Efficacy of anti-T-lymphocyte globulin-Fresenius as an induction agent in deceased-donor renal transplantation: A cohort study

YUN-XIA CHAI, JIAN-LEI JI, SHU-JUAN LI, YAN-WEI CAO, XIAO-XIA SUN, QING-HAI WANG, TAO HUANG, ZHEN DONG and HONG-YANG WANG

Department of Kidney Transplantation, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, P.R. China

Received March 2, 2019; Accepted September 24, 2019

DOI: 10.3892/etm.2020.8451

Abstract. Anti-T-lymphocyte globulin (ATG) is frequently used in the induction regimen of renal transplantation, but its dose has not been standardized. In the present study, the efficacy of different ATG-Fresenius (ATG-F) doses was assessed in recipients of renal transplantation. A total of 131 adult recipients of renal transplantation who received ATG-F induction between August 2015 and July 2018 were included. The incidence of biopsy-confirmed acute rejection, graft function, as well as graft and patient survival within 12 months post-transplant, was assessed, and adverse events, including hematologic and infection-associated side effects, were compared between patients receiving a cumulative ATG-F dose of <7 or ≥7 mg/kg. The incidence of biopsy-confirmed acute rejection was similar between patients receiving cumulative doses of <7 and ≥7 mg/kg (7.5 vs. 4.7%, P=0.766). The incidence of infection within 12 months was lower in the ATG-F <7 mg/kg group compared with that in the ≥7 mg/kg group (26.9 vs. 50.0%, P=0.006), but the incidence of pneumonia did not differ between the ATG-F <7 and ≥7 mg/kg groups (10.4 vs. 20.3%, P=0.117). The incidence of urinary infection was higher in the ≥7 mg/kg group than in the <7 mg/kg group (20.4 vs. 7.46%, P=0.033), while the extent and duration of anemia and lymphopenia was similar between groups. There was no difference in graft function, delayed graft function, as well as overall and graft survival between the groups. In conclusion, a moderate reduction in the cumulative ATG-F dose was not associated with an increased risk of acute rejection, while the risk of infection was reduced. Optimization of the ATG-F dose for induction may facilitate the reduction of the risk of infection without compromising the induction efficacy in renal transplant recipients.

Correspondence to: Dr Zhen Dong or Dr Hong-Yang Wang, Department of Kidney Transplantation, The Affiliated Hospital of Qingdao University, 57 Haier Road, Qingdao, Shandong 266000, P.R. China
E-mail: dong266000@163.com
E-mail: why19850804@163.com

Key words: anti-T-lymphocyte globulin, acute rejection, kidney transplantation

Introduction

Induction is recommended for all renal transplantation (RT) recipients, except for haplo-identical living related-donor transplantations (1). Anti-T-lymphocyte globulins (ATGs), which may effectively attenuate the risk of acute rejection and improve graft survival, is frequently used for induction in solid organ transplantation (2). ATG-Fresenius (ATG-F; Neovii-Biotech), a highly purified rabbit polyclonal anti-human T-lymphocyte immunoglobulin derived from immunizing rabbits with the Jurkat T-Lymphoblast cell line, is one of the best-characterized types of ATGs (3). Short-term induction is more preferable due to the prominent toxicity associated with long-term administration (4). However, the optimal dose, the maximal tolerable cumulative dose and the dosing frequency of ATG-F remain undefined despite the fact that ATG-F has been in use for many years. Kaden *et al* (5,6) attempted to re-schedule the timing of ATG-F induction from the post-operative period to the pre-operative period and use a single high dose (9 mg/kg) for induction, and they revealed that the reschedule increased the rates of graft and patient survival compared to those receiving routine triple-drug maintenance therapy. However, Meier-Kriesche *et al* (7) indicated that ATG-F reduced the risk of acute rejection but also caused serious adverse effects in the renal graft recipients, including higher mortality linked to cardiovascular or infectious episodes and a higher incidence of advanced malignancy. In addition, Chen *et al* (8) reported that a regimen consisting of a cumulative ATG-F dose of 6 mg/kg (2 mg/kg/day during the operation and on post-operative days 1 and 2) provided adequate protection from acute rejection.

At the Affiliated Hospital of Qingdao University (Qingdao, China), a cumulative ATG-F dose of 7 mg/kg based on actual body weight has been consistently used for the induction of renal transplantation. However, doses are rounded to the nearest vial size and the range of the dose lies between 400 and 600 mg; this practice may result in administering a cumulative dose of <7 mg/kg for overweight patients but ≥7 mg/kg for underweight ones. The absence of randomized controlled trials and controversial data from the existing literature

points to the requirement for data to facilitate the selection of optimal ATG-F induction doses for recipients of kidney graft, particularly under the circumstance of ATG-F provided with triple immunosuppressive maintenance. Therefore, in the present study, the efficacy and safety associated with different cumulative doses of ATG-F induction were assessed in renal transplant recipients receiving a steroid-containing maintenance regimen.

Materials and methods

Enrollment of participants. The present retrospective single-center cohort study included adult renal transplant recipients who received a deceased donor graft at the Affiliated Hospital of Qingdao University (Qingdao, China) between August 2015 and July 2018. All participants received ATG-F induction and were maintained on tacrolimus, enteric-coated mycophenolate sodium (EC-MPS) and prednisone. According to the institutional protocol, the indications for ATG-F induction included the following: i) Chinese ethnicity; ii) receipt of deceased donor renal transplant; iii) panel reactive antibody (PRA) between 0 and 10%, or a negative pre-operative PRA but a positive history in the waiting list; or iv) a history of blood transfusion within 3 months prior to surgery. Patients were excluded if they had a history of prior non-renal transplantation, received a simultaneous non-renal transplant, underwent desensitization, experienced primary graft non-function, received a positively cross-matched renal graft, or received any experimental medications or ATG-F for non-protocol-based indications.

Categorization of study participants based on ATG-F doses. Eligible patients were divided into 2 groups, including the cumulative ATG-F dose <7 mg/kg group (group 1) and the ≥7 mg/kg group (group 2) based on the pre-operative actual body weight.

The induction regimen of ATG-F consisted of 2 mg/kg administered on post-operative day (POD) 0 and POD 1, followed by another 1.5 mg/kg on POD 2 and POD 3, for a cumulative dose of 7 mg/kg. Doses were rounded to the nearest vial size (100 mg) and capped at 200 mg based on the 2 mg/kg schedule on POD 0 and 1, and 100 mg based on the 1.5 mg/kg schedule on POD 2 and 3. Dose modifications were not allowed for patients with leukopenia or thrombocytopenia. The cumulative ATG-F dosages for group 1 and 2 were 442.19±77.08 mg (400-600 mg) and 485.93±58.27 mg (400-600 mg), respectively (P<0.001). Corticosteroids were administered according to the following schedule: Intravenous methylprednisolone 500 or 750 mg given intra-operatively followed by another 500 mg on POD 1 and 2, and oral prednisone starting at 16 mg on POD 3 with gradual tapering to 4 mg by POD 90. In addition, oral tacrolimus 0.05-0.06 mg/kg every 12 h was initiated within 24 h of renal transplantation, with the trough levels set at 8-10 ng/ml between POD 0 and 30, 6-8 ng/ml between POD 31 and 180, and 5-7 ng/ml after POD 181. Oral EC-MPS 540 or 720 mg was administered every 12 h on POD 0. All patients received prophylaxis for *Pneumocystis jiroveci* infection using trimethoprim/sulfamethoxazole for 6-12 months, except those presenting with severe leukopenia or having a serum creatinine level exceeding 2 mg/dl. Prophylaxis against cytomegalovirus (CMV) was not routinely administered.

Table I. Comparison of clinical features between groups 1 and 2.

Parameter	Group 1 (n=67)	Group 2 (n=64)	P-value
Age (years)	41.9±10.1	39.5±10.5	0.751
Sex, Male (n, %)	59 (88.1)	43 (67.2)	0.330
ABW (kg)	73.4±13.5	59.6±9.3	0.009
BMI (kg/m^2)	24.3±3.69	20.7±2.85	0.047
Follow up (days)	480 (90-1140)	610 (125-1145)	0.584
Indication for transplant (n, %)			0.632
CGN	45 (67.2)	48 (75.0)	
IgAN	6 (9.0)	5 (7.8)	
DN	8 (11.8)	6 (9.4)	
HTN	2 (3.0)	1 (1.6)	
PCKD	3 (4.5)	1 (1.6)	
Other	3 (4.5)	3 (4.6)	
Dialysis mode (n, %)			0.655
Preemptive	3 (4.5)	5 (7.8)	
HD	57 (85.1)	54 (84.4)	
PD	7 (10.4)	5 (7.8)	
Dialysis duration	12	12	0.268
HLA mismatch	2.8±1.3	3.0±1.2	0.363

Values are expressed as n (%) or the mean ± standard deviation. Group 1, <7 mg/kg ATG-F; group 2, ≥7 mg/kg ATG-F. ATG-F, anti-T-lymphocyte globulin-Fresenius; CGN, chronic glomerulonephritis; IgAN, IgA nephropathy; HTN, hypertensive nephropathy; DN, diabetic nephropathy; PCKD, polycystic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; HLA, human lymphocyte antigen; BMI, body mass index; ABW, actual body weight.

Endpoint definitions. The primary endpoint was incident biopsy-confirmed acute rejection (BCAR) within 12 months after transplantation, based on the Banff histologic criteria (9). Secondary endpoints included incident infections (all), pneumonia, urinary tract infection; CMV or BK viruria and viremia, BK virus nephropathy (BKVN), hematologic adverse effects including anemia, leukopenia, thrombocytopenia and lymphopenia; delayed graft function, as well as overall patient and graft survival. Graft function was assessed via measuring serum creatinine levels at 12 months. BK virus was screened by PCR-based assays at 1, 3, 6, 9 and 12 months after transplantation, or as required when serum creatinine increased for unknown reasons. PCR assays for CMV were performed at 1, 3, 6 and 12 months after transplantation in the presence of symptoms and signs suggestive of CMV infection. Delayed graft function was defined according to a urine output level of <0.5 ml/kg/h, a decline in serum creatinine <10% from pre-transplant levels within 24 h, or a requirement for hemodialysis within 1 week after transplantation. Primary non-function of renal grafts was defined as recipients requiring maintenance

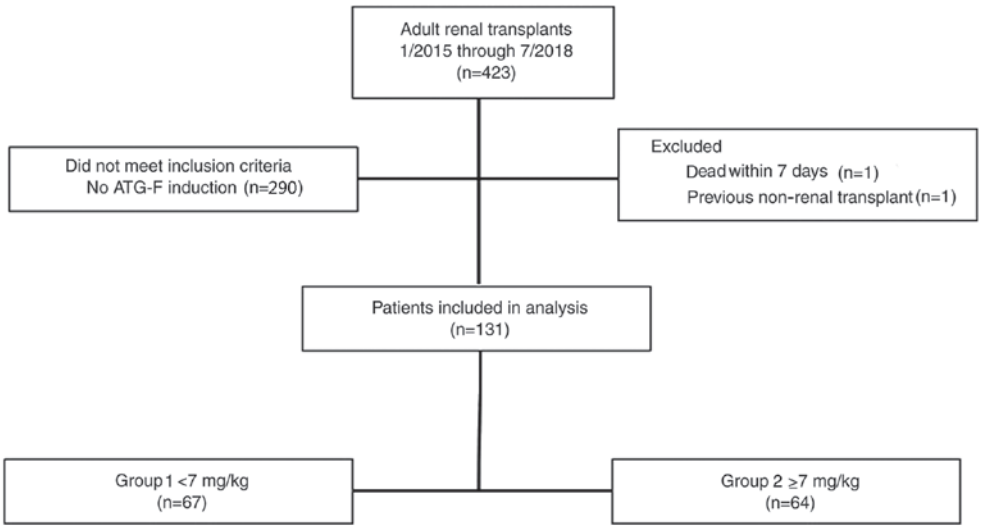

Figure 1. Flow chart for the enrollment of patients in the present study. ATG-F, anti-T-lymphocyte globulin-Fresenius.

Table II. Clinical features of the donors.

Parameter	Group 1 (n=34)	Group 2 (n=32)	P-value
Age (years)	39.1±9.9	40.7±13.1	0.576
Sex, Male (n, %)	28 (82.4)	26 (81.3)	0.908
Cause of death (n, %)			0.972
Traumatic brain injury	18 (52.9)	16 (50.0)	
Encephalorrhagia	14 (41.2)	14 (43.8)	
Other	2 (5.9)	2 (6.2)	
Warm ischemic time (min)	8.2±4.3	8.7±4.6	0.650
Cold ischemic time (h)	7.6±2.7	7.7±2.3	0.872
Mean ATG-F dose (mg/kg)	5.90±0.93	8.24±1.05	<0.001
Cumulative ATG-F dose (mg)	442.19±77.08	485.93±58.27	<0.001
Incidence of delayed graft function (%)	7.4%	4.7%	0.766
Mean serum creatinine at 12 months (mg/dl)	1.23±0.64	1.19±0.58	0.165

Values are expressed as n (%) or the mean ± standard deviation. Comparison between groups 1 and 2 was performed using a Chi-square test. Group 1, <7 mg/kg ATG-F; group 2, ≥7 mg/kg ATG-F. ATG-F, anti-T-lymphocyte globulin-Fresenius.

dialysis or re-transplantation, excluding those who died with functional grafts.

Statistical analysis. The Student's t-test and one-way analysis of variance were used to compare continuous variables. Categorical variables were compared using the χ^2 test. Continuous variables are expressed as the mean ± the standard deviation. A P-value <0.05 was deemed significant. All statistical analyses were performed using SPSS 21 (IBM Corp.).

Results

Clinical characteristics of study participants. Of the 423 renal transplantations performed between August 2015 and July 2018, 131 cases were included in the final analysis (Fig. 1). Participants in the two dose groups were well matched with regard to demographics and immunological risk factors aside from by body weight and body mass index (Table I). The clinical features of the donors are presented in Table II. There was no significant difference between groups 1 and 2 in terms of age, sex, cause of death or duration of ischemia. The mean ATG-F dose in group 1 was significantly lower than that in group 2 (5.90±0.93 vs. 8.24±1.05 mg/kg, P<0.001). The cumulative ATG-F dosages in groups 1 and 2 were 442.19±77.08 mg (400-600) and 485.93±58.27 mg (400-600), respectively (P<0.001). The trough levels of tacrolimus were similar between the two groups during the follow-up period (Fig. 2 and Table III). All participants were maintained on a steroid-containing regimen and continued the triple maintenance immunosuppression for 12 months (Table III). The overall incidence of delayed graft function was 6.1% and the

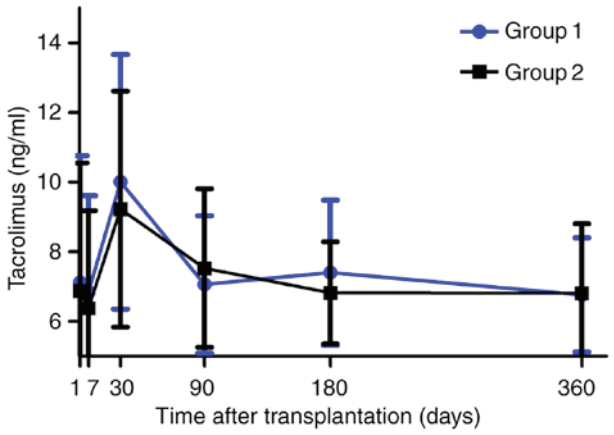

Figure 2. Tacrolimus trough concentrations of patients with ATG-F induction during the follow-up period (group 1, <7 mg/kg ATG-F vs. group 2, ≥7 mg/kg ATG-F). The Student's t-test was used to analyze the differences in Tacrolimus trough concentrations. ATG-F, anti-T-lymphocyte globulin-Fresenius.

Table III. Mean trough tacrolimus levels in subjects on maintenance immunosuppression and immunosuppression at 12 months.

A, Mean trough tacrolimus levels in subjects on maintenance immunosuppression (ng/ml)

Post-operative day	Group 1 (n=67)	Group 2 (n=64)	P-value
7	6.9±2.8	6.8±3.3	0.255
30	9.9±3.7	9.7±3.7	0.397
90	7.1±2.0	7.4±2.3	0.196
360	6.8±1.6	6.9±1.9	0.175

B, Immunosuppressive drug use at 12 months

Regimen	Group 1 (n=67)	Group 2 (n=64)	P-value
TMP	65	62	0.645
CMP	2	2	

Values are expressed as the mean ± standard deviation or n. Group 1, <7 mg/kg ATG-F; group 2, ≥7 mg/kg ATG-F. ATG-F, anti-T-lymphocyte globulin-Fresenius; T, tacrolimus; M, enteric-coated mycophenolate sodium; P, prednisone; C, cyclosporine.

incidence did not differ between the two groups (7.4 vs. 4.7%, P=0.766; Table II).

Comparison of endpoints between the two dose groups. There was no significant difference with regard to overall patient and graft survival between the 2 groups. At 12 months after transplantation, all patients in group 1 were alive, whereas 98.4% of patients were alive in group 2 (P=0.306; Fig. 3A). One patient from group 2 died during the follow-up period due to pulmonary infection. Graft survival was 100 and 98.4% in group 1 and 2, respectively (P=0.374; Fig. 3B). Allograft loss occurred in 1 patient from group 2 during follow-up due to T cell-mediated acute rejection. There was no difference regarding creatinine-based graft function between groups 1 and 2 (1.23 vs. 1.19 mg/dl, P=0.165; Table II) or the primary endpoint BCAR at 12 months between the two groups. The cumulative ATG-F dose did not influence the rates of BCAR within the first 12 months after transplantation (Table IV).

Table IV. Rates of BCAR at 12 months.

BCAR grade (n, %)	Group 1 (n=67)	Group 2 (n=64)	P-value
≥1A	5 (7.4)	3 (4.7)	0.766
1	4 (6.0)	2 (3.1)	0.718
2	1 (1.5)	1 (1.6)	0.496

Values are expressed as n (%). Group 1, <7 mg/kg ATG-F; group 2, ≥7 mg/kg ATG-F. ATG-F, anti-T-lymphocyte globulin-Fresenius; BCAR, biopsy-confirmed acute rejection.

Comparison of side effects between the two dose groups. Regarding adverse effects, no differences in CMV infection rates (60.5 vs. 66.6%, P=0.560), CMV-associated diseases (7.4 vs. 7.8%; P=0.800) or BKVN (1.6 vs. 3.0%, P=0.968) were observed between groups 1 and 2. Group 1 had a lower incidence of BK viremia (7.5 vs. 23.3%, P=0.022) and BK viruria (50.0 vs. 76.7%, P=0.023) than group 2. The overall incidence of infection (26.9 vs. 50.0%, P=0.006) and urinary tract infection (7.5 vs. 20.3%, P=0.033) within 12 months was significantly lower in group 1 than in group 2. In addition, the incidence of pneumonia within 12 months was similar in groups 1 and 2 (10.4 vs. 20.3%, P=0.117). Similarly, the incidence of anemia, lymphopenia, thrombocytopenia and leukopenia did not differ between the two groups (Fig. 4). Induction using ATG-F depleted circulating lymphocytes to <500 cells/mm^3, and lymphocyte depletion persisted until POD 90 in 3.2% of patients. However, the degree and the duration of lymphopenia did not differ between the two groups.

Discussion

The dose of ATG-F used for induction in renal transplantation that is able to provide adequate protection against acute rejection with a low incidence of complications is a subject under intense investigation. The present results provide additional evidence regarding weight-based dosing strategies of ATG-F induction in adult patients receiving renal transplantation with moderate immunologic risk.

The total ATG-F dosage for induction therapy was relatively constant for all patients at the Affiliated Hospital of Qingdao University. The mean ATG-F dosage was calculated using total dosages divided by the mean body weight. As a result, the mean ATG-F dosage was lower in patients with higher body weight. In the present study, transplant recipients were effectively protected from acute rejection based on ATG-F induction using a cumulative dose of <7 mg/kg in combination with a tacrolimus-based steroid-containing triple

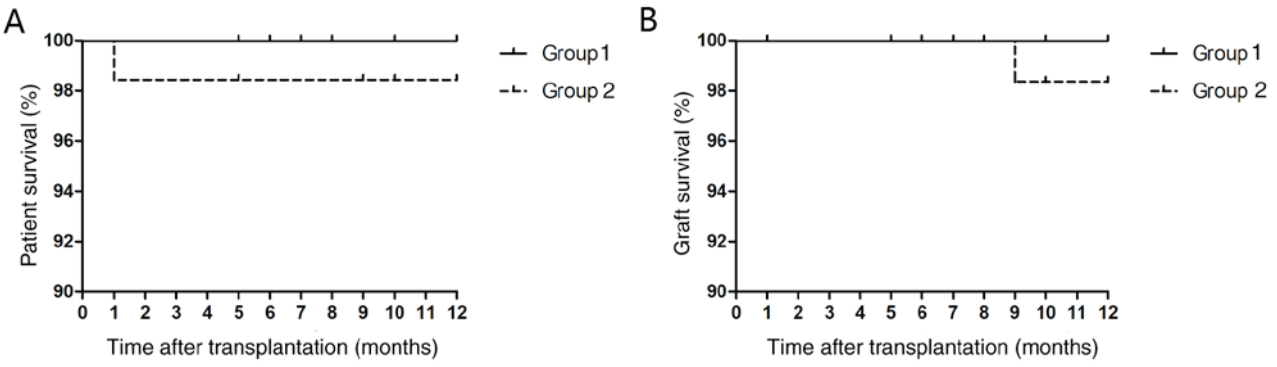

Figure 3. Kaplan-Meier analysis of (A) patient and (B) graft survival in groups 1 and 2 during the follow-up period. Log-rank test was used to analyze the differences in patient and graft survival between groups. Group 1, <7 mg/kg ATG-F; group 2, ≥7 mg/kg ATG-F; ATG-F, anti-T-lymphocyte globulin-Fresenius.

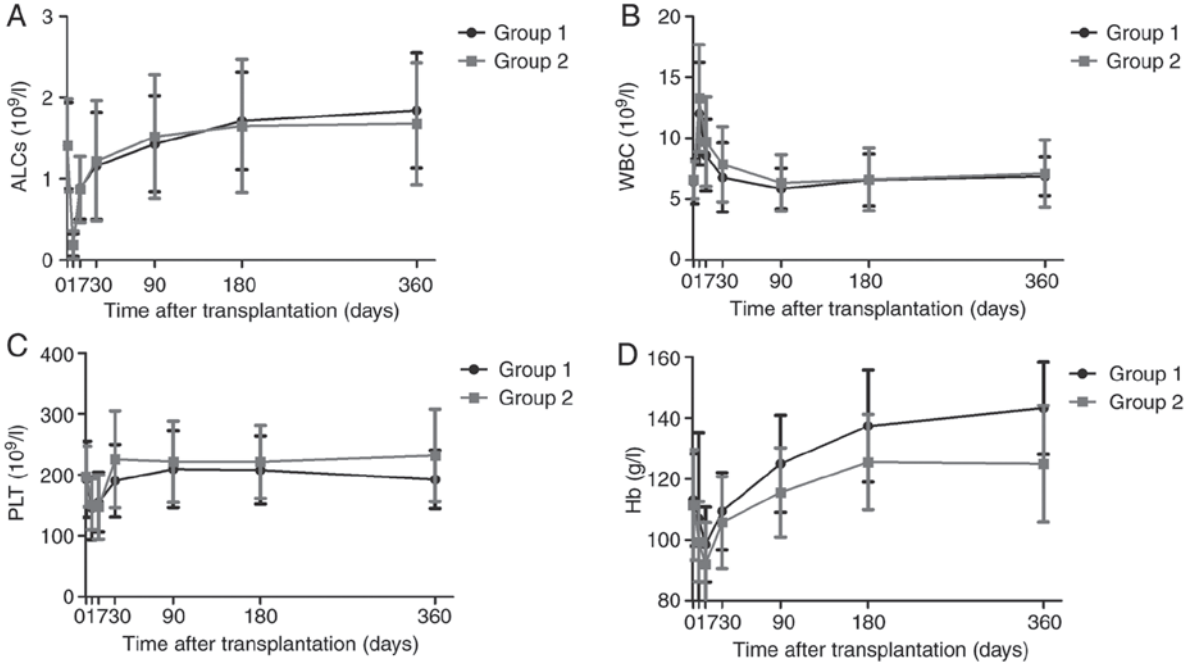

Figure 4. Hematologic effects of ATG-F induction following renal transplantation. (A) ALC, (B) total WBC count, (C) PTL counts and (D) Hb. The Student's t-test was used to analyze the differences in ALC, WBCs, PTLs and Hb levels. Group 1, <7 mg/kg ATG-F; group 2, ≥7 mg/kg ATG-F. ATG-F, anti-T-lymphocyte globulin-Fresenius; ALC, absolute lymphocyte count; WBC, white blood cell; PLT, platelet; Hb, hemoglobin.

maintenance immunosuppression. The mean ATG-F dose in the study participants was 7.05±1.54 mg/kg. Overall patient survival and death-censored graft survival at 12 months were 99.2%, whereas the incidence of BCAR ≥1A at 12 months was only 6.1% (8/131). The present results clearly indicate that an induction regimen consisting of a lower ATG-F dose did not increase the risk of acute rejection.

Kaden *et al* (10,11) indicated that a single pre-operative ATG bolus (ATG-F at 9 mg/kg) for prophylaxis against rejection induced a drastic reduction in T-cell counts that lasted for at least 5 days, and this regimen resulted in a lower risk of rejection compared with that in graft recipients receiving a regimen of triple immunosuppressants only. Yussim and Shapira (12) reported a higher acute rejection rate when graft recipients were given the same dose of ATG-F and a triple maintenance immunosuppression regimen consisting of a calcineurin inhibitor, an anti-proliferative agent and steroids. Similarly, Samsel *et al* (13) studied the effect of high-dose ATG bolus administration on revascularization among renal graft recipients receiving a triple maintenance immunosuppression regimen consisting of steroids, mycophenolate mofetil (converted to azathioprine 4 months later) and cyclosporine. The incidence of acute rejection at 12 months in that study was 22.5%. Earlier studies also examined the efficacy of different ATG-F doses in combination with a triple maintenance immunosuppression regimen in these patients. Chen *et al* (8) compared the efficacy and safety between rabbit anti-thymocyte globulin and anti-T lymphocyte globulin in renal transplant patients receiving allografts from donors who had suffered cardiac death, and indicated a higher rate of acute rejection (19.4%) but similar 1-year graft (97%) and patient survival (100%) in those receiving ATG-F compared with those determined in the present study. Shang *et al* (14) indicated that the rate of acute rejection at 12 months was 15.4% but the 1-year patient and graft survival was 94.9% among recipients who received ATG-F 1.5 mg/kg daily for

4 days in combination with a standard triple immunosuppression regimen. In that study, the incidence of post-operative infection was 35.9% (14).

The results of the present study indicated that differences in the dose of ATG-F were not associated with changes in the risk of opportunistic infections, hematologic toxicities or the duration of lymphopenia. A total of 10 patients developed CMV-associated diseases, including diarrhea, abdominal pain or fever, and all had good outcomes. In China, CMV is an endemic disease and most individuals are positive for CMV IgG. Considering the fact that CMV-associated pneumonia is rare at our institute, preemptive therapy for CMV instead of routine prophylaxis with valgancyclovir or ganciclovir was preferred for all recipients, although all patients tested positive for CMV IgG.

ATG-F has been widely used in the induction phase of solid-organ transplantation for decades, but the optimal dosage and duration remain elusive. Most existing studies have used rabbit ATG, a drug that completely differs from ATG-F with regard to the production process, usage, dosage and treatment efficacy. A number of studies used ATG-F as the induction regimen and a single ATG bolus (9 mg/kg) was the most common approach (10,11). Although the present study was retrospective, a comparison group was present, and important results regarding the optimal dosage and outcomes of ATG-F were obtained.

Acute rejection remains one of the major causes of graft loss after solid organ transplantation (15). The proliferation of leukocytes is one of the underlying mechanisms that increase acute rejection after initial reperfusion injury (16). ATGs are immunosuppressive agents widely used in the induction of immunosuppression after renal transplantation. The efficacy of ATG preparations relies on its potent capacity to deplete T lymphocytes of the graft, thereby preventing or treating episodes of acute rejection in transplantation (3). In the present study, patients from the low-dose group exhibited a similar degree of lymphocyte depletion compared with those in the high-dose group. In addition, the incidence of acute rejection did not differ between the two groups.

The present study is limited by its retrospective design and its non-randomized single-center nature. Confounding factors, including adherence to the maintenance immunosuppression regimen or adjustment of mycophenolate dose, were not collected for analysis. Recipients at the highest immunologic risk were excluded from the present study, including those who were ABO incompatible, had a positive cross-match result and those who received desensitization or steroid avoidance. The results of the present study suggested that a modest reduction in the ATG-F dose for induction is associated with a lower risk of infection and does not increase the risk of acute rejection when used in combination with tacrolimus-based steroid-containing triple maintenance immunosuppression in graft recipients with low immunologic risk.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YXC, HYW and ZD conceived and designed the study; JLJ, SJL and YWC collected data; XXS, QHW and TH analyzed and interpreted the data; YXC drafted the manuscript; ZD and HYW revised the manuscript; ZD had primary responsibility for the final content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Qingdao, China; no. QYFY WZLL 22519). All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. Written informed consent was obtained from all individual participants included in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Yilmaz M, Sezer TO, Kir O, Öztürk A, Hoşcoşkun C and Töz H: Use of ATG-fresenius as an induction agent in deceased-donor kidney transplantation. Transplant Proc 49: 486-489, 2017.
2. Pennington CA, Tischer SM, Lee E, Lee S, Sindelar J Jr and Park JM: Evaluation of a weight-based rabbit anti-thymocyte globulin induction dosing regimen for kidney transplant recipients. Pharmacotherapy 35: 748-754, 2015.
3. Beiras-Fernandez A, Thein E and Hammer C: Induction of immunosuppression with polyclonal antithymocyte globulins: An overview. Exp Clin Transplant 1: 79-84, 2003.
4. Morton RL, Howard K, Webster AC, Wong G and Craig JC: The cost-effectiveness of induction immunosuppression in kidney transplantation. Nephrol Dial Transplant 24: 2258-2269, 2009.
5. Kaden J, Strobelt V and May G: Short and long-term results after pretransplant high-dose single ATG-fresenius bolus in cadaveric kidney transplantation. Transplant Proc 30: 4011-4014, 1998.
6. Kaden J, Völp A and Wesslau C: High graft protection and low incidences of infections, malignancies and other adverse effects with intra-operative high dose ATG-induction: A single centre cohort study of 760 cases. Ann Transplant 18: 9-22, 2013.
7. Meier-Kriesche HU, Arndorfer JA and Kaplan B: Association of antibody induction with short- and long-term cause-specific mortality in renal transplant recipients. J Am Soc Nephrol 13: 769-772, 2002.
8. Chen GD, Lai XQ, Ko DS, Qiu J, Wang CX, Han M, Li J, Huang G, He XS and Chen LZ: Comparison of efficacy and safety between rabbit anti-thymocyte globulin and anti-T lymphocyte globulin in kidney transplantation from donation after cardiac death: A retrospective cohort study. Nephrology (Carlton) 20: 539-543, 2015.
9. Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, Halloran PF, Baldwin W, Banfi G, Collins AB, *et al*: Banff 07 classification of renal allograft pathology: Updates and future directions. Am J Transplant 8: 753-760, 2008.

10. Kaden J, May G, Müller P, Groth J, Strobelt V, Eger E and Wohlfahrt L: Intraoperative high-dose anti-T-lymphocyte globulin bolus in addition to triple-drug therapy improves kidney graft survival. Transplant Proc 27: 1060-1061, 1995.
11. Kaden J, May G, Strobelt V, Groth J and Müller P: Intraoperative T-cell depletion prior to completion of anastomoses by high-dose single ATG bolus as a new approach to improve long-term results after kidney transplantation. Transplant Proc 29: 344-347, 1997.
12. Yussim A and Shapira Z: Single-bolus high-dose ATG for prophylaxis of rejection in renal transplantation - a prospective, randomized study. Transpl Int 13 (Suppl 1): S293-S294, 2000.
13. Samsel R, Pliszczyński J, Chmura A, Korczak G, Włodarczyk Z, Cieciura T, Lagiewska B, Glyda M, Wyzgal J, Paczek L, *et al*: Safety and efficacy of high dose ATG bolus administration on rewascularization in kidney graft patients - long term results. Ann Transplant 13: 32-39, 2008.
14. Shang W, Feng G, Gao S, Wang Z, Pang X, Li J, Liu L, Feng Y, Xie H, Zhang S, *et al*: Reduced ATG-F dosage for induction in pediatric renal transplantation: A single-center experience. Pediatr Transplant 18: 240-245, 2014.
15. Brennan DC, Daller JA, Lake KD, Cibrik D and Del Castillo D; Thymoglobulin Induction Study Group: Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med 355: 1967-1977, 2006.
16. Beiras-Fernandez A, Chappell D, Hammer C, Beiras A, Reichart B and Thein E: Impact of polyclonal anti-thymocyte globulins on the expression of adhesion and inflammation molecules after ischemia-reperfusion injury. Transpl Immunol 20: 224-228, 2009.