

EXECUTIVE SUMMARY

REPORT OF THE XENOTRANSPLANTATION ADVISORY COMMITTEE OF THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

THE PRESENT STATUS OF XENOTRANSPLANTATION AND ITS POTENTIAL ROLE IN THE TREATMENT OF END-STAGE CARDIAC AND PULMONARY DISEASE

D.K.C. Cooper*, A.M. Keogh*,
J. Brink, P.A. Corris, W. Klepetko, R.N. Pierson III,
M. Schmoeckel, R. Shirakura, L. Warner-Stevenson

* Co-chairs

In August 1999, the President of the International Society for Heart and Lung Transplantation (ISHLT), Robert Kormos, set up a Xenotransplantation Advisory Committee charged with drawing up a white paper on the present status of xenotransplantation and its potential role in the future of the treatment of patients with end-stage cardiac and pulmonary diseases. The committee, which included members from a wide geographic background as well as diverse professional interests, has considered this topic in a global context.

In particular, it has considered the need for a new source of thoracic organs for transplantation, the potential of xenotransplantation to fulfill this need in comparison with other therapeutic modalities, the immune barriers and potential complications of clinical xenotransplantation, as well as some of its ethical, regulatory and financial aspects. Consideration was given to the results believed to be necessary in experimental models before progression to a clinical trial should be undertaken, the criteria of selection of patients for the initial clinical trials, and the necessary results that would need to be obtained in the clinical trials to pursue this field of therapy further. Finally, an assessment was made as to whether the state of the science was adequate at this stage to initiate a clinical trial, what regulatory mechanisms would be advisable to oversee such a trial, and who or what body should financially support such a trial. We would emphasize that the field of xenotransplantation research, particularly that involving thoracic organ transplantation, should be reviewed at intervals and revisions made to our conclusions and recommendations (see below).

There is an urgent and steadily increasing need for a greater supply of donor thoracic organs worldwide. Xenotransplantation offers the possibility of an unlimited supply of hearts and lungs that could be available electively when required. Pig organs transplanted into nonhuman primates are rejected by antibody-mediated mechanisms, which provide major immunologic barriers that have not yet been overcome. Having reviewed the literature on xenotransplantation, we present a number of conclusions on its present status with regard to thoracic organs, and we make a number of recommendations relating to eventual clinical trials.

Although pig hearts have been demonstrated to function in a heterotopic site in nonhuman primates for periods of several weeks, median survival of orthotopically transplanted hearts is currently less than one month. No transplanted pig lung has functioned for even 24 hours. Current experimental results indicate that a clinical trial at present would be premature. There is a potential risk, hitherto undetermined, of the transfer of an infectious organism with the donor pig organ to the recipient, and possibly to other members of the community. A clinical trial of xenotransplantation should not be

undertaken until experts in microbiology and the relevant regulatory authorities consider this risk to be minimal.

A clinical trial should be considered when an approximate 60% survival of life-supporting pig organs in nonhuman primates has been achieved for a minimum of 3 months, with at least 10 animals surviving for this minimum period of time. Furthermore, there should be evidence that longer survival (>6 months) can be achieved. These results should be achieved in the absence of life-threatening complications from the immunosuppressive regimen used. The relationship between the presence of anti-HLA antibody and anti-pig antibody and their cross-reactivity, and the outcome of pig organ xenotransplantation in recipients previously sensitized to HLA antigens require further investigation. We recommend that the initial patients entered into a clinical trial of cardiac xenotransplantation should be those who are unacceptable for allotransplantation or who are acceptable for allotransplantation but who are unlikely to survive until a human cadaveric organ becomes available and in whom bridging by a mechanical assist device is not possible.

Both the initial clinical trial and all subsequent clinical xenotransplantation procedures for the foreseeable future should be regulated by national bodies that should have wide-reaching government-backed control over all aspects of the trials. We recommend coordination and monitoring of these trials through an international body, such as the International Society for Heart and Lung Transplantation, and the setting up of a registry to record and widely disperse the results of these trials.

Xenotransplantation has the potential to solve the problem of donor organ supply, and therefore research in this field should be actively encouraged and supported.

CONCLUSIONS

1. There is a need for an increased supply of donor thoracic organs worldwide.
2. Xenotransplantation offers the possibility of an unlimited supply of organs for heart and lung transplantation. These organs would be available when required, enabling the operative procedure to be carried out electively.
3. There are many questions relating to the immunologic problems of xenotransplantation that have not yet been answered.
4. The results of experimental non-life-supporting heart or lung transplantation do not reflect those of life-supporting thoracic organ transplantation, and are not acceptable as a sufficient basis on which to proceed to a clinical trial.
5. There is insufficient evidence to conclude that the immune response to a cardiac or pulmonary xenograft used to bridge a patient to an allograft will or will not be detrimental to the function of the subsequent allograft.
6. There is insufficient evidence to conclude that the presence of B and/or T cell allosensitization (e.g. from previous blood transfusion, pregnancy or allograft) will or will not be detrimental to the function of a subsequent xenograft.
7. There are remaining questions relating to the function and growth of the pig heart and lungs in the human metabolic environment that are as yet unanswered. Although the evidence is that a pig heart can function satisfactorily in the orthotopic position in a primate, evidence with regard to porcine lung function is inadequate to come to a conclusion in this respect.
8. There is a potential risk, hitherto undetermined, of the transfer of an infectious organism with the donor pig organ to the recipient, and possibly to other members of the community.

9. The current experimental results indicate that a clinical trial of HTx at present would be premature.
10. Experimental lung xenotransplantation is in an extremely primitive stage of development and no consideration of a clinical trial can be given at the present time.
11. Thoracic organ xenotransplantation, when successful, will almost certainly require increased health care spending.
12. Xenotransplantation of thoracic organs theoretically has immense potential, and research in this area should be encouraged and supported.

RECOMMENDATIONS

1. Every effort should be made to improve the medical treatment of patients with advanced heart and lung disease to minimize the number needing organ transplantation.
2. Every effort should be made to increase the number of human cadaveric organs that become available.
3. A clinical trial of xenotransplantation should be undertaken only when experts in microbiology and the relevant regulatory authorities consider the potential risks of transfer of a porcine-related infection from the recipient of a pig thoracic organ to other members of the community to be minimal. The recommendations that follow are based on the assumption that this recommendation will be fulfilled.
4. Both the initial clinical trial and all subsequent clinical xenotransplantation procedures for the foreseeable future should be regulated by national bodies that should have wide-reaching government-backed control over all aspects of the trials, including the power to halt them, if deemed necessary.
5. All clinical trials should be monitored by an international body that would coordinate the trial and disperse information widely. The ISHLT could play a leading role in this respect and maintain a registry of the results of all clinical trials.
6. A clinical trial of xenotransplantation should be undertaken only when 60% survival of life-supporting pig-to-nonhuman primate transplants for a minimum of 3 months has been achieved in a series of consecutive experiments with a minimum of 10 animals surviving for this period of time. If the xenograft is being implanted with the intention of it providing permanent replacement of the native organ, evidence must be provided of some nonhuman primates surviving at least 6 months. Ideally, a 50% 6-month survival should be achieved, but consideration could be given to a clinical trial even if this goal is not attained if all other aspects of the experimental work were encouraging. These goals should be achieved in the absence of the development of life-threatening complications from the immunosuppressive regimen used.
7. A bridging trial should be initiated only when there is substantial evidence that the immune response to the xenograft will not be detrimental (by the development of a cross-reactive antibody or cellular response) to the subsequent allograft.
8. The relationship between the presence of anti-HLA antibody and anti-pig antibody and their cross-reactivity needs to be investigated further. The outcome of pig organ xenotransplantation in recipients previously sensitized to HLA antigens by an allograft, pregnancy or blood transfusion requires further investigation.
9. The initial patients entered into a clinical trial of xenotransplantation should be those who are unacceptable for allotransplantation but who do not have such severe concomitant disease or other factors that would greatly diminish the potential for success of the trial. The results of permanent support by a mechanical assist device are currently uncertain, and the availability of this form of experimental therapy does not preclude a clinical trial of permanent cardiac xenotransplantation, and does not render such a trial unethical.

10. A second group who could be considered are those acceptable for allotransplantation but who are unlikely to survive until a human cadaveric organ becomes available and in whom bridging by a mechanical assist device is not possible or is unavailable. A xenograft bridge should not be employed if a mechanical assist device would fulfill this role and is available when required.
11. The decision to initiate a clinical trial of heart or lung xenotransplantation does not need to await the performance of previous trials of cell or kidney xenotransplantation.
12. Although the initial clinical trial should ideally not include infants and children, but only adult patients who are able to give fully-informed consent, infants and children should not be absolutely precluded from the trial.
13. An initial clinical trial conducted in a small number of patients (e.g., ten) should not be expanded until minimum follow-up has been for an adequate period of time to assess the results, which we suggest should be a minimum of 3 months. We recognize that this period is inadequate to assess the potential for medium- and long-term complications.
14. The initial clinical trials should be carried out as an extension of a planned experimental program, and should ideally be performed or directed by those who have been involved in the experimental development of the protocol.
15. The status of research into xenotransplantation should be reviewed at intervals and the above recommendations should be revised as necessary.
16. In order to protect the integrity and assure the ongoing success of clinical trials, the ethical issues surrounding xenotransplantation should be further explored. This includes the ethical considerations expressly identified and discussed in this report, as well as shared concerns and differences between nations, cultures and religious traditions within the broader international community.