Modest dose anti-thymocyte globulin administered intraoperatively is safe and effective in kidney transplantations: a retrospective study

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ABSTRACT

Background: Anti-thymocyte globulin (ATG) as induction therapy in renal transplantation is facing the dilemma of reducing the incidence of acute rejection (AR) and delayed graft function (DGF) or increasing risks of infection and malignancy. The purpose of this study was to delineate the safety and efficiency of the optimal ATG dosage.

Methods: We retrospectively evaluated 91 deceased donor kidney transplant recipients (KTRs) in our institution between March 2011 and January 2019. The patients were classified into three groups based on induction therapy: (1) Group 1: modest-dose ATG (three mg/kg) intraoperatively ($N = 21$); (2) Group 2: low-dose ATG (1–1.5 mg/kg) intraoperatively ($N = 23$); (3) Group 3: basiliximab 20 mg both on day 0 and 4 ($N = 47$). In Groups 1 and 2, all patients received a daily low-dose program (1–1.5 mg/kg each day) with target dosage of six mg/kg. Induction therapy was combined with standard immunosuppressive regimen consisting of calcineurin inhibitors, mycophenolate/the mammalian target of rapamycin inhibitors and corticosteroids.

Results: There was no significant difference in patient characteristics among groups. The outcomes of infection rate, biopsy-proven acute rejection, post-transplant diabetes mellitus, graft survival, and patient survival were similar among groups. Compared to the daily low-dose ATG regimen, the intraoperative modest-dose regimen did not cause more dose interruption and hence was more likely to reach the target ATG dosage. The intraoperative modest-dose regimen also seemed to reduce the rate of DGF.

Discussion: In recent years, a trend of using a "lower" dose of ATG has seemed to emerge. Our results suggest intraoperative modest-dose ATG followed by daily low-dose ATG regimen was safe and effective in cadaveric renal transplantations for preventing DGF, AR, and graft loss.

INTRODUCTION

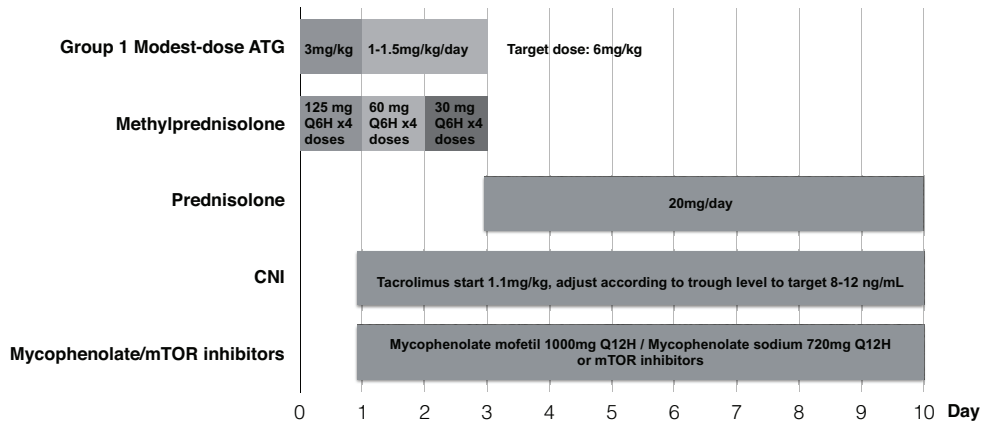
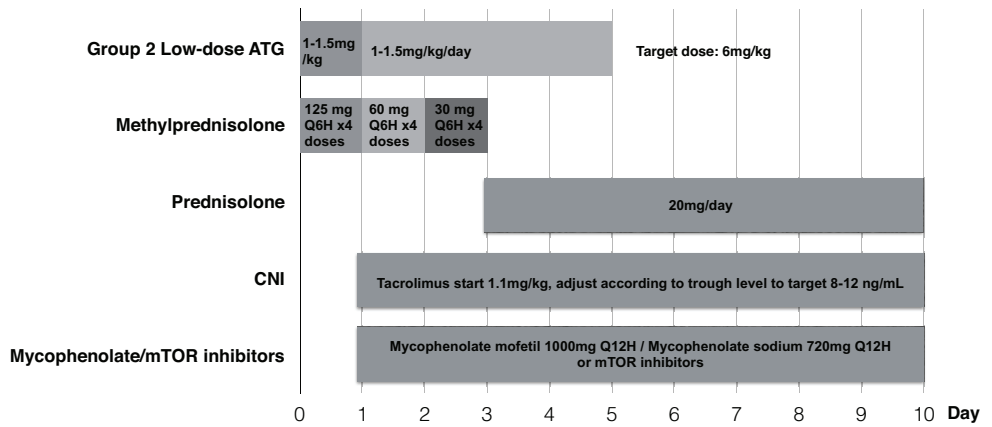
Anti-thymocyte globulin (ATG) induction therapy is known to reduce the incidence of acute rejection (AR), delayed graft function (DGF), and graft loss in renal transplantation (*Ciancio, Burke & Miller, 2007*; *Erickson et al., 2010*; *Kainz et al., 2010*; *Knoll, 2008*; *Mourad et al., 2012*; *Schenker et al., 2011*; *Siedlecki, Irish & Brennan, 2011*; *Thiyagarajan, Ponnuswamy & Bagul, 2013*). It is recommended for recipients with moderate to high risk of AR and DGF (*Bia et al., 2010*; *Kasiske et al., 2009*), though the risk of infection and malignancy might be increased (*Clesca et al., 2007*; *Laftavi et al., 2011*; *Meier-Kriesche, Arndorfer & Kaplan, 2002*; *Mourad et al., 2012*; *Schenker et al., 2011*). Currently, the timing of administration and the ideal dosage of ATG induction therapy remain inconclusive as most clinical studies have been carried out on patients with different immunological risk and in the context of varying maintenance regimens (*Mourad et al., 2012*; *Schenker et al., 2011*). Nevertheless, in recent years, a trend of using a "lower" dose of ATG has seemed to emerge. The purpose of this study was to examine the safety and efficiency of intraoperative modest-dose ATG followed by daily low-dose ATG regimen in cadaveric renal transplantations.

PATIENTS AND METHODS

We retrospectively evaluated 155 adult kidney transplant recipients (KTRs) who received either standard or expanded criteria deceased donor in our institution from March 2011 to January 2019. Patients were excluded because of not-receiving induction therapy ($N = 10$), or receiving living donor kidney transplantation ($N = 54$). A total of 91 patients were enrolled in our study.

Based on the recommendations from kidney disease: improving global outcomes (KDIGO) guidelines (*Kasiske et al., 2009*), we used rabbit ATG (Thymoglobuline®, Genzyme) induction therapy in intermediate to high risk patients and chose basiliximab for low immunologic risk recipients. According to the guidelines, low immunologic risk was defined as first-time transplant recipients who have less than 20% panel-reactive antibodies. Intermediate risk was defined as transplant recipients with panel-reactive antibodies between 20% and 80%. All the enrolled patients were classified into three groups: (1) Group 1: Recipients were administered modest-dose ATG (three mg/kg) intraoperatively after patient was anesthetized in the operation room ($N = 21$); (2) Group 2: Recipients were administered low-dose ATG (1–1.5 mg/kg) intraoperatively ($N = 23$); (3) Group 3: Patients received basiliximab with 20 mg dose on day 0 and 4 ($N = 47$). In Groups 1 and 2, all patients received a daily low-dose program (1–1.5 mg/kg each day) with target dosage of six mg/kg. Standard maintenance immunosuppressive regimen consisting of calcineurin inhibitors, mycophenolate/the mammalian target of rapamycin inhibitors and corticosteroid was used in the three groups (Fig. 1). This study was approved by the Institutional Review Board of The Kaohsiung Chang Gung Memorial Hospital (Approval number: 201801012B0).

Baseline donor and recipient characteristics, operative variables, and post-transplantation outcomes including incidence of DGF, infection, malignancy, biopsy-proven acute rejection (BPAR), post-transplant diabetes mellitus (PTDM), graft survival and patient

A. Group 1 Intraoperative modest-dose ATG

B. Group 2 Low-dose ATG

C. Group 3 Basiliximab

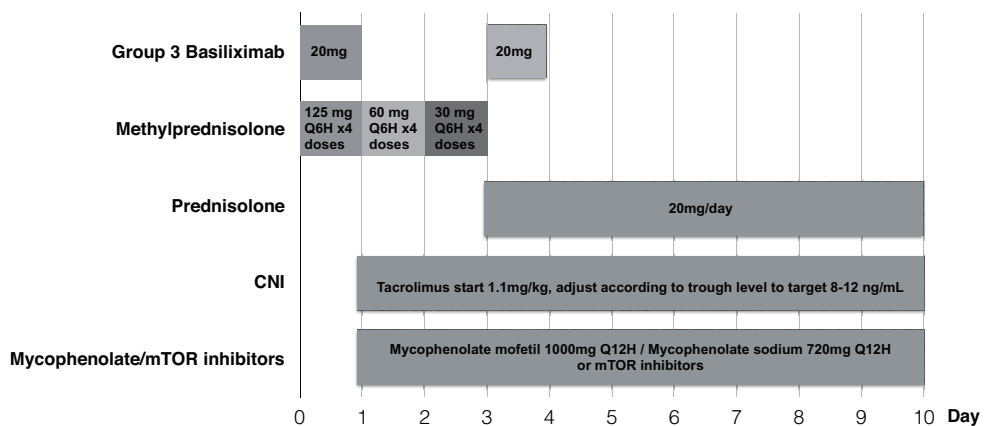



Figure 1 **Immunosuppressive regimens in the three groups.** (A) Group 1 Intraoperative modest-dose ATG, (B) Group 2 Low-dose ATG, (C) Group 3 Basiliximab.

survival were evaluated during the first post transplantation year. Renal biopsies were performed based on the recommendation of KDIGO guidelines (*Kasiske et al., 2009*). IBM® SPSS® Statistics Base Version 24 software was used for all statistical analyses. Arithmetic values were calculated and expressed as mean ± SD. Baseline demographic data among patient groups were analyzed using one-way ANOVA for continuous variables and Pearson Chi-square test for dichotomous variables. Two-sided p-values less than 0.05 were considered to indicate statistical significance.

RESULTS

Among the three study groups, there were no significant differences in general characteristics of both donor and recipient including gender, age, body mass index, comorbidities (e.g., hypertension, diabetes mellitus, coronary artery disease, cerebral vascular accident), preoperative dialysis duration, warm ischemia time, kidney donor profile index, and kidney donor risk index (Table 1). In Group 1, 21 patients received intraoperative modest-dose ATG (three mg/kg). The mean administered cumulative ATG dosage was 4.54 ± 1.43 mg/kg. In Group 2, 23 patients received low dose ATG (1–1.5 mg/kg) intraoperatively, and their mean administered cumulative ATG dosage was 4.04 ± 1.78 mg/kg. The ATG therapy was held or ceased if leukocytopenia (WBC < 2,500/uL), thrombocytopenia (platelet < 100,000/uL), or high-grade fever episode occurred (>38.5 ℃). The trend of ATG dose interruption or premature termination occurred less in Group 1 (14.3%) than Group 2 (26.1%) without significant difference. In Group 3, all patients receiving basiliximab completed the two doses on day 0 and day 4 as suggested.

There were no significant differences in all-cause infection, cytomegalovirus infection, BK virus infection, urinary tract infection, BPAR, PTDM, graft survival, and patient survival (Table 2).

We used the definition of requirement of dialysis in the first week following transplantation as DGF (*Thiyagarajan, Ponnuswamy & Bagul, 2013*). In our study, 31 patients were recorded as DGF after renal transplantation of which nine (42.9%) patients received intraoperative modest-dose ATG (Group 1), 14 (60.9%) patients received low-dose ATG (Group 2), and eight (17.0%) patients received basiliximab (Group 3). Compared to daily low dose ATG regimen, intraoperative modest-dose ATG induction seemed to offer less DGF, though the difference was not statistically significant.

DISCUSSION

Anti-thymocyte globulin induction therapy in kidney transplantation is suggested by most transplant guidelines, though the optimal dosage and administered timing are yet to be determined. *Kaden et al. (1995, 2011)* found a single high-dose bolus ATG given (nine mg/kg body weight) in reperfusion period could effectively improve kidney graft survival (*Du et al., 2016*; *Kaden, Strobelt & May, 1998*). Studies using single high-dose ATG were reported on efficacy in immunosuppression (*Kaden et al., 2009*; *Samsel et al., 2008*; *Yussim & Shapira, 2000*). However, full-dose ATG induction therapy (7–10 mg/kg) has been associated with increased infectious complications and morbidity in the early post-transplant period (*Clesca et al., 2007*; *Laftavi et al., 2011*). In recent years, a trend of using "reduced" dose of

Table 1 Recipient and donor characteristics.

	Group 1 intraoperative modest-dose ATG (N = 21)	Group 2 low-dose ATG (N = 23)	Group 3 basiliximab (N = 47)	p-value
Total ATG dosage (mg/kg)	4.54 ± 1.43	4.04 ± 1.78	0.62 ± 0.14	<0.001* (Group 1 = 2 > 3)
ATG dose interruption, N (%)	3 (14.3%)	6 (26.1%)	0 (0%)	0.004* (Group 2 > 3)
Gender (male)	8 (38.1%)	11 (47.8%)	22 (46.8%)	0.763
Age (year)	43.82 ± 17.28	49.47 ± 10.11	42.00 ± 11.05	0.068
BMI	22.33 ± 4.11	23.20 ± 3.58	23.52 ± 3.97	0.525
HTN, N (%)	15 (71.4%)	12 (52.2%)	30 (63.8%)	0.407
DM, N (%)	1 (4.8%)	1 (4.3%)	4 (8.5%)	>0.99
CAD, N (%)	0 (0%)	1 (4.3%)	1 (2.1%)	>0.99
CVA, N (%)	0 (0%)	1 (4.3%)	0 (0%)	0.484
Dialysis duration (year)	7.43 ± 4.84	10.45 ± 5.61	7.37 ± 5.15	0.061
OP time (min)	332.81 ± 67.88	323.30 ± 67.49	292.49 ± 41.65	0.011* (Group 1 > 3)
Warm ischemia time (min)	49.72 ± 13.01	45.25 ± 10.43	45.38 ± 9.32	0.314
KDPI (%)	59.30 ± 26.17	48.11 ± 26.30	44.98 ± 28.89	0.168
KDRI	1.16 ± 0.33	1.08 ± 0.47	1.01 ± 0.34	0.347

Note:

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CVA, cerebral vascular accident; OP, operation; KDPI, kidney donor profile index; KDRI, kidney donor risk index. Data was expressed as absolute and relative frequencies or mean ± SD.

* The p value < 0.05 was regarded as statistically significant.

ATG has emerged (*Gurk-Turner et al., 2008*; *Hardinger et al., 2005*; *Laftavi et al., 2011*; *Wong et al., 2006*). *Hardinger et al. (2005)* showed the efficacy of reduced dose of ATG induction (modest-dose ATG (three mg/kg) intra-operatively followed by 1.5 mg/kg on POD 1 and 2) in 40 low-risk renal transplant recipients. It has not yet been tested whether the initial dose can be further reduced. In our study, we show that the initial low dose (1.5 mg/kg) regimen could be safe because BPAR, graft survival, and patient survival characteristics did not differ between Groups 1 and 2.

The mean total dose of ATG was comparable in both Groups 1 (4.54 ± 1.43 mg/kg) and 2 (4.04 ± 1.78 mg/kg). *Gurk-Turner et al. (2008)* compared the incidence of BPAR during the first 12 months and the graft survival in KTRs treated with ≤7.5 mg/kg or >7.5 mg/kg ATG. They concluded that in high risk KTRs, total ATG doses ≤7.5 mg/kg are safe and effective in achieving a low rate of AR and graft outcomes comparable to higher doses. In line with our results, Klem et al. examined the 1-year AR rate, patient survival and graft survival in KTRs receiving a total 4.5 mg/kg or six mg/kg of ATG. They reported 1-year AR rates were 10% and 11% in the 4.5 mg/kg and six mg/kg cohorts, respectively, with 100% patient and graft survival at 1 year in both groups (*Klem et al., 2009*). In addition, compared to Group 2, Group 1 regimen did not result in more dose interruption and hence was more likely to reach the target ATG dosage.

Table 2 Clinical outcomes of the three groups.

	Group 1 intraoperative modest-dose ATG ($N = 21$)	Group 2 low-dose ATG ($N = 23$)	Group 3 basiliximab ($N = 47$)	p-value
Follow-up, month	24.14 ± 20.32	54.78 ± 16.09	41.40 ± 22.90	<0.001* (Group 2 > 3 > 1)
DGF	9 (42.9%)	14 (60.9%)	8 (17.0%)	0.001* (Group 2 > 3)
All cause infection	11 (52.4%)	12 (52.2%)	25 (53.2%)	0.996
CMV infection	2 (10.0%)	1 (4.5%)	2 (4.7%)	0.707
BKV infection	3 (15.8%)	2 (9.1%)	8 (19.0%)	0.672
UTI	8 (38.1%)	6 (26.1%)	17 (36.2%)	0.639
Malignancy	0 (0%)	4 (17.4%)	3 (6.4%)	0.090
BPAR	5 (23.8%)	1 (4.3%)	7 (15.6%)	0.182
PTDM	2 (9.5%)	2 (8.7%)	2 (4.3%)	0.624
Hospitalization days	19.38 ± 13.98	21.48 ± 13.24	18.72 ± 17.33	0.786
Graft survival (1 year)	21 (100.0%)	22 (95.7%)	46 (97.9%)	>0.99
Re-transplant	0 (0%)	0 (0%)	0 (0%)	–
Patient survival (1 year)	19 (90.5%)	23 (100.0%)	47 (100.0%)	0.051

Note:

OP, operation; DGF, delayed graft function; CMV, cytomegalovirus; BKV, BK virus; UTI, urinary tract infection; BPAR, biopsy-proven acute rejection; PTDM, post-transplant diabetes mellitus.

* The p value < 0.05 was regarded as statistically significant.

Notably, however, Group 1 in our study did show a lower DGF rate (42.9% vs. 60.9%). DGF is a major obstacle for long-term graft survival. Data from a prospective randomized clinical trial highlights the crucial role of intraoperative administration of ATG in reducing DGF (*Goggins et al., 2003*). This benefit disappeared when the initial dosing of ATG was reduced to as low as 1.5 mg/kg (*Brennan et al., 2006*). Based on these reported findings and our results, we would suggest initial modest-dose ATG is a more ideal induction regimen. By reducing DGF, the superiority of this initial modest-dose ATG induction regimen might be reflected in better long-term graft survival. Group 3 showed a significantly low DGF rate because this regimen, by guideline recommendations, was applied to the low immunologic risk recipients.

The risk of cancer, especially lymphoproliferative diseases, is one of the known side effects of anti-thymocyte induction agents (*Schenker et al., 2011*). Higher incidence of non-Hodgkin's lymphoma connected to antilymphocyte antibody induction has been previously described (*Cockfield et al., 1991*; *Hibberd et al., 1999*; *Opelz & Henderson, 1993*; *Samsel et al., 2008*). Nevertheless, in our study, the incidence of onset malignancy had no significant difference among the three groups. Although our study showed both modest-dose and low-dose ATG induction yielded comparable malignancy rates to basiliximab, longer follow-up periods are required to confirm this.

The main limitations of the current study were the small sample size and the unequal patient number in study groups. Although this phenomenon did truly reflect real world experience from a non-high volume kidney transplantation center, results from analysis on

these patients may limit its generalizability. Further prospective studies with larger numbers of patients are required to confirm these results.

CONCLUSIONS

We proposed a safe and effective ATG induction regimen in intermediate to high risk renal transplant recipients. In line with the trend of administering lower ATG dose in recent years, our dosing regimen not only confirmed the advantage of modest reduction of initial ATG dose to three mg/kg, but also demonstrated its potential benefits in less dose interruption and reducing DGF.

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Hui-Ying Liu conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Yuan-Tso Cheng conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Hao Lun Luo performed the experiments, analyzed the data, contributed reagents/ materials/analysis tools, approved the final draft.
- Chiang-Chi Huang performed the experiments, approved the final draft.
- Chien Hsu Chen performed the experiments, contributed reagents/materials/analysis tools, approved the final draft.
- Yuan-Chi Shen performed the experiments, contributed reagents/materials/analysis tools, approved the final draft.
- Wen-Chin Lee performed the experiments, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

The Kaohsiung Chang Gung Memorial Hospital granted Ethical approval to carry out the study within its facilities (Ethical Application Ref: 201801012B0).

Data Availability

The raw data are available in the Supplemental Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.7274#supplemental-information.

REFERENCES

Bia M, Adey DB, Bloom RD, Chan L, Kulkarni S, Tomlanovich S. 2010. KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. *American Journal of Kidney Diseases* **56(2)**:189–218 DOI 10.1053/j.ajkd.2010.04.010.

Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D. 2006. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *New England Journal of Medicine* **355(19)**:1967–1977 DOI 10.1056/NEJMoa060068.

Ciancio G, Burke GW, Miller J. 2007. Induction therapy in renal transplantation: an overview of current developments. *Drugs* **67(18)**:2667–2680 DOI 10.2165/00003495-200767180-00003.

Clesca P, Dirlando M, Park S-I, García R, Ferraz E, Pinheiro-Machado PG, Kushnaroff L, Tedesco-Silva H Jr, Medina-Pestana JO. 2007. Thymoglobulin and rate of infectious complications after transplantation. *Transplantation Proceedings* **39(2)**:463–464 DOI 10.1016/j.transproceed.2007.01.024.

Cockfield SM, Preiksaitis J, Harvey E, Jones C, Hebert D, Keown P, Halloran PF. 1991. Is sequential use of ALG and OKT3 in renal transplants associated with an increased incidence of fulminant posttransplant lymphoproliferative disorder? *Transplantation Proceedings* **23(1 Pt 2)**:1106–1107.

Du X, Wang W, Sun Z-J, Su LL, Zhang X-D. 2016. Meta-analysis on the safety and efficacy of the reperfusion use of a single high dose of anti-T-lymphocyte globulin fresenius in kidney transplantation. *Transplantation Proceedings* **48(6)**:2017–2022 DOI 10.1016/j.transproceed.2016.04.019.

Erickson AL, Roberts K, Malek SK, Chandraker AK, Tullius SG, Gabardi S. 2010. Analysis of infusion-site reactions in renal transplant recipients receiving peripherally administered rabbit antithymocyte globulin as compared with basiliximab. *Transplant International* **23(6)**:636–640 DOI 10.1111/j.1432-2277.2009.01042.x.

Goggins WC, Pascual MA, Powelson JA, Magee C, Tolkoff-Rubin N, Farrell ML, Ko DSC, Williams WW, Chandraker A, Delmonico FL, Auchincloss H, Cosimi AB. 2003. A prospective, randomized, clinical trial of intraoperative versus postoperative thymoglobulin in adult cadaveric renal transplant recipients. *Transplantation* **76(5)**:798–802 DOI 10.1097/01.TP.0000081042.67285.91.

Gurk-Turner C, Airee R, Philosophe B, Kukuruga D, Drachenberg C, Haririan A. 2008. Thymoglobulin dose optimization for induction therapy in high risk kidney transplant recipients. *Transplantation* **85(10)**:1425–1430 DOI 10.1097/TP.0b013e31816dd596.

Hardinger KL, Bohl DL, Schnitzler MA, Lockwood M, Storch GA, Brennan DC. 2005. A randomized, prospective, pharmacoeconomic trial of tacrolimus versus cyclosporine in combination with thymoglobulin in renal transplant recipients. *Transplantation* **80(1)**:41–46 DOI 10.1097/01.TP.0000162980.68628.5A.

Hibberd AD, Trevillian PR, Wlodarzcyk JH, Gillies AHB, Stein AM, Sheil AGR, Disney APS. 1999. Cancer risk associated with ATG/OKT3 in renal transplantation. *Transplantation Proceedings* **31(1–2)**:1271–1272 DOI 10.1016/S0041-1345(98)01992-7.

Kaden J, May G, Muller P, Groth J, Strobelt V, Eger E, Wohlfahrt L. 1995. Intraoperative high-dose anti-T-lymphocyte globulin bolus in addition to triple-drug therapy improves kidney graft survival. *Transplantation Proceedings* **27(1)**:1060–1061.

Kaden J, May G, Völp A, Wesslau C. 2009. Improved long-term survival after intra-operative single high-dose ATG-Fresenius induction in renal transplantation: a single centre experience. *Annals of Transplantation* **14(3)**:7–17.

Kaden J, May G, Völp A, Wesslau C. 2011. Factors impacting short and long-term kidney graft survival: modification by single intra-operative high-dose induction with ATG-Fresenius. *Annals of Transplantation* **16(4)**:81–91 DOI 10.12659/AOT.882223.

Kaden J, Strobelt V, May G. 1998. Short and long-term results after pretransplant high-dose single ATG-fresenius bolus in cadaveric kidney transplantation. *Transplantation Proceedings* **30(8)**:4011–4014 DOI 10.1016/S0041-1345(98)01322-0.

Kainz A, Korbely R, Soleiman A, Mayer B, Oberbauer R. 2010. Antithymocyte globulin use for treatment of biopsy confirmed acute rejection is associated with prolonged renal allograft survival. *Transplant International* **23(1)**:64–70 DOI 10.1111/j.1432-2277.2009.00950.x.

Kasiske BL, Zeier MG, Craig JC, Ekberg H, Garvey CA, Green MD, Jha V, Josephson MA, Kiberd BA, Kreis HA, McDonald RA, Newmann JM, Obrador GT, Chapman JR, Vincenti FG, Balk EM, Wagner M, Raman G, Earley A, Abariga S. 2009. Special issue: KDIGO clinical practice guideline for the care of kidney transplant recipients. *American Journal of Transplantation* **9(Suppl 3)**:S1–S157 DOI 10.1111/j.1600-6143.2009.02834.x.

Klem P, Cooper JE, Weiss AS, Gralla J, Owen P, Chan L, Wiseman AC. 2009. Reduced dose rabbit anti-thymocyte globulin induction for prevention of acute rejection in high-risk kidney transplant recipients. *Transplantation* **88(7)**:891–896 DOI 10.1097/TP.0b013e3181b6f38c.

Knoll G. 2008. Trends in kidney transplantation over the past decade. *Drugs* **68(Supplement 1)**:3–10 DOI 10.2165/00003495-200868001-00002.

Laftavi MR, Patel S, Soliman MR, Alnimri M, Kohli R, Said M, Pankewycz O. 2011. Low-dose thymoglobulin use in elderly renal transplant recipients is safe and effective induction therapy. *Transplantation Proceedings* **43(2)**:466–468 DOI 10.1016/j.transproceed.2011.01.039.

Meier-Kriesche HU, Arndorfer JA, Kaplan B. 2002. Association of antibody induction with short- and long-term cause-specific mortality in renal transplant recipients. *Journal of the American Society of Nephrology* **13(3)**:769–772.

Mourad G, Morelon E, Noël C, Glotz D, Lebranchu Y. 2012. The role of Thymoglobulin induction in kidney transplantation: an update. *Clinical Transplantation* **26(5)**:E450–E464 DOI 10.1111/ctr.12021.

Opelz G, Henderson R. 1993. Incidence of non-hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* **342(8886–8887)**:1514–1516 DOI 10.1016/S0140-6736(05)80084-4.

Samsel R, Pliszczynski J, Chmura A, Korczak G, Wlodarczyk Z, Cieciura T, Lagiewska B, Glyda M, Wyzgal J, Paczek L, Durlik M, Rowinski W. 2008. Safety and efficacy of high dose ATG bolus administration on rewascularization in kidney graft patients–long term results. *Annals of Transplantation* **13(1)**:32–39.

Schenker P, Ozturk A, Vonend O, Krüger B, Jazra M, Wunsch A, Krämer BK, Viebahn R. 2011. Single-dose thymoglobulin induction in living-donor renal transplantation. *Annals of Transplantation* **16(2)**:50–58 DOI 10.12659/AOT.881865.

Siedlecki A, Irish W, Brennan DC. 2011. Delayed graft function in the kidney transplant. *American Journal of Transplantation* **11(11)**:2279–2296 DOI 10.1111/j.1600-6143.2011.03754.x.

Thiyagarajan UM, Ponnuswamy A, Bagul A. 2013. Thymoglobulin and its use in renal transplantation: a review. *American Journal of Nephrology* **37(6)**:586–601 DOI 10.1159/000351643.

Wong W, Agrawal N, Pascual M, Anderson DC, Hirsch HH, Fujimoto K, Cardarelli F, Winkelmayer WC, Cosimi AB, Tolkoff-Rubin N. 2006. Comparison of two dosages of thymoglobulin used as a short-course for induction in kidney transplantation. *Transplant International* **19(8)**:629–635 DOI 10.1111/j.1432-2277.2006.00270.x.

Yussim A, Shapira Z. 2000. Single-bolus high-dose ATG for prophylaxis of rejection in renal transplantation–a prospective, randomized study. *Transplant International* **13(Suppl 1)**:S293–S294.