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Removal Dynamics of Autoantibodies, Immunoglobulins, and Coagulation Factors by Selective Plasma Exchange on Three Consecutive Days

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Abstract: Selective plasma exchange has been shown to be effective in various diseases, but no studies have assessed the benefits of daily treatment. We aimed to investigate the removal dynamics of immunoglobulins, fibrinogen, and factor XIII on three consecutive days in three patients. For mean processed plasma volumes of 1.06 × plasma volume, reductions of 79.6%, 49.3%, and 8.6% were seen for immunoglobulins G, A, and M, respectively. The reductions for fibrinogen and factor XIII were 18.4% and 13.0%, respectively. Removal dynamics were similar for immunoglobulin G-related autoantibodies and immunoglobulin G when using daily selective plasma exchange. Moreover, daily use effectively removed the immunoglobulin G while retaining the coagulation factors. When disease-specific autoantibodies are limited to immunoglobulin G, daily selective plasma exchange may be a useful and safe method of intensive induction treatment for plasmapheresis. However, further study is required in larger cohorts to confirm these findings. **Key Words:** Daily, Factor XIII, Fibrinogen, Immunoglobulin, Selective plasma exchange.

Plasmapheresis is often performed to treat autoimmune diseases, with efficacy in removing pathogenic autoantibodies, immune complexes, cryoglobulins, myeloma light chains, and cholesterol-containing lipoproteins from the plasma (1,2). Simple plasma exchange (PE), which uses a conventional plasma membrane separator, is the most common method. This involves passing the patient's blood through a device that separates plasma from other components, before replacing the plasma with either albumin solution or fresh frozen plasma (FFP) (3).

Although FFP contains all the noncellular components of normal blood, it is associated with increased risks of anaphylactoid reactions, citrate reactions, and virus transmission (1). Indeed, a previous study of PE for the treatment of Guillain–Barré syndrome indicated that FFP was significantly associated with more adverse events compared with albumin (4), whereas another indicated that adverse effects occurred more often with FFP than with albumin (5). Therefore, FFP should be avoided unless treatment is required for thrombotic thrombocytopenic purpura or if there is a high risk of hemorrhage (1). Albumin also benefits from having no risk of viral transmission and a decreased risk of anaphylactoid reactions (1). However, when using albumin as the replacement fluid in PE, important coagulation factors and immunoglobulins (Igs) are not replaced. Repeated PE with albumin as the replacement fluid can substantially reduce the concentrations of these key factors (6).

Selective PE (SePE) is a method of simple PE that uses a selective membrane plasma separator (Evacure Plus EC-4A10; EC-4A, Kawasumi Laboratories Inc., Tokyo, Japan) (7). The EC-4A device has a relatively small pore size of 0.03 μm, which is around one-tenth that of conventional plasma

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separators, such as the OP-05W (Asahi Kasei Medical Co. Ltd., Tokyo, Japan) (8). We have previously reported sieving coefficients (SCs) of 0.5, 0.17, and 0 for IgG, factor XIII (FXIII), and fibrinogen, respectively, when using the EC-4A device (8). Thus, SePE can remove approximately 50% of IgG, yet retain the coagulation factors, such as FXIII and fibrinogen. In three plasmaphereses performed on alternate days, we showed differences in the percent reductions of IgG and fibrinogen between the PE group and the SePE group: in the PE group, mean reductions were 82.0% and 80.9%, respectively; in the SePE group, the corresponding reductions were 75.4% and 29.3% (9). The effectiveness of SePE has recently been reported in immune-mediated disorders (i.e., neurological, dermatological), thrombocytopenia, and multiple myeloma (10–14).

When three plasmaphereses are performed, we can remove pathogenic autoantibodies more efficiently on an alternate-day basis than on a daily basis (6). However, if the patient is critically ill, daily therapy provides an intensive induction plasmapheresis. It has been reported, for example, that daily treatment with double filtration plasmapheresis (DFPP) correlated with better clinical response to treatment in patients with severe generalized myasthenia gravis (15). However, repeat DFPP with albumin replacement can reduce the concentrations of larger molecular substances, such as fibrinogen and FXIII (11,16), and thereby increase the risk of bleeding. Although SePE can retain fibrinogen and FXIII, no researchers have investigated the use of daily SePE in clinical practice.

In the present study, we investigated the removal characteristics of autoantibodies, IgG, IgA, IgM, fibrinogen, and FXIII when performing SePE on three consecutive days.

PATIENTS AND METHODS

Study design and patients

This was a retrospective observational study of patients who underwent SePE on three consecutive days between August 2016 and December 2016 at the medical hospital of Tokyo Medical and Dental University. We reviewed medical records and data related to the three SePE sessions and evaluated the processed plasma volumes (PPVs) and concentrations of disease-specific autoantibodies, fibrinogen, and FXIII before and immediately after SePE, if available. The study protocol was approved by the Medical Research Ethics Committee of our university (approval number M2017-231) and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, 2013).

Plasmapheresis

Plasmapheresis was performed using a Plasauto iQ21 blood purification system (Asahi Kasei Medical Co. Ltd., Tokyo, Japan) and SePE was performed using the EC-4A device. Albumin solutions were prepared by diluting 25% albumin in lactated Ringer's solution and 10% sodium chloride as a supplementary fluid during plasmapheresis. The albumin concentration in the supplementary fluid was equivalent to 0.75 that of the pre-SePE treatment levels based on a reported albumin SC of 0.73 when using the EC-4A device (8). To maintain the plasma osmotic pressure of the supplementary fluids, 10% sodium chloride was used in a 1/100 volume of diluted albumin solution. The targets for plasma osmotic pressure and sodium concentration were 280 mOsm/kg/H_2O and 138 mEq/L, respectively.

During SePE, blood flow and plasma separation were maintained at rates of 80–120 and 20–30 mL/min, respectively. An indwelling double-lumen catheter was inserted into the internal jugular vein or femoral vein. Plasma volume (PV) was calculated according to the following Equation (17):

$$PV = (BW/13) \times (100 - Ht)/100 \quad (1)$$

where BW indicates body weight (kg) and Ht indicates hematocrit (%).

The target reduction in IgG after one session of SePE was 50–53% and the PPV of SePE was set at approximately 1.1 × the PV (7). In a previous study, it was estimated that blood volume constituted 0.065 of BW (1); however, we estimated blood volume as BW divided by 13 (approximately 0.077 of BW). Therefore, 1.0 × PV in the previous report was approximately equivalent to 0.85 × PV in this report.

Data measurement and statistical analysis

We measured IgG (normal range: 868–1780 mg/dL), IgA (122–412 mg/dL), and IgM (normal range: 28–177 mg/dL) with a JCA-BM2250 automatic analyzer (JEOL Ltd., Tokyo, Japan). Fibrinogen (normal range: 185–370 mg/dL) and Ht (normal range: 40.8–49.6%) were measured using an XE-2100 automated hematology system (Sysmex Corp., Kobe, Japan). FXIII (normal range: 70–140%) was measured using a chromogenic assay. IgG antibodies associated with

desmoglein 1 (Dsg1Ab; normal range: <20 U/mL), IgG antibodies against BP180 (BP180Ab; normal range: <9 U/mL), and myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA; normal range: <3.5 U/mL) were measured by chemiluminescent enzyme immunoassay. Data for multiple values are presented as means ± standard deviation.

RESULTS

Three cases were included. Case 1 was a 54-year-old female with pemphigus vulgaris, case 2 was a 76-year-old female with bullous pemphigoid, and case 3 was a 74-year-old female with ANCA-associated microscopic polyangiitis. We evaluated the PPVs and concentrations of disease-specific autoantibodies (Dsg1Ab for case 1, BP180Ab for case 2, and MPO-ANCA for case 3), IgG, IgA, IgM, and fibrinogen before and immediately after each SePE treatment. However, we only evaluated the FXIII concentrations before and immediately after SePE in cases 1 and 2.

PPV and IgG, IgA, IgM, fibrinogen, and FXIII removal rates after one SePE session

Among the three cases, the mean PPV for one session of SePE was a PV of 1.06 ± 0.11. After one session of SePE, the mean reductions were 50.4% for IgG, 26.4% for IgA, 1.9% for IgM, 8.8% for fibrinogen, and 2.8% for FXIII. To account for changes in colloid osmotic pressure, the percent reductions of each parameter after one session were corrected using the following Equation (17):

$$Reduction\ rate = \{1 - [Ht_{pre} \times (1 - Ht_{post}/100) \times C_{post}]/ [Ht_{post} \times (1 - Ht_{pre}/100) \times C_{pre}]\} \times 100 \quad (2)$$

where Ht_{pre} and Ht_{post} refer to the Ht (%) before and immediately after each SePE session, and C_{pre} and C_{post} refer to the concentrations before and immediately after each SePE session.

Removal dynamics of IgG, IgA, and IgM for SePE on consecutive days

The removal dynamics of IgG, IgA, and IgM are shown in Figure 1; the percent reductions after three sessions of daily SePE were 79.6% ± 3.6%, 49.3% ± 10.6%, and 8.6% ± 4.5%, respectively.

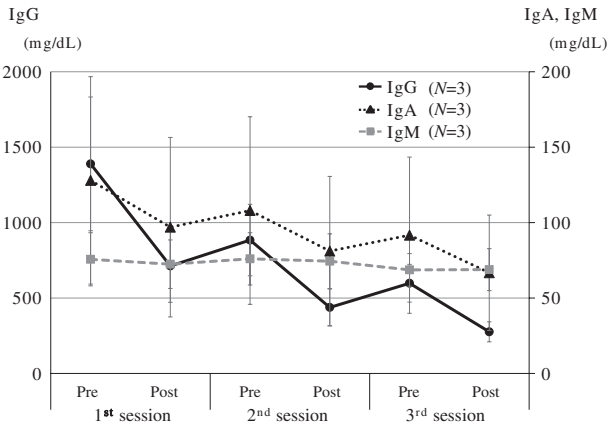

FIG. 1. Removal dynamics of IgG, IgA, and IgM during SePE on consecutive days. The pre- and post-data indicate the concentration of each parameter before and immediately after each SePE session, respectively. Ig, immunoglobulin; SePE, selective plasma exchange.

IgG levels decreased, but IgM levels did not change.

Removal dynamics of disease-specific autoantibodies for SePE on consecutive days

The removal dynamics of disease-specific autoantibodies and IgG are shown in Figure 2. In cases 1, 2, and 3, the reductions in IgG after three sessions of daily SePE were 81.1%, 75.5%, and 82.2%, respectively. Also, the reduction in Dsg1Ab after three sessions of daily SePE was 74.7% for case 1, the reduction in BP180Ab was 85.9% for case 2, and the reduction in MPO-ANCA was 76.8% for case 3. All disease-specific autoantibodies decreased, and the removal dynamics of disease-specific autoantibodies and IgG were similar. To account for changes in colloid osmotic pressure, the concentration of each parameter immediately after SePE was corrected for the Ht using Equation 3 (18), and the percent reductions of each parameter were corrected using Equation 4:

$$Corrected\ concentration = concentration \times Ht\ before\ SePE / Ht\ immediately\ after\ SePE, \quad (3)$$

$$Reduction\ rate\ after\ three\ sessions\ of\ daily\ SePE = [(concentration\ before\ the\ first\ SePE\ session - corrected\ concentration\ after\ the\ third\ SePE\ session) / concentration\ before\ the\ first\ SePE\ session] \times 100 \quad (4)$$

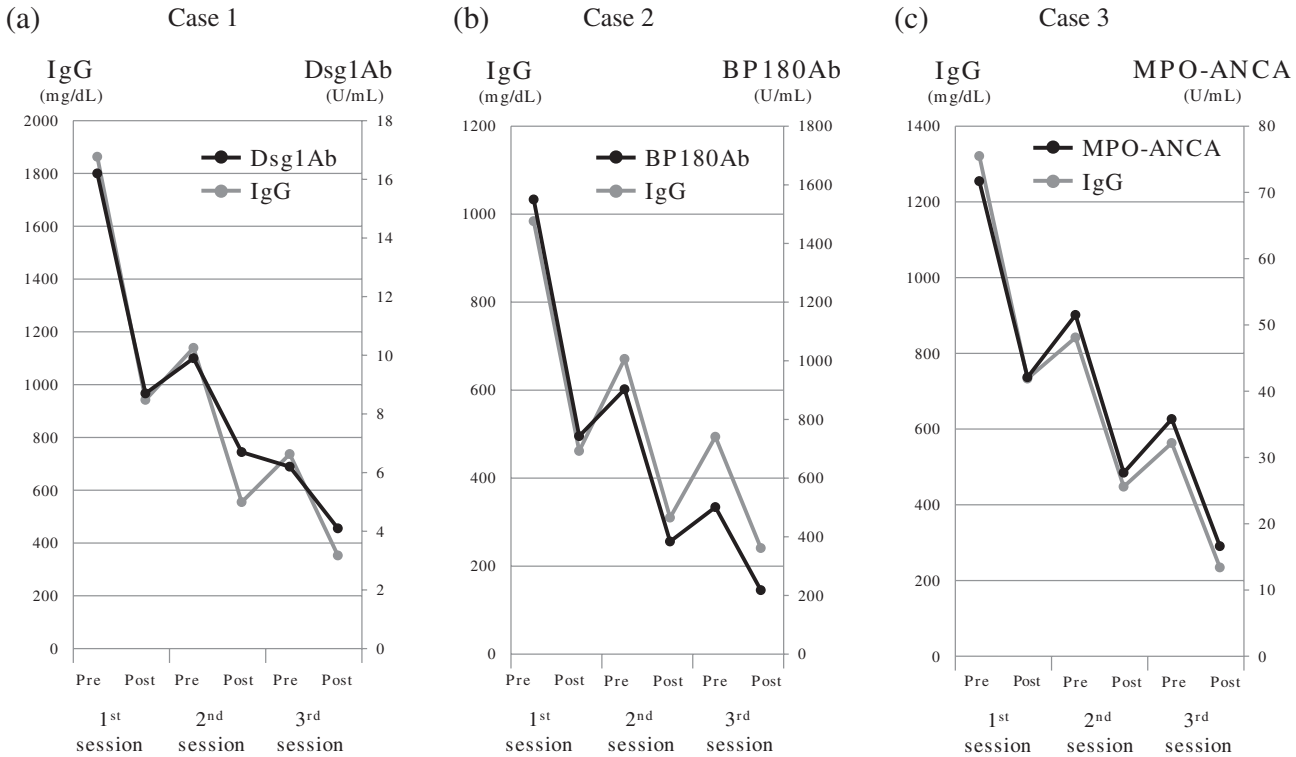

FIG. 2. Removal dynamics of IgG and disease-specific autoantibodies during SePE on consecutive days. Data are shown for case 1 (a), case 2 (b), and case 3 (c). The pre- and post-data indicate the concentration of each parameter before and immediately after each SePE session, respectively. BP180Ab, IgG antibodies against bullous pemphigoid 180; Dsg1Ab, IgG antibodies associated with desmoglein 1; Ig, immunoglobulin; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibodies; SePE, selective plasma exchange.

Removal dynamics of fibrinogen and FXIII for SePE on consecutive days

The removal dynamics of fibrinogen and FXIII are shown in Figure 3. The reductions after three sessions of daily SePE were 18.4% ±17.0% for fibrinogen and 13.0% ±2.4% for FXIII. The reductions of fibrinogen and FXIII after three sessions of daily SePE were suppressed to less than 20%, with similar removal dynamics for fibrinogen and FXIII.

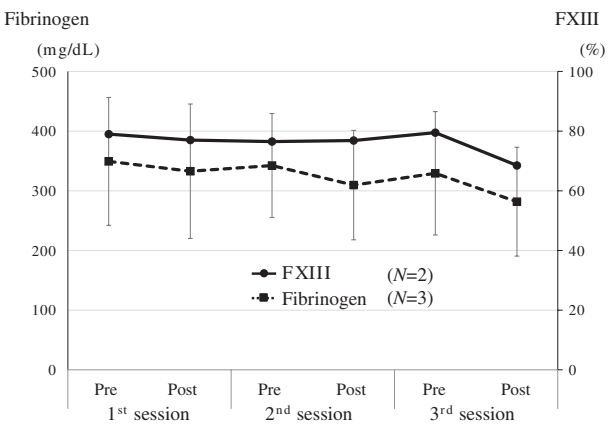

FIG. 3. Removal dynamics of fibrinogen and FXIII during SePE on consecutive days. The pre- and post-data indicate the concentration of each parameter before and immediately after each SePE session, respectively. FXIII, factor XIII; SePE, selective plasma exchange.

DISCUSSION

To the best of our knowledge, this is the first clinical report to describe the removal dynamics of disease-specific autoantibodies, Ig, fibrinogen, and FXIII during SePE performed on three consecutive days. We showed that daily SePE effectively removed IgG, while retaining coagulation factors, such as fibrinogen and FXIII.

Immunoglobulin G and autoantibodies are the most common targets of treatment by plasmapheresis (6). In autoimmune neurological diseases, the pathogenic role of a patient's antibodies has been suggested based on the correlation between antibody titers and clinical outcomes, with high IgG removal rates by plasmapheresis correlating with better clinical response (15,19). In this study, the mean reduction in IgG was 50.4% when the mean PPV was set at 1.06 for a session of SePE. This is consistent with our previous experience, when the reductions in IgG were 50%, 55%, and 60% for PPVs set at 1.0, 1.25, and 1.5 PV, respectively (7).

Very high PPVs during a single SePE treatment yield smaller reductions, as with PE (1). Even when increased from 1.0 to 1.5 PV, for example, there was only a 10% further decrease in IgG, implying that excessive PPV inefficiently increases the duration and cost of treatment (1). A previous report also indicated that each treatment should provide a PPV approximately 0.85 × to 1.2 × our PV, even in PE (1). Based on these findings, we set the target PPV to 1.1.

The removal rates of IgG after one session of PE, DFPP, SePE, and immunoadsorption using a tryptophan-immobilized column (IA) have been reported as approximately 63%, 56%, 50%, and 36%, respectively (9–12). Notably, PE can eliminate plasma proteins, DFPP can reduce the concentrations of larger molecular substances (e.g., IgG and IgM), and IA can remove pathogenic substances by semi-selective adsorption. Although repeated plasmapheresis is often used to treat autoimmune disease, we have only recently evaluated the removal rates after three sessions on alternate days (9). It was shown that the mean percent reductions of IgG were 82.0% for the PE group (PE–PE–PE), 76.4% for the PE/SePE group (PE-SePE-SePE), and 75.4% for the SePE group (SePE–SePE–SePE) (9). In the present study, the mean percent reduction in IgG after three sessions of daily SePE was 79.6%, which was similar after three sessions of PE on alternate days. However, SePE could not remove IgM. Daily SePE can therefore be considered useful for plasmapheresis if the target is limited to IgG. Only half of all IgG within the body is distributed within the plasma, so equilibration between body fluid compartments and variability in synthesis are probably responsible for the changes in IgG between sessions (1,6).

When comparing three plasmapheresis sessions performed daily or on alternate days, daily therapy causes the IgG concentration to decrease more rapidly. However, by the end of a course of therapy, or on the seventh day, both the plasma IgG concentration and the total body IgG tend to decrease more efficiently with alternate-day therapy (6). Thus, we can remove pathogenic substances more efficiently using an alternate-day approach rather than a daily approach, assuming we use the same amount of plasma (6). However, Trikha et al. reported that low-dose daily and alternate-day PE given with FFP replacement had similar efficacy and complication rates in patients with severe myasthenia gravis (20). If these parameters genuinely do not vary to a clinically relevant degree, daily plasmapheresis may be preferable because of the decreased duration of hospitalization and shorter use of indwelling catheters. Severity must also be considered when determining the frequency of therapy (6): if the patient is critically ill, daily SePE offers intensive induction therapy; by contrast, if the aim is to reduce levels of a molecule within a limited number of sessions, but there is no time pressure, plasmapheresis on alternate days may be more appropriate (6).

In this study, Dsg1Ab in case 1, BP180Ab in case 2, and MPO-ANCA in case 3 were studied as disease-specific autoantibodies; the dominant IgG subclasses of these are IgG3, IgG1/4, and IgG1/4, respectively (21–23). Daily SePE was able to remove these disease-specific autoantibodies effectively. Moreover, the removal dynamics of disease-specific autoantibodies and IgG during SePE were similar, because IgG was effectively eliminated by SePE regardless of the IgG subclass. When albumin replacement is used, IgG can be a surrogate marker for monitoring pathogenic autoantibody removal.

When applied with albumin replacement, both PE and DFPP have been shown to reduce fibrinogen and FXIII concentrations markedly (1,9,11,16,24). Similarly, IA causes a marked reduction in fibrinogen concentrations because tryptophan is a high-affinity fibrinogen adsorber (10,12,25). In one study, five sessions of DFPP caused fibrinogen levels to fall below 70 mg/dL in 44% of patients, with oozing developing at the puncture site of the central venous catheter and clinically overt bleeding occurring in approximately 19% and 3% of patients, respectively (24). In another report, repeated DFPP caused severe subcutaneous bleeding in a patient with decreased FXIII levels (16). A decrease in FXIII of <10%, which cannot be detected by the coagulation or bleeding time, can cause spontaneous bleeding, major postoperative bleeding, and delayed wound healing (11,16). Fibrinogen levels were regularly below 100 mg/dL after IA, increasing the risk of hemorrhage (25). By contrast, SePE retained fibrinogen and FXIII even after three consecutive days of therapy in the present study. Indeed, the mean percent reductions were only 18.4% for fibrinogen and 13.0% for FXIII, respectively, with both levels remaining within normal limits. On this basis, daily SePE can be considered safe for plasmapheresis, though fibrinogen may need to be used as a surrogate marker for monitoring the removal of FXIII when SePE is performed with albumin replacement.

Plasmapheresis can only remove pathogenic substances from the plasma, and usually has no ability to reduce the production of those substances. In autoimmune diseases, immunosuppressive therapy

is therefore essential to treat the cause of autoantibody production. However, IgGs except IgG3 has longer half-lives of 22 days (1), which suggests that autoantibodies may exist in the body for more than 3 weeks, even when immunosuppressive therapy is effective. Therefore, combining daily plasmapheresis and immunosuppressive therapy may offer a useful option for intensive induction treatment.

CONCLUSIONS

In this study, daily selective plasma exchange not only removed IgG-related autoantibodies and IgG effectively but also retained essential coagulation factors, such as fibrinogen and FXIII. When disease-specific autoantibodies are limited to IgG, daily selective PE is useful and safe for the intensive induction of plasmapheresis. The paucity of information on daily plasmapheresis means that further studies are needed to investigate the methods, therapeutic effects, and complications of this approach.

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Conflict of Interest: All authors have declared that there are no competing interests.

REFERENCES

1. Kaplan AA. Therapeutic plasma exchange: a technical and operational review. *J Clin Apher* 2013;28:3–10.
2. Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. *Am J Kidney Dis* 2008;52:1180–96.
3. Schwartz J, Padmanabhan A, Aqui N 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 seventh special issue. *J Clin Apher* 2016;31:149–62.
4. Bouget J, Chevret S, Chastang C, Raphael JC. Plasma exchange morbidity in Guillain-Barré syndrome: results from the French prospective, double-blind, randomized, multicenter study. The French Cooperative Group. *Crit Care Med* 1993;21:651–8.
5. McLeod BC, Sniecinski I, Ciavarella D et al. Frequency of immediate adverse effects associated with therapeutic apheresis. *Transfusion* 1999;39:282–8.
6. Hanafusa N. Theoretical basis of pathogenic substance removal during plasmapheresis. *Ther Apher Dial* 2011;15:421–30.
7. Ohkubo A, Okado T. Selective plasma exchange. *Transfus Apher Sci* 2017;56:657–60.
8. Ohkubo A, Kurashima N, Nakamura A, Miyamoto S, Iimori S, Rai T. Solute removal capacity of high cut-off membrane plasma separators. *Ther Apher Dial* 2013;17:484–9.
9. Miyamoto S, Ohkubo A, Seshima H et al. Removal dynamics of immunoglobulin and fibrinogen by conventional plasma exchange, selective plasma exchange, and a combination of the two. *Ther Apher Dial* 2016;20:342–7.
10. Ohkubo A, Okado T, Kurashima N et al. Removal kinetics of antibodies against glutamic acid decarboxylase by various plasmapheresis modalities in the treatment of neurological disorders. *Ther Apher Dial* 2014;18:231–7.
11. Nasu K, Hanafusa N, Nangaku M. Selective plasma exchange can reduce auto-antibodies in patients with bullous pemphigoid without affecting factor XIII and fibrinogen. *J Clin Apher* 2017;32:589–91.
12. Miyamoto S, Ohkubo A, Seshima H et al. Selective plasma exchange for the removal of pemphigus autoantibodies, fibrinogen, and factor XIII in pemphigus vulgaris. *Ther Apher Dial* 2017;21:226–31.
13. Nakae H, Fukuda H, Okuyama M, Igarashi T. Selective plasma exchange for critically ill patients accompanied with thrombocytopenia. *Ther Apher Dial* 2016;20:339–41.
14. Kawabe M, Yamamoto I, Katsuma A et al. Successful treatment of myeloma cast nephropathy using bortezomib-based chemotherapy plus selective plasma exchange. *CEN Case Rep* 2016;5:232–7.
15. Yeh JH, Chiu HC. Double filtration plasmapheresis in myasthenia gravis–analysis of clinical efficacy and prognostic parameters. *Acta Neurol Scand* 1999;100:305–9.
16. Seishima M, Shibuya Y, Kato G, Aoki T. Decreased factor XIII activity in a patient with subcutaneous bleeding after double filtration plasmapheresis. *Ther Apher Dial* 2009;13:229–31.
17. Kawanishi H, Mineshima M, Hirakata H, Akizawa T. Standard for hemodialysis and related therapies by the Japanese Society for Dialysis Therapy 2012. *J Jpn Soc Dial Ther* 2012;45:435–45.
18. Ohkubo A, Okado T, Kurashima N et al. Removal characteristics of immunoglobulin G subclasses by conventional plasma exchange and selective plasma exchange. *Ther Apher Dial* 2015;19:361–6.
19. Dalmau J, Gleichman AJ, Hughes EG et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–8.
20. Trikha I, Singh S, Goyal V, Shukla G, Bhasin R, Behari M. Comparative efficacy of low dose, daily versus alternate day plasma exchange in severe myasthenia gravis: a randomised trial. *J Neurol* 2007;254:989–95.
21. Bystryn JC, Rudolph JL. Pemphigus. *Lancet* 2005;366:61–73.
22. Jankásková J, Horváth ON, Varga R et al. Increased sensitivity and high specificity of indirect immunofluorescence in detecting IgG subclasses for diagnosis of bullous pemphigoid. *Clin Exp Dermatol* 2018;43:248–53.
23. Gao Y, Ye H, Yu F, Guo XH, Zhao MH. Anti-myeloperoxidase IgG subclass distribution and avidity in sera from patients with propylthiouracil-induced antineutrophil cytoplasmic antibodies associated vasculitis. *Clin Immunol* 2005;117:87–93.
24. Yeh JH, Chiu HC. Coagulation abnormalities in serial double-filtration plasmapheresis. *J Clin Apher* 2001;16:139–42.
25. Koessler J, Kobsar A, Kuhn S et al. The effect of immunoadsorption with the Immusorba TR-350 column on coagulation compared to plasma exchange. *Vox Sang* 2015;108:46–51.