Pig heart xenotransplantation as a bridge to allotransplantation

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With the increasing availability of pigs genetically engineered to protect their tissues from the human immune response, research into xenotransplantation is progressing steadily. One potential route to the clinic would be the use of a pig heart as a bridge to allotransplantation. This would only be ethical if the outcome was realistically estimated to be as good as, or better than, bridging with a mechanical device. The experimental results that would be required to warrant consideration of a clinical trial and the patients in whom bridging with a xenograft might be considered preferable to a mechanical device are discussed.

J Heart Lung Transplant 2010;29:838–40
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KEYWORDS:
- bridging to transplantation
- hearts
- pig
- mechanical support
- ventricular assist devices
- xenotransplantation

In 2000, one of us (D.K.C.C.) had the privilege of being co-chairperson of an International Society of Heart and Lung Transplantation (ISHLT) committee set up to review the potential of xenotransplantation of the heart.1 For reasons that can no longer fully be remembered, one of the committee’s conclusions was that bridging with a pig heart should not be an option if a mechanical circulatory support (MCS) device could be implanted.

Given recent advances in xenotransplantation and insights into outcomes with the current generation of MCS, we wished to reconsider whether there would be specific patient populations for whom there might be equipoise for xenotransplantation as a bridge to transplantation (BTT). In addition, the experience gained from such research would provide valuable clinical information on the potential of xenotransplantation as a permanent option for patients with end-stage cardiac failure. This information may be complementary to, or different from, that obtained from pig-to-non-human primate experimental studies.

During the past 10 years, there have been substantial advances in the field of MCS. The current generation of continuous-flow left ventricular assist devices (LVAD) is smaller, more durable, and has a superior adverse event profile to the previous generations of pulsatile LVADs.2 Survival with the current generation of LVADs as a BTT is about 90% at 6 months and 79% at 18 months.2,3 Outcomes are even better in less severely ill patients.2

When used as a BTT, an LVAD must provide support of sufficient duration until a suitable organ becomes available. Of those supported with an LVAD as a BTT, approximately 52% will have undergone heart transplantation at 1 year, and 35% will be alive with the device in place. Hence, any technology applied to a group eligible for LV support alone would need to demonstrate similar durability.2 Lastly, patients who receive a continuous-flow LVAD as a BTT have substantial improvements in functional status, with 83% of patients becoming New York Heart Association functional class I or II after 6 months of support.

In contrast to LVAD support, those who require support with a biventricular assist device (BiVAD) have substantially worse outcomes, with 1 year survival of <50%.2 They also have a substantially worse adverse event profile than those who receive LVAD support alone, particularly when...
compared with the current generation of continuous-flow LVADs. The incidence of bleeding with BiVADs is higher as a consequence of the more advanced state of the patient’s heart failure and the more extensive surgery required during implantation. Such bleeding leads to a greater requirement for blood products and thus an increased likelihood of human leukocyte antigen (HLA) sensitization, which, in turn, may make it difficult to obtain a compatible donor organ. Given this, the population, or a subset of the population, of patients who require BiVAD support may be the most appropriate individuals to consider when designing a trial of xenotransplantation.

Achieving equipoise to bridge a patient to transplant with a pig heart could be achieved if the results were realistically anticipated to be comparable to, or better than, those of the currently available BiVAD or total artificial heart technology; that is, a 50% survival at 6 months, the capability of effective support of patients for 6 to 9 months until a donor heart is obtained, with a reasonable functional capacity and quality of life, and in the relative absence of complications of immunosuppressive therapy, such as infection and malignancy. Alternatively, a pig heart might be indicated if any particular MCS device is not possible in a particular patient. However, the poor outcomes after BiVADs are largely related to the patient’s advanced heart failure state, with substantial renal, hepatic, and nutritional compromise; therefore, these patients may also be at high risk after xenotransplantation.

Preliminary requirements in animal models

To achieve equipoise even in this severely ill population, the field of xenotransplantation will also need to meet acceptable outcomes in the pig-to-non-human primate model. We would suggest that a clinical trial should not be considered until the following parameters have been met in such a model:

1. Heterotopically-placed pig heart grafts survive and function fairly consistently (eg, 7 of 10) for at least 6 months.
2. Orthotopically-placed pig heart grafts survive and function fairly consistently (eg, 7 of 10) for > 3 months, with some primates surviving > 6 months; this follows the ISHLT guidelines of 2000.1
3. Absence of life-threatening consumptive coagulopathy.4,5
4. Low incidence of immunosuppression-related complications, such as infection and malignancy.6

These suggested survival figures may seem lower than those required to justify a clinical trial, but these suggested goals take into consideration the significantly greater difficulty in maintaining immunosuppressed non-human primates under experimental conditions, such as the inability to provide intensive care and monitoring in comparison to the conditions available to human patients.

Patient selection

Although there are no absolute consensus guidelines for VAD implantation, criteria have been developed to help optimize patient selection and outcome.7–10 Thus patients who may be considered for a trial of xenotransplantation include:

1. Those with significant right heart dysfunction and/or persistent ventricular dysrhythmias that are not suitable candidates for LV support alone (with or without temporary right ventricular support) and thus would require BiVAD support.
2. Small adults and children with a body surface area of < 1.5 m² in whom it may occasionally be difficult to insert a suitable assist device, and in particular, those who are at high risk with the current generation of pediatric MCS devices.
3. Patients not considered candidates for any of the currently available MCS systems due to anatomic considerations or pre-existing thrombophilia.
4. Infants and children with congenital heart disease, such as ventricular septal defect, tetralogy of Fallot, and complex malformations, whose survival after the insertion of a device is < 25%.

Potential contraindications to bridging with a pig heart include sepsis, elevated pulmonary vascular resistance, dysregulated coagulation, and possibly postcardiotomy failure, such as those requiring extracorporeal membrane oxygenation.

Special issues

Several other points are worthy of consideration.

1. Sensitization to HLA. The current evidence is that even if sensitization to pig antigens develops, this does not result in sensitization to HLA11 and therefore would not preclude allotransplantation.
2. Informed consent. This should be obtained as early as feasible in the course of the progression of heart failure when BiVAD support is becoming likely, to give the patient and his or her family an opportunity to fully consider the potential advantages and disadvantages.12 An attempt to obtain informed consent when the patient is deteriorating rapidly is not ideal.
3. Cost. Bridging with a pig heart is likely to be equally expensive as MCS implantation, but as with MCS, the costs will hopefully decrease with experience.
4. Induction of B-cell tolerance. There have been reports of the induction of tolerance to A or B blood group carbohydrate antigens after ABO-incompatible heart allotransplantation in infants.13,14 Because the major pig antigen against which humans have natural preformed antibodies is also a carbohydrate (Galα1,3Gal), it is possible that if the pig heart transplant occurs in infancy,15 tolerance to this carbohydrate antigen will develop. More importantly, GTKO pigs are now available, and, if non-Gal antigens are also found to be carbohydrate structures, then tolerance to these antigens may develop. This might, in fact, allow long-term survival of a pig heart in
an infant who is receiving T-cell–directed immunosuppressive therapy alone.

In conclusion, although heterotopically transplanted pig hearts have functioned for almost 6 months in non-human primates and orthotopically transplanted pig hearts for almost 2 months, we are not yet ready to undertake a clinical trial of pig heart transplantation, even as a BTT in high-risk patients. However, as new genetically engineered pigs steadily become available, it is likely we shall be in such a position within a few years. It is not too early to consider the future possibility of bridging as a first step toward permanent implantation of a pig heart. The above comments are intended to stimulate consideration of this topic.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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