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.

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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

associated with the more tolerant strategy regarding treatment of grade 2 rejection.

It is important to recognize, however, that some grade 2 rejections do evolve into more virulent forms. We also know that repetitive nontreated rejection may result in impaired long-term graft dysfunction. It has been our experience at the University of Kentucky that one predictor of myocyte necrosis is the persistence of grade 2 rejection on previous biopsies, even late after transplantation.

In addition, there is biochemical and molecular evidence that cellular damage does occur in the presence of grade 2 rejection. Apoptosis, or programmed cell death, has been reported to occur in up to 50% of grade 2 biopsies, compared to its absence in grade 0 or 1A biopsies. If confirmed, this would suggest the grade 2 rejection is, in fact, associated with significant heart cell injury. If this is the case, perhaps we need to reassess treatment of grade 2 in the context of new immunosuppressant therapy.

May I have the one slide, please? As you know, we recently completed a double-blind, controlled, multi-center trial that assessed the safety and efficacy of mycophenolate versus azathioprine. We found that the use of this agent was associated with a reduction in the requirement for rejection treatment from 73.7% to 65.7% and a reduction in 1-year mortality from 11.4% to 6.2%.

With these observations in mind, I would like to ask Dr. Baumgartner several questions. How similar were the study groups with respect to induction and maintenance therapy since this was a retrospective analysis performed over a 10-year time period? Also, since it has been suggested that there may be a correlation between ischemic time and degree of rejection, would you comment on preservation techniques and ischemic times for the two cohorts?

Finally, it would be helpful to hear your thoughts regarding the treatment of patients with two consecutive, biopsy-proven, grade 2 rejections. What agents, if any, would you recommend using?

DR. WILLIAM A. BAUMGARTNER (Baltimore, Maryland): In answer to Dr. Mentzer's questions, we have not used induction therapy since the beginning. The patients were treated similarly for maintenance immunosuppression, except that around 1991 we switched to a triple drug immunosuppressive protocol. There is some difference in the immunosuppression from early to late, although the biopsy analysis demonstrating grade 2 rejection were unequivocal between the two groups.

You mentioned ischemic time and the occurrence of subsequent rejection. There is no question that this is an important point. Our preservation technique continues to be crystalloid cardioplegia and submersion in ice.

One of the important points I think, as you pointed out, is that the ischemic time is also associated with both 1- and 3-year mortality. This is particularly important in view of the recent decision by HCFA indicating that regionalization or nationalization of donor allocation is going to be discussed. We all feel that this will adversely affect our patients. You asked about two consecutive episodes of grade 2-A rejection. Based upon these results, we are still fairly conservative. We will continue to follow them with weekly to ten-day biopsies. We will not treat two biopsies, but a third positive one we will go ahead and treat. We will treat with oral prednisone and no other augmented immunosuppressant.

DR. WALTER H. MERRILL (Nashville, Tennessee): I think the authors are correct. Moderate rejection episodes in the absence of hemodynamic compromise do not necessarily require additional immunotherapy. My questions are as follows: First, did the maintenance prophylactic therapy for infection change over the time course of this study? Second, did specific treatment of episodes of moderate rejection lead to an increased risk of death from infection? Or was there merely an increased risk of infection which was potentially treatable and curable?

Finally, this study specifically excluded patients who experienced moderate rejection within three months of transplantation. In view of the fact that some studies have indicated early acute rejection episodes may increase the risk for the occurrence of late rejection episodes, could the authors tell us how they treat episodes of moderate rejection that occur less than 3 months from the time of transplantation?

DR. WILLIAM A. BAUMGARTNER (Baltimore, Maryland): The first question was what we do for infection prophylaxis. We haven't changed our protocol for bacterial coverage. We use Ancef for the perioperative period. We have changed our CMV prophylaxis based upon the data that suggest that CMV may contribute to the development of coronary artery disease. Patients who are positive for CMV undergo prophylaxis in the hospital with ganciclovir and continue with acyclovir for three months after discharge.

In regard to deaths from infection, we had only five deaths, two in the treated group and three in the nontreated group. It is interesting to note that the two patients who died in the treated group died from infection within 6 months of treatment. So we assume that the infection episodes were more severe in the treated group.

In regard to how do we treat grade 2 rejection less than 3 months following transplantation, we treat grade 2 rejection with oral steroids and taper. I also think there is good evidence in the literature to show that when rejection occurs within the first 3 months of transplantation, it can be an aggressive form and progress to grades 3-A and 3-B.

DR. ERIC A. ROSE (New York, New York): The systemization of endomyocardial biopsy grading of rejection represented by the ISHLT scoring system has provided a measurement standard allowing rationalization of diagnosis and management of subclinical rejection.

The benign nature of mild cellular infiltrates and biopsies of ISHLT grade 1 and, conversely, the potentially dangerous natural history of untreated grade 3 biopsies have allowed tailoring of immunosuppressive therapy to minimize morbidity due to rejection and infection. Histologic grade 2 rejection however represents a fairly frequent finding whose significance has been controversial.

The Hopkins investigators now present a carefully analyzed series with such moderate focal rejection who have been managed with watchful waiting rather than augmented immunosuppression.

The experience was accumulated over an 8-year period and contrasted with a comparable retrospective control group who prior to 1990 were treated with boosts of immunosuppressive agents. The data convincingly demonstrate that subsequent grade 3 rejection frequency is no higher in the untreated group, while infectious morbidity was significantly diminished compared to the untreated cohort.

Untreated patients had also had comparable long-term survival and frequency of graft atherosclerosis. However, this observation applies only to grade 2 rejection observed more than three months after transplantation, and the authors have continued to treat grade 2 rejection in the early postoperative period. In addition, the

median time of the observed grade 2 rejection in this study actually exceeded one year after transplantation.

I have the following questions for Dr. Baumgartner. What was the frequency of early grade 2 biopsy histology in both groups? You have already mentioned that you do continue to treat early grade 2 rejection. Has your maintenance immunosuppression regimen changed over the course of this study since 1991? And lastly, have you modified your protocol of scheduled surveillance biopsies? In particular, do you continue to do routine surveillance biopsies beyond the first year after transplantation?

DR. WILLIAM A. BAUMGARTNER (Baltimore, Maryland): The maintenance immunosuppression issue is certainly of significance. We started out with cyclosporine and prednisone for the first few years of our program and then subsequently switched to a triple drug immunosuppression when Dr. Bolman and his group showed that this was an important aspect of maintenance immunosuppression that influenced survival. Although there was a difference in immunosuppressive protocols, the analysis was based on the histologic picture of the biopsy. So we felt that even though there was a difference, that this would not influence the histologic appearance of grade 2 rejection.

You asked whether we modified our protocol for the number of biopsies that we do posttransplantation. And we have. I think there has been increasing data to suggest that late rejection, that is rejection occurring after a year, is very infrequent in patients undergoing transplantation. However, it still occurs. We have now modified our protocol so patients undergo biopsy every 3 months for the first 2 years and then twice a year after that. At that point in time, if we do find grade 2 rejection, we do not treat. We only treat rejection of higher grades.

DR. FRANK C. SPENCER (New York, New York): My question has probably been answered several times. The histologic changes seen are those that may occur with a chronic inflammatory process from any cause. How can you determine that these histologic abnormalities are due to rejection and not due to an inflammatory process of unknown cause? Separately, how many patients had similar Grade 2 histologic abnormalities on two consecutive biopsies?

DR. WILLIAM A. BAUMGARTNER (Baltimore, Maryland): It is a very good question, Dr. Spencer. We occasionally hover over the microscope in trying to figure out whether this is rejection, especially in patients who are out beyond a year, especially if they had no evidence of infection. Sometimes this can be manifested as toxoplasmosis, which presents as an infiltrate. Viral infiltrates can also occur, but it is fairly rare. If there is no evidence of infection and titers are not elevated, then I think we can safely assume that this is rejection and not infection.