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XENOTRANSPLANTATION

Editorial

Assessment of infectious risk in clinical xenotransplantation: The lessons for clinical allotransplantation

The infectious risk of clinical xenotransplantation is unknown. Based on experience with human allotransplantation, it has been assumed that the potential exists for the transmission of infection with the viable cells or tissues of a xenograft [1–4]. This risk was amplified by concerns regarding the unique potential risk of the transmission of zoonotic infectious agents of animal (swine) origin into human recipients for which diagnostic tools did not exist and the behavior of which was unpredictable in the immunosuppressed human graft recipient. The terms "xenosis," "direct zoonosis," and "xenozoonosis" were used to suggest the potential for the emergence of novel pathogens in xenotransplantation. Basic research has resulted in a series of important observations including the molecular cloning of the porcine endogenous retroviruses (PERV), the PERV receptors, and the identification of PERV-AC with the potential to infect human cells in vitro [5–7]. Molecular diagnostic tools have been developed for other pig-derived pathogens comparable with those affecting human allograft recipients including porcine cytomegalovirus (PCMV), porcine lymphotropic herpesvirus (PLHV2), porcine circoviruses, and hepatitis E virus. Assays also exist for common pathogenic viruses (e.g., adenovirus, parvovirus, encephalomyocarditis virus, porcine reproductive and respiratory syndrome virus, Aujesky's Disease, enterovirus B), bacteria (*Salmonella*, *Leptospira* and *Yersinia* species, *Mycoplasma hyopneumoniae*), and parasites (*Cryptosporidium* and *Isospora* species) affecting swine. In pig-to-primate xenotransplantation, additional diagnostic tools were developed for primate (baboon and macaque) CMV and other herpesviruses given the intensity of immunosuppression required for sustained xenograft function in the non-human primates. The U.S. Food and Drug Administration, the World Health Organization, and other national authorities issued guidance documents related to xenotransplantation [8–12]. This experience allowed the development of consensus guidelines under the auspices of the World Health Organization regarding the assessment of donor animals and human recipients of porcine xenografts to prevent infectious transmission events [13].

Despite this impressive progress, the actual risk of disease transmission in xenotransplantation remains unknown. Early clinical data from a period prior to optimal assay development suggested that transmission events were uncommon and might be unrecognizable among the *expected* infections occurring in immunocompromised transplant recipients [14–17]. However, significant progress has been made in the microbiology of xenotransplantation, notably in the screening of source animals for clinical trials of xenotransplantation. This observation is exemplified by the report by Wynyard et al. [18] on the "Microbiological Safety of the First Clinical Pig Islet Xenotransplantation Trial in New Zealand," a report of a New Zealand Government-approved clinical trial of alginate-encapsulated porcine islet cell transplants in fourteen patients suffering hypoglycemic unawareness. Each patient received between 5000 and 20 000 islet equivalents as a single dose from Auckland Island strain donor pigs. A number of components of the trial merit comment. In advance of the trial, pigs and islet preparations were tested for 26 microorganisms (15 viruses, 10 bacterial species, and one protozoan) using molecular and immunological assays. Recipients were found to be negative on testing for PERVs and other microorganisms at multiple time points up to 1 yr following transplantation. Of note, the colony of donor swine is derived from a herd from the Auckland Islands and have been further isolated since 1999 in a biosecure facility. These data support the safety of this trial using these donor animals. The data are quite encouraging for the field, but cannot predict the safety of subsequent trials using whole, vascularized organs (and a much larger cell mass) or other donor herds.

The approach developed to assure the safety of clinical xenotransplantation has provided much of the framework for the prevention of "donor-derived infection" in human allotransplantation [19]. In both settings, the absolute prevention of

the transmission of infection with transplantation is impossible; such a goal would make life-saving transplants unavailable. In human allotransplantation, outbreaks of disease (e.g., SARS coronavirus, West Nile virus) or local epidemiology (Chagas' disease, endemic fungi) affecting organ donors disproportionately affect immunosuppressed allograft recipients. Donor screening for all potential pathogens is impossible. In clinical xenotransplantation, a level of safety has been developed beyond that available for human organ donors given the availability of closed herds of donor swine that can be routinely tested for a battery of potential human pathogens. Microbiological assays can be standardized and the proficiency of the laboratories validated by expert, reference laboratories. Only in xenotransplantation have recipient surveillance programs been mandated to detect both known and previously unknown or unexpected pathogens even in the absence of infectious syndromes. In the future, this may incorporate new technologies (e.g., broad-range primers or high-throughput sequencing of nucleic acids) to look for unknown pathogens. As new technologies are applied to xenotransplantation, the safety of allotransplantation may also be further enhanced.

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References

1. Fishman JA. Infection and xenotransplantation. Developing strategies to minimize risk. Ann N Y Acad Sci 1998; 862: 52–66.
2. Fishman JA, Patience C. Xenotransplantation: infectious risk revisited. Am J Transplant 2004; 4: 1383–1390.
3. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357: 2601–2614.
4. Mattiuzzo G, Scobie L, Takeuchi Y. Strategies to enhance the safety profile of xenotransplantation: minimizing the risk of viral zoonoses. Curr Opin Organ Transplant 2008; 13: 184–188.
5. Akiyoshi DE, Denaro M, Zhu H et al. Identification of a full-length cDNA for an endogenous retrovirus of miniature swine. J Virol 1998; 72: 4503–4507.
6. Takeuchi Y, Patience C, Magre S et al. Host range and interference studies of three classes of pig endogenous retrovirus. J Virol 1998; 72: 9986–9991.
7. Wood JC, Quinn G, Suling KM et al. Identification of exogenous forms of human-tropic porcine endogenous retrovirus in miniature Swine. J Virol 2004; 78: 2494–2501.
8. First World Health Organization Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials: Changsha, China, 19–21 November 2008. The Changsha Communique. Xenotransplantation 2008; 16: 61–63.
9. U.S. Food and Drug Administration. PHS Guideline on Infectious Disease Issues in Xenotransplantation, 2001. https://www.federalregister.gov/articles/2001/01/29/01-2419/phs-guideline-on-infectious-disease-issues-in-xenotransplantation-availability.
10. U.S. Food and Drug Administration. Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans, 2003.
11. World Health Organization. WHO consultation on xenotransplantation – WHO/EMC/ZOO/98.1 (Guidance Document) 1997.
12. World Health Organization. OECD/WHO Consultation on Xenotransplantation Surveillance – WHO/CDS/CSR/EPH/2001.2 (Guidance Document) 2000. http://www.who.int/transplantation/publications/OECD_WHO.pdf.
13. Fishman JA, Scobie L, Takeuchi Y. Xenotransplantation-associated infectious risk: a WHO consultation. Xenotransplantation 2012; 19: 72–81.
14. Garkavenko O, Croxson MC, Irgang M et al. Monitoring for presence of potentially xenotic viruses in recipients of pig islet xenotransplantation. J Clin Microbiol 2004; 42: 5353–5356.
15. Paradis K, Langford G, Long Z et al. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. The XEN 111 Study Group. Science 1999; 285: 1236–1241.
16. Heneine W, Tibell A, Switzer WM et al. No evidence of infection with porcine endogenous retrovirus in recipients of porcine islet-cell xenografts. Lancet 1998; 352: 695–699.
17. Patience C, Patton GS, Takeuchi Y et al. No evidence of pig DNA or retroviral infection in patients with short-term extracorporeal connection to pig kidneys. Lancet 1998; 352: 699–701.
18. Wynyard S, Nathu N, Garkavenko O et al. Microbiological safety of the first clinical pig islet xenotransplantation trial in New Zealand. Xenotransplantation 2014; 21: 309–323.
19. Fishman JA, Greenwald MA, Grossi PA. Transmission of infection with human allografts: essential considerations in donor screening. Clin Infect Dis 2012; 55: 720–727.