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ORIGINAL ARTICLE

Experience of therapeutic plasma exchange in rheumatic diseases: Albumin may be a suitable substitute for plasma

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ABSTRACT

Objectives: In this study, we aimed to assess the value of therapeutic plasma exchange (TPE) in the treatment of rheumatic diseases and compare the safety of different replacement fluids used in TPE.

Patients and methods: A total of 727 TPE procedures in 285 patients (57 males, 228 females; mean age: 39.7±15.4 years; range, 13 to 79 years) with rheumatic diseases between January 2011 and February 2019 were retrospectively analyzed. Data including demographic and clinical characteristics of the patients were recorded. Treatment response to TPE and adverse events were evaluated in all patients.

Results: Indications for TPE included 13 different disorders, with the majority being systemic lupus erythematosus (up to 50%). The mean number of TPE sessions was 2.55±1.00 per patient and the mean exchange plasma volume was 2,270±256 mL per session. Combined plasma and albumin was the most frequently used replacement fluid (69.5%), followed by albumin and plasma in 20.5% and 10.0% of episodes, respectively. Up to 73.7% (210/285) patients achieved clinical improvement after TPE treatment. Adverse events occurred in 15.1% (110/727) of all the procedures, and allergic reaction (34.5%) was the most common event. The overall incidence rate of complication was similar among the three types of replacement fluids (p=0.214).

Conclusion: Based on our study results, TPE is an invasive, but safe, useful and, sometimes, essential tool with an acceptable risk/benefit ratio for most rheumatic diseases. Albumin can be used as a feasible substitute for plasma in case of shortage of blood resources.

Keywords: Adverse events, albumin, replacement fluids, rheumatic diseases, therapeutic plasma exchange.

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification procedure which can partly or absolutely remove pathogenic substances from the blood, such as multifarious toxic substances, immunoglobulins (Igs), various auto-antibodies and circulating immune complexes and, then, replace the separated plasma with replacement fluids, including fresh frozen plasma (FFP) or certain concentrations of human albumin through centrifugal or membrane filtration devices.[1-3] Since the first use by Abel et al.[4] in 1914, TPE has been widely applied in numerous conditions, including neurological, hematological, nephrological, dermatological, and even rheumatic disorders.[5-10] It is widely accepted that the development of most rheumatic diseases are mainly mediated by disordered immune regulations and production of various profile autoantibodies.[11] Consequently, it is of great significance to alleviate the symptoms and improve the prognosis for rheumatic diseases via eliminating harmful substances from blood,

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although the specific pathogenesis of majority of those entities have been not clearly elucidated, yet. Encouragingly, TPE has been more and more commonly applied to treat connective tissue diseases (CTDs) due to increased data on the evidence-based applications over the extension of indications for TPE.[12-14] A better understanding of pathophysiology of autoimmune disorders and the advancement of apheresis technology further support the role of TPE as a part of the treatment for several rheumatic entities.

The TPE is designed to physically and temporarily remove circulating antibodies and immune complexes, which is considered to be an alternative therapy, when medical treatments fail to control disease activity timely or as a supplementary therapy aiming at optimizing the prognosis, in addition to traditional treatment regimen. In general, TPE is not applied as frequently in rheumatic disorders as glucocorticoids or immunosuppressive agents. In some cases, TPE showed important advantages, when patients presented with inflammatory storm or certain life-threatening acute complications, such as rapidly progressive interstitial lung disease (RP-ILD) or diffuse alveolar hemorrhage (DAH).[15-18]

However, due to insufficient large-scale trials on TPE, there is no specific recommendations associated with apheresis for most rheumatic disorders. Besides, there is, thus far, no uniform database recording the TPE-associated adverse events (AEs) and benefits of TPE in the treatment of rheumatic disorders. Therefore, in the present study, we aimed to share our experiences and therapeutic effects of TPE in patients with a variety of rheumatic diseases to explore the clinical efficacies and the incidence rates of AEs among different replaced fluids.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Department of Rheumatology and Immunology of Tongji Hospital between January 1st, 2011 and February 1st, 2019. A total of 727 TPE procedures in 285 patients (57 males, 228 females; mean age: 39.7±15.4 years; range, 13 to 79 years) with rheumatic diseases were included. The following data were collected: age, sex, the amount and types of replacement fluids, indications for TPE, vascular access site, the treated plasma volume (PV), the American Society for Apheresis (ASFA) category, treatment response and complications in all procedures. Data about the adjuvant therapies were not collected due to a wide range of indications subject to TPE. However, TPE is a temporary measure and usually requires subsequent medical management including immunosuppressive or immunomodulatory agents, such as cyclophosphamide or intravenous immunoglobulin (IVIG), tailored to specific condition of each individual to avoid the rebound of disease activity.

All patients enrolled were routinely prescribed with acid-citrate-dextrose type A solution given to avoid hypocalcemia. Due to the relatively lower risk of complications associated with the peripheral access, most of our patients adopted the peripheral venous access (PVA), for instance, the anterior cubital vein, as the vascular access. In general, PVA was selected in most cases, except for the poor condition in blood vessel. Central venous catheterization (CVC) or femoral venous catheterization (FVC) would be considered, if the peripheral vessels of patients were in poor conditions. When an arteriovenous fistula is present, it is selected preferentially as the vascular access.

As the definition of treatment responses could vary with a wide range of indications of TPE, we set a series of uniform criteria and used common terminology to evaluate the treatment responses to TPE rigorously. The clinical improvements of patients who underwent TPE were classified into the following three outcomes: complete remission (CR), partial remission (PR), and persistence/worsening. The CR was defined as normal laboratory examinations without clinical symptoms. The PR was defined as the achievement of laboratory indices improving up to at least 50%, compared to baseline and no occurrence of new clinical symptoms. Persistence/worsening was referred to a persistent/deteriorated condition of the laboratory indices and clinical symptoms.

The prescribed frequency and times of TPE performed were usually dependent on the laboratory indices and a comprehensive assessment of the disease severity. For most patients, TPE procedure was carried out every two days for an average of three sessions.

The specific number of procedures depended on the development of latent disorders, the corresponding international recommendations guidelines from the ASFA, the patients' response to the therapy, and the occurrence rate of any AE. All the TPE procedures were performed by centrifugal continuous flow cell separators (Haemonetics®; Fresenius Kabi AG, Bad Homburg, Germany) in our institution. The PV was calculated automatically by the instrument according to the patients' sex, height, and weight and hematocrit (Hct) level varied among different individuals in every process. The estimated plasma volume (EPV) was simply calculated from the patient's weight and Hct using the following formula: EPV=[0.065 × weight (kg)] × [1-Hct].[19] The blood flow rate was set to about 30 to 50 mL/min according to the individual's physical condition and the tolerance to device.

The main components of replacement fluids included FFP, virus-free plasma, 20% human albumin, and lactated Ringer' solution. Others contained artificial colloidal solution (hydroxyethyl starch injection), and normal saline were mainly used to flush the pipes of devices prior to TPE. A total of 20% human albumin could be utilized after being diluted with saline to prevent significant hemodynamic changes caused by high concentration solution. The selection of replacement fluids depended mainly on the patients' clinical condition, laboratory results, and supply of bloods products. A written informed consent was obtained from each patient. The study protocol was approved by the Institutional Review Board (IRB) of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval No: 2019-S1150). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (interquartile range [IQR]), while categorical variables were expressed in number and percentage. The chi-square test or Fisher's exact test were used to analyze differences in AE incidence rates among the subgroups divided by type of replacement fluids. The Spearman rank correlation coefficient test was used to analyze variables correlation. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

The demographics and the TPE procedural data of the study population are shown in Table 1. The total sessions of TPE were 727 with a mean number of 2.55±1.00 sessions per patient (Table 1). The total exchanged volume was 1,650,392 mL for all the subjects and the mean separated PV was 2,270±256 mL per session (range, 1,000 to 5,000 mL), corresponding to the 1.0 to 1.5 PV as traditionally recommended dose. Combination of plasma and 20% human albumin was the most frequently used replacement fluid in 69.5% patients. The patients utilizing human albumin as monotherapy accounted for 20.5% and yet the proportion of using plasma exclusively was barely 10.0%. The use of plasma was restricted by the limitation of blood resources. Scarcity of blood products could give rise to the emergence of this phenomenon. The TPE was performed through PVA in 98.2% and CVC in 1.8% of the enrolled cases.

As shown in Figure 1, the most common indication for TPE was systemic lupus erythematosus (SLE), accounting for 50.2%. The TPE was performed in patients with SLE who suffered from lupus crisis, lupus nephritis, or in severe disease activity. The other main indications for TPE were dermatomyositis/polymyositis (DM/PM), Sjögren's syndrome (SS), and overlap syndrome (OS), respectively. Other relatively rare indications of TPE included adult-onset Still's disease, CTDs, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), IgG4-related disease (IgG4-RD), systemic sclerosis (SSc), antiphospholipid syndrome (APS), rheumatoid arthritis (RA), hemophagocytic syndrome (HPS), and systemic vasculitis. The disease with the highest average TPE sessions was systemic vasculitis with 3.00 sessions per patient. The average number of procedures were lower in SSc with 2.00 sessions per patient (Table 1).

According to the improvement of patients' clinical symptoms and laboratory examinations,

Table 1. Demographic characteristics of patients and TPE procedural data

Diagnosis	n	Mean±SD	Mean age (year)	IQR	Sex (M/F)	Sessions	Mean sessions per patient†		Plasma	20% albumin, diluted	Plasma plus 20% albumin, diluted	ASFA category
						n	Mean	Min-Max	n*	n*	n*	
SLE	143		33.2	23.0-42.0	16/127	369	2.58	1-8	42	85	242	II
DM/PM	38	50.2±13.9			16/22	92	2.42	1-3	8	14	70	-
SS	21	42.2±14.8			2/19	55	2.62	1-7	1	15	39	-
OS	17	47.6±10.9			1/16	45	2.65	1-5	8	3	34	-
CTD	12	46.8±14.4			0/12	29	2.42	2-4	6	7	16	-
AOSD	12	36.3±13.5			3/9	33	2.75	2-4	2	8	23	-
AAV	10	59.5±7.3			5/5	28	2.80	1-6	2	2	24	I-III
IgG4-RD	9	52.0±15.7			7/2	20	2.22	1-4	1	4	15	-
SSc	8	44.5±16.4			0/8	16	2.00	1-3	1	4	11	III
APS	8	36.4±15.6			5/3	22	2.75	2-5	0	3	19	I
RA	3	32.3±17.6			1/2	7	2.50	2-3	0	1	6	-
Systemic vasculitis	2	20.5±6.4			1/1	6	3.00	3	2	3	1	II-III
HPS	2		55.0		0/2	5	2.50	2-3	0	0	5	III
Total	285		38	26.5-51.0	57/228	727	2.55	1-8	73	149	505	I-III

TPE: Therapeutic plasma exchange; IQR: Interquartile range; M/F: Male/Female; Min: Minimum; Max: Maximum; ASFA: the American Society for Apheresis; SLE: Systemic lupus erythematosus; DM/PM: Dermatomyositis/Polymyositis; SS: Sjögren's syndrome; OS: Overlap syndrome; CTD: Connective tissue disease; AOSD: Adult-onset Still's disease; IgG4-RD: IgG4-related disease; AAV: ANCA-associated vasculitis; Adult-onset Still's disease; SSc: Systemic sclerosis; APS: Antiphospholipid syndrome; RA: Rheumatoid arthritis; HPS: Hemophagocytic syndrome; * The number of TPE sessions; † Values were presented as mean (range: minimum to maximum) to clearly compare the specific number of TPE procedure among different diagnosis.

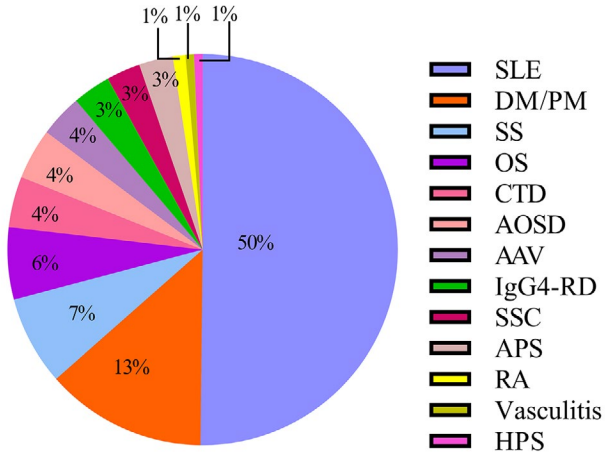

Figure 1. The distribution of indications for TPE in our study.

SLE: Systemic lupus erythematosus; DM/PM: Dermatomyositis/Polymyositis; SS: Sjögren's syndrome; OS: Overlap syndrome; CTD: Connective tissue disease; AOSD: Adult-onset Still's disease; AAV: ANCA-associated vasculitis; IgG4-RD: IgG4-RD: IgG4-related disease; SSC: Systemic sclerosis; APS: Antiphospholipid syndrome; RA: Rheumatoid arthritis; HPS: Hemophagocytic syndrome;

the outcomes of treatment responses to TPE procedures are presented in Table 2. A total of 73.7% patients achieved clinical improvement (CR and PR) after TPE procedures, with 8.8% patients achieved CR and 64.9% patients achieved PR, respectively. The patients in status of disease persistence or worsening after proper management of TPE procedures accounted for 26.3%. The treatment effects of TPE based on the classification of diseases indicated that IgG4-RD presented the highest clinical remission rate of all the patients with a 33.3% CR rate, followed by SS and SSc, with a CR of 23.8% and 12.5%, respectively. However, for the poor sample size of each disease except for SLE, there was a bias in the results. A weak correlation was found between the total number of TPE sessions, the volume of replacement fluid and the outcome of clinical remission ($r=0.130$, $p=0.028$ and $r=0.135$, $p=0.023$, respectively). No statistically significant correlation existed between the age, diagnosis and the outcomes of clinical improvement ($p>0.05$ for all comparisons). In addition, we found no significant difference of therapeutic response between different sexes (Table 3).

In our study, a total of 110 AEs related to TPE in 82 TPE procedures involving 64 patients were reported during all sessions, corresponding to 15.1% for the incidence of AEs (Table 4). The incidence rate of AEs was listed and classified by the type of replacement fluids. Allergic reactions were the most common complication, accounting for 34.5% of the AEs, followed by palpitation (16.4%) and dizziness/weak (13.6%),

Table 2. The comparisons of outcomes of clinical response to TPE among different diagnosis

Indications for TPE	Complete remission		Partial remission		Persistence/worsening		Total	
	n	%	n	%	n	%	n	TPE-related death
SLE	12	8.4	90	62.9	41	28.7	143	0
DM/PM	0	0	24	63.2	14	36.8	38	0
SS	5	23.8	14	66.7	2	9.5	21	0
CTD	1	8.3	7	58.4	4	33.3	12	0
OS	1	5.9	15	88.2	1	5.9	17	0
AOSD	1	8.3	8	66.7	3	25.0	12	0
AAV	1	10.0	5	50.0	4	40.0	10	0
IgG4-RD	3	33.3	5	55.6	1	11.1	9	0
APS	0	0	6	75.0	2	25.0	8	0
SSc	1	12.5	5	62.5	2	25.0	8	0
RA	0	0	3	100.0	0	0	3	0
HPS	0	0	1	50.0	1	50.0	2	0
Systemic vasculitis	0	0	2	100.0	0	0	2	0
Total	25	8.8	185	64.9	75	26.3	285	0

TPE: Therapeutic plasma exchange; SLE: Systemic lupus erythematosus; DM/PM: Dermatomyositis/polymyositis; SS: Sjögren's syndrome; CTD: Connective tissue disease; OS: Overlap syndrome; AOSD: Adult-onset Still's disease; AAV: ANCA-associated vasculitis; IgG4-RD: IgG4-related disease; APS: Antiphospholipid syndrome; SSc: Systemic sclerosis; RA: Rheumatoid arthritis; HPS: Hemophagocytic syndrome.

Table 3. The comparisons of outcomes of the clinical response to TPE and adverse events of TPE between different sex

	Sex				
	Male (n=57)		Female (n=228)		
Number of patient	n	%	n	%	*p*
Number of patient with AEs	15	26.3	49	21.5	0.332
Clinical response to TPE					
Complete remission	4	7.0	21	9.2	
Partial remission	38	66.7	147	64.5	0.868
Persistence/worsening	15	26.3	60	26.3	

TPE: Therapeutic plasma exchange; n: The number of patients involved in events; AEs: adverse events.

respectively. Other complications including hypotension, nausea, fever, catheter thrombosis, coagulation dysfunction, syncope, hypocalcemia-related symptoms, and infection were relatively rare, indicating no significant difference in risk for suffering from those complications whether plasma or albumin was used as replacement fluid. Severe events were much less common and no death associated with TPE was observed in our study. The allergic reactions related to use of plasma were manifested as mild-to-moderate symptoms of pruritus and urticaria in most of the patients, whereas only one case with SLE experienced severe anaphylactic shock during replacement process while using a combination of FFP and human albumin as replacement fluid. Fortunately, the patient was rescued immediately and back to normal without leaving any sequelae. The overall incidence rate of complications did not show a significant difference among the three types of replacement fluids (p=0.214), while plasma as replacement fluid was more often related to episode of anaphylaxis and dizziness/fatigue (p=0.003 and p=0.008, respectively). Correlation analyses showed that the incidence rate of AEs was weakly and positively correlated with the number of TPE sessions (r=0.153, p=0.010), but weakly inversely correlated with age (r=-0.168, p=0.005). No statistically significant correlation was found between sex, the volume of replacement fluids and the incidence rates of AEs (p>0.05 for all comparisons) (Table 3).

Table 4. The comparison of incidence rate of adverse events among subgroups classified by type of replacement fluid

	Plasma (%)		20% albumin (%)		Plasma plus 20% albumin (%)		Total cases (%)		
Adverse events	n	%	n	%	n	%	n	%	*p*
Allergic reactions	7	9.6	0	0	31	6.1	38	5.2	0.003*
Palpitation	3	4.1	6	4.0	9	1.8	18	2.5	0.121
Dizziness/weak	5	6.8	4	2.7	6	1.2	15	2.1	0.008*
Hypotension	0	0	4	2.7	3	0.6	7	1.0	0.070
Nausea	1	1.4	3	2.0	3	0.6	7	1.0	0.174
Fever	0	0	1	0.7	5	0.1	6	0.8	<0.999
Coagulation dysfunction	0	0	2	1.3	3	0.6	5	0.7	0.600
Catheter thrombosis	0	0	1	0.7	4	0.8	5	0.7	<0.999
Syncope	0	0	2	1.3	3	0.6	5	0.7	0.600
Hypocalcaemia related symptoms	0	0	0	0	3	0.6	3	0.4	<0.999
Infection	0	0	0	0	1	0.2	1	0.1	<0.999
Total	16	21.9	23	15.4	71	14.1	110	15.1	0.214

The events were recorded for each TPE procedure. TPE: therapeutic plasma exchange; n: the total number of TPE procedure in each type of replacement fluid.

DISCUSSION

It has been well documented that the overproduction of inflammatory cytokines and autoantibodies, as well as excessive deposition of immune complexes, play critical roles in the progression of rheumatic disorders.[11] The primary rationale of TPE procedure is to remove those pathogenic substances rapidly intended to achieve the goal of disease remission in a short period of time. The TPE is sparsely implemented in patients with rheumatic disorders due to a limited number of the ASFA Category I indications for them. This procedure has been tested in several rheumatic researches, since the initial use of TPE; however, these studies have definitely reported adverse effects or results which are insufficient to warrant recommendations for this technique.[20,21] As a result, data on TPE technical notes and AEs are limited in the rheumatism setting. To the best of our knowledge, this is one of the largest investigations on the applications of TPE in rheumatic diseases up to date. As a whole, data collected from our cohort indicated that patients achieving clinical improvement (including CR and PR) after TPE treatment were up to 73.7%, which is consistent with the previous studies.[22,23] Of note, SLE was the main indication for TPE in our study, representing 50% of all the cases, followed in a descending order by patients with DM/PM and SS. Combination of plasma and 20% human albumin was the most frequently used replacement fluid (69.5%), followed by human albumin and plasma in 20.5% and 10.0% of episodes, respectively. In consideration of great prospects for application of TPE, it is imperative for rheumatologists to further explore more appropriate indications and confirm the safety profile of TPE in rheumatic diseases.

The TPE was initially used in SLE under the prime rationale of eliminating the high titer autoantibodies and circulating immune complexes to control the disease activity. A randomized-controlled trial (RCT) study performed by Wei et al.[24] in 1983 showed that plasma exchange in mild SLE led to significant improvements in serological test results, including antibodies to deoxyribonucleic acid, the serum levels of IgG, IgM, IgA, and circulating immune complexes, while the frequency and degree of clinical improvement revealed no significant advantages over the controls. In contrast, the results from another RCT performed by Lewis et al.[20] indicated that TPE was not capable of improving the prognosis of SLE patients with renal involvements. However, for the treatment of severe SLE, particularly for the patients with DAH or neuropsychiatric lupus, the application of TPE achieved substantial clinical responses, compared to conventional therapies, based on anecdotal cases or non-controlled studies.[23,25,26] According to the latest guidelines recommended by the ASFA, SLE accompanied with severe complications was classified as a Category II indication for TPE,[27] corresponding to the reasons subject to TPE of SLE patients in our center. In our series, up to 62.9% SLE patients achieved PR and patients with CR accounted for 8.4%, which is an encouraging outcome, particularly in severe SLE or patients with involvement of kidney and or central nervous system.

In the present study, we attempted to apply TPE in the treatment of severe conditions of DM/PM, which were the second most common indications for TPE in our center. As far as we know, DM/PM patients with positive anti-melanoma differentiation-associated gene 5 (MDA5) antibody show a high prevalence of hyperferritinemia, elevated serum levels of cytokines, RP-ILD, and poor prognosis even with aggressive immunosuppressive therapies including high-dose glucocorticoids, calcineurin inhibitors, and IVIG.[28,29] Furthermore, hyperferritinemia and elevated cytokines are associated with severity and prognosis of DM-ILD.[30,31] As mentioned above, TPE can remove autoantibodies, elevated cytokines, and other immune reactants involved in the pathophysiology of autoimmune disease. Thus, we speculated that TPE could have therapeutic efficacy for patients with positivity of myositis-specific antibodies or elevated cytokines, particularly for anti-MDA5-positive patients. Our results indicated that 63.2% (24/38) patients achieved PR, which is an inspiring result due to the high fatality rate of severe DM/PM. The positive effects of TPE in acute phase of DM/PM were confirmed by several anecdotal cases,[15-17,32] although Miller et al.[21] reported that TPE failed to improve functional capacity or muscle strength in one RCT consisting of 39 subjects. It is uncertain whether TPE is responsible for remission in idiopathic inflammatory myositis, even with those

favorable outcomes. Nevertheless, further multi-center, large-scale clinical trials are needed to confirm the efficacy of this procedure for DM/PM.

The utility and efficacy of plasma exchange have been demonstrated in patients with catastrophic antiphospholipid syndrome, AAV, and hemophagocytic syndrome according to recommendations from the ASFA.[27] However, the clinical response to TPE of the aforementioned conditions did not reveal a favorable improvement in our institution, which was probably attributed to the small sample size of patients in these entities. A multi-center, prospective cohort study would more accurately evaluate the impact of TPE on prognosis of these patients. Furthermore, we expanded the applications of TPE into the treatment of SS, OS, CTD, AOSD, IgG4-RD, and RA, which have not been included in the recommendation guidelines from the ASFA so far. The majority of these patients were in high titer autoantibodies or hyperglobulinemia and had a poor response to conventional treatments, but showed a good response to the TPE. In particular, the clinical remission rates of IgG4-RD and SS patients in our study achieved a CR rate of 33.3% and 23.8%, respectively. Although the pathogenesis of IgG4-related disease is still unclear, measurement of IgG4 titers is a useful tool for monitoring disease activity in patients with IgG4-RD.[33] The reduction of Ig and cytokines may improve immunomodulatory imbalance and systemic inflammation in IgG4-RD patients. We extrapolated that PE might exert a therapeutic effect by removing pathological and etiological molecules from the plasma in IgG4-RD. The application of TPE in refractory IgG4-RD with excessive IgG and IgG4 protein productions could be an alternative treatment option in the future based on those favorable findings.

The incidence rate of TPE-related AEs varied in different regions, ranging from 3.4 to 9.9% in the US[34,35] and from 10.9 to 60% in other countries outside the US.[36-38] The result from our study indicated that the incidence rate of TPE-related AEs in rheumatic treatment was 15.1%, and plasma-induced allergic reaction was the most frequent complication, which is in line with a previous report.[37] Other common AEs included palpitations, dizziness/fatigue, nausea, and hypotension, accounting for 16.4%, 13.6%, 6.4%, and 6.4% in all episodes, respectively. Occurrence of these complications might be a result of the slight hemodynamics changes caused by the process of extracorporeal circulation, as well as the underlying diseases.

As opposed to a previous report,[36] hypotension occurred less frequently in our study, a possible explanation for which is that the hemodynamic changes caused by centrifugal filtration device are less and slighter due to the lower requirement for blood flow rate compared to the membrane filtration devices. It can be illustrated, in part, by the fact that centrifugal filtration device is a safer option, particularly for patients with hemodynamic instability. Hypotension seemed more likely to occur, when albumin was used as a replacement solution alone, although there was no statistically significant difference ($p=0.070$). The possible reasons may be a too low colloid osmotic pressure and refilling of the intravascular volume. Complications such as coagulation dysfunction, catheter thrombosis, syncope, hypocalcemia and infection were relatively rare, which were mainly attributed to the precautions in advance and operators' professional and skilled techniques. Notably, all patients complicated with catheter thrombosis and catheter-related infection were adopted CVC/FVC as the vascular access in our study. This result indicates that there is a higher security while using superficial veins as vascular access, compared to CVC or FVC. There was a weakly negative correlation ($r=-0.168$, $p=0.005$) between the age and the frequency of AEs, suggesting that the younger patients were more susceptible to suffer AEs. A plausible explanation is that younger patients are prone to presenting more active and prompt immune response to external stimulus.

Considering the shortage of blood resources, we also compared the incidence rate of AEs among different types of solutions to optimize the use of replacement fluids in clinical practice. The analyses of AEs showed that the overall incidence rate of complications was not significantly different among the three types of replacement fluids ($p=0.214$), while allergic reactions and dizziness/weakness seemed to be more frequent in plasma group. This result may be explained by the fact that FFP is prone to anaphylactic reactions for being rich in Igs and complements.[2] It is necessary to monitor the serum albumin level closely for patients undergoing plasma as primary

replacement fluid to reduce the occurrence rate of dizziness. Thus, the use of albumin as replacement fluids in TPE seems to be safer than that of plasma alone. Albumin can be used as a feasible substitute for plasma under the circumstance of scarcity of blood products, although the cost of albumin is higher. In general, TPE is a complex and expensive treatment modality, but a helpful procedure. Considering the high costs of this procedure, we should explore more cost-effective replacement fluids and management strategies to reduce the costs.

There are several limitations to the present study. First, selective bias and information bias were inevitably in this study due to its single-center and retrospective nature, although the patients were enrolled consecutively. Second, there is a lack of uniform international consensus criteria for the evaluation of clinical response currently, which could have led to the assessment results with a certain subjectivity. Third, we did not include the adjuvant therapies that might have an impact on outcome into analysis, which may have affected the accuracy of efficacy assessment of TPE. Fourth, the sample size of several diseases is small, such as RA and HPS, which may have influenced the accurate evaluation of clinical remission rates. Finally, due to the variety of disease entities included and the high heterogeneity of research cases, the clinical improvement results may be controversial to some extent. Hence, further RCTs with a larger sample size should be carried out to assess the efficacy of this procedure and recommend more rational indications for TPE in the future. On the other hand, the main strength of this study is that it is the first study to report the technical notes, clinical responses, and complications related to TPE in the Chinese population with rheumatic diseases. Notably, TPE has frequently showed its unique superiority to several rheumatic diseases and, therefore, it is essential for rheumatologists to confirm the safety profile and risks of this procedure in rheumatic treatments.

In conclusion, TPE is an invasive, but safe, useful and, sometimes, essential tool with an acceptable risk/benefit ratio for most rheumatic disorders, particularly in refractory cases, although not all indications for TPE are proven as effective based on the limited evidence. Furthermore, we suggest that albumin can be used as a feasible substitute for plasma in the case of shortage of blood resources. Further multi-center RCTs are needed to confirm the safety profile and the efficacy of TPE and to determine more proper indications for this procedure.

Declaration of conflicting interests

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