

ORIGINAL ARTICLE

Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation

Daniel C. Brennan, M.D., John A. Daller, M.D., Ph.D., Kathleen D. Lake, Pharm.D.,
Diane Cibrik, M.D., and Domingo Del Castillo, M.D.,
for the Thymoglobulin Induction Study Group*

ABSTRACT

BACKGROUND

Induction therapy reduces the frequency of acute rejection and delayed graft function after transplantation. A rabbit antithymocyte polyclonal antibody or basiliximab, an interleukin-2 receptor monoclonal antibody, is most commonly used for induction.

METHODS

In this prospective, randomized, international study, we compared short courses of antithymocyte globulin and basiliximab in patients at high risk for acute rejection or delayed graft function who received a renal transplant from a deceased donor. Patients taking cyclosporine, mycophenolate mofetil, and prednisone were randomly assigned to receive either rabbit antithymocyte globulin (1.5 mg per kilogram of body weight daily, 141 patients) during transplantation (day 0) and on days 1 through 4 or basiliximab (20 mg, 137 patients) on days 0 and 4. The primary end point was a composite of acute rejection, delayed graft function, graft loss, and death.

RESULTS

At 12 months, the incidence of the composite end point was similar in the two groups ($P=0.34$). The antithymocyte globulin group, as compared with the basiliximab group, had lower incidences of acute rejection (15.6% vs. 25.5%, $P=0.02$) and of acute rejection that required treatment with antibody (1.4% vs. 8.0%, $P=0.005$). The antithymocyte globulin group and the basiliximab group had similar incidences of graft loss (9.2% and 10.2%, respectively), delayed graft function (40.4% and 44.5%), and death (4.3% and 4.4%). Though the incidences of all adverse events, serious adverse events, and cancers were also similar between the two groups, patients receiving antithymocyte globulin had a greater incidence of infection (85.8% vs. 75.2%, $P=0.03$) but a lower incidence of cytomegalovirus disease (7.8% vs. 17.5%, $P=0.02$).

CONCLUSIONS

Among patients at high risk for acute rejection or delayed graft function who received a renal transplant from a deceased donor, induction therapy consisting of a 5-day course of antithymocyte globulin, as compared with basiliximab, reduced the incidence and severity of acute rejection but not the incidence of delayed graft function. Patient and graft survival were similar in the two groups. (ClinicalTrials.gov number, NCT00235300.)

From the Renal Division, Washington University School of Medicine, Barnes-Jewish Hospital, St. Louis (D.C.B.); the University of Texas Medical Branch, Galveston (J.A.D.); the Departments of Internal Medicine and Surgery, University of Michigan, Ann Arbor (K.D.L., D.C.); and the Hospital Reina Sofia, Cordoba, Spain (D.D.C.). Address reprint requests to Dr. Brennan at Washington University School of Medicine, Renal Division, Campus Box 8126, St. Louis, MO 63110, or at dbrennan@wustl.edu.

*The principal investigators of the Thymoglobulin Induction Study Group are listed in the Appendix.

N Engl J Med 2006;355:1967-77.

Copyright © 2006 Massachusetts Medical Society.

TWO EVENTS OCCURRING EARLY IN THE post-transplantation period, acute rejection and delayed graft function, negatively affect graft survival.¹⁻³ Patients with delayed graft function have an increased risk of acute rejection, and graft survival is superior in patients who do not have delayed graft function or acute rejection as compared with those who have either or both.⁴⁻⁷ The up-regulation of immunogenic molecules during brain death and during the subsequent procurement of organs predisposes allografts from deceased donors to acute rejection and delayed function. Induction therapy is specific therapy given at the time of transplantation to lower the incidence of acute rejection or to prevent or treat delayed graft function. Currently, almost 70% of kidney-transplant recipients receive induction therapy with either rabbit antithymocyte globulin (Thymoglobulin, Genzyme), a lymphocyte-depleting polyclonal antibody that targets multiple immunologic epitopes,⁸⁻¹² or basiliximab (Simulect, Novartis Pharmaceuticals) or daclizumab (Zenapax, Roche Pharmaceuticals), non-lymphocyte-depleting monoclonal antibodies that target the interleukin-2 receptor.¹³

Historically, rabbit antithymocyte globulin has been administered intravenously daily for 7 to 14 days after transplantation. Initiating this treatment during transplantation is generally associated with a lower incidence of delayed graft function and a trend toward a lower incidence of acute rejection.^{14,15} Short courses and prolonged courses appear to have similar efficacy.¹⁶ Basiliximab, the most commonly used interleukin-2 receptor antagonist,¹³ is administered both intraoperatively and on postoperative day 4. We compared the safety and efficacy of basiliximab and antithymocyte globulin (each administered intraoperatively and over the next 4 days) in patients with a high risk of acute rejection or delayed graft function who received a renal allograft from a deceased donor.

METHODS

STUDY DESIGN

This prospective, randomized, international study was designed to compare the safety and efficacy of rabbit antithymocyte globulin and of basiliximab for induction therapy in patients who were at high risk for acute rejection or delayed graft function and who received a renal transplant from a deceased donor. The design, data collection, and

analysis were performed by a sponsor, Genzyme, which holds the primary data. All the authors reviewed the data, vouch for the veracity and completeness of the data and data analyses, and wrote the manuscript.

The study was approved by the institutional review board at each site, and written informed consent was obtained from all patients. All patients were randomly assigned to receive either antithymocyte globulin or basiliximab before transplantation, according to 1:1 variable-block randomization at each investigative center. The treatment assignments were randomized at an independent center. Patients were followed for 12 months or until they were withdrawn from the study or were lost to follow-up (Fig. 1).

INCLUSION AND EXCLUSION CRITERIA

Only adult candidates for renal transplants from deceased donors were considered for enrollment. Eligibility was determined according to the duration of cold ischemia and other donor and recipient risk factors (Table 1). One or more of these factors, which put the recipient at high risk for acute rejection or delayed graft function, were required for eligibility.

Patients were excluded if they had been receiving immunosuppressive therapy before transplantation; had received an investigational medication within the past 30 days; had a known contraindication to the administration of antithymocyte globulin or basiliximab; were suspected or known to have an infection or were seropositive for hepatitis B surface antigen (HBsAg), antibody against hepatitis B core antigen (anti-HBcAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV); or had had cancer (except nonmelanoma skin cancer) within the previous 2 years. Pregnant women, nursing mothers, and women of child-bearing potential who were not using condoms or oral contraceptives were excluded.

INDUCTION THERAPY

Patients in the antithymocyte globulin group were given acetaminophen and diphenhydramine before receiving antithymocyte globulin (1.5 mg per kilogram of body weight given intravenously), which was reconstituted according to the package insert. Treatment with antithymocyte globulin was initiated intraoperatively, before graft reperfusion. Subsequent doses were given daily through day 4, for a total dose of 7.5 mg per kilogram. The

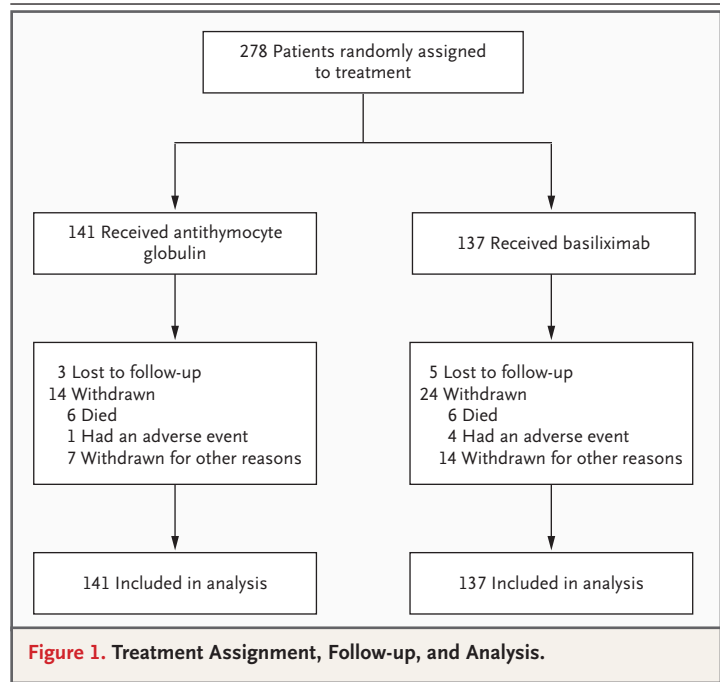
dose was decreased by 50% in patients with platelet counts of less than 80,000 per cubic millimeter or an absolute neutrophil count of less than 3000 per cubic millimeter. If the platelet count was less than 50,000 per cubic millimeter or the absolute neutrophil count was less than 1500 per cubic millimeter, then antithymocyte globulin was withheld. Basiliximab (20 mg) was administered intravenously according to the instructions of the manufacturer, which called for a first infusion before graft reperfusion, followed by a second infusion on day 4. Neither premedication nor dose adjustments were recommended by the manufacturer. According to the protocol, either antithymocyte globulin or basiliximab could be discontinued or interrupted if the patient refused to take it or if a serious adverse event that was severe and related to infusion occurred.

MAINTENANCE THERAPY

Both groups received maintenance immunosuppressive therapy involving cyclosporine (modified), mycophenolate mofetil, and prednisone. The first dose of cyclosporine (6 to 8 mg per kilogram given orally, divided into two doses) was initiated in each patient when any of the following events took place: urinary output reached or exceeded 1.5 liters per day for 2 consecutive days; the serum creatinine level was 3.0 mg per deciliter (265 μ mol per liter) or less on 2 consecutive days; or the serum creatinine level decreased to less than 50% of the pretransplantation level. If treatment with cyclosporine had not been initiated before day 4, the drug was begun then, since it was prespecified that the cyclosporine level in each patient had to reach the therapeutic range (defined according to local institutional standards) by day 10.

Treatment with mycophenolate mofetil (1.0 g given orally twice a day) was initiated before transplantation and was continued postoperatively once the patient could tolerate oral medications. The dose was adjusted by the investigators at their discretion, and the dose was reduced or the drug withheld if the absolute neutrophil count was less than 3500 per cubic millimeter.

Methylprednisolone (7 mg per kilogram given intravenously) was administered before the initial intraoperative dose of antithymocyte globulin or basiliximab. A standard corticosteroid taper was used to reduce the dose of prednisone or its equivalent to 5 mg by 6 months (see the Supplementary Appendix, available with the full text of



this article at www.nejm.org). The taper schedule and corticosteroid dose were adjusted at the discretion of the investigator if biopsy-proven acute rejection occurred.

CONCOMITANT THERAPY

Patients who received basiliximab were not permitted to receive rabbit antithymocyte globulin, except for the treatment of biopsy-proven acute rejection. Primary immunosuppressive therapy with tacrolimus, azathioprine, sirolimus, or other agents was prohibited. However, a switch to other immunosuppressive therapy was permitted after a documented episode of rejection. Patients with severe gastrointestinal intolerance to mycophenolate mofetil could be given azathioprine instead.

PROPHYLAXIS AGAINST INFECTION

Patients who were seropositive for cytomegalovirus (CMV) before transplantation and patients who received an organ from a donor who was seropositive for CMV received ganciclovir (orally or intravenously) for at least 14 days, beginning on day 1, followed by maintenance therapy with oral ganciclovir through day 90. Each investigator determined the dose on the basis of standard criteria. Antifungal and antibacterial medications were administered on the basis of the standards at each center.

Table 1. Eligibility Criteria According to Allograft Cold-Ischemia Time.*

Duration of Cold Ischemia	Required Risk Factors
<16 Hr, or ≤30 hr and any machine perfusion	If donor had a heartbeat, the donor had to be older than 50 yr or have a serum creatinine level >2.5 mg/dl (220 μmol/liter); if donor did not have a heartbeat, no further recipient risk factors required†
16–24 Hr	One donor or recipient risk factor†
>24 Hr	No additional risk factors required
>30 Hr and some machine perfusion	No additional risk factors required

* All information available before transplantation was considered.

† Donor risk factors were cold ischemia for more than 24 hours, donor age older than 50 years, donor without a heartbeat, donor with acute tubular necrosis, and donor requiring high-dose inotropic support. Recipient risk factors were repeated transplantation, panel-reactive antibody value exceeding 20% before transplantation, black race, and one or more HLA antigen mismatches with the donor.

EFFICACY END POINTS

The primary efficacy end point was a composite of the first occurrence of biopsy-proven acute rejection, delayed graft function, graft loss, or death; the incidence of each of these end points was also studied. All episodes of acute rejection were confirmed by biopsy, with histologic characteristics described according to the Banff criteria with the use of microscopy.¹⁷ Delayed graft function was defined as the need for dialysis within the first week after transplantation. Slow graft function was defined as a serum creatinine level exceeding 3.0 mg per deciliter on day 5 that did not require treatment with dialysis.⁶

CLINICAL ASSESSMENT

Demographic and baseline data included the age, sex, and race or ethnic group of the donor and recipient, the weight and height of the recipient, the cold-ischemia time, the panel-reactive antibody value before transplantation and at its peak, the CMV serostatus of the donor, and the presence or absence of a heartbeat in the donor. Laboratory data — including hemoglobin level, white-cell and platelet counts, cyclosporine trough level, and serum creatinine level — were measured at baseline, days 0 through 5, day 14, and months 1, 2, 3, 6, 9, and 12. Thrombocytopenia was defined as a platelet count of less than 80,000 per cubic millimeter; leukopenia was defined as a white-cell

count of less than 2500 per cubic millimeter. Safety data included all adverse events and serious adverse events. Frequencies of infection, cancer, and CMV disease were also calculated.

STATISTICAL ANALYSIS

We calculated that 240 patients would have to be enrolled for the study to have a statistical power of 80% to detect a significant difference between the two groups, with the use of a two-sided test and a significance level of 5%, given an incidence of the primary end point of 27.0% with antithymocyte globulin and 45.3% with basiliximab.¹⁸ The study design included an interim assessment and the subsequent readjustment of enrollment to 340 patients, because the interim differences between the two groups (particularly with regard to delayed graft function) were smaller than expected.¹⁹ The data and safety monitoring committee recommended the discontinuation of the study after 278 patients had been enrolled. This decision was made because of the statistical improbability of showing a change in the primary end point if more patients were enrolled.

All analyses were performed on the basis of the intention-to-treat principle. Categorical variables were summarized as counts and percentages, and continuous variables as means with standard deviations. Categorical data were compared with the use of Fisher's exact test, and continuous variables with the use of the Wilcoxon–Mann–Whitney test or the t-test. The incidences of graft rejection, graft loss, and death were calculated with the use of survival-analysis techniques. All tests were two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Eleven European centers enrolled 95 patients and 17 U.S. centers enrolled 183 patients between May 2, 2000, and March 6, 2002. Of these 278 patients, 141 were randomly assigned to receive antithymocyte globulin and 137 were randomly assigned to receive basiliximab. The baseline and demographic characteristics of the two groups were similar (Table 2). The mean (±SD) numbers of risk factors for acute rejection or delayed graft

Table 2. Baseline Characteristics of Recipients and Donors and Transplantation Characteristics.*

Characteristic	Antithymocyte Globulin (N=141)	Basiliximab (N=137)	P Value
Recipient			
Age — yr	51.3±13.1	49.7±13.0	0.27
Sex — no. (%)			0.55
Female	62 (44.0)	55 (40.1)	
Male	79 (56.0)	82 (59.9)	
Race or ethnic group — no. (%)†			0.77
White	85 (60.3)	89 (65.0)	
Black	41 (29.1)	39 (28.5)	
American Indian	1 (0.7)	0	
Asian	4 (2.8)	3 (2.2)	
Other	10 (7.1)	6 (4.4)	
Weight — kg	73.7±16.2	76.0±16.0	0.26
Height — cm	168.6±10.8	169.9±10.5	0.19
Body-mass index	26.0±5.0	26.5±5.1	0.46
Donor			
Age — yr			0.96
Mean	46.8±17.5	46.9±17.3	
Median	51.0	51.0	
Sex			0.16
Female	64 (45.4)	51 (37.2)	
Male	76 (53.9)	86 (62.8)	
Unknown	1 (0.7)	0	
Race or ethnic group†			0.97
White	107 (75.9)	103 (75.2)	
Black	11 (7.8)	9 (6.6)	
Asian	2 (1.4)	2 (1.5)	
Other	19 (13.5)	20 (14.6)	
Unknown	2 (1.4)	3 (2.2)	
Transplantation			
Duration of cold ischemia — hr	25.4±8.6	27.1±8.4	0.09
Cold ischemia lasting >24 hr — no. (%)	73 (51.8)	84 (61.3)	0.26
Repeated transplantation — no. (%)	16 (11.3)	13 (9.5)	0.83
Cytomegalovirus serologic status — no. (%)			0.14
Donor positive, recipient negative	21 (14.9)	31 (22.6)	
Donor and recipient positive	66 (46.8)	52 (38.0)	
Donor negative, recipient positive	33 (23.4)	29 (21.2)	
Donor and recipient negative	8 (5.7)	14 (10.2)	
Unknown	13 (9.2)	11 (8.0)	
Donor without heartbeat — no. (%)	7 (5.0)	6 (4.4)	1.00
Donor older than 50 yr — no. (%)	75 (53.2)	74 (54.0)	0.90
Panel-reactive antibody — %			0.86
Before transplantation	6.3±19.0	5.7±17.1	
Peak	14.0±28.2	13.5±27.7	0.68

* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Race or ethnic group was self-reported by recipients and reported by the investigator for donors.

function were similar among recipients in the antithymocyte globulin group and those in the basiliximab group (0.6 ± 0.75 and 0.6 ± 0.79 , respectively; $P=0.96$), as well as among donors (1.4 ± 0.78 and 1.4 ± 0.71 , respectively; $P=0.83$). The mean duration of the hospital stay did not differ significantly between the antithymocyte globulin group and the basiliximab group (13.2 ± 8.3 and 12.6 ± 7.9 days, respectively; $P=0.38$); the mean duration was 9.7 ± 5.5 days in the United States and 19.1 ± 8.9 days in Europe ($P<0.001$).

INDUCTION AND MAINTENANCE THERAPIES

Basiliximab was initiated intraoperatively in 96.7% of all patients who were assigned to receive it, and 96.4% received the intended two doses. The average total dose of basiliximab was 39.3 ± 3.8 mg per patient (0.54 ± 0.13 mg per kilogram). Rabbit antithymocyte globulin was initiated before reperfusion in 87.9% of all patients assigned to receive it, and 68.8% received the intended five doses. One patient (0.7%) received six doses, and another (0.7%) received seven doses. At least four doses were administered in 87.2% of patients. The major reasons for stopping or reducing the antithymocyte globulin dose were leukopenia (in 45.2% of patients), thrombocytopenia (11.9% of patients), or both (14.3% of patients). These conditions resolved by day 14, on average (Fig. 2). The incidences of acute rejection, infection, and cancer did not differ significantly according to whether patients received full or reduced doses of antithymocyte globulin. The average total dose of antithymocyte globulin was 474.2 ± 147.5 mg (6.5 ± 1.5 mg per kilogram), and the minimum and maximum doses were 1.3 mg per kilogram and 9.8 mg per kilogram, respectively. Graft loss less than 24 hours after transplantation was the reason that 3.6% of patients did not receive the second dose.

The use of maintenance immunosuppressive therapy in the two groups was generally similar. However, at 12 months, more patients in the antithymocyte globulin group than in the basiliximab group were receiving mycophenolate mofetil (20.2% vs. 10.3%, $P=0.05$).

EFFICACY END POINTS

At 12 months, the incidence of the primary end point did not differ significantly between the antithymocyte globulin group (50.4%) and the basiliximab group (56.2%, $P=0.34$) (Table 3). There were fewer patients with biopsy-proven acute re-

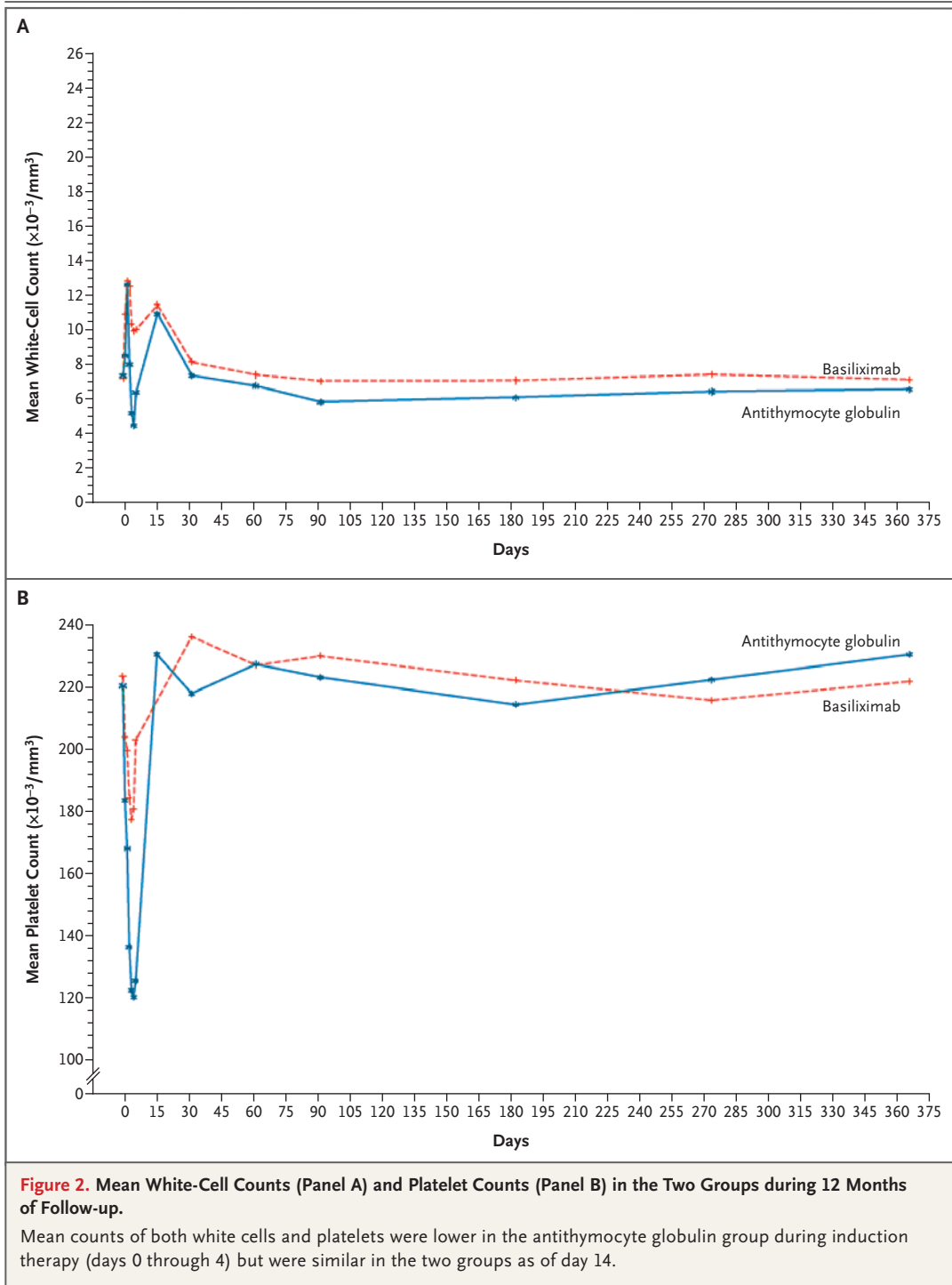
jection in the antithymocyte globulin group than in the basiliximab group (15.6% vs. 25.5%, $P=0.02$) (Table 3). The incidence of acute rejection tended to be lower among blacks and nonblacks receiving antithymocyte globulin than among those receiving basiliximab. The incidence did not differ significantly between blacks and nonblacks in both groups combined ($P=0.14$). The incidence also did not differ significantly between patients (in both groups combined) in the United States and those in Europe ($P=0.28$). There were no episodes of rejection with a Banff grade of III (a severe episode of rejection consisting of marked arteritis involving the intima or transmural arteritis with fibrinoid deposits and necrosis of the medial smooth muscle cells). Severe rejection, as indicated by the need for antibody treatment, was less frequent among patients receiving antithymocyte globulin than among those receiving basiliximab (1.4% vs. 8.0%, $P=0.005$).

The incidence of delayed graft function was similar in the antithymocyte globulin group (40.4%) and the basiliximab group (44.5%, $P=0.54$), as was the incidence of slow graft function (23.4% and 26.3%, respectively; $P=0.49$). The mean number of hemodialysis treatments was similar in the antithymocyte globulin group and the basiliximab group (3.2 ± 3.0 and 3.1 ± 2.9 , respectively; $P=0.62$). The incidence of graft loss was also similar among patients receiving antithymocyte globulin (9.2%) and those receiving basiliximab (10.2%), as were the incidences of death (4.3% and 4.4%, respectively) and the causes of graft loss and death.

SAFETY

The two agents were associated with a similar overall incidence of adverse events and serious adverse events (Table 4). Immediately after transplantation, leukopenia and thrombocytopenia were more common among patients who received antithymocyte globulin than among those who received basiliximab ($P<0.001$). By day 14, there were no significant differences noted (Fig. 2).

Overall, the incidence of infection was higher in the antithymocyte globulin group than in the basiliximab group (85.8% vs. 75.2%, $P=0.03$). This difference appeared to be attributable to a greater frequency of urinary tract infections in the antithymocyte globulin group (39.0%, vs. 27.0% in the basiliximab group; $P=0.04$) and non-CMV viral infections (21.3% vs. 11.7%, $P=0.04$). The incidence of CMV disease was lower in the antithy-



mocyte globulin group than in the basiliximab group (7.8% vs. 17.5%, $P=0.02$). Antibiotic prophylaxis was administered according to each center's protocol, and it was used in fewer patients receiving antithymocyte globulin than patients receiving basiliximab (18.9% vs. 30.9%, $P=0.03$).

There were no significant differences between the two groups in the incidence of cancer, including post-transplantation lymphoproliferative disease, though there were five cases of cancer in the antithymocyte globulin group and only one in the basiliximab group (Table 4). All cancers ap-

Table 3. Efficacy End Points 12 Months after Transplantation.

End Point	Antithymocyte Globulin (N=141)	Basiliximab (N=137)	P Value
	<i>no. of patients (%)</i>		
Composite of acute rejection, delayed graft function, graft loss, and death	71 (50.4)	77 (56.2)	0.34
Biopsy-proven acute rejection	22 (15.6)	35 (25.5)	0.02
No. of black recipients/total no. of such recipients	8/41 (19.5)	13/39 (33.3)	0.14
No. of nonblack recipients/total no. of such recipients	14/100 (14.0)	22/98 (22.4)	0.07
No. of recipients in United States/total no. of such recipients	13/91 (14.3)	21/92 (22.8)	0.07
No. of recipients in Europe/total no. of such recipients	9/50 (18.0)	14/45 (31.1)	0.12
Antibody-treated acute rejection	2 (1.4)	11 (8.0)	0.005
Delayed graft function	57 (40.4)	61 (44.5)	0.54
Graft loss	13 (9.2)	14 (10.2)	0.68
From death	4 (2.8)	3 (2.2)	
From acute rejection	1 (0.7)	1 (0.7)	
From primary nonfunction	1 (0.7)	4 (2.9)	
From graft thrombosis	0	4 (2.9)	
From chronic rejection	2 (1.4)	1 (0.7)	
From infection	1 (0.7)	1 (0.7)	
From toxic effects of cyclosporine	1 (0.7)	0	
From recurrent disease	1 (0.7)	0	
From hypertension	1 (0.7)	0	
From urinary fistula	1 (0.7)	0	
Death	6 (4.3)	6 (4.4)	0.90
From cardiovascular disease	2 (1.4)	5 (3.6)	
From pulmonary disease	1 (0.7)	1 (0.7)	
From gastrointestinal disease	2 (1.4)	0	
From unknown cause	1 (0.7)	0	

pear to have been successfully treated, and none were fatal during follow-up.

Hemoglobin levels between the groups did not differ significantly at any point during the study. At 12 months, the mean, median, and range of the serum creatinine levels were 2.0 ± 1.45 , 1.7, and 0.7 to 12.0 mg per deciliter (177 ± 128 , 150, and 62 to 1061 mmol per liter), respectively, in the antithymocyte globulin group and 1.8 ± 0.75 , 1.7, and 0.8 to 6.6 mg per deciliter (159 ± 66 , 150, and 71 to 583 mmol per liter), respectively, in the basiliximab group. These measures did not differ significantly between the two groups ($P=0.51$).

DISCUSSION

In our trial, immunoprophylaxis with antithymocyte globulin, as compared with basiliximab, did not reduce the incidence of delayed graft function among patients at high risk for delayed graft function or acute rejection who received a renal transplant from a deceased donor. It is possible that the injury associated with prolonged cold ischemia and an advanced age of the donor or recipient were too great to prevent delayed graft function. A possible alternative explanation is the finding that the use of an interleukin-2 receptor antagonist such

Table 4. Frequency of Adverse Events at 12 Months.*

Adverse Event	Antithymocyte Globulin (N = 141)	Basiliximab (N = 137)	P Value
	<i>no. of patients (%)</i>		
Total events	140 (99.3)	135 (98.5)	0.62
Serious events	103 (73.0)	99 (72.3)	0.89
Leukopenia	47 (33.3)	20 (14.6)	<0.001
Thrombocytopenia	15 (10.6)	8 (5.8)	0.19
All infections	121 (85.8)	103 (75.2)	0.03
Urinary tract	55 (39.0)	37 (27.0)	0.04
Probable bacterial or other	87 (61.7)	70 (51.1)	0.09
Confirmed bacterial	74 (52.5)	51 (37.2)	0.01
Cytomegalovirus	11 (7.8)	24 (17.5)	0.02
Viral other than cytomegalovirus	30 (21.3)	16 (11.7)	0.04
Fungal	20 (14.2)	20 (14.6)	1.00
Protozoal	0	1 (0.7)	0.49
Cancer	5 (3.5)	1 (0.7)	0.21
Post-transplantation lymphoproliferative disease	3 (2.1)	0	0.13
Renal-cell carcinoma in native kidney	1 (0.7)	1 (0.7)	1.00
Cutaneous squamous-cell carcinoma	1 (0.7)	0	1.00

* Leukopenia was defined as a white-cell count of less than 2500 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 80,000 per cubic millimeter. Values for each type of infection do not sum to the total number of infections because some patients had more than one type of infection.

as basiliximab is associated with a trend toward a lower incidence of delayed graft function than that with placebo.²⁰

We found that the incidence and severity of acute rejection were lower in the antithymocyte globulin group than in the basiliximab group. The incidence of biopsy-proven acute rejection among patients who received basiliximab was more than 1.5 times that among those who received antithymocyte globulin, and the severity of rejection was also greater, since the need for antibody treatment was more than 6 times that in the antithymocyte globulin group. These results were achieved even though the dose and duration of antithymocyte globulin therapy were lower than those in previous reports.

The incidences of adverse events and serious adverse events were similar in the two groups, but the types of events differed. The higher initial incidence of leukopenia in the antithymocyte globulin group was anticipated. The white-cell counts in our trial did not distinguish between lymphopenia, which is essential to the efficacy of antithy-

mocyte globulin, and leukopenia, which potentially compromises resistance to infection. Absolute neutrophil counts might have been more useful than white-cell counts in comparing the safety of the two induction agents, because neutrophil counts more accurately predict the risk of infection related to leukopenia. Most centers now reduce the dose of antithymocyte globulin by one half for patients with an absolute neutrophil count of less than 1200 per cubic millimeter and withhold the dose if the absolute neutrophil count is less than 800 per cubic millimeter.

Urinary tract infections were more common among patients in the antithymocyte globulin group than among those in the basiliximab group. Antibiotic prophylaxis was used less frequently in the antithymocyte globulin group than in the basiliximab group. The study design stipulated the use of prophylaxis against CMV disease for the first 3 months. The incidence of CMV disease was lower in the antithymocyte globulin group than in the basiliximab group, which may have been due to the greater incidence of rejection episodes,

and a greater need for antibody therapy to treat rejection, in the basiliximab group. There were more cases of cancer in the antithymocyte globulin group, but not significantly more.

A small French, multicenter study compared rabbit antithymocyte globulin and basiliximab in patients at low risk for acute rejection or delayed graft function (50 patients per group).²¹ Rabbit antithymocyte globulin was not administered intraoperatively in that study, but there was a trend toward a lower incidence of delayed graft function in the antithymocyte globulin group (6%) than in the basiliximab group (14%), though no significant differences were seen in the incidence of acute rejection. In that study, 94% of patients receiving rabbit antithymocyte globulin did not receive cyclosporine until after day 6, whereas all patients receiving basiliximab started receiving cyclosporine on day 0 or day 1, which may constitute a selection bias. No antiviral prophylaxis was used, but the incidences of clinical CMV disease in the antithymocyte globulin group (12%) and the basiliximab group (6%) did not differ significantly.

A French study at three centers compared rabbit antithymocyte globulin (in 53 patients) and basiliximab (in 52 patients); all the patients were at low risk for acute rejection and delayed graft function and were undergoing a standard maintenance regimen of cyclosporine, mycophenolate mofetil, and corticosteroids.²² In that study, rabbit antithymocyte globulin was not used intraoperatively. There was no significant difference between the antithymocyte globulin group and the basiliximab group in the incidence of delayed graft function (30.2% and 28.8%, respectively) or

acute rejection (9.4% and 9.6%, respectively). No specific prophylaxis against CMV disease was used. Cytomegalovirus infection was more common in the rabbit antithymocyte globulin group than in the basiliximab group (41.5% vs. 21.2% of patients).

Our study has certain limitations. It was not a blinded trial; the identity of the induction agent could be deduced from the lymphopenia that occurs with rabbit antithymocyte globulin. However, the treatment assignments were randomized at an independent center. We do not believe that the lack of blinding influenced the study, since the end points were objective and did not involve subjective interpretation.

In conclusion, our study, which was relatively large, compared induction therapy with rabbit antithymocyte polyclonal antibody and induction therapy with basiliximab, an interleukin-2 receptor antagonist, in patients at high risk for acute rejection or delayed graft function who received a renal transplant from a deceased donor. Intraoperative use of antithymocyte globulin did not lower the incidence of delayed graft function in this high-risk population but did reduce the incidence and severity of acute rejection.

Supported by SangStat Medical Corporation and Genzyme.

Dr. Brennan reports having received grant support, consulting fees, and lecture fees from Genzyme, Novartis, Astellas, Pfizer, Roche, and Wyeth. Dr. Daller reports holding equity ownership in Genzyme. Dr. Lake reports being an employee of Roche. Dr. Cibrik reports having received consulting fees and grant support from Novartis and Astellas. Dr. Del Castillo reports having received consulting fees from Novartis, Astellas, Roche, and Wyeth and lecture fees from Novartis and Genzyme. No other potential conflict of interest relevant to this article was reported.

We thank Dr. Carolyn Sawyer and Kimberly Knolhoff for critical review and assistance with preparation of the manuscript.

APPENDIX

The principal investigators of the Thymoglobulin Induction Study Group are as follows: **United States** — Saint Barnabas Medical Center — L. Bonomini; Washington University and Barnes-Jewish Hospital — D.C. Brennan; Westchester Medical Center — K.M.H. Butt; University of Michigan Hospital — D. Cibrik; University of Alabama at Birmingham — R. Gaston; Emory University Hospital — C. Gausch; University of Texas Medical Branch — K. Gugliuzza; Medical College of Wisconsin — S. Hariharan; Carolinas Medical Center — D. Hayes; Rush University — S.C. Jensik; California Pacific Medical Center — S. Katznelson; University of California, Los Angeles — E. Kendrick; Yale University School of Medicine — M.I. Lorber; Allegheny General Hospital — D. Nghiem; University of Kentucky Medical Center — D. Ranjan; Life Link Transplant Institute — C. Wright; Medical College of Georgia — J.J. Wynn; **France** — Hôpital Foch — M. Delahousse; Centre Hospitalier Universitaire de Rangueil — D. Durand; Hôpital Edouard Herriot — N. Lefrancois; Centre Hospitalier Universitaire de Grenoble — P. Vialtel; **Germany** — Universität Erlangen-Nürnberg — R. Schmieder; Universitätsklinik Eppendorf — R. Stahl; **Spain** — Hospital 12 de Octubre — A. Andres; Hospital Reina Sofia — D. Del Castillo; Hospital Clinico y Provincial — F. Oppenheimer; Hospital de Cruces — P. Gomez Ullate; **United Kingdom** — Freeman Hospital — D. Talbot.

REFERENCES

1. Cecka JM, Cho YW, Terasaki PI. Analyses of the UNOS Scientific Renal Transplant Registry at three years — early events affecting transplant success. *Transplantation* 1992;53:59-64.
2. Gjertson DW. Determinants of long-term survival of adult kidney transplants: a 1999 UNOS update. In: Cecka M, Terasaki PI, eds. *Clinical transplants 1999*. Los Angeles: UCLA Immunogenetics Center, 2000:341-52.
3. Hariharan S. Long-term kidney transplant survival. *Am J Kidney Dis* 2001;38: Suppl 6:S44-S50.
4. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States,

- 1988 to 1996. *N Engl J Med* 2000;342:605-12.
5. Lindholm A, Ohlman S, Albrechtsen D, Tufveson G, Persson H, Persson NH. The impact of acute rejection episodes on long-term graft function and outcome in 1347 primary renal transplants treated by 3 cyclosporine regimens. *Transplantation* 1993; 56:307-15.
 6. Humar A, Johnson EM, Payne WD, et al. Effect of initial slow graft function on renal allograft rejection and survival. *Clin Transplant* 1997;11:623-7.
 7. Shoskes DA, Halloran PF. Delayed graft function in renal transplantation: etiology, management and long-term significance. *J Urol* 1996;155:1831-40.
 8. Bourdage JS, Hamlin DM. Comparative polyclonal antithymocyte globulin and antilymphocyte/antilymphoblast globulin anti-CD antigen analysis by flow cytometry. *Transplantation* 1995;59:1194-200.
 9. Zand MS, Vo T, Huggins J, et al. Polyclonal rabbit antithymocyte globulin triggers B-cell and plasma cell apoptosis by multiple pathways. *Transplantation* 2005; 79:1507-15.
 10. Michallet MC, Preville X, Flacher M, Fournel S, Genestier L, Revillard JP. Functional antibodies to leukocyte adhesion molecules in antithymocyte globulins. *Transplantation* 2003;75:657-62.
 11. Bonnefoy-Berard N, Revillard JP. Mechanisms of immunosuppression induced by antithymocyte globulins and OKT3. *J Heart Lung Transplant* 1996;15:435-42.
 12. Woodside KJ, Hu M, Meng T, Hunter GC, Sower LE, Daller JA. Differential effects of interleukin-2 blockade on apoptosis in naive and activated human lymphocytes. *Transplantation* 2003;75:1631-5.
 13. The U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. 2004 OPTN/SRTR annual report. (Accessed October 13, 2006, at <http://www.optn.org/AR2004/default.htm>.)
 14. Brennan DC, Flavin K, Lowell JA, et al. A randomized, double-blinded comparison of thymoglobulin versus Atgam for induction immunosuppressive therapy in adult renal transplant recipients. *Transplantation* 1999;67:1011-8. [Erratum, *Transplantation* 1999;67:1386.]
 15. Goggins WC, Pascual MA, Powelson JA, et al. A prospective, randomized, clinical trial of intraoperative versus postoperative thymoglobulin in adult cadaveric renal transplant recipients. *Transplantation* 2003;76:798-802.
 16. Agha IA, Rueda J, Alvarez A, et al. Short course induction immunosuppression with thymoglobulin for renal transplant recipients. *Transplantation* 2002;73: 473-5.
 17. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int* 1999; 55:713-23.
 18. Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. New York: John Wiley, 1981:41-2.
 19. Wittes J, Brittain E. The role of internal pilot studies in increasing the efficiency of clinical trials. *Stat Med* 1990;9:65-71.
 20. Sandrini S. Use of IL-2 receptor antagonists to reduce delayed graft function following renal transplantation: a review. *Clin Transplant* 2005;19:705-10.
 21. Lebranchu Y, Bridoux F, Buchler M, et al. Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. *Am J Transplant* 2002;2:48-56.
 22. Mourad G, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D. Sequential protocols using basiliximab versus antithymocyte globulins in renal-transplant patients receiving mycophenolate mofetil and steroids. *Transplantation* 2004;78:584-90.

Copyright © 2006 Massachusetts Medical Society.

COLLECTIONS OF ARTICLES ON THE JOURNAL'S WEB SITE

The *Journal's* Web site (www.nejm.org) sorts published articles into more than 50 distinct clinical collections, which can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronological order, with the most recent first.