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One Year Results of Preoperative Single Bolus ATG-Fresenius Induction Therapy in Sensitized Renal Transplant Recipients

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ABSTRACT

Sensitization in kidney transplantation is associated with more acute rejections, inferior graft survival, and an increase in delayed graft function. This study was designed to evaluate the efficacy and safety of preoperative single bolus antithymocyte globulin (ATG) induction therapy in sensitized renal transplant recipients.

Methods. Fifty-six cadaveric donor kidney transplant recipients were divided into two groups: Group I (nonsensitized group, $n = 30$) and group II (sensitized group, PRA>10%, $n = 26$). ATG was given as a single preoperative bolus induction therapy to group II (ATG IV; 9 mg/kg). The group I patients were treated with mycophenolate mofetil preoperatively as induction therapy. The basic immunosuppressive regimen included tacrolimus (FK-506) or cyclosporine, mycophenolate mofetil, and prednisolone. After hospital discharge, patients were followed on a routine outpatient basis for 12 months.

Results. Acute rejection episodes (ARE) occurred in 20% (6/30) of group I and 15.38% (4/26) of group II patients (P = NS). Infections occurred in eight patients (26.7%) as 11 episodes (36.7%), averaging 1.4 episodes per infected patient in group 1, and 6 patients (23.1%) for a total of 10 episodes (38.5%), averaging 1.7 episodes per infected patient, in group II (P = NS). Occurrence of side effects and hospital stay were almost comparable in the two groups. No delayed graft function was observed in either group. The 12-month actuarial patient and graft survival were 100% in Group I and II.

Conclusion. A preoperative single bolus ATG induction therapy was an effective and safe therapeutic measure, yielding an acceptable acute rejection rate in presensitized renal transplant recipients.

ALTHOUGH many new drugs have emerged into the immunosuppressive armamentarium during the last decade, acute rejection episodes (ARE) constitute a major problem in kidney transplantation (KT), representing a leading cause of chronic graft dysfunction and late graft loss.[1,2] The survival of kidney transplantations in sensitized patients is shorter than that in nonsensitized patients, and the difficulty of transplanting sensitized patients increases proportionately to the patient's panel reactive antibody (PRA) titer. Due to high PRA scores, many patients are eventually dropped from their center's waiting list and never receive a transplant. So new immunosuppressive modalities have been developed to reduce the incidence and severity of allograft rejection episodes among sensitized renal transplant recipients.

Rabbit antithymocyte globulin (ATG) is a polyclonal antihuman antibody directed against a number of T-cell antigens. Although its precise mechanism of action is unclear, its use as an induction immunosuppressive agent results in reduced rates of delayed graft function and acute rejection, with better 1-year graft survival and renal function in both sensitized[3] and unsensitized recipients.[4] Recently it has been shown that a single intraoperative bolus induction therapy of ATG was effective to reduce ARE and improve 1- and 3-year graft survival without increasing the incidence of infections, especially CMV disease.[5] Here, we

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report our findings on the clinical benefit of inclusion of ATG (Fresenius) as a bolus induction therapy in sensitized renal transplant recipients. Both efficacy as graft survival and function, and safety, as number and types of side effects, were examined in 26 sensitized renal transplant recipients.

MATERIALS AND METHODS

Patient Demographics

Between July 2002 and June 2004, a total of 56 patients were assigned to group II ($n = 26$), who received a single preoperative bolus therapy of ATG (Fresenius), or group I ($n = 30$), who were treated with mycophenolate mofetil preoperatively as induction therapy. Donors were cadavers. The recipient and donor demographics were comparable in the two groups (Table 1).

Pre-transplant Status

Donor-recipient blood group matching was identical in all patients. The HLA-AB/DR matching between donors and recipients of two groups is shown in Table 1 (P = NS). Immunologic low risk was defined as PRA score <10%, with exclusions of those recipients of previous KT, multiple pregnancies or multiple blood transfusions. Group I patients were immunologic low risk; and the PRA scores of group II patients were all are above 10% (Table 1).

Immunosuppressive Therapy

In group II, a bolus of 9 mg/kg of ATG was given 2 hours before operation, lasting until after the completion of the vascular anastomoses. To reduce the side effects of ATG, 40 mg methylprednisolone was administered intravenously before ATG administration. MMF was started 6 hours before the operation at a dose of 1 g in group I as induction therapy. All the patients in the two groups received 500 mg of intravenous methylprednisolone during the operation and a 3-day bolus of intravenous methylprednisolone therapy (8 mg/kg per day) posttransplantation.

Table 1. Demographics, Pretransplant Status, and Immunosuppressive Regimen of Patients

Characteristic	Group I	Group II
Number	30	26
Gender distribution (M:F)	21:9	14:12
Age ($X \pm$ S.D.)	40.8 ± 8.16	43.1 ± 9.39
Donor age ($X \pm$ S.D.)	26.27 ± 4.28	26.88 ± 3.69
Pretransplant dialysis (months)	10.4 ± 17.9	10.5 ± 7.64
PRA score (%)		
<10	30	0
10–20	0	4
20–50	0	13
>50	0	9
HLA mismatching		
0	0	0
1	3	1
2	6	8
3	10	8
>3	11	9
Immunosuppressive regimen		
Neoral/MMF/Prednisone	18	10
FK506/MMF/Prednisone	12	16
Conversion (Neoral to FK506)	2	0

Maintenance immunosuppression did not differ between the two groups, including a calcineurin inhibitor (CsA Neoral or tacrolimus), combined with prednisone and MMF. Two patients in group 1 were converted from Neoral to FK506 because of gingival hyperplasia (Table 1).

Diagnosis of ARE

To avoid the complications of percutaneous kidney biopsy, ARE in the first week posttransplantation were diagnosed by progressive elevation of serum creatinine (>20% of baseline creatinine); response to antirejection therapy; and clinical signs of rejection including fever (>38.0°C), decreased urinary output, pain over an enlarged kidney graft, hypertension, and color Doppler increased kidney graft size and elevated vascular resistance index (>0.8). After the first week posttransplantation, percutaneous kidney biopsy was performed in cases of functional deterioration, and kidney pathology classified using the updated Banff classification.[6]

Diagnosis of Infection

Urine culture was performed routinely after the catheter was removed on day 5 after transplantation. Thereafter, urine culture was obtained weekly on a routine basis and more frequently when indicated. The urine was considered infected if greater than 100,000 organisms mL^{-1} were present or it was culture positive. Cultures were also taken from other sites (eg, sputum) when patients had persistently elevated leukocyte counts or episodes of fever. Bronchoscopy and bronchial lavage were performed when a pulmonary infiltrate was present and sputum samples were inadequate. Chest X-rays were taken every other day during the first week posttransplantation, then weekly until patient discharge. Polymerase chain reaction test for cytomegalovirus, herpes simplex, herpes zoster, and Epstein-Barr virus were performed before transplantation and when needed after grafting. Viral infections were diagnosed on the basis of a positive test or histological proof of tissue invasion.

Patient Follow-up

Patients were monitored daily while hospitalized, once weekly for 1 to 3 months, twice monthly for 4 to 6 months, and once monthly thereafter for up to 12 months posttransplantation. Patients were monitored for the signs of ARE, serum creatinine, infections, and side effects.

Statistical Analysis

Data were presented as mean values ± S.D. or as percent of total using student's t test and chi-square test to assess statistical significance. $P < .05$ were considered significant.

RESULTS

Acute Rejection Episodes (ARE)

ARE occurred in 6 of 30 patients (20%) in group I between 3 and 165 days posttransplantation (Table 2). There were three patients in the first week and three patients beyond the first month posttransplantation (46.2 ± 62.3 days, median 25 days). For group II, ARE occurred in 4 of 26 patients (15.38%) between 4 and 11 days posttransplantation, (6.5 ± 3.1 days, median 5.5 days) except one patient. The difference between two groups was not significant