Decreased infections in cardiac transplant recipients on cyclosporine with reduced corticosteroid use

MARGARET J. GORENSEK, MD; ROBERT W. STEWART, MD; THOMAS F. KEYS, MD; MARTIN C. MCHENRY, MD; DAVID L. LONGWORTH, MD; SUSAN J. REHM, MD; THERESA BABIAK, BS

■ Fifty patients undergoing orthotopic cardiac transplantation were monitored over 34 months for evidence of infection. Four separate immunosuppressive protocols were used during the course of the study; the most recent protocol (protocol 4) employed significantly lower overall steroid dosages than the earlier protocols (protocols 1, 2, and 3). All immunosuppressive regimens used cyclosporine, and azathioprine was added in the last three protocols. Statistical techniques to compare the occurrence of infection in protocols 1, 2, and 3 v protocol 4 showed that patients in protocol group 4 ($n=21$) had significantly more time free of pneumonia ($P=.02$) and major infections ($P=.04$) and marginally more time free of symptomatic cytomegalovirus infection ($P=.08$) than patients in protocol groups 1, 2, and 3 ($n=29$). The median incidence of major infection per month was lower for protocol group 4 ($P=.02$). The time free of viral infection did not differ significantly between the two groups ($P=.75$) nor did the median incidence of rejection per month ($P=.19$). The authors conclude that reduction of steroid dosages in cardiac transplant patients receiving cyclosporine is associated with a significant decrease in the incidence of clinically important infections.
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INFECTION remains the most common cause of significant morbidity and mortality in transplant recipients, despite the success that the potent new immunosuppressive agent, cyclosporine, has allowed.[1-4] Studies have shown that infection rates after cardiac transplantation were lower when cyclosporine and lower dosages of prednisone were used.[3-7] As the cardiac transplant program evolved at The Cleveland

Clinic, the relationship between steroids and infectious complications became obvious[8] and led to the use of increasingly lower amounts of steroid. We have used four protocols (protocols 1, 2, 3, and 4), each attempting to use lower steroid dosages than the earlier one. Because patients in protocol 4 received significantly less steroids, the incidence of infection was compared between this group and the combined group consisting of protocol groups 1, 2, and 3.

MATERIALS AND METHODS

Study population

Fifty-three patients undergoing orthotopic cardiac transplantation at the Cleveland Clinic from August 15,

TABLE 1
IMMUNOSUPPRESSIVE PROTOCOLS USED DURING THE STUDY

Dates	No. of patients	Immunosuppression		
		Glucocorticoids*	Cyclosporine	Azathioprine
Protocol 1 8/15/84–3/15/85	7	2.0 ± 1.2†	Preoperative Intravenous Bolus	None
Protocol 2 3/16/85–5/10/85	3	3.6 ± 1.4†	Preoperative Oral	2 mg/kg
Protocol 3 5/11/85–4/14/86	19	1.3 ± 1.0†	Preoperative Intravenous Continuous	2 mg/kg
Total, protocols 1, 2, 3	29			
Protocol 4 4/15/86–7/1/87	21	1.2 ± 1.2†	Postoperative Intravenous Continuous	2 mg/kg

*Average daily dosage (mg/kg/day) for post-transplant days 1–30 (mean ± SD). Includes daily prophylaxis in combination with therapy for rejection.
†The difference between protocols 1, 2, and 3 v protocol 4 was $P = .02$ (Wilcoxon rank sum test).

1984 to June 30, 1987 were followed up for evidence of infection. Three patients died during the immediate postoperative period and were not included in this study. Average length of follow-up was 17 months with a range of three to 34 months. The study population consisted of 38 males and 18 females. Eighty-two percent of patients were white and 18% black. Average age was 43.1 years with a range of 13 to 62 years. Underlying heart disease was cardiomyopathic in 48%, ischemic in 36%, and valvular in 16%. All patients were monitored for infection during their entire post-transplantation course until the end of the study.

Immunosuppression

Four separate immunosuppressive regimens were developed during the course of the study; all included tapering dosages of corticosteroids and cyclosporine, and azathioprine was added to the latter three regimens. (Patients in protocol 1 were started on azathioprine later after discharge.) These protocols have been described in detail in an earlier paper.[9] The major differences between the last protocol and the initial three protocols was the significantly lower steroid dosages ($P<.0001$ for the average daily steroid dose during the first postoperative month) and the postponement of cyclosporine administration until adequate renal function was established postoperatively.

The current immunosuppressive protocol, protocol 4, involves three drugs. Azathioprine, 2 mg/kg, is given intravenously as soon as the donor is identified, it is continued on a daily basis indefinitely, administration is switched to the oral route when digestive function returns, and it is withheld when leukopenia is noted. Corticosteroids, beginning with 500 mg of methylprednisolone during implantation, are rapidly tapered: 125 mg methylprednisolone every eight hours for three doses then 30 mg daily until the first biopsy. Thereafter, therapy is usually maintained at 20 mg of oral prednisone daily. Cyclosporine is started only when adequate renal function has been demonstrated, generally within two days of transplantation. The initial administration is a continuous intravenous regimen of about 1.5 mg/kg/day and adjusted to maintain the whole blood level at 330 ng/mL. By the end of the first week, the oral route is established with twice daily dosing to keep the trough level of cyclosporine at 250 ng/mL.

Rejection, as determined by endomyocardial biopsy, was treated by a three- to five-day course of increased corticosteroids. Larger dosages of steroids (1,000 mg methylprednisolone daily) were employed in protocols 1 and 2. In protocols 3 and 4, progressively lower dosages (50–200 mg prednisone daily) were employed, tailoring the amount in proportion to the histologic severity of rejection. A 10- to 14-day regimen of either Minnesota anti-lymphoblast globulin (ALG) or OKT-3 was used to treat severe rejection refractory to steroids.

The dosages of steroids employed in protocol 3 were actually intermediate between those used in protocols 1 and 2 v protocol 4, because protocol 3 represented an ongoing effort to decrease overall steroid use. In an attempt to transform the use of steroids for both prophylaxis and rejection therapy into one variable, we chose

TABLE 2
MAJOR INFECTIONS OCCURRING IN 18 OF 50 CARDIAC TRANSPLANT RECIPIENTS OVER 34 MONTHS

Pt. no. (race, sex)	Days post-transplant	Types of infections	Patient outcome
IMMUNOSUPPRESSIVE PROTOCOLS 1, 2, and 3 (n = 29)			
1	27	Disseminated CMV	
(43 WM)	58	*Pseudomonas aeruginosa, Serratia marcescens, Morganella morgagnii* pneumonia/sepsis	Died
	61	*Candida albicans* peritonitis	
3	264	CMV pneumonia	Died
(45 WM)	354	*Nocardia asteroides* vertebral osteomyelitis	
	355	*Candida albicans* deep skin abscess	
	460	*Enterococcus* and *Staphylococcus* epi/pneumonia	
	522	*Corynebacterium* JK bacteremia	
	543	*Pseudomonas aeruginosa* pneumonia	
	675	Coagulase-negative *Staphylococcus* sepsis/empyema	
8	71	*Pneumocystis carinii* pneumonia	Resolved
(38 WM)	754	*Mycoplasma pneumoniae* pneumonia	
11	294	*Nocardia asteroides* and CMV pneumonia	Died
(39 WF)	411	Cerebral nocardiosis	
	424	*Pseudomonas aeruginosa* sepsis/pneumonia	
13	38	*Aspergillus fumigatus* pneumonia	Died
(29 WM)	180	*Aspergillus* and CMV pneumonia	
	337	Coagulase-negative *Staphylococcus* bacteremia/empyema	
	345	*Pneumocystis carinii* pneumonia	
	360	*Aspergillus* tricuspid endocarditis/disseminated invasive aspergillosis	
15	17	*Citrobacter freundii, Enterococcus, Pseudomonas aeruginosa* peritonitis	Resolved
(55 WF)	221	*Pneumocystis carinii* pneumonia	
16	17	*Enterococcus* urosepsis	Resolved
(38 WF)			
17	61	*Pneumocystis carinii* and CMV pneumonia	Resolved
(54 WM)	580	*Mycoplasma pneumoniae* pneumonia	
18	18	*Staphylococcus aureus* B-*Streptococcus, Klebsiella pneumoniae* pneumonia	Resolved
(42 WM)	165	*Streptococcus pneumoniae* pneumonia	
19	28	*Candida albicans* and *Enterococcus* mediastinitis	Resolved
(19 BF)			
20	519	*Candida albicans* sternal osteomyelitis/chondritis	Resolved
(52 WM)			
23	154	*Streptococcus pneumoniae* bacteremia, presumed endocarditis	Resolved
(31 WF)			
27	9	*Serratia marcescens* and *Klebsiella pneumoniae* pneumonia	Died (other causes)
(45 WM)			
28	115	Pneumococcal pneumonia	
(58 WM)	287	Adenovirus, CMV, *Staphylococcus aureus* pneumonia	Resolved
29	5	*Enterobacter cloacae* and *Torulopsis glabrata* pneumonia	Died (other causes)
(24 WM)			
IMMUNOSUPPRESSIVE PROTOCOL 4 (n = 21)			
38	13	*Candida albicans* fungemia/sepsis	Resolved
(48 BM)	117	Pleural tuberculosis	
43	3	*Candida albicans* and *Enterococcus* sepsis	Died (other causes)
(52 WM)			
50	102	*Pneumocystis carinii* and CMV pneumonia	Resolved
(36 WM)			

CMV = cytomegalovirus

TABLE 3
COMPARISON OF OCCURRENCE OF INFECTIONS IN CARDIAC TRANSPLANT RECIPIENTS BETWEEN IMMUNOSUPPRESSIVE PROTOCOL GROUPS

Type of infection	Protocol groups 1, 2, and 3 (n = 29)	Protocol group 4 (n = 21)	P*	Total events (% = No. events/50)
Major infections	15	3	.04	18 (36%)
Pneumonias	11	1	.016	12 (24%)
Bacteremias	6	2	N.S.	8 (16%)
Pneumocystis	4	1	N.S.	5 (10%)
Aspergillus/Nocardia	3	0	N.S.	3 (6%)
All CMV infections	21	14	N.S.	35 (70%)
Symptomatic CMV	9	2	.08	11 (22%)
Asymptomatic CMV	12	12	N.S.	24 (48%)
Herpes simplex infections	8	3	N.S.	11 (22%)
Herpes zoster infections	3	3	N.S.	6 (12%)
Urinary tract infections	8	4	N.S.	12 (24%)

*$P \le .05$ was considered significant; $P = .08$ was considered marginally significant.

cumulative steroid dosage as the single variable. For comparison between groups (Table 1), the variable chosen was the calculated mean daily steroid dosage for post-transplant days 1–30 (corrected for body weight). Protocol 4, the currently employed approach to both prophylaxis and rejection therapy, was compared to a combined group consisting of protocols 1, 2, and 3, both because protocol 4 represents an outgrowth of these earlier protocols and also because it constitutes a stable approach over a period of nearly 15 months and therefore creates a population large enough for meaningful analysis.

Definition of infection

A major infection was defined as an infection causing significant morbidity/mortality and requiring prolonged hospitalization, eg, pneumonia, sepsis, bacteremia/fungemia, or osteomyelitis. Pneumonias were classified as definite if positive cultures, microbiological stains, or histopathologic studies were obtained on actual lung tissue (by transbronchial or open lung biopsies, lung resection, or at autopsy). Pneumonias were classified as probable if patients presented with a characteristic clinical picture, changes on chest radiograph with either positive sputum or bronchoscopy cultures, stains on bronchioalveolar lavage for Pneumocystis carinii, or serologic evidence of infection. Bacteremias were defined by positive blood cultures for an organism with a consistent clinical picture. Urinary tract infections were defined by a characteristic clinical picture with pyuria and 10^5/mL organisms on urine culture. Cytomegalovirus (CMV) infections were defined by positive cultures of blood, urine, or tissue for CMV, seroconversion, significant in-

crease in CMV-IgG titers, or by typical histopathology on tissue stains. Patients with CMV infection who had fever and other evidence of organ involvement and no other source of infection were determined to have symptomatic CMV. Herpes simplex and herpes zoster infections were defined based on a characteristic clinical picture with or without positive vesicle or other tissue cultures. The remaining miscellaneous infections were defined on the basis of characteristic clinical pictures with positive tissue or fluid cultures for the organism involved.

Statistical methods

Time to infection was analyzed using Kaplan-Meier techniques. Differences between the two protocol curves were tested using the logrank statistic. Incidence and rejection rates per months were analyzed using a nonparametric technique (Wilcoxon Rank Sum test).[10]

In addition, Kaplan-Meier survival analysis was employed to look at major infections as a risk factor for mortality, and at overall comparison of actuarial survival between the two immunosuppressive protocol groups.[11] Occurrence of rejection episodes was also examined between the two protocol groups using a t-test comparison to look for differences in average number of rejections per patient in the two groups.

RESULTS

Thirty-eight major infections occurred in 18 of 50 patients (36%), for an average of 0.76 events/patient. Thirty-four events occurred in groups 1, 2, and 3 and four in group 4. The types of infections occurring in
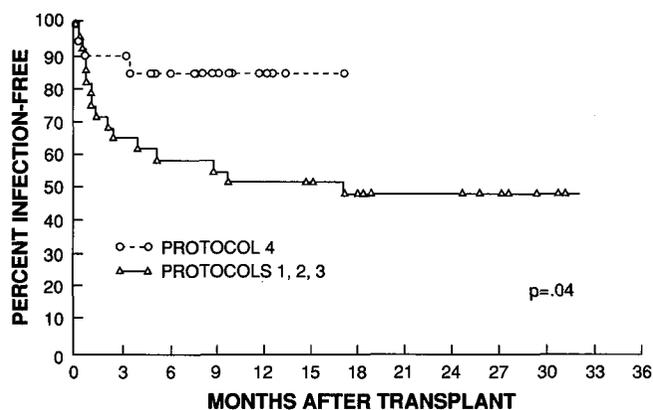
FIGURE 1. Freedom from major infections following cardiac transplantation, based on immunosuppressive protocol groups.

FIGURE 2. Actuarial survival following cardiac transplantation, based on occurrence of major infections.

these patients, their time of occurrence, and patient outcome are listed in Table 2. Table 3 compares the occurrence of various types of infection between the two groups and the overall infections in the 50 patients. There was a statistically significant difference in major infections (P=.04), pneumonias (P=.016), and symptomatic CMV infections (P=.08) between the two groups. The median incidence of major infections/month was lower for protocol group 4 (P=.02). Figure 1 illustrates the Kaplan-Meier plots of freedom from major infection between the two protocol groups. Although too few cases occurred to allow statistical comparison between the episodes of Nocardia, Aspergillus, and Pneumocystis infections between the two groups, there were no instances of Aspergillus or Nocardia infections in group 4 v three instances in groups 1–3 and only one episode of Pneumocystis infection in group 4 v four episodes in groups 1–3. No difference occurred in the number of total viral infections between the two groups; a marginal difference in symptomatic CMV infection (P=.08) was noted in group 4.

Ten patients died during the course of the study. Infection was the direct cause of death in four cases; all four patients were in protocol groups 1–3. Infection was a significant contributing factor to death in three additional cases; two of these were in groups 1–3. As illustrated in the Kaplan-Meier survival curves (Figure 2), major infection was determined to be a significant risk factor for mortality (P=.02) following cardiac transplantation.
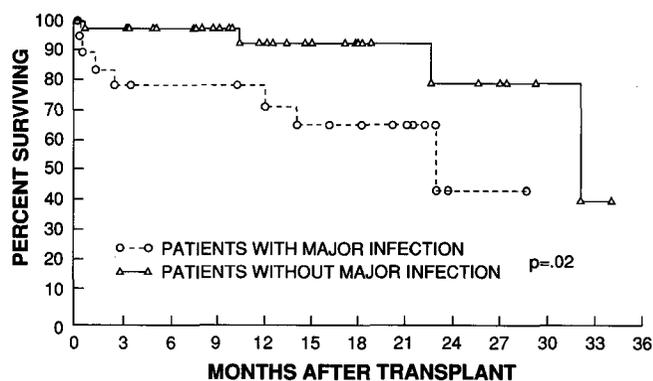
A total of 125 episodes of rejection occurred in 29 patients in groups 1–3 v 88 episodes in 21 patients in group 4. Comparing all episodes of rejection (accelerating mild, moderate, severe) there was no significant difference between the groups (P=.75). Forty-five moderate and severe rejections occurred in 29 patients in groups 1–3 v 30 rejections in 21 patients in group 4 (P=.80). The median incidence of rejection/month was also not different between the two groups (P=.19).

Although the difference in actuarial survival following cardiac transplantation was not significant between the two immunosuppressive protocol groups (P=.84), the follow-up was shorter in group 4, and only a small number of patients remained at the end in both groups.

DISCUSSION

Infection still continues to be an important cause of morbidity and mortality following cardiac transplantation.[1,4] With the advent of cyclosporine, a dramatic decrease in post-transplantation infection rates has been reported from many transplant centers.[2,5,12-14] Hoflin et al,[2] from Stanford, described a significantly lower mortality rate in their cyclosporine-treated cardiac transplant recipients, as well as a decreased incidence of infectious complications including pneumonias and Aspergillus, Nocardia, Pneumocystis, and active viral infections. Similar improvements in infectious complications and decreased mortality in heart transplant patients treated with cyclosporine were reported at the

Texas Heart Institute.[13,14]

Griffith et al,[7] at the University of Pittsburgh, postulated that the significant decrease in infections noted in their heart transplant patients receiving cyclosporine was largely due to the lowered steroid dosages used when cyclosporine was employed. This observation was further supported by the experience from the Columbia Medical Center in New York; by employing overall lower dosages of cyclosporine and oral prednisone for maintenance immunosuppression than previously reported, Dresdale et al[5] were able to achieve a much lower incidence of infectious complications. They concluded that both the form and dosage of steroid were critical factors for subsequent infections and discounted the belief that larger initial steroid dosages after transplantation were necessary to prevent rejection. They thought that lowered steroid dosages could safely be used to maintain immunosuppression and treat rejection with acceptable short-term results.

The present study also supports the critical role of steroids in increasing susceptibility of cardiac transplant recipients to infectious complications. An earlier study from this institution involving a detailed multivariate analysis of risk factors for cytomegalovirus infection following cardiac transplantation identified increased corticosteroid administration as the major significant risk factor for symptomatic or clinically important CMV infection.[8] By continuing to use lower steroid dosages, a significant decrease was noted not only in symptomatic CMV infections ($P=.08$), but also in pneumonias ($P=.02$) and other major infections ($P=.04$), without significant increases in rejection ($P=.75$).

This study demonstrates that larger steroid dosages remain a major risk factor for infectious complications in cardiac transplant recipients receiving cyclosporine and that reducing corticosteroids should further decrease infectious complications and subsequent morbidity and mortality in patients undergoing heart transplantation.

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