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ORIGINAL ARTICLE

Comparison of two dosages of thymoglobulin used as a short-course for induction in kidney transplantation

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Summary

Thymoglobulin is used effectively as an induction agent in kidney transplantation, but the optimal dose is not well established. We evaluated the degree and durability of T-cell clearances with two different thymoglobulin regimens in adult kidney transplant recipients (KTR). Seven KTR received a 3-day thymoglobulin-based induction of 1.0 mg/kg/day while nine received 1.5 mg/kg/day, in addition to maintenance immunosuppression. Lymphocyte subsets were monitored for 6 months. Renal function, infections and malignancies were monitored for 24 months. T-cell subsets were significantly lower by day 30 with the thymoglobulin 1.5 mg/kg/day regimen when compared with the 1.0 mg/kg/day regimen; this trend was sustained at 6-month ($CD3^+$: 438 ± 254 vs. 1001 ± 532 cells/mm^3, $P = 0.016$). Renal function between the two groups was not significantly different at 6- and 24-months post-transplant. One case of BK Virus viremia in the 1.5 mg/kg/day thymoglobulin group was detected. No acute rejection episodes, cytomegalovirus infections, or malignancies were noted in either group. Thymoglobulin induction was efficacious in both groups, but with a significantly sustained T-cell clearance in the 1.5 mg/kg/day regimen. A more profound T-cell clearance within the first 6 months postinduction therapy may translate into a decreased risk of immunological injury and improved long-term outcome after kidney transplantation.

Introduction

In recent years, polyclonal anti-lymphocyte globulins have become an integral part of immunosuppressive regimens in many transplant centers [1]. Because of their broad specificity, these agents have been used successfully not only for the treatment of acute rejection and graft versus host reaction, but more recently as part of induction therapy in kidney as well as other solid organ transplantation [2–6].

Thymoglobulin® (Thymo; Genzyme, Cambridge, MA, USA), a rabbit-derived polyclonal antibody, contains a variety of antibodies specific for T-cell epitopes, including CD2, CD3, CD4, $CD8^+$, CD11a, CD18, CD25, HLA-DR and HLA class I [7,8]. Anti-thymocyte globulin treatment induces a dose-dependent lymphocytopenia in blood as well as T-cell depletion in spleen and lymph nodes [9]. T-cell apoptosis in peripheral lymphoid tissue is an important mechanism of depletion [10]. The remaining T-cells in peripheral lymphoid organs are coated by antibodies and have a down-modulated surface expression of CD2, CD3, CD4 and CD8 molecules with a decreased responsiveness in mixed leukocyte reaction [9].

Despite extensive clinical use of Thymo for induction immunosuppression in adult kidney transplant recipients

(KTR), the ideal dose and duration of therapy are still empirical in many centers where various protocols exist, and over-immunosuppression remains a concern. For example, previous studies have reported the use of Thymo in dosages ranging from 4.2 to 10.5 mg/kg (total cumulative dose) for induction therapy in adult KTR with variable success [11–17]. In an attempt to better delineate the degree and durability of T-cell clearance with Thymo, as well as its safety profile, we analyzed our recent experience with the use of two different 3-day regimens of Thymo induction therapy (1.0 vs. 1.5 mg/kg/day) in adult KTR.

Materials and methods

Study design

This study was approved by the Massachusetts General Hospital Investigational Review Board. Between April 2002 and January 2003, we recruited patients, 18 years old or older, who were scheduled to receive a primary deceased or living unrelated donor kidney transplant. Patients were excluded from the study if they had: (i) multiple organ transplants, (ii) serological evidence of Human Immunodeficiency Virus type-1, Human T-lymphotropic Virus type 1, or active hepatitis B and C, (iii) previous exposure to lymphocyte depleting therapies, (iv) recent or current exposure to other investigational drugs or (v) a history of malignancy within 5 years prior to transplant (other than treated skin malignancies).

Immunosuppression regimen

Induction protocol

Patients received three consecutive days of Thymo as part of their induction immunosuppressive protocol. The first seven patients received Thymo 1.0 mg/kg/day (group A) and the subsequent nine patients received Thymo 1.5 mg/kg/day (group B). The first dose was given, intra-operatively (periperfusion) of the allograft, as described previously [14]. Common adverse effects noted with Thymo infusion include fevers, shivering, hypertension, peripheral edema, tachyarrhythmia, myalgia, dyspnea and gastrointestinal symptoms; hematological complications include leukopenia and thrombocytopenia. All these adverse effects were monitored closely during and after the infusion.

Maintenance therapy

Post-transplant, once the patient had adequate urine output and the serum creatinine was <5 mg/dl, they were started on twice daily 0.05 mg/kg of tacrolimus (Prograf; Astellas, Deerfield, IL, USA), with target trough levels of 8–12 ng/ml. Patients were additionally maintained on steroids and mycophenolate mofetil [(MMF), CellCept; Roche, Nutley, NJ, USA]. At our institution, this is the current maintenance regimen of choice given their immunosuppressive properties and our success rates using it. Methylprednisolone (100 mg) was administered intravenously before each Thymo infusion and then converted to oral prednisone and tapered slowly over 6 months to a dose not <5 mg/day. MMF was begun at an initial dose of 1 g twice daily at the time of transplantation; this was lowered to 500 mg twice daily if diarrhea, esophagitis, gastritis, leukopenia or thrombocytopenia occurred. Living unrelated KTR received a dose of tacrolimus 0.05 mg/kg the night before transplantation.

Antimicrobial prophylaxis

Oral candidal prophylaxis was provided by clotrimazole three times daily for the first 5 days post-transplant. Trimethoprim–sulfamethoxazole (80/400 mg) was provided daily for 6 months for bacterial and pneumocystis carini pneumonia prophylaxis. For patients allergic to sulfa, atovaquone (1500 mg/day) and levofloxacin (250 mg/day) were substituted for trimethoprim–sulfamethoxazole. For cytomegalovirus (CMV) prophylaxis, ganciclovir was given intravenous initially while the patients were in the hospital and then switched to oral daily valganciclovir (Valcyte 450 mg; Roche) for 6 months when either donor or recipient had serological evidence of previous CMV exposure. Famvir (500 mg/day) was administered for 6 months when neither donor nor recipient had serological evidence of previous exposure to CMV.

Data collection

Lymphocyte count on days 3, 7, 30, 90 and 180 post-transplant were measured in all patients. Total lymphocyte count was calculated on a dual platform by multiplying the white blood cell count differential with the percentage of $CD45^+$ cells in the lymphocyte light scatter gate [18]. T-cell $CD3^+$, total $CD4^+$, total $CD8^+$ and B-cell ($CD19^+$) subsets were analyzed by flow cytometry using the FACSCalibur® cytometer (Becton Dickenson, Franklin Lakes, NJ, USA) and CellQuest® (Becton Dickenson, Franklin Lakes, NJ, USA) acquisition and analysis software [18]. This method quantitated the absolute number of T-cells ($CD3^+$), total $CD4^+$, total $CD8^+$, B cells ($CD19^+$), and natural killer (NK) cells. By examining the fluorescence intensity of the CD5, OKT3 (CD3) and Leu4 (CD3) antibodies, we can determine whether or not the drug bound effectively and saturated the remaining T-cells. Whole blood specimens are stained with no prior washing to preserve the absolute number of cells present.

Serum creatinine, complete blood count and trough tacrolimus levels were also assessed serially for 24 months.

Glomerular filtration rates (GFR) were estimated by the Cockcroft–Gault equation [19]. Patients were also evaluated for malignancies throughout the study. Infections such as cytomegalovirus (CMV) and BK virus (BKV) were monitored at 24 months post-transplant in all patients. CMV antigenemia was measured by direct immunofluorescence of CMV infected peripheral leukocyte; these samples were analyzed within 24 h of collection. BKV replication in urine and plasma was measured using the BKV-specific, real-time polymerase chain reaction method (Taqman ABI Prism 7700; Applied Biosystem, Foster City, CA, USA) [20].

Statistical analysis

All results are expressed as mean ± standard error of the mean. Observations within each group were evaluated by paired *t*-test.Observations between the groups were compared using the unpaired *t*-test for continuous variables and Fisher's exact test for categorical variables. A two-tailed *P*-value of <0.05 was considered significant.

Results

Patient characteristics

There were no significant differences in baseline demographics or patient characteristics between group A (Thymo 1.0 mg/kg/day) and group B (Thymo 1.5 mg/kg/day; Table 1). Thymo infusion was not associated with any immediate adverse effects.

Allograft function

No episodes of acute rejection or delayed graft function (requiring dialysis post-transplant) occurred in either group in 24 months of follow-up. There were no significant differences in renal function pretransplant (serum creatinine: 7.5 ± 0.6 vs. 9.5 ± 1.2 mg/dl, $P = 0.209$; GFR: 11.7 ± 1.3 vs. 11.0 ± 1.9 ml/min, $P = 0.762$) between groups A and B (Table 1). Renal function improved immediately post-transplant and remained stable with no significant difference between groups A and B after 6 months (serum creatinine: 1.1 ± 0.1 vs. 1.4 ± 0.1 mg/dl, $P = 0.069$; GFR: 74.9 ± 11.7 vs. 65.0 ± 5.2 ml/min, $P = 0.418$) and after 24 months post-transplant (serum creatinine: 1.0 ± 0.1 vs. 1.4 ± 0.1 mg/dl, $P = 0.078$; GFR: 76.8 ± 18.5 vs. 68.5 ± 9.8 ml/min, $P = 0.365$). There was also no significant difference detected in serum creatinine when 6 months was compared with 24 months within each group (group A: $P = 0.669$, group B: $P = 0.942$). When group A was compared with group B, the average tacrolimus trough level (7.92 ± 0.71 vs. 7.80 ± 0.51 ng/ml; $P = 0.883$), average prednisone dose (6.42 ± 0.74 vs. 7.50 ± 0.32 mg/day; $P = 0.324$) and average MMF dose (1.70 ± 0.20 vs. 1.40 ± 0.18 g/day; $P = 0.305$), respectively, were not significantly different at 6 months as well as at 24 months post-transplant. Levels of mycophenolic acid were not measured. On average, tacrolimus was initiated 3.2 + 0.2 vs. 3.1 + 0.1 days post-transplant when group A was compared with group B ($P = 0.121$).

Lymphocyte subsets

Results of T-cell subsets are expressed as the absolute number of $CD3^+$ cells. Baseline pretransplant lymphocyte counts were within the normal range ($CD3^+$: 679 ± 105 cells/mm^3 and total $CD4^+$: 493 ± 96 cells/mm^3). There was excellent initial T-cell clearance in both groups, with a dose-dependent lymphocytopenia (Table 2). However, when group A was compared with group B, cell counts were significantly lower by post-transplant day 30 in group B ($CD3^+$: 1027 ± 230 vs. 262 ± 70 cells/mm^3, $P = 0.002$ and total $CD4^+$: 483 ± 40 vs. 95 ± 20 cells/mm^3, $P < 0.001$; Figs 1 and 2). This difference in T-cell absolute $CD3^+$ counts (940 ± 193 vs. 438 ± 85 cells/mm^3, $P =$

Table 1. Baseline characteristics and demographics.

	Group A (thymoglobulin 1.0 mg/kg/day; *n* = 7)	Group B (thymoglobulin 1.5 mg/kg/day; *n* = 9)	*P*-value
Age (mean ± SEM)	51 ± 4	51 ± 3	0.881
Female gender (%)	5 (71)	4 (44)	0.358
Ethnicity			
White race	5	9	0.175
Asian/Hispanic	2	0	
Organ source			
Deceased donor	5	4	0.358
Living donor	2	5	
HLA mismatch	4.7 ± 0.3	4.3 ± 0.4	0.483
PRA (%)	15.7 ± 14.1	5.1 ± 3.8	0.43
Serum creatinine (mg/dl)	7.5 ± 0.6	9.5 ± 1.2	0.209
Glomerular filtration rate (ml/min)	11.7 + 1.3	11.0 + 1.9	0.762

Table 2. Lymphocyte clearances and hematological profiles after thymoglobulin induction.

Days post-transplant	3	7	30	90	180
Thymoglobulin 1.0 mg/kg/day (group A)					
CD3† (nl: 860–2820)	14 ± 11	156 ± 111	1027 ± 230*	1015 ± 206*	940 ± 193*
CD4† (nl: 500–1950)	5 ± 2	57 ± 44	483 ± 40*	530 ± 91*	400 ± 76*
CD8† (nl: 300–1040)	11 ± 3	98 ± 67	525 ± 168*	507 ± 117	487 ± 149
CD19† (nl: 60–400)	72 ± 26	186 ± 89	206 ± 83	454 ± 248	146 ± 68
Total lymphocyte†	99 ± 26	370 ± 172	1408 ± 314*	1509 ± 406*	1298 ± 349*
WBC‡ (nl: 4.5–11.0)	8.0 ± 1.9	8.7 ± 1.9	7.1 ± 0.9	6.1 ± 1.0	5.7 ± 0.9
Platelets‡ (nl: 150–350)	180 ± 13	251 ± 36	272 ± 21	254 ± 22	226 ± 26
Thymoglobulin 1.5 mg/kg/day (group B)					
CD3† (nl: 860–2820)	10 ± 6	53 ± 22	262 ± 70*	323 ± 81*	438 ± 85*
CD4† (nl: 500–1950)	3 ± 1	18 ± 6	95 ± 20*	105 ± 22*	111 ± 13*
CD8† (nl: 300–1040)	12 ± 6	44 ± 16	188 ± 47*	240 ± 55*	363 ± 72
CD19† (nl: 60–400)	55 ± 18	180 ± 84	122 ± 34	71 ± 30	54 ± 13
Total lymphocyte†	193 ± 95	225 ± 98	425 ± 117*	568 ± 121*	633 ± 91*
WBC‡ (nl: 4.5–11.0)	6.3 ± 1.4	9.3 ± 1.6	7.0 ± 1.3	5.6 ± 1.1	6.7 ± 1.4
Platelets‡ (nl: 150–350)	159 ± 22	207 ± 38	270 ± 50	268 ± 46	204 ± 27

nl, normal.
*Showed significant difference of at least $P < 0.05$ when comparing group A versus group B.
†Values are expressed as cells/mm^3.
‡Values are expressed as $\times 10^3$/mm^3.

0.022) and total CD4$^+$ absolute counts (400 ± 76 vs. 111 ± 13 cells/mm^3, $P < 0.001$) remained detectable at 6 months of follow-up (Figs 1 and 2). The vast majority of the total CD4$^+$ lymphocytes were CD3$^+$CD4$^+$ T-cells with <1% myeloid progenitor contamination, as measured by standard flow cytometric lymphocyte gating.

Although total CD8$^+$ subsets also had similar trends towards lower values in group A versus group B (525 ± 168 vs. 188 ± 47 cells/mm^3, $P = 0.030$) by day 30, this difference was not significant by day 180 (487 ± 149 vs. 363 ± 72 cells/mm^3, $P = 0.435$; Fig. 3). The CD4$^+$/CD8$^+$ ratio (day 3: 0.5 vs. 0.2, $P = 0.789$; day 180: 0.8 vs. 0.3, $P = 0.029$), respectively, decreased in both groups A and B immediately postinduction therapy and remained significantly low in follow-up at 6 months. Initially, 2 weeks post-transplant, the remaining natural killer (NK) cell population decreased the lymphocyte CD4$^+$/CD8$^+$ ratio; these NK cells expressed CD8$^+$but not CD3$^+$. Six-months post-transplant, reconstituted CD3$^+$CD8$^+$ T-cells composed a greater percentage of the total CD8$^+$ lymphocytes. Although there was a trend for lower CD19$^+$ cell count in group B, it did not reach a significant difference when compared with the group A.

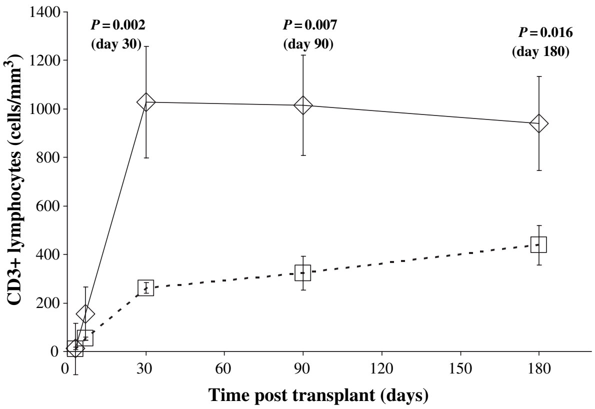

Figure 1 CD3$^+$ lymphocytes in thymoglobulin regimen 1.0 mg/kg/day (◇) versus 1.5 mg/kg/day (□). Normal CD3$^+$ lymphocyte range is 860–2820 cells/mm^3.

Hematological profile

One patient in group B had a pretransplant platelet count of 65×10^3/mm^3, but it rose spontaneously above 100×10^3/mm^3 by day 14. There were two cases of transient leukopenia (WBC < 3×10^3/mm^3), and another two cases of thrombocytopenia (platelets < 100×10^3/mm^3) on post-transplant day 3 in group B, but all recovered spontaneously by day 14. None of these cases required any treatment to achieve normal levels. Overall, there was no significant difference between groups A and B in terms of their hematological profile pretransplant (WBC: 5.7 ± 0.4 vs. 9.7 ± 1.7 × 10^3/mm^3, $P = 0.080$ and platelets: 247 ± 19 vs. 232 ± 54 × 10^3/mm^3, $P = 0.811$) and 6 months post-transplant (WBC: 5.7 ± 0.9 vs. 6.7 ± 1.4 × 10^3/mm^3, $P = 0.595$ and platelets: 226 ± 26 vs. 204 ± 87 × 10^3/mm^3, $P = 0.588$) respectively (Table 2).

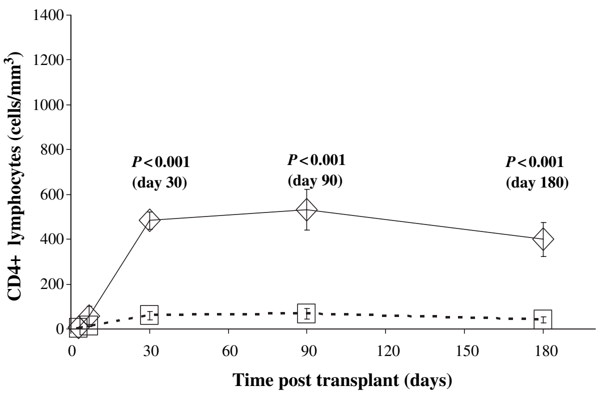

Figure 2 $CD4^+$ lymphocytes in thymoglobulin regimen 1.0 mg/kg/day (◇) versus 1.5 mg/kg/day (□). Normal $CD4^+$ lymphocyte range is 500–1950 cells/mm^3.

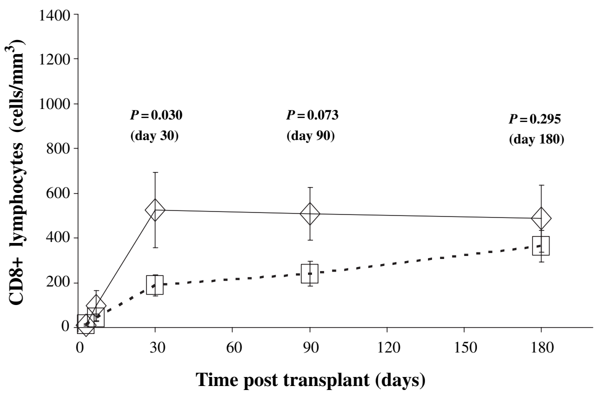

Figure 3 $CD8^+$ lymphocytes in thymoglobulin regimen 1.0 mg/kg/day (◇) versus 1.5 mg/kg/day (□). Normal $CD8^+$ lymphocyte range is 300–1040 cells/mm^3.

Complications

Patient and graft survival at 24 months in follow-up were 100% in both groups. One patient in group B who developed transient BKV viruria and viremia at 6 months; however, with lowering of his tacrolimus dosage, his viremia resolved within 2 months thereafter. No cases of malignancies, CMV antigenemia, lymphoproliferative disease or other infections were noted in either group within the first 6 months and subsequently 24 months post-transplant. In 2 years of follow-up, one patient (age 60, nondiabetic) developed cellulitis in the left leg 5 months post-transplant and another patient (age 72, diabetic) in group B developed osteomyelitis in the right toe, which required amputation.

Discussion

Several clinical studies have examined whether induction therapy, with varying dosages (ranging from 4.2 to 10.5 mg/kg total) of Thymo administered daily or intermittently, would be safe and effective in kidney transplantation (Table 3). Among these studies, there were varying degrees of success with acute rejection episodes, ranging from 3.6% to 19%, and some with significant side effects including high infection rates. Yet, the optimal dosage and regimen are still not well established, and excessive impairment of the cell-mediated immunity may increase the risk of opportunistic infections and post-transplant malignancies.

In the current study, Thymo induction therapy with either dose provided rapid initial T-cell depletion and allowed a delay in the institution of calcineurin inhibitors post-transplant until adequate allograft function was established. By such delay, we avoided the early nephrotoxicity of the calcineurin inhibitors and consequently no significant difference in renal function between the two groups was seen. Both Thymo regimens produced excellent lymphocyte depletion within 3-days post-transplant as attested by very low CD3, CD4 and CD8 cell counts. Anti-lymphocyte antibodies coat the T-cells and are subsequently cleared from the peripheral blood by the immune system [21]. We saw a dose-dependent clearance of lymphocytes in peripheral blood with a significantly more profound and sustained depletion of $CD3^+$ and $CD3^+CD4^+$ starting after day 30 and up to 180 days post-transplant with the Thymo 1.5 mg/kg/day regimen (group B) when compared with the 1.0 mg/kg/day regimen (group A). Use of these antibodies is usually associated with a low incidence of acute rejection and *in vitro* donor-specific hyporesponsiveness [3,12,22]. Although no acute rejection episodes with either regimen were seen in our patients, it is important to note that the slower recovery of $CD3^+$ and $CD3^+CD4^+$ cells with Thymo 1.5 mg/kg/day regimen might imply additional immunological benefit and thus, possibly better long-term graft survival. Others have shown that recovery of these T-cell subsets early post-transplant may be related with poorer long-term graft function [23].

Interestingly, total $CD8^+$ cells rose rapidly in both groups after day 30 causing a shift in the $CD4^+/CD8^+$ ratio immediately after transplant in both groups. This difference reached significant difference between the groups ($P = 0.029$) at 6 months post-transplant. Initially, the rise of the total $CD8^+$ in the first few weeks is most likely due to remaining NK cells rather than $CD3^+CD8^+$ T-cells; thereafter, the proportion of $CD8^+$ cells starts to fill again with proliferating $CD3^+CD8^+$ T-cells. This was seen in all of our samples studied by flow cytometry. It has been reported that a rapid recovery of $CD8^+$ lymphocytes and a low percentage of total $CD4^+$ T-cells within the first month post-transplant may be associated with improved graft outcome [23]. Longer follow-up and larger trials may be necessary to evaluate further the significance of these findings.

Table 3. Recent thymoglobulin induction studies in kidney transplantation.

Reference	No. patients	Follow-up (months)	Thymo dose (total mg/kg)	Maintenance immunosuppression	Acute rejection (%)	Infections (%)	Leukopenia (%)	Thrombocytopenia (%)	Malignancy (%)	Graft Survival (%)
Djamali *et al.* [11]	16 vs. 23	12	6.6¶ vs. 9.1**	CsA, AZA, Pred	19 vs. 13††	50 vs. 69††	6.5 vs. 9††	12.5 vs. 0††	0	100
Agha *et al.* [12]	40 vs. 48	6–12	6.0** vs. 10.5**	CsA, AZA, Pred	5 vs. 4.2††	17 vs. 12.5††	20 vs. 56‡‡	35 vs. 10‡‡	0	95 vs. 98††
Peddi *et al.* [13]	41	11.3	4.2¶	CNI, MMF, Pred	12.2	2.4	9.8	7.3	0	93
Goggins *et al.* [14]	27 vs. 31	15.1	4.6** vs. 4.8**	CNI, MMF, Pred	3.6 vs. 16‡‡	3.7 vs. 6.5††	NA	NA	NA	100
Buchler *et al.* [15]	240	12	8.8**	CNI, MMF/AZA, Pred	14	43	16	17	3	95
Haririan *et al.* [16]	36* vs. 52†	19	>4.5** vs. 40 mg	Tac/SRL,MMF,Pred	14 vs. 29††	5.6 vs. 7.7††	NA	NA	NA	86 vs. 81††
Hardinger *et al.* [17]	134‡ vs. 66§	12	NA	CNI, MMF/AZA, Pred	4 vs. 6††	4 vs. 6††	NA	NA	2 vs. 0††	95 vs. 100††

*Thymoglobulin.
†Basiliximab.
‡Tac, Tacrolimus.
§CsA, Cyclosporine; Pred, Prednisone; AZA, Azathioprine; CNI, calcineurin inhibitor; MMF, Mycophenolate Mofetil; SRL, Sirolimus; NA, not available.
¶Intermittent dosing.
**Daily dosing.
††NS, nonsignificant.
‡‡$P < 0.05$.

Induction therapy is slowly becoming predominant in kidney transplantation and currently approximately 70% of the US centers are using induction regimens [1]. Nevertheless, there are some apprehensions regarding its immediate as well as long-term side effects. Besides the few cases of transient cases of leukopenia and thrombocytopenia in our study, there were no other immediate adverse effects. Infusion of methylprednisolone before each Thymo dose most likely provided an anti-inflammatory effect and protection against such adverse reactions of fevers, shivering and hypertension. Nowadays, an emerging concern is BKV nephropathy, which has been linked to over-immunosuppression. In our study, only one case of BKV viruria and viremia occurred in the Thymo 1.5 mg/kg regimen. Induction therapy itself probably does not cause increased susceptibility to such an infection. Rather, as previously suggested, factors such as ischemia, pro-inflammatory cytokines and immune injury, in combination with high doses of tacrolimus and mycophenolate mofetil, may render the renal allograft susceptible to invasive BKV infection [24,25].

When our study is compared with previous studies, the Thymo dosages studied here were lowered and with less complications, yet just as effectual [11–17]. In summary, induction therapy with either Thymo regimen for three consecutive days, with maintenance of tacrolimus, prednisone and MMF, was safe and successful with no acute rejection episodes or post-transplant complications during 6 months and subsequently at 24 months of follow-up. While there was no apparent clinical benefit with the use of higher dose Thymo in this study thus far, it provided a significantly more effective and sustained T-cell clearance over the first 6 months, which can lead to reduce alloreactivity and, subsequently may decrease the risk of chronic rejection. Although the present study was not designed and sufficiently powered to elucidate this question, we were able to test the possible clinical advantages of more sustained T-cell clearances. It has been reported that higher lymphocyte counts after treatment with polyclonal preparations are associated with higher rejection rates and possibly decrease graft survival [3]. The lower Thymo dose is less immunosuppression but it may be more advantageous to use the slightly higher Thymo dose for the potential long-term gain given the minimal difference in complications thus far noted.

Whether a more profound and sustained T-cell clearance post-transplant will translate into a decreased risk of immunological injury and improved long-term outcomes after renal transplantation remains to be determined in larger prospective randomized studies. Meanwhile, our data emphasized that a short-course (3-day) induction therapy with either 1.0 or 1.5 mg/kg/day of thymoglobulin appears to be a practical, safe and efficacious strategy for standard initial immunosuppression in adult KTR.

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