Letter to the Editor
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Successful Desensitization by Post-Centrifugal Plasma Filtration in Two Highly Sensitized Heart and Lung Transplant Recipients

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Dear Editor,

The presence of donor-specific antibodies (DSAs) not only increases the incidence of antibody-mediated rejection (AMR) but also leads to other complications, such as increased frequency of high-grade T cell-mediated rejection, chronic lung allograft dysfunction, bronchiolitis obliterans syndrome, cardiac allograft vasculopathy, and poor allograft survival in heart and lung transplant recipients [1-3]. Sensitized patients have a lower five-year survival rate than non-sensitized patients (65% vs. 74%), and rejection occurs more acutely and severely in the former than in the latter [3, 4]. We describe successful desensitization using post-centrifugal plasma filtration (PCPF) in two heart and lung transplant recipients with multiple DSAs. There is no report of desensitization treatment using PCPF in heart and lung transplant recipients. This retrospective study was approved by the Institutional Review Board at Pusan National University Yangsan Hospital, Yangsan, Korea (No. 05-2015-106).

One patient (Case 1, Table 1) was admitted on May 2015 for heart transplantation and showed high levels of four preformed DSAs, with a cumulative mean fluorescence intensity (MFI) of 35,035 at admission. As high DSA levels can predispose to AMR, the patient was desensitized. Two and 10 sessions of PCPF were performed before and after transplantation, respectively, using Com.Tec (Fresenius, Kabi, Germany). The primary plasma separator was a plastic disposable kit (PL1; Fresenius), and the secondary plasma fractionator was a 2A column (Evaflux; Asahi Kasei Medical, Japan) with an albumin sieving coefficient of 0.62. To reduce the AMR risk, rituximab, corticosteroid, and bortezomib were administered. Multiple treatments with immunosuppressants and 12 sessions of PCPF reduced the DSA MFI from 35,035 to 4,559 (Fig. 1A). Moreover, only two of the four DSAs were detected. The patient recovered from the rejection episode and was alive on day 1,774 post-transplantation.

Another patient (Case 2, Table 1), a candidate for lung transplantation, admitted on January 2016, presented high levels of

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Table 1. Baseline characteristics of the two patients with DSAs

Case	Sex	Age (yr)	Diagnosis	Recipient			Donor			DSA (initial MFI strength)			Pre-transplant		Outcome (days)	
				HLA A	HLA B	HLA DR	HLA A	HLA B	HLA DR	Class I	Class II	Cumulative MFI	CDC (T/B)	FCM (T/B)	Rejection	Alive/ Dead
1	F	32	Dilated cardiomyopathy	11/24	07/54	04/04	24/24	51/52	14/15	B52 (9,135), B51 (2,484)	DR14 (14,616) DR15 (8,800)	35,035	Positive/ Positive	Positive/ Positive	AMR episode	Alive (1,774)
2	F	54	Acute interstitial pneumonia	33/33	44/44	07/13	02/11	13/48	12/14	A2 (2,752), B48 (7,093), B13 (3,079)		12,924	Negative/ Negative	Positive/ Positive	No	Alive (1,474)

Abbreviations: AMR, antibody-medicated rejection; CDC, complement-dependent cytotoxicity crossmatch; DSA, donor-specific antibody; FCM, flow cytometry crossmatch; HLA, human leukocyte antigen; MFI, mean fluorescence intensity; T/B, T cell/B cell.

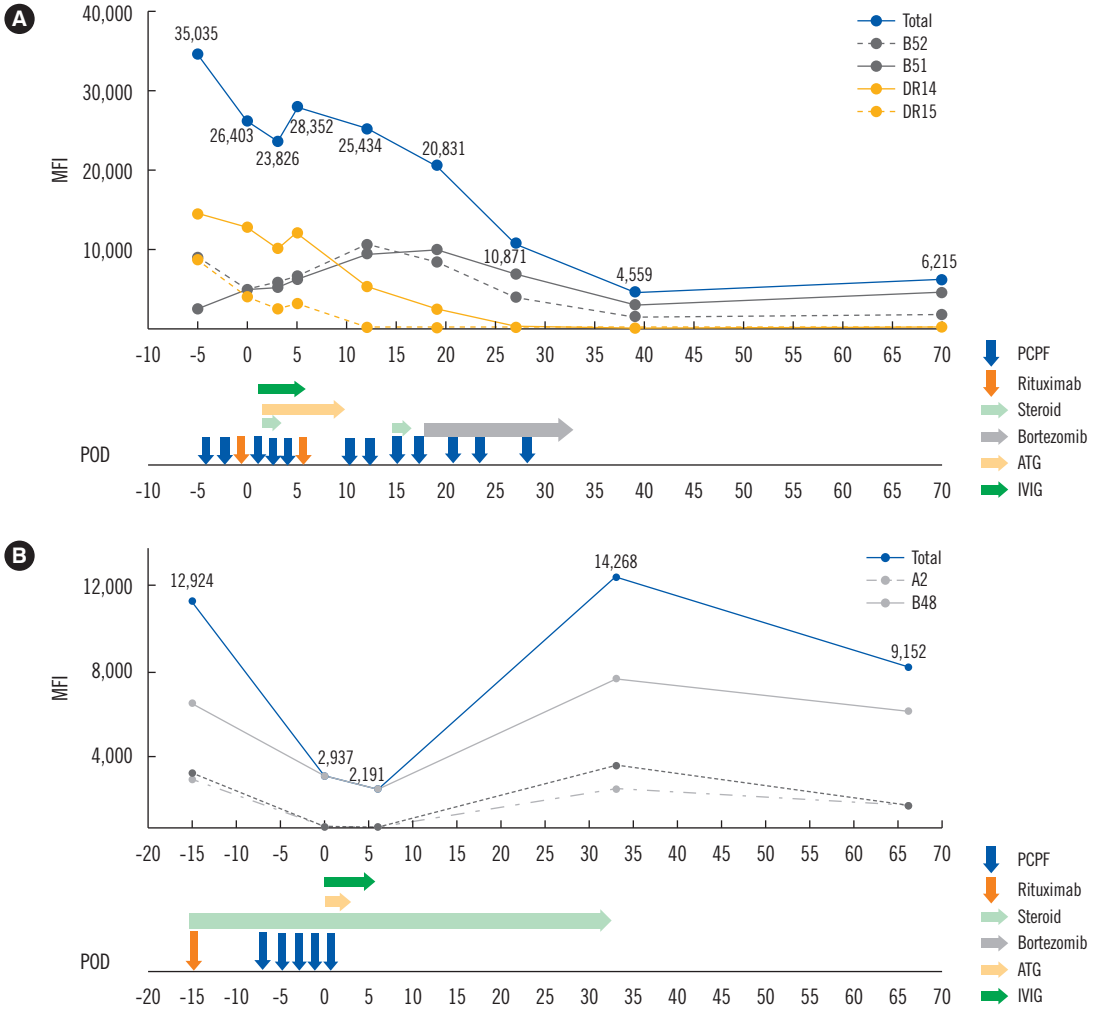

Fig. 1. Changes in DSAs with desensitization treatment. (A) A heart transplant recipient (Case 1, Table 1) with preformed DSAs and (B) a lung transplant recipient (Case 2, Table 1) who underwent desensitization before donor matching.
Abbreviations: ATG, anti-thymocyte globulin; DSA, donor-specific antibody; IVIG, intravenous immunoglobulin; MFI, mean fluorescence intensity; PCPF, post-centrifugal plasma filtration; POD, postoperative day.

46 anti-HLA antibodies (Abs); of these, five showed MFI > 10,000; 27 showed MFI 3,000-10,000, and 14 showed MFI < 3,000. High DSA levels were predicted for this patient, and initial desensitization with rituximab before and during PCPF was scheduled. Four PCPF sessions were performed before the operation or donor matching to reduce anti-HLA Ab levels. A

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matched donor was found after four sessions of PCPF, and the cumulative MFI of three DSAs decreased from 12,924 to 2,937 on the day of transplantation (Fig. 1B). DSA MFI values increased to 14, 268 one month after transplantation, and the patient was subjected to another PCPF session. The patient was alive on day 1,474 post-transplantation.

Rituximab (375 mg/m^2) and plasmapheresis should be administered as pre-transplantation treatment to the highly sensitized patients. Intravenous immunoglobulin (IVIg; 1-2 g/kg) and anti-thymocyte globulin (0.75-1.5 mg/kg) were administered as induction therapy. Depending on the patient condition, steroids and bortezomib may be administered [3-5]. IVIg therapy is at the core of most desensitization protocols and provides protection against infectious complications [6]. Within one week of IVIg administration, a 33% decrease in panel-reactive Ab was observed in heart transplant recipients, and a >80% reduction in cytotoxicity was achieved with repeated doses [1]. Recently, therapeutic monoclonal Abs have been used to prevent graft rejection [3]. Rituximab, a chimeric anti-CD20 monoclonal Ab, has no effect on plasma cells, but does affect B cells [3]. Therapeutic plasma exchange (TPE) also decreases intravascular IgG levels, with an efficacy comparable to that of IVIg, but it requires a longer treatment period. Bortezomib is a reversible 26S proteasome inhibitor that decreases plasma cell levels and has other pleiotropic immunomodulatory effects [6]. Bortezomib treatment reduced alloantibody levels in heart transplant recipients [7]. In this study, two patients with high DSA levels were treated with rituximab and/or bortezomib, with no graft loss. Positive T cell flow cytometry crossmatch is a risk factor for AMR [4]. An MFI of 3,000-5,000, a widely recognized flow cytometry crossmatch-positive cutoff, is considered a target for desensitization treatment [8].

In cases of cadaveric transplantation, the donors are not known in advance, and thus, the desensitization treatment before transplantation is shorter after donor selection. As TPE replaces all plasma, drugs are also removed. Similar to immunoadsorption, PCPF removes only Ig in the plasma that do not pass through the secondary filter. Therefore, it is possible to remove plasma Abs while perpetuating the effects of the drug, which is more effective for desensitization treatment. Our study has some limitations; the treatment method would differ according to the condition of each patient, and owing to the small number of patients, the usefulness of the desensitization protocol could not be statistically validated. In conclusion, we report two patients with high levels of preformed DSAs who underwent PCPF before transplantation. Although the desensitization period was short owing to the critical condition of the patients, the transplantation was successful. This study shows that successful desensitization in heart and lung transplant recipients can be achieved under favorable circumstances.

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AUTHOR CONTRIBUTIONS

Conceptualization: HHK. Investigation and data curation: HGJ, DHK, WHC, JSK, SYL and HJY. Writing-original draft preparation and writing: HJL. Writing-review and editing: KHS and HJL. Supervision: HHK. Approval of final manuscript: all authors.

CONFLICTS OF INTEREST

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