# Plasmapheresis in the Treatment of Early Acute Kidney Allograft Dysfunction

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***Objective:*** **To evaluate the efficacy of plasmapheresis (PP) in kidney transplant recipients with acute humoral rejection (AHR).**

***Patients and Methods:*** **A retrospective review was conducted of all kidney allograft recipients who had undergone PP rescue therapy for early acute allograft dysfunction diagnosed as AHR at Shaheed Labbafinejad Medical Center from 1995 to 2002.**

***Results:*** **Twelve patients (4 men and 8 women; median age, 32 years; age range, 15-68 years) with AHR were treated with PP. The median time from transplantation to AHR was 6 days (range, 2-7 days). PP was performed in 2 to 11 sessions (median, 8.5 sessions) in the patients studied. Eight patients responded to that treatment, and their creatinine value normalized. Those responders were monitored for a median of 162.5 weeks (range, 69.3-484.7 weeks), and all had a functioning allograft during the follow-up period except for 1 patient in whom the graft failed 154 weeks after transplantation. In the 4 remaining patients (nonresponders), the allograft failed within the first posttransplant month. The median time from the acute serum creatinine elevation to the initiation of PP was 6 days in responders and 18.6 days in nonresponders (*P* = .37).**

***Conclusions:*** **We suggest that PP with or without other therapeutic measures may have a role in the salvage of grafts with early acute dysfunction that is resistant to conventional therapy. Our findings indicate that graft survival in patients with AHR who respond to PP can be comparable to that in other kidney recipients.**

**Key words:** *Kidney transplantation, Plasmapheresis, Allograft rejection, Humoral rejection, Serum creatinine level*

Acute humoral rejection (AHR) of a kidney allograft is defined as the rapid deterioration of allograft function that is mediated by antibody generation against the donor's antigens. The incidence of AHR ranges from 3% to 10% among kidney transplant patients, and approximately 20% to 30% of patients with acute rejection have a humoral component [1]. One-year graft survival does not exceed 15% to 50% in patients with AHR, a significant number of whom experience graft loss [2, 3]. AHR is often indicated by early and severe rejection that is resistant to steroids and antilymphocyte therapy [4]. A few isolated reports have suggested a role for plasmapheresis (PP) in the treatment of AHR, but the effectiveness of that treatment has not been established [5, 6]. PP is most often administered in combination with immunosuppressants such as mycophenolate mofetil plus tacrolimus or with intravenous immunoglobulin (IVIG) [2, 7]. It has been shown that treatment with PP leads to an acceptable rate of graft survival [8], although few studies in the literature have addressed that issue. We report the role of PP in the treatment of 12 kidney recipients with early acute allograft dysfunction that was diagnosed as AHR and their renal allograft outcome in our center.

## Patients and Methods

A retrospective review was conducted of all kidney allograft recipients who underwent PP rescue therapy for AHR at Shaheed Labbafinejad Medical Center from November 1995 to May 2002. AHR was diagnosed in patients with acute allograft dysfunction that did not respond to antirejection therapy

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and that exhibited at least 1 of the following characteristics: typical histologic features of antibody-mediated rejection, a positive donor-specific post-transplant cross-match, the positive result of a post-transplant panel reactive antibody (PRA) screen, or the positive result of a pretransplant PRA screen. Patients who did not meet those criteria were excluded. All pertinent information about the study subjects was obtained from their medical records. The patients had been fully instructed about their therapeutic options and had provided informed consent.

### Immunosuppression

All patients received prophylactic immunosuppression consisting of cyclosporine (3-4 mg/kg/d), azathioprine (1-2 mg/kg/d), and prednisolone (40-50 mg/d). A combination of antilymphocytic agents and pulse steroid therapy was administered to all patients in whom rejection occurred after the first 4 or 5 postoperative days. Pulse steroid therapy was discontinued when PP rescue therapy was initiated. If no response to conventional antirejection therapy occurred in 3 days, PP was performed.

### Treatment protocol

The standard PP rescue therapy consisted of the removal of 2 L of plasma with the replacement of 100% of the volume removed. The replacement fluid was given as 50% fresh frozen plasma and 50% albumin (5% solution). The patients underwent PP for 90 minutes every other day by means of a COBE Spectra cell separator (COBE 2997, COBE BCT, Lakewood, Colo, USA). Treatment with PP was discontinued when a clinical improvement was noted, complications supervened, or dialysis was required. Response to treatment was defined as improved urinary output and a significant decrease in the serum creatinine level.

### Statistic analyses

We used the Mann-Whitney *U* test to compare continuous variables between groups. Survival analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 9.0, SSPS Inc, Chicago, Ill, USA) by means of the Kaplan-Meier method.

## Results

Twelve patients (4 men and 8 women; median age, 32 years; age range, 15-68 years) were treated with PP for AHR. The median time from transplantation to serum creatinine elevation was 6 days (range, 2-7 days). All patients had received a kidney from a living-unrelated donor and had had more than 4 HLA mismatches. All patients had a negative cross-match before transplantation, but in 6 patients, the cross-match was positive at the time of rejection. In 6 patients, the result of a PRA screen was positive before transplantation (range, 5%-40%). At the time of rejection, the result of a PRA screen was positive in 7 patients (range, 10%-100%). A renal biopsy was performed in 1 patient. Antirejection therapy consisted of antithymocyte globulin in all patients, and 9 of those individuals also received pulse steroid therapy. PP was performed in 2 to 11 sessions (median, 8.5 sessions) (Table).

Eight patients responded to the treatment

**Table**. Demographic and clinical characteristics of patients with acute humoral rejection

| Patient No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Response to PP | N | N | N | N | P | P | P | P | P | P | P | P |
| Age (y) | 68 | 19 | 23 | 50 | 43 | 19 | 45 | 32 | 16 | 15 | 32 | 38 |
| Sex | M | F | F | F | M | F | F | F | F | M | F | M |
| Biopsy result | - | - | - | P | - | - | - | - | - | - | - | - |
| Pulse steroid therapy | P | P | N | P | N | P | P | P | N | P | P | P |
| ATG | P | P | P | P | P | P | P | P | P | P | P | P |
| Posttransplantation cross-match | P | N | P | N | P | N | P | P | N | P | N | N |
| Pretransplantation PRA | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 0 | 5 | 6 | 10 | 40 |
| Posttransplantation PRA | 100 | 100 | 100 | - | 10 | 10 | - | - | - | 70 | 100 | - |
| Interval from transplantation to AHR | 6 | 6 | 4 | 6 | 3 | 6 | 6 | 6 | 2 | 4 | 7 | 7 |
| Time to PP initiation | 3 | 27 | 10 | 28 | 3 | 17 | 6 | 6 | 15 | 14 | 5 | 6 |
| PP sessions (no.) | 10 | 2 | 10 | 10 | 7 | 10 | 5 | 4 | 10 | 4 | 2 | 11 |
| Creatinine level, PP treatment, day zero | 8.8 | 8.5 | 11.8 | 4.9 | 9.8 | 8 | 5.7 | 6.1 | 10.5 | 3.5 | 4.3 | 8.5 |
| Creatinine level, PP treatment, day 10 | 6.9 | - | 6.5 | 3.4 | 7.7 | 3.0 | 3.2 | 3.9 | 10.4 | 2.2 | 2.7 | 3.1 |
| Creatinine level, PP treatment, day 30 | - | - | - | - | 2.4 | 1.4 | 1.7 | 2.8 | 5.6 | 1.7 | 1.9 | 4.5 |
| Current creatinine level | - | - | - | - | .6 | 1.4 | - | 1.4 | 1.8 | 1.3 | 1.3 | 2.5 |

PP, Plasmapheresis; N, negative; P, positive; M, male; F, female; ATG, antithymocyte globulin; PRA, panel reactive antibodies; AHR, acute humoral rejection.

described above, and their creatinine values normalized. In those individuals, the median serum creatinine level at days zero, 10, and 30 after the initiation of PP was 7.05 mg/dL, 3.12 mg/dL, and 2.15 mg/dL, respectively. Those patients were monitored for a median of 162.5 weeks (range, 69.3-484.7 weeks), and all had a functioning allograft during the follow-up period except for 1 patient in whom the graft failed 154 weeks after transplantation. In the 4 remaining patients (the nonresponders), the allograft failed within the first posttransplant month. Three of those 4 failed allografts demonstrated a posttransplant PRA of 100%. The median time from the serum creatinine elevation to the initiation of PP was 6 days in responders and 18.6 days in nonresponders ($P = .37$). Overall, the 2-year graft survival was 66.7% (mean survival time, 5.6 years; 95% CI, 3.1-8.1).

## Discussion

In this study, we showed that PP could preserve a kidney allograft in 75% of patients who were diagnosed as having AHR. Although AHR was not biopsy-proven in most of the patients studied, various clinical characteristics and the results of laboratory analyses rendered a diagnosis of AHR likely in those individuals and suggested the value of an alternative treatment such as PP. Biopsy was not performed in most of the patients in this retrospective study because of our prompt initiation of treatment before the confirmed diagnosis of AHR and because of the risk of kidney rupture during the first few postoperative days. PP rescue therapy led to a relatively acceptable graft survival rate in these patients, and in only 1 patient who demonstrated a good response to PP did the graft fail during the 2-year follow-up period.

AHR is associated with a high rate of graft loss in patients treated with conventional therapy, and no definitive treatment has been identified for that type of allograft failure. PP is thought to remove antibodies produced by the antibody-mediated immune reaction in the recipient and has been used successfully as a preemptive therapy in crossmatch–positive transplant recipients [7, 9]. PP has also been used as rescue therapy in patients with AHR. In 1984, Banowsky and colleagues used PP to treat steroid-resistant rejection in 32 patients and reported a 60% initial response to therapy and a 56.6% graft survival rate 2 years after treatment [10]. A higher response rate was achieved when PP was combined with other treatments. In a study of 18 patients, the combination of PP and an aggressive immunosuppressive regimen produced an improvement in 78% of the patients with AHR [11]. In a report by Pascual and colleagues [4], the role of PP and mycophenolate mofetil plus tacrolimus in decreasing the level of donor-specific alloantibodies and treating AHR in 5 patients was discussed. PP is now combined with IVIG (which exerts an alloantibody-suppressive effect) in most transplant centers. At the time of our early experiments with the prevention of allograft dysfunction, IVIG had not yet been suggested for that purpose in the literature. Thereafter, although we knew that IVIG could be helpful in preventing renal allograft failure, the high cost and unavailability of that agent in the drug market of Iran prevented our prescribing it.

Montgomery and colleagues used the combination of PP and IVIG to treat patients with AHR [7] and prevented graft loss in 9 of their 10 study subjects. Rescue therapy with PP and IVIG was shown to be successful in 71% to 90% of patients with AHR and enabled a 2-year graft survival rate of 70% to 80% [2, 7, 12]. Even though treatment with PP and IVIG offers an opportunity for graft salvage, no clinical trial has studied the effectiveness of PP or IVIG alone. No definite protocol for the use of PP has been established, and the average number of PP sessions required and the most advantageous time for their administration have not been determined. Our findings failed to show a significant difference in the duration of treatment or the time from the serum creatinine elevation to the initiation of PP in responders versus nonresponders. However, the time from the serum creatinine elevation to the initiation of PP was slightly shorter in the responders (median, 6 days vs 18.6 days).

We acknowledge that our findings are based on the limited experience from a single transplant center. Also, we could not use definite criteria to diagnose AHR. Montgomery and colleagues used a broad set of criteria (which are similar to our diagnostic criteria) in the diagnosis of AHR, but their subjects demonstrated a 90% response to the combination of PP and IVIG [7]. There are also reports of successful outcomes in cases of steroid-resistant rejection, regardless of the pathophysiologic mechanism [13]. Those results are sufficiently encouraging to warrant considering the use of PP in patients with acute allograft dysfunction that is resistant to conventional therapy.

In conclusion, we suggest that PP with or without other therapeutic measures may have a role in the salvage of grafts with acute dysfunction that is resistant to conventional therapy. Our findings indicate that patients who respond to PP can demonstrate graft survival comparable to that in other

kidney recipients. However, corroborative evidence provided by clinical trials is needed to clarify the use of PP in this group of patients.

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