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The comparative efficacy and safety of basiliximab and antithymocyte globulin in deceased donor kidney transplantation: a multicenter cohort study

Su Yeon Hong[1,3], Young Soo Kim[1,3], Kyubok Jin[4,5], Seungyeup Han[4,5], Chul Woo Yang[1,2], Byung Ha Chung[1,2,*], Woo Yeong Park[4,5,*]

For further information on the authors' affiliations, see ***Additional information****.*

Background: Generally, an induction agent is chosen based on the conditions of the deceased donor and the recipient. Antithymocyte globulin (ATG) is preferred in relatively high-risk conditions. No clear evidence indicates which induction agent is safer or more efficient for deceased donor kidney transplantation (DDKT). This study compares the efficacy and safety of basiliximab (BSX) and ATG according to donor characteristics in DDKT.

Methods: A total of 724 kidney transplant recipients from three transplant centers were enrolled, and propensity score matching was performed. Based on a donor age of 60 years, donor kidney with acute kidney injury (AKI), and Kidney Donor Profile Index (KDPI) score of 65%, we investigated how the choice of induction therapy agent affected the posttransplant clinical outcomes of delayed graft function (DGF), acute rejection (AR), infectious complications, and allograft and patient survival.

Results: AR and DGF did not differ significantly according to induction agent in elderly/young donor, AKI/non-AKI, and high-KDPI/low-KDPI subgroups. The infection rate did not show meaningful differences. The differences in death-censored allograft survival and patient survival rates between induction agents were not statistically significant.

Conclusion: Our study suggests that BSX can produce clinical outcomes similarly favorable to those of ATG even in DDKT cases with relatively poor donor conditions. Nonetheless, the donor and recipient conditions, immunological risk, and infection risk must be all taken into consideration when choosing an induction agent. Therefore, clinicians should carefully select the induction therapy agent for DDKT based on the risks and benefits in each DDKT case.

Keywords: Basiliximab, Delayed graft function, Graft rejection, Graft survival, Kidney transplantation, Thymoglobulin

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Correspondence: Woo Yeong Park
Department of Internal Medicine, Keimyung University School of Medicine, 1095 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Republic of Korea.
E-mail: parkwy2015@dsmc.or.kr
ORCID: https://orcid.org/0000-0003-2662-2898

Byung Ha Chung
Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea. E-mail: chungbh@catholic.ac.kr
ORCID: https://orcid.org/0000-0003-0048-5717

*Woo Yeong Park and Byung Ha Chung contributed equally to this study as co-corresponding authors.

Introduction

The incidence of end-stage renal disease (ESRD) is increasing worldwide. Kidney transplantation (KT) is one promising option for ESRD patients because it provides good quality of life after transplantation and a high survival rate. However, kidney donors are scarce, which leads to prolonged transplant waiting times and is associated with mortality among ESRD patients on the waiting list [1]. In December 2017, 19,807 patients were on the Korean Network for Organ Sharing waiting list for KT [2,3]. During the past decade in Korea, a 22.4% annual increase was recorded in the KT waiting list. The median wait time for KT from a deceased donor (DD) was 4.5 ± 2.7 years [3]. In Korea, 5.2 patients a day die while waiting for KT [4]. Using kidneys from donors with acute kidney injury (AKI) or elderly DDs is one attractive strategy to expand the donor pool. Although posttransplant clinical outcomes and prognosis in those cases are controversial, many previous studies have reported that KT from elderly DDs or DDs with AKI is a negative risk factor for delayed graft function (DGF), acute rejection (AR), and allograft survival [4,5]. The Kidney Donor Profile Index (KDPI) scoring system for DDs is widely used to predict postoperative graft function, and a high KDPI score is a well-known risk factor for allograft failure [6].

To compensate for those risk factors and enable successful KT, induction therapy is important. Antithymocyte globulin (ATG) and basiliximab (BSX) are the most widely used induction therapies in KT [7]. ATG is a lymphocyte depleting polyclonal antibody that targets multiple immunologic epitopes. BSX is a non-lymphocyte-depleting monoclonal antibody that targets interleukin-2 receptor (IL-2R). Previous studies have compared the efficacy and safety of ATG and BSX in KT in terms of clinical outcomes and complications. Webster et al. [8] reported no differences in allograft failure between BSX and ATG, but ATG showed a lower biopsy-proven AR (BPAR) rate 1 year after the transplant than did BSX. More recently, a prospective randomized study was performed to compare ATG (1.5 mg/kg from day 0 to day 4) and BSX (20 mg on day 1 and day 4) in deceased-donor KT (DDKT) patients at high risk for AR and DGF [9]. The ATG group had lower incidence and severity of AR. However, DGF and the graft survival and patient survival rates showed no statistically significant differences between the two induction therapies [10]. Furthermore, other studies found that patients who received BSX had a lower incidence of infection than those who received ATG [11,12]. Despite the various previous studies, recent randomized studies have failed to demonstrate which induction therapy is more efficient. Therefore, the purpose of this study was to compare the efficacy and safety of ATG and BSX as induction therapy for DDKT cases in which the donor characteristics are poor.

Methods

Study population

A total of 724 kidney transplant recipients (KTRs) who received KT at one of three transplant centers between October 1996 and July 2019 were enrolled, excluding 53 KTRs with no information about induction therapy or graft function after KT or with follow-up loss. The KTRs were divided into ATG-DDKT (252 KTRs) and BSX-DDKT (472 KTRs) groups. After propensity score (PS) matching, we used subgroups based on donor age of 60 years, donor kidney AKI, and KDPI score of 65% (elderly vs. young DDs, DDs with AKI vs. DDs without AKI, and DDs with high KDPI vs. DDs with low KDPI) to investigate how the induction therapy agent affected posttransplant clinical outcomes. We conducted re-matching within each subgroup based on cohort PS. The study population flow chart and patient distribution are presented in Fig. 1.

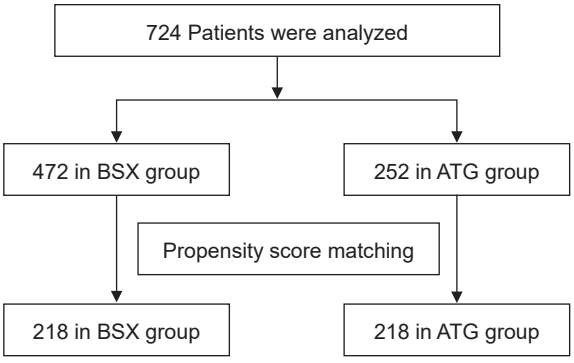

Figure 1. Flow chart of the study population. A total of 724 kidney transplant recipients was divided into ATG-DDKT and BSX-DDKT groups, and propensity score matching was performed. ATG, antithymocyte globulin; BSX, basiliximab; DDKT, deceased donor kidney transplantation.

First, the ATG-DDKT and BSX-DDKT groups were subdivided into young-DDKT and elderly-DDKT subgroups based on a donor age of 60 years at the time of donation (<60 years vs. ≥60 years). When re-matching was conducted within each subgroup, the young-DDKT group contained 358 cases (83.3%), and the elderly-DDKT group contained 72 cases (16.7%).

Second, each group was subdivided into AKI-DDKT and non-AKI-DDKT subgroups based on whether the DD had AKI, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The AKI-DDKT group contained 286 cases (68.8%), and the non-AKI-DDKT group contained 130 cases (31.2%).

Third, each group was subdivided into high KDPI-DDKT and low-KDPI-DDKT subgroups based on KDPI scores. We defined high KDPI score as that greater than 65%, the median KDPI score in this cohort. The KDPI scores were calculated using the KDPI calculator on the Organ Procurement and Transplantation Network website (https://optn.transplant.hrsa.gov/data/allocation-calculators/kdpi-calculator/). The high-KDPI-DDKT group contained 226 cases (57.7%), and the low-KDPI-DDKT group contained 166 cases (42.3%).

We then investigated the effects of choice of induction therapy agent in those groups in terms of both short- and long-term clinical outcomes.

In all patients in the BSX-DDKT group, 20 mg/day of BSX was administered on the operation day and postoperation day 4. In the ATG-DDKT group, ATG was given from the operation day to postoperation day 4. The standard dose of ATG was body weight × 1.25 mg/day, but that dose was halved when the white blood cell (WBC) count was 2,000/mm^3 to 3,000/mm^3 or the platelet count was lower than 75,000/mm^3 but higher than 50,000/mm^3. When the WBC count was less than 2,000/mm^3 or the platelet count was lower than 50,000/mm^3, ATG treatment was stopped.

Clinical parameters and outcomes

We retrospectively analyzed the medical records of both donors and recipients. The baseline donor data were age, sex, body mass index (BMI) (kg/m^2), history of diabetes mellitus (DM) and hypertension (HTN), donor death due to cerebrovascular accident (CVA), cold ischemic time, KDPI, and serum creatinine (as an assessment of kidney function from the day of admission to the day of KT). The baseline and follow-up estimated glomerular filtration rates (eGFRs) were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. We collected the following baseline recipient data: age, sex, BMI, history and duration of dialysis before KT, number of previous KTs, cause of ESRD, history of DM and HTN, number of human leukocyte antigen (HLA) mismatches, immunosuppressant type for induction and maintenance, and percentage of panel-reactive antibodies (PRAs). BPAR was diagnosed by the Banff classification. DGF was defined as the need for dialysis within the first week after KT because of unrecovered allograft function. Infection complications included BK virus nephropathy, *Pneumocystis jirovecii* pneumonia, CMV viremia, and other infections that could cause graft failure or patient death. The death-censored allograft survival rate was defined as the rate from KT to the return to dialysis except for allograft loss due to patient death. The patient survival rate was defined as the rate from KT to death by any cause.

The primary outcomes were a comparison of the death-censored allograft survival rate of KTRs according to induction therapy agent in subgroups formed according to donor age, presence of AKI, and KDPI score. The secondary outcomes were incidence of DGF and BPAR, infection rate, and patient survival rate between the ATG-DDKT and BSX-DDKT groups according to donor age, presence of AKI, and KDPI score. The causes of allograft failure included BPAR (both T-cell-mediated rejection and antibody-mediated rejection [AMR]), biopsy-proven chronic AMR, chronic allograft dysfunction, biopsy-proven BK virus-associated nephropathy, and biopsy-proven recurrent primary glomerulonephritis. Chronic allograft dysfunction was diagnosed when the allograft findings showed non-specific chronic tissue injury without evidence of rejection or when no allograft biopsy was performed within 1 year of allograft failure, and allograft function showed gradual deterioration for several years before allograft failure.

This study was approved by the Institutional Review Boards (IRBs) of Seoul St. Mary's Hospital (No. XC15RIMI0061K), Uijeongbu St. Mary's Hospital (No. XC15RIMI0061U), and Keimyung University Dongsan Hospital (No. 2021-07-041). The requirement for informed consent was waived by the IRBs of those three centers because the clinicians explained to all donor families and all recipients pri-

or to KT that personal data associated with the donor and recipient's clinical course would be used for research purposes, and all information identifying individuals was protected. As a retrospective medical record study, our study did not use any distinguishable personal identification information. Furthermore, all methods were performed in accordance with the relevant guidelines and regulations. The three transplant centers involved in this study have never performed transplantation with kidneys procured from prisoners, and this study did not include them in this study population.

Statistical analysis

We applied a PS matching analysis to minimize the influence of potential confounding biases and increase comparability between the BSX and ATG groups. The following variables were used to calculate the PSs in a multivariate logistic regression model: donor and recipient age, sex, BMI, PRA class I + II >30%, DM, HTN, perioperative eGFR, KDPI score, donor kidney AKI, and CVA as the cause of donor death. PS re-matching within each subgroup was performed based on the cohort PS. A 1:1 PS matching method was applied based on the greedy 8-1-digit matching algorithm.

Continuous variables with normal distributions in the entire cohort are expressed as mean with standard deviation and were analyzed using independent t-test. Categorical variables in the entire cohort are expressed as number with percentage and were analyzed by chi-square test. The statistical analysis of the PS cohort used paired t-test and the McNemar test. The death-censored graft survival and patient survival rates were analyzed using Kaplan-Meier curves and log-rank tests. After confirming the proportional hazard (PH) assumption, a conditional Cox PH regression analysis was used to investigate how the choice of induction therapy agent affected the clinical outcomes of DDKT and to find independent risk factors for allograft failure while considering confounding variables: transplant year (1996–2005 vs. 2006–2012 vs. 2013–2019), transplant center, recipient age, recipient sex, recipient BMI, donor age, donor sex, donor BMI, cold ischemic time, HLA mismatch number, PRA summation quantity, KDPI score, and donor kidney AKI. Any p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS version 19.0 (IBM Corp.), and the PS matching analysis was performed by the 'MatchIt' packages in R version 4.1.1 (R Foundation for Statistical Computing).

Results

Comparison of baseline characteristics according to induction therapy

The demographic and clinical data of the patients who underwent DDKT are shown in Table 1 according to the induction therapy agent used. The donors and recipients in the ATG group were older than those in the BSX group (p = 0.002). The donors in the ATG group had more frequent underlying DM than those in the BSX group (p = 0.02). The KDPI score (p = 0.04) and incidence of donors with AKI (p < 0.001) were higher in the ATG group, which also had more highly sensitized patients (PRA class I + II >30%) and lower donor preoperative eGFR than the BSX group (p < 0.001). On the other hand, the ratio of patients with previous KT was lower (p = 0.003) in BSX group. Among the operative characteristics, no difference was observed between the two groups in terms of mean cold ischemic time or HLA mismatch numbers, but brain death due to CVA was significantly higher in the BSX group (p = 0.001). The majority of renal disease in both groups was related to chronic glomerulonephritis. No significant differences between the two groups were observed in respect to donor sex, recipient BMI, dialysis duration, and etiology of recipient ESRD. Because the BSX and ATG groups differed significantly in various factors, we used PS matching to minimize the influence of potential confounding biases and increase the comparability of the groups.

Comparison of clinical outcomes according to induction therapy agent in all patients

Comparisons of postoperative patient survival and death-censored graft survival after induction with BSX versus ATG in the PS-matched cohort are shown in Fig. 2. Death-censored graft survival did not differ significantly after induction with BSX and ATG (p = 0.61). The patient survival rates with BSX and ATG were 93.3% and 94.2%, respectively (p = 0.86). In the PS-matched cohort, the incidence of AR (25.2%

Table 1. Comparison of clinical and laboratory parameters according to induction therapy agent used in KT recipients

Variable	Entire cohort (n = 724)			PS-matched cohort (n = 436)		
	Basiliximab KT (n = 472)	ATG KT (n = 252)	p-value	Basiliximab KT (n = 218)	ATG KT (n = 218)	p-value
Donor						
Age at KT (yr)	44.9 ± 14.7	48.2 ± 12.7	0.002	48.00 ± 13.3	47.7 ± 12.5	0.76
Sex, male:female	312:160	180:72	0.14	160:58	152:66	0.45
Body mass index (kg/m^2)	23.1 ± 3.6	23.9 ± 3.6	0.004	23.9 ± 3.7	23.8 ± 3.6	0.85
Hypertension	100 (21.2)	50 (19.8)	0.67	48 (22.0)	44 (20.2)	0.70
Diabetes mellitus	37 (7.8)	34 (13.5)	0.02	26 (11.9)	22 (10.1)	0.64
Cause of donor death-CVA	343 (72.7)	154 (61.1)	0.001	144 (66.1)	148 (67.9)	0.74
Preoperative eGFR (mL/min/1.73 m^2)	91.6 ± 44.1	70.2 ± 45.1	<0.001	73.8 ± 41.0	74.2 ± 44.9	0.90
KDPI score, ≥65	228 (48.3)	142 (56.3)	0.04	125 (57.3)	123 (56.4)	0.91
Acute kidney injury	219 (46.4)	182 (72.2)	<0.001	146 (67.0)	150 (68.8)	0.67
Recipient						
Transplant year			<0.001			<0.001
1999–2005	8 (1.7)	0 (0)		0 (0)	0 (0)	
2006–2012	208 (44.1)	10 (4.0)		94 (43.1)	10 (4.6)	
2013–2019	256 (54.2)	242 (96.0)		124 (56.9)	208 (95.4)	
Age at KT (yr)	49.0 ± 10.0	51.4 ± 9.9	0.002	49.6 ± 9.3	51.1 ± 9.7	0.09
Sex, male:female	290:182	134:118	0.03	134:84	109:109	0.03
Body mass index (kg/m^2)	23.2 ± 3.8	23.3 ± 3.5	0.73	23.6 ± 4.3	23.3 ± 3.7	0.44
Hypertension	401 (85.0)	193 (76.6)	0.005	185 (84.9)	172 (78.9)	0.15
Diabetes mellitus	92 (19.5)	58 (23.0)	0.27	44 (20.2)	46 (26.1)	0.91
Dialysis duration (yr)	7.80 ± 6.78	9.77 ± 13.91	0.04	7.74 ± 8.60	10.25 ± 14.84	0.03
Previous KT	38 (8.1)	38 (15.1)	0.003	12 (5.5)	34 (15.6)	0.001
Cause of ESRD			0.32			0.03
Glomerulonephritis	212 (44.9)	127 (50.4)		82 (37.6)	113 (51.8)	
Diabetes mellitus	81 (17.2)	47 (18.7)		37 (17.0)	36 (16.5)	
Hypertension	86 (18.2)	38 (15.1)		49 (22.5)	36 (16.5)	
Others	93 (19.7)	40 (15.9)		50 (22.9)	33 (15.1)	
Cold ischemic time (min)	248.2 ± 118.5	257.4 ± 135.1	0.38	240.4 ± 117.2	255.9 ± 132.1	0.20
HLA mismatch number	3.57 ± 1.50	3.68 ± 1.57	0.36	3.83 ± 1.36	3.70 ± 1.53	0.38
PRA class I + II, >30%	55 (11.7)	100 (39.7)	<0.001	27 (12.4)	27 (12.4)	>0.99

Data are expressed as mean ± standard deviation, number only, or number (%).
ATG, antithymocyte globulin; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease, HLA, human leukocyte antigen; KDPI, Kidney Donor Profile Index; KT, kidney transplant; PRA, panel reactive antibody; PS, propensity score.

vs. 23.9%, p = 0.82), infection rate (4.1% vs. 6.0%, p = 0.50), and DGF (20.6% vs. 22.5%, p = 0.72) did not differ significantly. Across the entire cohort, all patients showed similar results (Table 2; Supplementary Fig. 1, available online).

Comparison of clinical outcomes according to donor age

We compared postoperative patient survival and death-censored graft survival after induction with BSX or ATG according to donor age in the PS-matched subgroups. The elderly group (donor age of ≥60 years) contained 72 patients, and the young group (donor age of <60 years) contained 358 patients. In the elderly group, death-censored graft survival did not differ significantly between the BSX and ATG groups (p = 0.88). Likewise, in the young group, death-censored graft survival did not differ significantly between the BSX and ATG groups (p = 0.50). The patient survival rates in the elderly group after treatment with BSX and ATG were 93.9% and 92.6%, respectively (p = 0.97). Likewise, the patient survival rates in the young group

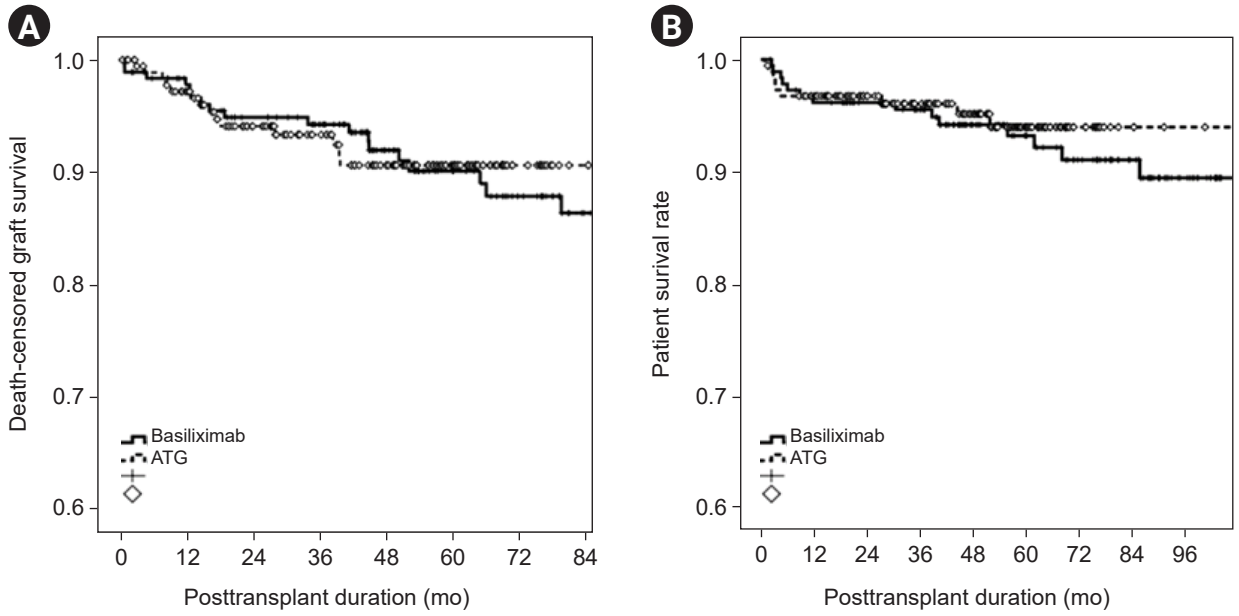

Figure 2. Death-censored graft and patient survival in the matched cohort according to induction therapy. (A) Death-censored graft survival in the matched cohort (p = 0.61). (B) Patient survival in the matched cohort (basiliximab, 93.3%; ATG, 94.2%; p = 0.86). ATG, antithymocyte globulin.

Table 2. Comparison of AR, infection rate, and delayed graft function according to induction therapy

Variable	Entire cohort (n = 724)			PS-matched cohort (n = 436)		
	Basiliximab (n = 472)	ATG (n = 252)	p-value	Basiliximab (n = 218)	ATG (n = 218)	p-value
AR	109 (23.1)	60 (23.8)	0.83	55 (25.2)	52 (23.9)	0.82
Infection rate	24 (5.1)	13 (5.2)	0.97	9 (4.1)	13 (6.0)	0.50
DGF	90 (19.1)	59 (23.4)	0.17	45 (20.6)	49 (22.5)	0.72

Data are expressed as number (%).
AR, acute rejection; ATG, antithymocyte globulin; DGF, delayed graft function; PS, propensity score.

were 91.9% and 94.5% after treatment with BSX and ATG, respectively (p = 0.80). The incidence of AR (BSX, 27.8% vs. ATG, 22.2%; p = 0.79), the infection rate (BSX, 8.3% vs. ATG, 5.6%; p = 0.66), and DGF (BSX, 19.4% vs. ATG, 16.7%; p = 0.74) did not differ significantly in the elderly group. As in the elderly group, the incidence of AR (BSX, 24.0% vs. ATG, 24.0%; p > 0.99), infection rate (BSX, 3.9% vs. ATG, 5.6%; p = 0.61), and DGF (BSX, 20.7% vs. ATG, 23.5%; p = 0.61) did not differ significantly according to the induction therapy agent used in the young group (Table 3). The entire cohort analysis results are summarized in Supplementary Table 1 (available online).

Comparison of clinical outcomes according to acute kidney injury in donor

We compared postoperative patient survival and death-censored graft survival after induction with BSX or ATG according to the presence of donor kidney AKI in the PS-matched subgroups. The AKI group contained 286 patients, and the non-AKI group contained 130 patients. In the AKI group, death-censored graft survival did not differ significantly between the patients who received BSX and those who received ATG induction therapy (p = 0.90). Likewise, in the non-AKI group, death-censored graft survival did not differ between BSX and ATG (p = 0.25). The patient survival rates in the AKI group after treatment with BSX and ATG

Table 3. Comparison of AR, infection rate, and DGF according to induction therapy in elderly and young propensity score matched subgroups

Variable	Elderly (n = 72)			Young (n = 358)		
	Basiliximab (n = 36)	ATG (n = 36)	p-value	Basiliximab (n = 179)	ATG (n = 179)	p-value
AR	10 (27.8)	8 (22.2)	0.79	43 (24.0)	43 (24.0)	>0.99
Infection rate	3 (8.3)	2 (5.6)	0.66	7 (3.9)	10 (5.6)	0.61
DGF	7 (19.4)	6 (16.7)	0.74	37 (20.7)	42 (23.5)	0.61

Data are expressed as number (%).
AR, acute rejection; ATG, antithymocyte globulin; DGF, delayed graft function.

Table 4. Comparison of AR, infection rate, and DGF according to induction therapy in donor AKI and non-AKI propensity score matched subgrou

Variable	AKI (n = 286)			Non-AKI (n = 130)		
	Basiliximab (n = 143)	ATG (n = 143)	p-value	Basiliximab (n = 65)	ATG (n = 65)	p-value
AR	40 (28.0)	33 (23.1)	0.40	12 (18.5)	17 (26.2)	0.41
Infection rate	6 (4.2)	6 (4.2)	>0.99	4 (6.2)	6 (9.2)	0.75
DGF	39 (27.3)	41 (28.7)	0.89	4 (6.2)	6 (9.2)	0.73

Data are expressed as number (%).
AKI, acute kidney injury; AR, acute rejection; ATG, antithymocyte globulin; DGF, delayed graft function.

were 93.8% and 95.2%, respectively (p = 0.95). In the non-AKI group, the patient survival rates were 91.8% and 92.0% in patients treated with BSX and ATG, respectively (p = 0.67). The incidence of AR (BSX, 28.0% vs. ATG, 23.1%; p = 0.40), infection rate (BSX, 4.2% vs. ATG, 4.2%; p > 0.99), and DGF (BSX, 27.3% vs. ATG, 28.7%; p = 0.89) did not differ significantly by induction therapy in the AKI group. Likewise, the incidence of AR (BSX, 18.5% vs. ATG, 26.2%; p = 0.41), infection rate (BSX, 6.2% vs. ATG, 9.2%; p = 0.75), and DGF (BSX, 6.2% vs. ATG, 9.2%; p = 0.73) did not differ significantly in the non-AKI group (Table 4). The entire cohort analysis results are summarized in Supplementary Table 2 (available online).

Comparison of clinical outcomes according to Kidney Donor Profile Index score

We compared postoperative patient survival and death-censored graft survival after induction with BSX and ATG according to KDPI score in the PS-matched subgroups. The high-KDPI group (KDPI score of >65%) contained 226 patients, and the low-KDPI group contained 166 patients. In the high-KDPI group, death-censored graft survival did not differ significantly between the patients who received BSX and those who received ATG induction therapy (p = 0.39). Likewise, in the low-KDPI group, death-censored graft survival did not differ significantly between patients who received BSX and those who received ATG (p = 0.55). The patient survival rates in patients treated with BSX and ATG were 92.7% and 95.1%, respectively, in the high-KDPI group (p = 0.46) and 96.2% and 95.8% in the low-KDPI group (p = 0.63). The incidence of AR (BSX, 25.7% vs. ATG, 28.3%; p = 0.77), infection rate (BSX, 6.2% vs. ATG, 5.3%; p = 0.78), and DGF (BSX, 23.0% vs. ATG, 26.6%; p = 0.64) did not differ between induction therapies in the high-KDPI group. Likewise in the low-KDPI group, the incidence of AR (BSX, 21.7% vs. ATG, 15.7%; p = 0.42), infection rate (BSX, 3.6% vs. ATG, 6.2%; p = 0.63), and DGF (BSX, 19.3% vs. ATG, 20.5%; p = 0.85) did not differ significantly between induction therapies (Table 5). The entire cohort analysis results are summarized in Supplementary Table 3 (available online).

Discussion

Due to a shortage of organ donors and ethical issues, DDKT is a promising option for ESRD patients. Moreover, kidneys from donors with AKI, elderly DDs, and donors with high KDPI scores have recently become widely used to maximize

Table 5. Comparison of AR, infection rate, and DGF according to induction therapy in high-KDPI and low-KDPI propensity score matched subgroups

Variable	High-KDPI (n = 226)			Low-KDPI (n = 166)		
	Basiliximab (n = 113)	ATG (n = 113)	p-value	Basiliximab (n = 83)	ATG (n = 83)	p-value
AR	29 (25.7)	32 (28.3)	0.77	18 (21.7)	13 (15.7)	0.42
Infection rate	7 (6.2)	6 (5.3)	0.78	3 (3.6)	5 (6.2)	0.63
DGF	26 (23.0)	30 (26.5)	0.64	16 (19.3)	17 (20.5)	0.85

Data are expressed as number (%).
AKI, acute kidney injury; AR, acute rejection; ATG, antithymocyte globulin; DGF, delayed graft function.

the number of donor candidates. Due to improvements in KT strategies including induction therapy agents, the criteria for DDs have been expanded. Induction therapy plays an important role in transplantation by lowering the incidence of AR and thereby improving allograft survival [13]. Currently, almost 80% of KTRs in the United States receive induction therapy with either BSX or ATG [9]. In general, BSX is used for immunologically low-risk patients, and ATG is used for high-risk patients. However, the effects of selecting one induction immunosuppressant over the other in DDKT remain unclear, and the choice of induction agent remains controversial [14]. Therefore, we compared the efficacy and safety of ATG and BSX as induction therapy in DDKT patients whose donor condition was relatively poor.

A series of trials have demonstrated that induction therapy with ATG or BSX reduces the risk of early AR episodes after KT versus controls. In 2010, the Cochrane Collaboration published a meta-analysis of randomized controlled trials that compared BSX induction with placebo and with ATG [15]. Compared with placebo, the BPAR rates were 30% lower with BSX (1-year relative risk [RR], 0.72; 95% confidence interval [CI], 0.64–0.81), and graft loss was reduced (1-year RR, 0.75; 95% CI, 0.62–0.90). Brennan et al. [9] compared patients at high risk of AR or DGF who received DDKT with ATG (1.5 mg/kg from day 0 to day 4) with those who received BSX (20 mg on day 1 and day 4) as induction therapy. Their ATG patients had a lower incidence and lower severity of AR. A long-term follow-up study of those patients showed that the incidence of AR requiring antibody treatment in patients with ATG was lower than that in patients who received BSX [16].

The TAXI study compared DGF in high-risk DDKT recipients who received IL-2R antibody vs. ATG. Those ATG patients had a lower incidence of both rejection and DGF 1 year after transplant [17]. Jeong et al. [18] found that low-dose ATG (1 mg/kg on days 0, 1, and 2) significantly reduced the rates of DGF and AR compared with BSX in high-risk recipients (DGF, p = 0.035; AR, p = 0.004). Based on those previous studies, ATG is considered to have higher immunosuppressive effects than BSX and is expected to have clinical outcome benefits in DDKT with poor donor condition [19].

ATG is also considered to carry a higher risk of infection. Various previous studies have reported that patients who receive BSX have a lower incidence of infection than those who receive ATG [20–22]. About the cause for that difference, Liu et al. [23] said that it might be related to the different drug mechanisms. BSX is a monoclonal antibody that targets CD25 and binds to the α-chain of IL-2R, making it a potent inhibitor of IL-2-mediated T-cell proliferation. CD25 participates in lymphocyte differentiation, activation, and proliferation. CD8 T cells respond to viral infections and also participate in defense against bacterial and protozoal infections. Because most CD8 cells express IL-2R β and γ chains, CD25 therapy (BSX) might not impair the cytotoxic T-cells that contribute to the control of infection.

In previous studies, the death-censored graft and patient survival rates were similar between the two induction therapies [24–26]. Likewise, the differences in graft and patient survival rates between induction agents were not statistically significant in our study. We calculated a log minus log survival plot to test the assumption of PHs. Each risk factor graph curve had a constant vertical distance, indicating that our data satisfy the PH assumption. Furthermore, we conducted the Schoenfeld residual test to confirm that finding and found a Schoenfeld p-value of >0.05, which indicates that our study model meets the PH assumption. In our multicollinearity check, the variance inflation factor was less than 10 (range, 1.00–1.93). In our multivariable analysis using a conditional Cox regression hazard model,

induction therapy agent was not a significant risk factor for allograft failure (hazard ratio [HR], 1.73; 95% CI, 0.87–3.44; p = 0.12). Neither DD AKI (HR, 1.43; 95% CI, 0.63–3.23; p = 0.40) nor elderly DD (HR, 1.00; 95% CI, 0.96–1.05; p = 0.87) alone showed significance in the multivariable analysis, which agrees with previous reports. High KDPI score alone showed significance for allograft failure (HR, 4.15; 95% CI, 1.31–13.13; p = 0.02) (Table 6).

In addition to those results, which confirm those in previous studies, our results here provide interesting information that was not reported in previous studies. We found that induction therapy itself did not notably influence long-term clinical outcomes, including the incidence of AR and DGF. Neither AR nor DGF differed significantly by induction agent, not only in the total study population, but also in the elderly/young donor, AKI/non-AKI, and high-KDPI/low-KDPI subgroups. Our study suggests that BSX can produce clinical outcomes that are similarly favorable to those with ATG even in DDKT cases in which the donor condition is relatively poor. Therefore, using ATG induction therapy in high-risk DDKT as a matter of protocol or habit might not be an appropriate strategy.

Our study has some limitations, as suggested in our previous reports using this cohort. First, because it was a retrospective study, our study has a possibility of selection bias. To overcome that limitation and reduce the effects of confounding factors, we used PS matching and a relatively large number of KTRs from multiple centers. In addition, we adjusted our results to consider the transplant center and transplant year in the multivariable analysis. Second, not all KTRs corresponding to donors included in this study were included in our analysis because some organs were transferred to another institution according to the organ distribution rule in Korea, which could have induced bias during the analysis. Well-designed, stratified, prospective multicenter studies are required to overcome these issues.

In conclusion, clinicians should select an induction therapy agent carefully in DDKT. The donor and recipient conditions, immunological risk, and infection risk must all be considered. Selection of induction therapy agent should be individualized based on the risks and benefits in each DDKT case.

Additional information

[1]*Transplant Research Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[2]*Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[3]*Division of Nephrology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Republic of Korea*
[4]*Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea*
[5]*Keimyung University Kidney Institute, Daegu, Republic of Korea*

Table 6. Risk factors for allograft failure in deceased donor KT (propensity score matched cohort)

Risk factor	Unadjusted HR (95% CI)	p-value	Adjusted HR[a] (95% CI)	p-value
Induction therapy				
ATG vs. basiliximab	1.70 (0.78–3.71)	0.18	1.73 (0.87–3.44)	0.12
Donor				
Age	1.01 (0.95–1.07)	0.81	1.00 (0.96–1.05)	0.87
Sex, female vs. male	1.75 (0.51–5.98)	0.37	1.19 (0.59–2.41)	0.63
AKI by KDIGO, 1 vs. 0	0.33 (0.04–3.21)	0.34	1.43 (0.63–3.23)	0.40
KDPI score, ≥65 vs. <65	5.00 (0.58–42.79)	0.14	4.15 (1.31–13.13)	0.02
Recipient				
Age	0.94 (0.87–1.01)	0.09	1.00 (0.96–1.03)	0.85
Sex, female vs. male	1.75 (0.51–5.98)	0.37	1.19 (0.62–2.29)	0.60
Previous KT, yes vs. no	0.67 (0.11–3.99)	0.66	1.01 (0.30–3.44)	0.99
PRA class I + II, >30% vs. ≤30%	0.40 (0.14–1.16)	0.09	0.47 (0.21–1.03)	0.06
HLA mismatch number	1.00 (0.68–1.47)	>0.99	0.99 (0.79–1.25)	0.95

AKI, acute kidney injury; ATG, antithymocyte globulin; CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio; KDIGO, Kidney Disease Improving Global Outcomes; KDPI, Kidney Donor Profile Index; KT, kidney transplantation; PRA, panel reactive antibody.
[a]Adjusted by recipient age, recipient sex, donor sex, donor age, HLA mismatch number, PRA summation quantity, donor kidney AKI, and KDPI score.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization: BHC, WYP
Data curation: SYH, YSK, KJ, SH
Funding acquisition: BHC
Formal analysis: SYH, YSK, KJ, WYP
Supervision: SH, CWY, BHC, WYP
Validation: SH, CWY
Writing–original draft: SYH, BHC, WYP
Writing–review & editing: SYH, WYP, BHC
All authors read and approved the final manuscript.

ORCID

Su Yeon Hong, https://orcid.org/0000-0002-7574-5045
Young Soo Kim, https://orcid.org/0000-0001-8478-0566
Kyubok Jin, https://orcid.org/0000-0002-7836-8863
Seungyeup Han, https://orcid.org/0000-0002-7561-6534
Chul Woo Yang, https://orcid.org/0000-0001-9796-636X
Byung Ha Chung, https://orcid.org/0000-0003-0048-5717
Woo Yeong Park, https://orcid.org/0000-0003-2662-2898

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