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Prophylactic Use of Rabbit Antihuman Thymocyte Immunoglobulin in Renal Transplantation

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ABSTRACT

INTRODUCTION: Patients receiving a renal transplant were studied to: (1) evaluate the efficacy and safety of a prophylactic application of rabbit antihuman thymocyte immunoglobulin (ATG-R) plus immunosuppressive therapy, and (2) compare the outcomes to those of a control group of patients receiving only immunosuppressive therapy.

METHODS: A total of 922 recipients receiving allograft renal transplantation in our hospital were enrolled between May 2003 and March 2009. Patients with inferior conditions in pregnancy history, blood transfusion history, repeated transplantation, panel reaction antibody, lymphocytotoxicity test, and human leukocyte antigen matching were assigned to the experimental group (n = 156). They received conventional immunosuppressive therapy plus a single-bolus preoperative high dose (1.5 mg/kg) and a short-term postoperative low dose (0.5-1 mg/kg) of ATG-R prophylactic treatment. A control group (n = 766) received only the immunosuppressive therapy. The incidence rates of delayed graft function (DGF), acute rejection (AR) within 6 months and lung infection within 6 months, and the 1-year patient and kidney survival rates of the patients in the experimental and control groups were compared.

RESULTS: The incidence of DGF was significantly lower in the experimental group than the control group (1.92% vs 8.49%; $P < .01$). The incidence of AR within 6 months was also lower in the experimental group (5.13% vs 10.97%; $P < .05$). There were no significant group differences in the incidence of lung infection within 6 months or 1-year patient and kidney survival rates. Survival rates for transplant recipients were 98.72% and 98.43% for the experimental group and control group, respectively.

CONCLUSION: A preoperative high dose and a postoperative short-term low dose of prophylactic ATG-R could markedly reduce the incidence of DGF and AR but not increase the incidence of lung infection in highly sensitive renal transplant recipients. This protocol may be an effective and feasible ATG immune-induction therapy.

Abbreviations and Acronyms

AR = acute rejection
ATG-R = rabbit antihuman thymocyte immunoglobulin
DGF = delayed graft function
HLA = human leukocyte antigen
PRA = panel reaction antibody
WBC = white blood cell count.

Drug abbreviations

AZa = azathioprine
CsA = cyclosporine A
FK-506 = tacrolimus
MMF = mycophenolate mofetil
MP = methylprednisolone
MZR = mizoribine
Pred = prednisone

KEYWORDS: Renal transplantation; Rabbit antihuman thymocyte immunoglobulin; Prophylactic application.

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original study

Prophylactic Use of Rabbit Antihuman Thymocyte Immunoglobulin in Renal Transplantation

INTRODUCTION

Renal transplantation has become the conventional therapy for end-stage renal disease in recent years, but common complications such as acute rejection (AR) and delayed graft function (DGF) are still important determinants for its success or failure. Inhibiting the occurrence of AR and DGF is the key to transplantation success.

Prophylactic use of rabbit antihuman thymocyte immunoglobulin (ATG-R) before and after renal transplantation surgery has been adopted by many foreign transplant centers. Several studies have shown that ATG could promote the recovery of renal parenchymal damage and significantly reduce the occurrence of AR and DGF [1]. However, the application of ATG has also led to adverse reactions such as varying degrees of infection, thereby affecting patient and kidney survival rates. Further research is needed. In the present investigation, patients receiving a renal transplant were studied to: (1) evaluate the efficacy and safety of a preoperative high-dose (1.5 mg/kg) and postoperative short-term low-dose (0.5-1 mg/kg) prophylactic application of ATG-R plus immunosuppressive therapy, and (2) compare the outcomes to those of a control group of patients receiving only immunosuppressive therapy.

METHODS

Study Design

The investigation is retrospective. Data were obtained from the database of the authors' hospital between May 2003 and March 2009.

Participants

A total of 922 patients (518 male; 404 female) participated in the investigation. Their mean age was 48.1 years (range, 14-77 years). All patients received an allograft renal transplant. Data from patients who died during the perioperative period from heart or liver failure with normal graft function were excluded from the study.

Group Enrollment

Experimental group absolute enrollment criteria. Patients with 1 of the following criteria were allocated into the experiment group: (1) panel reaction antibody (PRA) > 20%, (2) lymphocytotoxicity test > 5%, (3) blood transfusion received more than 2 times, (4) second renal transplantation.

Experimental group relative enrollment criteria. Patients with more than 2 of the following criteria were also allocated into the experiment group: (1) 2.5% < PRA < 20%, (2) lymphocytotoxicity test 4% to 5%, (3) more than 2 pregnancies, (4) blood transfusion, (5) second renal transplantation, (6) 1-2 human leukocyte antigen (HLA) matches.

A total of 156 patients met the inclusion criteria for the experimental group. The remaining 766 patients served as the control group.

Administration of Immunosuppressive Therapy

Patients in both the experimental and control groups received immunosuppressive therapy. The drugs used for this therapy were: cyclosporine A (CsA), mycophenolate mofetil ([MMF] CellCept; Hoffmann-La Roche Inc, Basel, Switzerland), mizoribine (MZR), azathioprine (AZa), prednisone (Pred), and tacrolimus (FK-506).

The drugs were administered in the following combinations: CSA + MMF / MZR / AZa + Pred or FK506 + MMF / MZR / AZa + Pred in 2 groups, respectively. The treatment protocols of the 2 groups had no statistically significant difference.

The initial dosage of CsA was 6-7 mg/kg, which was then adjusted according to: CsA concentration was 250-350 ng/mL in 1 month, 200-300 ng/mL in 2-3 months, 150-250 ng/mL in 4-6 months. The initial dosage of FK-506 was 0.1-0.15 mg/kg, which was adjusted according to: FK506 concentration was 8-10 ng/mL in 1 month, 7-9 ng/mL in 2-3 months, 6-8 ng/mL in 4-6 months. MMF 1 g was taken at 1 hour preoperatively and the postoperative dosage was 1-1.5 g/d. Methylprednisolone (MP) 1 g was given preoperatively and during the operation; the MP dose was reduced to 0.5 g daily within 3 days after the operation. On the 4th day after the operation, prednisone 40-50 mg was given; it was reduced to 10 mg as the maintenance dosage 30 days after the operation. For the patients with ATG-R induction, immunosuppressive dosage was usually reduced.

Administration of ATG-R

In addition to the immunosuppressive therapy, the experimental group received ATG-R. First, patients were given dexamethasone 5 mg. Then, ATG-R (1-1.5 mg/kg) was intravenously infused preoperatively for 3 hours. Three to 5 days after the operation, 0.5-1mg/kg ATG-R was given 1 to 3 times. The medication duration and dosage were adjusted according to the physical condition of the patients. The ATG-R dose was reduced and duration was shortened in patients who were lean; the dose was increased proportionately in physically strong patients and continued to 7 days after the operation. For patients with confirmed AR, ATG-R (1-1.5 mg/kg) was given for 3-5 days.

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The occurrence of side effects such as chills, fever, tachycardia, vomiting, dyspnea, and peripheral thrombophlebitis was closely monitored. If adverse reactions occurred, we slowed the drip rate or stopped infusion to ease the symptoms. Peripheral blood leukocytes and platelet counts were determined daily during treatment, and blood cell count was observed for 2 weeks after treatment. When platelet count was < 80 × 10^9/L or white blood cell count (WBC) was < 2.5 × 10^9/ L, drug dosage was reduced; when platelet was < 50 × 10^9/ L or WBC was < 1.5 × 10^9/ L, ATG-R was discontinued.

Diagnostic Criteria for Acute Rejection

Diagnosis of AR was judged according to a comprehensive analysis of the following criteria: (1) clinical manifestations such as hypourocrinia, elevated blood pressure, fever, weight gain, or gas pains in the transplanted renal region; (2) serum level of creatinine elevated by more than 15%; (3) increased urinary protein; (4) color Doppler ultrasound indicating an increase of the vascular resistance index; (5) renal graft biopsy and pathological examination showing antibody-mediated rejection and T-cell mediated rejection (according to Banff 97 guidelines); (4) clinical symptoms that were improved by antirejection treatment.

Diagnosis and Treatment of Delayed Graft Function

Patients were diagnosed as having DGF if they needed hemodialysis maintenance treatment within 2 weeks after transplantation, excluding the possibility of ureteral obstruction, renal artery stenosis, or AR. These patients accepted hemodialysis, reduction of CsA or FK506 dosage to half, activating blood circulation, and removal of blood stasis treatment.

Diagnostic Criteria for Lung Infection

Patients were diagnosed as having lung infection if they had a chest X-ray showing lamellar and plaque shadows or interstitial tissue change, plus 1 of the following: (1) cough and expectoration (recent occurrence or aggravation of original respiratory symptoms); (2) fever; (3) lung signs of consolidation or crackles; (4) blood WBC > 10 × 10^9 or < 4 × 10^9.

Data Analysis

The incidence rates of delayed graft function (DGF), acute rejection (AR) within 6 months and lung infection within 6 months, and the 1-year patient and kidney survival rates of the patients in the experimental and control groups were compared. SPSS 10.1 statistical software (Chicago, IL, USA) was used for statistical analysis. PRA and HLA matches in the 2 groups were compared with a rank sum test. The lymphocytotoxicity test and donor kidney source were compared with a chi-square test. The Mann-Whitney test was used to compare the incidence of AR, DGF, and infection between the 2 groups. A probability < .05 was considered statistically significant.

RESULTS

Group Characteristics

Table 1 contains the characteristics of the patients in the experimental and control groups. There were no statistically significant differences in age, sex, or the administration of immunosuppressive agents between the 2 groups (P > .05). There were significant group differences in pregnancy history (P < .01), blood transfusion history (P < .01), repeated transplantation (P < .01), PRA (P < .01), lymphocytotoxicity test (P < .01), and HLA matches (P < .05). In all significantly different comparisons, the experimental group had lower scores than the control group.

Outcomes

Table 2 contains the number of patients experiencing DGF, AR, lung infection, and graft and recipient survival for the patients in the experimental and control groups. The incidence of DGF in the experimental group and the control group was 1.92% and 8.49%, respectively; the incidence was significantly lower in the experimental group (P < .01). The incidence of AR within 6 months in the experimental group and the control group was 5.13% and 10.97%, respectively; the incidence was significantly lower in the experimental group (P < .05). The incidence of lung infection within 6 months in the experimental group and the control group was 9.62% and 9.66%, respectively; the group comparison was not significantly different. One-year graft survival rates were 98.08% and 97.91% for the experimental group and control group, respectively; no significant group difference was found. One-year survival rates for transplant recipients were 98.72% and 98.43% for the experimental group and control group, respectively; the group difference was not significant.

Adverse Events

Experimental group. In the experimental group, 6 patients (3.85%) had systemic side effects due to ATG-R; the side effects included fever (n = 2), vomiting (n = 3), and dyspnea (n = 1). These side effects disappeared by slowing down the rate of infusion and administration of dexamethasone. No severe allergic reactions were observed. Seven patients developed leukopenia, 4 patients developed lymphopenia, and 3 patients developed thrombocytopenia. Among these 14 patients, 10 patients recovered after withdrawal of ATG-R and reduction of the dosage of MMF, 3 patients recovered after administration of drugs to increase WBC and platelets, and 1 patient died due to leukopenia and infection.

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Table 1. Characteristics of the Patients in the Experimental and Control Groups; Probability of Significant Group Differences (N = 922).
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Characteristic	Experimental Group (n = 156)	Control Group (n = 766)	*P*
Age, years			
Mean	47.7	48.3	>.05
Range	14-77	15-75	
Gender, n			
Males	95	421	>.05
Females	61	345	
Pregnancy history, n			
Once	18	165	<.05
More than 2 times	26	87	
Repeated transplantation, n			
Second	11	0	<.01
Third	2	0	
Panel reaction antibody, %			
0	105	718	
1-10	21	30	<.01
11-20	24	18	
> 20	6	0	
Lymphocytotoxicity test, %			
0-3	26	649	
4-5	123	117	<.01
6-10	3	0	
11-15	4	0	
Human leukocyte antigen matches, matching sites			
4-6	8	81	<.05
3-4	52	406	
1-2	96	289	
Immunosuppressive agents, n			
CSA+Pred+MMF/MZR/AZa	92/4/7	513/21/29	>.05
FK506+Pred+MMF/MZR/AZa	45/2/6	188/5/10	

Control group. In the control group, 43 patients developed leukopenia, 10 patients developed lymphopenia, and 14 patients developed thrombocytopenia. Most of the patients recovered after adjusting the dosage of MMF; 8 patients recovered after using drugs to increase WBC and platelets; 2 patients died due to leukopenia and infection.

DISCUSSION

ATG is a polyclonal antilymphocyte serum. It contains specific antibodies that act directly against a variety of T cell surface-active molecules (eg, CD2, CD3, CD4, CD8, CD18, HLA-DR) and could quickly reverse T cell-induced graft rejection. At present, there are 3 types of ATG: ATG-R and ATG-F are derived from a rabbit, and ATGAM is derived from a horse. ATG-R is most commonly used [2]. Studies have shown that ATG-R was significantly superior to ATGAM in reducing the AR of renal transplants and improving recipient tolerance [3]. In a study on heart transplantation, ATG-R and ATG-F was more successful in reducing the incidence and lessening the adverse consequences of AR when compared with OKT3 [4,5]; ATG-R and ATG-F had similar effects to OKT3 in other aspects [6].

So far, the majority of trials have used ATG on the basis of strict triple medication, which reduced the occurrence of AR but at

Table 2. Outcome Measures for Patients in the Experimental and Control Groups Following Treatment for Renal Transplantation; Probability of Significant Group Differences (N = 922). doi: 10.3834/uij.1944-5784.2010.12.04t2

Outcome Measure	Experimental Group (n = 156)		Control Group (n = 766)		*P*
	n	%n	n	%n	
Acute Rejection incidence[a] Antibody-mediated rejection T-cell mediated rejection	8 3 5	5.13	84 29 55	10.97	<.05
Delayed graft function incidence	3	1.92	65	8.49	<.01
Lung infection incidence[a]	15	9.62	74	9.66	>.05
Graft survival rate, 1 year	153	98.08	750	97.91	>.05
Recipient survival rate, 1 year	154	98.72	753	98.43	>.05

[a]Within 6 months

the same time inevitably increased the incidence of infection [7,8]. Regarding the lasting role of ATG in the removal of T cells and regulation of cell surface molecules, some recent trials have reduced the maintenance dose of other immunosuppressive agents [9].

We adjusted the prophylactic treatment protocol of ATG-R based on the summary of domestic and foreign experiences. A high dose was given preoperatively and the dosage and frequency were reduced after the operation. When compared with the control group, patients in the experimental group had inferior conditions for PRA, the lymphocytoxicity test, and HLA matches, among other characteristics. Results of the study showed that the incidence of DGF and AR was significantly lower in the experimental group than the control group. There were no significant group differences in the incidence of infection within 6 months or 1-year patient and kidney survival rates. These results demonstrated the efficacy and safety of prophylactic use of ATG-R.

Kyllönen et al [10] performed a randomized trial in which patients were divided into: (1) a treatment group that received a preoperative high-dose single-bolus ATG (9 mg/kg) induction treatment, (2) a comparison group receiving 2 doses of basiliximab (Simulect; Novartis Pharmaceuticals Corp, East Hanover, NJ, USA) induction, and (3) a comparison group receiving the traditional CsA triple therapy. The results showed that the incidence of DGF in the 3 groups was 5.7%, 24.1%, and 15.9%, respectively. DGF was significantly lower in the group receiving the single-bolus high dose of ATG than in the other 2 groups (*P* = .025). AR incidence was 11.3%, 12.1% and 20.5%, respectively. One-year graft survival rates were 98.1%, 90.6%, 96.6% and 5-year graft survival rates were and 96.6%, 93.2%, 84.1%, respectively. These results indicated that ATG induction therapy could significantly reduce the incidence of DGF and, when used in combination with relatively low doses of CsA, could significantly reduce posttransplant dialysis and improve graft survival.

Some conflicting results have been reported. Sheashaa et al [11] found that, although the conventional single-bolus high-dose ATG induction therapy could significantly reduce the incidence of AR, no obvious influence on the function of the transplanted kidney or patient and kidney survival rates was observed. Wang et al [12] also performed a single-bolus high-dose ATG induction therapy trial. Recipients were divided according to PRA into a nonsensitive group (n = 30) and a sensitive group (PRA > 10%; n = 26). Patients in the sensitive group were given a high dose of ATG (9 mg/kg) induction therapy preoperatively. The results showed that the incidence of AR in the 2 groups was 20% and 15.38%, respectively; the incidence of AR was significantly lower for patients in the sensitive group. Infection rates were 26.7% and 36.7%, respectively; the incidence of infection was higher for patients in the sensitive group. These data suggested that administering a preoperative bolus of ATG was a safe and effective method that could significantly reduce the incidence of transplant rejection.

In the present study, 3 patients (1 in the experiment group; 2 in the control group) died due to leukopenia and infection. Monitoring of blood leukocyte is required during the entire course of ATG treatment. During the period when the leukocyte

is descending quickly, monitoring should be done every day. If the leukocyte falls between 2,000 and 3,000 cells/mL^3, the ATG dosage should be reduced by half. If the leukocyte falls below 2,000 cells/mL^3, the ATG administration should be stopped.

CONCLUSIONS

A preoperative high dose and a postoperative short-term low dose of prophylactic ATG-R could markedly reduce the incidence of DGF and AR but not increase the incidence of lung infection in highly sensitive renal transplant recipients. This protocol may be an effective and feasible ATG immune-induction therapy.

Conflict of Interest: none declared

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