A Phase I/II Randomized Open-Label Multicenter Trial of Efalizumab, a Humanized Anti-CD11a, Anti-LFA-1 in Renal Transplantation

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Leukocyte function associated antigen-1 (LFA-1) has a multifaceted role in the immune response, including adhesion and trafficking of leukocytes, stabilizing the immune synapse of the MHC-TCR complex and providing costimulation signals. Monoclonal antibodies to the CD11a chain of LFA-1 have been seen to result in effective immunosuppression in experimental models. Efalizumab, a humanized IgG1 anti-CD11a, is approved for use in psoriasis and may provide effective immunosuppression in organ transplantation. Thirty-eight patients undergoing their first living donor or deceased renal transplant were randomized to receive efalizumab 0.5 or 2 mg/kg weekly subcutaneously for 12 weeks. Patients were maintained on full dose cyclosporine, mycophenolate mofetil and steroids or half dose cyclosporine, sirolimus and prednisone. At 6 months following transplant patient survival was 97% and graft survival was 95%. Clinical biopsy-proven acute rejection in the first 6 months after transplantation was confirmed in 4 of 38 patients (11%). Three patients (8%) developed post transplant lymphoproliferative disease, all treated with the higher dose efalizumab and full dose cyclosporine. The two doses of efalizumab resulted in comparable saturation and modulation of CD11a. This phase II trial suggests that efalizumab may warrant further investigation in transplantation.

Introduction

The incidence of acute graft rejection and short-term graft survival in renal transplantation have shown considerable improvement in the past decade (1,2). However the gains obtained from the reduction of acute rejection and improvement in graft survival in the first year following transplantation has not resulted in a commensurate increase in long-term graft survival (3). Both immune and non-immune mechanisms (particularly the nephrotoxicity associated with the use of calcineurin inhibitors) limit the extended survival of renal allografts (4–7). Novel, more effective immunosuppression may lead to less reliance on maintenance immunosuppression agents that result in nephrotoxicity, accelerated glomerular senescence and exacerbation of cardiovascular risk factors (8,9). This approach may be particularly useful for recipients of renal allografts from extended criteria donors and/or those that develop delayed graft function. Biologic agents that target novel targets such as costimulation pathways or adhesion pathways have been shown to induce tolerance in rodents and prolong graft survival in nonhuman primates (10–21). An important therapeutic target for inhibition with biologic agents is the leukocyte function associated antigen 1 (LFA-1), best known as a classic adhesion molecule (22,23). LFA-1 is a member of the heterodimeric B2 integrin family, consisting of a noncovalently linked unique alpha chain (CD11a) and a beta chain (CD18) which is common to other B2 integrins. The importance of the adhesion molecules LFA-1/ICAM interactions as part of the early events in T-cell

activation has been recently elucidated by several groups and has been shown to be necessary for T-cell activation, T-cell helper and B-cell responses, natural killer cell cytotoxicity and antibody-dependent cytotoxicity (23,24). LFA-1 functions as an adherence molecule, plays a role in stabilizing the immune synapse of the TCR-MHC complex and participates in costimulation. In fact, LFA-1 ligation activates some of the same signaling pathways as CD28 ligation, suggesting that LFA-1 can provide important costimulatory signals (23,25). The ability of LFA-1 to provide costimulatory signals has implications for regimens where the goal is drug minimization with excellent graft acceptance (26,27). Several pilot studies have explored blockade of adhesion molecules with the use of murine anti-ICAM-1 or anti-LFA1 monoclonal antibodies in kidney transplantation with mixed results (28–30). A large randomized prospective trial in recipients of deceased donor kidneys treated with a 10-day course of odulimomab, a murine anti-LFA1 antibody, showed comparable efficacy and safety to antilymphocyte therapy (31). Efalizumab is a humanized IgG1 version of a murine anti-CD11a monoclonal antibody and has been used both experimentally and in clinical studies in patients with psoriasis (32–39). In phase III studies in moderate-to-severe psoriasis efalizumab, administered by subcutaneous injection, was found to be safe, well tolerated and effective (34,35). This phase II open-label multicenter, multidose study was performed to evaluate the safety, pharmacokinetics/pharmacodynamics (PKs/PDs) and biological activity of subcutaneously administered efalizumab in patients receiving a primary renal transplant.

Materials and Methods

Patients selection

Patients undergoing their first living donor or deceased donor renal transplant were enrolled in the study. Living related HLA identical recipients were excluded. Other inclusion criteria were, recipients 18–65 years of age, weight < 120 kg, negative serology for human immunodeficiency virus, hepatitis B surface antigen and hepatitis C antibody, be at least one antigen (HLA-A, B, DR) mismatch with the donor, donor age ≤ 65 years of age and a cold ischemia time ≤ 30 h. Patients underwent a protocol kidney biopsy at 3 months after transplantation with follow-up to 6 months.

Treatments administered

The study drug, efalizumab, was to be weekly administered by subcutaneous injection for 12 consecutive weeks. In this study 2 doses of efalizumab, 2 and 0.5 mg/kg, were evaluated. In psoriasis studies, the higher dose (2.0 mg/kg) of efalizumab saturated and down-modulated circulating T-cell CD11a for 14 days ($T_{1/2}$ = 6 days), achieved saturation of tissue lymphocytes and produced immunologic quiescence in inflamed psoriatic plaques. The lower dose (0.5 mg/kg) did not maintain full saturation for 7 days when used as monotherapy by psoriasis subjects (36). This lower dose was chosen in transplant recipients in order to examine the PK and PD effects of efalizumab when used in combination with other immunosuppressive agents. Patients were randomized to one of two efalizumab treatment groups. Subjects in Group I received an initial dose of 0.5 mg/kg efalizumab up to 36 h prior to transplantation. The dose was maintained at 0.5 mg/kg for all subsequent weekly administrations. Subjects in Group II received an initial dose of 0.7 mg/kg efalizumab and the dose was increased to

Table 1: Efalizumab dose and concomitant immunosuppression

Dose of efalizumab	Group I 0.5 mg/kg	Group II 2.0 mg/kg
A: Half-dose CsA*+ sirolimus + prednisone	N = 9	N = 9
B: Full-dose CsA** + MMF + prednisone	N = 10	N = 10
Totals (n = 38)	N = 19	N = 19

CsA = cyclosporine; MMF = mycophenolate mofetil.
*Initial dose 5 mg/kg/day.
**Initial dose 10 mg/kg/day.

2.0 mg/kg for all subsequent weekly administrations. Subjects who missed three doses of efalizumab during the treatment period were discontinued from the study. Patients who experienced delayed graft function requiring renal replacement therapy were maintained on the efalizumab treatment unless antilymphocyte therapy was initiated. Patients who developed acute rejection that required therapy with polyclonal antilymphocyte antibodies or OKT3 were discontinued from additional efalizumab administrations.

Immunosuppression

The study was designed to explore the PK, PD and safety of efalizumab with different immunosuppressive regimens incorporating full dose cyclosporine with mycophenolate mofetil (MMF) or low dose cyclosporine with sirolimus.

Patients in Groups I and II were treated with maintenance immunosuppression regimen consisting of either half-dose cyclosporine (5 mg/kg/day), sirolimus and prednisone (arms IA and IIA) or full dose cyclosporine (10 mg/kg/day), MMF and prednisone (arms IB and IIB) (Table 1). The target whole blood trough level of cyclosporine is shown in Table 6.

Patients enrolled in arms IA and IIA were treated with sirolimus, first dose 15 mg on day of surgery and then 5 mg daily and adjusted to maintain blood levels between 5 and 15 ng/mL. If cyclosporine was withheld because of delayed graft function, the maintenance dose of sirolimus could be increased to maintain blood levels at 10–20 ng/mL until cyclosporine was initiated. Patients in arms IB and IIB received MMF 1–1.5 g b.i.d.

The first dose of corticosteroids was 125–250 mg of methylprednisolone prior to the initial subcutaneous administration of efalizumab and was tapered after transplantation as per transplant center are. Complete steroid withdrawal was not allowed during the study.

Kidney function was assessed using a calculated glomerular filtration rage (mL/min) formula by Nankivell.

Method of Assigning Subject to Treatment Groups

Patients were initially enrolled in Group I. Because the goal was to obtain early safety experience at the dose of efalizumab 0.5 mg/kg/week prior to exposing subjects to 2.0 mg/kg/week, enrollment into Group II occurred after enrollment into Group I was completed. Within each group, patients were randomized to maintenance immunosuppression regimens A or B (Table 1).

All patients signed an informed consent approved by each center's Committee on Human Research.

Table 2: Summary of demographic characteristics for all subjects

| Characteristic | Group I | | Group II | | Total N = 38 |
	Group IA (N = 9)	Group IB (N = 10)	Group IIA (N = 9)	Group IIB (N = 10)	
Sex					
Female	4 (44%)	3 (30%)	4 (44%)	5 (50%)	16 (42%)
Male	5 (56%)	7 (70%)	5 (56%)	5 (50%)	22 (58%)
Race					
Caucasian	5 (56%)	5 (50%)	6 (67%)	1 (10%)	17 (45%)
African American	1 (11%)	2 (20%)	1 (11%)	4 (40%)	8 (21%)
Other races	3 (33%)	3 (30%)	2 (22%)	5 (50%)	13 (35%)
Age, years (mean ± SD)	48 ± 16	43 ± 13	45 ± 11	49 ± 11	46 ± 13
Type of donor					
Living related	4 (44%)	1 (10%)	4 (44%)	1 (10%)	10 (26%)
Living unrelated	2 (22%)	4 (40%)	2 (22%)	2 (20%)	10 (26%)
Deceased	3 (33%)	5 (50%)	3 (33%)	7 (70%)	18 (47%)
Cold ischemia time[1]					
N (deceased donors)	3	5	3	7	18
Mean ± S.D., home	23 ± 6	17 ± 6	19 ±10.6	21 ± 8	20 ±7
	22	13	18	17	18
HLA type mismatch					
Median	3	5	4	4	4

[1]Cold ischemia time is summarized only for the 18 subjects who received a renal transplant from a deceased donor.

Therapy of Acute Rejection

All suspected clinical rejection episodes had to be confirmed by a kidney biopsy within 24-h of steroid pulse therapy. Patients who developed steroid-resistant rejection or who had a rejection that required treatment with polyclonal antilymphocyte agents or OKT3 did not receive any additional administrations of efalizumab.

PKs and PDs Analysis

Blood samples for PK analysis of efalizumab, cyclosporine and flow cytometry were obtained at baseline and at day 1, 2, 28, 56, 84, 98, 112, 140 and 168. Efalizumab levels were measured by an ELISA assay (38,39). On days 0 (prior to transplantation), 28 and 56, PK samples for efalizumab were collected prior to dosing and 4–6 h following dosing. For all other administrations of efalizumab, samples were collected immediately prior to dosing. Samples for human anti-human antibodies (HAHA) were obtained prior to transplantation and at days 56, 84, 112 and 168 after transplantation.

Statistical Analysis

Due to the lack of control groups and the small size of the study, no formal statistical testing was performed. In general, continuous variables were summarized showing the sample size, mean, median, standard deviation and range. Categorical variables were summarized using frequency and proportion. All safety, efficacy, PK and PD data were summarized for those subjects who receive any amount of efalizumab. Safety was assessed through a summary of adverse events, laboratory test results, changes in vital signs and determination of antibody formation to efalizumab. In case of missing data, the summary statistics were based on available data. The sample size for this study was based primarily on safety considerations. A total of 36 subjects (18 subjects each in the low and high efalizumab dose groups) would provide more than 80% power to detect the difference in the acute rejection rate (40% for the historical control vs. 20% for the combined efalizumab groups) or in the delayed graft function rate (30% for the historical control vs. 15% for the combined efalizumab group). The power calculation was based on a one-sided 10% significance level using one sample binomial distribution (n = 36). No adjustment was made for the multiple endpoints.

Results

A total of 38 subjects were enrolled in the trial, with 19 subjects in both Groups I and II with a similar distribution among the subgroups (IA, IB, IIA and IIB). Table 2 shows the patient distribution in the various dose groups and subgroup treatment groups as well as a summary of demographic characteristics. A total of 20 of 38 (53%) subjects received a renal transplant from a living donor, with equal distributions for living related or living unrelated donors. More subjects in Arm B received a renal transplant from a deceased donor (50% in IB, 70% in IIB) than subjects in Arm A (33% in each arm), regardless of dose of efalizumab. Cold ischemia time for the 18 subjects who received a deceased renal transplant ranged from 9 to 36 h with an overall median time of 18 h. The longest median ischemia time was reported for Group IA (22 h), with the other three groups reporting similar median ischemia times (13–18 h). One subject had a cold ischemia time greater than 30 h (36 h for Subject 4005 in Group IIB). HLA

Table 3: Target and achieved trough whole blood levels of CsA

Group	Month 1 target (ng/mL) min–max	Month 1 achieved (ng/mL) min–max (mean)	Month 2 target (ng/mL) min–max	Month 2 achieved (ng/mL) min–max (mean)	Month 3 target (ng/mL) min–max	Month 3 achieved (ng/mL) min–max (mean)
IA	100–250	97–253 (179)	100–200	109–472 (205)	50–200	87–251 (145)
IIA	100–250	73–441 (236)	100–200	73–365 (192)	50–200	81–204 (128)
IB	250–400	125–421 (283)	200–350	145–337 (251)	>200	120–323 (215)
IIB	250–400	132–416 (263)	200–350	97–386 (278)	>200	128–378 (215)

type mismatches among the subjects and their respective donors ranged from 1 to 6 mismatches, with the majority of subjects (84%) having at least three mismatches. A total of 14 (37%) subjects had at least five and as many as six HLA type mismatches with their respective donors. The only notable difference in the distribution of HLA type mismatches among the four treatment groups was that more subjects in Arm B had 5 or 6 mismatches than subjects in Arm A, regardless of dose of efalizumab (40–50% vs. 22–33%).

Thirty-one of 38 (82%) of patients received at least 10 of 12 treatments with efalizumab and completed the study. Six (16%) of the 38 subjects discontinued the study drug and later were discontinued from the study prematurely; of these 5 (13%) discontinued due to an adverse event and 1 (3%) withdrew consent. In addition, 1 (3%) of the subjects experienced an adverse event and discontinued the study drug prematurely but remained in the study and completed the study assessments. Three of 38 received antilymphocyte therapy for DGF. Table 3 shows that the targeted trough levels of cyclosporine were in general achieved.

Efficacy

At 6 months following transplantation patient survival was 97% and graft survival was 95%. Clinical biopsy-proven acute rejection in the first 6 months after transplantation (during the first 3 months of therapy and 3 months of follow-up) was confirmed in 4 of 38 patients (11%). All four rejections were mild and were treated and reversed with corticosteroid pulse therapy (Table 4).

Table 4: Cumulative clinically suspected biopsy-proven acute rejection at 6 months

	Group IA	Group IIA	Group IB	Group IIB
Incidence of biopsy proven rejections	1/9 (11%)	1/9 (10%)	1/10 (10%)	1/10 (11%)
Banff grade	IA	IA	IB	IA
Days post-transplant	52	90	115	70
Donor type	Deceased	Deceased	Living unrelated	Deceased

At 3 months after transplantation, 18 patients agreed to undergo a protocol kidney biopsy. Two of 18 were found to have mild subclinical acute rejection (Banff grade IA) and neither was treated with acute therapy. Thus, the overall biopsy-confirmed acute rejection rate at 6 months including clinical and subclinical rejections totaled 6 of 38 (16%). Of the 18 deceased donor recipients in the study, 2 (11%) experienced delayed graft function after the transplant. Of the 20 living donor recipients 1 (5%) experienced delayed graft function.

Two (5%) subjects died during the study. Of the subjects who died, one in Group IIA died from complications of pancreatitis at day 70 post transplant and the other in Group IIB died from complications following surgery to repair a ruptured ileum secondary to PTLD. Of the subjects who experienced a graft loss, one in Group IA experienced graft loss due to an infarction of the kidney secondary to thrombosis and the other in Group IB experienced graft loss due to primary nonfunction secondary to thrombosis resulting from an atherectomy performed during the transplant procedure. Both graft losses were reported as technical complications.

At 6 months, the median GFR for the four treatment groups (IA, IB, IIA, IIB) combined was 59 mL/min and there was no significant difference between the groups.

Safety Results

All subjects who received at least 1 dose of efalizumab were included in the safety analysis. Table 5 summarizes

Table 5: Adverse events in the first 6 months

	Dose group				
	IA N = 9	IB N = 10	IIA N = 9	IIB N = 10	Combined (N = 38)
Drug-related AE	3 (33%)	2 (20%)	5 (56%)	6 (60%)	16 (42%)
Drug-related serious AE	1 (11%)	0 (0%)	2 (22%)	5 (50%)	8 (21%)
CMV infections	1 (11%)	0 (0%)	1 (11%)	0 (0%)	2 (5%)
PTLD	0 (0%)	0 (0%)	0 (0%)	3 (30%)	3 (8%)

the adverse events in the first 6 months after transplantation. Forty-two percent of patients were reported to have a drug-related adverse event, and 8 patients (8%) had serious adverse events. Two patients had cytomegalovirus (CMV) infections. A major concern of this study was the occurrence of PTLD in 3 of 38 patients (8%). All 3 patients with PTLD were in Group IIB, representing 30% of patients treated with the regimen of the higher dose efalizumab, 2 mg/kg, and full dose cyclosporine, MMF and prednisone. The PTLD cases were diagnosed at days 105, 138 and 183. One patient had been treated with OKT3 for delayed graft function and presented on day 105 with fever, malaise and leukopenia. This patient had a slightly elevated Epstein Barr (EB) virus level by polymerase chain reaction and the kidney biopsy showed a diffuse plasma cell infiltrate which cleared after reduction of immunosuppression. The dose of cyclosporine was decreased and MMF was discontinued. A repeat biopsy on day 145 was negative for any evidence of ongoing PTLD. The patient had a full recovery without any residual effect. The second patient presented on day 138 with severe abdominal pain and was diagnosed with a perforated jejunum. A biopsy obtained from the site of the perforation revealed a lymphoid B-cell neoplasm consistent with PTLD. The patient's immunosuppressive agents were decreased and she was successfully treated with chemotherapy. The third patient with PTLD presented on day 174 with progressive abdominal pain. Initial work-up was negative and he was discharged. He was readmitted on day 188 with recurrence of the abdominal pain. At that point he had free air under the diaphragm and a laparotomy revealed a small bowel perforation (ruptured ileum), which required a small bowel resection with primary anastomosis. A biopsy of the small bowel showed evidence of PTLD. Despite a reduction of the immunosuppressive agents, the patient continued to deteriorate and died soon after of sepsis.

PK and PD analysis

Table 6 shows the mean PK parameters of plasma efalizumab. Patients who received the higher dose efalizumab (Group II) achieved higher plasma trough levels and AUC than patients treated with the lower dose efalizumab (Group I). The two groups had overlapping effective half-lives and clearance of efalizumab. In addition PK results suggest that the different maintenance immunosuppressive medications did not modify the PKs of efalizumab.

The effect of efalizumab therapy on circulating lymphocytes was assessed by monitoring cell counts, lymphocyte subsets and CD11a expression. Mean white blood cells (WBC) increased 61% (Group IA) to 113% (Group IIA) on day 2 due to an increase in the mean granulocyte count. The mean granulocyte count returned to near pretreatment levels by day 28. The mean lymphocyte count was decreased on day 2 from 27% (Group IIB) to 78% (Group IB) of the pretreatment level. Mean lymphocyte counts returned to near or above baseline levels on day 28, were elevated on day 56 and then returned to near baseline levels after drug clearance. Both B and T lymphocyte counts followed the general pattern of total lymphocyte counts. Mean NK cell counts were unchanged during treatment. There was, however, a general decline in mean NK cell counts at day 168. Mean CD11a expression, measured by using an antibody to another CD11a epitope that was not cross-blocked, was decreased after efalizumab administration, reaching a steady state on day 2 of 15% to 34% of baseline that persisted for the course of treatment. Mean available efalizumab binding sites declined to less than 8%

Table 6: Pharmacokinetic parameters of plasma efalizumab in patients receiving weekly subcutaneous doses of efalizumab

Group	Dose	C_{trough} (µg/mL)	Time-end days	Effective half-life days	AUCss (µg/mL day)	CL (mL/d/kg)
		Mean ± SD median (min–max)				
IA	0.5 mg/kg/wk	7.35 ± 3.41	52 ± 20	10.4 ± 4.0	51.4 ± 4.0	13.0 ± 8.6
(N = 9)	× 12 SC	8.95 (2.66–10.2)	55 (24–84)	11.0 (4.8–16.6)	62.6 (18.6–71.4)	8.04 (7.09–26.5)
		(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 6)
IB	0.5 mg/kg/wk	7.92 ± 4.81	51 ± 13	10.2 ± 2.6	55.4 ± 33.7	19.5 ± 21.7
(n = 10)	× 12 SC	9.62 (1.27–13.3)	57 (32–61)	11.4 (6.4–12.2)	67.3 (8.89–93.1)	7.38 (5.35–56.8)
		(n = 7)	(n = 7)	(n = 7)	(n = 7)	(n = 7)
IIA	0.7 mg/kg SC	35.2 ± 14.9	69 ± 12	13.8 ± 2.4	246 ± 105	11.7 ± 10.6
(n = 9)	2.0 mg/kg/wk	39.9 (8.63–48.1)	65 (57–86)	13.0 (11.4–17.2)	279 (60.4–337)	7.19 (5.96–33.1)
	× 11 SC	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 6)
IIB	0.7 mg/kg SC	33.5 ± 16.1	67 ± 18	13.4 ± 3.6	234 ± 112	11.7 ± 8.5
(n = 10)	2.0 mg/kg/wk	31.3 (9.07–55.9)	60 (39–89) (n = 7)	12.0 (7.8–17.8) (n = 7)	219 (63.5–391)	9.19 (5.43–31.3)
	× 11 SC	(n = 8)	(n = 7)	(n = 7)	(n = 8)	(n = 8)

Time-end = time after last dose when efalizumab level fell below 0.039 µg/mL (detection level).
Effective half-life was evaluated as one-fifth of time-end.
C_{trough} = concentration of efalizumab on day 77 or 84.
AUCss = C_{trough}*7 days.
Clss = last dose/AUCss, clearance of efalizumab during the week after the last dose.
SC = subcutaneous administration.

of pretreatment levels by Day 2 and remained less than 4% during treatment. CD11a expression and available binding sites returned to pretreatment levels by day 168, 3 months after the last administration of efalizumab. There was no difference in the extent of CD11a down modulation or degree of saturation between the two dosing groups, although recovery of CD11a expression was slightly delayed in the high dose efalizumab group.

HAHA response

Antibody response to efalizumab was assessed in 33 of the 38 subjects using a double antigen assay. The minimum quantifiable concentration was 6.25 RU/mL. None of the subjects tested had a persistent HAHA response to efalizumab. Only 1 of 33 (3%) evaluable subjects had a detectable antibody response. The magnitude of the antibody response was 6.76 RU/mL on day 112 and on subsequent testing at day 168 showed no detectable antibody response.

Discussion

The purpose of this trial was to assess the safety, immunogenicity, PK and PD of efalizumab. Subcutaneous administration of efalizumab was associated with few acute side effects. The use of efalizumab at 0.5 mg/kg dosed weekly appeared to be safe with both immunosuppressive regimens (Groups IA and IB). In the arm combining efalizumab at 2.0 mg/kg dosed weekly with full dose cyclosporine/MMF/prednisone (Group IIB), there were three cases of PTLD. The early appearance of PTLD in subjects receiving this regimen is consistent with the observation that the use of intense immunosuppression, in particular with biologic agents, can lead to the early appearance of PTLD in susceptible subjects (9,40,41). This is emphasized by the fact that no cases of PTLD were observed in the arm combining efalizumab at 2.0 mg/kg weekly with half-dose cyclosporine/sirolimus/prednisone (Group IIA). Whether the high incidence of PTLD in Group IIB patients was related to overimmunosuppression (high dose efalizumab in combination with full dose cyclosporine) or an aberrant cluster of cases remains to be determined. Efalizumab therapy *per se* in psoriasis has not been associated with the occurrence of PTLD (34–36). Drug-related adverse events were more common in Group II (11/19 subjects) than in Group I (5/19 subjects). The 7 patients who experienced serious adverse events that were considered to be possibly related to the study drug included PTLD (3/38), CMV (2/38), pancreatitis (1/38) and peritonitis (1/38). There were two deaths, one arising from complications associated with the PTLD.

Only 4 of 38 patients were diagnosed with clinical biopsy-proven acute rejection. Two additional patients had subclinical rejection on a protocol kidney biopsy done at 3 months after transplantation. All the rejections were mild and were reversed with steroid pulse therapy. There was no graft loss from rejection. The results of this study suggest that efalizumab is potentially biologically active, but a larger trial will be required to assess preliminary efficacy and to more clearly establish the safety of efalizumab, especially in regards to PTLD.

The PK evaluation of efalizumab showed that the average drug concentrations and AUC in patients treated with 2 mg/kg were significantly higher than patients treated with 0.5 mg/kg (Table 6). The two immunosuppressive regimens (half-dose cyclosporine, sirolimus, prednisone or full-dose cyclosporine, MMF, prednisone) did not have an effect on the PKs of efalizumab. Of interest was that the trough concentrations per unit dose of efalizumab in renal transplant patients tended to be higher and the clearance lower than those observed in previous studies in psoriasis patients (38,39). There are several possible explanations for this slower clearance in renal transplant patients as compared to psoriasis patients. First, a larger number of activated T cells in the skin of psoriasis patients may result in greater local uptake of efalizumab, resulting in lower bioavailability particularly at the low doses. Second, it is possible that there may be direct effects of the immunosuppressive drugs on the clearance of efalizumab (39,42).

Efalizumab therapy resulted in both saturation of the binding site on CD11a as well as its down-modulation. CD11a expression and available binding sites returned to pretreatment levels by day 168. There was no difference in the extent of CD11a modulation or degree of saturation between the dosing groups (0.5 vs. 2.0 mg/kg).

The 0.5 mg/kg/week efalizumab regimen resulted in comparable saturation and down-modulation of CD11a as the higher dose regimen, was associated with similar efficacy but had fewer adverse events than the higher dose of efalizumab when used with either full-dose cyclosporine, MMF and prednisone or half-dose cyclosporine, sirolimus and prednisone.

The induction regimen of efalizumab used in this trial with weekly administration for 12 weeks is the prototype for the new generation of biologic agents that are being developed for chronic use (43). Costimulation blockade with belatacept administered intravenously chronically in renal transplant recipients with a CNI-free regimen showed comparable efficacy to a cyclosporine-based regime at 1 year following transplantation (9). This phase I/II trial of efalizumab suggests that this humanized monoclonal antibody may warrant further investigation as a novel biologic immunosuppressive agent for organ transplantation.

Acknowledgment

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