

Graft

<http://gft.sagepub.com>

Induction with a Single Intraoperative Dose of OKT-3: A Novel Approach to Reduce Early Renal Allograft Rejection

Harold C. Yang, Michael J. Holman, Mohammad S. Razaque and Nasimul Ahsan

Graft 2002; 5; 344

DOI: 10.1177/1522162802005006004

The online version of this article can be found at:
<http://gft.sagepub.com/cgi/content/abstract/5/6/344>

Published by:

 SAGE Publications

<http://www.sagepublications.com>

Additional services and information for *Graft* can be found at:

Email Alerts: <http://gft.sagepub.com/cgi/alerts>

Subscriptions: <http://gft.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Induction with a Single Intraoperative Dose of OKT-3: A Novel Approach to Reduce Early Renal Allograft Rejection

Nasimul Ahsan, Michael J. Holman, Mohammad S. Razzaque, and Harold C. Yang

When serious complications have resulted in limited use of antibody induction therapies, in noninduction tacrolimus (FK506) and cyclosporine oral solution (modified) (Neoral® CsA) protocols, acute rejection remains in excess of 15% in kidney transplantation. This study compared the efficacy of single-dose OKT-3 induction and noninduction regimens in kidney transplant recipients treated with FK506/CsA-based immunosuppression. From a pool of 158 patients transplanted consecutively between January 1996 and December 1997, 124 patients were prospectively followed for a minimum of 12 months. All patients received either FK506 or CsA as the primary immunotherapy. Other immunosuppressive agents were mycophenolate mofetil and prednisone. All patients received prophylactic oral ganciclovir (500 mg bid for 3 months). Group A ($n = 49$), all cadaveric, received a single dose (5 mg) of intraoperative intravenous OKT-3; Group B ($n = 29$), all cadaveric, received no antibody induction; and Group C ($n = 46$), all living related, received no antibody induction. Patients were followed for episodes of biopsy-proven acute rejection within 6 months posttransplant and patient-graft survival within 12 months posttransplant. As expected, compared to Groups A and B, Group C had the least human leukocyte antigen (HLA) mismatches, cold ischemia times, and %Panel Reactive Antibody. Other demographic characteristics (Group A vs. B vs. C), including donor age (31.8 ± 2.2 vs. 30.8 ± 3.2 vs. 38.4 ± 1.6 years), patient age (45.4 ± 2.3 vs. 50.7 ± 2.4 vs. 36.9 ± 2.5 years), % male (63 vs. 72 vs. 48), % Caucasian (84 vs. 90 vs. 91), cytomegalovirus status, and causes of renal failure, were comparable. Acute rejection occurred in 4% of patients in the single-dose OKT-3 induction group (Group A) compared to 24% in the noninduction cadaveric allograft group (Group B) and 15% in the noninduction living-related allograft group (Group C) ($P < 0.02$). Of these, steroid-resistant rejection episodes were higher in Groups B (4/7) and C (5/7) than in Group A (0/2). At the end of 12 months, patient survival rates were 93.9% for Group A, 93.1% for Group B, and 100% for Group C ($P = ns$). The corresponding graft survival rates were 93.9%, 93.1%, and 96.6%, respectively ($P = ns$). The functions of renal allograft at 12 months as measured by serum creatine (mg/dl \pm SEM) were comparable in all 3 groups (Groups A vs. B vs. C = 1.47 ± 0.1 vs. 1.47 ± 0.1 vs. 1.52 ± 0.1). Infection (both bacterial and viral) occurred in 20.4% of patients in Group A compared to 37.9% in Group B and 45.7% in Group C ($P < 0.05$). The results show that when compared with single-dose OKT-3 induced cadaveric transplant patients, episodes of acute rejection and infectious complications are significantly higher in noninduced cadaveric recipients and better HLA-matched living-related recipients. The authors conclude that single-dose intraoperative OKT-3 administration is a novel approach that allows significant reduction in early posttransplant acute rejection in recipients of kidney transplants and is well tolerated.

Nasimul Ahsan, MD
Division of Nephrology and
Transplantation, Department of Medicine
UMDNJ-RWJUH, MEB 412
One Robert Wood Johnson Place
New Brunswick, New Jersey, USA 08904
Tel.: 732.235.6955
Fax: 732.235.8696
e-mail: ahsanna@umdnj.edu

Introduction

Since its introduction as an induction agent, OKT-3, a monoclonal antibody, has been recognized as first-line and steroid-resistant rejection therapy in solid organ transplantation.¹ Several studies have shown that induction therapy with OKT-3 is more effective than noninduction protocols in preventing acute rejection, groups receiving OKT-3 induction experience significantly fewer rejection episodes, and, perhaps most important, graft survival is increased in the OKT-3 group.²⁻⁴ Unfortunately, OKT-3 induction is not without its drawbacks. Serious complications, including adverse drug reactions, an increased infection rate, and higher cost, have been associated with its use.^{5,6} The conventional OKT-3 induction protocol is 5 mg intravenously 1 time per day for 10 to 14 days.¹ A number of groups have explored "low"-dose protocols in an attempt to minimize the side effects of these agents. These low-dose regimens are effective in preventing acute rejection, but little difference is demonstrated in the complication profile.⁷⁻¹⁰

With the introduction of several new immunosuppressant agents (e.g., FK506, cyclosporin A [CsA], mycophenolate mofetil [MMF], and rapamune), many centers have been using noninduction protocols. However, despite superior efficacy, acute rejection remains in excess of 15% with the new agents.¹¹⁻¹³ This study compared the efficacy of single-dose intraoperative OKT-3 induction and noninduction regimens in kidney transplant recipients.

Patients and Methods

This study was performed at the Milton S. Hershey Medical Center, Hershey, Pennsylvania. Patient entry began in January 1996 and continued until December 1997. A total of 168 renal transplants were conducted during this time, and 124 patients were eligible for the study.

Patients were considered eligible for the study if they were receiving a first cadaveric or living-related renal transplant and were at least 18 years old. Patients were excluded if they were recipients of prior organ transplants ($n = 8$) or multiorgan transplants ($n = 6$) or developed postoperative acute tubular necrosis (ATN) ($n = 20$) requiring prolonged antibody therapy. ATN was defined by urine output of less than 40 cc/h, failure to decrease serum creati-

nine by 20% within 12 to 24 hours, and/or need for dialysis. All patients received either tacrolimus or microemulsion cyclosporin as the primary immunotherapy. Patients receiving cadaveric allografts were divided into 2 groups: single dose (5 mg) of intraoperative intravenous OKT-3 (Group A) or no OKT-3 induction (Group B). A third group of patients who were recipients of living-related allografts and did not receive antibody induction was also studied (Group C).

OKT-3 (5 mg) (Orthoclone OKT3, Cilag, Raritan, NJ) was administered intravenously after induction of anesthesia. Oral tacrolimus (0.08 mg/kg; Fujisawa Healthcare, Inc., Deerfield, IL) or cyclosporine oral solution (modified) (CsA 4 mg/kg; Novartis Pharmaceutical Co., East Hanover, NJ), plus MMF (1500 mg; Hoffman-La Roche, Nutley, NJ) and intravenous methylprednisolone (500 mg), were administered prior to transplantation. Tacrolimus and CsA were administered on a schedule of 2 divided doses of 0.16 to 0.2 mg/kg/day and 8 to 10 mg/kg/day, respectively. Tacrolimus target whole-blood trough levels were 5 to 15 ng/ml (IMx[®] Tacro II assay, Abbott Laboratories, Abbott Park, IL) after the third month of follow-up. Corresponding target CsA levels were 100 to 300 ng/ml (Mono-TDx assays, Abbott Laboratories, Abbott Park, IL). Posttransplant oral methylprednisolone was administered at a daily dose descending from 2 to 0.15 mg/kg per day at the end of 180 days. All patients concomitantly received oral 500 mg MMF twice daily. Trimethoprim-sulfamethoxazole was administered in both treatment groups for *Pneumocystis carinii* prophylaxis. Oral ganciclovir 500 mg twice per day for 3 months was administered in all patients regardless of donor-recipient CMV status. Episodes of renal allograft dysfunction were defined by (a) an increased serum creatinine concentration of 0.3 mg/dl or greater; (b) a doubling of serum creatinine concentration, as compared with baseline or serum nadir; (c) oliguria; (d) an elevation of body temperature (above 38°C); (e) swelling and tenderness of graft; and (f) reduced graft blood flow by Doppler ultrasonography (after excluding hydronephrosis). Biopsy of the graft was required to confirm the diagnosis of the first episode of acute rejection in each patient prior to or within 24 hours of commencement of

ACUTE TUBULAR NECROSIS:

A kidney disorder that results in damage to the renal tubule cells, leading to acute renal failure. Acute tubular necrosis can result from any condition that deprives the kidney of oxygen (ischemia).

antirejection treatment, unless the procedure was medically contraindicated.

Acute rejection was treated similarly in all groups with recycling oral prednisolone 2 mg/kg per day for 3 days with subsequent taper. Steroid-resistant rejection was treated by the addition of OKT-3 (5 mg/d intravenously for 5 to 10 days).

Statistical Analysis

The primary endpoint of the study was treatment failure, defined by the occurrence of graft rejection that was confirmed histologically by core needle biopsy, graft loss, or patient death during the first 6 months following transplant. The proportion of patients experiencing biopsy-proven acute rejection, an infectious complication (during the first 6 months posttransplant), and 1-year patient/graft survival was analyzed using the Fischer exact test. Continuous baseline variables, such as patients' and donors' age, patients' weight, and cold ischemia time, were compared between treatment groups using 2-way analysis of variance (ANOVA) and Fischer exact tests when appropriate. Results are reported as mean \pm SEM when indicated. Differences were considered significant at $P < 0.05$.

Results

A total of 124 patients were included in the study (49 in Group A, 29 in Group B, 46 in Group C). All patients had a minimum follow-up of 12 months after transplant. Overall, the 3 groups were comparable with respect to age, weight, gender, CMV status, and cause of renal failure. As expected, compared to Groups A and B, Group C had the least human leukocyte antigen (HLA) mismatches, cold ischemia times, and %PRA (Table 1).

Efficacy Endpoints

During the first 6 months following transplant, episodes of acute rejection occurred in 4% of patients in the single-dose OKT-3 induction group (Group A) compared to 24% in the noninduction cadaveric allograft group (Group B) and 15% in the noninduction living-related allograft group (Group C) ($P < 0.02$) (Fig. 1). There was a total of 16 acute rejection episodes, 2 in Group A and 7 each in Groups B and C. Of these, steroid-resistant rejection episodes were higher in Groups B (4/7)

and C (5/7) than in Group A (0/2). Histopathology demonstrated BANFF grade I/II/III: Group A = 2/0/0, Group B = 2/3/2, and Group C = 1/3/3 ($P = ns$). At the end of 12 months, patient survival rates were 93.9% for Group A, 93.1% for Group B, and 100% for Group C ($P = ns$). The corresponding graft survival rates were 93.9%, 93.1%, and 96.6%, respectively ($P = ns$) (Fig. 2). The functions of renal allograft as measured by serum creatine (mg/dl \pm SEM) were comparable in all 3 groups (Groups A vs. B vs. C = 1.47 ± 0.1 vs. 1.47 ± 0.1 vs. 1.52 ± 0.1) (Fig. 3).

Five patients died (4%) during the first 12 months—3 patients (1 myocardial infarction, 1 sepsis, and 1 malignant melanoma) in Group A, 2 patients (1 myocardial infarction and 1 sepsis) in Group B—and are reflected in the incidence of graft loss. There were 2 graft losses in Group C due to acute vascular rejection. The mean time (days \pm SEM) to the first episode of acute rejection was 52 ± 20 days for Group A, 52 ± 11 days for Group B, and 32 ± 6 days for Group C.

Out of 42 infectious complications (both bacterial and viral), 20.4% (10/49) occurred in Group A compared to 37.9% (11/29) in Group B and 45.7% (21/46) in Group C ($P < 0.05$) (Table 2). Compared to Group A (0%), a trend to higher incidence of infections was seen following episodes of rejection in Group B (27.6%) and Group C (19.5%).

Discussion

In this prospective study, we compared single-dose intraoperative OKT-3 induction with noninduction protocols in recipients of kidney transplants. The distinctive feature of this study is that in patients treated with FK506 or microemulsion cyclosporine in combination with MMF, intraoperative single-dose OKT-3 induction lowered acute rejection rates to single digits. The incidence of acute rejection was 4% in the OKT-3 induction group (Group A) compared to 24% (noninduction, cadaveric renal transplants) in Group B and 15.2% (noninduction, living-related renal transplants) in Group C ($P < 0.02$) (Fig. 1). All groups had comparable 1-year graft and patient survival rates. In addition, the incidence of infection was significantly less in Group A (20.4%) in

HUMAN LEUKOCYTE ANTIGEN:

A genetic fingerprint on white blood cells and platelets that is composed of proteins that play a critical role in activating the body's immune system to respond to foreign organisms.

Table 1 | DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

	GROUP A	GROUP B	GROUP C
Number	49	29	46
Gender (% male)	63	72	48
Patients' age (years \pm SEM)	45 \pm 2.3	51 \pm 2.4	37 \pm 2.5
Donors' age (years \pm SEM)	32 \pm 2.2	31 \pm 3.2	38 \pm 1.6
Race (% white)	84	90	91
Patients' weight (kg \pm SEM)	72.4 \pm 3.0	81 \pm 2.0	62.4 \pm 1.1
HLA-DR mismatch (%)			
0	24	24	39
1	40	56	48
2	36	20	13
Cold ischemia time (hours \pm SEM)	16.5 \pm 0.9	18 \pm 0.8	2.9 \pm 0.1*
Panel-reactive antibody (% \pm SEM)	8 \pm 3.3	4.9 \pm 2.9	0.6 \pm 0.3
Causes of ESRD, <i>n</i> (%)			
Diabetes	9 (18)	7 (24)	9 (19)
Glomerulonephritis	10 (20)	3 (10)	11 (23)
Polycystic kidneys	6 (12)	7 (24)	2 (4)
Autoimmune diseases	3 (6)	1 (3)	4 (8)
Hypertension	9 (18)	6 (21)	3 (6)
Dialysis (%)	84	79	79
Duration of dialysis (months \pm SEM)	33.5 \pm 3.9	35 \pm 6.2	12.5 \pm 2.2
CMV status (%) (donor/recipient)			
D+/R+	34.7	44.8	31.1
D+/R-	30.6	20.7	26.7
D-/R+	12.2	20.7	26.7
D-/R-	30.4	13.8	15.6
Immunosuppression regimen, <i>n</i> (%)			
FK506	24 (49)	21 (72)	28 (61)
Microemulsion CsA	25 (51)	8 (18)	18 (39)

HLA = human leukocyte antigen; DR is a locus on the HLA system; ESRD = end-stage renal disease; CMV = cytomegalovirus; CsA = cyclosporin A.

* $P < 0.05$, Group C compared with Groups A and B.

comparison to Groups B and C (37.9% and 45.7%, respectively) ($P < 0.05$). Furthermore, our patients experienced none of the side effects commonly associated with OKT-3 induction during or following the operation.

Secondary both to the drug's success as an antirejection agent and the increased risk of nephrotoxicity associated with cyclosporine prophylaxis, the use of OKT-3 as an induction agent has been explored. Recently, several studies supporting the use

of OKT-3 as an induction agent have been published. In 1993, Norman et al. demonstrated that OKT-3 patients had significantly fewer rejection episodes (51% vs. 66%), a longer time to initial rejection (46 days vs. 8 days) and fewer rejections per patient (0.82 vs. 1.14) when compared to noninduction patients.² Several additional studies have affirmed these results.^{3,4}

Unfortunately, OKT-3 induction is not without its drawbacks, including significant adverse drug

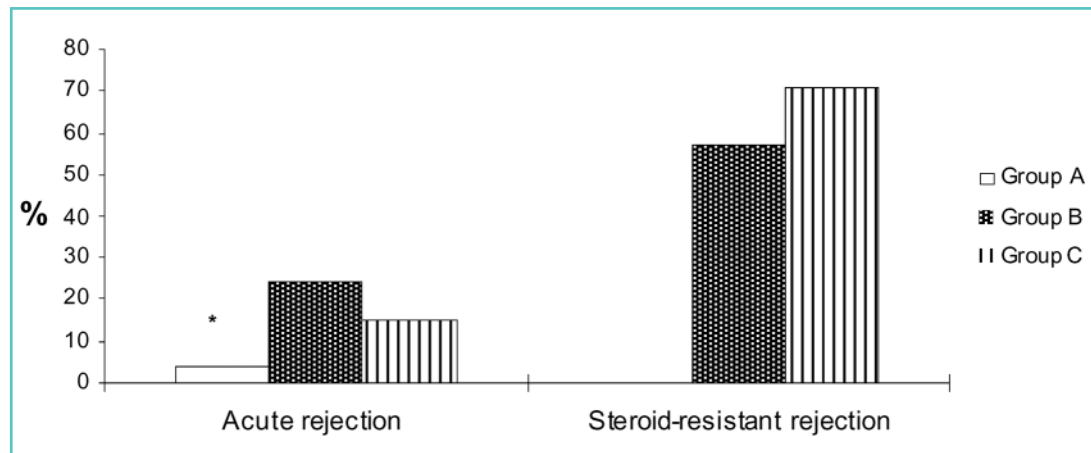


Figure 1. Incidence of first episode of biopsy-proven acute rejection. * $P < 0.05$, Group A vs. Groups B and C.

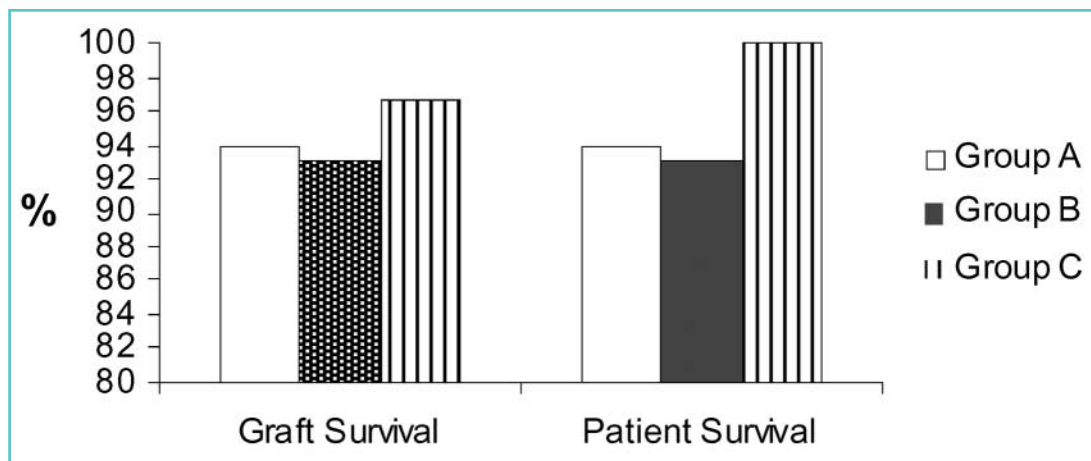


Figure 2. Graft and patient survival at 1 year following transplant.

reactions, elevated infection rates, and increased cost. Nearly 92% of patients experience hyperpyrexia and chills with the initial dose of OKT-3.⁵ Known as the “cytokine release syndrome,” this reaction is believed to result from lymphocyte opsonization and clearance with resulting significant cell lysis and cytokine release. Other reported side effects include flash pulmonary edema, aseptic meningitis, and seizures. Perhaps the most significant complication associated with prolonged OKT-3 use is infection. Studies show that an increased incidence of infection is associated with multiple exposures to the drug.⁵ Finally, with the current strong focus on cost containment, economic issues

must be considered. OKT-3 induction (5 mg/d for 10 to 14 days) is estimated to add \$8000 to the cost of transplantation.⁶

In response to these concerns, a number of groups have examined “low-dose” induction protocols. The conventional OKT-3 induction protocol is 5 mg intravenously per day for 10 to 14 days. The low-dose protocols have dosing schedules ranging from 0.5 to 2.5 mg intravenously per day for 10 to 14 days. The goal is to maintain the reduction in rejection episodes seen with the conventional protocol while decreasing the adverse side effects. Unfortunately, although all the studies reported that the low-dose protocols were effective in reducing

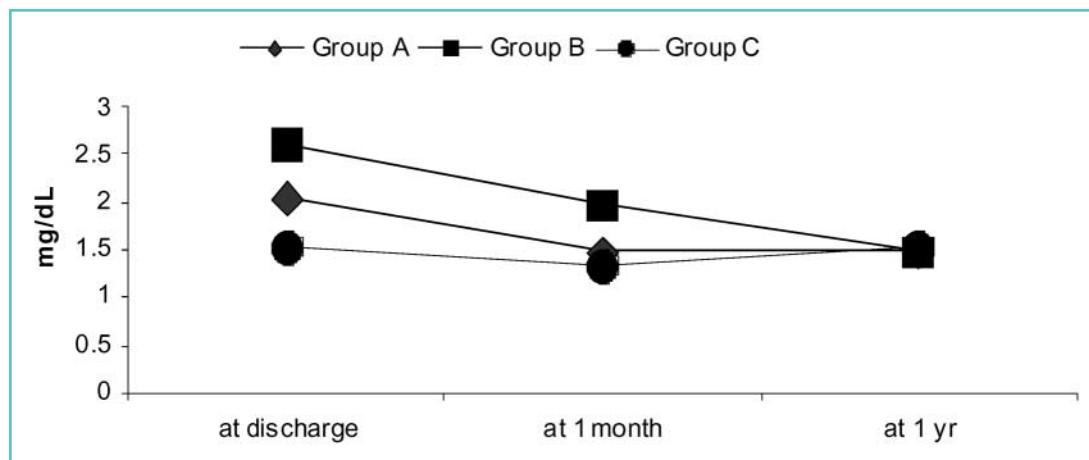


Figure 3. Allograft function as measured by serum creatinine (mg/dl).

rejection, no significant difference in the side effect profile was noted.⁷⁻¹⁰

Unable to limit the side effects of OKT-3 induction and with the introduction of several new immunosuppressive agents (e.g., tacrolimus [FK506], microemulsion CsA, MMF), many centers have turned to noninduction protocols using these agents. In recent randomized, multicenter clinical studies, use of these agents significantly reduced the rate of biopsy-proven rejection or treatment failure during the first 6 months after transplantation.¹¹⁻¹⁴ However, although these new noninduction protocols have proven to be more effective than the previous noninduction protocols, acute rejection remains in excess of 15% in kidney transplantation. Aware of the correlation of acute rejection episodes with decreasing graft survival, as well as the significant organ shortage facing the United States, we feel this level of acute rejection is unacceptable. Induction using OKT-3 had been proven effective in reducing acute rejection; overall, the goal was to maximize the antirejection benefits while minimizing side effects.^{2,7-10}

While considering the issues surrounding OKT-3 induction, we developed the novel concept of intraoperative single-dose induction. Previous work has shown a 5 mg total dose (0.5 mg/d for 10 days) to be as effective as conventional dosing in preventing acute rejection.⁸ We believed OKT-3 has such profound anti-T cell activity that a single 5-mg dose given intraoperatively would also prove effective.

Our single-digit (4%) acute rejection rate substantiates our hypothesis. Our cadaveric renal allograft group, which received single-dose intraoperative induction (Group A), experienced significantly fewer rejection episodes than Group B, the noninduction cadaveric renal allograft group, and more than that of Group A, the living-related renal allograft induction group. Due to the nonrandomized nature of our study, a disproportionately higher number of patients in Groups B and C received FK506-based primary immunotherapy. A subgroup analysis, however, failed to demonstrate any significant differences in episodes of rejection between FK506- and CsA-based groups. In this regard, it is important to note that a recent multicenter randomized trial comparing FK506 plus MMF or azathioprine and CsA plus MMF showed similar efficacy in preventing first episodes of biopsy-proven acute rejection in recipients of kidney transplantation.¹⁴

Perhaps most significant was the difference in the incidence of infection between the groups. A greater incidence of infection has been associated with the use of OKT-3, which becomes more significant with multiple exposures to the drug.⁵ Our study revealed that significantly fewer infections in the induction group (Group A) compared to the noninduction groups (Groups B and C) and a trend to a higher incidence of infection following rejection episodes in Groups B and C were noted. We believe that the decreased incidence of acute

OPSONIZATION:

The process by which bacteria are altered in such a manner that they are more readily and more efficiently engulfed by phagocytes.

Table 2 | INFECTIOUS COMPLICATIONS

	GROUP A	GROUP B	GROUP C
Number	49	29	46
Total infection, <i>n</i> (%)	10 (20.4)	11 (37.9)	21 (45.7)*
Bacterial, <i>n</i> (%)	5 (10.2)	7 (24.1)	12 (26.1)
Fungal, <i>n</i> (%)	2 (4.1)	0	0
Viral, <i>n</i> (%)	3 (6.1)	4 (13.3)	9 (19.6)
Cytomegalovirus (CMV), <i>n</i> (%)	2 (4.1)	3 (10.3)	4 (8.7)
Infection following rejection episodes	0	8 (27.3)	9 (19.6)
Infection following steroid resistant rejection	0	4 (13.8)	5 (10.8)

**P* < 0.05, Group A compared with Groups B and C.

rejection of the induction group results in decreasing the exposure to highly immunosuppressive rescue therapies and their coincident opportunistic infections.

In addition, an intraoperative protocol would eliminate the adverse drug reactions associated with serial dosing, including cytokine release syndrome. The complication of flash pulmonary edema is reduced secondary to the controlled fluid status and the secured airway (via the endotracheal tube). As expected, patients reported no side effects, nor did the transplant surgeons or anesthesiologists note any significant changes in physiologic parameters intraoperatively.

Finally, there is the economic issue. The average cost of conventional OKT-3 induction is estimated at \$8000,⁶ and the total administration cost of our single-dose protocol was approximately \$800. Past studies suggest that the long-term cost of convention induction therapy with OKT-3 is offset by decreased hospitalization costs for rejection episodes. To date, we have not reviewed the cost data among our groups. It is plausible, however, that if \$8000 is offset long term, our cost may not only be offset but prove more economic than non-induction protocols.

In summary, our result shows that when compared with single-dose OKT-3 induced cadaveric transplant patients, episodes of acute rejection and infectious complications are significantly higher in the noninduced cadaveric recipients and better HLA-matched living-related recipients. In conclusion, single-dose intraoperative OKT-3 induction,

when used in combination with either FK506/MMF or CsA/MMF, significantly reduces episodes of acute rejection to less than 10%.

Acknowledgment

The authors are enormously grateful to Christopher Y. Lu, MD, University of Texas Southwestern Medical Center (Dallas, TX), for the editorial review and helpful suggestion in preparation of this manuscript.

REFERENCES

- Burk ML, Matuszewski KA. Muromonab-CD3 and antithymocyte globulin in renal transplantation. *Ann Pharmacother* 1997;31:1370-7.
- Norman DJ, Kahana L, Stuart FP Jr, Thistlethwaite JR Jr, Shield CF III, Monaco A, et al. A randomized clinical trial of induction therapy with OKT3 in kidney transplantation. *Transplantation* 1993;55:44-50.
- Beilman GJ, Shield CF III, Hughes JD, Kelley HK, Ward LG, Beck D. The effects of intraoperative administration of OKT3 during renal transplantation. *Transplantation* 1993;55:490-3.
- Abramowicz D, Goldman M, De Pauw L, Vanherweghem JL, Kinnaert P, Vereerstraeten P. The long-term effects of prophylactic OKT3 monoclonal antibody in cadaver kidney transplantation: a single-center, prospective, randomized study. *Transplantation* 1992;54:433-7.
- Thistlethwaite JR Jr, Stuart JK, Mayes JT, Gaber AO, Stuart FP. Use of a brief steroid trial before initiating OKT3 therapy for renal allograft rejection. *Am J Kidney Dis* 1988;11:94-8.
- Shield CF III, Jacobs RJ, Wyant S, Das A. A cost-effectiveness analysis of OKT3 induction therapy in cadaveric kidney transplantation. *Am J Kidney Dis* 1996;27:855-64.
- Oh HK, Provenzano R, Tayeb J, Salmay N, Jones B. Two low-dose OKT3 induction regimens following renal transplantation: clinical experience at a single center. *Clin Transplant* 1998;12:343-7.
- Parlevliet KJ, ten Berge RJ, Raasveld MH, Surachno J, Wilmink JM, Schellekens PT. Low-dose OKT3 induction therapy following renal transplantation: a controlled study. *Nephrol Dial Transplant* 1994;9:698-703.
- Alloway R, Kotb M, Hathaway DK, Gaber LW, Vera SR, Gaber AO. Randomized double-blind study of standard versus low-dose OKT3 induction therapy in renal allograft recipients. *Am J Kidney Dis* 1993;22:36-43.

10. Norman DJ, Kimball JA, Bennett WM, Shihab F, Batiuk TD, Meyer MM, et al. A prospective, double-blind, randomized study of high- versus low-dose OKT3 induction immunosuppression in cadaveric renal transplantation. **Transpl Int** 1994;7:356-61.
11. Frei U, Taesch S, Niese D. Use of Sandimmun CsA in renal transplant patients. International Sandimmun CsA Study Group. **Transplant Proc** 1994;26:2928-31.
12. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. **Transplantation** 1997;63:977-83.
13. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. **Transplantation** 1995;60:225-32.
14. Johnson C, Ahsan N, Gonwa T, et al. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (CsA) with mycophenolate mofetil after cadaveric kidney transplantation. **Transplantation** 2000;69:834-41.