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The effect of Daclizumab in a high-risk renal transplant population

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Abstract: Introduction: African–American (AA) renal transplant recipients have a higher incidence of acute rejection when compared to Caucasian renal transplant recipients. This higher rejection rate holds true even with the addition of several of the newer immunosuppressive agents (e.g. mycophenolate mofetil (MMF) and Rapamycin). Acute rejection rates among Hispanic (H) renal transplant recipients are higher in some settings, while lower or the same as in Caucasians in other settings. IL-2 receptor antibodies have been shown to decrease rejection rates when added to a regimen of cyclosporine (CsA), azathioprine and prednisone. Limited data are available on these agents in conjunction with triple CsA, MMF and prednisone therapy, particularly in higher risk group patients. We studied the effect of the addition of the IL-2 receptor antibody Daclizumab to a CsA, MMF, prednisone regimen in a group of African–American and high-risk Hispanic renal transplant recipients.
Methods: This was a non-randomized, prospective study. A total of 49 renal transplant recipients (29 African–American and 20 Hispanic) were studied and followed. A simultaneous cohort of 56 (31 African–American and 25 Hispanic) renal transplant recipients receiving CsA, MMF and prednisone with no standard induction agent served as the control group. The study cohort received the same regimen with the addition of Daclizumab at 1 mg/kg for five doses over 10 wk. Multivariate analysis was performed to isolate independent factors influencing the study's results.
Results: A total of 56 patients in the control group and 49 patients in the Daclizumab group received an average follow-up of 17.1 ± 6.9 and 12.7 ± 5.1 months, respectively. Acute rejection rates were lower in the Daclizumab group as compared to the control group 26.4% versus 49.3% per patient years, respectively. A total of eight recurrent rejections in 6 patients occurred in the control group and none in the Daclizumab arm. Graft loss at this follow-up was no different between the groups.
Conclusion: The addition of Daclizumab to a regimen of CsA, MMF and prednisone decreases acute rejection episodes in a high-risk group of African–American and Hispanic renal transplant recipients.

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Key words: African–American – Daclizumab – high risk – Hispanic – immunosuppression – induction – kidney transplantation

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It is well recognized that African–American (AA) renal transplant recipients have an increased incidence of acute rejection when compared to Caucasian patients (1–3). The recent approval of agents, e.g. mycophenolate mofetil (MMF), tacrolimus and Rapamycin, have all decreased acute rejection rates when compared to their control group (4–6). However, each of these studies demonstrated either higher rejection rates or need for higher drug dosages in African–American patients (7–10).

The use of antibody induction in reducing rejection in high-risk patients such as African–American renal transplant recipients has been addressed

in previous studies with generally favorable results (11–13). However, these studies only evaluated polyclonal anti-lymphocytic antibodies or OKT3. In addition, none of these studies addressed the effect of antibody induction when added to regimens utilizing newer immunosuppressive agents such as MMF.

Daclizumab is a humanized IgG monoclonal antibody that binds to the alpha chain of the IL-2 receptor (14–16). Phase III trials utilizing Daclizumab in a regimen of cyclosporine (CsA), with or without azathioprine, and prednisone demonstrated a significant decrease in early acute rejection episodes (14–16). However, limited information is available on the efficacy of Daclizumab in African–American renal transplant recipients, particularly in conjunction with MMF therapy.

Due to the heterogeneity of the population identified as Hispanic, it has been difficult to assess this group's risk status. In our own program we noted that our Hispanic population suffered acute rejection rates higher than Caucasians and similar to that of African–Americans (45% in African–Americans and Hispanics versus 25% in Caucasians). This higher acute rejection rate in African–American and Hispanic renal transplant recipients was in the setting of a no-induction CsA, MMF and prednisone regimen.

We therefore studied the effect of the addition of Daclizumab to a regimen of CsA, MMF and prednisone in this high-risk group of renal transplant recipients.

Materials and methods

A total of 49 African–American and Hispanic renal transplant recipients constituted the study group. A simultaneous cohort of patients (56 African–American and Hispanics) was used as the control group. Study and control patients were transplanted between January 1998 and October 1999 and followed until February 2000. The control group received a regimen of calcineurin inhibitor, along with MMF at 1 g b.i.d. and solumedrol starting at 250 mg i.v. once a day for the first 3 days and then prednisone tapered to 10 mg once a day by 3 months. Cyclosporine 12-h trough levels were targeted to be 250–350 ng/mL (by monoclonal TDX) during the first 3 months and then 200–300 for the rest of the year. The study group of 49 patients received an identical protocol with the exception of the addition of Daclizumab at 1 mg/kg per dose given every 2 wk for a total of five doses over an 8-wk time period. All 49 patients completed the full course of Daclizumab treatment. In both cohorts, all patients received the micro-emulsion formulation of CsA with the exception of 9 patients in each group who 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-square test as appropriate compared the demographic characteristics between the two groups. 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 the Breslow 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, primary non-function, and donor type (living/cadaveric). Test results were considered statistically significant at $p < 0.05$. All statistical analysis was performed using SPSS software (Version 9.0 for Windows 95, SPSS, Inc., Chicago, IL, USA).

Results

As demonstrated in Table 1, the baseline demographics were not significantly different between the two cohorts with exception for a higher percentage of PRA prior to transplantation in the Daclizumab group, and a significantly longer follow-up in the control group. There was a lower

Table 1. Demographics

	Daclizumab (n = 49)	Controls (n = 56)	p
Age (yr)	42.8 ± 11.2, 21–65	40.1 ± 14.8, 27–67	ns[a]
Gender (male/female)	29/20 (59%)	32/24 (57%)	ns[b]
Race (AA/H)	29/20 (59%)	31/25 (54%)	ns[b]
Diabetes (yes/no)	11/45 (16%)	4/14 (20%)	ns[b]
Repeat tx (yes/no)	8/41 (16%)	9/47 (16%)	ns[b]
Donor (LD/CAD)	11/38 (22%)	22/34 (39%)	ns[b]
Induction (yes/no)	13/36 (27%)	19/37 (34%)	ns[b]
Fk506/CsA	9/40 (18%)	9/47 (16%)	ns[b]
AB mismatch	1.93 ± 1.2, 0–4	2.16 ± 1.3, 0–4	ns[a]
DR mismatch	0.81 ± 0.74, 0–2	0.89 ± 0.71, 0–2	ns[a]
PRA%	22.8 ± 31, 0–98	1.5 ± 7.4, 0–49	<0.05[a]
Cold ischemia (h)	14.7 ± 8.1, 1–31	13.2 ± 11.8, 0.5–37.5	ns[a]
DGF (yes/no)	18/31 (37%)	13/43 (23%)	ns[b]
Follow-up (months)	12.7 ± 5.1, 5–24	17.1 ± 6.9, 5–24	<0.05[a]

[a] Independent sample t-test.
[b] Chi-square.

Table 2. Rejection episodes

	n	%	Time post-transplant
First rejection			
Daclizumab	12	24.5	5.4 ± 4.3*, 0.2–14.9
Control	21	37.5	2.2 ± 3.1*, 0.2–11.1
Second rejection			
Daclizumab	0	0	na
Control	6	10.7	8.4 ± 4.9, 3.9–14.9
Third rejection			
Daclizumab	0	0	na
Control	2	3.6	15.5 ± 3.0, 13.3–17.6

* $p < 0.05$ by independent sample t-test.

incidence of living as opposed to cadaver donation in the Daclizumab group (22%) as opposed to the control group (39%) but the difference did not reach statistical significance. There was a trend to a higher incidence of delayed graft function in the Daclizumab group (37%) as opposed to the control group (23%); however, this difference was not statistically significant.

As shown in Table 2, there was a total of 12 rejections in the Daclizumab group as opposed to 29 in the control group. Of the 29 rejection episodes in the control group 21 where first rejections (37.5%), six were repeat rejections (10.7%) at least 3 months after the first episode, and two were third rejections. In the Daclizumab group none of the patients experienced a repeat rejection. First rejection episodes occurred significantly earlier in the control patients (2.2 ± 3.1 months post-transplant) as opposed to in the Daclizumab treated patients (5.4 ± 4.3 months post-transplant, $p < 0.05$).

As shown in Table 3, during the first year of follow-up, 11 rejection episodes (26.4% per 100 patient years) occurred in the Daclizumab group as compared to 25 rejection episodes (49.3% per 100 patient years) in the control group.

Fig. 1 shows that the Daclizumab group had a significantly higher rejection free survival as compared to the control group. There was also a significantly higher incidence of repeat rejections in the control group as compared to the Daclizumab group by Kaplan–Meier analysis as shown in Fig. 1.

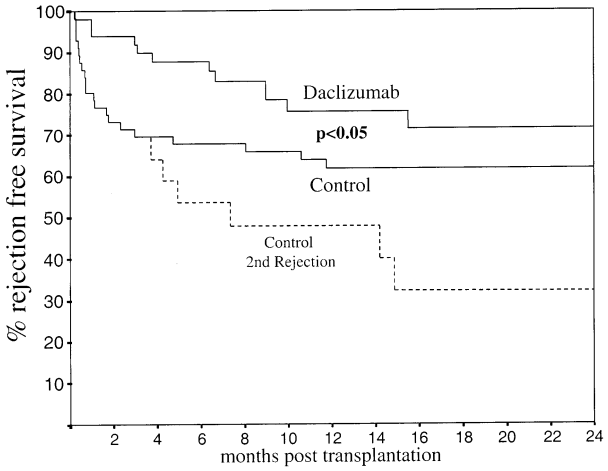

Fig. 1. Rejection free survival for first and second rejection.

Fig. 2 shows that the cumulative risk for a first rejection episode was significantly lower in the Daclizumab-treated group by Cox proportional hazard analysis. The only two significant protective factors from first acute rejection by Cox proportional hazard model were Daclizumab therapy (RR 0.34, CI 0.12–0.94) and living donation (RR 0.34, 0.11–0.99).

Discussion

To our knowledge, this is the largest study to assess the efficacy of the addition of an IL-2 receptor antibody to a-MMF based triple therapy regimen in a high immunologic risk population. In this population of African–American and high-risk Hispanic renal transplant recipients, the addition of Daclizumab for a 10-wk/five-dose course was associated with a significantly improved rejection free survival as compared to the control group by Kaplan–Meier analysis. The number of patients with an acute rejection episode trended lower in the Daclizumab group than in the control group (24.5% vs. 37.5%). However, when the total number of rejection episodes was taken into account a clear superiority in event free survival was noted in the Daclizumab group. It is interesting to note that at the time of this follow-up, eight recurrent rejections have occurred in the control group and none in the Daclizumab group.

Table 3. Total number of rejection episodes (first and subsequent) limited to the first year of follow-up

	n	Episodes per 100 patients (%)	Mean follow-up years	Episodes per 100 patient years (%)
Daclizumab	11	22.4	0.85	26.4
Control	25	44.6	0.91	49.3
All	36	34.3	0.88	39.0

The demographics for both groups were relatively equal with the Daclizumab group having a higher average PRA level and the control group having a longer follow-up period. Both these factors were taken into account by the multivariate analysis. In addition, CsA (and where applicable tacrolimus) concentrations were not different between the groups, nor were MMF or prednisone doses. There was an equal number of patients on tacrolimus in the study and the control group and the use of tacrolimus versus Neoral was also accounted for by the multivariate analysis and had no impact on the results.

The rejection rate in our control arm was very similar to the rejection rate noted for African–American patients in the 2-g arm of the phase 3 MMF study. Therefore, it is likely that our population offers a fair representation of this high-risk group.

Hispanic patients comprise a very heterogeneous group of people, in our population. Hispanic patients had rejection rates similar to those for African–Americans (45%) and higher than those for Caucasians (25%). The addition of Daclizumab to this group showed the same beneficial effect as observed for the African–American group.

Daclizumab clearly increased the time to a first rejection when compared to the control group. However, there did seem to be a tendency for the Daclizumab group to have an increased number of patients suffering a first acute rejection episode after the first 6 months. This raises the possibility that the drug is merely shifting rejections over to a later time period. While this is possible, it may be more important to look at the total number of rejection episodes as opposed to patients developing rejection. If looked at in this light, the difference in number of rejection episodes does not narrow over time. The best interpretation of these data may be that Daclizumab offers significant protection during the time of its activity and thereafter patients return to their baseline risk having been covered during the most vulnerable immunologic time period.

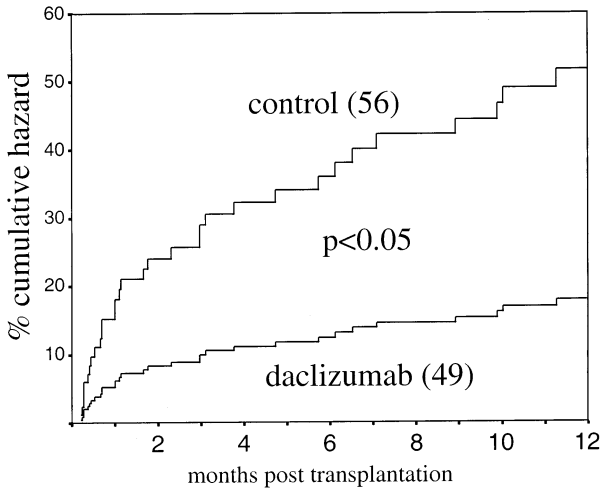

Fig. 2. Cumulative risk for a first acute rejection during the first year of follow-up by Cox proportional hazard

In summary, our study demonstrates that the addition of the IL-2 receptor antibody Daclizumab to a triple therapy regimen significantly decreases the number of rejections and number of recurrent rejection episodes in African–American and a high-risk group of Hispanic renal transplant recipients. Whether this effect will translate into better long-term graft survival will need to be addressed by a longer follow-up and a larger number of patients.

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