A Randomized Prospective Trial of Cardiac Xenografts vs. Current Standard-Of-Care Cardiac Transplant for Treatment of End-Stage Congestive Heart Failure

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A. Study Purpose and Rationale

Cardiac transplant is a valuable treatment for people with symptomatic congestive heart failure. While fewer than 5001o of patients with New York Heart Association class III or IV heart failure survive two years even with optimal medical management, [11] cardiac transplant recipients have a 50% survival rate approaching ten years. [21 The success of transplantation, especially since the emergence of cyclosporine and other immunosuppressive medicines in the 1980s, is reflected in the increase in the number of people officially waiting for heart transplantation on the registry list of the United Network for Or an Sharing (UNOS); between December 1987 and August 1998 the waiting list for donor hea rts rew from 646 to 4097 names. [2] However, the availability of human donor organs and ice total number of transplants per year have stabilized during this period, with a corresponding increase in the rate of death among patients waiting for a human heart to become available, estimated at 3001b. [2,3] The use of left ventricular assist devices (LVADs) to augment the function of a failing heart has been used with some success as a "bridge" to transplant but has yet to gain approval as a long-term alternative to transplant. [4,5]

Xenotransplantation, or the use of donor organs from a species different from the recipient, offers a solution to the current shortage of human donor organs. Since the 1960s, when Reemstra and StarzI both performed a limited number of kidney transplant procedures using primate donors and human recipients, [6,7] xenotransplantation has been clinically limited by problems of rejection unique to cross-species molecular and cellular interactions, including hyperacute rejection and delayed xenograft rejection. Over several years, knowledge of the mechanisms governing rejection of xenografts has increased, and techniques have been developed to alter potential donors transgenically. Specifically, the possibility of using pig hearts for cardiac transplant has been an active area of research. The current prevailing opinion is that the use of pigs as donors is ethically superior to the use of primates such as baboons or chimpanzees; moreover, they are currently bred in quantity for food, and their hearts are suitably sized and structured for transplantation into humans. Trials of pig-to-primate transplantation have already met with limited success, with graft survival of up to 24 days even using limited immunosuppression. [8] It is not inconceivable that Phase I trials of xenotransplantation may occur within the next several years, likely starting with carefully selected "compassionate need" cases of patients who fail to meet current age limitations for consideration for transplant.

While it is not possible to propose a xenotransplantation clinical trial based on our current technology, research has produced several promising strategies to reduce xenograft-specific causes of rejection. Hyperacute rejection may eventually be overcome through some combination of 1) depletion or inactivation of xenoreactive natural antibodies (XNAs) in -humans; 2) transgenic elimination of XNA antigen targets; and 3) transfer of human antigens into donor cells to inhibit activation of complement. [9-15] The process of delayed xenograft rejection occurs 3 to 4 days after transplantation, and current efforts to overcome this barrier include genetic manipulation of the endothelial cells in the donor heart as well as inactivation of the monocytic and natural killer cells which mediate this process. [16-18]

For the purpose of this exercise, I will propose a Phase II trial to compare the outcome of patients receiving xenografts with the those receiving the current standard of care, namely, the possibility of a human heart transplant after placement on the national registry. Clearly, Phase I evaluation of safety and efficacy would come first and would form the basis for the preparation of xenografts and post-transplant

care of patients receiving these organs; I will not speculate on the details of such preparation and care at this time.

An alternative study design might use xenografts as a "bridge" to human organ transplant, but this approach fails to address the problem of the critical shortage of human donor organs. Over 4000 patients died in 1996 alone while awaiting an organ transplant (including 744 patients listed for heart and 48 listed for heart-lung transplants); Hancock estimates that another 100,000 die each year having failed to qualify for placement on the transplant waiting list. [15] While some physicians argue that stringent pre-transplant evaluation is necessary to ensure that each organ is "used" to its greatest potential, [19] others believe that the process of selecting (and eliminating) transplant candidates is often a subconscious form of health care rationing based on poorly-considered "medical futility" arguments. [20] A recent study also suggests that women, African-Americans, and patients in low-income regions are less likely to be listed for transplant. [21] To realize the maximum benefit of xenografts for all patients, they must be demonstrated to be at least the equals of transplanted human organs.

B. Study Design and Statistical Analysis

In order to enroll a suitable number of patients in this study, several different transplant programs will participate. Multi-center participation will be limited to transplant programs which perform at least twelve heart transplants per year (the national average in 1997); [2] the possibility of LVAD placement will also be a requirement.

One way to conduct this study would be to recruit all eligible patients at time of listing for transplant and subsequently randomize each consenting patient to control (human) or experimental (pig) transplant. However, the striking differences in the two treatment options are such that patients may be unwilling to enroll, entrusting their future to a random decision. Many doctors would also have ethical concerns about such a study, and may find that the introduction of such randomization damages their rapport with the patient. Zelen has proposed a method of study design involving pre-randomization which addresses these concerns and, by providing more definitive information to each patient at the time of recruitment, increases enrollment overall. [221 This method is schernatized in Figure 1 on the next page and works as follows:

- At the time that patients are to be listed for transplant, all patients at participating transplant centers are randomized into a smaller (Group A) and a larger (Group B) population. The size and composition of each group is clarified below.

- Group A is considered the control group for the study. They are listed with UNOS as eligible for human heart transplant and are not offered the possibility of xenotransplant. They receive treatment which is currently standard-of-care as well as the rigorous pretransplant and post-transplant care which all transplant patients currently enjoy. Because they are not subjected to any additional risks or testing than that which is a normal part of their care, their consent to function as control patients is not requested.

Group A - study control not offered xenotransplant
All eligible patients randoimrization
Figure 1. Randomization of eligible patients by Zelen's method. [22]

- All patients in Group B are offered their choice of either human transplant or xenotransplant. Those choosing human transplant are discarded from Group B, listed with UNOS, and receive care identical to those in Group A; however, they are not counted as either control patients in this study. The smaller subset of patients in Group B who agree to xenotransplantation (which we can call Group B') undergo non-emergent xenotransplantation within 72 hours of enrollment. To preserve the structure of this study and to minimize "lost" time while a patient is neither listed with UNOS nor preparing for xenotransplant, the

decision to undergo xenotransplantation must be made within 7 days, after which patients will automatically be registered with UNOS and ineligible to receive a xenograft.

To determine the randomization of patients between Group A and Group B, during the six months prior to the inception of this study, all patients listed for transplant at the participating medical centers will be asked the following question at the time of UNOS registry: "While cardiac transplantation is a very effective treatment for heart failure, more than half of all patients spend at least a year waiting for a human heart to become available, and about 3001o of all patients die before a human heart becomes available. A few patients have ben transplanted with hearts from pigs specifically modified for transplantation into humans. If you were offered the option of participating in a study where you would receive a pig heart within the next three days, would you choose to wait for a human heart or would you choose to receive a pig heart?" The results of Phase I studies as well as the details of the medical regimen for xenotransplant patients would also be made available as part of the questionnaire.

Based on the results of the above questionnaire, the population of Group B would be tailored such that the profile of those people likely to enroll would be similar both to Group A and to the population of transplant patients as a whole. For example, if patients over the age of 50 were (on average) three times less likely to choose xenotransplantation than the transplant population as a whole, then patients over age 50 would be over-represented by a factor of three in Group B during randomization. Possible confounding variables which should be considered during randomization include age, gender, weight, blood type, ethnic or racial group, and likely UNOS status at the time of enrollment, which are independent predictors of survival. [23,13]

The primary endpoint for this study will be two year survival from the time of listing for transplant (Group A) or the time of xenotransplantation (Group B). Patients in either group who undergo LVAD or are listed for retransplantation statistically will be considered transplant failures, which will be a concurrent endpoint. There is no potential to cross over between groups. The survival rates for patients in both groups will be used to construct Kaplan-Meier plots. An independent statistical review board will follow the study populations at regular intervals for adverse effects or significant differences in the two groups prior to the primary endpoint. Secondary endpoints will include total number of days hospitalized; measures of cardiac function such as ejection fraction by MUGA, pulmonary artery oxygen saturation, and maximal oxygen consumption on exercise(V02); cumulative dose of steroid per patient; rate and degree of rejection on biopsy within the first 6 months, I year, and 2 years; and validated subjective measures of quality of life. [24,25]

For purposes of power analysis in this study, the predicted mortality in the control group two years subsequent to the time of enrollment is about 40%. This estimate includes the mortality of patients who die after registration with UNOS but prior to transplantation, which was estimated at 30% (and increasing) based on data from 1988 to 1991. [3] This 30% figure may be an underestimate; UNOS reports that in 1996 over 5% of patients listed for heart transplant remained on the waiting list for greater than one year, and while listed, the incident death rate for these patients was 395 deaths per 1000 patient-years. [2]. Additionally, patients who are listed for transplant but are subsequently removed from the list are not statistically counted as deaths, although a substantial portion are presumably removed due to co-morbidities which develop as a result of prolonged time on the waiting list. However, as a result of this study, the number of patients listed for transplant will be reduced and the waiting time may show a corresponding decrease. Patients who undergo transplant have a known mortality of approximately 15% at one year and 20% at two years counted from the time of the surgery. [2]

Power analysis determines that a sample size of 180 patients - 90 each in Groups A and B - is necessary to demonstrate statistical significance for a 2001o absolute reduction in mortality with 80% confidence. It is important to note that demonstration of equivalence between the two groups is also clinically relevant. The goal of this study will be to enroll at least 30 patients per year in Group B, which would allow the study to be completed in a total of five years.

C. Study Procedures

Participation in this study does not add to the rigorous level of care for patients who are either awaiting transplant or are post-transplant. Care of the post-transplant patient involves frequent follow-up visits to the transplant physician with intense medical management of regimens for immunosuppression, blood pressure management, lipid profile modification, and treatment of other complications including diabetes, infections and/or toxic side effects from immunosuppressants. [261 Invasive assessment of cardiac function and screening for asymptomatic rejection is also crucial. For patients in this study, right heart catheterization and cardiac biopsy will be performed at least every three months during the first year post-transplant; the frequency may be increased or, after the -first year, decreased accordingly depending upon pathologic evidence of graft rejection at the discretion of the treating physician. A sample from each biopsy of each patient will be reviewed by a pathologist who is not otherwise involved in this study to determine rejection rates for the two groups.

D. Study Drugs and E. Study Devices

Because it is unclear what additional drugs may be needed to prevent xenograft rejection, these issues will not be addressed.

E. Study Questionnaires

As discussed in detail in section B, a single question will be asked of transplant candidates who are not participants in this study. Questionnaires intended to measure subjective quality of life, including the Life Satisfaction score and the Well-being score have previously been described. [251

F. Study subjects and H. Recruitment of Subjects.

Many programs have already established strict criteria, based on general guidelines, which patients must pass prior to listing with LJNOS for transplantation. [27-3 11 Indications for transplant include class III or IV heart failure due to left ventricular dysfunction, refractory angina, refractory cardiac arrhythmia, and diastolic heart failure. Other surgical remedy (revascularization, correction of valvular abnormalities) must be considered and either rejected or ineffective. Physiologic testing is also important; patients with decreased maximal oxygen consumption on exercise (VO2< 14 ml/kg/min) and low pulmonary vascular resistance (less than 2.5 Wood units) are considered good candidates. Some comorbid illnesses are considered absolute contraindications to transplantation, including diabetes mellitus with evidence of microangiopathy, current or past history of malignancy, cirrhosis, and some major psychiatric illnesses; other comorbidities are considered on a case-by-case basis. At most centers, the maximum age at time of listing is 65.

For purposes of the current study, all patients who are considered candidates with an indication of congestive heart failure between the age of 18 and 65 will be eligible for enrollment excepting: 1) candidates listed for simultaneous multiple organ transplantation; 2) patients with prior heart transplants listed for second heart transplant; 3) patients who have undergone emergent LVAD implantation prior to listing for transplant.

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