

ORIGINAL ARTICLE

Daclizumab to Prevent Rejection after Cardiac Transplantation

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ABSTRACT

BACKGROUND

Daclizumab, a humanized monoclonal antibody against the interleukin-2 receptor, reduced the risk of rejection without increasing the risk of infection among renal-transplant recipients and, in a single-center trial, among cardiac-transplant recipients. We conducted a multicenter, placebo-controlled, double-blind study to confirm these results in cardiac-transplant patients.

METHODS

We randomly assigned 434 recipients of a first cardiac transplant treated with standard immunosuppression (cyclosporine, mycophenolate mofetil, and corticosteroids) to receive five doses of daclizumab or placebo. The primary end point was a composite of moderate or severe cellular rejection, hemodynamically significant graft dysfunction, a second transplantation, or death or loss to follow-up within six months.

RESULTS

By six months, 104 of 218 patients in the placebo group had reached the primary end point, as compared with 77 of the 216 patients in the daclizumab group (47.7 percent vs. 35.6 percent, $P=0.007$), a 12.1 percent absolute risk reduction and a 25 percent relative reduction. The rate of rejection was lower in the daclizumab group than in the placebo group (41.3 percent vs. 25.5 percent). Among patients reaching the primary end point, the median time to the end point was almost three times as long in the daclizumab group as in the placebo group during the first 6 months (61 vs. 21 days) and at 1 year (96 vs. 26 days). More patients in the daclizumab group than in the placebo group died of infection (6 vs. 0) when they received concomitant cytolytic therapy.

CONCLUSIONS

Daclizumab was efficacious as prophylaxis against acute cellular rejection after cardiac transplantation. Because of the excess risk of death, concurrent or anticipated use of cytolytic therapy with daclizumab should be avoided.

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CARDIAC TRANSPLANTATION HAS BECOME commonplace in the 22 years since the approval of cyclosporine. Nevertheless, progress in immunosuppression has been slow, in part because the heart is a vital organ and acute allograft rejection can include hemodynamic compromise, irreversible graft injury, and death. Furthermore, the immunosuppressive therapy used to prevent rejection predisposes patients to infection, which continues to be the leading cause of death in the year after cardiac transplantation.^{1,2} In a prior report of a single-center evaluation of 55 heart-transplant recipients, there was a striking decrease in the rate of rejection, by a factor of 2.8, among patients receiving daclizumab, a monoclonal antibody against the α subunit of the interleukin-2 receptor, with no increase in the rate of infection.³

A common immunosuppression protocol for cardiac transplantation includes cyclosporine, mycophenolate mofetil, and corticosteroids (triple therapy). The results of a multicenter, double-blind, placebo-controlled clinical trial involving 650 cardiac-transplant recipients⁴ suggested that treatment with mycophenolate mofetil, a purine analogue, reduced the rate of rejection and improved survival but had a higher incidence of nonfatal, opportunistic infections as compared with azathioprine therapy.

An alternative to standard triple therapy at the time of cardiac transplantation has been the use of augmented immunosuppression, commonly termed "induction immunotherapy," with antilymphocyte antibodies. These cytolytic agents, used in more than 40 percent of initial heart transplantations,² include the murine monoclonal antibody muromonab-CD3 and other antithymocyte or antilymphocyte agents (e.g., ATGAM and Thymoglobulin). Retrospective evaluations from a large, multi-institutional database have suggested that cytolytic therapy reduces the risk of early rejection but increases the risk of infection.^{1,5} Despite the widespread use of induction immunotherapy, no randomized, multicenter trial has been conducted in cardiac-transplant recipients.

Daclizumab functions as an immunosuppressant by antagonizing interleukin-2-mediated proliferation of T cells.⁶ Daclizumab has been shown to decrease the risk of rejection of renal transplants, with no increased incidence of infection.^{7,8} On the basis of a prior report of decreased rejection rates,³ we conducted a multicenter, double-blind, random-

ized, placebo-controlled trial designed to test the efficacy of daclizumab induction immunotherapy as prophylaxis against cardiac rejection.

METHODS

PATIENTS

Patients older than 13 years of age receiving their first cardiac allograft were recruited at 31 transplantation centers in the United States, Canada, Germany, and Sweden between August 28, 1999, and April 29, 2001, and after transplantation were randomly assigned in a double-blind manner to receive either daclizumab or placebo in combination with cyclosporine, mycophenolate mofetil, and corticosteroids. Patients known to be in need of cytolytic therapy at the time of transplantation or those requiring ventricular assist devices after surgery were excluded. Each participating institutional review board approved the study protocol, and written informed consent was obtained from all patients.

TREATMENTS

Daclizumab, 1 mg per kilogram of body weight (up to 100 mg), or placebo was administered intravenously within 12 hours after transplantation and on days 8, 22, 36, and 50. Maintenance immunosuppressive therapy included mycophenolate mofetil (1.5 g twice daily) and a microemulsion of cyclosporine (1 to 4 mg per kilogram intravenously or 2 to 6 mg per kilogram orally, initiated within 72 hours after transplantation). The dose of mycophenolate mofetil could be adjusted in the event of adverse effects. The doses of cyclosporine were adjusted to maintain the usual trough levels at each center. Methylprednisolone (500 to 1000 mg) was intravenously administered perioperatively, or oral prednisone or its equivalent was given at a daily dose of 0.5 to 1 mg per kilogram through day 14; the dose was reduced to 0.2 mg per kilogram by day 28 and to 0.10 to 0.15 mg per kilogram by day 90. Corticosteroids could be discontinued electively after day 180. All patients received statins. Antibiotics to prevent *Pneumocystis carinii* pneumonia were administered for one year. Patients at high risk for cytomegalovirus (CMV) disease (CMV-negative recipients whose donors were CMV-positive) received prophylactic ganciclovir (up to 5 to 10 mg per kilogram per day for two weeks, followed by treatment according to the practice of the individual center).

BIOPSY

Endomyocardial biopsies were performed on the days of the second through fifth daclizumab infusions and then every 2 weeks up to 3 months, monthly up to 6 months, and then every 2 months up to 12 months after transplantation. Biopsy specimens were read by the local center pathologist in accordance with the criteria of the International Society for Heart and Lung Transplantation (ISHLT).⁹

END POINTS

The primary efficacy end point was a composite end point at six months consisting of the first of any one of the following: a biopsy showing acute cellular rejection of grade 3A or higher; hemodynamic compromise, treated with inotropic agents and pulsed doses of immunosuppressants, whether or not a biopsy was done and regardless of the grade of the biopsy; death; a second transplantation; or loss to follow-up. Hemodynamic compromise was defined by any or all of the following: an ejection fraction of 30 percent or less or a 20 percent decrease in the ejection fraction from baseline, a fractional shortening of no more than 20 percent or a 25 percent decrease from baseline, or a cardiac index of less than 2.0 liters per minute per square meter or a 25 percent decrease from baseline. Secondary efficacy end points included the composite end point at 12 months, patient and graft survival at 6 and 12 months, and the time to the first occurrence of the composite end point within 6 and 12 months.

STATISTICAL ANALYSIS

The number of patients enrolled in the study was based on a two-sided alpha level of 2.5 percent, an assumed rate of acute rejection of 40 percent in the placebo group, and a statistical power of 80 percent to detect a 40 percent reduction in the rejection rate in the daclizumab group, with an expected dropout rate of 20 percent. The sample size was calculated with the use of the normal approximation of the binomial, with continuity correction.

The Cochran–Mantel–Haenszel general association test, with stratification according to center, was used to test the null hypothesis of no difference between groups. A 95 percent confidence interval was calculated for the difference in the weighted averages (weighted according to center size) of the rejection rates. Logistic regression was used to test for interactions between center and treatment group. The time-to-event data were analyzed with the use

Table 1. Baseline Characteristics of the Patients and Donors.*

Characteristic	Placebo Group (N=218)	Daclizumab Group (N=216)	P Value
Patients			
Male sex — no. (%)	177 (81.2)	171 (79.2)	0.60
Race or ethnic group — no. (%)†			0.28
White	193 (88.5)	185 (85.6)	
Black	15 (6.9)	23 (10.6)	
Asian	2 (0.9)	0	
Other	8 (3.7)	8 (3.7)	
Age — yr			
Mean	53.1±11.9	52.4±11.0	0.54
Median	56.0	54.0	
Range	13–74	18–72	
Weight — kg	79.9±15.6	80.0±13.9	0.94
Indication for transplantation — no. (%)			0.88
Coronary artery disease	68 (31.2)	64 (29.6)	
Dilated cardiomyopathy	138 (63.3)	138 (63.9)	
Other	12 (5.5)	14 (6.5)	
UNOS waiting-list status or equivalent — no. (%)‡			0.85
1A	50 (22.9)	46 (21.3)	
1B	83 (38.1)	88 (40.7)	
2	83 (38.1)	82 (38.0)	
Intraaortic balloon pump — no. (%)	8 (3.7)	18 (8.3)	0.04
Left ventricular assist device — no. (%)	16 (7.3)	18 (8.3)	0.70
Most recent PRA <10% — no. (%)	205 (94.0)	194 (89.8)	0.11
CMV status — no. (%)			
Donor and recipient positive	136 (62.4)	136 (63.0)	0.90
Donor positive, recipient negative	50 (22.9)	47 (21.8)	0.77
Donors			
Duration of cold ischemia — min	192.0±67.2	186.0±57.0	0.32
Age — yr			0.08
Mean	29.8±12.5	32.0±13.2	
Median	26.0	28.0	

* Plus-minus values are means ±SD. UNOS denotes United Network for Organ Sharing, PRA panel reactive antibody test, and CMV cytomegalovirus.
 † Race or ethnic group was determined by patient report.
 ‡ Data were unavailable for two patients in the placebo group.

of Kaplan–Meier product-limit estimates. Dosing information was summarized at 6 months and 12 months and compared in the two groups by means of the blocked Wilcoxon rank-sum test. Analyses of efficacy were conducted according to the intention to treat unless otherwise noted. Analyses of safety included only patients who had received at least one

Table 2. Efficacy Results at 6 and 12 Months.*

Result	Placebo Group (N=218)	Daclizumab Group (N=216)	P Value
<i>no. (%)</i>			
6 Months			
Primary end point	104 (47.7)	77 (35.6)	0.007
First biopsy-proven rejection	90 (41.3)	55 (25.5)	
ISHLT grade 3A	78 (35.8)	50 (23.1)	
ISHLT grade 3B	11 (5.0)	4 (1.9)	
ISHLT grade 4	1 (0.5)	1 (0.5)	
Hemodynamic compromise	3 (1.4)	6 (2.8)	
Death	7 (3.2)	14 (6.5)	
Second transplantation	0	0	
Lost to follow-up	4 (1.8)	2 (0.9)	
12 Months			
Composite end point	116 (53.2)	97 (44.9)	0.06
First biopsy-proven rejection	101 (46.3)	73 (33.8)	
ISHLT grade 3A	89 (40.8)	67 (31.0)	
ISHLT grade 3B	11 (5.0)	5 (2.3)	
ISHLT grade 4	1 (0.5)	1 (0.5)	
Hemodynamic compromise	3 (1.4)	6 (2.8)	
Death	8 (3.7)	16 (7.4)	
Lost to follow-up	4 (1.8)	2 (0.9)	

* The composite clinical end point was the first occurrence of any of the following: cellular rejection, hemodynamically significant graft dysfunction, a second transplantation, death, or loss to follow-up (see the Methods section for additional details). Data on efficacy results at 6 and 12 months were censored at the time of the first event. ISHLT denotes International Society for Heart and Lung Transplantation.

dose of placebo or daclizumab; if a patient received daclizumab any time after randomization, he or she was included in the daclizumab group.

The study was designed by Roche Laboratories, with the assistance of a subgroup of the principal investigators (listed in the Appendix). The data were collected and held by Roche Laboratories. The writing committee had full access to the data and was fully involved in the data analysis, which was performed by the sponsor's statistician. The committee vouches for the veracity and completeness of the reported data.

RESULTS

PATIENT POPULATION

The 434 patients were well matched at baseline (Table 1). There were no significant differences be-

tween groups in the percentages of ABO-identical or ABO-compatible allografts and HLA-A, B, or DR antigen mismatches (data not shown).

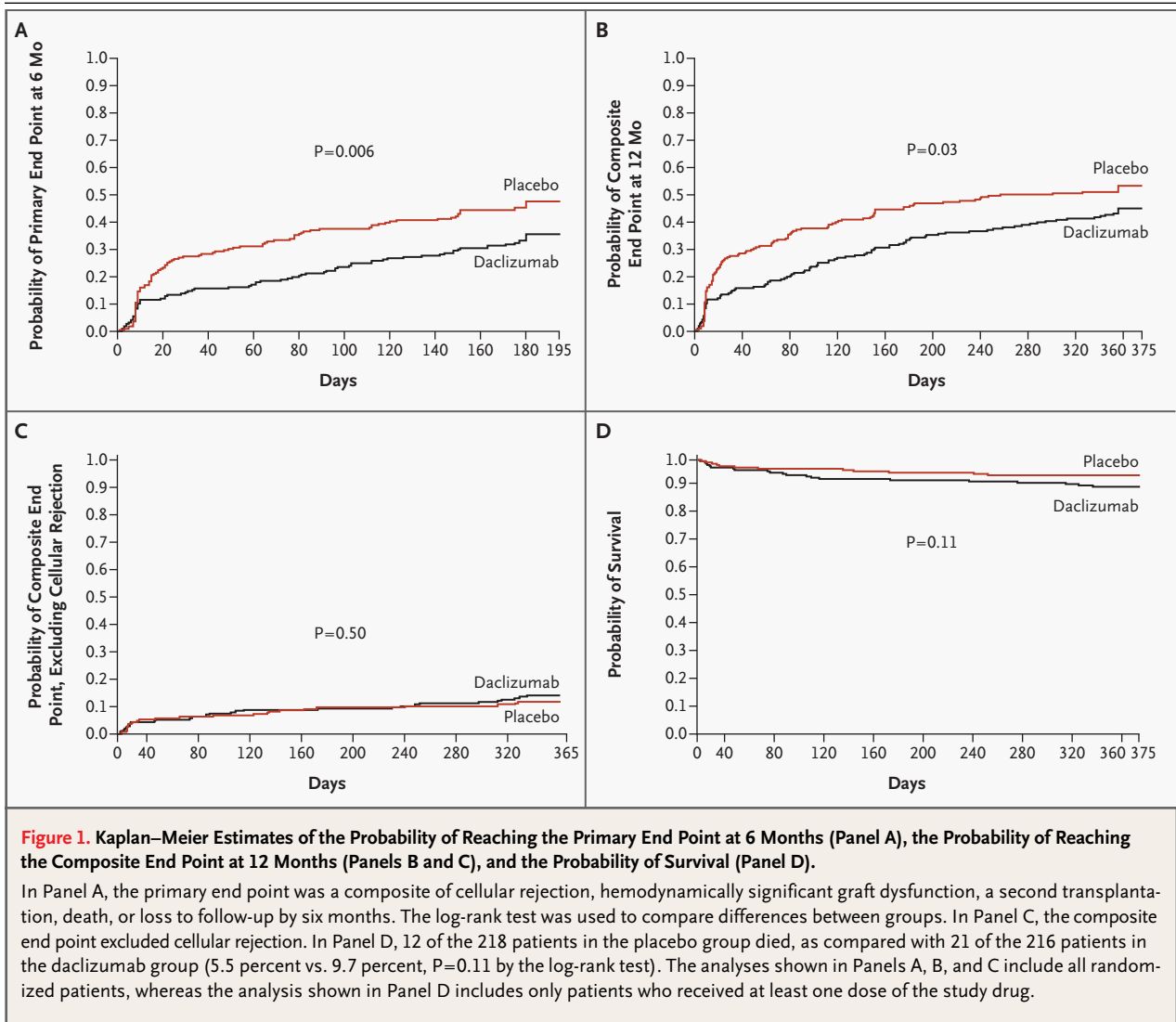
Adherence to the study protocol was excellent, with 81.8 percent of patients receiving at least four doses of study drug according to the protocol. The concomitant use of maintenance immunosuppression was well balanced: the median daily dose of cyclosporine was 355 mg in the placebo group and 344 mg in the daclizumab group from day 0 to 90 and 313 mg and 300 mg, respectively, from day 91 to 180; the median daily dose of mycophenolate mofetil was 2915 mg and 2918 mg, respectively, from day 0 to 90 and 2716 mg and 3000 mg, respectively, from day 91 to 180; and the median cumulative doses of maintenance corticosteroids were 3401 mg and 3354 mg, respectively, from day 0 to 90 and 900 mg and 855 mg, respectively, from day 91 to 180. By six months, 31 patients in the placebo group (14.2 percent) and 24 patients in the daclizumab group (11.1 percent) were not taking corticosteroids.

EFFICACY

By six months, 104 of the 218 patients in the placebo group had reached the primary end point, as compared with 77 of the 216 patients in the daclizumab group (47.7 percent vs. 35.6 percent), a 12.1 percent absolute risk reduction and a 25 percent relative reduction ($P=0.007$) (Table 2 and Fig. 1). Corticosteroids were used to treat rejection in 111 placebo recipients, as compared with 78 daclizumab recipients (50.9 percent vs. 36.1 percent). In the group of patients who met the primary end point, the observed difference was heavily influenced by the smaller number of daclizumab-treated patients who had acute rejection of ISHLT grade 3A or higher (55, as compared with 90 in the placebo group; 25.5 percent vs. 41.3 percent) (Table 2). Among the patients who reached the primary end point during the first six months of follow-up, the median time to reach the end point was approximately three times as long among patients in the daclizumab group as among patients in the placebo group (61 vs. 21 days), and this favorable outcome was also observed during the first year of follow-up (median time to reach the secondary end point, 96 vs. 26 days).

OPPORTUNISTIC INFECTIONS AND CANCER

The incidence of any opportunistic infection, including CMV infection and CMV disease, was similar in the two groups (Table 3). Cancer rates were also similar in the two groups (Table 3).



MORTALITY

At one year, Kaplan–Meier estimates of survival according to the intention to treat did not differ significantly between groups (Fig. 1D), even though the majority of patients had a United Network for Organ Sharing (UNOS) waiting-list status of 1A or 1B (Table 1). At six months, 10 patients in the placebo group had died from various causes according to the intention to treat, as compared with 16 in the daclizumab group; at one year, the numbers were 12 and 21, respectively (Table 4). Mortality rates were similar when analyzed according to the actual treatment received (Table 4).

Deaths from infection were more frequent among patients in the daclizumab group who also received cytolytic therapy than among patients in

the placebo group who also received cytolytic therapy (6 of 40 [15.0 percent] vs. 0 of 37 [0 percent]) (Table 4). Although cytolytic therapy was prohibited by the study protocol (other than to treat rejection), patients were required to undergo randomization and receive the study drug within 12 hours after their return to the intensive care unit after the heart transplantation.

Predictably, some patients had postoperative changes in their clinical course after randomization, most commonly worsening renal function, for which investigators discontinued cyclosporine and substituted renal-sparing cytolytic therapy (Table 4). Another common indication for cytolytic therapy was suspected acute rejection. A total of 77 patients received cytolytic therapy (37 in the placebo group

Table 3. Rates of Opportunistic Infection or Cancer.*

Variable	Placebo Group (N=207)	Daclizumab Group (N=216)
	<i>no. of patients (%)</i>	
Serious opportunistic infection in 1st 6 mo†	16 (7.7)	15 (6.9)
Bronchopulmonary aspergillosis	1 (0.5)	1 (0.5)
Candida	2 (1.0)	4 (1.9)
CMV	12 (5.8)	11 (5.1)
Herpes zoster	1 (0.5)	1 (0.5)
Any opportunistic infection in 1st 12 mo†	80 (38.6)	71 (32.9)
Bronchopulmonary aspergillosis	2 (1.0)	2 (0.9)
Candida	18 (8.7)	20 (9.3)
CMV	50 (24.2)	43 (19.9)
Herpes simplex	15 (7.2)	12 (5.6)
Herpes zoster	11 (5.3)	9 (4.2)
Cryptococcal meningitis	0	1 (0.5)
Cancer		
By 6 mo	5 (2.4)	7 (3.2)
By 12 mo	11 (5.3)	11 (5.1)
Post-transplantation lymphoproliferative disorder	1 (0.5)	1 (0.5)

* The analysis included all patients who received at least one dose of placebo or daclizumab. CMV denotes cytomegalovirus.

† Some patients had more than one type of opportunistic infection.

and 40 in the daclizumab group), most of them (81.8 percent) within the first 30 days after transplantation. Of the 21 patients in the daclizumab group who died, 8 also received cytolytic therapy within the first 30 days, and 6 of these 8 patients died from infection. In comparison, of the 11 patients in the placebo group who died, 2 received cytolytic therapy within the first 30 days, and neither died from infection.

DISCUSSION

This clinical trial was undertaken to evaluate the efficacy of daclizumab, a humanized monoclonal antibody that binds to the interleukin-2 α receptor on activated lymphocytes, to reduce the risk of rejection in patients undergoing cardiac transplantation who were given triple-drug immunosuppressive therapy including cyclosporine, mycophenolate mofetil, and corticosteroids. The primary end point was a composite of any of the following within six months after transplantation: acute cellular rejection of ISHLT grade 3A or higher on endomyocar-

dial biopsy, hemodynamically significant graft dysfunction requiring augmented immunosuppression and inotropes regardless of biopsy results, second transplantation, death, or loss to follow-up. The incidence of the primary end point at six months was 35.6 percent in the daclizumab group and 47.7 percent in the placebo group. This 12.1 percent absolute risk reduction resulted primarily from a reduction in the incidence of acute cellular rejection.

By binding the interleukin-2 α receptor on the surface of activated T cells, daclizumab inhibits interleukin-2-mediated proliferation of T cells and thus has an immunosuppressive effect. One dose of daclizumab has an elimination half-life of approximately 20 days.⁶ We administered five doses of daclizumab, the first in the immediate post-transplantation period, with four additional doses given through week 7; hence, an immunosuppressive effect was expected to persist for up to 120 days in adults (unpublished data).

Among patients who met the primary end point in the first six months, the median time to reach the end point was three times as long among patients in the daclizumab group as among patients in the placebo group. This prevention of rejection is clinically important, since the reduction in the risk of rejection occurred within the first few weeks after transplantation, when immunosuppression is most intensive and the need to treat acute cellular rejection, usually with high doses of corticosteroids, may increase the incidence of complications, such as impaired wound healing, infection, or glucose intolerance. The decreased overall incidence of rejection in the daclizumab group was attained without an increased incidence of any serious opportunistic infections. This finding has previously been reported in studies of daclizumab after renal transplantation.^{7,8}

Survival exceeded 90 percent in both groups at one year and substantially exceeded the UNOS one-year survival rate of 85.3 percent among 4927 first-time cardiac-transplant recipients in the United States during the same period (1999 to 2001).¹⁰ As compared with the UNOS study, we had fewer patients with a UNOS waiting-list status of 1A (22 percent, as compared with 36 percent), more patients with a status of 2 (38 percent, as compared with 27 percent), and similar numbers with a status of 1B (39 percent and 37 percent, respectively), which may have contributed in part to these favorable outcomes. However, in the UNOS study, the one-year survival rates were 81.1 percent among patients with a status of 1A, 87.2 percent among those with

Table 4. Rates of Death and Cytolytic Therapy.*

Variable	Placebo Group	Daclizumab Group	Absolute Difference (95% CI)
Intention-to-treat analysis (randomized population) — no. (%)			
Total no.	218	216	
Deaths			
6 Mo	10 (4.6)	16 (7.4)	2.8 (–2.10 to 7.74)
12 Mo	12 (5.5)	21 (9.7)	4.2 (–1.22 to 9.66)
Analysis according to treatment received (at least 1 dose of placebo or daclizumab) — no. (%)			
Total no.	207	216	
Deaths			
6 mo	10 (4.8)	16 (7.4)	2.6 (–2.45 to 7.60)
12 mo	11 (5.3)	21 (9.7)	4.4 (–1.06 to 9.88)
Causes of death — no.			
0–6 Mo†			
Sepsis	0	6	
Multiorgan failure	3	1	
Anoxic encephalopathy	0	2	
Cardiac arrest	2	0	
Other‡	5	7	
7–12 Mo			
Acute myocardial infarction	1		
CMV infection		1	
Cryptococcal meningitis		1	
Multiorgan failure		1	
Myocardial infarction		1	
Sudden death from cardiac causes		1	
Cytolytic therapy — no. (%)			
0–30 days	31 (15.0)	32 (14.8)	
For renal insufficiency	17 (8.2)	18 (8.3)	
For other indications	14 (6.8)	14 (6.5)	
Cumulative to 6 mo	35 (16.9)	35 (16.2)	
Cumulative to 12 mo	37 (17.9)	40 (18.5)	
Receipt of cytolytic therapy from 0–30 days — no./total no. (%)			
Death within 6 mo	2/31 (6.5)	4/32 (12.5)	
Death within 12 mo	2/31 (6.5)	8/32 (25.0)	
Receipt of cytolytic therapy from 0–12 mo — no./total no. (%)			
Death within 6 mo	2/37 (5.4)	8/40 (20.0)	
Death within 12 mo	2/37 (5.4)	8/40 (20.0)	
Death from infection	0	6/40 (15.0)	

* Cytolytic therapy included muromonab-CD3 and antithymocyte or antilymphocyte agents. CMV denotes cytomegalovirus.

† Causes of death did not differ significantly between groups in intention-to-treat analyses or analyses according to the treatment received.

‡ In the daclizumab group, each of the following caused one death: arteriovenous malformation, heart failure, cerebral hemorrhage, cerebral infarction, mediastinal abscess, pulmonary embolism, and squamous-cell carcinoma. In the placebo group, one death was caused by each of the following: brain herniation, mesenteric occlusion, shock, sudden death from cardiac causes, and thrombotic thrombocytopenic purpura.

a status of 1B, and 87.9 percent among those with a status of 2. Thus, even though our population had fewer patients with a status of 1A and more patients with a status of 2, the overall survival rate still substantially exceeded those in the contemporaneous UNOS study.

More patients in the daclizumab group than in the placebo group died during the first 12 months after transplantation. The annual mortality rate in the placebo group (5.3 percent) was similar to the 6.2 percent observed among 289 patients treated with the same mycophenolate mofetil dosing protocol in an earlier trial.⁴ A comprehensive review of the clinical courses of the patients who died revealed that 8 of the 21 patients who died in the daclizumab group (38.1 percent) had also received cytolytic therapy and that 6 of these 8 patients (75.0 percent) had died from infection. Cytolytic therapy has previously been shown to be an independent risk factor for infection after transplantation.^{4,5} In contrast, only 2 of the 11 patients who died in the placebo group had also received cytolytic therapy (18.2 percent), and neither death was associated with infection.

The cytolytic therapy given to the daclizumab group that most likely resulted in a very high level of immunosuppression was an unintended result of the double-blind study design. Some investigators, who did not know whether the patient had received daclizumab or placebo, used cytolytic therapy for complications in the early postoperative period, such as serious renal insufficiency necessitating delayed administration of cyclosporine. Therefore, the patients in the daclizumab group who also received cytolytic therapy had a high level of immunosuppression as a result of treatment with up to five drugs (the cytolytic agent, daclizumab, cyclosporine, mycophenolate mofetil, and corticosteroids), which may have increased the risk of serious infection. Furthermore, because of the double-blind study design, investigators continued administering study drug regardless of whether a patient was also receiving cytolytic therapy. This drug combination may have contributed to the increased numbers of patients who died from infection in this trial.

Our findings provide provocative although not definitive evidence of an increased risk of fatal infection when daclizumab is used in conjunction with cytolytic therapy. Such combined ongoing use of daclizumab after the administration of T-cell-deplet-

ing antibodies was not intended to be part of the trial design and does not represent the current standard of care. Combined use of daclizumab and cytolytic antibodies should be avoided in routine clinical practice, including in patients undergoing transplantation who are expected to require cytolytic therapy to avoid renal dysfunction from calcineurin inhibitors. Patients who receive daclizumab soon after transplantation and require treatment for suspected or biopsy-proven rejection should preferentially be treated with high-dose corticosteroids rather than cytolytic therapy. If the use of a T-cell-depleting antibody is thought to be indicated, daclizumab therapy should be discontinued.

The clinical relevance of the prespecified primary end point as opposed to other end points, such as long-term allograft survival or freedom from allograft vasculopathy, raises more fundamental questions regarding the prevention of moderate rejection. Evaluations of large registries have shown a relationship between the occurrence of cellular rejection and extended survival.² Our 6-month efficacy and 12-month safety design did not permit these issues to be addressed. Future studies of daclizumab and other immunosuppressive approaches in cardiac transplantation will need to account for these important long-term clinical outcomes and whether the use of surrogate markers (e.g., intravascular changes on ultrasonography) will permit truncation of follow-up.

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APPENDIX

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