

## Comparison of the Clinical Outcomes between Anti-thymocyte Globulin and Basiliximab Induction Therapy in Deceased Donor Kidney Transplantation: Single Center Experience

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**Background:** The aim of this study is to evaluate the clinical outcomes between anti-thymocyte globulin (ATG) and basiliximab induction in deceased donor kidney transplantation (DDKT).

**Methods:** Between May 2006 and February 2015, 40 patients underwent DDKT at our institution. Three cases (7.5%) of them were lost during the following-up schedule. In this study, ATG induction criteria were donor age > 50 years old or donor creatinine level > 1.3 mg/dL except hepatitis B virus positive and hepatitis C virus positive recipients. Recipients were divided into two groups: the ATG group (n=20) and the basiliximab group (n=17).

**Results:** The 1-year patient survival in the ATG group was 89.4% compared to 93.8% in the basiliximab group ( $P=0.989$ ). Graft survival for a 1 year in the ATG and the basiliximab group was 89.1% and 93.8%, respectively ( $P=0.967$ ). Incidences of acute rejection episodes were more prevalent in the basiliximab group (15.0% vs. 29.4%,  $P=0.428$ ). The glomerular filtration rate level by period of recipients was not different in both group (12th month,  $64.60 \pm 16.17$  mg/dL vs.  $68.51 \pm 18.60$  mg/dL,  $P=0.544$ ). The overall complications during the follow-up were not significantly different in both groups (90.0% vs. 76.5%,  $P=0.383$ ).

**Conclusions:** The results showed that there was no difference in the patient survival and graft survival between induction of ATG and basiliximab of the DDKT were not different. Therefore, use of both induction agents led to a good patient and graft survival and ATG might be a safe and preferable agent for relatively poor renal function of donor in kidney transplantation.

**Key Words:** Antithymocyte globulin, Basiliximab, Kidney transplantation

**중심 단어:** 항가슴샘세포 글로블린, 바실릭시맙, 신장이식

### INTRODUCTION

After kidney transplantation, acute rejection is associated with shortened kidney allograft survivals(1). Therefore, in-

duction therapy has been used to prevent acute cellular rejection at the time of transplantation. In the almost center, anti-thymocyte globulin (ATG, Thymoglobulin, Genzyme, Cambridge, MA, USA) and basiliximab (Simulect, Novartis Pharmaceutical Corp., Basel, Switzerland) have been used as an induction therapy for many years. Are there any differences between two agents for induction therapy in terms of safety and efficacy? We did not yet come to the conclusion of this question. Brennan et al.(1) reported that ATG showed superior results in preventing acute cellular rejection in high risk patients. But, Liu et al.(2) concluded that basiliximab may be safer and more preferable option

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for the induction therapy in kidney transplantation. Neidlinger and Sollinger(3) proposed also that there was insufficient evidence to justify the use of ATG induction in kidney transplantation. So the aim of this study is to evaluate the clinical outcomes between ATG and basiliximab induction in deceased donor kidney transplantation (DDKT).

## MATERIALS AND METHODS

### 1. Patients and study design

Between May 2006 and February 2015, 40 patients have undergone DDKT at department of surgery at Konyang University Hospital, Daejeon, Korea. Three cases (7.5%) of them were lost in the following-up. Recipients were divided into two groups: the ATG group (n=20) and the basiliximab group (n=17). We applied ATG induction criteria by the following donor age >50 years old or donor creatinine level >1.3 mg/dL except hepatitis B virus positive and hepatitis C virus positive recipients. Patients who did not meet the ATG induction criteria received basiliximab induction therapy. The following characteristics were evaluated retrospectively: recipient age, recipient sex, recipient body mass index (BMI), panel reactive antibody, donor age, donor sex, donor BMI, renal disease cause, brain death cause, time on dialysis, cold ischemic time (CIT), operation time, hospital stay day, complications, glomerular filtration rate (GFR) level by period, human leucocyte antigen (HLA) mismatches, delayed graft function (DGF), and acute T-cell mediated rejection through the medical records. DGF was defined as (1) anuria, (2) the failure of the serum creatinine level to decrease by 25% during the first 24 hours after transplantation, and (3) the need for dialysis within the first week after transplantation.

### 2. Immunosuppressive therapy

Patients of ATG group received ATG daily for 5 days induction therapy (1.5 mg/kg/day). ATG was diluted in an isotonic solution to make a total volume of 250 mL and then administered by slow, regular intravenous infusion within the 12-hour period prior to revascularization of the graft. Patients of basiliximab group were given basiliximab, which was administered in two separate 20 mg doses by bolus intravenous injection, the first dose within 2 hours before re-

vascularization of the graft and the second dose on day 4 posttransplant.

The maintenance of immunosuppressive regimens was standard triple therapy consisting of tacrolimus, mycophenolate mofetil (MMF) and prednisone throughout the study. MMF was administered on first postoperative day at a dose of 750 mg twice daily. Tacrolimus was administered on third day posttransplant in the ATG group at a dose of 0.1 mg/kg/day and administrated on first postoperative day in the basiliximab group. The dosage was subsequently adjusted to give a trough concentration of between 8~10 ng/mL during 3 months, 5~8 ng/mL during the next 6 months.

All the patients received 500 mg of intravenous methylprednisolone prior to revascularization of the graft during the operation and first day posttransplant. Later, its dose is tapered out. Oral prednisone was subsequently prescribed at a daily dose of 20 mg until 1 month. Then the daily dose was tapered to 5 mg within a year.

### 3. Statistical analysis

Statistical analysis was performed using the Student t-test, the Mann-Whitney test, the chi-square test, and the log-rank test. The Kaplan-Meier method was used to calculate overall patient and graft survivals. Statistical significance was accepted for  $P < 0.05$ , and statistical analysis was carried out using PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA.).

## RESULTS

### 1. Demographic and clinical data

The demographic and clinical data of the patients that underwent DDKT were shown in Table 1. No significant differences between two groups were observed in respect to age, sex, and etiology of chronic renal disease in terms of recipient's characteristics. The majority of renal disease in both groups was related to diabetes mellitus nephropathy. All patients in the both group were first renal transplantation (100%). The mean follow-up period in the ATG and the basiliximab group was  $28.7 \pm 18.2$  months in ATG group and  $38.2 \pm 24.0$  months respectively. All recipients of both group had no donor-specific antibody. Donor age was not significantly different between two groups ( $P=0.185$ ).

**Table 1.** Demographic and clinical data

Variable	ATG (n=20)	Basiliximab (n=17)	P-value
Recipient factor			
Age (yr)	51.3±11.4	48.0±8.1	0.312
Male	14 (70.0)	12 (70.6)	1.000
Female	6 (30.0)	5 (29.4)	
Pre-NTx dialysis (mo)	28.7±27.7	57.7±35.2	0.010
Body mass index (kg/m <sup>2</sup> )	23.2±2.5	22.7±3.1	0.630
Renal disease cause			
Diabetes mellitus	10 (50.0)	12 (70.6)	0.413
Hypertension	7 (35.0)	4 (23.5)	
Glomerulonephritis	3 (15.0)	1 (5.9)	
No. of transplantation			
First	20 (100.0)	17 (100.0)	1.000
Follow-up months	28.7±18.2	38.2±24.0	0.193
Preoperative PRA I ≥30%	1 (0.05)	0	1.000
Preoperative PRA II ≥30%	0	0	
Donor factor			
Age (yr)	45.0±16.3	38.5±12.7	0.185
Male	20 (100.0)	13 (76.5)	0.036
Female	0	4 (23.5)	
Body mass index (kg/m <sup>2</sup> )	24.2±4.0	23.0±3.9	0.355
Cause of brain death			
Cerebrovascular accident	10 (50.0)	12 (70.6)	0.204
Hypoxic brain damage	4 (20.0)	2 (11.8)	0.667
Trauma	6 (30.0)	3 (17.6)	0.462
Preoperative creatinine (mg/dL)	1.50±0.59	1.07±0.36	0.014
Operative factor			
Mean CIT (min)	208.4±58.2	201.0±57.7	0.703
Operation time (min)	241.8±52.3	235.3±54.1	0.716
HLA mismatch	4.6±1.6	4.6±1.2	0.980
Hospital stays	18.5±7.6	15.5±3.2	0.142

Data are presented as mean±SD or number (%).

Abbreviations: ATG, anti-thymocyte globulin; Pre-NTx, pre-nontransplantation; PRA, panel reactive antibody; CIT, cold ischemic time; HLA, human leukocyte antigen.

All donors of ATG group were male. Donor BMI of both group was also not significantly different ( $24.2\pm 4.0$  kg/m<sup>2</sup> vs.  $23.0\pm 3.9$  kg/m<sup>2</sup>,  $P=0.355$ ). Causes of brain death were not significantly different between two groups. Preoperative creatinine level of donor in the ATG group was higher than the basiliximab group ( $1.50\pm 0.59$  mg/dL vs.  $1.07\pm 0.36$  mg/dL,  $P=0.014$ ). In operative characteristics, no difference was observed between two groups in terms of operation time, mean CIT, HLA mismatch, and hospital stays.

## 2. Postoperative complications

Postoperative complications in the two groups were shown in Table 2. Complications during the follow-up peri-

ods were not significantly different in both groups. No significant difference was observed between two groups in terms of total patient numbers of complication (90% vs. 76.5%,  $P=0.383$ ). In terms of cytomegalovirus, no difference was observed between two groups (45.0% vs. 23.5%,  $P=0.300$ ). Infection rate was higher in ATG induction group, but the statistical difference was not found (80.0% vs. 58.8%,  $P=0.279$ ). There was only one case of BK nephropathy in ATG group (5.0% vs. 0.0%,  $P=1.000$ ).

## 3. Postoperative patient survival and graft survival after induction of ATG vs. basiliximab

Comparisons of the postoperative patient survival and

**Table 2.** Comparison of the postoperative complications after induction of ATG versus basiliximab

Variable	ATG (n=20)	Basiliximab (n=17)	P-value
Infection	16 (80.0)	10 (58.8)	0.279
Bacterial infection	8 (40.0)	5 (29.4)	0.731
Pneumonia	3 (15.0)	4 (23.5)	0.680
Urinary tract infection	3 (15.0)	1 (5.9)	0.609
Others	2 (10.0)	0	
Viral infection	13 (65.0)	6 (35.3)	0.103
Cytomegalovirus	9 (45.0)	4 (23.5)	0.300
BK nephropathy	1 (5.0)	0	1.000
Others	3 (15.0)	2 (11.8)	
Fungal infection	2 (10.0)	0	0.489
Graft AVF	0	1 (5.9)	0.459
Avascular necrosis	0	1 (5.9)	0.459
Surgical complications			
Ureter stricture	1 (5.0)	0	1.000
Ureter leakage	1 (5.0)	0	1.000
Bladder rupture	0	1 (5.9)	0.459
Total numbers	18 (90.0)	13 (76.5)	0.383

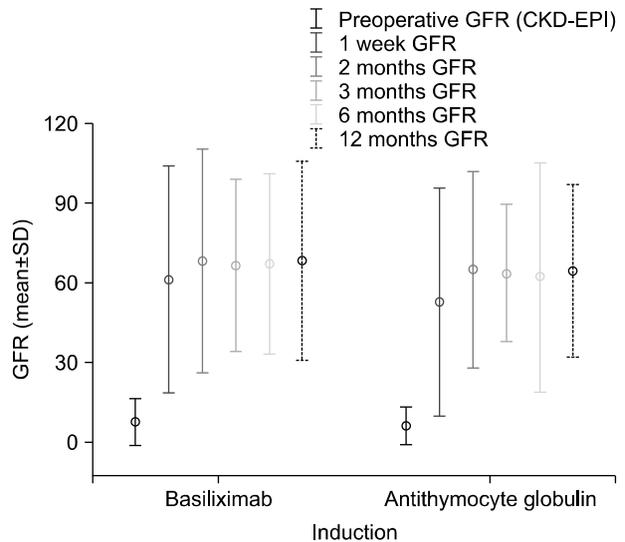
Data are presented as number (%).  
Abbreviations: ATG, anti-thymocyte globulin; AVF, arteriovenous fistula.

graft survival after induction of ATG versus basiliximab were shown in Table 3. The 1-year patient survival in the ATG group and basiliximab was 89.4% and 93.8%, respectively ( $P=0.989$ ). Graft survival at 1 year was 89.1% and 93.8% in the ATG and the basiliximab group respectively ( $P=0.967$ ). Also death-censored graft survival at 1 year was 94.7% and 100% in the ATG and the basiliximab group respectively ( $P=0.344$ ). Incidence of acute T-cell mediated rejection was more prevalent in the basiliximab group (15.0% vs. 29.4%,  $P=0.428$ ). Incidence of antibody mediated rejection and graft loss were not significantly different. There was one case of graft loss in both groups, respectively. The cause of graft loss in ATG group was chronic allograft nephropathy and cause of graft loss in basiliximab was acute tubular necrosis. DGF was also not significantly different in both groups (15.0% vs. 11.8%,  $P=1.000$ ). GFR (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) level by period of recipients was not different in both group (12th month:  $65.51 \pm 18.60$  mg/dL vs.  $64.60 \pm 16.17$  mg/dL,  $P=0.544$ ) (Fig. 1).

**Table 3.** Comparison of the postoperative patient survival and graft survival after induction of ATG versus basiliximab

Variable	ATG (n=20)	Basiliximab (n=17)	P-value
Delayed graft function	3 (15.0)	2 (11.8)	1.000
Acute T-cell mediated rejection	3 (15.0)	5 (29.4)	0.428
Antibody mediated rejection	1 (5.0)	1 (5.9)	1.000
Graft loss	1 (5.0) <sup>a</sup>	1 (5.9) <sup>b</sup>	1.000
Death	2 (10.0)	2 (11.8)	1.000
1 Year patient survival rate (%)	89.4	93.8	0.989
1 Year graft survival rate (%)	89.1	93.8	0.967
1 Year graft survival rate <sup>c</sup> (%)	94.7	100.0	0.344

Data are presented as number (%).  
Abbreviation: ATG, anti-thymocyte globulin.  
<sup>a</sup>By acute tubular necrosis; <sup>b</sup>By chronic allograft nephropathy;  
<sup>c</sup>Death censored graft survival.



**Fig. 1.** Comparison of the glomerular filtration rate (GFR) (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) level by period after induction of antithymocyte globulin versus basiliximab. GFR level by period of recipients was not different in both group ( $P=0.544$  at 12th month).

## DISCUSSION

Induction therapy is specific therapy given at the time of transplantation to lower the incidence of acute rejection and thus improve allograft survival. Currently, almost 70% of kidney transplantation recipients received induction therapy with either basiliximab or ATG(1). ATG is a lymphocyte-depleting polyclonal antibody that targets multiple immuno-

logic epitopes. And basiliximab is a non-lymphocyte-depleting monoclonal antibodies that target the interleukin-2 (IL-2) receptor(1).

In this single center study of 37 DDKT performed in adults, we treated the induction therapy for all patients of DDKT with basiliximab or ATG. We applied ATG for relatively poor renal function of donor, which were donor age >50 years old or donor creatinine level >1.3 mg/dL and patients who did not meet the ATG induction criteria received basiliximab induction therapy. Nonetheless, there was no statistical difference in postoperative complication, acute T-cell mediated rejection and 1-year patient and graft survival between both groups.

Various previous studies reported that basiliximab had lower incidence of infection(1,2,4,5). Similar to those results, our study shows that the infection rate was higher in ATG than basiliximab group, but there was no significant difference (61.5% vs. 38.5%,  $P=0.279$ ). About the cause of different incidence of infection between basiliximab and ATG, Liu et al.(2) said that it may be related to their different mechanisms. ATG interacts with and depletes all kinds of T lymphocytes. But basiliximab is a monoclonal antibody that binds to the  $\alpha$ -chain of the IL-2 receptor (IL-2R) with an affinity approximating that of IL-2 itself, and is therefore a potent inhibitor of IL-2-mediated T-cell proliferation. CD8 cytotoxic T-cells may not be impaired by CD25 therapy because most CD8 cells express IL-2R  $\beta$  and  $\gamma$  chains, allowing expansion of CD8 cells without significant contribution from the  $\alpha$ -chain of the IL-2R. Thus it may contribute to the control of infection.

An acute rejection is still the biggest complication to improve the survival of renal transplantation. It increases not only the incidence of early stage kidney non-function and other complications and the treatment cost, but also is an important risk factor leading to late kidney graft loss(6). Thus any treatment to prevent and decrease early stage acute rejections would help increase the long-term survival of patients and grafts(7). An incidence of acute rejection was reported in 20%~50%(4,6,8-10). In many studies, there was no significant difference on acute rejection between ATG and basiliximab(2,3,5,10-14), whereas some other studies have report that ATG induction group showed lower incidence of acute rejection(1,15,16). In this study, the in-

cidence of acute rejection was 15.0% in ATG group and 29.4% in basiliximab group, respectively. Acute rejection was more prevalent in the basiliximab group than ATG group, but there was no statistical significance ( $P=0.428$ ) which these results were similar to other previous studies.

In this study, despite of small cases of DDKT, DGF, the 1-year patient survival, 1-year graft survival and GFR level by period of recipients were not significantly different in both groups. We found no significant intergroup differences in patient survivals and graft survivals. In many studies, DGF rate was 6%~40%, 1-year survival rate was about 90%(5,6,9,11,13,14,16). Our study showed similar results, but we applied ATG criteria to donor of relatively poor renal function. In other words, ATG would be considered as a safe and efficient induction agent even if the donor has a poor renal function.

BK virus associated nephropathy (BKVAN) is major cause of progressive destruction of allograft in kidney transplantation(17,18). An incidence of BKVAN was 1%~10% of kidney transplant patients and its incidence is increasing recently(19). BK virus (BKV) is a member of the human polyomavirus family(20) and infection with the virus is common and a majority of adult population is seropositive for the virus(21). BKV resides dormant in uroepithelial cells and is not known to cause tissue damage in immunocompetent individuals(22). However, the virus can become reactivated in the setting of immunodeficiency (e.g., secondary to HIV infection or immunosuppressive medications), and result in cellular damage and organ dysfunction(23). Dadhania et al.(24) reported that steroid maintenance therapy and induction with ATG are independent risk factors for BKV replication in renal allograft recipients treated with tacrolimus and MMF. In our study, BK nephropathy was only one case and found in ATG group. On 9 weeks after kidney transplantation, this patient was diagnosed BKV nephropathy and acute rejection simultaneously and was treated with steroid pulse therapy and leflunomide. In order to improve the outcomes of BKVAN, Gautam et al.(25) reported that routine BKV surveillance is effective, and it tends to detect BKV replication earlier, allowing reduction of immunosuppression, which results in good outcomes with renal preservation.

There were a few limitations: first, small sample size and

second, short-term follow-up length. These factors might have influenced on the results of this study. A long-term follow-up and further studies may be required to evaluate the influence of these induction agents on complications after DDKT.

## CONCLUSION

The results showed that patient survival and graft survival after induction of ATG vs. basiliximab of the DDKT were not different. Infection rate was higher in ATG induction group but episodes of acute T-cell mediated rejection were more prevalent in basiliximab induction group. The statistical significance was not found between both groups. Therefore, both induction agents led to a good patient and graft survival and ATG might be safe and preferable agent for relatively poor renal function of donor in kidney transplantation. Because of the small number of patients in the study and the short-term outcome, these results should be confirmed with larger cohorts to find out the long-term benefits of these two induction therapy.

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