ORIGINAL ARTICLE

Therapeutic Apheresis and Dialysis

WILEY

Performance, clinical effectiveness, and safety of immunoadsorption in a wide range of indications

Kornelius Fuchs[1] | Silke Rummler[2] | Wolfgang Ries[3] |
Matthias Helmschrott[4] | Jochen Selbach[5] | Friedlinde Ernst[6] |
Christian Morath[7] | Adelheid Gauly[8] | Saynab Atiye[8] |
Manuela Stauss-Grabo[8] | Mareike Giefer[8]

[1]Department of Neurology, University Hospital, Regensburg, Germany

[2]Institute for Transfusion Medicine, University Hospital, Jena, Germany

[3]Internal Medicine, Department of Nephrology, Diakonissenkrankenhaus, Flensburg, Germany

[4]Department of Cardiology, University Hospital Heidelberg, Heidelberg, Germany

[5]Department of Nephrology, Caritas Hospital, Bad Mergentheim, Germany

[6]Center for Internal Medicine and Dialysis, Kempten, Germany

[7]Department for Dialysis, Nierenzentrum Heidelberg, Heidelberg, Germany

[8]Fresenius Medical Care, Global Medical Office, Bad Homburg, Germany

Correspondence

Adelheid Gauly, Fresenius Medical Care Deutschland GmbH, Global Medical Office, Else-Kröner-Strasse 3, 61352 Bad Homburg, Germany.
Email: adelheid.gauly@fmc-ag.com

Funding information

Fresenius Medical Care Deutschland GmbH

Abstract

Immunoadsorption is well known to selectively remove immunoglobulins and immune complexes from plasma and is applied in a variety of autoimmune diseases and for desensitization before, or at acute rejection after organ transplantation. Performance, safety, and clinical effectiveness of immunoadsorption were the aim of this study. This prospective, noninterventional, multicentre cohort study included patients treated with immunoadsorption (Immunosorba or GLOBAFFIN adsorbers) for any indication. Clinical effectiveness was assessed after termination of the patient's individual treatment schedule. Eighty-one patients were included, 69 were treated with Immunosorba, 11 with GLOBAFFIN, one patient with both adsorbers. A majority of patients was treated for neurological indications, dilated cardiomyopathy, and before or after kidney or heart transplantation. Mean IgG reduction from pre- to post-treatment was 69.9% ± 11.5% for Immunosorba and 74.1% ± 5.0% for GLOBAFFIN, respectively. The overall IgG reduction over a complete treatment block was 68%–93% with Immunosorba and 62%–90% with GLOBAFFIN depending on the duration of the overall treatment. After termination of the immunoadsorption therapy, an improvement of clinical status was observed in 63.0%, stabilization of symptoms in 29.6%, and a deterioration in 4.9% of patients. Changes in fibrinogen, thrombocytes, and albumin were mostly classified as noncritical. Overall, the treatments were well tolerated. Immunoadsorption in routine clinical practice with both GLOBAFFIN and Immunosorba has been safely performed, was well tolerated by patients, and effective in lowering immunoglobulins with an improvement or maintenance of clinical status, thus represents an additional therapeutic option for therapy refractory immune disorders.

KEYWORDS

clinical effectiveness, dilated cardiomyopathy, immunoadsorption, neurology, transplantation

1 | INTRODUCTION

Immunoadsorption, also known as immunoapheresis, is an adsorptive procedure in an extracorporeal circuit to remove circulating antibodies and antibody complexes from the blood of patients with different immune disorders or rejection reactions [1].

Autoimmune diseases are conditions in which immune responses are directed toward endogenous cells, tissues, and antigens. Formation of antibodies against the body's own tissue may affect nearly all organ systems.

In organ transplantation, the immune system recognizes the transplanted organ as foreign tissue, and the resulting inflammation associated with a rejection reaction can lead to the loss of the transplanted organ.

Immunoadsorption, in contrast to nonspecific plasma exchange, offers the advantage of specificity, that is, only antibodies and immune complexes are removed and other important plasma constituents, for example, albumin and coagulation factors remain with the patient. An accompanying substitution with plasma or colloidal solutions is thus not required. This allows larger plasma volumes to be treated than with plasma exchange, enhancing reduction rates of IgG antibodies or autoantibodies and immune complexes [2], with a low rate of side effects [3].

Immunoadsorption is considered as a therapeutic option in a wide variety of autoimmune diseases and for desensitization before organ transplantation or at acute antibody mediated rejection [4–7]. It is indicated in all diseases in which circulating, disease-causing immune factors have been identified to be involved in the onset and progression of the disease. Usually, the procedure is applied in patients in whom other conventional therapies, such as pharmacological therapies, are not successful [7].

Clinical experience on immunoadsorption in some rare autoimmune diseases is still based on case reports only. Large, prospective, randomized trials are lacking for most indications, since low frequency of patients in such indications prevent adequately powered studies [1]. Other reasons are the different severity of the disease in patients, inconsistent treatment regimens, the high cost of treatment associated with the often unresolved reimbursement in the respective health care system. Placebo-controlled trials for efficacy are hardly possible, since in seriously ill patients a control (sham) treatment is ethically not acceptable [8].

Nevertheless, more documented clinical data on indications and clinical effectiveness of immunoadsorption has been requested for years by many stakeholders, among those clinicians and regulatory bodies. Accordingly, the noninterventional study described in the following has been designed to examine current clinical practice of immunoadsorption with the Immunosorba and GLOBAFFIN systems (Fresenius Medical Care, Bad Homburg, Germany) in view of the range of treated indications, of clinical performance, clinical effectiveness, and safety of the procedure.

2 | PATIENTS AND METHODS

2.1 | Study objectives

The objectives of this noninterventional study were performance in terms of the capability of the adsorbers Immunosorba and GLOBAFFIN (Fresenius Medical Care) to reduce immunoglobulins (IgG, IgM, IgA), clinical effectiveness, and safety and tolerability of the intervention in clinical application.

2.2 | Study design

This study was a prospective, noncomparative, noninterventional, multicenter cohort study, performed between July 2013 and April 2018 in six German tertiary care hospitals or centers specialized in extracorporeal therapies.

Clinical and treatment-related data were collected from patients eligible for the study based on inclusion and exclusion criteria over a maximum period of 24 months after first treatment with the Immunosorba or GLOBAFFIN system. Assignment of patients to the immunoadsorption system and treatment regimens followed clinical practice established in the participating hospitals.

2.3 | Patients

Adult patients, able to give informed consent with any indication for immunoadsorption, who were scheduled to be treated with the Immunosorba or GLOBAFFIN adsorber were eligible to be recruited in the study.

2.4 | Immunoadsorption treatments and documented parameters

Immunoadsorption treatments included plasma separation by centrifugation or plasma filtration, according to centre practice. Anticoagulation followed usual and patient-adjusted practice by heparin, citrate (acid-citrate-dextrose, ACD-A solution), or a combination of both. The

immunoadsorption procedure involved with both systems a pair of adsorbers, which were alternately used while the other one was being regenerated. Assignment of patients to the Immunosorba or the GLOBAFFIN system, frequency and overall duration of the immunoadsorption therapy was performed according to the physician's judgment, based exclusively on medical criteria. The adsorber pair was reused within the same patient until completion of the planned treatment regimen or insufficient IgG lowering. Patients were allowed to switch the adsorber type if necessary. Depending on the indication, the immunoadsorption therapy included one to several apheresis cycles per patient, each with three or more apheresis treatments.

Demographic, clinical, laboratory, and treatment parameters were collected at enrolment in the study and/or pre- and post-treatment according to availability given by the clinical routine of the respective centers. Plasma volume was calculated with the formula by Retzlaff et al. [9], modified by Sprenger et al. [10] Laboratory analysis was performed following usual methods in the hospitals' laboratories. Performance of the immunoadsorption system was assessed through pre- to post-treatment reduction rates of IgG and for specificity of IgA and IgM. After termination of the last immunoadsorption session of the respective treatment regimen, clinical effectiveness of the treatment was evaluated by the attending physician or referral specialist in view of improvement, stabilization, or deterioration of the clinical status based on disease specific criteria. Where appropriate, patient follow-up was assessed for up to 2 years with disease specific scores namely the van-der-Meché score in Guillain-Barré syndrome (GBS) [11], the Barthel Index (BI), [12] and the modified Rankin scale (MRS) [13] in autoimmune encephalitis.

Safety and tolerability of the immunoadsorption treatments was assessed based on pre- and post-treatment laboratory parameters, and documentation of adverse device effects (ADEs).

2.5 | Ethical considerations

Within the study only CE-certified products were used. The study and related documents were approved by independent ethics committees at the study sites. Patients were enrolled in the study after having given informed consent in writing. The study was executed in compliance with the Declaration of Helsinki in the version applicable at the time the study was conducted.

The study was registered at Deutsches Register Klinische Studien (DRKS) under the ID DRKS00005097.

2.6 | Statistical analysis

No formal sample size estimation was performed. In order to reflect the average frequency of patients with indications for immunoadsorption in the participating centers within a certain time period and approximately the proportion of use of the two adsorbers in clinical practice, 50 patients treated with Immunosorba and 30 patients treated with GLOBAFFIN should be included.

All data were analyzed descriptively. Dichotomous and categorical variables are given as absolute numbers and relative frequencies, continuous variables as mean ± SD, or median (range) as appropriate.

Following the noninterventional nature of the study, all patients with at least one documented apheresis treatment were included in the analysis population, which was used for all performance, clinical effectiveness, and safety analyses.

To assess the applied treatment patterns and their potential impact on treatment success, the treatment schedules were categorized according to overall treatment duration (regimen 1: <5 days, regimen 2: 6–10 days, regimen 3: 11–40 days, regimen 4: >40 days).

Statistical significance of changes of laboratory parameters was tested with the Wilcoxon-Mann–Whitney-Test.

All analyses were performed with SAS V9.4 (SAS Institute, Inc.).

3 | RESULTS

3.1 | Study population

A total of 81 patients scheduled for treatment with immunoadsorption for various indications were recruited in six centers, in 69 patients the Immunosorba, in 11 patients the GLOBAFFIN system was used. In one patient, both systems were applied consecutively. Of note, the GLOBAFFIN system was used in one of the six centers only.

Patients were in average 51 years old, 53% were male (Table 1). The majority of patients was treated for neurological indications, most frequently for multiple sclerosis (N = 17), myasthenia gravis (N = 10), autoimmune encephalitis (N = 9), and inflammatory polyneuropathies (N = 8). Further, immunoadsorption was applied for desensitization before transplantation or at acute graft rejection (N = 8). Also dilated cardiomyopathy (DCM) was treated in a significant number of patients (N = 8). Twenty-one patients were treated for further neurological or other indications (Table 2).

TABLE 1 Patient characteristics at study enrolment

	All patients N = 81	Immunosorba N = 70	GLOBAFFIN N = 12
Age (years)	51.0 ± 15.6	50.4 ± 15.1	55.0 ± 18.6
Gender (% male)	53	56	33
Body weight (kg)	78.8 ± 17.5	78.4 ± 15.5	81.2 ± 26.6

3.2 | Treatment patterns of immunoadsorption

In total, 443 Immunosorba and 156 GLOBAFFIN treatments were documented in this study (Table 3). In the entire study population, patients received between 2 and 50 (median 5) immunoadsorption treatments, which were distributed over a period of between 2 days and 2 years, with a median of 6 days. The majority of patients were treated with treatment schedules including less than 10 treatments, only in single cases higher number of sessions were performed (Figure 1). The most homogeneous treatment patterns were reported for patients with DCM (all eight patients received 3–5 treatments within 5 days), multiple sclerosis (14 of 17 patients received 3–5 treatments within 3–9 days), and myasthenia gravis (8 of 10 patients received 3–5 treatments within 3–6 days). Of all 81 patients in the study population, 12 received 10 or more treatments, of which 7 even received 20 or more treatments.

Most of the patients (48.1%) received treatments within 5 days and could be allocated to treatment regimen 1. The remaining patients were allocated equally to regimen 2 (6–10 days), regimen 3 (11–40 days), and regimen 4 (>40 days) with 13.6%, 18.5%, and 19.8%, respectively (Table S1). Even within the same indication, different treatment regimens were applied (Table S2).

Vascular access for the immunoadsorption was in the majority of treatments via peripheral veno-venous or central venous access (Table 3). Plasma separation was performed predominantly by centrifugation (91.4%), only in single cases plasmafiltration was applied (8.6%). In average 2.2 plasma volumes were treated per session, with slightly higher values in the cohort being treated with Immunosorba than in that treated with GLOBAFFIN. This was achieved in an average duration of the immunoadsorption session of 261 ± 52 min, ranging from 126 to 348 min (Table 3). The introduction of a new pair of adsorbers in patients on long treatment regimens was at the discretion of the treating physician and was usually based on a reduced lowering of IgG.Anticoagulation was mostly performed with citrate (ACD-A-solution), or with both, ACD-A and heparin in one treatment. Only in few cases, heparin alone, or alternating ACD-A and heparin, was used.

Citrate was applied in a ratio relative to plasma flow between 1:75 and 1:10. No IgG substitution after the immunoadsorption sessions was reported.

3.3 | Performance of immunoadsorption

In total, IgG levels pre- and post-treatment were documented in 230 treatments in 29 patients for Immunosorba and in 143 treatments in 12 patients for GLOBAFFIN. The mean relative reduction (RR) of IgG achieved by treatment was 69.9% ± 11.5% for Immunosorba with in average a 1.9-fold treated plasma volume and 74.1% ± 5.0% for GLOBAFFIN with in average a 2.0-fold treated plasma volume (Figure 2). In 77.7% of these treatments, the RR of IgG was ≥60% (67.4% with Immunosorba and 91.6% with GLOBAFFIN, respectively). In the treatments with RR of IgG < 60%, a deviation between prescribed and treated plasma volume of more than 10% occurred in 36.8% of treatments, which was significantly different to the frequency among treatments achieving a RR of IgG of ≥60% (23.4%, $p = 0.014$). Reasons for this deviation between prescribed and treated plasma volume were mostly either medical or technical complications.

In a few cases with repeated treatments over a longer period of time, low reduction rates were observed preceding the introduction of a new adsorber pair.

After the immunoadsorption treatment a partial recovery of IgG plasma concentration occurs and plasma IgG concentrations are reduced stepwise over the entire treatment cycle as shown exemplary in the group of patients with DCM, who were treated relatively uniformly three to five times within 5 days (Figure 3). Consequently, the overall reduction of IgG over all applied treatments is higher than for the individual treatment. It ranged from 68% to 93% with Immunosorba and from 83% to 90% with GLOBAFFIN (Table S3).

Patients within therapy regimen 1, who are treated on consecutive days within 5 days showed higher overall RR rates of IgG (RR of 91.8% for Immunosorba) than patients in treatment regime 4 (RR of 67.8% for Immunosorba and 83.1% for GLOBAFFIN), who were treated over a longer time period and longer intervals between treatments or treatment cycles.

The immunoglobulins IgM and IgA also adsorb to the immunoadsorbers but to a markedly lower extent than IgG. The mean RR of IgM from pre- to post-treatment was 13.4% ± 8.6% for Immunosorba and 19.4% ± 5.8% for GLOBAFFIN (Figure 2). The mean RR of IgA from pre- to post-treatment was 14.0% ± 7.1% for Immunosorba and 15.6% ± 4.1% for GLOBAFFIN (Figure 2).

TABLE 2 Indications treated with immunoadsorption (by adsorber)

Indications for immunoadsorption	All patients N = 81		Immunosorba N = 70		GLOBAFFIN N = 12	
	No. of patients	No. of treatments by patient, range	No. of patients	No. of treatments by patient, range	No. of patients	No. of treatments by patient, range
Neurological indications						
Multiple sclerosis	17	2–12	15	2–12	2	7–8
Myasthenia gravis	10	3–18	10	3–18		
Autoimmune encephalitis	9	3–20	6	3–7	3	10–20
Inflammatory polyneuropathies	8	2–50	7	2–50	1	25
Optic neuritis[a]	4	4–29	3	4–6	2	16–29
Stiff-Person syndrome	4	3–12	4	3–12		
Guillain-Barré syndrome	3	6–32	1	32	2	6–8
Idiopathic inflammatory myopathies	2	4–20	2	4–20		
Lambert-Eaton syndrome	1	3	1	3		
Morvan syndrome	1	4	1	4		
Myelitis (unknown etiology)	1	7	—		1	7
Suspected autoimmune cerebellar ataxia differential diagnosis spinocerebellar ataxia	1	5	1	5		
Systemic cerebral arthritis and collagenosis	1	9			1	9
Transplantation						
Acute humoral rejection (heart transplantation)	3	6–9	3	6–9		
Acute humoral rejection (kidney transplantation)	2	7–8	2	7–8		
AB0-incompatibility (transplantation)	2	3–6	2	3–6		
Human leukocyte antigen (HLA) immunization (heart transplantation)	1	4	1	4		
Cardiovascular indications						
Dilated cardiomyopathy	8	3–5	8	3–5		
Suspected thromboangiitis obliterans	1	5	1	5		
Other indications						
Diabetes Type 1 with insulin alloantibodies	1	3	1	3		
Pemphigus foliaceus	1	3	1	3		

[a]One patient with optic neuritis was treated consecutively with both adsorbers and is therefore included in both subgroups.

3.4 | Clinical effectiveness of immunoadsorption

The assessment of clinical effectiveness was performed by the treating specialist after completion of the patient's last immunoadsorption treatment. Overall, in 63.0% of patients an improvement of clinical status was observed, no change in 29.6% and a deterioration in 4.9% of the patients (Table 4).

3.4.1 | Multiple sclerosis

In patients being treated for multiple sclerosis, 94% showed clinical improvements after completion of the immunoadsorption cycles. Nine patients showed motor improvements of various type, seven patients in visual acuity and/or eyesight (Table S2). One patient showed no change in the clinical status, no patient showed any deterioration.

TABLE 3 Treatment parameters

	All patients N = 81	Immunosorba N = 70	GLOBAFFIN N = 12
Number of treatments	599	443	156
No. of treatments/patient, median (range)	5 (2–50)	5 (2–50)	9.5 (6–29)
Duration of treatment (first to last IA session, days), median (range)	6 (2–715)	5 (2–711)	26 (14–715)
Method of plasma separation			
Plasma filtration (%)	8.6	10.0	0
Centrifugation (%)	91.4	90.0	100.0
Vascular access (% of treatments)			
Peripheral veno-venous	37.4	22.6	79.5
Central venous	42.2	49.9	20.5
Femoral vein	6.0	8.1	—
Arteriovenous fistula/shunt	13.2	17.8	—
Other	1.2	1.6	—
Treatment duration (min), mean ± SD (range)	261 ± 52 (126–348)	262 ± 54 (126–348)	253 ± 41 (199–315)
Processed plasma volume per treatment (multiple of patient's plasma volume)	2.21 ± 0.54	2.26 ± 0.54	1.88 ± 0.36
Anticoagulation (%)			
Citrate (ACD-A)	57	60	42
Heparin	5	6	0
ACD-A + heparin	32	33	25
ACD-A, heparin alternating	6	1	33

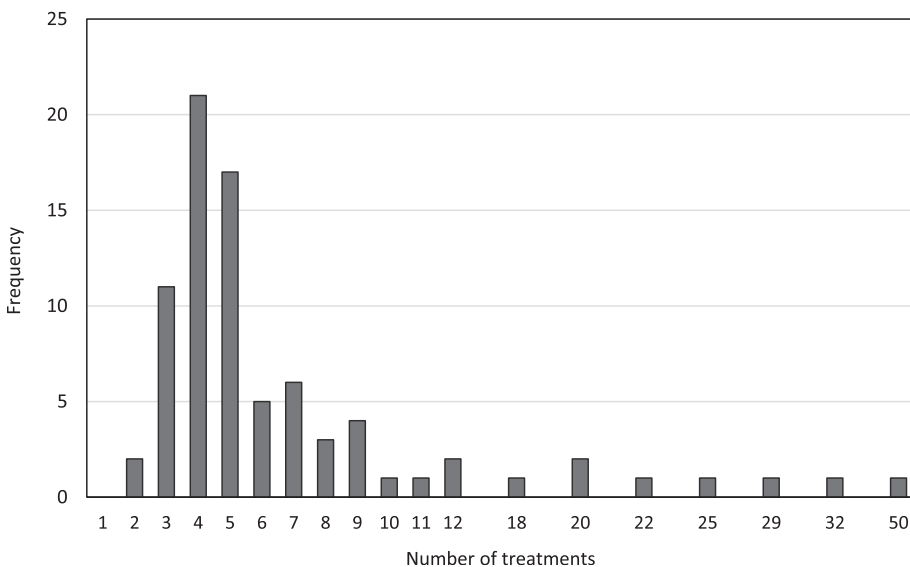Abbreviations: ACD-A, acid-citrate-dextrose solution; IA, immunoadsorption.

FIGURE 1 Distribution of immunoadsorption treatment frequency

3.4.2 | Myasthenia gravis

From the patients treated for myasthenia gravis, 80% showed clinical improvements after completion of the immunoadsorption cycles. The extent of paresis improved in three patients, in five patients symptoms of dysphagia, dyspnea, and dysarthria improved. On the other hand, there were also two patients showing deteriorations of these symptoms together with double images and/or ptosis (Table S2).
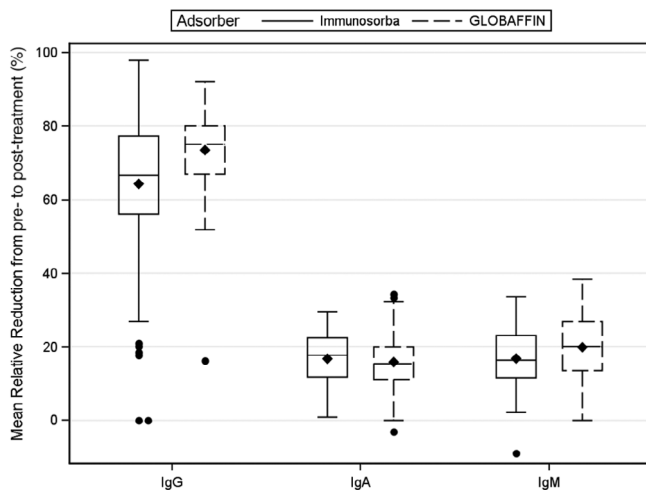
FIGURE 2 Mean relative reduction of IgG, IgA, and IgM with Immunosorba and GLOBAFFIN of patient averages of suited treatments. The plots show the interquartile range (IQR; box), mean (square), median (line), minimum and maximum value within the IQR ± 1.5 IQR (whiskers), and outliers (circles)
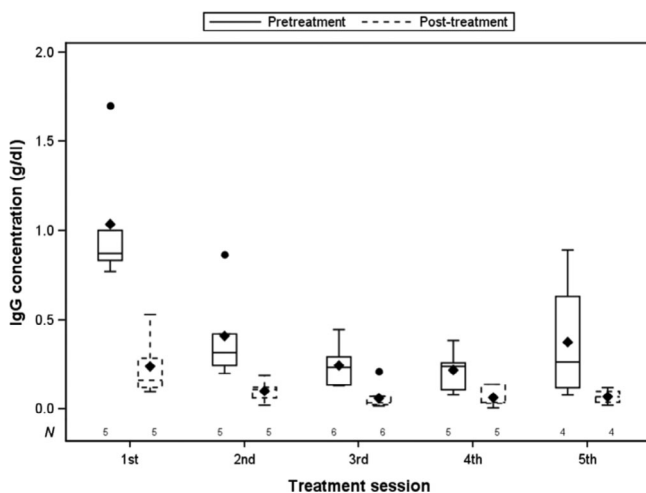

FIGURE 3 Course of IgG from first to fifth treatment in the patient group with dilated cardiomyopathy. The plots show the interquartile range (IQR; box), mean (square),median (line), minimum and maximum value within the IQR ± 1.5 IQR (whiskers), and outliers (circles)

3.4.3 | Autoimmune encephalitis

In patients with autoimmune encephalitis, two out of nine patients showed improvements of cognitive abilities and gait disorders. In six patients, no change was observed, indicating a maintenance of the clinical status with no worsening of the symptoms and one patient showed deterioration of the clinical status in terms of motor activity and incontinence (Table S2). The BI and MRS were determined in six and five patients, respectively, after termination of the treatment cycle and 6 and 12 months later (Table S4). The clinical assessment was confirmed with both indices except in one patient showing an improvement of clinical status directly after immunoadsorption, who did not show changes of BI over the 1-year follow-up.

3.4.4 | Inflammatory polyneuropathies

Four out of eight patients treated for inflammatory polyneuropathies improved in terms of motor function, sensitivity, or walking capacity. The other four patients showed no change of clinical status (Table S2).

3.4.5 | Guillain-Barré syndrome

In the three patients with GBS, two patients showed improvements of clinical status after completion of the immunoadsorption cycles in terms of gait disorders and paraparesis of the lower extremities, and one patient was unchanged (Table S2). Accordingly, the van-der-Meché-Score improved in two patients from 4 and 5 points to 1 point each after 6 months and was unchanged in one patient (Table S5).

3.4.6 | Dilated cardiomyopathy

After completion of the immunoadsorption cycles, three out of the eight patients with DCM showed a clinical improvement in terms of physical capacity, New York Heart Association (NYHA) status, or left ventricular function, whereas four showed no change and one a deterioration of clinical status, as a left ventricular assist device had to be implanted (Table S2). During the follow-up period of up to 1 year, the NYHA status and the left ventricular ejection fraction (LVEF) improved and worsened in two patients each. In the other four patients, no change of NYHA status and either no change of LVEF or variable values were observed (Table S6).

3.4.7 | Transplantation

Eight patients were treated before heart or kidney transplantation for desensitization or at onset of acute graft rejection. Two patients with AB0 incompatibility received successfully a kidney transplant. Parallel to a negative antibody titer, plasma creatinine decreased and glomerular filtration rate (GFR) recovered 3 and 12 months after apheresis treatment and transplantation (Tables S2 and S7).

TABLE 4 Clinical effectiveness (improvement/no change/deterioration) by indication; clinical outcome assessment by patient after termination of individual immunoadsorption treatment schedule

Indication	N	IMP	NC	DET	NA
Neurological indications					
Multiple sclerosis	17	16 (94.1%)	1 (5.9%)	—	—
Myasthenia gravis	10	8 (80%)	—	2 (20%)	—
Autoimmune encephalitis	9	2 (22.2%)	6 (66.7%)	1 (11.1%)	—
Inflammatory polyneuropathies	8	4 (50%)	4 (50%)	—	—
Optic neuritis	4	3 (75%)	1 (25%)	—	—
Stiff-Person syndrome	4	—	3 (75%)	—	1 (25%)
Guillain-Barré syndrome	3	2 (66.7%)	1 (33.3%)	—	—
Idiopathic inflammatory myopathies	2	1 (50%)	1 (50%)	—	—
Lambert-Eaton syndrome	1	—	1 (100%)	—	—
Morvan syndrome	1	1 (100%)	—	—	—
Myelitis (unknown etiology)	1	1 (100%)	—	—	—
Suspected autoimmune cerebellar ataxia differential diagnosis spinocerebellar ataxia	1	—	1 (100%)	—	—
Systemic cerebral arthritis and collagenosis	1	1 (100%)	—	—	—
Transplantation					
Acute humoral rejection (heart transplantation)	3	3 (100%)	—	—	—
Acute humoral rejection (kidney transplantation)	2	1 (50%)	1 (50%)	—	—
AB0 incompatibility (transplantation)	2	2 (100%)	—	—	—
Human leukocyte antigen (HLA) immunization (heart transplantation)	1	—	—	—	1 (100%)
Cardiovascular indications					
Dilated cardiomyopathy	8	3 (37.5%)	4 (50%)	1 (12.5%)	—
Suspected thromboangiitis obliterans	1	1 (100%)	—	—	—
Other indications					
Diabetes Type 1 with insulin alloantibodies	1	1 (100%)	—	—	—
Pemphigus foliaceus	1	1 (100%)	—	—	—
All patients	81	51 (63%)	24 (29.6%)	4 (4.9%)	2 (2.5%)

Abbreviations: DET, deterioration; IMP, improvement; NA, no assessment possible; NC, no change.

Of two patients with acute humoral rejection after kidney transplantation, one patient's kidney function was unchanged directly after apheresis and deteriorated slightly after 3 and 12 months, whereas the other patient showed an improvement of kidney function in terms of plasma creatinine and GFR at Month 3, but a worsening at Month 12 (Tables S2 and S8).

Stabilization of cardiopulmonary condition or pump power was recorded for the three patients treated for acute humoral rejection after heart transplantation (Table S2). One further patient scheduled to be treated for HLA immunization before heart transplantation could not be assessed, since an infection precluded the execution of organ transplantation (Table 4).

3.5 | Safety and tolerability

From the study population of 81 patients, 36 patients experienced a total of 143 ADEs. Out of 443 Immunosorba treatments 17%, and out of 156 GLOBAFFIN treatments 18% of sessions were affected by an ADE in this study (Table 5), indicating a similar safety profile of both adsorbers. In the Immunosorba cohort, hypocalcemia ($N = 14$; 20%) and hypokalemia ($N = 12$; 17.1%) was occurring in the highest percentage of patients. Hypocalcemia was observed in 6.6%, and hypokalemia in 7.9% of treatments (Table S9).

In the GLOBAFFIN cohort, hypercalcemia ($N = 4$; 33% of all patients) was, with 8.3% of treatments, the most frequently observed ADEs (Table S9).

TABLE 5 Safety data on immunoadsorption

	Immunosorba	GLOBAFFIN
Frequency of adverse device effects and incidents		
No. of patients	70	12
No. of patients with ADE	28 (18%)	8 (67%)
No. of sessions with ADE	77 (17%)	28 (18%)
Total no. of ADE	108	35
Incidents	0	0

Change of laboratory parameters from pre- to postapheresis						
	N	Immunosorba	*p* value	*N*	GLOBAFFIN	*p* value
Fibrinogen (mg/dL)	18	−43.0 ± 12.7	<0.0001	11	−86.4 ± 34.0	0.001
Albumin (g/dL)	6	−0.47 ± 0.26	0.031	11	−0.54 ± 0.15	0.001
Hemoglobin (g/dL)	25	−0.12 ± 0.6	0.135	11	−0.38 ± 0.39	0.010
Leukocytes (10^3/μl)	26	1.03 ± 1.9	0.002	11	0.28 ± 0.5	0.175
Thrombocytes (10^3/μl)	25	−16.0 ± 14.0	<0.0001	11	−25.0 ± 18.1	0.005

Abbreviation: ADE, adverse device effect.

Fibrinogen decreased significantly both with Immunosorba and with GLOBAFFIN. The RR of fibrinogen was in average 17.8% and 30.7% with Immunosorba and GLOBAFFIN, respectively. Hypofibrinogenemia (defined as <150 mg/dL for transplant patients, <100 mg/dL for all other patients) was recorded once pretreatment, and in five sessions posttreatment. Thrombocyte count decreased significantly both with Immunosorba and with GLOBAFFIN, to a higher extent with the latter (Table 5). No bleeding events were reported with either adsorber.

4 | DISCUSSION

This noninterventional clinical study collected real-world evidence on the application of immunoadsorption using the Immunosorba and GLOBAFFIN adsorber. This study setting allowed the admission of patients with a wide range of clinical indications for immunoadsorption, and obtaining information on how this therapy is carried out in clinical practice.

A majority of patients was treated with immunoadsorption for various neurological indications, such as multiple sclerosis, myasthenia gravis, or inflammatory polyneuropathies. Besides these, immunoadsorption was applied for desensitization before or after kidney or heart transplantation, for DCM, and few cases with dermatological or other indications. Also apheresis registries confirm the therapeutic potential of immunoadsorption and other apheresis procedures for a wide variety of indications, with neurological indications being also the most frequent among immune mediated diseases in the World Apheresis Registry [14].

Patients were treated with heterogeneous treatment regimens and only for few indications a typical treatment schedule seems to be established by today. Patients with DCM are typically treated five times within a short interval of 1 week [15], similar to—with exceptions—patients with multiple sclerosis [16]. Also patients with myasthenia gravis were mostly treated with a similar short treatment regimen, due to the need associated with acute exacerbation of the disease [17]. Variable treatment patterns likely reflect the need for patient individualized therapies based on the indication, the patients' different clinical conditions, and disease progression.

The categorization of treatment patterns allows to compare patients with similar treatment schedules with regard to the overall reduction of IgG levels and to distinguish between patients suffering from an acute exacerbation of the disease or requiring immunoapheresis treatments for a short period of time (e.g., patients in need for a transplantation) and patients suffering from a chronic type of disease, which requires regular treatments with several days or weeks in between.

Reduction of IgG concentration was effective and comparable between GLOBAFFIN and Immunosorba columns. Selective IgG adsorption is based on high affinity of the ligand in the immunoadsorber to the Fc domain of IgG [18]. The adsorber is virtually not saturable due to the alternating regeneration of the two adsorbers, and thus performance is related to the treated plasma volume [2]. However, only approximately 45% of IgG is accessible

in the intravascular space and IgG delivery from other compartments into the circulation is limited within the usual treatment time of an apheresis session of a few hours [19]. Rebound of antibodies occurs either through de novo synthesis or through redistribution between intra- and extravascular spaces. Particularly in regimens with treatments performed on consecutive days, rebound is limited, so that also pretreatment IgG levels are step-by-step lowered and a greater overall reduction of plasma IgG levels is achieved than for schedules with longer intervals between treatments.

We demonstrated a high binding-specificity of the Immunosorba and GLOBAFFIN columns for IgG. However, both adsorbers also bind with a lower affinity IgM and IgA. The relevance of IgA and IgM for the progression of immune-mediated diseases and of their removal on the clinical effectiveness of immunoadsorption is not uniform across different indications, and is only occasionally addressed [20,21].

An improvement of the patients' clinical status as assessed after a patient's individual termination of all immunoadsorption sessions was reported from about two thirds of patients. In further approximately 30% of patients a stable clinical status under immunoapheresis was reported. In view of the severity of the underlying autoimmune diseases, the stabilization of symptoms is also considered as therapeutic response to immunoadsorption therapy and, especially in neurological disorders, immunoadsorption is often recommended as maintenance therapy by the American Society for Apheresis (ASFA) [4]. The clinical effect is suggested to be attributable to the removal of autoimmune antibodies or immune complexes, supported by an immunomodulatory effect of the ligand (protein A) on the adsorber [22,23].

In a recently published retrospective study, clinical effectiveness of immunoadsorption in neurological indications as assessed with disease specific scores was even 91%. This was achieved with an average of 7.1 treatments, while the mean apheresis dose in terms of treated plasma volumes per session was lower than in our study [24].

For multiple sclerosis and optic neuritis, that are often associated, a response rate with improvement of the clinical status of 94% and 75%, respectively, has been observed in the present study, similar to that summarized in a recent meta-analysis [25]. Most patients with multiple sclerosis and optic neuritis were treated with less than seven treatments within up to 14 days as recommended by the ASFA for acute attacks/relapse [4]. Few patients were treated more frequently and over a longer period of time with individually adjusted intervals for maintenance treatment. Autoantibodies associated to demyelinating diseases may contribute to the pathophysiology of multiple sclerosis [26]. A recent prospective randomized study compared immunoadsorption with plasma exchange in multiple sclerosis patients specifically with an acute relapse. The authors found a response rate of 61.3% directly and of 86.7% 4 weeks after immunoadsorption [27].

In myasthenia gravis, antibodies against the acetylcholine receptor or other proteins of the neuromuscular junction can be detected in a large proportion of patients [28]. Plasmapheresis or immunoadsorption are indicated in situations of acute exacerbations of the disease [28]. In the present study, immunoadsorption successfully improved clinical status in terms of voluntary muscle function in the majority of patients immediately after the application of 3–5 treatment sessions within up to 6 days. The clinical effectiveness of immunoadsorption in patients in an acute myasthenia crisis was similarly described by Köhler et al. based on the Besinger score [17]. Long-lasting efficacy of immunoadsorption on patients' clinical status over an 8-year follow-up was reported by Schneidewind et al. Despite the fact that antibody levels after 6 years were higher than the pre-treatment levels, myasthenia gravis status improved, possibly by additional immunomodulatory effects [29].

Autoimmune encephalitis is associated to antibodies directed to surface receptors and ion channels on neurological tissues [30]. In the present study, two out of nine patients showed an improvement in terms of cognitive abilities and gait disorder and in five patients no change of the clinical status was observed indicating a maintenance without further worsening of the clinical symptoms. Only in one patient a worsening of clinical status after immunoadsorption was observed. Our findings are in contrast to previous studies, where an improvement, assessed with disease specific scores, could be found in 60% and 64% of patients [31,32]. This different response rate could be associated with the type of antibodies involved in the pathophysiology of individual cases. Patients with antibodies against cell surface epitopes tend to show a higher response rate than those with intracellular antigens. Moreover, accessibility of antibodies in the circulation and redistribution from the cerebrospinal fluid may play a role [19]. These results demonstrate the importance of patient individualized therapies including the assessment of the specific IgG antibodies involved in the patient's disease.

In the eight patients with inflammatory polyneuropathy, heterogeneous treatment patterns were observed, from two treatments within 2 days up to 50 treatments over 2 years, which may be an expression of different manifestations of the disease. Improvements in terms of motor function and/or sensibility were achieved in four patients, in the other four patients no change of clinical status was observed. Little and inconclusive evidence on the clinical effectiveness of immunoadsorption in this indication is

existing at present, as both, worsening of clinical parameters [33], and an improvement of overall disability was reported [34].

In two out of three patients with GBS, a treatment success was observed with a short treatment regimen following ASFA treatment recommendations [4]. One patient treated 32 times over a period of 498 days reflects also previously described cases with persistent neurological deficits requiring additional treatments [35].

Immunoadsorption is considered an option to desensitize patients in case of AB0-incompatibility, presence of HLA-antibodies before transplantation, or at antibody-mediated rejection [36]. The clinical usefulness was shown in a study involving 48 patients with AB0 incompatibility treated with immunoadsorption, whose rate of patient and graft survival as well as graft function was comparable to AB0 compatible patients [37]. The results observed in our study are also in line with previously published experience on treatment of acute humoral rejection [38].

In DCM, cellular and humoral immune disturbances including antibodies against cardiac cell proteins contribute to its pathogenesis and progression [39]. For DCM the treatment schedule of 3–5 consecutive treatments without repeated cycles is well established, possibly since only low antibody rebound has been observed in DCM patients [40]. A responder rate of DCM to immunoadsorption of 40%, similar to ours, has previously been reported in a cohort of 93 patients [40]. Other studies also found improvements in cardiac function and cardiopulmonary exercise capacity [41,42].

Mean fibrinogen concentration decreased both with Immunosorba and GLOBAFFIN. Post-treatment values <100 mg/dL were recorded with GLOBAFFIN in only 5 out of 135 treatments with available fibrinogen data. No bleeding events were reported, neither in association to these low levels nor in other treatments with either adsorber. The RR of fibrinogen was less than or similar to reduction rates observed in other studies [43,44]. It is also lower than with total plasma exchange, where fibrinogen reductions by more than 60% were reported [43]. Together with the moderate decrease of thrombocyte count found in our study, and absence of bleeding events, the immunoadsorption with both adsorbers can be considered as safe in view of bleeding risk.

A moderate serum albumin decrease was observed with both adsorbers, and is known from these and other types of immunoadsorbers, but, depending on patient group, mostly not considered as critical [20,45].

The treatments with both adsorbers were well tolerated and reported ADEs did not cause incidents, serious adverse events, or deaths. Better tolerability of immunoadsorption than plasma exchange has been observed and explained by the fact that plasma replacement solutions are not required with immunoadsorption [17]. Many documented symptoms are also reported from studies with the present adsorbers and also other brands [46]. However, the most often reported hyper- or hypocalcemia were not reported with similar frequency from other studies and registries, covering not only immunoadsorption but also other apheresis modalities [46–48]. The occurrence may be associated to citrate anticoagulation and calcium substitution strategies being heterogeneously applied as postadsorber Ca-infusion, orally, or without Ca substitution. These results highlight the need of close monitoring of the anticoagulation process, especially blood ionized calcium levels, and the adjustment of the anticoagulation depending upon both the coagulation status and medical history of the patient.

The strength of this study is the cohort size and the patients representing a wide range of diseases being treated with immunoadsorption. This reflects the different degree to which immunoadsorption has been acknowledged as a potential therapy option in patients affected by autoimmune diseases and being resistant to other, mostly pharmacological therapies.

The study has certain limitations inherent to its observational nature. Only clinical data and laboratory measurements were documented as they were collected in clinical routine, so that missing data was a fact and performance analysis based on immunoglobulin measurements and safety analysis based on laboratory analysis had to rely on the available data. In many indications only small numbers of patients were included, so that interpretation on, for example, the association of treatment schedule and clinical effectiveness should be done with caution. Focusing investigations on specific indications and aiming at higher patient numbers are warranted.

5 | CONCLUSION

In conclusion, the application of immunoadsorption in routine clinical practice has been safely performed and was well tolerated by the patients regardless of the adsorber used. Immunoadsorption with both GLOBAFFIN and Immunosorba is effective in lowering immunoglobulins and improving clinical status presumably associated with autoimmune processes and graft incompatibility or rejection. Observed side effects reflect the known pattern of extracorporeal therapies as previously reported from clinical practice. Thus, immunoadsorption with both adsorbers GLOBAFFIN and Immunosorba represents an additional therapeutic option for therapy refractory immune disorders.

ORCID

Adelheid Gauly https://orcid.org/0000-0002-2554-0711

REFERENCES

1. Braun N, Bosch T. Immunoadsorption, current status and future developments. Expert Opin Investig Drugs. 2000;9:2017–38.
2. Belak M, Borberg H, Jimenez C, Oette K. Technical and clinical experience with protein A immunoadsorption columns. Transfus Sci. 1994;15:419–22.
3. Kihm JP, Schwenger V. Plasmapherese und Immunadsorption auf der Intensivstation. Nephrol Ther. 2011;6:149–54.
4. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, 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;34:171–354.
5. Ronspeck W, Brinckmann R, Egner R, Gebauer F, Winkler D, Jekow P, et al. Peptide based adsorbers for therapeutic immunoadsorption. Ther Apher Dial. 2003;7:91–7.
6. Niedermeier A, Eming R, Pfütze M, Neumann CR, Happel C, Reich K, et al. Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). Arch Dermatol. 2007;143:192–8.
7. Malchesky PS. Therapeutic apheresis: why? Ther Apher Dial. 2015;19:417–26.
8. Biesenbach P, Schmaldienst S, Smolen JS, Horl WH, Derfler K, Stummvoll GH. Immunoadsorption in SLE: three different high affinity columns are adequately effective in removing autoantibodies and controlling disease activity. Atheroscler Suppl. 2009;10:114–21.
9. Retzlaff JA, Tauxe WN, Kiely JM, Stroebel CF. Erythrocyte volume, plasma volume, and lean body mass in adult men and women. Blood. 1969;33:649–61.
10. Sprenger KB, Huber K, Kratz W, Henze E. Nomograms for the prediction of patient's plasma volume in plasma exchange therapy from height, weight, and hematocrit. J Clin Apher. 1987;3:185–90.
11. van der Meche FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. N Engl J Med. 1992;326:1123–9.
12. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61–5.
13. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–7.
14. Stegmayr B, Mortzell Henriksson M, Newman E, Witt V, Derfler K, Leitner G, et al. Distribution of indications and procedures within the framework of centers participating in the WAA apheresis registry. Transfus Apher Sci. 2017;56:71–4.
15. Staudt A, Hummel A, Ruppert J, Dörr M, Trimpert C, Birkenmeier K, et al. Immunoadsorption in dilated cardiomyopathy: 6-month results from a randomized study. Am Heart J. 2006;152:712.
16. Rolfes L, Pfeuffer S, Ruck T, Melzer N, Pawlitzki M, Heming M, et al. Therapeutic apheresis in acute relapsing multiple sclerosis: current evidence and unmet needs—a systematic review. J Clin Med. 2019;8:1623.
17. Köhler W, Bucka C, Klingel R. A randomized and controlled study comparing immunoadsorption and plasma exchange in myasthenic crisis. J Clin Apher. 2011;26:347–55.
18. Sanchez AP, Cunard R, Ward DM. The selective therapeutic apheresis procedures. J Clin Apher. 2013;28:20–9.
19. Fassbender C, Klingel R, Köhler W. Immunoadsorption for autoimmune encephalitis. Atheroscler Suppl. 2017;30:257–63.
20. Scheibenbogen C, Loebel M, Freitag H, Krueger A, Bauer S, Antelmann M, et al. Immunoadsorption to remove ß2 adrenergic receptor antibodies in Chronic Fatigue syndrome CFS/ME. PLoS One. 2018;13:e0193672.
21. Parmentier SP, Rosenkranz E, Schirutschke H, Opgenoorth M, Quick C, Hoelig K, et al. Comparing the efficacy of three techniques to reduce isoagglutinin titers in AB0 incompatible kidney transplant recipients. Atheroscler Suppl. 2017;30:253–6.
22. Schneidewind-Müller JM, Winkler RE, Tiess M, Müller W, Ramlow W. Changes in lymphocytic cluster distribution during extracorporeal immunoadsorption. Artif Organs. 2002;26:140–4.
23. Matic G, Bosch T, Ramlow W. Background and indications for protein A-based extracorporeal immunoadsorption. Ther Apher. 2001;5:394–403.
24. Klingele M, Allmendinger C, Thieme S, Baerens L, Fliser D, Jan B. Therapeutic apheresis within immune-mediated neurological disorders: dosing and its effectiveness. Sci Rep. 2020;10:7925.

25. Lipphardt M, Wallbach M, Koziolek MJ. Plasma exchange or immunoadsorption in demyelinating diseases: a meta-analysis. J Clin Med. 2020;9:1597.

26. Egg R, Reindl M, Deisenhammer F, Linington C, Berger T. Anti-MOG and anti-MBP antibody subclasses in multiple sclerosis. Mult Scler. 2001;7:285–9.

27. Dorst J, Fangerau T, Taranu D, Eichele P, Dreyhaupt J, Michels S, et al. 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. EClinicalMedicine. 2019;16: 98–106.

28. Sieb JP. Myasthenia gravis: an update for the clinician. Clin Exp Immunol. 2014;175:408–18.

29. Schneidewind JM, Zettl UK, Winkler RE, Ramlow W, Tiess M, Michelsen A, et al. The outcome in myasthenia gravis patients—an eight-year follow-up after finishing immuno-absorption therapy. Transfus Apher Sci. 2001;24:95–8.

30. Newman MP, Blum S, Wong RCW, Scott JG, Prain K, Wilson RJ, et al. Autoimmune encephalitis. Intern Med J. 2016; 46:148–57.

31. Heine J, Ly L-T, Lieker I, Slowinski T, Finke C, Prüss H, et al. Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study. J Neurol. 2016;263: 2395–402.

32. Dogan Onugoren M, Golombeck KS, Bien C, Abu-Tair M, Brand M, Bulla-Hellwig M, et al. Immunoadsorption therapy in autoimmune encephalitides. Neurol Neuroimmunol Neuro-inflamm. 2016;3:e207.

33. Hadden RDM, Bensa S, Lunn MPT, Hughes RAC. Immunoadsorption inferior to plasma exchange in a patient with chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Neurosurg Psychiatry. 2002;72:644–6.

34. Galldiks N, Burghaus L, Dohmen C, Teschner S, Pollok M, Leebmann J, et al. Immunoadsorption in patients with chronic inflammatory demyelinating polyradiculoneuropathy with unsatisfactory response to first-line treatment. Eur Neurol. 2011;66:183–9.

35. Marn Pernat A, Buturović-Ponikvar J, Svigelj V, Ponikvar R. Guillain-Barré syndrome treated by membrane plasma exchange and/or immunoadsorption. Ther Apher Dial. 2009; 13:310–3.

36. Salvadori M, Tsalouchos A. Therapeutic apheresis in kidney transplantation: an updated review. World J Transplant. 2019; 9:103–22.

37. Speer C, Kälble F, Nusshag C, Pego da Silva L, Schaier M, Becker LE, et al. Outcomes and complications following ABO-incompatible kidney transplantation performed after desensitization by semi-selective immunoadsorption - a retrospective study. Transpl Int. 2019;32:1286–96.

38. Böhmig GA, Regele H, Exner M, Derhartunian V, Kletzmayr J, Säemann MD, et al. C4d-positive acute humoral renal allograft rejection: effective treatment by immunoadsorption. J Am Soc Nephrol. 2001;12:2482–9.

39. Staudt A, Schäper F, Stangl V, Plagemann A, Böhm M, Merkel K, et al. Immunohistological changes in dilated cardiomyopathy induced by immunoadsorption therapy and subsequent immunoglobulin substitution. Circulation. 2001; 103:2681–6.

40. Ohlow M-A, Brunelli M, Schreiber M, Lauer B. Therapeutic effect of immunoadsorption and subsequent immunoglobulin substitution in patients with dilated cardiomyopathy: results from the observational prospective Bad Berka Registry. J Cardiol. 2017;69:409–16.

41. Herda LR, Trimpert C, Nauke U, Landsberger M, Hummel A, Beug D, et al. Effects of immunoadsorption and subsequent immunoglobulin G substitution on cardiopulmonary exercise capacity in patients with dilated cardiomyopathy. Am Heart J. 2010;159:809–16.

42. Müller J, Wallukat G, Dandel M, Bieda H, Brandes K, Spiegelsberger S, et al. Immunoglobulin adsorption in patients with idiopathic dilated cardiomyopathy. Circulation. 2000;101: 385–91.

43. Zöllner S, Pablik E, Druml W, Derfler K, Rees A, Biesenbach P. Fibrinogen reduction and bleeding complications in plasma exchange, immunoadsorption and a combination of the two. Blood Purif. 2014;38:160–6.

44. Biesenbach P, Eskandary F, Ay C, Wiegele M, Derfler K, Schaden E, et al. Effect of combined treatment with immunoadsorption and membrane filtration on plasma coagulation—results of a randomized controlled crossover study. J Clin Apher. 2016;31:29–37.

45. Rostaing L, Allal A, Del Bello A, Sallusto F, Esposito L, Doumerc N, et al. Treatment of large plasma volumes using specific immunoadsorption to desensitize ABO-incompatible kidney-transplant candidates. J Nephropathol. 2016;5:90–7.

46. Mörtzell Henriksson M, Newman E, Witt V, Derfler K, Leitner G, Eloot S, et al. Adverse events in apheresis: an update of the WAA registry data. Transfus Apher Sci. 2016;54:2–15.

47. Malchesky PS, Koo AP, Skibinski CI, Hadsell AT, Rybicki LA. Apheresis technologies and clinical applications: the 2007 International Apheresis Registry. Ther Apher Dial. 2010;14: 52–73.

48. Norda R, Stegmayr BG. Therapeutic apheresis in Sweden: update of epidemiology and adverse events. Transfus Apher Sci. 2003;29:159–66.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.