

Low rate of infectious complications following immunoadsorption therapy without regular substitution of intravenous immunoglobulins

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Abstract

Introduction: Immunoadsorption (IA) is increasingly used instead of plasma exchange due to lower risk of side effects and a higher selectivity. As a consequence of the reduction of immunoglobulins (Ig), the rate of infectious complications might increase in those patients. We therefore aimed to investigate the infection rate following IA without intravenous IG (IVIG) substitution in our apheresis center, where patients do not receive IVIG on a regular basis.

Material and methods: We conducted a retrospective analysis of the IA treatments performed between 2010 and 2015 without IVIG substitution and collected data on patient age, diagnosis, number of IA treatments, serum levels of Ig, total protein, albumin, C-reactive protein (CRP) and infectious complications that occurred within 2 months after the IA treatment cycle.

Results: A total number of 52 patients (27 females) received at least 5 IA sessions using the following adsorbers: TheraSorb™-Ig (n = 3), TheraSorb™-Ig flex (n = 44), TheraSorb™ Ig pro (n = 1) and TheraSorb™-IgE (n = 5). The median number of treatment sessions was 8.8 [range 5–16], the median IgG reduction was 82 [11–99] %. Serum albumin was decreased by 8%. The median CRP levels remained normal until the end of therapy and within 2 months after that (3.10 and 4.30 mg/L respectively). Only 4 patients had infections (7.7%). Three of them received additional immunosuppressive therapy.

Conclusions: Immunoadsorption leads to a significant reduction of IgG. CRP as inflammatory marker is not affected. Even without substitution of IVIG the complication rate directly linked with IA is low and questionable.

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1. Introduction

Extracorporeal treatments became important tools in the therapy of diseases associated with pathogenic autoantibodies, mainly derived from the Ig subclass. Plasma exchange has been introduced in clinical practice more than 50 years ago and remains the most commonly used apheresis technique for a wide variety of autoimmune disorders. However, the necessity to substitute iso-oncotic fluid, mainly consisting either of albumin or fresh frozen

plasma and crystalloids, bears the risk of transmission of blood borne diseases, limits the exchanged plasma volumes, can cause fluid imbalance, coagulopathy, dilution thrombocytopenia and other undesirable effects of plasmapheresis [1]. In contrast, IA has a higher selectivity and overcomes a number of these specific risks.

Nowadays, IA as an extracorporeal treatment method is increasingly used instead of plasma exchange due to lower risk of side effects. Using highly specific adsorbers loaded with either immobilized sheep antigens against Ig [2], staphylococcal protein A [3], the synthetic peptide Gam 146 [4] or consisting of tryptophane, the selective removal of up to 90% of serum Ig with a single treatment session is

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possible. IA has shown the efficacy in a number of autoimmune disorders in neurology, hematology, nephrology, dermatology and others [5–16]. However, many issues on correlation of antibody titers reduction with disease symptoms, the effects on autoantibodies outside the vascular compartment, the possible influence on cytokines and other pathogenic mechanisms are not yet answered [1]. One of these open questions is the possible alteration/constraint of the immune system due to IA.

The efficacious depletion of immunoglobulins might increase the rate of infectious complications in those patients. Therefore, in many centers IVIG substitution is performed at the end of IA treatment cycles to compensate for this risk. We here aimed to investigate, whether patients have a high risk for infectious complications following IA treatment without IVIG substitution.

2. Material and methods

2.1. Participants and data collection

52 patients (27 females, median age 48 [7–89] years) who received IA without additional IVIG substitution between 2010 and 2015 at the Extracorporeal Treatment and Apheresis Center of the University Hospital Carl Gustav Carus in Dresden were included in the study. Data on patient age, diagnosis, number of IA treatments, levels of IgG, total protein, albumin, CRP and infectious complications that either occurred directly during the IA cycle or were reported during follow-up within two months were analyzed (see Table 1). Indications and patient numbers are given in Table 2.

2.2. Immunoabsorption

The daily therapeutic apheresis treatment was performed using reusable adsorber systems loaded with sheep-antigens directed against human Ig: TheraSorb™-Ig (n = 3), Ig flex (n = 44), Ig pro (n = 1) and the LIFE 18™ – Apheresis Unit (Miltenyi Biotec, Bergisch Gladbach, Germany). The more specific TheraSorb™-IgE adsorbers were used in 4 patients with atopic dermatitis and in one patient with severe Guillain–Barré syndrome (alternating with Ig-adsorber), who had extreme high levels of IgE.

Due to the potential relevance of persistent Ig reduction, only treatments cycles consisting of at least 5 IA sessions

Table 2

Indications for immunoabsorption in 52 patients.

Disease	n
Multiple sclerosis	11
Autoimmune encephalitis	5
Myasthenia gravis	3
Guillain–Barré syndrome	2
Chronic relapsing inflammatory optic neuropathy	1
Chronic inflammatory demyelinating neuropathy	1
Paraproteinemic motoric polyneuropathy	1
Multifocal acquired demyelinating sensory and motor neuropathy	1
Transverse myelitis	1
Cerebellar ataxia	1
Stiff man syndrome	1
Autoimmune autonomic ganglionopathy	1
Meningoencephalopathy of unknown origin	1
Suspected somatoform autonomic dysfunction	1
Atopic dermatitis	5
Pemphigus vulgaris	5
Bullous pemphigoid	1
Membranous glomerulonephritis	1
Lupus erythematosus with nephrotic syndrome	1
Acquired hemophilia	2
Thrombotic thrombocytopenic purpura	1
Evans syndrome	1
Thromboangiitis obliterans	3
JC virus under Rituximab	1

were included. The number of sessions varied from 5 to 16 with a median of 8.8.

2.3. Biochemical analysis

Protein serum levels were measured with Total Protein Gen.2, Albumin Gen.2, Tina-quant IgA Gen.2, Tina-quant IgM Gen.2, Tina-quant IgG Gen.2 and CRP Gen.3 (Roche/Hitachi Cobas c 701/702) in our routine clinical laboratory.

2.4. Statistics

All data are given as median and range. Microsoft Excel 2010 was used for data processing including figure's drawing.

3. Results

3.1. Changes in protein serum levels

The median IgG value was 8.14 [2.28–23.8] g/L prior to IA treatment and decreased to 1.55 [0.22–14.7] g/L at the

Table 1

Patients and treatment characteristics.

n	Female	Age (years)	Adsorber TheraSorb™ (n)				Indications (n)					Treatment sessions (from–to, mean)
			IgG	Ig Flex	Ig pro	Ig E	Neurology	Dermatology	Nephrology	Hematology	Other	
52	27 (52%)	46.8 ± 19.9	3	44	1	5 ^a	31	11	2	4	4	5–16, 8.8

^a The TheraSorb™-IgE adsorbers were used in 4 patients with atopic dermatitis and in one patient with severe Guillain–Barré syndrome alternating with Ig-adsorber.

end of the treatment cycles. The IgG levels at follow up were assessed in 16 subjects and achieved 75% of the initial pre-treatment values.

Before therapy, median serum total protein was 63.1 [39.8–85.2] g/L ($n = 47$) and albumin 41.3 [22.2–49.9] g/L ($n = 46$), at the end of the treatment 50.1 [33.9–69.6] g/L and 35.2 [21.0–45.9] g/L respectively ($n = 42$) and at follow up visit within 2 months 57.3 [40.9–71.2] g/L ($n = 29$) and 38.9 [20.0–48.6] g/L ($n = 20$) respectively. Following IA, the values were reduced by a median of 20 [3–44]% for total protein, 8 [2–35]% for albumin and restored up to 91% and 94% respectively to the follow up visit within two months (see Fig. 1).

The median CRP values remained within the normal range during the whole observation time: 3.40 [0.5–229] mg/L before ($n = 52$), 3.10 [0.6–97.0] mg/L ($n = 33$) after therapy and 4.30 [0.5–55.9] mg/L ($n = 38$) at follow up. The CRP values were increased over 10 mg/L before the start of IA in 12 patients and in 8 patients at the end of IA. Compared to the value before IA CRP was lower in 8 and higher in 4 patients with initially elevated values (over 10 mg/L) (see Fig. 2).

3.2. Infectious complications

Infections were reported in 4 patients (7.7%) within a 2 months follow-up. A 58 years old man with membranous glomerulonephritis under rituximab 100 mg weekly and prednisolone 7.5 mg/d suffered from a mild upper respiratory tract infection without fever. A 60 years old woman with paraneoplastic cerebellitis (due to a bronchial carcinoma) treated with Carboplatin/Etoposide and a 56 years old man with bullous pemphigoid took prednisolone 50 mg/d, mycophenolat mofetil 3 g/d and rituximab 1000 mg and

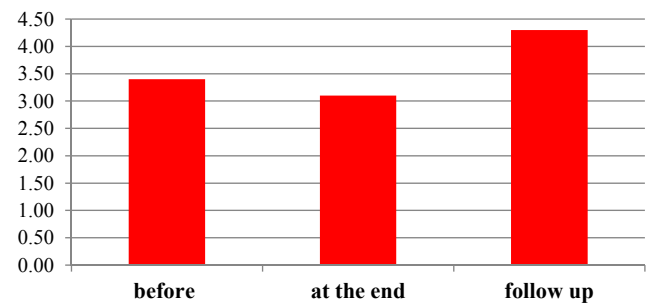


Fig. 2. CRP serum levels were not changed during IA treatment. The median CRP values remained within the normal range during the whole observation time: 3.40 mg/L before, 3.10 mg/L – after therapy and 4.30 mg/L – at follow up. The red columns represent the median serum concentration of CRP in mg/L before ($n = 52$), at the end ($n = 33$) and within 2 months after the therapy cycle ($n = 38$).

had subsequent clostridium-difficile enteritis. A 31 years old woman having a severe meningoencephalopathy of unknown origin was treated finally with high dose prednisolone. This patient died 2.5 weeks later from septic shock. Interestingly, the median IgG values at the end of IA cycle were lower (1.55 [0.08–14.7] g/L) in the infection free group compared to infectious patients (2.13 [0.62–6.21] g/L). The mean IgG reduction reflecting treatment efficacy is depicted in Fig. 3.

4. Discussion

We conducted a retrospective analysis of 52 IA cycles performed in patients with 24 different indications and without subsequent IVIG substitution, to investigate the rate of infectious complications potentially linked with the treatment-related Ig depletion. As expected, the reduction

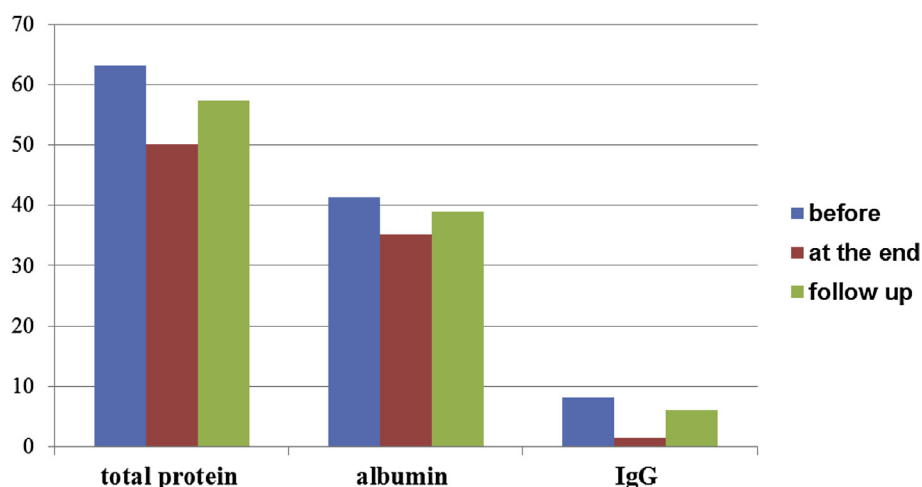


Fig. 1. The changes of protein serum levels during the observation time. The median IgG value was 8.14 [2.28–23.8] g/L and decreased to 1.55 [0.22–14.7] g/L at the end of the treatment cycle. The IgG levels in follow up were registered in only 16 subjects reaching 75% of the initial values. Following the IA treatment cycle, serum protein concentrations were reduced by a median of 21% for total protein, 8% for albumin and restored up to 91% and 94% of the initial levels respectively at the follow up visit (within a two months' time frame). The blue columns represent the median serum proteins concentrations in g/L before (total protein – $n = 47$; albumin – $n = 46$; IgG – $n = 52$), the red columns – at the end (total protein – $n = 42$; albumin – $n = 42$; IgG – $n = 52$) and the green columns – within 2 months after the therapy cycle (total protein – $n = 29$; albumin – $n = 20$; IgG – $n = 16$).

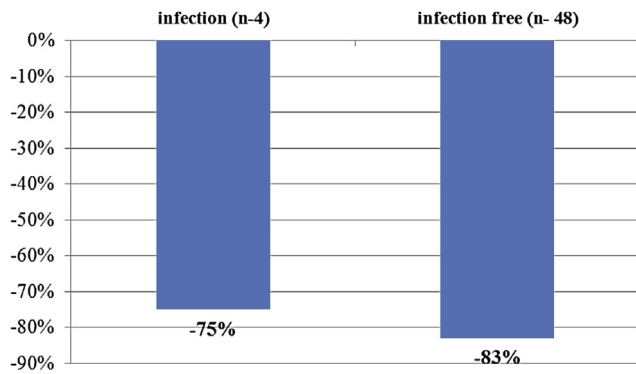


Fig. 3. **IgG serum levels in patients with and without infectious complication.** The median reduction of IgG levels in 48 patients with infection was even lower than this in 4 infection free persons (–75 and –83% respectively). The blue columns represent the relative percentage reduction of IgG serum concentrations in g/l to the end of the therapy cycle.

of IgG serum levels at the end of the treatment was significant (82%), whereas the total serum protein and albumin levels were only slightly decreased. CRP as a marker of systemic inflammation was not affected and varied within normal range during the course of therapy and thereafter. Infections occurred in only 4 patients (7.7%), three of them receiving additional immunosuppressive therapy. Intriguingly, the median IgG levels at the end of IA cycle were higher in the group with subsequent infections (2.13 g/L) than in infection free patients (1.55 g/L) (the mean reduction rates were 75 and 83% respectively). But this difference cannot be statistically evaluated because of the sharp contrast in size of patients groups (4 infections versus 48 subjects without complications).

Some authors reported on immunodeficiency syndrome resulting from substantial reduction of Ig concentrations due to the combination of apheresis and immunosuppressives in cases of intensive care settings [17,18] and two of our four patients suffering from infections after the immunoadsorption cycle were also treated in the intensive care unit.

The combined protocol (IA, cyclophosphamide and prednisolone) for the treatment of acquired haemophilia also includes IVIG substitution (0.3 g/kg BW/d on days 5–7) [19]. In contrast to the patients reported here, IVIG are a part of the therapeutic protocol in acquired hemophilia. Weekly plasmapheresis or immunoadsorption and fortnightly administration IVIG (1 g/kg BW) were recommended for the treatment of high-risk pregnant patients with triple antiphospholipid positivity [20], and a five days immunoadsorption cycle with subsequent application of IVIG (0.5 g/kg BW) represented the therapeutic approach for patients with dilated cardiomyopathy [21]. As a consequence, several studies performed intravenous substitution of immunoglobulins, especially in persons with severe conditions. In critical myasthenic patients of intensive care unit IVIG (0.3–0.5 g/kg body weight (BW)/d) was administered after the 5 IA sessions [10]. Here, the

subsequent immunosuppressive medication with cyclophosphamide and prednisolone until remission could partly justify the giving of IVIG in this case to support the depressed humoral immunity.

In numerous publications on IA in chronic patients suffering from refractory autoimmune syndromes, IVIG substitution is not mentioned. A retrospective analysis in 16 SLE patients who underwent long-term IA showed no severe infections during IA without concomitant cyclophosphamide [22]. However, high disease activity increased the overall risk for complications (up to 33%), especially in persons who took cyclophosphamide in addition to IA. Due to the fact that we treated only one subject with active SLE, we can't provide comparable data for this specific group of patients.

The majority of our patients (though including only one with lupus erythematosus) also received immunosuppressants (steroids, cyclophosphamide, cyclosporine, carboplatin, mycophenolat mofetil, etoposide, monoclonal antibodies), but despite a high number of treatments, high efficacy with respect to Ig reduction and wide range of diseases the infection rates were rather low.

A prospective, randomized trial of Oxford rheumatologists [23] demonstrated a similarly low incidence of infections in patients receiving combined IA and IVIG (0.14 g/kg BW) and in the control group treated using IA alone. The infection rate among our patients during a follow-up period of 2 months was in a line with this study. Of note, the aforementioned trial reported a high incidence of serious side-effects resulting from IVIG infusion necessitating the termination of treatment in 24% of the patients. Considering the risk for complications and the costs of this preventive treatment, there is further reasonable doubt with respect to the necessity of IVIG substitution therapy.

Given the fact that serum IgG increased up to 75% of the initial value in our patients within 2 months, the low rate of infectious complication despite substantial depletion of IgG following IA treatment could be mainly attributed to a fast restoration of serum Ig. Moreover, in parallel with the reduction of the humoral factors IA may also stimulate/activate the cellular immune response [1], partly explaining its positive effects on pathogenesis of autoimmune disorders.

The retrospective design of our study resulted in some limitation with respect to the observation time and data collection from different documentation processes in the individual departments, referring their patients to our apheresis center. Nevertheless, despite of some absent laboratory parameters after therapy and during follow up, the number of treatments which could be analyzed completely, is very high.

5. Conclusions

IA leads to a significant reduction of IgG and a slight decrease of serum total protein and albumin levels. CRP

was unaffected. We showed that even without regular substitution of IVIG after intensive IA treatment, the rate of infections directly linked with IA is low. Therefore, this costly strategy with potential additional side effects should be tested in a larger prospective study, especially in patients with high disease activity and immunosuppressive therapy.

Author contributions

S. Tselmin: data gathering and analyzing, writing the first draft of publication.

U. Julius: data interpretation and editing.

SR. Bornstein, B. Hohenstein: idea of the study, data interpretation and editing.

Conflict of interests

S. Tselmin: no financial relationships or conflicts of interest regarding the content herein.

U. Julius travel expenses by Aegerion, Diamed, Fresenius Medical Care, Kaneka; honoraria from Aegerion, Amgen, Chiesi, Sanofi, Kaneka, Diamed, Fresenius Medical Care.

SR. Bornstein declared no conflict of interest.

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