Basiliximab reduces the incidence of acute cellular rejection in live-related-donor kidney transplantation: A three-year prospective randomized trial

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ABSTRACT: *Background:* **The aim of this work was to investigate the benefit of basiliximab induction therapy in living-related-donor kidney transplantation.**
Methods: **One hundred adult recipients of a first kidney allograft were randomized into two treatment groups, one to receive basiliximab and the second as a control. All patients received maintenance triple immunosuppressive therapy (steroids, cyclosporine microemulsion and azathioprine). The patients were followed up for a minimum of three years. The end points for evaluation included the incidence of acute rejection episodes, severity of rejection, cumulative steroid dose, patients' and graft survival.**
Results: **Basiliximab significantly reduced the proportion of patients who experienced an acute rejection in the first year (18/50) compared to the control group (31/50). At three years there were 26 acute rejections in the basiliximab group and 36 in control group. The cumulative steroid dose at three and 12 months was significantly lower in the basiliximab group. The overall incidence of post-transplant complications was comparable in the two groups.**
Conclusions: **Prophylactic basiliximab is well tolerated and significantly reduces the incidence of acute rejection episodes in living-related-donor kidney transplantation.**

Key words: *Basiliximab, Kidney transplantation, Acute rejection*

INTRODUCTION

The benefits of induction therapy using anti-T-cell antibodies are established (1-4). However, these agents may give rise to several side effects (5,6). Monoclonal antibodies against IL-2 receptor have now been introduced and tested in the clinical setting (7). It is claimed that these agents allow selective immunosuppression without morbidity or over-immunosuppression (8). Although there are reports of their therapeutic advantage in cadaveric renal transplantation (9-11), experience in the living-related-donor setting is limited (12).
The purpose of this investigation was to determine the safety and efficacy of one of these agents, Basiliximab (Simulect®, Novartis, Basel, Switzerland) in patients receiving living-related-donor transplants in one center.

PATIENTS AND METHODS

Study design. One hundred adult patients receiving their first transplant from a living-related-donor were studied, between June 1998 and June 1999. Eligible patients were prospectively randomized into two treatment groups, one to receive basiliximab, and the second as control. Basiliximab was given intravenously in two doses of 20 mg each, the first 2 hours preoperatively and the second on day 4 after transplantation. All patients in both groups received triple immunosuppressive therapy (steroids, cyclosporine microemulsion and azathioprine). Steroids were given by intravenous infusion, 500 mg on the day of transplantation (day 0) and 250 mg the next day, followed by oral prednisolone 1.5 mg/kg/day, gradually tapered to 0.3 mg/kg /day at the end of the first month and 0.15 mg/kg/day at the ninth month and there-

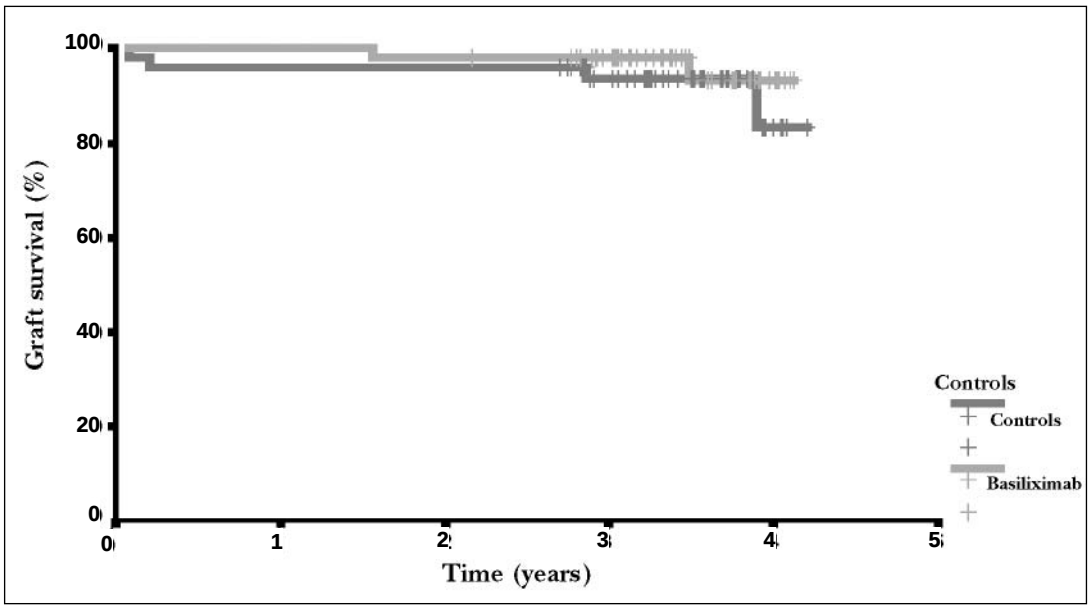

Fig. 1 - Actuarial Graft Survival.

after. Oral azathioprine 1 mg/kg/day was given from the third day after transplantation. Oral cyclosporine (Neoral) was started two days before transplantation, 8 mg/kg/day in two divided doses, and was readjusted according to the whole blood trough level which was kept between 200-300 ng/mL during first month, 125-150 ng/mL till the end of the sixth month and 100-125 ng/mL thereafter. Patients were regularly followed up clinically and biochemically for evidence of rejection and side effects.

A rise in serum creatinine of 0.2 mg/dL above the baseline was an indication for graft biopsy to check for acute rejection, cyclosporine nephrotoxicity or other pathologies. Biopsy-proven episodes of rejection were graded according to the Banff 97 classification (13). Acute rejection episodes were treated by intravenous steroids.

End points for evaluation. The observation period was at least 36 months. Graft and patients' survival was recorded, the number of biopsy-proven rejection episodes was noted, and the cumulative steroid dose was calculated. The incidence and type of side effects

TABLE I - DEMOGRAPHIC CHARACTERISTICS

	Basiliximab (n=50)	Control (n=50)
1. Age (y) (mean±SD)	32.9 ± 9.9	32.5 ± 10.8
2. Sex (M/F)	44/6	41/9
3. Body weight (kg) (mean±SD)	62.6 ± 13.1	63.7 ±15.1
4. Duration of dialysis (y) (mean±SD)	1.6 ± 3.2	1.4 ± 1.3
5. History of third party blood transfusion	26	27
6. Hepatitis C (PCR)	6	7
7. Hepatitis B (HbsAG)	0	2
8. HLA and DR mismatching		
Less than three mismatches	9	9
Three mismatches	34	31
Four or more mismatches	7	10
9. Mixed lymphocytic response (number)		
1-3:1	25	29
> 3:1	3	5
10. Consanguineity		
Parents	12	14
Siblings	29	24
Offspring and others	9	12

related to basiliximab therapy were observed. Graft function was assessed by serial serum creatinine and creatinine clearance measurements.

Statistical analysis. Continuous data were compared using the t-test. The chi-square test was employed for comparison of simple proportions. Patient and graft survival was computed using the Kaplan-Meier technique. Differences in survival were calculated by the log-rank test. A P value of less than 0.05 was considered statistically significant.

RESULTS

Table I confirms that the randomization process was valid. The two groups were similar as regards their demographic and tissue matching characteristics. Figure 1 illustrates the actuarial graft survival of the two groups. The basiliximab treated patients had marginally better graft survival (96% vs 92% three years post-transplantation). This diffefence did not reach statistical significance.

TABLE II - REJECTION EPISODES, BANFF GRADING AND CUMULATIVE STEROID THERAPY

	Basiliximab n	Control n	P-value
Number of patients who experienced an acute rejection episode during the first 12 months	18	31	0.009
Number of acute rejection episodes during the first 12 months	29	45	0.009
Severity of rejection (Banff grading):			
- Borderline and grade I	27	35	
- Grade II and grade III	2	10	0.008
Number of patients who experienced acute rejection episodes during the 36-month follow-up	26	36	0.039
Number of acute rejection episodes during the 36 months	42	54	0.042
Protocol biopsy at the end of follow-up to check for subclinical rejection			
- No rejection	12	6	
- Rejection	1	-	0.16
Number of patients who had chronic rejection biopsy during the 36-month follow-up	2	6	0.19
Cumulative steroid dose (g, mean ± SD):			
- During the first 3 months	3.9 ± 1.4	4.7 ± 1.6	0.018
- During the first 12 months	8.6 ± 2.3	9.9 ± 2.7	0.010

TABLE III - MEDICAL COMPLICATIONS DURING THREE YEARS' FOLLOW-UP

	Basiliximab n	Control n
Infections:		
CMV infection		
- Fever and serology	2	2
- CMV pneumonitis	1	1
Herpes Zoster	2	6
Urinary tract infection	3	5
Cutaneous infection	2	2
Urinary tuberculosis	1	1
Malignancy:		
- Cutaneous Kaposi's sarcoma	1	1
Diabetes mellitus	4	7
Hypertension	37	43
Transient high liver enzymes	18	24
Persistent high liver enzymes	2	-
Avascular hip necrosis	4	3
Proteinuria		
- Less than one gram	15	9
- Nephrotic	1	3

TABLE IV - GRAFT FUNCTION

	Basiliximab (mean ± SD)	Control (mean ± SD)
Serum creatinine (mg/dL):		
1 month	1.37 ± 0.47	1.45 ± 0.52
3 months	1.37 ± 0.36	1.43 ± 0.63
6 months	1.39 ± 0.03	1.40 ± 0.39
12 months	1.43 ± 0.04	1.45 ± 0.40
36 months	1.51 ± 0.45	1.56 ± 0.45
Creatinine clearance (mL/min):		
12 months	75.04 ± 14.08	72.0 ± 12.9
36 months	76.56 ± 12.93	72.26 ± 13.7

After three years, only one patient in the control group had died, of cytomegalovirus pneumonitis and respiratory failure. There were no deaths in the basiliximab group.

The incidence and the severity of acute rejection episodes among the basiliximab treated patients was significantly lower than among controls (Tab. II). In addition, the cumulative steroid dose required during the first three and the first 12 months was higher among controls. Some patients had no rejection episodes in the three-year follow-up period but agreed to a graft biopsy to test for subclinical rejection.

There was no difference in the incidence or distribution of late medical complications in the two groups (Tab. III). Similarly, the quality of graft function was similar, as determined by the slope of serum creatinine or by creatinine clearance (Tab. IV).

DISCUSSION

Acute rejection is an important risk factor for the development of chronic allograft failure (14). Moreover, acute rejection episodes are morbid events in themselves, requiring intensification of immunosuppression and hospital admission (15). Induction therapy with ATG or OKT3 reduced the incidence of acute rejection episodes in the cadaveric setting (3, 16), with only marginal differences in therapeutic efficacy. However, a high incidence of side effects was reported with OKT3 (3). Reports on the use of these agents in living-donor transplantation are few but the incidence and severity of acute rejection appears to be lower than with cadaveric transplants. The potential benefits must be weighed against the risks of over-immunosuppression with increased susceptibility to opportunistic viral infections and post-transplant lymphoproliferative disease (17).

Recently, safe and effective prophylactic therapy has been achieved with high-affinity humanized or chimeric monoclonal antibodies (daclizumb and basiliximab respectively). These target the interleukin-2 receptor (9-11). The chimeric monoclonal antibody basiliximab specifically binds the α subunit (CD 25) of the interleukin-2 receptor on activated T-lymphocytes through competitive antagonsim of interleukin-2 (18). Kovarik et al reported that basiliximab was well tolerated, with no evidence of cytotoxic release syndrome, hypersensitivity reactions or anti-idiotype antibody response (19).

The efficacy of basiliximab in preventing acute rejection was evaluated in two multicentric double-blind, randomized phase III trials which both used cyclosporine and corticosteroids for maintenance treatment. In the first trial (European/Canadian), only cadaveric kidneys were used (10). In the second (US Simulect Renal Study Group), 29% of the organs were from living donors (11). The European/Canadian group reported that the addition of basiliximab was associated with a 32% reduction in the proportion of patients with biopsy-confirmed acute rejection episodes, compared with placebo. There was no difference in the histological severity of rejections or in the numbers of patients who experienced more than one rejection episode (10). Nevertheless, there was no advantage in one-year graft and patient survival. No clinically relevant differences were found between the treatment groups in terms of changes in laboratory indices or vital signs, particularly in leucocyte or lymphocyte counts, at any time.

In the American trial (11) a similar significant therapeutic benefit was noted as regards the incidence of acute rejection episodes. These were reduced from 58% to 42% among the cadaveric cases and from 47% to 28% among living-donor transplants. The adverse event profile was comparable to the control group. The basiliximab treated patients also had significantly higher mean creatinine clearance over the one-year follow-up period.

In a third trial (20), the efficacy and safety of basiliximab were studied in renal transplant patients receiving triple therapy with cyclosporine, azathioprine and prednisone. The conclusions were the same. The investigators reported that basiliximab significantly reduced the incidence of first acute rejection and the risk of recurrent rejection in kidney transplant patients given the triple therapy. They had also claimed that this regimen may offer better protection from acute rejection than basiliximab with dual therapy, not including azathioprine.

Our study only comprised living-related first kidney transplants. Several end-points were chosen for assessing the efficiency of induction immunotherapy using this agent. The post-transplantation follow-up lasted more than three years. We recorded the incidence of acute rejection episodes, their severity as determined histopathologically, and the cumulative steroid doses required during this period. The basiliximab treated group had a lower incidence of acute rejection episodes which were generally less severe, and the cumulative steroid doses were smaller at 12 months post-transplantation. All these findings were statistically significant. During follow-up graft survival of the patients who received induction immunotherapy was marginally better than the control group, but the difference did not reach statistical significance. The adverse effect profile was comparable in both groups. These observations are similar to those reported in the cadaveric setting (10, 11).

While the US simulect study group reported better graft function in the basiliximab-treated group, we did not notice this advantage in terms of serial serum creatinine or creatinine clearance at 12 months and three years. This may be because the majority of patients in US trial received cadaveric kidneys, where the functional benefits resulting from prevention of acute rejection will be more pronounced.

The two large studies (10, 11) reported results up to one year after transplantation. Our results extended beyond three years and showed a significant reduction of acute rejection and its severity in this period. The incidence of biopsy-confirmed chronic rejection was marginally higher in the control group.

The results of our trial indicate that induction therapy using basiliximab has a clear therapeutic benefit in living-related-donor kidney transplantation. Longer follow-up and frequent biopsies are needed to verify this in the long term. The potential consequences of over-immunosuppression should be observed and reported. Amlot et al, in a phase I-II trial (21), reported that two out of 24 cadaveric renal transplant recipients experienced lymphoproliferative disorders (basiliximab was given as six spaced doses between 2.5 and 25 mg). Another issue still to be addressed is the possibility of reducing or eliminating corticosteroids or calcineurin inhibitor-based immuno-suppression in patients receiving this induction therapy.

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References

1. Sollinger H, Kaplan B, Pescovitz M, Philosophe B, Roza A, Brayman K, Somberg K. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. Transplantation 2001; 72: 1915-9.
2. Brennan DC, Flavin K, Lowell JA, Howard TK, Shenoy S, Burgess S, Dolan S, Kano JM, Mahon M, Schnitzler MA, Woodward R, Irish W, Singer GG. A randomized, double-blinded comparison of thymoglobulin versus ATGAM for induction immunosuppressive therapy in adult renal transplant recipients. Transplantation 1999; 67: 1011-8.
3. Bock HA, Gallati H, Zürcher RM, Bachofen M, Mihatsch MJ, Landmann J, Thiel G. A randomized prospective trial of prophylactic immunosuppression with ATG-Fresenius versus OKT3 after renal transplantation. Transplantation 1995; 59: 830-40.
4. Yussin A, Shapira Z. Single-bolus high-dose ATG for prophylaxis of rejection in renal transplantation - a prospective randomized study. Transpl Int 2000; 13 (suppl 1): S293-4.
5. Henry ML. Induction therapy. Current Opinion in Organ Transplantation 1997; 2: 49-53.
6. Danovitch GM. Immunosuppressive medications and protocols for kidney transplantation. In Danovitch GM Ed. Handbook of kidney transplantation (3rd ed). Boston: Lippincott and Wilkins 2001; 62-111.
7. Maes BD, Vanrenterghem J. Anti-interleukin-2 receptor monoclonal antibodies in renal transplantation: Editorial comments. Nephrol Dial Transplant 1999; 2824-6.
8. Olyaei AJ, Thi K, de Mattas A, Bennett WM. Use of basiliximab and daclizumab in kidney transplantation. Prog Transplant 2001; 1: 33-9.
9. Nashan B, Light S, Hardie IR, Lin A, Johnson RJ. Reduction of acute renal allograft rejection by daclizumab. Transplanta-

tion 1999; 67: 110 -5.
10. Nashan B, Moore R, Amlot P, Schmidt AG, Abeywickrama K, Soulillou JP. Randomized trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. Lancet 1997; 350: 1193-8.
11. Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. Transplantation 1999; 67: 276-84.
12. Mulloy LL, Wright F, Hall ML, Moore M. Simulect (Basiliximab) reduces acute cellular rejection in renal allografts from cadaveric and living donors. Transplant Proc 1999; 31: 1210-3.
13. Racusen L, Solez K, Colvin R, Bonsib S. The Banff 97 working classification of renal allograft pathology. Kidney Int 1999; 55: 713-23.
14. Humar A, Hassoun A, Kandaswamy R, Payne WD, Sutherland D, Matas A J. Immunologic factors: The major risk for decreased long-term renal allograft survival. Transplantation 1999; 68: 1842-6.
15. Danovitch GM. Immunosuppressive medications for renal transplantation. Kidney Int 2001; 59: 388-402.
16. Opelz GF. Efficacy of rejection prophylaxis with OKT_3 in renal transplantation. Transplantation 1995; 60: 1220-4.
17. The EBPG expert group on renal transplantation. European best practice guidelines for renal transplantation (part 1). Nephrol Dial Transplant 2000; 15 (suppl 7): S60.
18. Onrust SV, Wiseman LR. Basiliximab. Drugs 1999; 57: 207-13.
19. Kovarik J, Wolf P, Cisterne J, Mourad G, Lebranchu Y, Lang P, Bourbigot B, Cantrovich D, Girault D, Gerbeau C, Schmidt AG, Soulillou J P. Disposition of basiliximab, an interleukin-2 receptor monoclonal antibody, in recipients of mismatched cadaver renal allografts. Transplantation 1997; 64: 1701-5.
20. Ponticelli C, Yussim A, Cambi V, Legendre C, Rizzo G, Salvadori M, Kahn D, Kashi SH, Salmela, K, Fricke L, Garcia-Martinez J, Lechler R, Heemann U, Monteon F, Ortuno J, Amenabar J J, Arias M, Nicholson ML, Sperschneider H, Abendroth D, Gracida C, Lao M, Sever MS, Lameire N, Sanchez Fructuoso A, Basci A, Segoloni G, Conolly J, Altieri P, Akoh J, Prestele H, Girault D. Basiliximab significantly reduces acute rejection in renal transplant patients given triple therapy with azathioprine. Transplant Proc 2001; 33: 1009-10.
21. Amlot PL, Rawlings E, Fernando ON, Griffin PJ, Heinrich G, Schreier MH, Castaigne JP, Moore R, Sweny P. Prolonged action of a chimeric interleukin-2 receptor (CD 25) monoclonal antibody used in cadaveric renal transplantation. Transplantation 1995; 60: 748-56.

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