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## INTERLEUKIN-2-RECEPTOR BLOCKADE WITH DACLIZUMAB TO PREVENT ACUTE REJECTION IN RENAL TRANSPLANTATION

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## ABSTRACT

**Background** Monoclonal antibodies that block the high-affinity interleukin-2 receptor expressed on alloantigen-reactive T lymphocytes may cause selective immunosuppression. Daclizumab is a genetically engineered human IgG1 monoclonal antibody that binds specifically to the  $\alpha$  chain of the interleukin-2 receptor and may thus reduce the risk of rejection after renal transplantation.

**Methods** We administered daclizumab (1.0 mg per kilogram of body weight) or placebo intravenously before transplantation and once every other week afterward, for a total of five doses, to 260 patients receiving first cadaveric kidney grafts and immunosuppressive therapy with cyclosporine, azathioprine, and prednisone. The patients were followed at regular intervals for 12 months. The primary end point was the incidence of biopsy-confirmed acute rejection within six months after transplantation.

**Results** Of the 126 patients given daclizumab, 28 (22 percent) had biopsy-confirmed episodes of acute rejection, as compared with 47 of the 134 patients (35 percent) who received placebo ( $P=0.03$ ). Graft survival at 12 months was 95 percent in the daclizumab-treated patients, as compared with 90 percent in the patients given placebo ( $P=0.08$ ). The patients given daclizumab did not have any adverse reactions to the drug, and at six months, there were no significant differences between the two groups with respect to infectious complications or cancers. The serum half-life of daclizumab was 20 days, and its administration resulted in prolonged saturation of interleukin-2 $\alpha$  receptors on circulating lymphocytes.

**Conclusions** Daclizumab reduces the frequency of acute rejection in kidney-transplant recipients. (N Engl J Med 1998;338:161-5.)

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**A**CUTE rejection is a strong risk factor for chronic rejection in recipients of renal grafts from cadaveric donors.<sup>1</sup> This fact has prompted the development of new immunosuppressive agents designed to reduce the incidence and severity of acute rejection.<sup>2-6</sup> All these agents, however, achieve reductions in the frequency and severity of acute rejection at the price of generalized immunosuppression, with its attendant risks of opportunistic infection and cancer.

One potential target for more specific immunosuppressive therapy with monoclonal antibodies is

the interleukin-2 receptor.<sup>7</sup> The high-affinity interleukin-2 receptor is composed of three noncovalently bound chains: a 55-kd  $\alpha$  chain (also referred to as CD25 or Tac), a 75-kd  $\beta$  chain, and a 64-kd  $\gamma$  chain.<sup>7</sup> This receptor is present on nearly all activated T cells but not on resting T cells. The interaction of interleukin-2 with this high-affinity receptor is required for the clonal expansion and continued viability of activated T cells. A variety of rodent monoclonal antibodies directed against the  $\alpha$  chain of the receptor have been used in animals and humans to achieve selective immunosuppression by targeting only T-cell clones responding to the allograft.<sup>8-13</sup> Daclizumab, a molecularly engineered human IgG1 incorporating the antigen-binding regions of the parent murine monoclonal antibody, offers the potential for greater therapeutic use of interleukin-2-receptor blockade.<sup>14-17</sup> We compared the efficacy of daclizumab with placebo for the prevention of acute rejection in renal-transplant recipients.

## METHODS

## Study Design

We performed a randomized, double-blind, placebo-controlled trial at 11 transplantation centers in the United States, 3 in Canada, and 3 in Sweden. Adults receiving first renal allografts from cadaveric donors were eligible for the study. Patients were excluded if they were receiving multiple organ transplants or had a positive crossmatch for T-cell lymphocytes. The protocol was approved by the institutional review board or ethics committee at each participating center, and all patients gave written informed consent.

## Immunosuppressive Treatment

All patients received cyclosporine, azathioprine, and prednisone. The first dose of cyclosporine was given during the period from 12 hours before to 24 hours after transplantation.

Daclizumab (Zenapax, Hoffmann-LaRoche) or placebo was

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\*Other members of the Daclizumab Triple Therapy Study Group are listed in the Appendix.

administered intravenously over a period of 15 minutes. Each patient received five doses of either daclizumab (4 mg per kilogram of body weight, to a maximum of 100 mg per dose) or placebo (0.2 mg of polysorbate 80 per milliliter in 67 mM phosphate buffer). The first dose was administered within 24 hours before transplantation, with subsequent doses given two, four, six, and eight weeks after transplantation.

#### Primary and Secondary End Points

The primary end point of the study was the incidence of biopsy-confirmed acute rejection within the first six months after transplantation. All patients with an unexplained rise in the serum creatinine concentration or one or more symptoms of acute rejection (fever, pain over the graft, or a decrease in urinary volume) were required to undergo a renal biopsy within 24 hours after the initiation of antirejection therapy, which consisted initially of intravenous methylprednisolone (7 mg per kilogram per day) for three days. The histologic diagnosis of rejection was based on the presence of acute tubulitis or vasculitis and was made by the pathologist at each institution. Patients were considered to have presumptive rejection if they received a course of antirejection therapy in the absence of histologic confirmation of rejection. The diagnosis of any subsequent episodes of rejection in patients presenting with renal dysfunction was based on clinical criteria, such as the absence of evidence of nephrotoxicity or of urinary tract obstruction or infection, with a biopsy for confirmation performed at the investigator's discretion.

Secondary end points included patient survival and graft survival at one year, the time to the first episode of acute rejection, the number of acute rejection episodes per patient, the need for antilymphocyte therapy (OKT3 or polyclonal antithymocyte globulin) because of glucocorticoid-resistant rejection (defined as the absence of a response to intravenous methylprednisolone pulse therapy), graft function (as indicated by the serum creatinine concentration and glomerular filtration rate), and the cumulative dose of prednisone in the first six months after transplantation.

#### Pharmacokinetic Measurements

Blood samples were collected immediately before and after (for trough and peak concentrations, respectively) the first and fifth infusions of daclizumab or placebo and on days 70 and 84 after transplantation. A sandwich enzyme-linked immunosorbent assay was used to measure daclizumab in serum.<sup>18</sup>

In 20 consecutive patients at one U.S. center (University of California, San Francisco), lymphocyte analysis was performed to determine the saturation of the interleukin-2-receptor  $\alpha$  chain, with the use of methods reported previously.<sup>17</sup>

#### Glomerular Filtration Rate

The glomerular filtration rate was measured in all patients with functioning grafts six months after transplantation. Measurements were based on iohexol, radioisotope, or inulin clearance.

#### Statistical Analysis

Differences in categorical variables between the two groups were determined with the use of the Mantel-Haenszel test (with stratification according to center). Differences in the time to the first biopsy-confirmed episode of rejection were determined with the use of the log-rank test (with stratification according to center). The log-rank test was also used to analyze the time to graft failure (or death with a functioning graft) because of the small number of events reported. Kaplan-Meier estimates of the probability of patient survival and graft survival and the cumulative probability of biopsy-confirmed rejection were plotted over time. Differences in the number of presumptive or biopsy-confirmed rejection episodes per patient in the first six months were analyzed with a normal regression model. The serum creatinine concentrations, glomerular filtration rates, and cumulative doses of prednisone administered during the first six months after trans-

plantation in the two groups were compared with the use of the Wilcoxon rank-sum test. Logistic-regression analysis was used to determine the effects of various factors on the probability of biopsy-confirmed rejection. Proportional-hazards analysis was used to determine the effects of various factors on the time to biopsy-confirmed rejection. The results of lymphocyte and interleukin-2-receptor assays were compared with the use of Student's *t*-test. All statistical tests were two-sided.

All patients randomly assigned to a treatment group were included in the primary analyses of efficacy and safety, according to the intention-to-treat principle. Values are reported as means  $\pm$  SD.

## RESULTS

A total of 260 patients were enrolled in the study: 134 patients were assigned to the placebo group, and 126 to the daclizumab group. The two groups were similar with respect to age, sex, race, cause of end-stage renal disease, presence or absence of panel-reactive anti-HLA antibodies, number of HLA-DR mismatches between donor and recipient, and duration of cold ischemia for the graft (Table 1).

All patients received at least one dose of the study drug, and 107 of the patients in the placebo group (80 percent) and 107 of those in the daclizumab group (85 percent) received all five doses. Graft function was delayed in 39 patients in the placebo group (29 percent) and 27 patients in the daclizumab group (21 percent). The early use of prophylactic antilymphocyte therapy for delayed graft function led to the discontinuation of the study drug in nine patients in the placebo group (7 percent) and nine in the daclizumab group (7 percent).

#### Efficacy

Daclizumab prophylaxis resulted in a significant reduction in the incidence of biopsy-documented acute rejection during the first six months after transplantation (22 percent, vs. 35 percent in the placebo group;  $P=0.03$ ; odds ratio, 0.5; 95 percent confidence interval, 0.3 to 0.9) (Table 2). The proportion of patients with presumptive or biopsy-confirmed acute rejection and the number of rejection episodes per patient were also lower in the daclizumab group, and the time to the first rejection was longer. There was a trend toward a reduction in the number of patients with two or more rejection episodes and the number receiving antilymphocyte preparations for severe rejection in the daclizumab group. The beneficial effect of daclizumab was not influenced by delayed graft function, initial use of other antilymphocyte therapies, or exclusion of patients who did not receive all five infusions of the study drug (data not shown).

The patient-survival rates at one year were 98 percent in the daclizumab group and 96 percent in the placebo group (Table 3). The graft-survival rates in the daclizumab and placebo groups were 95 and 90 percent, respectively. None of the patients in the daclizumab group but three of those in the placebo group died of infections: one each of aspergillosis,

INTERLEUKIN-2-RECEPTOR BLOCKADE WITH DACLIZUMAB TO PREVENT REJECTION IN RENAL TRANSPLANTATION

TABLE 1. BASE-LINE CHARACTERISTICS OF RENAL-ALLOGRAFT RECIPIENTS.\*

CHARACTERISTIC	PLACEBO (N = 134)	DACLIZUMAB (N = 126)
Age — yr	47±13	47±13
Sex — no. of patients (%)		
Male	81 (60)	74 (59)
Female	53 (40)	52 (41)
Race or ethnic group — no. of patients (%)		
White	81 (60)	84 (67)
Black	27 (20)	24 (19)
Other	26 (19)	18 (14)
Cause of renal failure — no. of patients (%)		
Glomerulonephritis	40 (30)	33 (26)
Diabetes mellitus	29 (22)	32 (25)
Hereditary or polycystic kidney disease	20 (15)	24 (19)
Hypertension	19 (14)	18 (14)
Other	26 (19)	19 (15)
Panel-reactive serum antibodies — no. of patients (%)†		
0–10%	121 (90)	113 (89)
11–49%	10 (7)	12 (10)
50–100%	3 (2)	1 (1)
No. of HLA-DR mismatches — no. of patients (%)‡		
0	22 (16)	19 (15)
1	62 (46)	49 (39)
2	40 (30)	50 (40)
Graft cold-ischemia time — hr	21±9	22±8

\*Plus-minus values are means ±SD. Percentages may not sum to 100 because of rounding.

†Panel-reactive antibodies are anti-HLA antibodies that have a cytotoxic effect on lymphocytes obtained from a panel of donors from the general population.

‡Data were missing for some patients.

TABLE 2. ACUTE REJECTION EPISODES IN THE FIRST SIX MONTHS AFTER RENAL TRANSPLANTATION IN THE PLACEBO AND DACLIZUMAB GROUPS.

REJECTION	PLACEBO (N = 134)	DACLIZUMAB (N = 126)	P VALUE
One or more biopsy-confirmed episodes — no. of patients (%)	47 (35)	28 (22)	0.03
One or more biopsy-confirmed or presumptive episodes — no. of patients (%)	52 (39)	32 (25)	0.04
Two or more biopsy-confirmed or presumptive episodes — no. of patients (%)	18 (13)	9 (7)	0.08
Mean no. of episodes/patient	0.6	0.3	0.01
Time to first episode — days*	30±27	73±59	0.008
Episode requiring antilymphocyte therapy — no. of patients (%)†	19 (14)	10 (8)	0.09

\*Plus-minus values are means ±SD.

†Antilymphocyte therapy consisted of OKT3 or polyclonal antilymphocyte globulin.

TABLE 3. CAUSES OF DEATH AND RENAL-GRAFT FAILURE AT ONE YEAR IN THE PLACEBO AND DACLIZUMAB GROUPS.

CAUSE	PLACEBO (N = 134)	DACLIZUMAB (N = 126)
	no. of patients (%)	
Death	5 (4)	3 (2)
Infection or lymphoma	3 (2)	1 (1)
Cardiovascular cause	1 (1)	0
Pulmonary embolism	1 (1)	0
Intracerebral bleeding	0	1 (1)
Suicide	0	1 (1)
Graft failure	13 (10)	6 (5)
Death	5 (4)	3 (2)
Rejection	3 (2)	1 (1)
Technical cause	4 (3)	2 (2)
Primary nonfunction	1 (1)	0

coccidioidomycosis, and pseudomonas sepsis. One patient in the daclizumab group died of lymphoma.

The mean serum creatinine concentrations six months after transplantation were the same in the two groups (1.7±0.7 mg per deciliter [150±60 μmol per liter]). The mean glomerular filtration rate was 55±23 ml per minute in the daclizumab group and 52±22 ml per minute in the placebo group. The average daily doses of prednisone and cyclosporine did not differ between the groups at any time during the study, nor was there a difference in the mean trough whole-blood cyclosporine concentrations at any time.

Adverse Events

The administration of daclizumab was not associated with any immediate side effects. There was no significant difference in reported adverse events between the two groups (Table 4). One patient in the placebo group and two patients in the daclizumab group had lymphoma during the first year after transplantation.

Pharmacokinetic Data

Pharmacokinetic data were available for 92 patients in the daclizumab group. The mean serum half-life of daclizumab was 20 days.

Circulating Peripheral-Blood Lymphocytes and Interleukin-2 α-Chain Receptor

There were no differences in absolute lymphocyte numbers between the placebo and daclizumab groups before transplantation or for six months afterward. Circulating CD3+ cell concentrations and T-cell subgroups were not measured, because they were not affected by daclizumab therapy in an earlier study.<sup>17</sup> There was a significant decrease in the percentage of circulating lymphocytes that stained with anti-

**TABLE 4.** ADVERSE EVENTS AT SIX MONTHS IN THE PLACEBO AND DACLIZUMAB GROUPS.

ADVERSE EVENTS	PLACEBO (N=134)	DACLIZUMAB (N=126)
	no. of patients (%)	
Serious event*	13 (10)	6 (5)
Fever	16 (12)	11 (9)
Sepsis and bacteremia	9 (7)	4 (3)
Pneumonia	4 (3)	3 (2)
Fungal infection	27 (20)	21 (17)
Fungemia	2 (1)	0
Local infection	25 (19)	21 (17)
Local infection†	70 (52)	59 (47)
Cellulitis and wound infection	4 (3)	7 (6)
Urinary tract infection	44 (33)	34 (27)
Other	38 (28)	36 (29)
Any viral infection†	32 (24)	29 (23)
Viremia	12 (9)	12 (10)
Local infection	21 (16)	20 (16)
Cytomegalovirus infection	14 (10)	15 (12)
Viremia	10 (7)	12 (10)
Tissue infection	4 (3)	3 (2)

\*Serious adverse events were defined as complications other than death or rejection that prolonged or required hospitalization and were possibly or probably related to the study drug.

†Some patients had more than one type of infection.

CD25 antibody starting 10 hours after transplantation and lasting up to four months in the daclizumab group (data not shown). Similarly, there was a significant decrease in the percentage of circulating lymphocytes that stained with the fluorescein-conjugated antibody 7g7, which binds to an interleukin-2  $\alpha$ -chain-receptor epitope distinct from the epitope recognized by daclizumab and reflects total interleukin-2 $\alpha$ -receptor expression (data not shown).

### DISCUSSION

We found that the patients receiving daclizumab in addition to maintenance therapy with three immunosuppressive agents had a lower frequency of biopsy-confirmed acute rejection in the first six months after transplantation than the patients receiving placebo with the three immunosuppressive agents. In addition, the time to the first episode of acute rejection was significantly prolonged, and the mean number of episodes per patient significantly reduced in the daclizumab group. These results were obtained without a concomitant increase in infectious complications or cancers. The efficacy of daclizumab is probably related to its selective target, the  $\alpha$ -chain component of the high-affinity interleukin-2 receptor, which is present almost exclusively

on activated T cells. Use of the drug thus spares other immunocompetent cells.<sup>7</sup>

Only 10 percent of daclizumab is composed of murine sequences, which are from the antigen-binding regions of the parent antibody. These sequences are inserted into human immunoglobulin with the use of molecular biologic techniques.<sup>14</sup> Our study highlights the advantages of this type of antibody, including its prolonged serum half-life, approaching that of human IgG, and the absence of functional immunogenicity associated with its use.<sup>15,16,19,20</sup>

The exact mechanism or mechanisms of action of daclizumab are not known. A likely mechanism is that it binds to circulating lymphocytes with interleukin-2  $\alpha$ -chain receptors but does not activate the receptors, and the cells therefore have no free interleukin-2  $\alpha$ -chain receptors available for activation by interleukin-2. In addition, the decline in the percentage of circulating lymphocytes expressing CD25 (measured by staining with 7g7 antibody) without an accompanying decrease in the absolute number of lymphocytes suggests that the expression of interleukin-2 receptors is down-regulated or the shedding of the daclizumab-bound interleukin-2  $\alpha$  chain is increased.

In conclusion, when added to therapy with cyclosporine, azathioprine, and prednisone, daclizumab reduces the frequency of acute rejection and improves short-term graft survival in renal-transplant recipients.

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### APPENDIX

In addition to the authors, the following investigators participated in the Daclizumab Triple Therapy Study Group: *Victoria General Hospital, Halifax, N.S., Canada* — B. Kibert; *Huddinge Hospital, Huddinge, Sweden* — G. Tyden; *University of Minnesota, Minneapolis* — A. Matas; *Beth Israel Deaconess Medical Center, Boston* — M. Shapiro; *Tampa General Hospital, Tampa, Fla.* — G. Chan; *Vancouver General Hospital, Vancouver, B.C., Canada* — P. Keown; *University of California, San Francisco* — M. Lantz; *University of Alberta, Edmonton, Alta., Canada* — K. Solez; and *Hoffmann-LaRoche, Nutley, N.J.* — A. Lin, I. Patel, K. Nieforth, A. Wolitzky, and J. Hakimi.

### REFERENCES

1. Ferguson R. Acute rejection episodes — best predictor of long-term primary cadaveric renal transplant survival. *Clin Transplant* 1994;8:328-31.
2. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation* 1995; 60:225-32.
3. Vincenti F, Laskow DA, Neylan JF, Mendez R, Matas AJ. One-year follow-up from an open-label trial of FK506 in primary kidney transplantation: a report of the U.S. Multicenter FK506 Kidney Transplantation Group. *Transplantation* 1996;61:1576-81.
4. Morris RE. Mechanisms of action of new immunosuppressive drugs. *Kidney Int Suppl* 1996;53:S-26-S-38.
5. Kahan BD. Sirolimus: a new agent for clinical renal transplantation. *Transplant Proc* 1997;29:48-50.
6. Gruber SA, Chan GLC, Canafax DM, Matas AJ. Immunosuppression in renal transplantation. II. Corticosteroids, antilymphocyte globulin, and OKT3. *Clin Transplant* 1991;5:219-32.

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