

Ten-year Follow-up of Basiliximab Induction Therapy for Live-donor Kidney Transplant: A Prospective Randomized Controlled Study

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Abstract

Objectives: The effect of basiliximab induction therapy on long-term patient and graft survival is not clear. We sought to evaluate if there is any advantage to routine basiliximab induction on the long-term outcome of living-related donor kidney transplants.

Materials and Methods: One hundred adult recipients with their first kidney allograft were randomized into 2 treatment groups; 1 group received basiliximab, and the second served as a control. All patients received a maintenance triple immunosuppressive therapy (steroids, cyclosporine, microemulsion, and azathioprine). We followed them for 10 years.

Results: Basiliximab reduced the proportion of patients who experienced an acute rejection in the first year (18/50) when compared with the control group (31/50) ($P = .009$), and in 10 years (28/50) when compared with controls (37/50) ($P = .059$). The cumulative steroid dosage used throughout the study was significantly lower in the basiliximab group. The overall incidence of posttransplant complications was comparable among the 2 groups. There was no significant difference in patient and graft survival; 10-year patient and graft survival were 92% and 76% for basiliximab and 90% and 68% for the control group.

Conclusions: Routine basiliximab induction significantly reduces the incidence of acute rejection without any noticeable effects on the long-term renal transplant outcome.

Key words: Basiliximab, IL2 receptor antagonists, Renal transplant

Introduction

Minimizing acute rejection after renal transplant remains a clinical priority in view of its prognostic implications for subsequent graft loss.^{1, 2} Induction therapy is a common practice in many transplant centers to prevent occurrence of acute rejection after kidney transplant. It has been reported that interleukin-2 receptor antagonists (IL-2RAs) may provide selective immunosuppression without augmented morbidity and/or over-immunosuppression.³⁻⁵

In adult recipients, a series of multicenter, randomized trials in the late 1990s consistently demonstrated a 30% to 40% reduction in the incidence of biopsy-proven acute rejection with addition of IL-2RA induction to a regimen of cyclosporine and steroids, with or without azathioprine.⁶⁻⁹

We previously reported that the use of routine basiliximab induction in live-donor renal transplant significantly reduced the incidence of acute rejection in the first year but without beneficial effects on patient and graft survival up to 7 years after transplant.¹⁰⁻¹² To the best of our knowledge, this is the first study that evaluates long-term consequences of routine basiliximab induction therapy in live-donor renal transplant after 10 years' follow-up.

Patients and Methods

This study was a prospective, randomized study where 100 adult patients who had received their first live-donor renal transplant in our institution between June 1998 and June 1999 entered the study after obtaining informed consent. The study protocol was

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approved by our local institutional ethics committee and conforms with the ethical guidelines of the 1975 Helsinki Declaration.

Immunologic workup

Before transplant, all patients and their live donors had an immunologic workup including the cross-match and tissue typing for human leucocyte antigen (HLA) class I with standard lymphocyte microtoxicity test. Whereas HLADRB*1 allele typing was done by INNO-LiPA (Innogenetics Biologicals, Gent, Belgium) through 3 steps: (1) DNA extraction by Generation Capture Column Kit (GENTRA CORP, Houston, TX, USA); (2) polymerase chain reaction amplification; and (3) detection of HLADRB*1 where the LiPA HLA typing is a line probe assay based on the reverse hybridization principle.¹³

Study design

Patients were randomly assigned to 1 of the 2 treatment groups. The participant physicians were necessarily aware of the randomized treatment in all cases. One group received basiliximab, the second served as a control. Basiliximab was given intravenously in 2 doses (20 mg each); the first was given 2 hours preoperatively and the second on day 4 after transplant. All patients in both groups received triple immunosuppressive therapy (steroids, cyclosporine microemulsion, and azathioprine).

A rising serum creatinine of 17.68 $\mu\text{mol/L}$ above the baseline was an indication for a graft biopsy to determine the probable histopathologic diagnosis of either rejection, cyclosporine nephrotoxicity, or other diseases. We assessed the histopathologic findings using Banff Schema, 1997.¹⁴ Acute rejection episodes were treated by intravenous steroids.

Endpoints of evaluation

The observation period was a minimum of 120 months; graft and patient survival were determined; the number of biopsy-proven rejection episodes was noted; cumulative steroid dosage was calculated; incidence and type of possible adverse effects secondary to basiliximab therapy were observed; and graft function was assessed by serial estimation of serum creatinine and creatinine clearance.

Statistical analyses

To compare continuous data, the *t* test was used. The chi-square test was used to compare simple

proportions. Patient and graft survival were computed using Kaplan-Meier technique. Differences in survival were calculated by the log-rank test. Values for *P* less than .05 were considered statistically significant.

Results

The demographic characteristics of both groups are summarized in Table 1. There was a statistically significant reduction in the incidence as well as in the severity of acute rejection among the basiliximab-treated patients during the first year of follow-up.

Table 1. Demographic characteristics of both groups¹.

Variable ²	Basiliximab (n=50)	Control (n=50)
Age (y) (mean $\pm$ SD)	32.9 $\pm$ 9.9	32.5 $\pm$ 10.8
Sex (M/F)	44/6	41/9
Body weight (Kg) (mean $\pm$ SD)	62.6 $\pm$ 13.1	63.7 $\pm$ 15.1
Duration of dialysis (y) (mean $\pm$ SD)	1.6 $\pm$ 3.2	1.4 $\pm$ 1.3
History of third party blood transfusion	26	27
Hepatitis C	6	7
Hepatitis B	0	2
HLA and DR mismatching		
Less than 3 mismatch	9	9
3 Mismatches	34	31
4 Or more mismatches	7	10
Mixed lymphocytic response (number)		
1-3:1	25	29
> 3:1	3	5
Consanguinity		
Parents	12	14
Siblings	29	24
Offspring and others	9	12
Original kidney disease		
Chronic pyelonephritis	11	10
Glomerulonephritis	9	8
End-stage kidney (histopathologic diagnosis)	4	4
Amyloid	2	1
Uncertain (small kidneys)	24	26

¹*P* value > .05

²All continuous variables are presented as a means $\pm$ standard of deviation and qualitative variables as a sum number of patients.

At the end of the 10th year of follow-up, there was a trend toward a lower incidence of acute rejection in the basiliximab group. Furthermore, the basiliximab-treated group had a significantly less-severe acute rejection. The cumulative steroid dosage required during the first year and/or the 10-year period was higher among the control group. However, at the end of the follow-up, there was no significant difference in the prevalence of chronic allograft nephropathy in both groups (Table 2).

The majority of acute rejection episodes in both groups responded to methyl prednisolone therapy; however, we used antithymocyte globulin to treat

Table 2. Rejection episodes, Banff grading, and cumulative steroid therapy.

Variable ¹	Basiliximab (n=50)	Control (n=50)	P
Number of patients who experienced acute rejection episodes during the first year	18	31	.009
Number of acute rejection episodes during the first 12 months	29	45	.009
Severity of rejection (Banff grading):			
Borderline and grade I	27	35	.008
Grade II and grade III	2	10	
Number of patients who experienced acute rejection episodes during the 10-year follow-up	28	37	.059
Severity of rejection episodes (Banff grading) during the 10 years			.032
- Borderline and grade I	41	44	
- Grade II and grade III	3	11	
Number of acute rejection episodes during the 10 years	44	55	.061
Number of patients who had chronic allograft nephropathy (biopsy based) during the 10-year follow-up	12	17	.271
Cumulative steroid dosage (g) (mean $\pm$ SD)			
- During the first year	8.6 $\pm$ 2.3	9.9 $\pm$ 2.7	.010
- During the 10-year follow-up	27.3 $\pm$ 3.5	29.1 $\pm$ 4.3	

¹All continuous variables are presented as a means $\pm$ standard of deviation, and qualitative variables as a sum number of patients.

steroid-resistant severe rejection (grade 2 and grade 3) for 2 patients in the basiliximab group and 4 patients in the control group. Moreover, 1 patient in the control group did not respond to antithymocyte globulin and returned back to hemodialysis.

After 10 years, 4 patients died in each group owing either to cardiovascular-related, or severe pneumonia and respiratory failure. There was no difference in the

Table 3. Medical complications during 10 years follow up¹.

	Basiliximab (number)	Control (number)
Infection		
Cytomegalovirus infection	4	4
Herpes zoster	2	6
Urinary tract infection	4	5
Pneumonia	2	2
Urinary tuberculosis	1	1
Malignancy		
Cutaneous Kaposi sarcoma	2	3
Diabetes mellitus	5	7
Hypertension	39	43
Persistent high liver enzymes	3	1
Avascular hip necrosis	4	4
Histopathologic diagnoses (other than rejection):		
Acute cyclosporine nephrotoxicity (histopathologic)	5	4
Hemolytic uremic syndrome	1	1
Pyelonephritis	0	1
Recurrence of original kidney disease	1	1
Graft failure	12	16

¹P > .05

incidence or distribution of late medical complications among the 2 groups (Table 3). Histopathologic diagnoses rather than rejection are summarized in Table 3.

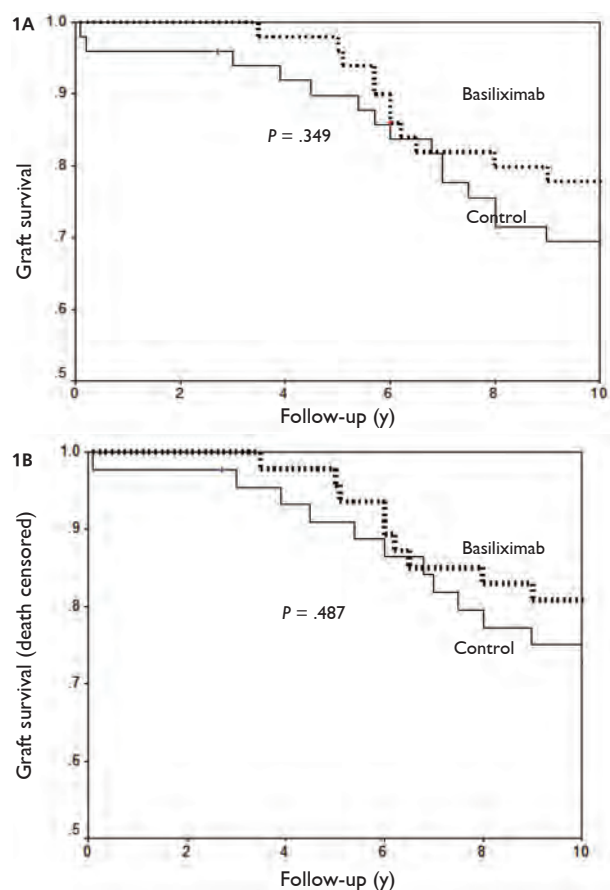
There was no significant difference between both groups regarding graft function (as determined by estimation of serum creatinine and creatinine clearance). Also, we did not find a difference between either group regarding cyclosporine level (Table 4).

Figures 1 and 2 illustrate the actuarial graft and patient survival of the 2 groups. There was no

Table 4. Graft function and cyclosporine levels¹.

	Basiliximab (mean $\pm$ SD)	Control (mean $\pm$ SD)
Serum creatinine (μ mol/L) :		
At the end of the first year	126.41 $\pm$ 3.54	128.18 $\pm$ 35.36
At 10th year of follow-up	150.28 $\pm$ 70.72	141.44 $\pm$ 44.2
Creatinine clearance (mL/min)		
At the end of the first year	75.04 $\pm$ 14.08	72.0 $\pm$ 12.9
At 10th year of follow-up	64.1 $\pm$ 15.2	65.5 $\pm$ 14.1
Cyclosporine levels		
At the end of the first year (ng/mL)	147.24 $\pm$ 10.72	144.46 $\pm$ 12.05
At 10th year of follow-up	113.3 $\pm$ 13.6	116.2 $\pm$ 14.4

¹P > .05

**Figure 1.** Graft survival.

1A. Actuarial graft survival.

1B. Death censored graft survival.

significant difference in patient and graft survival; 10-year patient and graft survival were 92% and 76% for basiliximab and 90% and 68% for control group.

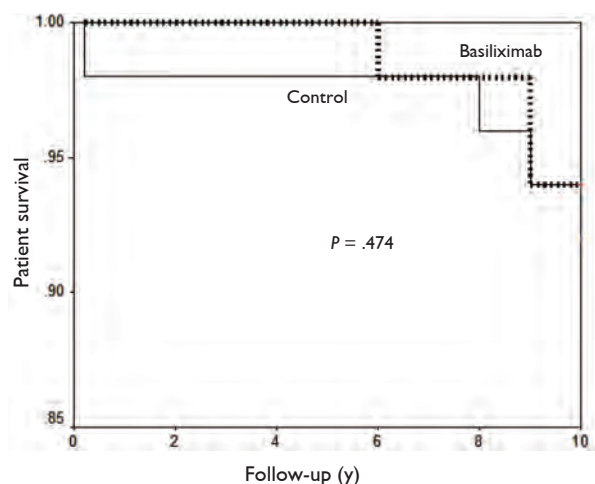


Figure 2. Actuarial patient survival.

Discussion

Since their introduction as induction therapeutic agents in the field of clinical transplantation, interleukin-2 receptor antagonists, basiliximab, and daclizumab continue to prove effective in preventing acute rejection episodes as well as being well-tolerated drugs.^{15, 16}

Although, the additive immunosuppressive effect of basiliximab is short-lived to cover the critical period immediately after renal transplant, we sought to explore if the addition of basiliximab to the triple immunosuppressive regimen including steroids, cyclosporine microemulsion, and azathioprine will improve the long-term outcome of renal transplant.

Nevertheless, Baudouin and associates reported the occurrence of anaphylactic shock caused by immunoglobulin E sensitization after retreatment with basiliximab¹⁷; none of our patients experienced such a complication.

Many published reports comparing basiliximab to antithymocyte globulin as induction therapy failed to prove superiority of the latter to the former in view of better patient and graft survival rates¹⁸⁻²⁰ or incidence of acute rejection²⁰ and without the hemodynamic and pulmonary adverse effects encountered with antithymocyte globulin.¹⁹

Almetuzumab has not been shown to be better than basiliximab regarding long-term patient and graft survival rates.²¹ Moreover, alemtuzumab induction therapy was comparable to basiliximab in a

prednisone-free maintenance immunosuppressive protocol for ethnically diverse population of kidney transplant recipients.²²

Basiliximab therapy may be considered an economic savings during the first year after transplant owing to a reduction in the cost of hospitalization, graft biopsy, and treating acute rejection especially steroid resistant episodes.^{23, 24}

Our results show that the 10-year graft survival was 76% and 68% for basiliximab and control group. This difference is not necessarily irrelevant. Just because a difference is not statistically significant does not mean there is no difference. With larger patient numbers, such a difference might become statistically significant. In conclusion, basiliximab induction is safe, and significantly reduces the incidence and severity of acute rejection in the first year after renal transplant; however, this was not translated to improve patient and graft survival in the long term.

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