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Regulation of Clinical Xenotransplantation—Time for a Reappraisal

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Abstract

The continual critical shortage of organs and cells from deceased human donors has stimulated research in the field of cross-species transplantation (xenotransplantation), with the pig selected as the most suitable potential source of organs. Since the US Food and Drug Administration concluded a comprehensive review of xenotransplantation in 2003, considerable progress has been made in the experimental laboratory to improve cell and organ xenograft survival in several pig-to-nonhuman primate systems that offer the best available models to predict clinical outcomes. Survival of heart, kidney, and islet grafts in nonhuman primates is now being measured in months or even years. The potential risks associated with xenotransplantation, for example, the transfer of an infectious microorganism, that were highlighted in the 2003 Food and Drug Administration guidance and subsequent World Health Organization consensus documents have been carefully studied and shown to be either less likely than previously thought or readily manageable by donor selection or recipient management strategies. In this context, we suggest that the national

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regulatory authorities worldwide should re-examine their guidelines and regulations regarding xenotransplantation, so as to better enable design and conduct of safe and informative clinical trials of cell and organ xenotransplantation when and as supported by the preclinical data. We identify specific topics that we suggest require reconsideration.

The continual critical shortage of organs and cells from deceased human donors has stimulated research in the field of cross-species transplantation (xenotransplantation), with the pig selected as the most suitable potential source of organs. Research has progressed rapidly in recent years, largely through the availability of an increasing number of genetically engineered pigs and of novel immunosuppressive agents. Survival of heart, kidney, and islet grafts in nonhuman primates is now being measured in months or even years.[1]

Since the US Food and Drug Administration (FDA) concluded a comprehensive review of xenotransplantation in 2003 (http://www.fda.gov/cber/guidelines.htm), considerable progress has been made in the experimental laboratory to improve cell and organ xenograft survival in several pig-to-nonhuman primate systems that offer the best available models to predict clinical outcomes. Meanwhile, the increasing number of deceased human donor organs used for clinical transplantation has failed to keep pace with an expanding candidate waitlist, and a significant number of waiting patients die without receiving a donor organ (http://optn.transplant.hrsa.gov/).

Risks

The potential risks associated with xenotransplantation, for example, the transfer of an infectious microorganism, that were highlighted in the 2003 FDA guidance and subsequent World Health Organization (WHO) consensus documents have been carefully studied and shown to be either less likely than previously thought or readily manageable by donor selection or recipient management strategies (see hereafter). As such, we consider that the risk-benefit ratio associated with pig-to-human transplantation of organs and tissues has changed dramatically since the FDA and other national (UKXIRA, MedSafe, etc) and international (WHO) regulatory bodies last completed their careful assessments in the first half of the last decade.

In this context, we suggest that the national regulatory authorities worldwide should re-examine their rules and regulations regarding xenotransplantation to better enable design and conduct of safe and informative clinical trials of cell and organ xenotransplantation when and as supported by the preclinical data.

Unmet Clinical Needs

We feel it is important to place this recommendation in context. Despite 5 decades of concerted effort, the gap between the supply of organ allografts and demand for them has widened significantly. Many initiatives to increase the number of human organs that are used for transplantation have succeeded, for example, the use of expanded donors or donors after circulatory death, organ pairing, and the like, and have been widely adopted internationally

as a consequence of progressive, culturally sensitive policy and education initiatives. Unfortunately, even though donor management options and donor acceptance criteria have been significantly expanded, optimistic projections that waiting lists would shrink have not been realized.

The results associated with various mechanical devices as an alternative to transplantation have improved significantly over the past decade, especially in cardiac support, whereas there remain several short- and long-term problems.[2,3] However, while ventricular assist devices play an increased role in the management of patients with cardiac failure, even for that population, there remains a large unmet need, and patients suffering from failure of other vital organs at present have no similar option.

Other options for overcoming the shortage of deceased human donors in general have not made as much progress as xenotransplantation.[4] Specifically, although there has been progress in stem cell research, tissue engineering and regenerative medicine, and blastocyst complementation, we believe that these technologies remain less advanced than xenotransplantation.[4] Although we support continued investment in each of these fields, given the major, well-defined barriers facing each of them, we do not expect that any of them will have significant clinical effect in the near future and believe that xenotransplantation provides the best near-term solution to the organ shortage that limits organ transplantation.

Preclinical Progress

Progress in xenotransplantation has been achieved by systematic study of the scientific barriers. Each identified barrier has been addressed, either by genetic engineering of the organ-source pig or by availability and application of novel immunosuppressive and anti-inflammatory agents.[1,5]

Genetically engineered pig heart transplants have functioned in a heterotopic position in baboons for more than 2 years, only failing after all immunosuppressive therapy had been discontinued.[6–9] Genetically engineered pig kidneys have supported life in baboons and monkeys for more than 6 months and, in one case, for almost a year[10–12] (Iwase H and Adams A, verbal personal communications). Both genetically engineered and wild-type pig islets have maintained insulin-independent normoglycemia in diabetic monkeys for periods of more than a year and, in 1 case, for almost 3 years.[13–17] Genetically engineered mesencephalic pig cells have reduced the physical features of a Parkinson-like disease in monkeys for more than 1 year.[18] Even in the difficult pig-to-baboon liver transplantation model, there has been significant improvement in graft survival, to almost 1 month in 2 recent instances.[19–21]

Preclinical results are rapidly approaching consensus benchmarks intended to trigger consideration of clinical trials. Indeed, clinical trials of decellularized pig corneal transplantation[22] and encapsulated pig islet transplantation[23,24] are already underway, and consideration is being given to the selection of patients for initial clinical trials of pig solid organ xenotransplantation.[25]

PERV

More recent experience has suggested that the risk of porcine endogenous retrovirus (PERV) infection in human recipients is less than anticipated.[26–28] Based on the molecular sequencing of PERV, both genomic screening and quantitative assays for circulating PERV have been developed.[29] These advances have allowed development of testing methods for source animals, organs, and human recipients.[30] Although persistent microchimerism in xenograft recipients may pose some risk of delayed donor-derived infection, no transmission to human xenograft recipients or in preclinical pig-to-primate studies has been demonstrated.[31,32] Burn patients treated with wild-type skin transplants did not develop evidence of infection.[27] Available antiviral agents also have activity against PERV.[33–35] Multiple intrinsic mechanisms seem to further limit the infectivity of PERV for human cells despite the presence of PERV receptors.[36] A variety of other approaches have been suggested including the selection of pigs with reduced PERV loci, including those used in a New Zealand clinical trial without evidence of PERV transmission, though this trial was in nonimmunosuppressed patients.[28] The same observation was made after the transplantation of encapsulated pig islets in patients in a second clinical trial in Argentina.[37] It is possible that newer molecular techniques including short interfering RNA technology[38–41] or the generation of PERV knockout swine using CRISPR-Cas9 technology[42,43] could limit or completely exclude PERV transmission.

Proposals

On the basis of these considerations, we would propose the following topics as candidates for reconsideration by national and international regulatory authorities.

1. The archiving of samples from both source pig and human recipient to enable investigation in the event of an unexpected complication after a xenotransplant.

   It was originally suggested that archiving of tissues should be maintained for up to 50 years. Considering the much lower risk now envisioned for PERV-induced disease[26,32,44,45] and the unwieldy logistics and high cost of such prolonged archiving, we believe that this requirement should be relaxed. It is anticipated that most infections associated with the presence of exogenous microorganisms will occur early after transplantation, but it is unknown how, when, or whether a PERV-related complication might present. However, new technologies may be applied to archived specimens (eg, high-throughput sequencing) to detect organisms not originally noted in screening assays for donor animals or not detected in nonimmunosuppressed hosts.

   Further clarification and guidelines are required on a number of points that include the following. Who will be responsible for maintaining the archives? Will it be the academic or clinical center carrying out the clinical trial or a company sponsoring a trial? Will the national regulatory authorities play any role in this archiving? Where will the tissues be archived and under what level of security? Who will bear the cost of storage of the archived samples?

2. *The monitoring of patients and their relatives and close friends after a xenotransplant*.

   For the same reasons as described for archiving above and because life-long monitoring, even if deemed advantageous, would be difficult and not likely enforceable, we suggest that such prolonged monitoring may be neither necessary nor advisable and therefore should be reconsidered.

3. *Pigs with multiple genetic modifications*.

   It needs to be made clear whether a pig with multiple genetic modifications will be considered as a single "product" or whether each genetic modification needs to be assessed and approved separately. Our present understanding is that, in the United States, a pig with multiple genetic modifications will be considered as a single entity. Separate assessment will almost certainly delay the clinical introduction of this potentially life-saving form of therapy. A related concern that should be clarified is whether a pig with a specific pattern of genetic modifications will be approved as a source of 1 specific organ or of all organs.

4. *The inclusion in the immunosuppressive treatment regimen of a drug that is not yet clinically approved by the national regulatory authority*.

   Guidance is sought about what circumstances might make it possible to use an investigational drug together with a genetically engineered pig, neither of which has yet been approved. For example, could islets from a genetically engineered source pig, presumably one with multiple hitherto unapproved genetic modifications, be combined with an investigational T-cell costimulation blockade agent or other investigational drug or device (eg, for immunoisolation)? This is not unprecedented in numerous islet allotransplant trials that have included investigational islet products and off-label use of immunosuppressants.[46] If adequately supported by preclinical efficacy and safety data, might a drug that is approved for other indications be used for off-label use in combination with an investigational genetically engineered pig organ?

Progress in xenotransplantation research is now relatively rapid. As such, we believe it is timely for the previously mentioned points, and others that may emerge, to be reappraised as the basis for informing clinical trials of xenotransplantation.

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