing studies with non-regenerating tryptophan adsorbers blood volumes of about 2 L were processed in each IA session, regenerating adsorbers allow 2-fold to 2.5-fold overall plasma volumes to be treated, equivalent to about 5 liters for a man with a body weight of 70 kg.

Since reduction of immunoglobulins correlates directly to the amount of treated plasma volume, highly effective removal rates of 72% to 87% for immunoglobulin G, and lower, but still relevant rates of 56% for immunoglobulin A and 46% for immunoglobulin M have been reported. Although removal of immunoglobulins seems promising from a pathophysiological point of view, there is little evidence regarding clinical efficacy of IA with regenerating systems for specific neurological diseases [5,6]. The only study including a total number of 16 patients did not report any objective outcome parameters, and

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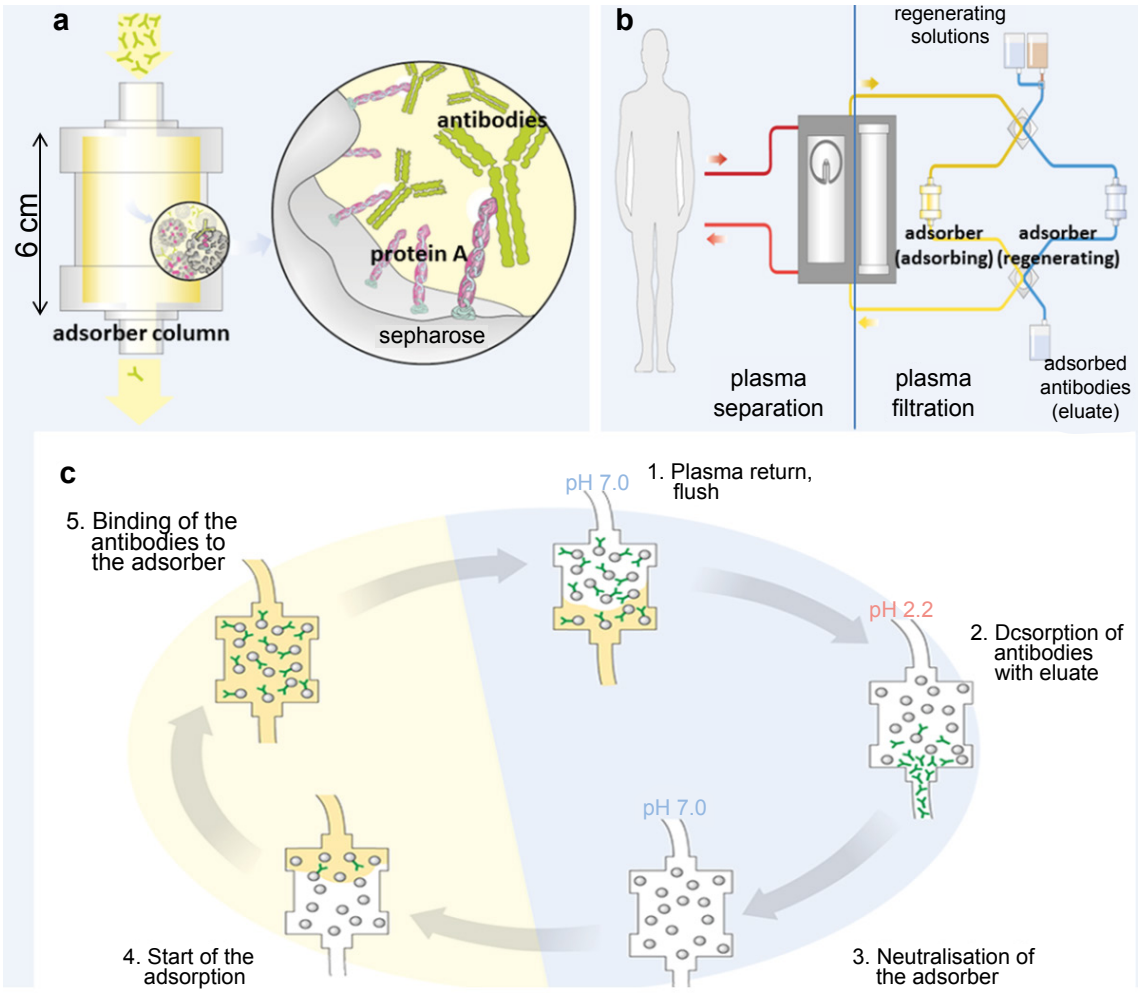

Figure 1: Principle of IA with regenerating columns.
a: IA of immunoglobulins by protein A, fixed in sepharose gel, **b:** Blood is separated in cells and plasma (left); plasma is filtered (right) in one adsorber column, while the other, **c:** column is regenerated by regenerating solution; columns alternate between adsorbing and regenerating cycles Adsorbing (yellow) and regenerating (blue) cycle of adsorber column.

number of cases for specific disorders was too low to demonstrate statistical significances [5]. The aim of this prospective and systematic study was to provide efficacy and tolerability data in patients with steroid-refractory MS and optic neuritis (ON) which could serve as basis for future randomized controlled studies.

Methods

Study design and participants

Between 07/2013 and 01/2016 a total of 25 patients aged 32.8 ± 13,5 with steroid-refractory MS and ON were recruited into the study. All patients fulfilled diagnostic criteria of relapsing-remitting MS or clinically isolated syndrome (CIS) as well as definition for relapse [7]. There was no restriction regarding time interval since occurrence of actual relapse. All patients had received treatment with high-dose intravenous steroids with 1000 mg methyl-prednisolone for 5 days. We also included patients who received a second treatment cycle of 2000 mg methylprednisolone for 5 days. "Steroid-refractory" was defined as residual, clinically relevant deficit after steroid therapy with an EDSS score of at least 1.0. Demographic and clinical characteristics of included patients are presented in (Table 1). Patients with clinically relevant infection were excluded.

The authors are treating physicians of the included patients and have access to identifying patient information. The study was purely observational, meaning that no additional invasive or non-invasive procedures were applied and treatment was performed in concordance with current national guidelines of MS and CIS, therefore representing standard care. The study itself comprises systematic and standardized data collection as well as statistical analysis. All patients who fulfilled the inclusion criteria above have been included, regardless of their clinical outcome (Table 1).

Procedures and outcomes

IA was performed on 5 consecutive days using an adsorber system (ADAsorb, medicap clinic GmbH, Ulrichstein, Germany) with regenerating protein A columns (Immunosorba, Fresenius Medical Care, Bad Homburg, Germany) as described above. Protein A is a cell wall protein from *Staphylococcus aureus* which selectively binds human immunoglobulins. Patient's 2-fold overall plasma volume as calculated on the basis of body weight was processed on the first day and 2.5-fold plasma volume was processed on day 2-5. In order to process such high blood volumes in acceptable time frames, a central nervous catheter in the jugular vein was placed in each patient. Heparin and citrate were used as anticoagulants. Since citrate decreases serum calcium levels which

Patient No.	Age	Sex	Diagnosis	2nd cycle of MP (UHD)	Latency (days)	EDSS before IA	EDSS day 5 of IA	EDSS 2 weeks after IA
1	15	F	ON	No	15	5.0	5.0	0.0
2	44	F	ON	Yes	116	2.0	0.0	0.0
3	54	F	ON	No	26	4.0	1.0	1.0
4	21	M	MS	No	25	2.0	2.0	2.0
5	48	M	MS	No	157	3.0	3.0	2.0
6	24	F	MS	No	15	3.5	2.0	3.5
7	17	F	ON	No	28	1.0	1.0	0.0
8	29	F	MS	Yes	135	1.0	1.0	1.0
9	36	F	MS	No	28	1.0	1.0	0.0
10	56	M	ON	No	46	4.0	4.0	5.0
11	23	F	MS	Yes	55	6.0	6.0	3.0
12	26	F	MS	Yes	90	2.5	2.5	1.0
13	20	F	ON	No	19	4.0	2.0	2.0
14	23	F	ON	Yes	31	2.0	1.0	1.0
15	15	M	MS	No	26	3.5	3.0	2.0
16	16	F	ON	Yes	70	1.0	1.0	1.0
17	46	F	MS	No	33	4.5	4.5	4.5
18	56	F	MS	No	134	4.5	4.5	4.5
19	37	M	MS	No	103	6.0	5.5	5.0
20	47	F	ON	Yes	145	2.0	2.0	1.0
21	24	F	ON	Yes	69	1.0	1.0	1.0
22	42	F	ON	No	15	4.0	4.0	2.0
23	43	F	MS	No	28	9.5	9.0	8.0
24	28	F	ON	Yes	51	4.0	4.0	2.0
25	29	M	ON	No	78	5.0	5.0	5.0
Mean ± SD	32.8 ± 13.5				61.6 ± 45.8	3.4 ± 2.0	3.0 ± 2.1	2.3 ± 2.0

Latency indicates the time span from first symptoms of relapse to start of IA therapy; MS: Multiple Sclerosis; ON: Optic Neuritis; MP: Methyl Prednisolone; UHD: Ultra-High Dose (2 g methyl-prednisolone/day for 5 days).

Table 1: Demographic data and clinical characteristics of subjects.

might result in paresthesia, serum calcium levels were continuously monitored during IA and calcium was substituted when necessary. No prophylactic antibiotics were given, and immunoglobulins were not substituted after therapy.

Although IA and PE are recommended therapies in steroid-refractory relapse according to current national guidelines, we carefully monitored patients before, during, and after IA because of the procedure`s innovative nature. Laboratory data (blood count, coagulation, electrolytes and C-reactive protein) were collected before and daily during IA to control for infections, coagulation disorders and electrolyte disturbances. Urinary tract infection was ruled out before IA by urinary status. During IA, heart rate, blood pressure, respiratory frequency, and oxygen saturation were continuously monitored. Patients stayed in hospital during IA sessions, which were conducted in the apheresis center of our Neurological Department.

Statistical analysis

Standardized outcome parameters were collected in hospital before (day 0) and last day of IA treatment (day 5) as well as 14 days after last IA session (day 19) in our outpatient clinic. EDSS was measured by a certified investigator. Visual acuity was measured by an ophthalmologist. Adverse events were recorded by anamnesis, clinical examination and monitoring data as described above.

To compare outcome parameters before and after IA, Wilcoxon test was used. All data is given as mean ± standard deviation. Level of significance was set at p=0.05. For statistical analyses, SPSS Statistics 21 (IBM) was used.

Results

General findings

A total number of 25 patients (6 male, 19 female) with steroid-refractory relapse of MS (N=12) or ON (N=13) were treated by IA between 07/2013 and 01/2016 and therefore included in the study. Age of patients was between 15 and 56 years (32.8 ± 13.5).

Latency since actual relapse ranged from 15 to 157 days (61.6 ± 45.8), and latency since last administration of intravenous methyl-prednisolone ranged from 6 to 152 days (42.6 ± 40.7). All patients had received 1000 mg methyl-prednisolone for 5 days, and 9/25 patients (36%) had received 2000 mg methyl-prednisolone for 5 days additionally. One patient had been treated with 2 cycles of plasma exchange.

Adverse events

No serious adverse events occurred. Minor, transient side effects included mild edema (N=4), palpitations (N=2), flush (N=1), and taste disturbance (N=1). Laboratory abnormalities were transient and asymptomatic. Most common were leukopenia (16%), anemia (20%), thrombopenia (48%), hypokalemia (28%), and hypoproteinemia (72%). Decreases of leukocytes and erythrocytes were mild in all cases, but thrombocytes showed significant decreases up to 50% in some cases. In case of hypokalemia and hypoproteinemia, we substituted potassium and protein. In 2 cases we found marginal increases of C-reactive protein and leukocytes, without clinical signs of infection and without need of antibiotic therapy. No relevant changes of heart

rate, blood pressure, respiratory frequency, or oxygen saturation were recorded during IA sessions.

Efficacy

Overall, EDSS improved significantly from 3.4 ± 2.0 before IA to 3.0 ± 2.1 (p=0.011) directly after IA and further to 2.3 ± 2.0 (p=0.001) 2 weeks after IA (Figure 2 and Table 1).

In the MS subgroup, EDSS improved from 3.9 ± 2.4 before IA to 3.7 ± 2.3 (p=0.059) directly after IA and further to 3.0 ± 2.2 (p=0.016) 2 weeks after IA. In the ON subgroup, visual acuity improved from 0.39 ± 0.33 before IA to 0.53 ± 0.36 (p=0.042) directly after IA and further to 0.66 ± 0.36 (p=0.01) 2 weeks after IA (Figure 3).

EDSS improved from 3.0 ± 1.5 before IA to 2.4 ± 1.8 (p=0.066) directly after IA and further to 1.6 ± 1.7 (p=0.01) 2 weeks after IA in this subgroup. In the subgroup of patients with short latency since relapse (defined as time span of less than 6 weeks between first symptoms of actual relapse and begin of IA), EDSS improvement (from 3.7 ± 2.3 before IA to 2.2 ± 2.3 after 2 weeks; p=0.007) was larger than in the subgroup of patients with long latency (from 3.2 ± 1.8 before IA to 2.4 ± 1.8 after 2 weeks), but improvement in the long-latency group was still significant (p=0.028, Figure 4).

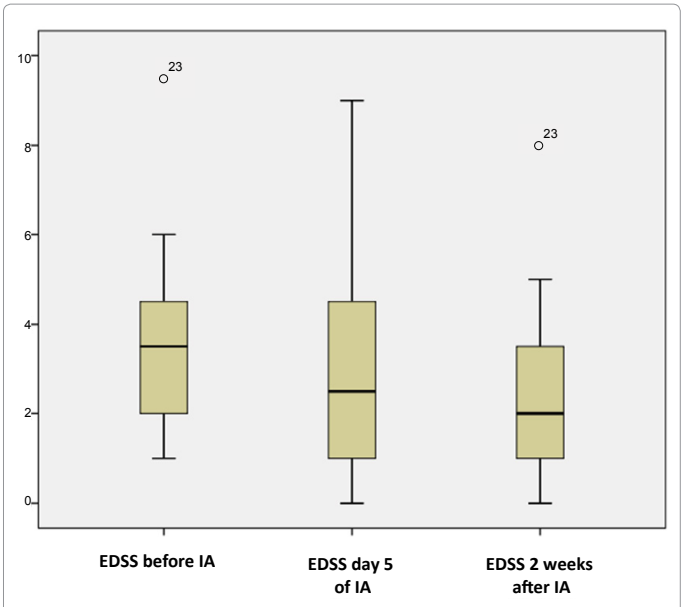

Figure 2: EDSS in all patients. EDSS before IA (left), directly after IA (middle), and 2 weeks after IA (right).

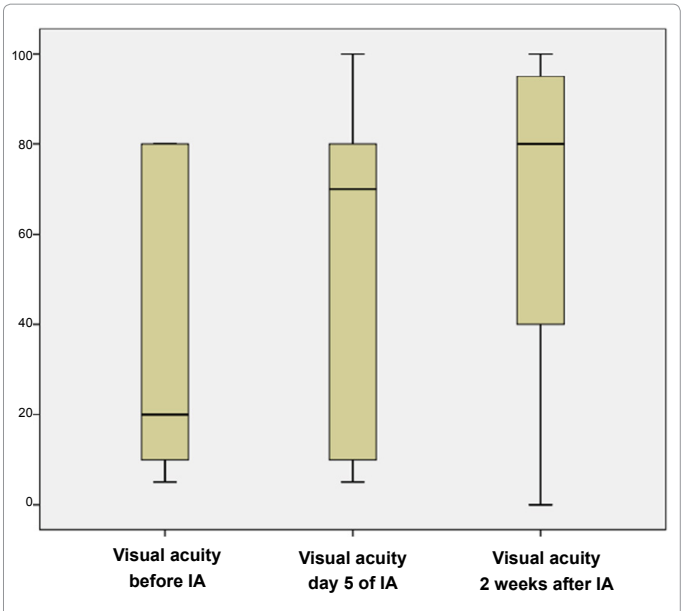

Figure 3: Visual acuity in patients with ON Visual acuity in ON subgroup before IA (left), directly after IA (middle), and 2 weeks after IA (right).

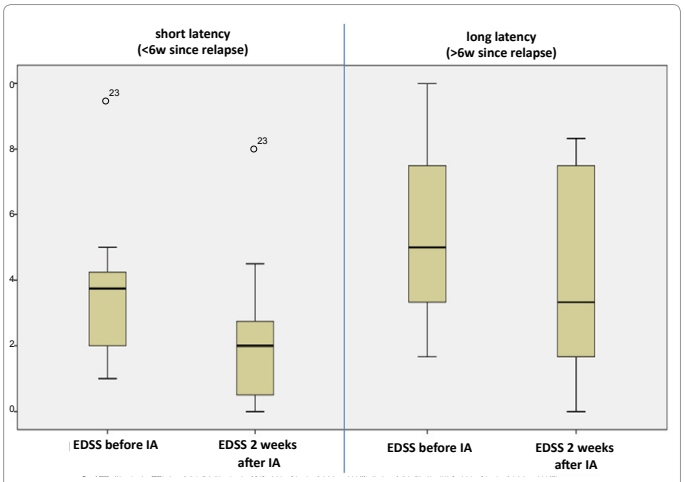

Figure 4: EDSS and latency since relapse EDSS in subgroup of patients with short latency since relapse (left; ≤ 6 weeks between first symptoms of actual relapse and start of IA) and in subgroup of patients with long latency (right; >6 weeks between first symptoms of actual relapse and start of IA).

Patients who had received ultra-high dose prednisolone (2 g for 5 days) in addition to high dose prednisolone (1 g for 5 days) improved from 2.4 ± 1.7 to 1.2 ± 0.8 (p=0.027) in EDSS, patients who had received high dose prednisolone alone improved from 4.0 ± 2.0 to 2.9 ± 2.3 (p=0.007).

Overall response rate (defined as improvement of at least 0.5 points in EDSS) was 64% (58.3% in the MS subgroup and 69.2% in the ON subgroup).

Discussion

Strengths and limitations

Although IA is increasingly recognized as a well-tolerated, low risk therapy option for a wide range of autoimmune neurologic disorders, systematic prospective data regarding tolerability and efficacy for specific disease entities are missing. Furthermore, most studies investigating IA used non-regenerating tryptophan adsorbers which are limited by their adsorbing capacity leading to lower blood volumes which could be processed. Because of low evidence, IA remains a second-line therapy for most neurologic disorders. In MS and ON, most national and international guidelines consider IA along with PE as therapy option in case of steroid-refractory relapse. The major strength of this study is that it offers systematic prospective efficacy and tolerability data for IA with regenerating columns for a specific neurological disease for the first time, using objective measurements and uniform treatment protocols. Main limitations of this study are absence of a randomized controlled design and limited number of outcome parameters available. Therefore results have to be considered as preliminary and are meant to support realization of a randomized controlled multi-center study with a larger number of subjects.

Tolerability

In agreement with all existing studies so far, we found that IA was very well tolerated with no serious adverse events occurring [5,6,8-11]. Most notably, paresthesia due to calcium loss related to anticoagulation with citrate as reported before could be avoided in all cases by frequent serum calcium controls and substitution [5].

As in the study by Hohenstein et al, no clinically relevant infection during or after IA occurred; only 2 patients showed marginal increases of C-reactive protein and leukocytes [5]. No antibiotic treatment was necessary, and no prophylactic antibiosis or post-interventional substitution of immunoglobulins was given. Although IA is regarded as specific for immunoglobulins, previous studies have shown that other plasma components might be eliminated to a lesser extent as well. Zollner et al. [9] showed that fibrinogen was lowered during IA but, as in our study, no bleeding complications occurred. Apart from coagulation alterations which are directly related to anticoagulation with heparin and citrate during IA, we found significant decline of thrombocytes up to 50% in some patients. Since we also found decreases of erythrocytes and leukocytes to a lesser extent, we assume that a certain loss of cells during IA has to be taken into account due to mechanical damage and/or residuals in the tube system. In one patient, we considered heparin-induced thrombocytopenia type II (HIT II) due to significant loss of thrombocytes; in this case anticoagulation was switched from heparin to argatroban during IA without any problems. In context of HIT II it has to be considered that antibody diagnostics might be false-negative due to removal of antibodies during IA. However, on a clinical level no symptoms related to coagulation alterations were detected in any patient.

On a laboratory level, we also commonly detected hypokalemia and hypoproteinemia which could be substituted without problems. Especially substitution of proteins should be considered during IA to prevent edema, which still occurred in a minority of patients to a slight extent. Other minor and transient clinical symptoms included palpitations, flush, and taste alteration sporadically. It has also been reported that IA can be safely performed during pregnancy which is important since use of steroids is restricted in this situation [11].

Efficacy

We found that IA was effective in most patients. Overall, we found a highly significant (p=0.001) mean improvement of EDSS by 1.1 after 2 weeks and a response rate of 64%. Existing literature investigating efficacy of IA with regenerating columns in MS or ON is very limited. Hohenstein et al. [5] reported clinical improvement in 4 of 4 MS patients, but specific outcome parameters are not reported.

Studies which investigated the effect of non-regenerating tryptophan adsorber systems reported response rates between 66% and over 80% [8,10,12]. In this context inclusion criteria have to be considered. In our study, we included patients with very long latencies up to 157 days since relapse. More than 50% of our patients had a latency of >6 weeks, which was generally regarded as a time span after which PE is no longer effective while data for IA are missing in this regard [13]. Importantly, although IA was more effective in patients with short latency, we still found a significant improvement for patients with long latency as well. Despite of high share of patients with long latency since relapse in our study population we still found response rates in the range of existing literature referring to non-regenerating adsorbers. We therefore believe that IA with regenerating adsorbers might be more effective, although studies comparing both procedures are needed in this regard.

IA was almost equally effective in patients with MS and patients with ON who did not meet criteria for MS and were classified as CIS. In ON, mean visual acuity improved by 0.27 (p=0.01) after 2 weeks and response rate was 69% which is comparable to results of Koziolek et al. [3] who found an improvement of visual acuity of 0.32 after 3 days and a response rate of 73%. Again, long latencies since relapse in our study population have to be considered.

Importantly, although we found a clinically relevant and statistically significant effect at last day of IA already, main improvement occurred within the following 2 weeks according to our data. This is in agreement with existing literature which suggests that first clinical effects are commonly noted as soon as day 3 of IA and that improvement might continue after IA [3,8].

Another important question is whether or not patients who do not benefit from high dose prednisolone should receive a second cycle of prednisolone therapy with ultra-high dose (UHD, 2 grams per day for 5 days) first before considering IA. In this study we included patients with and without ultra-high dose prednisolone therapy and found significant effects for both subgroups.

There is little data addressing the question which method of apheresis should be preferred in steroid-refractory relapse. Although IA offers several advantages over PE as described above and generally higher response rates are reported, evidence level for PE is higher considering the existence of randomized controlled studies [14,15]. Studies which compare both methods directly are largely missing; Mühlhausen et al. [16] reported no significant differences between IA and PE in retrospective data of 140 patients, although further details are not given. Therefore a randomized prospective trial comparing IA and PE in steroid-refractory relapse is needed.

In summary, our study provides preliminary evidence that IA with regenerating columns is a well-tolerated, low-risk, and effective therapy option in steroid-refractory MS and ON. Our data suggest that IA should be considered even in patients with latencies >6 weeks since relapse. All results have to be confirmed by a randomized controlled study, which should also address the questions whether to prefer IA or PE and whether or not ultra-high dose steroid therapy should precede apheresis.

Summary

We believe that the following conclusions can be drawn from our data:

1. IA is very safe with no relevant adverse events or complications in our group of patients.
2. IA improved EDSS in MS and ON as well as visual acuity in ON.
3. Improvement was significant even in patients with very long latencies (>6 weeks) since relapse.
4. Therefore IA should be considered as therapy option for patients with steroid-refractory relapse, and further prospective studies are needed to decide if IA should be considered as first-line therapy.
5. Randomized controlled studies are needed to compare PE, IA, and UHD prednisolone in steroid-refractory relapse as well as different IA techniques.

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