

Chronic Renal Failure as a Possible Risk Factor for Allergic Reaction in Therapeutic Plasma Exchange Using Fresh Frozen Plasma

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Abstract: The incidence of allergic reactions in patients with chronic renal failure during plasma exchange using fresh frozen plasma is not well known. We retrospectively reviewed 62 patients who underwent plasma exchange between January 2013 and May 2018. The most common indication for plasma exchange was desensitization/preconditioning for kidney transplant (61.3%, 38/62). The incidence of allergic reactions was significantly higher in patients with chronic renal failure than patients without (57.1% vs. 25.0%,

$P = 0.029$). Also, the incidence of allergic reactions tended to be higher in peritoneal dialysis patients (75%, 3/4) than in hemodialysis (58.8%, 10/17) and preemptive kidney transplant (58%, 11/19). These results suggested the relationship of chronic renal failure and the incidence of allergic reactions in patients undergoing therapeutic plasma exchange using fresh frozen plasma. **Key Words:** Allergic reactions, Chronic renal failure, Desensitization, Kidney transplant, Therapeutic plasma exchange.

Transfusion related reactions are commonly seen during therapeutic plasma exchange (TPE) using fresh frozen plasma (FFP) (1). The most common symptom is mild allergic reactions such as hives and urticarial reactions (1–3).

Since 1988, we have performed 300 kidney transplants. In the last 5 years, approximately 30% of kidney transplant recipients in our center required TPE for desensitization (highly sensitized or ABO blood type incompatible) and preconditioning (focal segmental glomerulosclerosis) (2,4,5). We came to know that these patients experienced higher incidence of allergic reactions for unknown reasons than patients with other indications such as liver failure (2–4). There is no previous study to investigate the impact

of chronic renal failure (CRF) on the incidence of allergic reactions during TPE.

The aim of this study is to investigate the relationship between CRF and the incidence of allergic reactions during TPE.

MATERIALS AND METHODS

Patients

We retrospectively reviewed 62 patients who underwent TPE from January 2013 to May 2018 at Japanese Red Cross Kumamoto Hospital. We divided 62 patients into two groups: allergy group ($n = 29$) and non-allergy group ($n = 32$).

Allergic reactions during TPE were defined as Type I immediate reaction such as anaphylaxis, angioedema, bronchospasm, urticarial (hives) and hypotension based on Gell and Coombs classification (6,7). We defined CRF as patients on dialysis or advanced chronic kidney disease stage more than grade 5 (estimated glomerular filtration rate < 15 mL/min) (8).

This study was approved by the Institutional Ethics Committee of Japanese Red Cross Kumamoto Hospital (approval number 18–45) in

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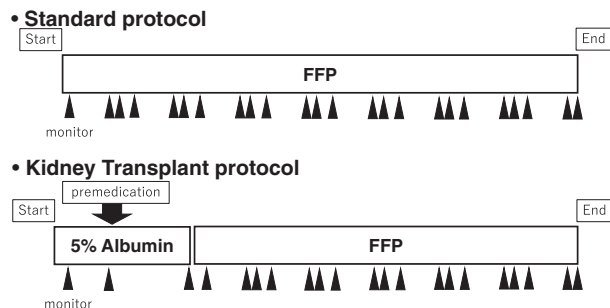


FIG. 1. Therapeutic plasma exchange protocols at Japanese Red Cross Kumamoto Hospital. Premedications: diphenhydramine 10 mg iv and hydrocortisone 100 mg iv. Abbreviations: FFP: fresh frozen plasma. Black arrows showed monitoring patients.

accordance with the current standard for human research. Informed consent was waived because of the retrospective nature of the study.

TPE protocol

We performed TPE without simultaneous hemodialysis to all patients following our own protocols (Fig. 1). For non-kidney transplant patients, we performed standard TPE protocol (replacement with FFP only). Because of the large number of kidney transplant patients, we performed consecutive TPE using 5% albumin then FFP to minimize the usage of FFP. TPE using 5% albumin only (no FFP) was excluded in the present study. Plasma separation was performed using a membrane with “Plasmaflow OP-05 W” (Asahi Kasei Medical Co., Tokyo, Japan). Based on the patients’

body plasma volume, the amount of replacement fluids (5% albumin + FFP or FFP) were adjusted (9).

Due to the high incidence of allergic reactions to FFP, most of the CRF patients received premedication including intravenous diphenhydramine 10 mg and hydrocortisone 100 mg just before the replacement with FFP (Fig. 1).

Immunosuppression and desensitization protocol for highly sensitized or ABO blood type incompatible kidney transplantation

All kidney transplant recipients received our standard immunosuppression regimen including tacrolimus/cyclosporine, mycophenolate mofetil, and methyl prednisolone. Desensitization therapy (Fig. 2) consisted of rituximab (100–200 mg/body) twice on days –13 and –1 or once on day –1, approximately one to three sessions of double filtration plasmapheresis (DFPP) + one session of TPE before kidney transplantation, and mycophenolate mofetil (1000 mg/day) + methyl prednisolone (10 mg/day) from day –14. In case of focal segmental glomerular sclerosis, we performed two sessions of TPE without any DFPPs.

Monitoring during administration of FFP

Following our protocol, we strictly monitored the patient’s vital signs and symptoms for 5 min after starting FFP administration, then at 15 min and at the end (10).

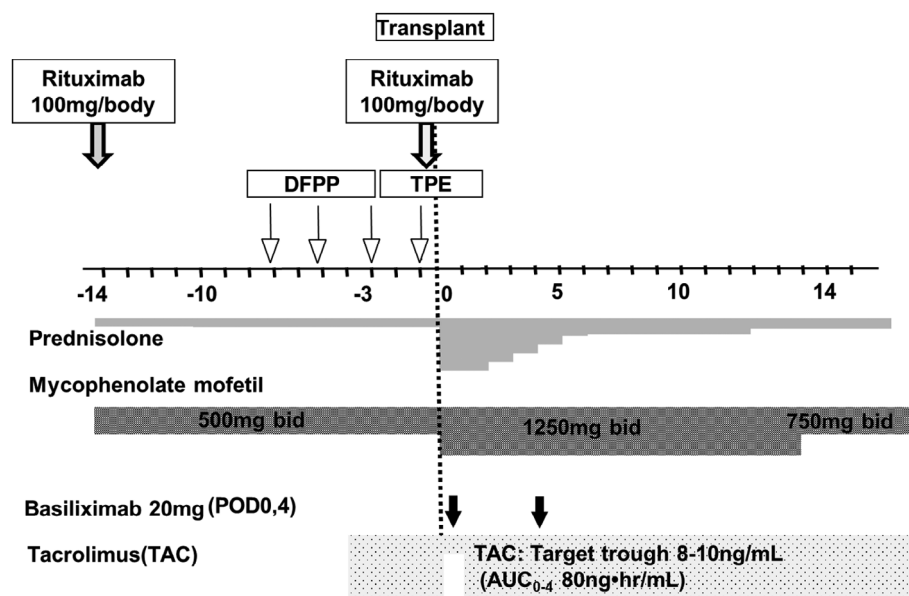


FIG. 2. Transplant desensitization protocol at Japanese Red Cross Kumamoto Hospital. Abbreviations: AUC, area under curve; DFPP, double filtration plasma pheresis; POD, post-operative date; TAC, tacrolimus; TPE, therapeutic plasma exchange.

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, IL, USA). Non-parametric analysis was used to compare continuous variables and Pearson's chi-square test was used for categorical data. Multivariate analysis was performed with stepwise logistic regression model. $P < 0.05$ was taken as statistically significant. Sub-group analysis was performed based on the types of dialysis.

RESULTS

The characteristics of patient are shown in Table 1. Allergic reactions were seen in 29 cases

TABLE 1. Characteristics of patients

	Allergy N = 29	Non-allergy N = 33	P
Age, median (IQR)	53.0 (44.3–64.5)	57.3 (47.3–66.4)	0.28
Sex, male: female	17:12	17:16	0.58
BMI, kg/m ² , median (IQR)	21.2 (19.0–25.6)	22.8 (19.4–24.5)	0.72
CRF, % (N)	82.8 (24)	54.5 (18)	0.029
ACE inhibitor, % (N)	13.8 (4)	0 (0)	0.027
FFP, mL, median (IQR)	2880 (1920–3360)	2880 (2400–3360)	0.51
Indications, (N)	Preconditioning for kidney transplant (22) • ABO i (21) • FSGS (1) AMR (3) HUS (1) TTP (1) MM (1) Wegener's granulomatosis (1)	Preconditioning for kidney transplant (16) • ABO i (14) • FSGS (2) Acute liver failure (3) TTP (3) SLE (2) MM (2) AMR (1) RPGN (1) HUS (1) Adult Still's disease (1) Diffuse alveolar hemorrhage (1) Neuromyelitis optica (1) Thrombotic disease, unknown causes (1)	

Abbreviations: ABO i, ABO blood type incompatible; ACE, angiotensin-converting-enzyme; AMR, antibody mediated rejection; BMI, body-mass index; CRF, chronic renal failure; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; IQR, interquartile range; MM, multiple myeloma; RPGN, rapidly progressive glomerulonephritis; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

(46.8%, 29/62) and were significantly higher in patients with CRF than patients without (57.1% vs. 25.0%, $P = 0.029$). Angiotensin-converting enzyme (ACE) inhibitors were used for 14% of patients in the allergy group while none in the non-allergy group ($P = 0.027$). The most common indications for TPE was preconditioning/desensitization for kidney transplant (61.3%, 38/62).

The incidence of allergic reactions was as follows: Urticaria (66%, 19/29), rash (34%, 10/29), and nausea (3%, 1/29). No one had anaphylactic reactions, and no one required TPE interruption. None of the allergic reactions were seen during the albumin part of the kidney transplant protocol but during FFP part.

In multivariate analysis (including age, CRF, and ACE inhibitors), CRF was significantly associated with allergic reactions (odds ratio 4.38 [95% confidence interval 1.23–15.6], $P = 0.023$).

The incidence of allergic reactions tended to be higher in patients on peritoneal dialysis (75%, 3/4) than on hemodialysis (58.8%, 10/17) and recipients who underwent preemptive kidney transplant (58%, 11/19) although there was no significant difference.

DISCUSSION

Allergic, anaphylactoid, and anaphylactic reactions result from the release of vasoactive substances from mast cells and basophils (2). The incidence of allergic transfusion reactions has been estimated at <1% to 3% of all transfusions (11–13). Most allergic reactions are mild and limited to urticarial, pruritis, and/ or flushing (11). Also, they are commonly associated with FFP and platelet transfusions (11,13). The rate of allergic reactions to FFP reported range from 1:591 to 1:2184 plasma units transfused (12,13).

In contrast to anaphylactic reaction, allergic reactions are likely to be underreported or dismissed because the symptoms are often minimal (14). To monitor the adverse reactions of the patients undergoing TPE, we established a team in our dialysis unit. Our incidence of allergic reactions was likely higher compared to the previous reports because of this monitoring team (1–3,15).

Our study showed the negative impact of CRF on the incidence of allergic reactions while TPE using FFP and/or albumin. The relationship between CRF and uremic pruritus is well-known, affecting up to 46% of hemodialysis patients (16–20) but the pathophysiology of uremic pruritus is not fully understood and is likely to be multifactorial (16). Subclinical or overt uremic neuropathy, skin or nerve

inflammation in the context of kidney failure-associated chronic systemic inflammation, or an increase in activity of μ -opioid receptors due to kidney failure have all been implicated (16–25). These underlying factors might evoke urticarial or allergic reactions in CRF patients, especially in peritoneal dialysis patients who are thought to have higher levels of certain uremic toxins (25,26), although there was no statistical difference in the present study.

Similar to the present study, Hisamichi et al. (27) reported the higher incidence of allergic reactions in patients with younger age and indications other than hepatic insufficiency as risk factors for allergic reactions in initial TPE using FFP. In contrast to our study, they mainly focused on liver failure, not on CRF due to the small number. On the other hand, the study supported our results and essentially we observed similar phenomenon; possible risk of CRF for allergic reaction in TPE using FFP.

Although most of the CRF patients received kidney transplant protocol in our study, Schmidt et al. (15) reported (in their 185 patients undergoing 912 TPEs) that the incidence of adverse events was not different by the type of replacement fluids including FFP alone, FFP with albumin and albumin alone. Thus, the protocol difference between standard TPE protocol (TPE using FFP) and kidney transplant protocol (TPE using FFP and albumin) would have little impact on the allergic reactions. ACE inhibitor is also a well-known cause for allergic reactions through the blockade of kinase I and II, inactivating enzymes of bradykinin (28). Thus, we included age (27) and ACE inhibitors into the multivariate analysis and concluded the independent impact of CRF on allergic reactions for patients undergoing TPE.

There are some limitations in this study. This is a retrospective study in a single institution. For kidney transplant recipients, they were educated to report any kind of adverse event to health care providers during TPE session. These factors might affect the high incidence of allergic reaction. Although there is no strong evidence to support that anti-histamine premedication decreases the incidence of allergic reactions (11,29,30), this premedication could have alleviated the incidence of allergic reactions for kidney transplant protocol patients. However, the incidence of allergic reactions was still higher in CRF patients than the others.

CONCLUSION

The incidence of allergic reactions in patients with chronic renal failure (CRF) was significantly higher

than patients without CRF. The mechanism remains unknown, but our results showed that CRF may be a possible risk factor for allergic reaction in therapeutic plasma exchange using fresh frozen plasma. Further studies are needed to confirm the pathophysiology of this phenomenon.

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Conflict of Interest: None.

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