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Conservative Management of Late Rejection After Heart Transplantation

A 10-Year Analysis

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Objective

Immunosuppressive regimens for rejection after heart transplantation have been modified to reduce infectious complications without diminishing rejection treatment efficacy. A review of a single institutional series was performed to evaluate the influence of conservative management of grade 2 rejection on long-term outcomes after heart transplantation.

Methods

Before 1990, patients with late (>3 months after transplant) grade 2 rejection were treated with supplemental immunosuppressive drugs. Beginning in 1990, patients with late grade 2 rejection were treated conservatively by maintaining the current immunosuppressive regimen without additional therapy. The groups were compared for survival, incidence of subsequent rejection, and incidence of subsequent infection.

Results

One hundred twelve patients had one or more episodes of isolated, late grade 2 rejection; 39 (35%) were treated with supplemental immunosuppression (treated group) and 73 (65%) received no additional therapy (nontreated group). The mean time from transplantation to the first episode of isolated grade 2 rejection was 15.6 months in the treated group and 17.8 months in the nontreated group. Graft survival at 5 and 10 years was 69% and 51%, respectively, in the treated group and 67% and 41%, respectively, in the nontreated group ($p = 0.77$).

The rates for overall subsequent rejection were 0.031 episodes/patient-month in the treated group and 0.029 episodes/patient-month in the nontreated group ($p = 0.64$). The rates for early rejection within 6 months of initial grade 2 rejection were 0.044 episodes/patient-month in the treated group and 0.035 episodes/patient-month in the nontreated group ($p = 0.56$). The rates for overall subsequent infection were 0.018 episodes/patient-month in the treated group and 0.012 episodes/patient-month in the nontreated group ($p = 0.05$). The rates for early infection within 6 months of initial grade 2 rejection were 0.070 episodes/patient-month in the treated group and 0.032 episodes/patient-month in the nontreated group ($p = 0.04$). Group comparisons demonstrated a significantly lower incidence of infection in the nontreated group.

Conclusions

Conservative management of late grade 2 rejection neither adversely affects survival nor increases the incidence of subsequent short-term or long-term rejection. This approach lowers the early and late incidence of infection after rejection and may reduce other complications from aggressive supplemental immunosuppression.

Orthotopic heart transplantation remains the treatment of choice for end-stage cardiac failure, and long-term outcomes over the past several years have consistently improved. Modification of immunosuppressive regimens has played a central role in reducing the severity of rejection and infection, the major causes of death after cardiac transplantation.

Rejection documented on endomyocardial biopsy to be greater than or equal to grade 3A, defined by the International Society of Heart and Lung Transplantation (ISHLT) as multifocal moderate rejection,[1] is usually treated with supplemental immunosuppression. Biopsies with scores equal to or less than ISHLT grade 1B, defined as diffuse,

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mild acute rejection, do not typically require additional therapy. Radovancevic and others[2] raised the issue of how to manage patients with focal moderate rejection, particularly in those individuals without evidence of clinical graft dysfunction. In addition, various grading mechanisms for rejection on endomyocardial biopsy prompted the standardization of the ISHLT grading system, which stratified grades 1B, 2, and 3A to assist the clinician in the treatment of moderate acute rejection and to allow comparison of data between transplant programs.[3]

Repeated episodes of rejection and infection affect long-term survival of the patients who received grafts and transplants. Alteration of any immunosuppressive regimen must maintain efficacy in treating rejection without increasing infectious complications. This study was conducted to evaluate the influence of conservative management of ISHLT grade 2 focal, moderate rejection on long-term outcomes after heart transplantation.

METHODS

Database Review

A retrospective review was performed of the Johns Hopkins Cardiac Surgery Transplantation Database. This database records and houses prospective data on all patients undergoing cardiac transplantation at The Johns Hopkins Hospital. Patient information was gathered beginning with the first transplant in July 1983 and concluding in July 1997. Each of the 258 patient records was reviewed for endomyocardial biopsy data and episodes of rejection and infection. The date of the first episode of grade 2 rejection (International Society of Heart and Lung Transplantation) occurring more than 3 months after transplantation as documented by endomyocardial biopsy was noted. The number of subsequent rejection episodes (grade 2 or higher), subsequent severe rejection episodes (grade 3 or higher), and subsequent infection episodes were recorded for each patient. Subtotals for the number of subsequent rejection and infection episodes occurring within 6 months of the initial grade 2 rejection episode also were recorded for each patient.

Patients were excluded from analysis if they had never had an episode of grade 2 rejection identified by endomyocardial biopsy during follow-up. Several patients were were excluded from analysis who had not had any episode of rejection, as were several early patients who had no available biopsy data. Patients in whom all grade 2 rejection episodes occurred within 3 months of transplantation were also excluded from analysis. After applying these strict exclusion parameters to assess the long-term incidence of grade 2 rejection and subsequent events, 112 patients met the study criteria. These patients were divided into two groups according to treatment strategy for the initial episode of grade 2 rejection; 39 (35%) patients underwent supplemental immunosuppression (treated group), and 73 (65%) patients were managed conservatively without additional therapy (nontreated group).

Table 1. INDICATIONS FOR TRANSPLANTATION

	Treated Group n = 39 (%)	Nontreated Group n = 73 (%)
Coronary artery disease	21 (54)	34 (47)
Primary	18 (46)	29 (40)
Graft (retransplantation)	3 (8)	5 (7)
Cardiomyopathy	16 (41)	34 (47)
Dilated	12 (31)	23 (32)
Hypertrophic	2 (5)	4 (5)
Familial	1 (2)	–
Postpartum	–	1 (1)
Idiopathic	1 (2)	6 (8)
Congenital heart disease	1 (2)	2 (3)
Myocarditis	–	2 (3)
Rheumatic heart disease	1 (2)	–
Hemochromatosis	–	1 (1)

Patient Demographics

There were 30 men and 9 women in the treated group, and 55 men and 18 women in the nontreated group. Mean patient age at the time of transplantation was 47.7 years in the treated group and 47.2 years in the nontreated group ($p = 0.91$). The most common indications for transplantation in either group were coronary artery disease and dilated cardiomyopathy. A summary of the indications for transplantation according to treatment group is listed in Table 1. Fisher's exact test analysis of the groups did not demonstrate a statistically significant difference according to indication for transplantation ($p = 0.60$).

Treatment of Grade 2 Rejection

Patients diagnosed with grade 2 rejection on endomyocardial biopsy before 1990 were treated with supplemental immunosuppression, most commonly pulse therapy with methylprednisolone or OKT3. Beginning in 1990, a conservative approach was initiated for grade 2 rejection, in which patients were maintained on their current immunosuppressive regimen without additional therapy. Patients who initially had grade 2 rejection, which progressed to more severe rejection on subsequent endomyocardial biopsy, were given supplemental immunosuppression as indicated by clinical signs and symptoms of congestive heart failure.

Statistical Analysis

The two patient groups (treated *versus* nontreated) were compared for actuarial patient survival, graft survival, and freedom from graft coronary atherosclerosis at 5 and 10 years by Kaplan-Meier methods. Rates of subsequent rejection, subsequent severe rejection (grade 3 or higher), and subsequent infection were determined for the treated group and the nontreated group, respectively. Rates for subsequent

Table 2. CAUSE OF DEATH AFTER GRADE 2 REJECTION

	Treated Group n = 17 (%)	Nontreated Group n = 14 (%)
Rejection	2 (12)	–
Infection	2 (12)	3 (21)
Graft coronary artery disease	8 (47)	5 (36)
Neoplasm	1 (6)	3 (21)
Diffuse alveolar damage	1 (6)	–
Sudden death	2 (12)	2 (14)
Renal failure	1 (6)	–
Multisystem organ failure	–	1 (7)

early (within 6 months of initial grade 2 rejection) rejection, early severe rejection (grade 3 or higher), and early infection also were determined for each group. These rates (in episodes per patient-month) were then compared between the treated group and the nontreated group using the incidence-rate test.

RESULTS

The first patient included in the series underwent transplantation in September 1983, and the final patient included in the series underwent transplantation in November 1996. Kaplan-Meier analysis for patient survival at 5 and 10 years in the treated group was 74% and 55%, respectively. In the nontreated group, patient survival at 5 and 10 years was 69% and 47%, respectively. These differences were not statistically significant ($p = 0.84$). The cause of death according to treatment group is summarized in Table 2.

Kaplan-Meier analysis for graft survival at 5 and 10 years in the treated group was 69% and 51%, respectively. In the nontreated group, graft survival at 5 and 10 years was 67% and 47%, respectively. These differences were not statistically significant ($p = 0.77$). Kaplan-Meier analysis for freedom from graft coronary atherosclerosis at 5 years was 53% in the treated group and 57% in the nontreated group. This difference was not statistically significant ($p = 0.63$).

The length of follow-up after the initial episode of grade 2 rejection was 602.4 patient-years; total follow-up was 286.1 patient-years in the treated group, and 316.3 patient years in the nontreated group. The mean time from transplantation to the initial episode of grade 2 rejection was 15.6 months in the treated group (range, 2.3–77.5 months). The mean time from transplantation to the initial episode of grade 2 rejection was 17.8 months in the nontreated group (range, 3.3–55.9 months). A total of 5264 biopsies were reviewed from the entire database of 258 patients; 2708 biopsies were performed in the study population of 112 patients. A total of 1164 biopsies were performed in the treated group and 1544 biopsies were performed in the nontreated group.

There were 105 subsequent episodes of rejection in the treated group and 109 subsequent episodes in the nontreated group after the initial grade 2 episode. There were 10 episodes of rejection in the treated group and 15 episodes in the nontreated group within 6 months of the initial episode of grade 2 rejection. There were 33 subsequent episodes of severe rejection (grade 3 or higher) in the treated group and 54 subsequent episodes in the nontreated group. There was one subsequent episode of severe rejection in the treated group and two subsequent episodes in the nontreated group within 6 months of the initial episode of grade 2 rejection. Rates of overall subsequent rejection, rejection within 6 months, severe rejection, and severe rejection within 6 months are summarized in Table 3. Comparison for any of these events using the incidence-rate test did not demonstrate a statistically significant difference in rejection rates between the groups.

There were 60 episodes of infection in the treated group and 45 episodes in the nontreated group after the initial episode of grade 2 rejection. There were 16 episodes of infection in the treated group and 14 episodes in the nontreated group within 6 months of the initial episode of grade 2 rejection. Rates of overall subsequent infection and infection within 6 months are summarized in Table 4. Comparison between the groups using the incidence-rate test demonstrated a significantly lower incidence of overall subsequent infection and infection within 6 months in the nontreated group.

A summary of subsequent infection episodes according to causative organism is listed in Table 5. Overall, viral and bacterial infections predominated in the treated group and the nontreated group. A similar pattern was noted among

Table 3. INCIDENCE OF SUBSEQUENT REJECTION

	Overall		Within 6 Months		Severe		Within 6 Months	
	n	Rate*	n	Rate*	n	Rate	n	Rate*
Treated group	105	0.031	10	0.044	33	0.01	1	0.004
Nontreated group	109	0.029	15	0.035	54	0.01	2	0.005
p value	0.64		0.56		0.07		1.00	

* All rates reported as episodes/patient month.

Table 4. INCIDENCE OF SUBSEQUENT INFECTION

	Overall		Within 6 Months	
	n	Rate*	n	Rate*
Treated group	60	0.018	16	0.070
Nontreated group	45	0.012	14	0.032
p value	0.05		0.04	

* All rates reported as episodes/patient month.

infection episodes occurring within 6 months of the initial episode of grade 2 rejection. Only five patients (total of 31 deaths) died as a result of infectious complications, two in the treated group and three in the nontreated group ($p = 1.00$). Both of the patients in the treated group died from infection within 6 months of the initial episode of grade 2 rejection. In contrast, all three patients in the nontreated group died more than 1 year after the initial episode of grade 2 rejection.

DISCUSSION

This study was conducted to evaluate the influence of conservative management of ISHLT grade 2 rejection on the long-term outcomes of survival, rejection, and infection after heart transplantation. The data are particularly encouraging in that there were no significant differences in patient or graft survival between the treated group and the nontreated group. This is consistent with the series reported by Hutter and associates[4] in which there was no increase in mortality among patients treated conservatively for moderate rejection. In contrast, Anguita and associates[5] noted a higher mortality rate in patients with a pattern of repeated grade 1B or 2 rejection; these patients did not receive supplemental immunosuppression in the absence of graft dysfunction. However, survival data for that series extended only to 3 years and probably reflects the early portion of the hazard function for rejection and mortality after heart transplantation.

Most investigators agree that rejection episodes are more frequent and more severe during the first 6 months after heart transplantation, and these episodes become less common as the time from operation increases. Spratt et al.[6] reported that only 2.5% of all endomyocardial biopsies more than 9 months after transplantation demonstrated rejection; all of these were of the moderate variety. Although moderate episodes of rejection may be less frequent in late follow-up, there has been some concern that these episodes may progress to more severe rejection. Brunner-La Rocca et al.[7] demonstrated that up to 20% of patients with grade 2 rejection will progress to a more severe form on rebiopsy at 7 to 10 days and have suggested that this may contribute to impaired long-term graft function and overall survival. El-Gamul et al.[8] noted that nearly 90% of grade 2 rejection occurring within 6 months of transplantation progressed to grade 3A rejection, as compared with 4% of late grade 2 episodes. Others have reported far smaller rates of progression. Winters et al.[9] demonstrated that approximately 85% of episodes of focal moderate rejection resolve spontaneously. Gleeson et al.[10] noted that more than 80% of such episodes occurring more than 1 year after transplantation cleared within 4 weeks of biopsy, and Lloveras et al.[11] reported that more than 80% of patients have only minimal or mild rejection on subsequent biopsy.

In our series, there was no statistically significant difference in the incidence of subsequent severe rejection between the groups, although there was a trend toward a slightly higher incidence in the nontreated group. This contrasts with the data reported by Anguita et al.,[5] who noted a 22% incidence of late severe rejection in patients with a pattern of repeated grade 1B or 2 rejections *versus* a 4% incidence in patients with a pattern of only grade 1A or 1B rejections. Nakhleh et al.[12] reported that endomyocardial biopsy may underestimate the degree of rejection, with up to 87% of biopsy specimens scored as grade 2 showing a lower grade of rejection when compared with the entire heart on autopsy. These observations may have some bearing on the utility of repeat biopsy during conservative management of patients with grade 2 rejection, because additional biopsies may reveal either progression of moderate rejection or documentation of more aggressive rejection not previously identified.

Conservative management of grade 2 rejection is particularly appealing when viewed in the context of endomyocardial biopsy. Many of these episodes are discovered on surveillance biopsy, and the patient has no evidence of clinical graft dysfunction. The spectrum of moderate rejection is somewhat controversial, and there is considerable difficulty in consistently identifying grade 2 rejection. Winters and McManus[13] assessed uniformity in interpretation of endomyocardial biopsies; more than 80% of discrepancies involved differentiating grade 2 lesions from grades 1A, 1B,

Table 5. CAUSES OF INFECTION AFTER GRADE 2 REJECTION

	Treated Group		Nontreated Group	
	Overall	Within 6 Months	Overall	Within 6 Months
Bacterial	26	9	11	6
Viral	13	3	15	5
Fungal	3	1	3	0
Protozoal	2	0	0	0
Mycobacterial	1	0	0	3
Unknown	15	3	16	0
Total	60	16	45	14

3A, and Quilty lesions. Other investigators reported discrepancy rates ranging from 10% to 20% and have noted the contribution of Quilty lesions, in particular, to these discrepancies.[14–18] Such variation in the accurate diagnosis of focal, moderate rejection strengthens the argument for a conservative approach to grade 2 rejection, reserving supplemental immunosuppression for patients with documented severe rejection or with clinical graft dysfunction.

A distinct advantage to the conservative approach to grade 2 rejection is the reduced infection rates that can be attributed to a less aggressive immunosuppression regimen. Supplemental immunosuppression can be associated with a related increase in short-term infection rates, and it is well-known that infection is one of the major risk factors for mortality. In the current patients, the early infection rate (within 6 months of initial grade 2 rejection episode) was reduced by 54% in the nontreated group (0.032 episodes/patient-month) compared with the treated group (0.070 episodes/patient-month). Long-term infection rates also were significantly lower in the nontreated group, although this difference was not as pronounced. A similarly low incidence in infection in patients more than 1 year after transplantation was demonstrated by Hutter and associates;[4] none of the infectious episodes in that series was associated with a treated rejection episode or resulted in mortality. It is of particular interest in this series of patients that both patient deaths from infection in the treated group occurred within 6 months of treatment of the initial episode of grade 2 rejection. The three patient deaths from infection in the nontreated group occurred at 13 months, 30 months, and 37 months after the initial episode of grade 2 rejection.

In conclusion, conservative management of late grade 2 rejection after heart transplantation in this series of patients was not associated with an increase in the incidence of subsequent rejection. Neither early rejection rates (within 6 months of initial grade 2 episode) nor subsequent severe rejection rates were significantly increased by this approach. The incidence of subsequent early infection and overall infection was significantly lower when supplemental immunosuppression was not used for treatment of focal moderate rejection. Finally, conservative management of grade 2 rejection does not adversely affect long-term survival after heart transplantation. Unless late grade 2 rejection is associated with clinical signs of heart failure, appropriate management should be observation with subsequent biopsy at 7 to 10 days.

References

1. Billingham ME, Cary NRB, Hammond ME, Kemnitz J, Marboe C, McCallister HA, Snovar DC, Winters GL, Zerbe A. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: heart Rejection Study Group. J Heart Lung Transplant 1990;9:587–593.
2. Radovancevic B, Birovljev S, Frazier OH. Treating cardiac allograft rejection: present approach - analysis of 100 consecutive patients. J Heart Lung Transplant 1990;9:288–291.
3. Billingham ME. Dilemma of variety of histopathologic grading systems for acute cardiac allograft rejection for acute cardiac allograft rejection by endomyocardial biopsy. J Heart Lung Transplant 1990;9:272–276.
4. Hutter JA, Wallwork J, English TAH. Management of rejection in heart transplant recipients: does moderate rejection always require treatment? J Heart Lung Transplant 1990;9:87–91.
5. Anguita M, Lopez-Rubio F, Arizon JM, Latre JM, Casares J, Lopez-Granados A, Mesa D, Gimenez D, Torres F, Concha M, Valles F. Repetitive nontreated episodes of grade 1B or 2 acute rejection impair long-term cardiac graft function. J Heart Lung Transplant 1995;14:452–460.
6. Spratt P, Sivathasan C, Macdonald P, Keogh A, Chang V. Role of routine endomyocardial biopsy to monitor late rejection after heart transplantation. J Heart Lung Transplant 1991;10:912–914.
7. Brunner-La Rocca HP, Sutsch G, Schneider J, Follath F, Kiowski W. Natural course of moderate cardiac allograft rejection (International Society for Heart Transplantation Grade 2) early and late after transplantation. Circulation 1996;94:1334–1338.
8. El-Gamel A, Doran H, Rahman A, Deiraniya A, Campbell C, Yonan N. Clinical importance of grade 2 cellular heart rejection [letter]. J Heart Lung Transplant 1996;15:319–321.
9. Winters GL, Loh E, Schoen FJ. Natural history of focal moderate cardiac allograft rejection. Is treatment warranted? Circulation 1995;91:1975–1980.
10. Gleeson MP, Kobashigawa JA, Stevenson LW, Moriguchi JD, Kawata N, Hamilton MA, Hage A, Drinkwater D, Laks H. The natural history of focal moderate rejection in orthotopic heart transplant recipients. J Am Coll Cardiol 1994;483A. Abstract.
11. Lloveras JJ, Escourrou G, Delisle MB, Fournial G, Cerene A, Bassanetti I, Durand D. Evolution of untreated mild rejection in heart transplant recipients. J Heart Lung Transplant 1992;11:751–756.
12. Nakhleh RE, Jones J, Goswitz JJ, Anderson EA, Titus J. Correlation of endomyocardial biopsy findings with autopsy findings in human cardiac allografts. J Heart Lung Transplant 1992;11:479–485.
13. Winters GL and McManus BM. Consistencies and controversies in the application of the International Society of Heart and Lung Transplantation Working Formulation for heart transplant biopsy specimens. J Heart Lung Transplant 1996;15:728–735.
14. Fishbein MC, Bell G, Lones MA, Czer LS, Miller JM, Harasty D, Trento A. Grade 2 cellular heart rejection: does it exist? J Heart Lung Transplant 1994;13:1051–1057.
15. Kemnitz J. Grade 2 cellular heart rejection: does it exist?: yes! [letter] J Heart Lung Transplant 1995;14:800–801.
16. Nielsen H, Sorensen FB, Nielsen B, Bagger JP, Thayssen P, Banndrup U. Reproducibility of the acute rejection diagnosis in human cardiac allografts. The Stanford Classification and the International Grading System. J Heart Lung Transplant 1993;12:239–243.
17. Sharples LD, Cary NRB, Large SR, Wallwork J. Error rates with which endomyocardial biopsy specimens are graded for rejection after cardiac transplantation. Am J Cardiol 1992;70:527–530.
18. White JA, Guiraudon C, Pflugfelder PW, Kostuk WJ. Routine surveillance myocardial biopsies are unnecessary beyond one year after heart transplantation. J Heart Lung Transplant 1995;14:1052–1056.

Discussion

DR. ROBERT M. MENTZER, JR. (Lexington, Kentucky): This study validates the clinical suspicion that lesser grades of acute cellular rejection have natural histories that may, in fact, be more benign than originally anticipated. Certainly, over-treatment of acute rejections carries the penalty of serious infectious complications, as documented in this review. Interestingly, the authors report a significant reduction in both early and late infections that was