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Comparison of single bolus ATG and Basiliximab as induction therapy in presensitized renal allograft recipients receiving tacrolimus-based immunosuppressive regimen

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Abstract

Presensitized renal allograft recipients require special management to improve their outcome, and there is no consensus on the optimal immunosuppressive strategy. We retrospectively analyzed clinical data of 82 patients, who were PRA positive pre-transplant (above 10%) and received single bolus ATG and basiliximab as induction therapy, and assessed safety and efficacy of two kinds of induction therapies. Patients of ATG group ($n=40$) received single bolus ATG (Fresenius, 9 mg/kg preoperatively) and those of basiliximab group ($n=42$) were given two doses of basiliximab (Simulect, Novartis, 20 mg) on days 0 and 4 post-transplant. All patients received standard triple immunosuppressive therapy with tacrolimus (FK-506), mycophenolate mofetil (MMF), and steroids. The follow-up time was 12 months. There was no hyperacute rejection in two groups, and delayed graft function occurred in two patients of ATG group and three of basiliximab group. After 12-month follow-up, more acute rejection (AR) episodes were observed in basiliximab group than ATG group (35.7% vs. 15%, $P=0.032$). Although highly significant differences were observed between ATG group and basiliximab group with respect to the incidence of thrombocytopenia ($P=0.001$), single bolus ATG was well tolerated. Incidences of other adverse events and infection episodes did not differ between two groups ($P>0.05$). One-year patient and graft survival was 95%, 92.5% and 95.2%, 88.1% in ATG and basiliximab group respectively ($P>0.05$). Both single bolus ATG and basiliximab induction therapy achieved similar one-year graft/patient survival. However, single bolus ATG yielded much lower AR rate than basiliximab without increase in infection episodes and severe adverse events.

Keywords: Kidney transplantation; ATG; Induction therapy; Basiliximab; Sensitization

1. Introduction

Sensitization was defined as the presence of HLA antibodies in the patient's serum and sensitized patients had acute rejection, delayed graft function, and graft failure at a significantly higher rate than those without antibodies [1]. The difficulty of transplanting sensitized patients increases proportionally to the patient's level of sensitization. To wait for compatible donors, these sensitized patients spend longer time on the waiting list and become tethered to dialysis. Intravenous gammaglobulin (IVIG) has been demonstrated to be a novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients [2]. However, IVIG is an expensive therapy, and most patients, especially those in China, cannot afford a four dose course of IVIG, which costs $25 000–$26 000 [2]. Therefore, it is urgent to design new immunosuppressive strategy manage sensitized recipients.

ATG has been widely used and proven effective in reducing the risk of AR after kidney transplantation. Most importantly, recent study has showed that a strategy combining sirolimus with ATG for high-risk recipients could lead to prompt recovery of renal function with a low risk of acute rejection episodes [3]. This approach, however, may expose recipients to overimmunosuppression, as evidenced by an increased incidence of cytomegalovirus (CMV) infection, post-transplant lymphoproliferative disease, and patient death with functioning graft [4]. To overcome this shortcoming,

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single bolus intraoperative induction therapy of ATG has been proposed and proven effective in reducing AR rate and improving 1- and 3-year graft survival without increasing the incidence of infections, especially CMV disease [5,6], the effectiveness of which in sensitized renal allograft recipients has been reported in our previous study [7].

Anti-CD25 mAbs, commercially available as basiliximab, have been used in renal transplantation for almost ten years. Although basiliximab cannot be indicated as a treatment of established acute rejection, the selective blockage of CD25 makes the basiliximab powerful rejection-preventing agents without significant added risk of infection, malignancy or other major side effects. It was demonstrated that both ATG and basiliximab, when used for induction therapy in a sequential protocol, are equally effective in terms of graft and patient survival as well as at preventing acute rejection. However, basiliximab is associated with a lower incidence of certain key adverse events, namely CMV infection, leukopenia, and thrombocytopenia [8].

In present study, we report the results of our retrospective study on the efficacy and safety of basiliximab versus single bolus ATG as induction therapy in sensitized renal transplant recipients.

2. Materials and methods

2.1. Patients and study design

A total of 82 presensitized renal recipients were enrolled into this retrospective study, which received their renal grafts from deceased donors in our center between January 2003 and December 2005. All the recipients received basiliximab or single bolus ATG as induction therapy. They were divided into ATG group ($n=40$), and basiliximab group ($n=42$). Informed consent was obtained from each patient, and the study conformed to the Declaration of Helsinki concerning medical research in humans. Presensitization was defined by the presence of HLA antibodies in the patient's serum pre-transplant (PRA > 10%), which was determined by ELISA technology (LAT-M, One Lambda Inc., CA, USA). Donor–recipient blood group matching was identical in all patients. HLA crossmatch of patients was negative (< 5%), which was determined by microdroplet assay of complement-dependent lymphocytotoxicity (CDC). Demographic characteristics of patients and donors, data of HLA mismatching, cold ischemia time, CMV status and other pre-transplant status of patients all are shown in Table 1 in details, which are comparable in two groups.

Table 1
Demographics, pre-transplant status and immunosuppressive regimen of patients

Characteristic	ATG group	Basiliximab	*P* value
Number	40	42	–
Females	13 (32.5%)	7 (16.6%)	0.095
Mean recipient age (years)	42.3 (9.6)	44.3 (10.1)	0.365
Mean donor age (years)	30.7 (7.5)	29.6 (7.1)	0.467
Original disease (%)			0.276
Glomerulonephritis	22 (55%.)	19 (45.2%)	
PCKD	1 (2.5%)	4 (9.5%)	
Hypertension	3 (7.5%)	1 (2.4%)	
Diabetes	1 (2.5%)	4 (9.5%)	
Unknown	13 (32.5)	14 (33.4%)	
Mean time on dialysis (months)	10.2 (9.5)	7.5 (5.0)	0.108
Current dialysis			1.000
Hemodialysis	38 (95%)	40 (95.2%)	
Peritoneal dialysis	2 (5%)	2 (4.8%)	
Mean cold ischemic time (h)	9.5 (2.9)	9.3 (2.4)	0.810
CMV status			0.825
Donor (P) /recipient (P)	8	6	
Donor (N) /recipient (P)	4	3	
Donor (P) /recipient (N)	5	7	
Donor (N) /recipient (N)	23	26	
PRA score (%)			0.900
10–30%	10 (25%)	12 (29%)	
30–50%	20 (50%)	21 (50%)	
>50%	10 (25%)	9 (21%)	
HLA mismatching	2.2 (0.7)	2.4 (0.7)	0.062

2.2. Immunosuppressive therapy

Patients of ATG group received single bolus ATG induction therapy (Fresenius, 9 mg/kg). ATG was diluted in an isotonic solution to a total volume of 500 mL and then administered by slow, regular intravenous infusion within the 6-h period prior to revascularization of the graft. Patients of basiliximab Group were given basiliximab (Simulect, Novartis), which was administered in two 20 mg doses by bolus intravenous injection, the first within the 2-h period before revascularization of the graft and the second on day 4 post-transplant. To prevent the side effects of ATG and basiliximab, 40 mg methylprednisolone (MP) was administered intravenously before induction therapy.

Maintenance immunosuppressive regimens were standard triple therapy consisting of FK-506, MMF and prednisone throughout the study. MMF was administered immediately after operation at a dose of 0.5–1 g twice daily. The dose of MMF was 0.5 g twice daily for patients with body weight < 50 kg, 0.75 g for 50–70 kg, and 1 g for > 70 kg. FK-506 was administered 2 days post-transplant at a dose of 0.1–0.12 mg/kg/day. The dosage was subsequently adjusted to give a trough concentration of between 10 and 13 ng/ml during the first month, 8–10 ng/ml within month 3, 6–8 ng/ml within month 6, then 4–6 ng/ml during the next six months.

All the patients received 500 mg of intravenous MP prior to revascularization of the graft during the operation and a 3-day bolus of intravenous MP therapy (8 mg/kg/day) post-transplant. Oral prednisone was subsequently prescribed at a daily dose of 20 mg. Then the daily dose was tapered to 10–15 mg in one year. Prophylaxis against CMV infection was given on a routine basis in this study, which consisted of ganciclovir (i.v. 500 mg/day) for 14 days post-transplant.

2.3. Diagnosis and treatment of acute rejection

The diagnosis of acute rejection was confirmed by percutaneous kidney biopsy and kidney pathology was classified using Banff 2003 criteria. Mild rejection episodes (Grade I A/B) were treated with MP i.v. at 8 mg/kg per day for 3 days. ATG (100 mg/day) was administered for moderate and severe episodes (Grade II A/B and III) or those resistant to steroids for 7–14 days.

2.4. Study assessments

The safety and tolerability of induction therapy were assessed by comparing the incidences in the two groups of adverse events (fever, serum sickness, leukopenia, or thrombocytopenia) and infections. A separate analysis was made of CMV infection, defined as positive antigenemia coupled with symptoms (e.g., malaise or fever).

The efficacy of basiliximab and ATG was assessed in the two groups by comparing the following parameters: incidences, severity and treatment failure of acute rejection, first acute rejection episode time, and graft/patient survival. Graft loss was defined as the need for regular dialysis or graftectomy. Serum creatinine levels were measured daily after transplantation until discharge, weekly during the first six months and then renal function was monitored biweekly. The first day reaching nadir serum creatinine was recorded in each patient, in order to evaluate the recovery of renal function. Efficacy was also assessed by comparing the rate of delayed graft function (DGF). DGF was defined as the need for dialysis during the first post-transplant week. The duration of post-transplant hospitalization was also compared among the two groups.

2.5. Statistical analyses

SPSS 13.0 was used for statistical analysis. The methods used in our study included chi-squared, *t* test, and repeated measures ANOVA. Results were considered significant when *P* was less than 0.05.