

## PREVENTION OF REJECTION IN CARDIAC TRANSPLANTATION BY BLOCKADE OF THE INTERLEUKIN-2 RECEPTOR WITH A MONOCLONAL ANTIBODY

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**ABSTRACT**

**Background** Alloantigen-activated T cells express the high-affinity interleukin-2 receptor. Specific blockade of this receptor with the human IgG1 monoclonal antibody daclizumab may prevent rejection of allografts after cardiac transplantation without inducing global immunosuppression.

**Methods** We randomly assigned 55 nonsensitized patients undergoing a first cardiac transplantation to receive either induction therapy with daclizumab (1.0 mg per kilogram of body weight), given intravenously within 24 hours after cardiac transplantation and every two weeks thereafter, for a total of five doses, or generalized immunosuppressive therapy. Concomitant immunosuppression was achieved in both groups with cyclosporine, mycophenolate mofetil, and prednisone. The primary end points were the incidence and severity of acute rejection, and the length of time to a first episode of biopsy-confirmed rejection.

**Results** Of the 55 patients in the study, 28 were randomly assigned to receive daclizumab and 27 served as the control group. During induction therapy, the mean frequency of acute rejection episodes (defined as a histologic grade of 2 or higher according to the classification of the International Society of Heart and Lung Transplants) was 0.64 per patient in the control group and 0.19 per patient in the daclizumab group ( $P=0.02$ ). Acute rejection developed in 17 of 27 patients in the control group (63 percent), as compared with 5 of 28 patients in the daclizumab group (18 percent; relative risk, 2.8; 95 percent confidence interval, 1.1 to 7.4;  $P=0.04$ ). Throughout follow-up, there were nine patients with episodes of acute rejection of histologic grade 3 in the control group, as compared with two in the daclizumab group ( $P=0.03$ ), and the time to a first episode of rejection was significantly longer in the daclizumab group ( $P=0.04$ ). There were no adverse reactions to daclizumab and no significant differences between the groups in the incidence of infection or cancer during follow-up.

**Conclusions** Induction therapy with daclizumab safely reduces the frequency and severity of cardiac-allograft rejection during the induction period. (N Engl J Med 2000;342:613-9.)

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**A**CUTE rejection episodes adversely affect short-term survival in recipients of cardiac transplants.<sup>1</sup> Rejection occurs most frequently during the first three months after transplantation, with the incidence decreasing exponentially thereafter.<sup>2</sup> Repeated or severe episodes of allograft rejection may lead to the development of

cardiac-allograft vasculopathy, the main cause of death after the first year in transplant recipients.<sup>3-6</sup> Accordingly, therapeutic strategies, such as the use of induction therapy with monoclonal or polyclonal antibodies in the perioperative period, have been advocated to decrease the frequency and severity of early allograft rejection.<sup>7</sup> The success of these nonselective agents has varied.<sup>7</sup> Allograft rejection is only delayed by their use, and the generalized immunosuppression they induce frequently increases the risk of opportunistic infection and cancer.

More selective agents that target key receptors, such as the interleukin-2 receptor on activated T cells, may be more effective than nonselective agents.<sup>8</sup> In vivo activation of the high-affinity interleukin-2 receptor by interleukin-2 promotes the clonal expansion of the activated T-cell population.<sup>9</sup> Daclizumab (Zenapax, Hoffmann-LaRoche, Nutley, N.J.) is a molecularly engineered human IgG1 monoclonal antibody that binds but does not activate the high-affinity interleukin-2 receptor. Because it consists of 90 percent human immunoglobulin sequences, daclizumab has low immunogenicity; its serum half-life is 21 days.

A previous study examined the administration of daclizumab to recipients of cadaveric renal transplants<sup>10</sup> and found decreases in the number of episodes of allograft rejection and an increase in the time to a first rejection episode without a concomitant increase in the incidence of infection or cancer. The purpose of the current study was to investigate the safety and efficacy of daclizumab with respect to the frequency and severity of acute rejection in nonsensitized recipients of first cardiac transplants.

**METHODS****Patients**

We recruited a total of 55 consecutive adult patients between January 1, 1998, and December 31, 1998. Patients were excluded if they were recipients of previous allografts or had a positive cross-match for T-cell lymphocytes. Patients were randomly assigned to receive standard triple immunosuppressive therapy either with or without daclizumab. Randomization was performed at the time of transplantation with the use of sealed envelopes. The protocol was approved by the institutional review board of Columbia-Presbyterian Medical Center, and all patients gave written informed consent.

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### Immunosuppressive Therapy

Triple-drug immunosuppressive therapy with cyclosporine, mycophenolate mofetil, and prednisone was administered to all the patients. Oral cyclosporine was given preoperatively at a dose of 1 to 2 mg per kilogram of body weight, according to the patient's creatinine clearance rate. Intravenous cyclosporine was administered as a continuous infusion at a dose of 1 to 2 mg per kilogram per 24 hours until the patient could receive oral medications. The doses of cyclosporine were adjusted to obtain a whole-blood trough level of 300 to 350 ng per milliliter, as measured with the use of a monoclonal assay (TDX, Abbott Laboratories, Abbot Park, Ill.), for the first six weeks after transplantation. Target trough levels decreased as the time after transplantation increased. After transplantation, muromonab-CD3 (OKT3) or antithymocyte globulin induction therapy was used instead of cyclosporine in patients with prolonged renal dysfunction (defined by a creatinine concentration  $>2.5$  mg per deciliter [ $221 \mu\text{mol}$  per liter]).

All the patients received 4 mg of azathioprine per kilogram orally before transplantation and then 2 mg per kilogram intravenously afterward until they were able to receive oral medications. The dose of mycophenolate mofetil was then increased to a maximum of 1500 mg twice daily over a period of three days.

Intravenous methylprednisolone was administered at a dose of 1 g intraoperatively and then 125 mg every eight hours for three doses. Prednisone or an equivalent dose of methylprednisolone was begun at 50 mg orally twice daily and tapered over the course of seven days to 15 mg orally twice daily. After each negative biopsy, the dose of prednisone was further tapered according to a standard schedule.

Daclizumab was given intravenously at a dose of 1 mg per kilogram within 24 hours after transplantation and every two weeks thereafter for a total of five doses.

### Biopsy Schedule, Histologic Grading of Rejection, and Treatment of Rejection

Endomyocardial biopsies were performed weekly for the first month after transplantation, every two weeks for the second month, monthly through month 6, and then every two months through month 12. Biopsy specimens were graded according to the standardized criteria of the International Society of Heart and Lung Transplants (ISHLT).<sup>11</sup> Acute allograft rejection was defined as a histologic grade of 2 or higher according to the ISHLT criteria. Patients with symptoms of heart failure or hemodynamic compromise were considered to have rejection even if the histologic grade was lower than 2. Hemodynamic compromise was defined as a pulmonary-capillary wedge pressure of more than 20 mm Hg, a cardiac index of less than 2 liters per minute per square meter of body-surface area, or a pulmonary arterial oxygen saturation of less than 50 percent. Both the ISHLT grade and the degree of hemodynamic compromise determined the type of treatment for a particular episode of rejection. All the patients underwent another biopsy 7 to 10 days after the treatment of an acute rejection episode.

### Immunologic Assays

#### HLA Typing

Serologic typing of HLA-A and HLA-B loci was performed by standard microcytotoxicity techniques. HLA-DR typing was performed by serologic analysis and DNA techniques with sequence-specific oligonucleotide primers and the polymerase chain reaction.

#### Lymphocyte-Growth Assay

A fragment of a biopsy specimen was placed in medium supplemented with recombinant interleukin-2 (5 U per milliliter) and examined at 48 hours with a phase-inverted microscope. A semi-quantitative scale (0 to 3) was used to score growth on the basis of circumferential T-cell aggregation.<sup>12</sup> A score of 1 or more was considered positive.

### Anti-HLA Antibodies

At the time of each endomyocardial biopsy, serum was screened for complement-mediated lytic activity, in the presence or absence of dithiothreitol, against T and B lymphocytes included in a panel of 70 of the most common HLA class I and class II antigens. Serum reactivity that persisted after treatment with dithiothreitol was considered to indicate the presence of IgG alloantibodies, whereas loss of reactivity indicated the presence of IgM alloantibodies. Serum reactivity with both T-cell and B-cell panels indicated the presence of anti-HLA class I antibodies. Serum reactivity with B-cell panels, but not with T-cell panels, indicated the presence of anti-HLA class II antibodies. Antibodies against both HLA class I and HLA class II antigens were considered present in cases in which serum reacted with both panels and B-cell reactivity exceeded T-cell reactivity by a factor of more than two. The presence of autoantibodies was considered to be ruled out by autologous serum crossmatching with recipient T cells and B cells. These combined methods have a high degree of sensitivity and specificity for anti-HLA class I and class II antibodies.<sup>13</sup>

### End Points

The primary end points of the study were the incidence of biopsy-confirmed rejection, the severity of rejection, and the length of time to a first treated episode of rejection. Secondary end points included the need for antilymphocytic therapy with muromonab-CD3 or antithymocyte globulin, the presence of immunologic indicators of alloreactivity, the duration of hospitalization after transplantation, the frequency of readmissions, and the incidence of infections and cancer. One-year survival and the mean daily doses of prednisone at each month after transplantation were also compared.

### Statistical Analysis

Differences in categorical variables between the two groups were evaluated by chi-square analysis. Continuous variables were compared between the groups with an unpaired Student's *t*-test. Kaplan-Meier plots with log-rank analysis were used to compare the time to a first rejection episode and survival in the two groups.

## RESULTS

A total of 55 patients were enrolled. Of these, 28 were randomly assigned to the daclizumab group and 27 to the control group by means of sealed envelopes. The base-line characteristics of the two groups were similar with respect to age, sex, donor's age, the need for prophylaxis against cytomegalovirus (given if either the donor or the recipient was seropositive), the presence of an HLA-DR match, and the duration of follow-up (Table 1). The duration of cold ischemia was slightly but significantly shorter in the control group than in the daclizumab group ( $P=0.05$ ).

All the patients in the daclizumab group received all five doses of the drug. The trough levels of cyclosporine were similar in the two groups throughout the follow-up period (Fig. 1A). The number of patients who were switched from cyclosporine to tacrolimus was the same in both groups. In the control group, one patient was switched because of neurotoxic effects, one because of frequent episodes of allograft rejection, one because of hirsutism, and one because of excessive gingival hyperplasia. In the daclizumab group, one patient was switched because of cyclosporine-induced hemolytic-uremic syndrome, two because of hirsutism, and one because of excessive gingival hyperplasia.

**TABLE 1.** CLINICAL CHARACTERISTICS OF THE STUDY PATIENTS.\*

CHARACTERISTIC	CONTROL GROUP (N=27)	DACLIZUMAB GROUP (N=28)
Age (yr)	50±13	53±14
Sex (no.)		
Male	21	22
Female	6	6
Age of donor (yr)	34±10	29±12
Cold-ischemia time (min)	173±60	209±69†
Cytomegalovirus prophylaxis (no.)	16	15
HLA match (no.)		
HLA-A	9	13
HLA-B	3	7
HLA-DR	9	13
Follow-up (days)	502±117	454±76

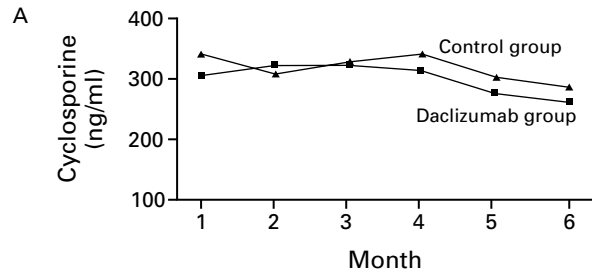
\*Plus-minus values are means ±SD.

†P=0.05.

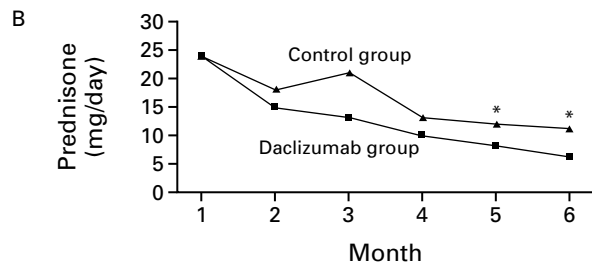
**Efficacy**

The period of induction therapy (based on the dosing regimen and the half-life of daclizumab) was three months. During this period, acute rejection (defined as a grade of 2 or higher according to the criteria of the ISHLT) developed in 17 of the 27 patients in the control group (63 percent), as compared with 5 of the 28 in the daclizumab group (18 percent; relative risk, 2.8; 95 percent confidence interval, 1.1 to 7.4; P=0.04). The time to a first rejection episode was significantly longer in the daclizumab group than in the control group (Fig. 2) (P=0.04). The effect on rejection was most evident in the first three months (Table 2), with a frequency of rejection episodes of 0.64 per patient in the control group as compared with 0.19 per patient in the daclizumab group (P=0.02). The frequency of rejection episodes after three months was similar in the two groups (0.54 in the control group vs. 0.50 in the daclizumab group, P=0.85). All rejection episodes after three months in the daclizumab group were managed with additional corticosteroids administered orally, except in the case of one patient whose first episode occurred at month 4 and who presented with cardiogenic shock, which led to death within 24 hours.

Overall, the severity of rejection episodes was also significantly lower in the daclizumab group than in the control group (Table 2), with only two episodes of grade 3 rejection in the daclizumab group, as compared with nine episodes in the control group (P=0.03), throughout the follow-up period. Moreover, none of the patients in the daclizumab group required rescue therapy with muromonab-CD3 or antithymocyte globulin for the treatment of rejection, whereas five patients in the control group did require such therapy (P=0.02). Similarly, fewer of the patients in



Month	Control group	Daclizumab group
1	340	304
2	309	323
3	327	322
4	342	313
5	302	276
6	285	262



Month	Control group	Daclizumab group
1	24	24
2	18	15
3	21	13
4	13	10
5	12	8
6	11	6

**Figure 1.** Cyclosporine Levels (Panel A) and Doses of Prednisone (Panel B) in the Control and Daclizumab Groups.

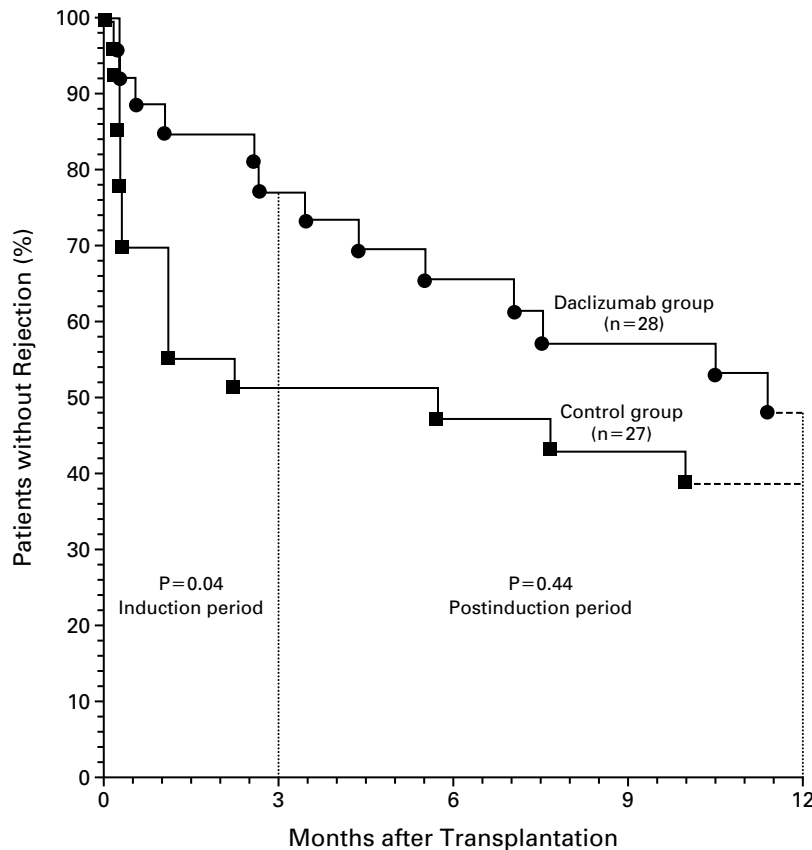
Values for cyclosporine and prednisone are means. Asterisks denote P=0.02.

the daclizumab group had multiple episodes of rejection (Table 2). This effect was most pronounced during the three-month induction period, when three patients in the control group and no patients in the daclizumab group had more than one episode of rejection (P=0.07).

**Secondary End Points**

The rate of use of antilymphocyte therapy was significantly lower in the daclizumab group than in the control group (six patients in the control group vs. one patient in the daclizumab group, P=0.04). One patient in the daclizumab group received muromonab-CD3 because of cyclosporine-induced nephrotoxic effects, whereas in the control group, five of the six patients who received antilymphocyte therapy were treated for hemodynamically significant rejection. The daily maintenance dose of corticosteroids was also significantly lower in the daclizumab group than in the control group by month 5, as shown in Figure 1B (P=0.02 at months 5 and 6).

The median duration of hospitalization after transplantation tended to be lower in the daclizumab group than in the control group (13 vs. 16 days), with more patients discharged within the first 14 days after transplantation (17 vs. 12 patients).



**Figure 2.** Kaplan–Meier Analysis of the Length of Time to a First Episode of Rejection in the Control and Daclizumab Groups.

The dashed portion of the curves represents the anticipated values for the completion of the study on the basis of the currently available data.

Overall survival at one year was similar in the two groups. There were four deaths in the control group, three of which occurred during the index hospitalization (two were due to rejection and one to infection). The death that occurred after the index hospitalization was due to overwhelming cytomegalovirus infection. There were two deaths in the daclizumab group, both after the index hospitalization. One was due to acute rejection, which occurred in the month after the completion of daclizumab therapy. The other death was due to pneumonia caused by influenza A virus or aspergillosis.

The incidence of production of anti-HLA antibodies was significantly lower among patients assigned to daclizumab. IgG anti-HLA antibodies developed in 6 of the 28 patients in the daclizumab group (21 percent), as compared with 19 of the 27 controls (70 percent,  $P < 0.001$ ). The lower rate in the daclizumab group was accounted for by parallel reductions in titers of IgG antibodies with specificity against either HLA class I or HLA class II antigens. Findings were similar with respect to the production of IgM anti-

HLA antibodies (10 percent in the daclizumab group vs. 45 percent in the control group,  $P = 0.01$ ).

In addition to the longer time to a first rejection episode in the daclizumab group, there was also a nonsignificant trend toward a longer time to a positive result on the lymphocyte-growth assay in the biopsy specimens from the patients in this group, as shown in Figure 3 ( $P = 0.27$ ). The one episode of rejection resulting in death that occurred after the three-month period of induction therapy was preceded by a positive finding on the lymphocyte-growth assay and the new onset of circulating anti-HLA antibodies. Of the other 12 episodes of rejection that occurred after induction therapy, 2 (17 percent) were preceded by positive lymphocyte-growth assays and 7 (58 percent) were preceded by the production of anti-HLA IgG antibodies.

#### Adverse Events

The administration of daclizumab was not associated with any short-term adverse reactions. There was no evidence of allergic reaction, the cytokine release

**TABLE 2.** SEVERITY AND FREQUENCY OF REJECTION EPISODES, IgG ANTIBODY PRODUCTION, AND POSITIVE RESULTS ON THE LYMPHOCYTE-GROWTH ASSAY DURING AND AFTER THE INDUCTION PERIOD.\*

VARIABLE	CONTROL GROUP (N=27)	DACLIZUMAB GROUP (N=28)	P VALUE
No. of grade ≥2 rejection episodes			
Total	27	17	0.09
During induction	17	5	0.007
After induction	10	12	0.72
No. of grade 2 rejection episodes			
Total	18	15	0.52
During induction	10	4	0.09
After induction	8	11	0.53
No. of grade 3 rejection episodes			
Total	9	2	0.03
During induction	7	1	0.03
After induction	2	1	0.54
No. of patients with ≥2 rejection episodes			
Total	7	5	0.47
During induction	3	0	0.07
After induction	4	5	0.76
Frequency of rejections (episodes/patient)			
Total	1.12	0.67	0.09
During induction	0.64	0.19	0.02
After induction	0.54	0.50	0.85
No. of patients with IgG antibodies			
Total	19	6	<0.001
During induction	14	4	0.004
After induction	5	2	0.04
No. of patients with positive lymphocyte-growth assay			
Total	13	10	0.26
During induction	10	7	0.27
After induction	3	3	0.26

\*The duration of the induction period was three months; the period after induction was nine months.

syndrome, fever, or myalgias. Similarly, there were no long-term adverse effects. Specifically, there were no cases of cancer in the daclizumab group, as compared with one case of polyclonal lymphoma in the control group.

The frequency of readmission to the hospital for any reason was similar in the two groups (17 readmissions in the daclizumab group vs. 21 in the control group). Infections accounted for the largest number of readmissions, and the incidence of readmission due to infection was the same in the two groups (11 readmissions in each group). The incidence of the most common cause of infection, cytomegalovirus, which was diagnosed on the basis of symptoms and serologic testing, was similar in the two groups (seven cases in the daclizumab group and five in the control group). The incidence of tissue-invasive cytomegalovirus infection requiring hospitalization and intravenous therapy with ganciclovir was also similar (six cases in the daclizumab group vs. four in the control group). The other infectious complications in the daclizumab group were one case each of pneumonia,

bronchitis, gastroenteritis, and pyelonephritis. In the control group, such complications were one case each of bronchitis, abscess of the frontal lobe, cellulitis, appendicitis, hepatitis, and pyelonephritis.

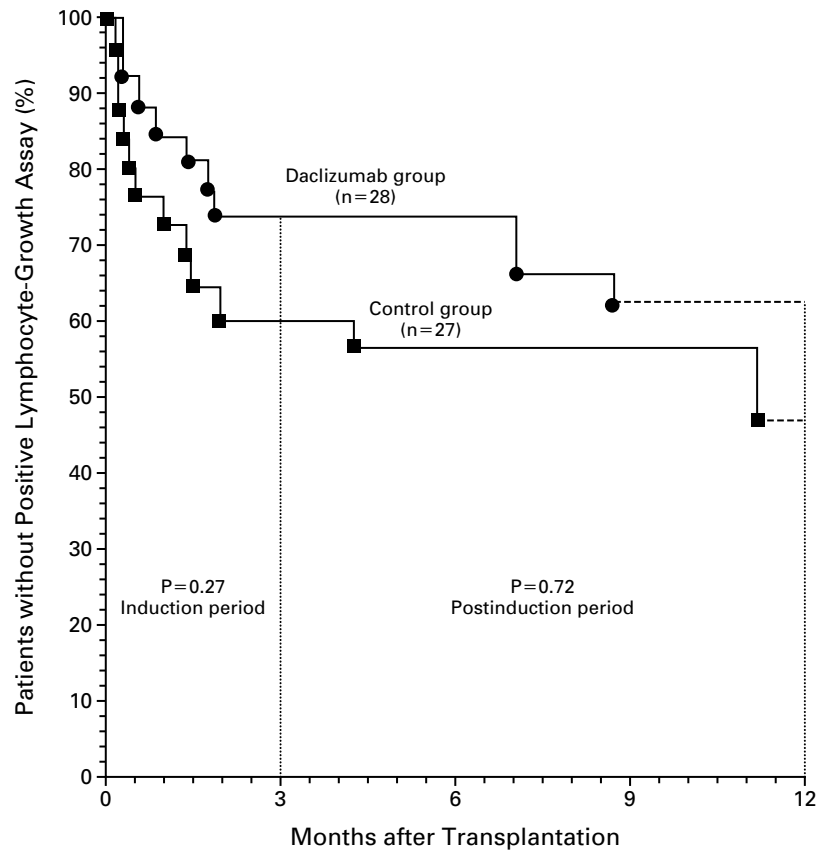
The frequency of readmission because of rejection was the same in the two groups (two in each group), and the frequency of readmission for any cause other than infection or rejection was similar (four readmissions in the daclizumab group and eight in the control group). Reasons for readmission included steroid-related psychosis (one in each group), generalized seizures (two in the control group), cholecystectomy (one in each group), duodenal ulcer (one in the control group), pain due to osteoporosis of the hip (one in the daclizumab group), hip replacement (one in the daclizumab group), optic neuritis (one in the control group), recurrent tamponade (one in the control group), and supraventricular tachycardia (one in the control group).

### DISCUSSION

As compared with generalized immunosuppressive therapy, induction therapy with daclizumab decreased the frequency of rejection, prolonged the time to a first rejection episode in the first three months after cardiac transplantation, and decreased the overall severity of rejection. In addition, as compared with the patients in the control group, those in the daclizumab group were less likely to need rescue therapy with antilymphocytic agents, needed less prednisone by the fifth month after transplantation, and were less likely to have immunologic reactivity against the allograft.

Daclizumab was more effective at reducing the frequency of rejection episodes in our patients than in a previously described series of renal-allograft recipients treated with daclizumab.<sup>10</sup> This may reflect the fact that we used mycophenolate mofetil instead of azathioprine, since it is superior to azathioprine in preventing allograft rejection when it is part of a triple-drug immunosuppressive regimen.<sup>14,15</sup>

There has been considerable debate about the value of induction therapy with monoclonal or polyclonal antibodies after cardiac transplantation. Monoclonal-antibody-based approaches, aimed at interrupting the activation of CD3 cells,<sup>7,16</sup> are extremely effective in terminating acute episodes of allograft rejection and in treating refractory rejection. However, the results of comparative studies of outcomes with and without monoclonal induction therapy have varied, with most studies demonstrating an effect on rejection that is maintained only while antibody therapy is ongoing.<sup>16</sup> Without repeated administration, these agents only delay the time to a first rejection episode without decreasing the overall frequency or severity of rejection.<sup>16</sup> At a mechanistic level, therefore, these agents appear to induce T-cell anergy and not clonal deletion.<sup>17,18</sup> Moreover, since neutralizing antimouse antibodies against the monoclonal agent inevitably develop after



**Figure 3.** Kaplan–Meier Analysis of the Length of Time to a Positive Lymphocyte-Growth Assay in the Control and Daclizumab Groups.

The dashed portion of the curves represents the anticipated values for the completion of the study on the basis of the currently available data.

10 to 14 days of treatment, prolonged or repeated courses are generally not possible. Therapy with monoclonal or polyclonal antibodies has also been associated with a greater incidence of opportunistic infection and cancer, probably because of the nonspecific T-cell suppression that results from such treatment. Frequent side effects, such as the cytokine release syndrome, allergic reactions, fever, and thrombocytopenia, also occur with these drugs.

Treatment with daclizumab resulted in a significant reduction in the frequency and severity of rejection during the treatment period, but after the cessation of therapy, the frequency of rejection increased to a level similar to that in the control group. This finding suggests that daclizumab has an immunomodulatory effect that is similar to that of other monoclonal antibody-based therapies (i.e., it induces clonal anergy rather than clonal deletion). However, daclizumab, a human monoclonal antibody directed against the interleukin-2 receptor, has several advantages over other induction agents. Given its unique composition, its use is not functionally immunogenic.<sup>19-21</sup> Its effective serum half-life is 21 days<sup>22</sup>; five doses thus provide sat-

uration for at least 3 months (as determined by receptor-saturation studies<sup>23</sup>), which covers the period of the highest incidence of cardiac-allograft rejection.<sup>2</sup> Moreover, this lack of immunogenicity makes possible prolonged courses and may permit repeated use of this agent for more than three months. Furthermore, rejection that occurred after the cessation of daclizumab therapy was generally preceded by the development of circulating IgG anti-HLA antibodies. Indeed, the one death due to acute rejection in the daclizumab group was preceded by both the formation of circulating IgG antibodies and a positive result on the lymphocyte-growth assay. Therefore, careful immunologic screening may identify patients who require prolonged, higher-dose, or repeated daclizumab therapy.

Interestingly, although the frequency of acute rejection episodes was significantly reduced during daclizumab therapy, the number of interleukin-2-activated T cells present in the allograft, as measured by the lymphocyte-growth assay, did not differ significantly between the groups. Doses of daclizumab that were suboptimal because of the biodistribution or because some patients had a more vigorous interleu-

kin-2 response than others, reflecting such fixed immunologic variables as HLA-DR mismatching, may account for this finding.

Daclizumab therapy also produced a marked reduction in the formation of anti-HLA antibodies that was sustained, even after induction therapy was stopped. The development of anti-HLA IgG antibodies after the cessation of daclizumab therapy generally preceded the onset of late rejection, suggesting that the lymphocyte-growth assay may be helpful in determining the optimal dose of daclizumab for recipients of heart transplants in the future. The fact that daclizumab affects the production of anti-HLA antibodies suggests that the drug has a prominent effect on the indirect pathway of recognition. The indirect pathway of CD4 T-cell activation plays an important part in the development of acute and chronic allograft rejection.<sup>24</sup> Whereas primary rejection appears always to be accompanied by recognition by the recipient's T cells of a dominant HLA-DR alloepitope presented by self-antigen-presenting cells,<sup>25,26</sup> recurrent episodes of rejection and the development of transplant-related coronary disease appear to result from the activation of antigen-specific B cells by soluble HLA-DR molecules.<sup>27-29</sup> Since the development of anti-HLA IgG antibodies to the graft has been associated with the development of cellular rejection<sup>13</sup> and graft atherosclerosis,<sup>30</sup> effective inhibition by interleukin-2-receptor blockade may thus favorably influence both the development of transplant-related coronary artery disease and long-term survival.

The short-term safety profile of daclizumab appears to be superior to that of other therapies based on monoclonal or polyclonal antibodies. The administration of daclizumab was not associated with any detectable signs of the cytokine release syndrome or allergic responses. The incidence of infection or cancer was not higher in the daclizumab group than in the control group. This finding may reflect the fact that more selective immunosuppression can be achieved or that the dose of prednisone can be tapered more rapidly with daclizumab therapy than with conventional immunosuppressive therapy.

In conclusion, daclizumab is an effective adjuvant immunomodulating agent in nonsensitized recipients of cardiac transplants. It has advantages over conventional induction therapy with muromonab-CD3 or antithymocyte globulin because it is more selective and because it can be used for prolonged and potentially repeated periods. Studies with larger cohorts are needed to address the short-term and long-term survival benefits for patients and should determine the optimal dosing schedules with the possible repeated use of daclizumab.

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