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Efficacy of Daclizumab in an African-American and Hispanic renal transplant population

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Abstract Current immunosuppressive regimens have decreased acute rejection rates during the 1st year after renal transplantation. However, this decrease has not been as marked in high-risk groups, such as African-American and Hispanic renal transplant recipients. We compared two simultaneous cohorts of altogether 36 African-American and Hispanic renal transplant recipients. Cohort one received a regimen of mycophenolate mofetil, prednisone, and a calcineurin inhibitor. The second cohort received the same protocol with the addition of Daclizumab (1 mg/kg for five doses given every 2 weeks). The median follow-up was 15.2 months (range 11.8–19.9 months). One patient in the Daclizumab-treated group and seven patients in the control group experienced an acute rejection episode. The rejection-free survival was significantly higher in the Daclizumab-treated group (94.4 %) as compared to the control group (66.7 %, Log-rank < 0.05) at 17 months after transplantation. A Cox Proportional Hazard model revealed lack of Daclizumab therapy as the only significant risk factor for acute rejection. (hazard ratio 7.0, 95 % CI = 1.1–48). The addition of the IL-2 receptor blocker Daclizumab to a triple therapy regimen may decrease early acute rejection in the high-risk groups of African-American and Hispanic patients.

Key words Kidney transplantation · High-risk population · Daclizumab · Immunosuppression

Introduction

Daclizumab is a humanized IgG monoclonal antibody that binds to the α chain of the IL-2 receptor [7]. Recently completed phase III studies have demonstrated the efficacy of Daclizumab in reducing episodes of acute rejection in primary renal transplants when added to a regimen of cyclosporine, azathioprine, and prednisone [2, 8]. Despite this evidence, limited data is available on the efficacy of Daclizumab in the high-risk groups of African-American and Hispanic renal transplant recipients. In addition, there is limited data on the safety and efficacy of Daclizumab when used in conjunction with regimens that incorporate mycophenolate mofetil.

It has been appreciated that African-American and Hispanic renal transplant recipients have an increased incidence of acute rejection as compared to Caucasian renal transplant recipients [1, 6]. This holds true even with triple drug regimens that include mycophenolate mofetil [5].

Table 1 Demographics (*AA* African-American; *H* Hispanic; *CAD* cadaveric; *LRD* living related; *PRA* panel-reactive antibody; *ATN* acute tubular necrosis)

	Daclizumab $n = 18$	Controls $n = 18$	P
Age (years)	41.4 ± 10.9 26–65	40.8 ± 11.1 24–64	[1]NS
Gender (m/f)	7 / 11	13 / 5	[2]< 0.05
Race (AA/H)	12 / 6	12 / 6	[2]NS
Diabetes (yes/no)	4 / 14	4 / 14	[2]NS
Donor (CAD/LRD)	10 / 8	14 / 4	[2]NS
FK506/CyA	3 / 15	3 / 15	[3]NS
HLA mismatch	2.58 ± 1.70 0–6	2.56 ± 1.75 0–5	[1]NS
PRA (%)	23.8 ± 32.2 0–93	4.2 ± 12.8 0–49	[1]< 0.05
Cold ischemia (hours)	14.5 ± 7.5 1.4–25.3	12.3 ± 11.6 0.5 ± 37.5	[1]NS
ATN (yes/no)	5 / 13	7 / 11	[2]NS
Follow-up (months)	6.07 ± 1.92 3.0–8.4	6.4 ± 2.3 3.1–11.1	[1]NS

[1] Independent sample t-test
[2] Chi-squared test
[3] Fisher's exact test

We examined the efficacy of Daclizumab when added to a triple therapy regimen consistenting of a calcineurin inhibitor, mycophenolate mofetil, and prednisone in an inner-city African-American and Hispanic renal transplant population, to determine whether this regimen could significantly improve the results obtained with traditional triple drug maintenance therapy.

Patients and methods

A total of 36 African-American and Hispanic renal transplant recipients were analyzed for this study. The setting was a tertiary care hospital in Newark, New Jersey. Simultaneous cohorts were compared from the time period of February 1998 to October 1999. One cohort (18 patients) received a regimen of a calcineurin inhibitor, along with mycophenolate mofetil at 1 g b.i.d. and solumedrol starting at 250 mg IV q.d. for the first 3 days and then prednisone tapered to 10 mg q.d. by 3 months. Cyclosporine (CyA) 12-h trough levels were targeted to be 250–350 ng/ml (by monoclonal TDX) during the first 3 months and then 200–300 ng/ml for the rest of the 1st year. A second cohort of 18 patients was evaluated who received an identical protocol with the exception of the addition of Daclizumab at 1 mg/kg per dose given every 2 weeks for a total of five doses over a 8 week period of time. All 18 patients completed the full course of Daclizumab treatment. In both cohorts, 15 patients received the microemulsion formulation of CyA while 3 patients received tacrolimus-based therapy. All patients in both cohorts received trimethoprim-sulfamethoxazole for pneumocystis carinii prophylaxis and acyclovir at 800 mg b.i.d. for cytomegalovirus (CMV) prophylaxis.

Independent sample t-test, chi-squared test, and Fisher's exact test as appropriate compared the demographic characteristics between the two groups. Immunosuppressive drug doses and blood chemistries among the study cohorts during the 1rst year of follow-up were compared by ANOVA analysis.

The rejection-free survival in the two study cohorts was displayed by Kaplan-Meier survival curves. Differences in rejection-free survival curves were estimated by Log-rank test.

Additionally, in a multivariate approach, a Cox Proportional Hazard regression was used to estimate the independent effect of Daclizumab therapy on the development of acute rejection in the two study cohorts while controlling for relevant risk factors. This model corrected for potential confounding variables such as race, gender, diabetes, HLA mismatch, cold ischemia time, acute tubular necrosis, and donor type (living vs cadaveric).

Test results were considered statistically significant at p values of less than 0.05. All statistical analyses were performed using SPSS software (Version 9.0 for Windows 95, SPSS, Chicago, Ill.).

Results

As demonstrated in Table 1 the baseline demographics did not differ between the two cohorts. Results are presented in Table 2. As seen in Table 2, CyA levels and (in the case of patients on tacrolimus) tacrolimus levels did not differ between the two groups. In addition, the mycophenolate mofetil doses were equivalent in the

Table 2 ANOVA comparison of immunosuppressive drug doses and blood chemistries during the 1 st year of follow-up (*MMF* mycophenolate mofetil; *Pred* prednisone)

	Cohort	1 month	3 months	6 months	P
MMF dose (mg/day)	Daclizumab Control	1944 ± 481 1833 ± 642	2115 ± 574 1846 ± 554	1666 ± 753 1750 ± 758	NS
CyA trough (ng/ml)	*Daclizumab *Control	258 ± 69 362 ± 108	233 ± 69 370 ± 141	243 ± 106 287 ± 112	NS
FK506 dose (mg/day)	Daclizumab Control	7.0 ± 4.6 5.3 ± 0.9	7.5 ± 7.7 5.0 ± 1.4	7.8 ± 3.8 5.0 ± 1.0	NS
FK506 trough (ng/ml)	Daclizumab Control	15.5 ± 4.9 12.7 ± 9.6	10.5 ± 3.3 10.1 ± 2.9	11.5 ± 8.7 10.7 ± 3.7	NS
Pred dose (mg/day)	*Daclizumab *Control	25.0 ± 4.1 43.3 ± 11.3	14.2 ± 5.4 22.2 ± 8.9	10.4 ± 1.1 13.9 ± 7.3	< 0.05

* $P < 0.05$ for comparison between Daclizumab and Control

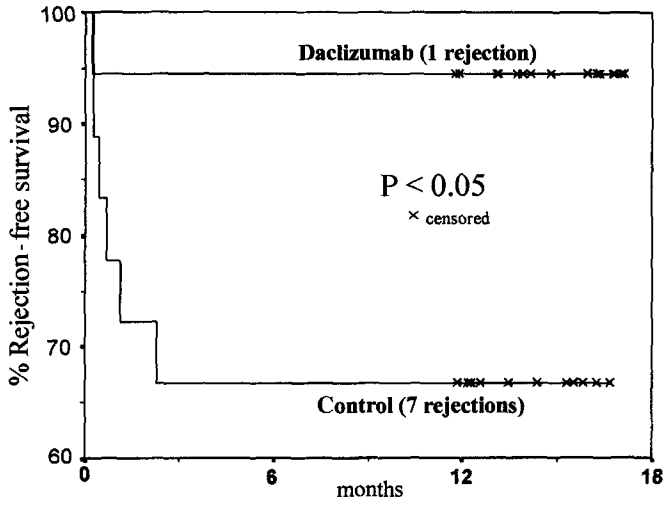

Fig. 1 Rejection-free survival in the Daclizumab-treated patients as compared to the control group

two groups. Prednisone doses were significantly higher in the control group. This was an effect of the higher incidence of rejection in the control group and the consequently increased steroid doses for the rejection treatment.

Only one rejection episode was noted in the Daclizumab group, while seven rejections were noted in the control group which resulted in a significantly different rejection-free survival among the two cohorts (Fig. 1, $p < 0.05$ by Log-rank). The incidence of CMV infections did not differ between the two groups. The Cox Proportional Hazard model revealed lack of Daclizumab therapy as the only significant risk factor for acute rejection (hazard ratio 7.0; 95 % CI = 1.1–48) and showed that the covariate factors of race, sex, diabetes, HLA mismatch, cold ischemic time, acute tubular necrosis (ATN), and donor type were not significant in explaining the difference in acute rejection rate found between the two groups. No patient lost their graft and no deaths occurred during the study period.

Discussion

Our study demonstrated that the addition of the IL-2 receptor blocker Daclizumab has the potential to decrease the incidence of early acute rejection in a subset of African-American and Hispanic patients, who tend to experience an increase in acute rejection rates as compared to Caucasian renal transplant recipients [1, 6]. This difference as demonstrated by multivariate analysis could not be ascribed to the particular calcineurin inhibitor used, calcineurin inhibitor concentrations, mycophenolate mofetil dose or prednisone dose.

New immunosuppressive regimens that include tacrolimus have been reported to decrease the incidence of acute rejection episodes in renal transplant recipients across racial barriers; however, African-Americans suffered higher rejection rates than Caucasians in these trials [4]. Mycophenolate mofetil, also demonstrated a significant decrease in acute rejection episodes in all study groups, but was less effective in African-American patients [3, 5].

Our study would indicate that the use of an IL-2 receptor blocker as an induction agent might be particularly helpful in the high-risk African-American and Hispanic renal transplant population by dramatically decreasing the incidence of acute rejection. It is worth pointing out that although the pharmacodynamic response of the IL-2 receptor blockade at dose regimens used in our study has been described to be in the order of 90 days [8], the protective effect from acute rejection seemed to last beyond the 1st year of transplantation in our study. Due to the short follow-up of our study, we could not make any conclusions on the issue of long-term graft survival, although given the substantial decrease in acute rejection, an improvement in long-term allograft survival might be expectable in African-American and Hispanic renal transplant recipients treated with Daclizumab induction therapy. The use of IL-2 receptor blockers in conjunction with newer immunosuppressive medications like Rapamycin in high-risk populations will need to be evaluated.

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