

Five-Year Follow Up of Thymoglobulin Versus ATGAM Induction in Adult Renal Transplantation

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Background. One-year results of a randomized, double-blinded trial of Thymoglobulin versus Atgam for induction therapy in renal transplantation revealed that Thymoglobulin was associated with higher event-free survival (94% vs. 63%), less acute rejection (4% vs. 25%), and better graft survival. This article compares the safety and efficacy of Thymoglobulin versus Atgam induction through 5 years.

Methods. Review and analysis of clinic records and electronic databases.

Results. At 5 years, event-free survival (73% vs. 33%, $P < 0.001$), graft survival (77% vs. 55%, $P = 0.047$), and freedom from rejection (92% vs. 66%, $P = 0.007$) were higher with Thymoglobulin versus Atgam. No additional cytomegalovirus (CMV) disease occurred after the first year with Thymoglobulin or Atgam (13% vs. 33%, $P = 0.056$). There were two cases of posttransplant lymphoproliferative disorder (PTLD) with the Atgam arm and none with Thymoglobulin. Thymoglobulin was associated with profound lymphopenia at 2 years after transplantation.

Conclusions. Thymoglobulin was associated with higher event-free survival, graft survival, and freedom from rejection without increased PTLD or CMV disease at 5 years compared with Atgam. The prolonged and profound lymphopenia may contribute to the long-term results associated with Thymoglobulin.

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We previously reported the 1-year results of a randomized, double-blinded trial of Thymoglobulin, rabbit-derived antithymocyte globulin (Thymoglobulin, SangStat, Fremont, CA) versus Atgam, equine-derived antithymocyte globulin (Atgam, Upjohn, Kalamazoo, MI) for induction immunosuppression. Use of Thymoglobulin was associated with an “event-free survival,” defined as freedom from acute rejection, graft loss, or death (94% vs. 63%, $P = 0.0005$), improved graft survival (98% vs. 83%, $P = 0.02$), less graft rejection (4% vs. 25%, $P = 0.014$), less severe rejection ($P = 0.02$), and less cytomegalovirus disease (CMV, 13% vs. 33%, $P = 0.056$) at 1 year (1).

Which induction agent is best for renal-transplant recipients in the short-term is controversial, and no long-term safety and efficacy data from prospective, randomized trials have been reported. The purpose of this article is to report 5-year outcomes in renal-transplant recipients who received Thymoglobulin or Atgam induction in a single-center, randomized, double-blind trial.

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MATERIALS AND METHODS

Study design, inclusion, and exclusion criteria and immunosuppressive regimens have been described previously (1). The trial was a randomized, single-center, double-blind trial of all adult renal-transplant recipients receiving induction immunosuppression. Patients receiving living-related human leukocyte antigen-identical renal allografts did not receive antilymphocyte induction therapy and were excluded.

Immunosuppression

All patients received quadruple sequential immunosuppression consisting of induction with Thymoglobulin or Atgam, followed by triple immunosuppressive therapy. Patients randomized to Thymoglobulin induction received 1.5 mg/kg per day intravenously up to 7 days beginning intraoperatively, through a central venous catheter. Patients randomized to Atgam induction received 15 mg/kg per day intravenously up to 7 days, beginning intraoperatively, through a central venous catheter. The study drug dose (Thymoglobulin or Atgam) was held temporarily at any time during therapy for any of the following reasons: serious adverse event, platelet count less than 50,000 cells/mm³, white blood cell count less than 2,000 cells/mm³. The study drug was decreased to half the dose at any time for one of the following reasons: platelet count between 50,000 and 75,000 cells/mm³, white blood cell count between 2,000 and 3,000 cells/mm³.

Maintenance immunosuppression consisted of cyclosporine (Neoral, Novartis Pharmaceuticals, East Hanover, NJ) with dose adjustments to maintain the 12-hour whole-blood trough level between 300 and 400 ng/mL for the first 1–3 months and then 150–300 ng/mL in conjunction with azathioprine and corticosteroids. Patients receiving a second transplant, those with an immunologic cause for end-stage renal disease, and those with severe gout requiring the use of allopurinol received mycophenolate mofetil.

Viral Prophylaxis

CMV infection and disease were defined previously (2, 3). For viral prophylaxis, 200 mg of acyclovir was administered twice daily for 3 months after transplant for herpes simplex prophylaxis when neither the donor nor recipient had serologic evidence of past exposure to CMV. When either the donor or recipient had serologic evidence of prior exposure to CMV, oral ganciclovir was given at 1,000 mg orally 3 times a day for 3 to 6 months as herpetic and CMV prophylaxis. Acute rejection episodes were determined by the presence of clinical signs including but not limited to fever, graft tenderness, and rise in serum creatinine and confirmed in all cases by biopsy evidence of rejection as defined by the Banff criteria.

Database and Patient Follow-up

Patients at our center are followed with a minimum of monthly laboratory tests and yearly clinic visits. Patients are tracked at least yearly, and their clinical status is reported to the United Network for Organ Sharing. Our center uses an electronic medical record (OTTR, HKS Medical Information Systems, Omaha, NE). In addition, a research nurse monitors and records all pertinent data from the medical records of all patients in a SAS database for research purposes (SAS version 8, Carey, NC).

Statistics

Differences in the characteristics of patients were tested with Student's *t* test for continuous variables, Fisher's exact test for binary categorical variables, chi-square for multivariate categorical variables, and the Mantel-Haenszel chi-square for ordered multivariate categorical variables. Incidence of CMV disease, graft loss, and death were calculated using survival analysis techniques. All statistical tests were two tailed.

RESULTS

Between May of 1996 and March of 1997, 72 consecutive patients were enrolled and randomized 2:1 in a double-blinded fashion to receive Thymoglobulin at 1.5 mg/kg versus Atgam at 15 mg/kg intravenously, intraoperatively, and then daily for at least 6 days (total of 7 days). The randomization was successful. There were no differences in baseline recipient or donor characteristics (Table 1). The mean recipient age was 47 years; 33% were black, 62% were male, 25% were diabetic, and 75% received deceased donor renal allografts. Only one patient had delayed graft function, requiring dialysis in the first week after transplantation. This patient was in the Thymoglobulin group, and the patient received one dialysis treatment for 1 hour for hyperkalemia immediately after transplantation. Five-year follow-up was available on 100% of patients enrolled in the trial.

Patient and Graft Survival

At 5 years after transplantation, the composite endpoint of freedom from death, graft loss, or rejection, "event-free survival," was higher with Thymoglobulin (73%) compared with Atgam (33%, $P < 0.001$) (Fig. 1). Patient survival was similar between the groups. Seven (15%) patients expired in the Thymoglobulin group at a mean of 2.8 ± 1.5 years (range 2 months–4.2 years) after transplant (Fig. 2). The rea-

sons for death included cardiovascular complications ($n=3$; pulmonary embolism, myocardial infarction, pulmonary hypertension), cancer ($n=2$; renal carcinoma, lung cancer), lung disease, and an intracranial bleed (Table 2). In the Atgam group, seven (29%) patients expired at a mean of 2.3 ± 1.0 years (range 1 month–3.5 years) after transplant. The reasons for death included cancer ($n=3$; metastatic gastric adenocarcinoma, multiple myeloma, colon cancer), infection ($n=2$; necrotic bowel and pneumonia), an intracranial hemorrhage, and a thrombotic cerebral vascular accident.

There was a statistically significant higher graft survival in the Thymoglobulin arm (Fig. 2). Actual 5-year graft survival was 77% in the Thymoglobulin arm and 54% in the Atgam arm, $P=0.046$. Eleven patients suffered graft loss in the Thymoglobulin arm for reasons including death with a functioning graft (DWFG, $n=7$), chronic allograft nephropathy ($n=2$), infection, and obstructive nephropathy. Eleven patients suffered graft loss in the Atgam arm for reasons including DWFG ($n=6$), chronic allograft nephropathy ($n=2$), early graft thrombosis ($n=2$), and urinary tract infection. The occurrence of DWFG was not statistically different between the two groups.

To explore the effect of antithymocyte globulins on long-term effects, several additional assessments were considered. Excluding early allograft caused by thrombosis, we saw that graft loss was not statistically different at 5 years with 23% (11/48) of patients in the Thymoglobulin arm versus 41% (9/22) of patients in the Atgam arm suffering graft loss ($P=0.11$). Although early events after transplantation have long-term effects, we wished to clarify whether Thymoglobulin was associated with a beneficial effect on late events independent of early events. Thus, we performed a Kaplan-Meier analysis of patients who had not had a composite endpoint event by 1 year posttransplantation. When excluding the first 12 months, 19% (8/43) of patients had a composite event in the Thymoglobulin arm and 47% (7/15) in the Atgam arm, $P=0.045$. Death-censored graft loss tended to be less with 10% (4/41) in the Thymoglobulin arm and 28% (5/18) in the Atgam arm, $P=0.07$. Last, a Cox proportional hazards analysis was performed using stepwise selection for variables: treatment group and donor, recipient, transplant, and immunosuppression characteristics. The only significant effect observed was treatment group.

Rejection, Maintenance Immunosuppression, and Safety

1 year after transplantation, Thymoglobulin patients had less graft rejection (4% vs. 25%). This was maintained at 5 years after transplantation, with a total of four episodes of acute rejection in the Thymoglobulin arm and eight episodes in the Atgam arm (8% vs. 34%, respectively, $P=0.0073$) (Fig. 3). In the Thymoglobulin group, two episodes of acute rejection had occurred within 6 months after transplantation and the other two between 1 and 3 years after transplantation. Of the eight patients in the Atgam group who experienced acute rejection, four were within the first 6 months after transplantation, two in months 6 through 12, and two episodes at greater than 4 years after transplantation. Four rejection episodes were classified as Banff grade II in the Atgam group and one in the Thymoglobulin group. Thus, the rejection episodes in the Atgam group tended to be more severe, with four

TABLE 1. Recipient and donor characteristics

Variable	Atgam (n=24)	Thymoglobulin (n=48)
Recipient characteristics ^a		
Age, years (mean±SD)	52±12	45±14
Percent of patients over 60 years	21	19
Race (%)		
White	17 (71)	30 (62)
Black	6 (25)	18 (38)
Sex (%)		
Female	9 (37)	18 (37)
Transplant type (%)		
Deceased Donor	19 (79)	35 (73)
Transplant number (%)		
First	23 (96)	44 (92)
Cause of ESRD (%)		
Hypertension	8 (33)	15 (31)
Diabetes	7 (29)	11 (23)
Glomerulonephritis	4 (17)	12 (25)
PCKD	3 (13)	6 (13)
Other	2 (8)	4 (8)
HLA match, mean	2.2	2.3
Donor characteristics		
Age, yrs (mean±SD)	28±16	40±37
Percent of patients over 60 yrs	4	10
Race (%)		
White	18 (75)	40 (83)
Black	4 (17)	7 (15)
Sex (%)		
Female	9 (37)	21 (44)
CMV status (%)		
Positive/positive	11 (46)	19 (40)
Positive/negative	5 (21)	8 (17)
Negative/positive	5 (21)	12 (25)
Negative/negative	3 (12)	9 (18)
Cold ischemia time, mean±SD, hrs	13.9±5.8	12.8±5.4
Delayed graft function, n (%)	0	1 (2)

^a There were no statistically significant differences between the groups.

ESRD, end-stage renal disease; PCKD, polycystic kidney disease; PRA, panel of reactive antibodies; HLA, human leukocyte antigen; CMV, cytomegalovirus.

(17%) patients considered steroid resistant and requiring antilymphocyte antibody treatment versus two (4%) patients in the Thymoglobulin group, $P=0.09$. The relatively small numbers of patients precluded an assessment of chronic rejection. However, of patients with functioning grafts at 5 years, serum creatinine levels were similar between the two groups. The mean 5-year serum creatinine was 1.9 ± 0.7 mg/dL in the Thymoglobulin arm ($n=37$) and 1.5 ± 0.7 mg/dL in the Atgam arm ($n=13$, $P=NS$).

The incidence of CMV disease was less with Thymoglobulin than Atgam at 5 years (13% vs. 33%, $P=0.056$), with no additional cases after the first year. At 5 years, a small number of patients ($n=6$) required crossover to tacrolimus or sirolimus. Cyclosporine concentrations were similar throughout the study period in both groups. As previously described (1), the antimetabolite was discontinued for ad-

verse effects or infection. Withdrawal of the antimetabolite occurred in 43% (16/37) of Thymoglobulin-treated patients, whereas in the Atgam arm, all surviving patients remained on an antimetabolite ($P=0.02$). Of those who remained on an antimetabolite, more patients in the Atgam arm remained on azathioprine ($P=0.02$), although the use of mycophenolate mofetil in the Thymoglobulin and Atgam groups was similar ($P=NS$).

Malignancy

There was a higher incidence of malignancy in the Atgam group compared with the Thymoglobulin group during the 5-year postoperative period (21% vs. 6%, $P=0.01$). There were two cases of posttransplant lymphoproliferative disorder (PTLD) in the Atgam arm and no cases in the Thymoglobulin arm. In the Thymoglobulin arm, three patients de-

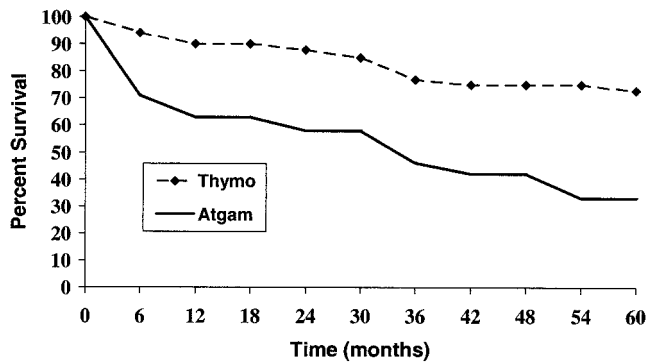


FIGURE 1. Composite endpoint. At 5 years after transplantation, the composite endpoint of freedom from death, graft loss, or rejection, event-free survival, was better with Thymoglobulin (73%) compared with Atgam (33%, $P < 0.001$).

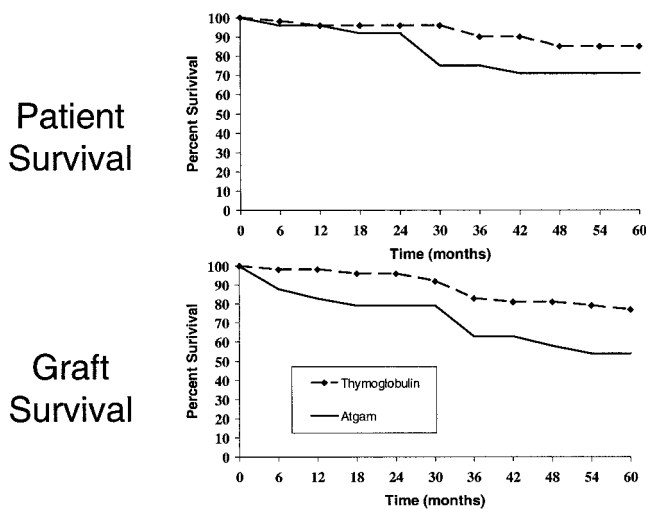


FIGURE 2. Patient and graft survival. Patient survival did not differ at 5 years. Despite a small number of patients treated, graft survival was significantly better in the Thymoglobulin arm (77%) versus the Atgam arm (54%, $P = 0.046$).

veloped malignancy including colon, renal, and lung carcinoma. Specifically, one patient in the Thymoglobulin group was diagnosed with adenocarcinoma of the colon 8 months after his transplant and underwent surgical resection. Another Thymoglobulin-treated patient was diagnosed with metastatic renal cell carcinoma and died 17 months after transplantation. The third patient, with a 22-pack per year history of smoking, was diagnosed with squamous cell cancer of lung 21 months after transplant and underwent left upper lung lobectomy. The patient expired 1 year after the diagnosis. In the Atgam group, five patients developed cancer, two of which developed a lymphoma. One patient was diagnosed with multiple myeloma 23 months after his transplantation and died 30 months after transplantation, and the other patient developed a plasmacytoma approximately 5 years after transplant. A patient with a history of metastatic colon cancer first diagnosed in 1989, requiring partial colectomy at that time, developed recurrent colon cancer with metastases to the peritoneum 29 months after transplant. Two months later, he

expired. Another patient developed myelodysplastic syndrome 1 month after transplantation and also developed basal cell carcinoma 4 years after transplantation. Last, grade II gastric adenocarcinoma was diagnosed in an Atgam-treated patient 38 months after transplant. The patient survived 4 months after the diagnosis.

Lymphocyte Analysis

Selected T-cell subsets at the time of antilymphocyte induction and the degree and duration of absolute lymphopenia ($< 1,000$ cells/ mm^3) were measured. Thymoglobulin suppressed CD3^+ T cells (median 0 cells/ mm^3 ; range 0–187 cells/ mm^3) to a greater extent than Atgam (median 16 cells/ mm^3 ; range 0–238 cells/ mm^3 , $P = 0.0001$) (Fig. 4). Thymoglobulin also suppressed CD5^+ T cells (median 2 cells/ mm^3 ; range 0–223 cells/ mm^3) to a greater extent than Atgam (median 17 cells/ mm^3 ; range 0–318 cells/ mm^3 , $P = 0.001$). Absolute lymphopenia developed rapidly upon administration of study medication and persisted for almost a full year among patients treated with Thymoglobulin but resolved by 14 days in patients receiving Atgam. Furthermore, the mean absolute lymphocyte count remained less than baseline among patients receiving Thymoglobulin throughout 1 year after transplantation ($P < 0.007$). In contrast, the absolute lymphocyte count was statistically less than baseline only at day 7 among patients who received Atgam. To determine the occurrence of CD4^+ suppression and inversion of the $\text{CD4}^+/\text{CD8}^+$ ratio, T-cell-marker analysis was obtained on 49% of all patients alive, free of malignancy, and with a functioning graft at 2 years after transplantation. Of these, 41% (18/44) of patients in the Thymoglobulin group and 68% (13/19) of patients in the Atgam group participated. The mean length of follow-up for these patients did not differ between the Thymoglobulin and Atgam groups and was 23 ± 8 months for Thymoglobulin patients and 22 ± 8 months for Atgam patients. The CD4^+ counts were lower for Thymoglobulin patients versus Atgam patients, 227 ± 38 cells/ mm^3 versus 466 ± 74 cells/ mm^3 , $P = 0.007$. The CD8^+ counts were similar for Thymoglobulin and Atgam 274 ± 69 cells/ mm^3 versus 327 ± 110 cells/ mm^3 , respectively, $P = \text{NS}$. The CD3^+ counts tended to be lower for Thymoglobulin 516 ± 93 cells/ mm^3 versus Atgam 825 ± 170 cells/ mm^3 , $P = 0.06$. There was also a trend toward a lower $\text{CD4}^+/\text{CD8}^+$ ratio in patients receiving Thymoglobulin compared with Atgam, 1.6 versus 2.4, $P = 0.103$.

DISCUSSION

The current study revealed that Thymoglobulin was associated with long-term, beneficial effects lasting 5 years after transplant with event-free survival, graft survival, and freedom from acute rejection that were higher in patients who received Thymoglobulin compared with patients who received Atgam. A Kaplan-Meier analysis of patients who had not had a composite endpoint event by 1 year posttransplantation revealed that use of Thymoglobulin was associated with a lingering benefit beyond the initial first year and extending to 5 years. The reason for these long-term associations may be related to the duration of lymphopenia. Absolute lymphopenia developed rapidly upon administration of study medication in both groups. We, and others, have re-

TABLE 2. Five-year outcomes

	Atgam (n=24)	Thymoglobulin (n=48)	P value
Total deaths, no. (%)	7 (29)	7 (15)	NS
Cause of death, no. (%)			NS
Cancer	3	2	
Infection	2	0	
Cardiac	1	3	
Bleed	1	1	
Pulmonary	0	1	
Total graft loss, no. (%)	11 (46)	11 (23)	0.047
Cause of graft loss, no. (%)			NS
Death with Function	6	7	
Acute Rejection	1	0	
Chronic allograft nephropathy	1	2	
Thrombosis	2	0	
Infection	1	1	
Obstructive nephropathy	0	1	
Acute rejection, no. (%)	8 (33)	4 (8)	0.007
Grade I	4	1	0.04
Grade II	4	3	
Steroid sensitive	4	2	0.09
Steroid Resistant	4	2	
CMV infection, no. (%)	8 (33)	6 (13)	0.056
Serum creatinine (mg/dL)	1.5±0.7	1.9±0.7	NS
Malignancy	5 (21)	3 (6)	0.01
PTLD	2 (4)	0	

PTLD, posttransplant lymphoproliferative disorder; CMV, cytomegalovirus.

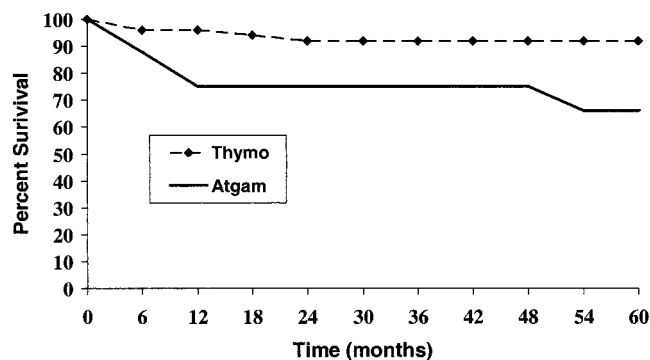


FIGURE 3. Freedom from acute rejection. At 5 years after transplantation, freedom from acute rejection occurred in 92% of Thymoglobulin-treated patients and 66% of Atgam-treated patients ($P=0.0073$).

vealed that prolonged lymphopenia has been associated with Thymoglobulin (1, 4–6). As previously reported, the mean absolute lymphocyte count remained less than baseline among patients receiving Thymoglobulin for the first year but resolved by day 14 in patients receiving Atgam (1). The present analysis extends our observations to 2 years and demonstrates long-term lymphopenia with CD3 and CD4 counts lower in the patients who received Thymoglobulin compared with Atgam. Rabbit polyclonal agents (of which Thymoglobulin is one) and not equine antilymphocytic agents (of

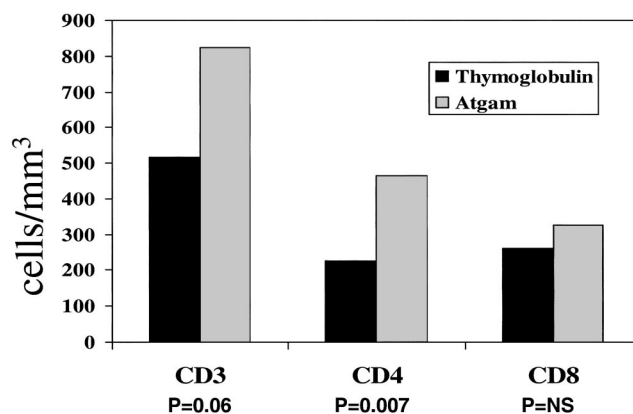


FIGURE 4. Lymphocyte subsets. The CD3+ counts tended to be lower for Thymoglobulin 516±93 cells/mm³ versus Atgam 825±170 cells/mm³, $P=0.06$. The CD4+ counts were lower for Thymoglobulin patients versus Atgam patients, 227±38 cells/mm³ versus 466±74 cells/mm³, $P=0.007$. The CD8+ counts were similar for Thymoglobulin and Atgam 274±69 cells/mm³ versus 327±110 cells/mm³, respectively, $P=NS$.

which Atgam is one) have been shown to result in long-term lymphocyte depletion and inversion of the CD4/CD8 ratio that may persist for years (6). The present study confirms the long-term lymphocyte depletion. The difference in the rate of recovery of the lymphopenia and the long-term duration of

the profound lymphopenia suggest that Thymoglobulin and Atgam have different mechanisms of action and that the observed differences were not simply from an inadequate dose of Atgam. Mechanisms, which have been proposed, include apoptosis in the central lymphocyte compartment, interference with leukocyte response to chemotactic signals, and inhibition of integrin-mediated cellular adhesion (7, 8).

In a recent trial, intraoperative administration of Thymoglobulin was associated with a reduced incidence of delayed graft function compared with postoperative administration (9). Intraoperative administration of both agents was used in this trial, and almost no delayed graft function was observed. Perhaps by eliminating the contribution of delayed graft function to acute rejection and poor graft survival we were able to see long-term differences between the two groups despite a relatively small number of patients in the trial.

It is unclear whether Thymoglobulin administration, *per se*, contributed to the long-term results. It is important to note that the graft survival in the Atgam arm was numerically lower but not statistically lower than national averages. This may be because of the relatively small numbers of patients enrolled in our study. Although the number enrolled was relatively small, this was a randomized, double-blinded, prospective study with 100% follow-up. Because of this design, the differences seen long term have a greater likelihood to reflect true differences as a result of the treatment rather than random events.

Viral infection and malignancy are concerns when using immunosuppressive therapy. Lymphopenia is felt to increase the likelihood of these two complications. CD4-cell depletion in particular has been associated a higher risk of squamous cell carcinoma (10). At 2 years after transplantation, CD4⁺ counts were significantly lower for Thymoglobulin-treated patients compared with Atgam-treated patients, but there was only a trend for lower CD4⁺/CD8⁺ ratios. CD3⁺ counts also tended to be lower. The absence of a significant difference in the CD3⁺ and CD4⁺/CD8⁺ ratios most likely reflects a type II error from small sample size. Overall, our data support persistent lymphopenia and immunomodulation with selective CD4⁺ depletion as possible mechanisms of action for Thymoglobulin. Despite this and the more profound CD4 depletion, there was a low incidence of cancer in the Thymoglobulin arm.

At 1 year, Thymoglobulin induction was associated with better event-free survival and prevention of rejection

compared with Atgam. At 5 years of follow-up, Thymoglobulin induction continued to be associated with higher event-free survival and reduced long-term acute rejection without an associated risk of PTLD and CMV disease compared with Atgam. Use of Thymoglobulin was also associated with profound lymphopenia at 2 years after transplantation that may explain, in part, the long-term results.

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