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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.

3. Results

3.1. Efficacy

There was no hyperacute rejection in two groups. During the 12-month follow-up period, 25 AR episodes were recorded in 21 patients and no patients suffered more than two episodes. The incidence of AR was 15% (6/40) in ATG group and 35.7% (15/42) in basiliximab group ($P=0.032$). The mean time of first AR episode was later in ATG group than that in basiliximab group (20.8±15.8 vs. 12.4±11.3), however, the difference did not reach statistical significance ($P=0.191$).

All AR episodes were confirmed by percutaneous kidney biopsy and data of pathological degrees was shown in Table 2. More grade IIA AR episodes were observed in basiliximab group, and no patients suffered grade IIA AR episodes in ATG group. But there was no significant difference ($P=0.112$).

AR episodes in ATG group were all reversed by MP bolus therapy. One out of ten patients was not sensitive to MP bolus therapy and reversed by ATG sequential therapy. There were 5 patients with grade IIA AR episode treated with ATG sequential therapy, of which 2 patients suffered graft loss due to treatment failure. Another patient in basiliximab group also suffered graft loss due to chronic rejection. Four patients died of severe pneumonia (2 patients in each group). One-year patient and graft survival was 95%, 92.5% and 95.2%, 88.1% in ATG and basiliximab group respectively. However, the difference did not reach statistical significance ($P=1.000$ and 0.764). (Table 2).

3.2. Renal function

As shown in Table 3, there was no statistical difference in mean baseline serum creatinine levels of two groups. DGF was seen in five patients: two in ATG group and three in basiliximab group. There was no significant difference. Mean serum creatinine (SC) levels of two groups at different time points post-transplantation were shown in Table 3, which were analyzed by repeated measures ANOVA. Results showed that mean SC levels of patients in two groups decreased markedly within the first month post-transplant. However, differences of SC levels among two groups did not reach statistical significance. According to the results, the conclusion could be drawn that SC levels fell gradually during the first month post-transplant and stable renal functions were recorded after month 3. When separate analysis was made of nadir serum creatinine (SC) levels, time to nadir SC level, and time to normal SC level respectively, no statistical difference was observed among two groups.

Table 2
Parameters of efficacy during the 12-month post-transplantation period

Characteristic	ATG group	Basiliximab	*P* value
Number	40	42	–
Patient survival (%)	38/40 (95)	40/42 (95.2)	1.000
10–30%	10/10 (100)	12/12 (100)	–
30–50%	19/20 (95)	20/21(95.2)	1.000
>50%	9/10 (90)	8/9 (88.9)	1.000
Graft survival (%)	37/40 (92.5)	37/42(88.1)	0.764
10–30%	10/10 (100)	12/12 (100)	–
30–50%	19/20 (95)	19/21 (90.5)	1.000
>50%	9/10 (90)	6/9 (66.7)	0.495
First AR time (day)	20.8 (15.8)	12.4 (11.3)	0.191
Patients with AR (%)	6 (15)	15 (35.7)	0.032
10–30%	1/10	1/12	1.000
30–50%	4/20	8/21	0.203
>50%	1/10	6/9	0.037
Pathology (First episode)			0.112
IA	4	5	
IB	2	5	
IIA	0	5	
IIB	0	0	
Treatment (Failure)			
MP	6	10(1)	
ATG	0	5(2)	
Hospital stay (day)	20.9 (9.8)	20.7 (10.1)	0.361

Table 3
Renal functions

Characteristic	ATG group	Basiliximab	*P* value
Serum creatinine (SC, μmol/L)			
Mean baseline SC	1026 (292)	1119 (292)	0.155
Day 1	565 (231)	671 (274)	0.198
Day 2	324 (211)	368 (282)	
Day 3	238 (211)	289 (338)	
Week 1	169 (159)	203 (243)	
Week 2	134 (147)	169 (230)	
Month 1	100 (51)	131 (99)	
Month 3	93 (23)	105 (24)	
Month 6	93 (21)	104 (22)	
Month 12	91 (19)	105 (25)	
Nadir serum creatinine	85 (21)	94 (23)	0.088
Time to nadir SC (day)	16 (10)	16 (15)	0.879
Time to normal SC (day)	9 (9)	9 (11)	0.479

3.3. Safety

Results for pertinent safety parameters are shown in Table 4. Thrombocytopenia, defined as a platelet count $<100\times10^9$/L, occurred in 11 patients (27.5%) in ATG group, which is much more than that of the Basiliximab Group ($P=0.001$). But none of the patients had a platelet count $<50\times10^9$/L and the platelet count of all patients suffering thrombocytopenia returned to normal level within 2–7 days without special treatments. Differences of incidences of other adverse events did not reach statistical significance.

Table 4
Side effects and infections in four groups

Characteristic	ATG group	Basiliximab	*P* value
Side effects			0.863
Fever	1	0	1.000
Serum sickness	1	0	1.000
Leukopenia	3	0	1.000
Thrombocytopenia	11	1	0.001
Infection			
Patient number	19/40	18/42	0.673
Episode number	31	28	
Pathogenic bacterium			0.895
Bacterial	14	15	
Viral	12	10	
Fungal	2	1	
Unknown	3	2	
Infection position			0.998
Respiratory system (Pneumonia)	12 (8)	12 (7)	
Urinary tract infection	12	10	
Oral infection	0	0	
Herpes zoster	7	6	
CMV infection	5	4	0.938

Thirty-seven patients suffered 59 infection episodes during one year post-transplantation, which were mainly caused by bacterium and virus. The majority of these infections affected the respiratory system or the urinary tract. Data in detail was shown in Table 4 and no significant difference was observed among two groups.

4. Discussion

There is an increasing proportion of highly sensitized patients with end-stage renal failure on transplant waiting lists. They have a markedly reduced probability to receive a suitable kidney allograft with a negative complement-dependent cytotoxicity crossmatch (CDCXM). Moreover, also in the presence of a negative CDCXM, sensitization in kidney transplantation was shown to be associated with inferior graft survival and an increase in delayed graft function [9–11]. To reduce AR episode and increase long-term survival, negative CDCXM, well HLA-matching allograft and induction therapy of biologics all are necessary for transplanting sensitized patients in our center. Well HLA-matching allograft is defined as HLA mismatch ≤ 3 and without the presence of the HLA antigen recognized by HLA antibody in the serum of recipient.

Induction therapy is administrated in order to reduce acute rejection episode, decrease or delay the use of maintenance immunosuppressive regimens, and most importantly benefit high-risk populations, such as pediatrics, African–Americans, and sensitized recipients [12]. The antibodies currently used as induction therapy are mainly polyclonal antithymocyte globulins (ATGs) and anti-interleukin 2 receptor (IL2R) antibodies (basiliximab and daclizumab) with different mechanisms (depletion of lymphocytes and IL2R blockade respectively). Different even contradictory results have been reported about induction therapy of daclizumab or ATG, especially in immunological high-risk patients [3,8,13–19]. This article reports the results of our study conducted to compare the efficacy and safety of basiliximab versus single bolus ATG as induction therapy in sensitized renal transplant recipients, in which maintenance immunosuppressive regimens and other concomitant treatments were identical.

Basiliximab could provide specific immunosuppression and has been shown to reduce the incidence of AR, with no significant increase in the risk of major adverse effects [20]. Basiliximab was also evaluated in high-risk patients [3,8,13,21]. Jirasiritham [14] concluded that the use of anti-IL-2 receptor antibodies as induction immunosuppression in immunological high-risk patients resulted in the same rate of acute rejection, severity of acute rejection, graft survival, and patient survival as recipients with normal immunological risk. However, compared with ATG group, Mariat [15] observed a higher incidence (50% vs. 19%) and increased severity of AR in basiliximab group in sensitized white patients with PRA greater than 20%. The study by Brennan [21] showed that the AR incidence of basiliximab group was 1.8 times lower than that of ATG group (14.2% vs. 25%), without a significant difference in the risk of serious adverse events. In present study, although similar 1-year patient/graft survivals were observed in both groups, patients of basiliximab group suffered more AR episode than those of ATG group, especially for those with PRA scores above 30% (46.7% vs. 16.7%). This suggested that single bolus ATG induction therapy can achieve lower AR incidence in renal graft recipients with positive PRA than basiliximab and should be selected preferentially.

Overimmunosuppression caused by ATG may result in severe infections, which are the main complications worried by researchers and limits the use of ATG seriously. Several studies showed that ATG was associated with not only better graft survival but increased incidence of lymphoproliferative disorder (PTLD), CMV disease, malignancy, and death resulted from overimmunosuppression [22,23]. To avoid overimmunosuppression caused by ATG, intraoperative bolus ATG Fresenius [24–27] and Thymoglobulin [28] administration were proposed and proven effective without an increase in viral or opportunistic infections. As shown in our study, similar infection incidence was observed in two groups (42.9% vs. 47.5%), suggesting that single bolus ATG induction therapy can markedly reduce the incidence of complications caused by overimmunosuppression without the decrease of ATG's efficiency in reducing AR episodes.

Both ATG and basiliximab were well tolerated, although more thrombocytopenia was seen in the ATG group. The thrombocytopenia was mild and transient and needed no additional treatment. No statistically significant differences were shown for fever, leucopenia, and serum sickness. Therefore, compared with basiliximab, single bolus ATG is associated with a similar incidence of certain key adverse events, which is lower than that of ATG used in a sequential protocol reported by others [3,8,18].

Longer follow-up time are desirable for definite conclusions, but the present study suggested that single bolus ATG induction therapy can achieve lower incidence of AR and should be administrated preferentially in the renal graft recipients with positive PRA.

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