Association of Antibody Induction with Short- and Long-Term Cause-Specific Mortality in Renal Transplant Recipients

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Abstract. A total of 73,707 primary renal transplants reported to the USRDS between 1988 and 1997 were examined to investigate the cause-specific risk for patient death associated with anti-lymphocyte antibody induction therapy (ABI). Cox proportional hazard models were used to estimate the relative risk of the use of ABI and patient death. All Cox models were corrected for potential confounding variables, such as age, gender, race, HLA mismatch, panel reactive antibody, delayed graft function, cold ischemia time, time since start of dialysis, etiology of end-stage renal disease, cytomegalovirus risk group, donor source (living or cadaveric), era effect, and immunosuppressive therapy. Primary study end points were patient death with functioning graft (DWFG) and overall patient death, including death after graft loss. Early patient death (deaths within the first 6 mo after renal transplantation) and late death (deaths after 6 mo post–renal transplantation) were investigated separately. Additionally, specific causes of death were investigated. ABI was associated with a significant risk for late death after renal transplantation (relative risk [RR] = 1.1; $P < 0.001$) but not for DWFG (RR = 0.94; $P = 0.10$). ABI conferred the highest RR for late malignancy–related death (RR = 1.35; $P < 0.001$). ABI was significantly associated with early deaths due to infection and cardiovascular causes (RR = 1.32 [$P < 0.001$] and RR = 1.27 [$P < 0.001$], respectively). Kaplan Meier plots confirmed that the risk of ABI for patient death secondary to infectious complications was increased predominately early after transplantation as opposed to late for malignancy-related death. ABI was associated with a significant relative risk for patient death secondary to cardiovascular causes and infectious complications early in the posttransplant period. In addition, ABI was associated with a significant risk for long-term malignancy-related death. The risk of ABI should be taken in context with potential benefits of this therapy.

Use of polyclonal anti-lymphocyte antibodies, derived either from equine sera (ALG, ATGAM) or from rabbit sera (ATG), immediately after renal transplantation for rejection prophylaxis (induction therapy) has been common clinical practice for several decades (1,2). In addition, the monoclonal anti–T cell agent OKT3 has also been widely used as an induction agent (3). The impact of these agents on long-term outcomes in renal transplantation remains controversial. However, strong evidence exists for efficacy (in terms of graft survival) in some subgroups of high-risk patients (*e.g.*, patients with high panel reactive antibodies [PRA], repeat transplantation, and delayed graft function [DGF]) (4–7).

For the most part, reports addressing the use of lymphocyte antibodies as induction agents in the literature have focused on the efficacy of these agents and have not explored the potential associated morbidity and mortality. The low incidence of some of the potential morbidities associated with antibody induction therapy and the long time to endpoints make it inherently difficult to ascertain differences through single-center reports. An association between posttransplant lymphoproliferative disorder and OKT3 has been noted after cardiac transplantation (8), and it is thought that a similar association exists among renal transplant recipients, particularly in Epstein-Barr virus–negative individuals (9,10). In addition, antibody induction has also been associated with a greater incidence of cytomegalovirus infection (11,12).

In a recent analysis of the United States Renal Data System (USRDS), no association could be ascertained between early sepsis and the use of antibody induction (13). However, a separate clinical study did note more infections with the use of OKT3 than with the use of a polyclonal antibody (14). Other than these reports, little else has been written on the potential morbidities associated with the use of these powerful antilymphocyte preparations. We analyzed USRDS renal transplant patient data to address the question of whether the use of either polyclonal antilymphocyte antibody induction therapy or OKT3 induction therapy were associated with either short- or long-term increased risk for cause-specific mortality.

Materials and Methods

The study population was composed of 73,707 primary adult renal transplant recipients registered in the USRDS database between 1988 and 1997. Patients were followed from transplant date until death or 1998. Primary study end points were patient death within 6 mo posttransplant (early death) and death after 6 mo after renal transplantation (late death). For late death, we investigated death with functioning graft (DWFG) and overall death, including death after graft loss, separately. Additionally, we analyzed cause-specific mortality

risks such as cardiovascular death, infection-related death, and death due to malignancy.

Kaplan Meier analyses were used to describe the cumulative risk for cause-specific mortality after renal transplantation in patients receiving antibody induction therapy as compared with patients who did not receive antibody induction therapy.

Cox proportional hazard models were used to estimate the relative risk (RR) associated between the use of antibody induction and the study end points. All Cox models were corrected for potential confounding variables, such as age, gender, race, HLA mismatch, PRA, DGF, cold ischemia time, time since the start of dialysis, etiology of end-stage renal disease, cytomegalovirus risk group, donor source, era effect, and immunosuppressive therapy. In the analysis for death after 6 mo, we also corrected the model for the occurrence of rejection within the first 6 mo after transplant.

A probability of type 1 error ($\alpha = 0.05$) was considered to be the threshold of statistical significance. All statistical analyses were performed using SPSS software (Version 10.0 for Windows NT, SPSS, Inc., Chicago, IL).

Results

Table 1 depicts the demographics of the patients studied. A total of 73,707 primary renal transplant patients were analyzed. One-third of all patients analyzed over this period of time received induction therapy. There was a trend for more African Americans, cadaveric transplants, and diabetics to receive induction therapy as opposed to other comparators. Table 2 depicts the distribution of posttransplant deaths among all patients. A total of 14,463 patients died during the study period. The majority of these patients died more than 6 mo posttransplantation. Cardiovascular disease was the most common cause of death, both short- and long-term, with little change in the proportion of death it accounted for between the short- and long-term.

Table 3 depicts the multivariate analysis for the risk of early deaths within 6 mo after renal transplantation. Antibody induction was associated with a significantly increased RR for overall patient death (RR = 1.13; confidence interval [CI] = 1.04 to 1.22; $P < 0.001$). Antibody induction was also significantly associated with an elevated risk for cardiovascular death (RR = 1.27; CI = 1.12 to 1.44; $P < 0.001$) and infection-related death (RR = 1.32; CI = 1.14 to 1.45; $P < 0.001$).

Table 4 depicts the multivariate analysis for the risk of late deaths (after 6 mo after renal transplantation). Antibody induction was associated with a significantly increased RR for overall patient death (RR = 1.10; CI = 1.05 to 1.15; $P < 0.001$). In contrast, antibody induction was not significantly associated with patient death with functioning graft (RR = 0.94; CI = 0.88 to 1.01; $P = 0.10$). Antibody induction was significantly associated with an elevated risk for cardiovascular death (RR = 1.17; CI = 1.10 to 1.25; $P < 0.001$), infection-related death (RR = 1.16; CI = 1.04 to 1.30; $P = 0.011$), and death due to malignancy (RR = 1.35; CI = 1.15 to 1.59; $P < 0.001$).

Figure 1 depicts the cumulative risk for infectious death by Kaplan Meier analysis. There was a significantly higher cumulative risk for infection-related death for patients receiving antibody induction *versus* no antibody induction death (7.8% increase over 8 yr of follow up; $P < 0.001$). Figure 2 depicts the cumulative risk for malignancy-related death. Patients receiving antibody induction had a significantly higher risk for malignancy-related death when compared with patients receiving no antibody induction (27% risk increase over 8 yr of follow up; $P < 0.001$).

Discussion

Our analysis indicates that standard antibody induction (ABI) with either polyclonal antilymphocyte antibodies or OKT3 is associated with a significantly increased risk for death after renal transplantation, including certain cause-specific mortalities. Antibody induction was associated with significantly increased risks for infectious and cardiovascular deaths during the first 6 mo after renal transplantation. The increased risk for infectious death would intuitively make sense. The greater immunosuppression caused by these agents might be expected to leave some patients more vulnerable to serious infections proximate to the time receiving these agents.

The increase in cardiovascular deaths in the early period after renal transplantation might be explained by either the procoagulant effects of these drugs or perhaps the stress of the cytokine release accompanying the administration of these biologic agents (15–17). The long-term cardiovascular risk might be related to early cardiovascular damage, which translates into increased late cardiovascular mortality.

The strongest association between antibody induction and mortality in the long term was observed with the risk for malignancy-related death. Antibody induction (*versus* patients who did not receive ABI) was associated with a 27% increased risk for malignancy-related death by univariate analysis and a

Table 1. Patient demographics

Parameter	Total (n)	No Induction (%)	Induction (%)
Gender			
male	44,214	67.8%	32.2%
female	29,263	68.5%	31.5%
Recipient race			
White	52,118	68.7%	31.3%
African American	16,767	64.0%	36.0%
other	4822	75.1%	24.9%
Primary diagnosis[a]			
GN	16,845	71.9%	28.1%
HTN	12,749	68.0%	32.0%
DM	19,469	62.5%	37.5%
Donor source			
living	18,297	80.8%	19.2%
cadaveric	55,410	63.9%	36.1%
Six antigen match			
yes	5381	87.0%	13.0%
no	68,326	66.6%	33.4%
Recipient age (yr)	43.5 ± 12.7	43.5 ± 12.9	43.6 ± 12.3
Donor age (yr)	33.9 ± 15.4	34.1 ± 15.2	33.7 ± 15.7
Time on dialysis (mo)	22.6 ± 28.0	22.1 ± 28.0	23.5 ± 28.1
Cold ischemia time (h)	17.3 ± 11.9	16.6 ± 12.1	18.7 ± 11.3

[a] GN, glomerulonephritis; HTN, hypertension; DM, diabetes mellitus.

Table 2. Causes of death

	All Posttransplantation Deaths	Early Deaths (<6 mo posttransplantation)	Late Deaths (>6 mo posttransplantation)
All deaths	14,463	3032	11,431
Cardiovascular death	5690 (39.3%)	1172 (38.7%)	4518 (39.5%)
Infectious death	2339 (16.2%)	794 (26.1%)	1545 (13.5%)
Malignancy death	778 (5.4%)	56 (1.8%)	722 (6.3%)
Other death	60.9%	66.6%	59.3%

Table 3. Multivariate analysis of the risk for death within 6 mo posttransplant, antibody *versus* no antibody induction[a]

Variable	Events (*n*)	RR	95% CI	*P*
All patient death	2943	1.13	1.04 to 1.22	< 0.001
Cardiovascular death	1150	1.27	1.12 to 1.44	< 0.001
Infectious death	790	1.32	1.14 to 1.45	< 0.001

[a] Cox model corrected for age, gender, race, HLA mismatch, % panel reactive antibodies (PRA), delayed graft function (DGF), cold ischemia time, dialysis time, etiology of end-stage renal disease, cytomegalovirus (CMV) risk group, donor source, era effect, and immunosuppressive therapy. RR, relative risk; CI, confidence interval.

Table 4. Multivariate analysis of the risk for death beyond 6 mo after renal transplantation; antibody *versus* no antibody induction[a]

	Events (*n*)	RR	95% CI	*P*
DWFG	4590	0.94	0.88 to 1.01	0.10
Overall death	11,404	1.10	1.05 to 1.15	< 0.001
Cardiovascular death	4503	1.17	1.10 to 1.25	< 0.001
Infectious death	1541	1.16	1.04 to 1.30	0.011
Cancer death	718	1.35	1.15 to 1.59	< 0.001

[a] Cox model corrected for gender, race, HLA mismatch, % PRA, DGF, cold ischemia time, dialysis time, etiology of end-stage renal disease, CMV risk group, donor source, era effect, immunosuppressive therapy, and occurrence of acute rejection within the first 6 mo posttransplant. DWFG, death with functioning graft.

Figure 1. Cumulative risk for infection-related death.
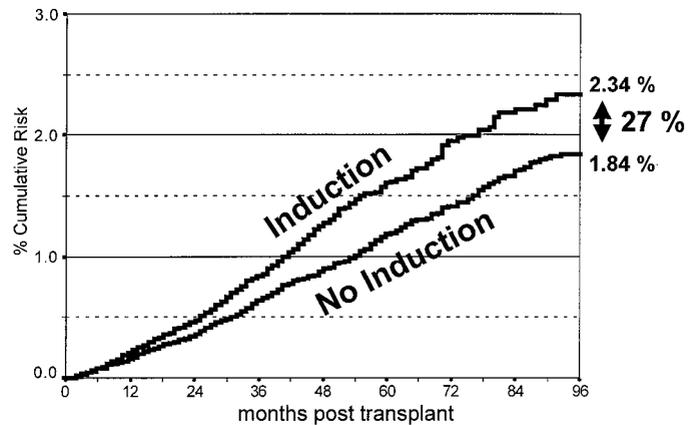
Figure 2. Cumulative risk for cancer-related death.

35% increased risk by multivariate analysis over the 8-yr follow-up period. It is important to note that the divergence in the Kaplan-Meier curve between the antibody induction group and the non-antibody induction group seems to continue as far out as 8 yr. It should also be noted that, although the incidence of malignant death is low, the incidence of malignancy must be considerably higher among the ABI group to achieve this markedly increased risk for the final end point of patient death.

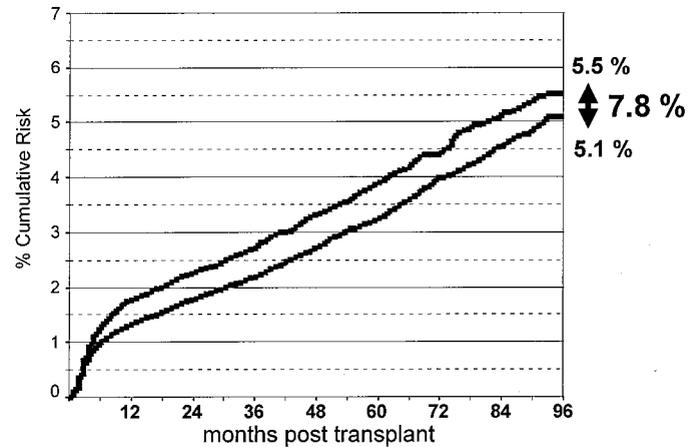It is interesting to note that although there was a significantly higher long-term risk for overall mortality in patients receiving antibody induction, no significant association between antibody induction and mortality could be detected when DWFG was the end point in the analysis. This further emphasizes the point that in studies aimed to detect the potential negative effects of therapies, patients need to be followed even after graft loss to the point when they resume maintenance dialysis treatment.

As opposed to previous analyses, we chose to follow patients throughout their lifetime, as patients with end-stage renal disease. The USRDS database allowed us to extend the follow-up beyond the return to dialysis and even after retransplantation as opposed to only during the period of primary graft

survival. This is one of the distinguishing points of this analysis, which might explain the differences among our results and those of previous studies.

Furthermore, we chose to split our analysis into early and late mortality risk. Our hypothesis was that the risk for certain end points would manifest mostly in the short term (*e.g.*, infection-related death) while others (*e.g.*, malignancy-related death) may only manifest after many years of follow-up. Antibody induction was associated with an increased mortality risk secondary to cardiovascular disease in the short and long term, reflecting a possible damage induced during time of administration of the drug but with variable latency before this damage translated into the final clinical end point of cardiovascular death.

This analysis is not a risk/benefit analysis for antibody induction therapy. Renal transplantation confers a significant survival advantage compared with maintenance dialysis (18). It is possible that if antibody induction therapy in certain high-risk groups extends the survival of the renal allograft, the effect of the longer period with a functioning graft would override the negative effect associated with antibody induction and ultimately constitutes a life expectancy gain. The present report merely quantifies the prior unknown association of antibody induction with patient death but does not address life expectancy differences in patients who potentially need antibody induction to maintain the function in their renal allograft. In addition, our study only investigated standard antibody induction therapy and not antibody use for treatment of rejection.

In conclusion, antibody induction with either polyclonal antilymphocyte agents or OKT3 is associated with a short-term increased risk of cardiovascular and infectious death. In addition, ABI is associated with a long-term increased risk of malignancy-related death. These results should be considered in any risk/benefit analysis of the use of these agents for induction therapy among renal transplant recipients.

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