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Limited Dose Monoclonal IL-2R Antibody Induction Protocol after Primary Kidney Transplantation

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This study prospectively compared immunoprophylaxis with a single intraoperative dose (2 mg/kg) of monoclonal interleukin-2 receptor (IL-2R) antibody vs. noninduction in kidney transplant recipients treated with tacrolimus (FK 506), mycophenolate mofetil (MMF) and a prednisone-based immunosuppression regimen.
One hundred recipients of first-kidney transplant were enrolled into the study to receive either anti-IL-2R monoclonal antibody, daclizumab (2 mg/kg intraoperatively, limited anti-IL-2R) or no induction (control). Each patient also received oral tacrolimus (dosed to target trough level 10–15 ng/mL), MMF (500 mg bid) and prednisone. The primary efficacy end-point was the incidence of biopsy proven acute rejection during the first 6 months post-transplant. The patients were also followed for 12-month graft function, and graft and patient survival rates.
Other than the donor's age being significantly lower in the control group, both groups were comparable with respect to age, weight, gender, race, human leukocyte antigen (HLA)-DR mismatch, panel reactive antibody (%PRA), cold ischemic time, cytomegalovirus (CMV) status, causes of renal failure, and duration and modes of renal replacement therapy (RRT).
During the first 6 months, episodes of first biopsy confirmed acute rejection was 3/50 (6%) in the limited anti-IL-2R group and 8/50 (16%) in the controls ($p < 0.05$). Twelve-month patient 100/98 (%) and graft survival 100/96 (%) were not statistically different. The group receiving limited anti-IL-2R did not have any adverse reactions.
Our study demonstrates that a limited (single) 2 mg/kg immunoprophylaxis dose with monoclonal IL-2R antibody (daclizumab) when combined with tacrolimus/MMF/steroid allows significant reduction in early renal allograft rejection to the single digit level. The therapy with anti-IL-2R antibody is simple and is well tolerated.

Key words: Anti-IL-2R antibody, induction immunoprophylaxis, kidney transplantation, limited dose, rejection

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Introduction

The development of new immunosuppressive agents is designed to reduce the incidence and severity of early acute post-transplant rejection (1–5). One potential target for more specific immunosuppressive therapy with monoclonal antibodies is the high affinity alpha chain of interleukin-2 receptors (IL-2R). Clinical investigation of murine anti-IL-2R monoclonal antibodies in renal transplantation has indicated that a complete blockade of IL-2R during the critical first post-transplant months allows effective immunoprophylaxis, especially in the early post-transplant period (6–13).

Efficacy of these agents however, is hampered by their short disposition half-lives in humans and by their immunogenicity in the form of neutralizing human antimouse antibodies. These inherent problems can be partially overcome by chimeric products and multiple dose regimens. Alternatively, as shown by saturation kinetics' studies, a simple limited loading dose of anti-IL-2R antibody coadministered with an immunosuppressant that inhibits IL-2 production could result in a complete blockade of IL-2R for several weeks (6–7 weeks) (14).

While effective, previous clinical trials in kidney transplants with anti-IL-2R antibody were performed with a cyclosporine/azathioprine/steroid-based therapy, the reported rejection rate was as high as 25%, and the regimen involved administrations of multiple doses of anti-IL-2R antibody, especially with daclizumab (15, 16). Recently, several newer immunosuppressants (e.g. tacrolimus, microemulsion cyclosporine, MMF and rapamycin) have been approved for clinical use in kidney transplants, and many investigators have reported early rejection rates of less than 20% using these agents (17–20).

With this in mind, the primary objective of the present study was to see if in kidney transplant recipients a simpler and more effective immunoprophylaxis could be obtained by combining a limited dose of the anti-IL-2R antibody daclizumab with newer immunosuppressants involving tacrolimus/MMF/steroid-based triple therapy.

Patients and Methods

A total of 100 consecutive renal transplant recipients were eligible for the study. The study was performed at the Pinnacle Health Transplant Program, Harrisburg, PA. Patients aged at least 18 years and receiving a first cadaveric or living-related renal transplant were considered eligible, and those who had already received organ transplants and multiorgan transplants were excluded. Patients were randomly selected to receive either the limited anti-IL-2R antibody, daclizumab (2 mg/kg of ideal body weight; Zenapax®, Hoffman-La Roche, Nutley, NJ) administered intravenously after induction of anesthesia or no induction (control). The time of daclizumab infusion took into account the possibility of immediate serious adverse reactions: times chosen were those at which the anesthesiologist could closely monitor the patient's airways and hemodynamic parameters. Oral tacrolimus (0.08 mg/kg Prograf®; Fujisawa Healthcare Inc., Deerfield, MI), plus mycophenolate mofetil (MMF, 1500 mg; Cell Cept® Hoffman-La Roche, Nutley, NJ) and intravenous methylprednisolone (500 mg) were administered before transplantation. Tacrolimus was administered on a schedule of two divided doses starting 0.16–0.2 mg/kg/day. Tacrolimus target whole-blood trough levels were maintained between 10 and 15 ng/mL (IMx® Tacro II assay, Abbott Laboratories, Abbott Park, IL) after the 3rd month of follow up. Post-transplant 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, reported elsewhere (21). Trimethoprim-sulfamethoxazole was administered in both treatment groups for *Pneumocystis carinii* prophylaxis. Oral ganciclovir (Cytovene®, Hoffman-La Roche, Nutley, NJ) 500 mg twice daily for 3 months was administered to all patients regardless of donor-recipient CMV status (22). Delayed graft function (DGF) was defined by a urine output of less than 40cc/h, failure to decrease serum creatinine by 20% within 12–24 h, and/or the need for dialysis. 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 or 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 first episode of acute rejection in each patient before or within 24 h of commencing the anti-rejection treatment, unless the procedure was medically contraindicated.

Acute rejection was treated similarly in all groups with an intravenous steroid (500 mg for 3 days) followed by recycling oral prednisolone 2 mg/kg per day for 3 days with a subsequent taper. Steroid-resistant rejection (when allograft function failed to improve after 3 doses of intravenous steroid) was treated by the addition of OKT-3 (5 mg/day intravenously for 5–10 days; Muromonab anti-CD3, Ortho Biotech, Cilag, NJ) or when commercially available by the addition of Thymoglobulin (1–1.5 mg/kg/day for 5–10 days; Sangstat Medical Corporation, NJ).

Statistical analysis

The sample size was calculated to detect a difference between the groups, to detect those experiencing rejection within 6 months post-transplant of 0.25 with 80% power and at a 5% significance level. The primary endpoint of the study was defined by the occurrence of acute graft rejection confirmed histologically by core needle biopsy during the first 6 months following transplant. Secondary parameters were episodes of infectious complications and 12-month graft function and patient/graft survival. All biopsies were reviewed by a pathologist unaware of the protocol and were graded according to the BANFF-97 scheme (23). The proportion of patients experiencing biopsy-proven acute rejection (during the first 6 months post-transplant), an infectious complication and 1-year graft function, and patient/graft survival were analyzed using Fischer's exact test. Continuous baseline variables, such as patient's and donor's age, patient's weight, panel reactive antibody (% PRA), and cold ischemia time were compared between the treatment groups using Student's *t*-tests. Results are reported as mean ± SEM when indicated. Differences were considered significant at $p < 0.05$.

Results

One hundred patients were included in the study (50 limited anti-IL-2R and 50 control). All patients had a minimum 12-month post-transplant follow up. With the exception of the donor's age (39.6 ± 2.4 vs. 32.5 ± 2.3 years, $p = 0.03$) there were no significant differences in patient demographic characteristics between the groups (limited anti-IL-2R vs. control) with respect to age (47.0 ± 2.0 vs. 47.0 ± 2.1 years), gender (% male: 66 vs. 64), race (% Caucasian: 96 vs. 90), transplant type (% cadaver: 75 vs. 66), HLA-DR mismatch, % PRA, overall cold ischemia time (8.0 ± 1.2 vs. 8.4 ± 1.2 h), causes of end-stage renal disease (ESRD), duration and methods of renal replacement therapy (RRT), and CMV D+/R− status (27 vs. 22%) (Table 1).

Efficacy end-points

Rejection. During the first 6 months following transplant there were 21 episodes of renal dysfunction (see Methods for definition), all of which had an increased serum creatinine concentration of 0.3 mg/dL or greater. Thirteen patients underwent diagnostic allograft kidney biopsy. Episodes of acute rejection occurred in 6% (3/50) of patients in the limited anti-IL-2R induction group compared with 16% (8/50) in the noninduction control group ($p < 0.05$) (Table 2). There was a total of 11 acute rejection episodes: three in the limited anti-IL-2R group and eight in the control group. Of these, steroid-resistant rejection episodes were 3/3 in the limited anti-IL-2R group and 5/8 in the control group ($p =$ NS). Histopathology demonstrated BANFF grades I, II, III: limited anti-IL-2R 1/2/0 and control 4/3/1 ($p =$ NS). Both steroid-resistant rejection groups had comparable demographics including the types of transplant, HLA types, and dose and serum levels of immunosuppressive agents.

Survivals and graft functions. At the end of 12 months, patient survival rates were limited anti-IL-2R vs. control, 100 vs. 98%, respectively. Corresponding graft survivals were 100 vs. 94%. The functions of renal allograft as measured by serum creatine (mg/dL ± SEM) were persistently higher in the control group at discharge (2.1 ± 0.1 vs. 2.9 ± 0.3; $p < 0.04$) and at months 1 (1.7 ± 0.2 vs. 1.9 ± 0.2), 3 (1.5 ± 0.1 vs. 1.8 ± 0.3), 6 (1.5 ± 0.1 vs. 1.7 ± 0.3) and 12 (1.5 ± 0.1 vs. 1.7 ± 0.2) (Figure 1). At the end of 12 months, the serum creatinine (mg/dL) levels of the patients who suffered steroid resistant acute rejections were as follows: limited anti-IL-2R 3.0 ± 0.3 (1.8–3.3) and control 2.56 ± 0.3 (2.1–3.3) (data reflects serum creatinine for 3/5 patients: one patient lost graft and another patient died before 12 months).

Immunosuppressive doses. Per protocol, tacrolimus dose was

Table 1: Demographic characteristics of the study population

	Limited anti-IL-2R (n = 50)	Control (n = 50)	p-value
Patient's age (y ± SEM)	47.0 ± 2.0	47.0 ± 2.1	
Donor's age (y ± SEM)	39.5 ± 2.4	32.5 ± 2.3	0.03
Gender (% male)	66	64	
Race (% Caucasian)	96	90	
Patient's weight (kg ± SEM)	81.40 ± 2.8	76.7 ± 2.7	
Type of transplant			
Cadaver (%)	35 (70)	33 (66)	
Living related	11 (22)	12 (24)	
Living unrelated	4 (8)	5 (10)	
HLA-DR mismatch (%)			
0	21	22	
1	20	19	
2	9	9	
Cold ischemia time (h ± SEM)	8.0 ± 1.1	8.4 ± 1.2	
Cadaver (h ± SEM)	16.9 ± 0.9	17.2 ± 1.0	
Living (h ± SEM)	3.1 ± 0.1	3.0 ± 0.1	
Panel-reactive antibody (% ± SEM)			
Historic	2.8 ± 0.6	3.5 ± 1.1	
Current	0.6 ± 0.2	0.5 ± 0.2	
Causes of ESRD (%)			
Diabetes	13 (26)	12 (24)	
Glomerulonephritis	19 (38)	15 (30)	
Polycystic kidneys	5 (10)	7 (14)	
Hypertension	4 (8)	5 (10)	
Reflux nephropathy	1 (2)	3 (6)	
Others	8 (16)	8 (16)	
RRT (%)			
None	10 (20)	9 (18)	
Hemodialysis	30 (60)	27 (54)	
Peritoneal	10 (20)	14 (28)	
Duration of RRT (mon. ± SEM)	23.2 ± 2.6	22.0 ± 2.0	
CMV status (donor/recipient)			
D+/R+	12	18	
D+/R−	13	11	
D−/R+	11	12	
D−/R−	14	9	

HLA-DR = human leukocyte antigen-DR
ESRD = end-stage renal disease
RRT = renal replacement therapy
CMV = cytomegalovirus

Table 2: Table 2: Incidence of first episode of biopsy-proven acute rejection. Graft and patient survival at 1-year transplant follow up

	Limited anti-IL-2R (n = 50)	Control (n = 50)	p-value
Delayed graft function (%)	12 (24)	10 (20)	
Rejection biopsy proven (%)	3 (6)	8 (16)	< 0.05
LRD/LURD/CRT	1/1/1	2/1/5	
Steroid resistant (%)	3/3 (100)	5/8 (62 5)	
LRD/LURD/CRT	1/1/1	2/1/2	
Onset of 1st rejection (days ± SEM)	42.6 ± 37	43 ± 46	
12-month patient survival (%)	50 (100)	49 (98)	
12-month graft survival (%)	50 (100)	47 (94)	

$p < 0.05$
DGF = delayed graft function
LRD = living-related donor
LURD = living-unrelated donor
CRT = cadaver renal transplant

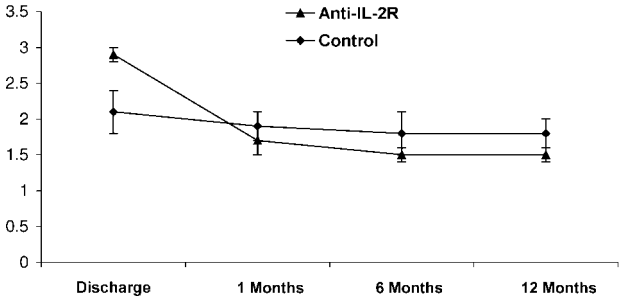

Figure 1: Allograft function following transplant as measured by serum creatinine (mg/dL).

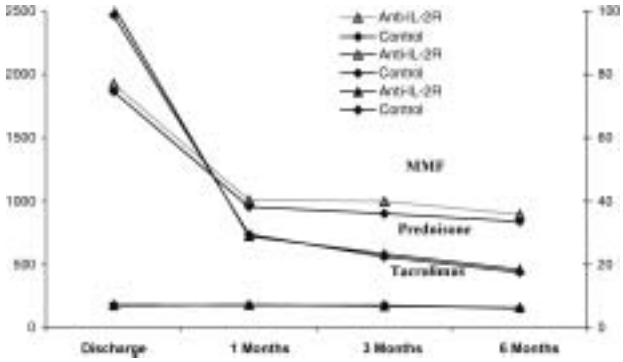

Figure 2: Daily drug doses (*X*-axis: time in months; *Y*-left-axis: MMF mg/day; *Y*-right/axis: prednisone mg/day and tacrolimus mg/day) during the study period.

adjusted to maintain the therapeutic ranges. At several time points and at the end of 6 months, there were no statistically significant differences between the groups (limited anti-IL-2R vs. control) with respect to the average daily dose of tacrolimus (6.3 ± 0.6 mg vs. 6.1 ± 0.6 mg), MMF (896 ± 74 mg vs. 840 ± 63 mg) and prednisone (18.3 ± 0.6 mg vs. 18.2 ± 0.6 mg (Figure 2).

Adverse effects. The administration of limited anti-IL-2R was not associated with any immediate adverse reactions. One control patient (2%) died of sepsis during the first 12 months, which is reflected in the incidence of graft loss. There were three graft losses in the control group as a result of primary nonfunction (one), rejection (one) and death with functioning graft (one). The mean time (days $\pm$ SEM) to the first episode of acute rejection was 42.6 ± 37 days for the limited anti-IL-2R group and 43 ± 46 days for the control group. Out of 17 infectious complications (both bacterial and viral), 12% (6/50) occurred in the limited anti-IL-2R group and 22% (11/50) in the control group (Table 3). In the control group there was no correlation between the episodes of higher infectious complications and additional immunotherapy required to treat the episodes of acute rejection.

Discussion

In this prospective study of kidney transplantation we explored immunoprophylaxis efficacy with a simple limited intraoperative dose of an anti-IL-2R antibody. The distinctive feature of this study was that unlike previous clinical trials with IL-2R antibodies, our patients received a single 2 mg/kg dose of daclizumab in a tacrolimus, MMF, and prednisone-based triple therapy regimen. Our study showed that during the first 6 months post-transplant, the incidence of first biopsy confirmed that acute rejection was 6% in the limited dose daclizumab induction group compared with 16% in the control group ($p < 0.05$). Both groups had comparable 1-year graft and patient survival rates.

Despite recent advances in the immunosuppressive regimen, early acute renal allograft rejection is a poor predictor of long-term allograft survival, and continues to be a significant clinical problem (1, 24–26). This fact has prompted the development of new immunosuppressive agents designed to reduce the incidence and severity of early acute post-transplant rejection (1–5). One potential target for more specific immunosuppressive therapy with monoclonal antibodies is the high affinity alpha chain of interleukin-2 receptors (anti-IL-2R). Clinical investigation of murine anti-IL-2R antibodies in renal transplantation has indicated a potential role for these agents in immunoprophylaxis, especially in the early post-transplant period (11–13). Recently, two engineered anti-IL-2R antibodies, basiliximab (chimeric product) and daclizumab (humanized product), were approved in the United States for prophylaxis against acute rejection in renal transplant recipients (15, 16).

Unfortunately, several factors including short disposition half-lives in humans and immunogenicity in the form of neutralizing human antimouse antibodies have limited the efficacy of these agents.

In case of basiliximab, chimerization has yielded a mAb with a prolonged half-life (1–2 weeks) and lack of antibody response (13), and chimerization has provided immunoprophylaxis for an extended period of time during the peri-transplant period (27). In a study with kidney transplant recipients, basiliximab (20 mg days 0 and 4) was administered in combination with cyclosporine and steroid: in this study the incidence of acute rejection was 29.8% in the basiliximab group and 44% in the control group, and the incidence of anti-idiotype antibody was 0.4% (16). On the other hand, daclizumab, the humanized product, required administration in multiple doses (each dose: 1 mg/kg at bi-weekly intervals for a total of five doses) in order to achieve the mean serum half-life of 20 days and saturation of IL-2R on circulating lymphocytes for 120 days. When administered in combination with cyclosporine, azathioprine and prednisone, the daclizumab group had a 22% acute renal allograft rejection (at 6 months) compared with the controls (35%) (16).

Although effective, the previous studies with both IL-2R antibodies were performed primarily with cyclosporine, azathioprine, and the steroid-based regimen, and the incidence of early rejection in the treatment group exceeded 20%. Recently, the introduction of newer, more immunosuppressive

Table 3: Adverse events and infectious complications

	Limited anti-IL-2R (n = 50)	Control (n = 50)	p-value
Total infection (%)	6 (12)	11 (22)	
Bacterial (%)	3 (6)	3 (6)	
Fungal (%)	0	1 (2)	
Viral (%)	3 (6)	8 (16)	
CMV (%)	5 (10)	1 (2)	
PE/DVT (%)	0	3 (6)	
MI/CHF (%)	4 (8)	1 (2)	
Cancer/lymphoma (%)	0	1 (2)	
Lymphocele (%)	0	1 (2)	

MI = myocardial infarction
CHF = congestive heart failure
DVT = deep vein thrombosis
PE = pulmonary embolism
CMV = cytomegalovirus

agents (tacrolimus, MMF, microemulsion cyclosporine, rapamycin) allows an overall reduction in early rejection episodes. With these agents in a noninduction regimen, some studies have reported a rejection rate of 15% or less (20, 21, 28). To this end we have shown that the coadministration of these newer immunosuppressive agents and the limited dosing (a single 5 mg intraoperative dose) of induction agents (e.g. OKT-3) could reduce acute rejection to below 10% (29).

Several investigators have claimed that the full benefit from IL-2R mAbs may be achieved when coadministered with an immunosuppressant that inhibits IL-2 production (30). Pharmacokinetic sampling was performed in two multicenter trials in which basiliximab was administered. Basiliximab clearance was 18 ± 8 mL/h when coadministered with MMF; significantly lower compared with a clearance of 37 ± 15 mL/h from a previous study of basiliximab with dual therapy ($p < 0.001$). As a consequence of the lower clearance of basiliximab, the durations of IL-2R saturation were prolonged in the presence of MMF (59 ± 17 days; range 28–94) compared with dual therapy (36 ± 14 days; range 12–91) (31). In a more recent pharmacokinetic and pharmacodynamic study, Vincenti et al. showed that a limited dosing of daclizumab in combination with a calcineurin inhibitor, MMF, and steroid resulted in prolonged blockade of IL-2R. In this saturation kinetic study, single 2 mg/kg doses of daclizumab resulted in prolonged blockade (42–70 days) of IL-2R (14). Daclizumab concentrations were maintained at 1 μg/mL (a concentration resulted in the complete suppression of IL-2R in circulating lymphocytes) for up to 43 ± 7 days after transplantation. Although the optimal immunoprophylaxis period for IL-2R mAb is currently unknown, investigators usually focused on the first 4–6 weeks after transplant as a critical period in renal transplantation. In another recent study, Kovarik et al. demonstrated that a single 40 mg dose of basiliximab could achieve and maintain adequate IL-2R saturating concentrations of 0.2μ g/mL during this critical period (32). Our current study was not designed to address the issues related to pharmacokinetics and pharmacodynamics and we did not perform any follow-up IL-2 receptor saturation kinetics. Nonetheless, our clinical results showed that an effective immunoprophylaxis could be obtained with a large single (limited dose) dose of anti-IL-2R, which was simple and obviously economic to administer. The combination of anti-IL-2R antibody with a newer immunosuppressive-based regimen that included tacrolimus (modulating production of IL-2) and MMF (prolonging the saturation of IL-2R) demonstrated a considerably more significant robust reduction in early rejection rate episodes than reported with phase III anti-IL-2R antibody clinical trials (15, 16).

In conclusion, our data in kidney transplantation substantiates the theory that immunoprophylaxis combined with a limited dose anti-IL-2R antibody protocol and administered in a tacrolimus/MMF/prednisone-based regimen allows a significant reduction in early acute rejection.

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