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COMMENTARY

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How the COVID-19 pandemic may impact public support for clinical xenotransplantation in the United States?

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Abstract

Many patients who would undergo organ transplantation cannot proceed due to the inability of human organ donation to satisfy medical needs. Xenotransplantation has the potential to offer unlimited availability of pig organs for transplantation, and pig-to-non-human primate models have demonstrated outcomes that may soon justify clinical trials. However, one of the unique ethical challenges faced by xenotransplantation is that the risk of introducing potential zoonotic disease into the community must be weighed along with the benefit to the patient. While most experts believe that zoonosis is manageable, apprehension over disease transmission from animal donors to human recipients remains a frequent concern of many who are undecided or opposed to clinical xenotransplantation. The COVID-19 pandemic represents a scenario (rapid worldwide spread of a highly contagious novel zoonotic disease with no natural defense in humans) that would seem to justify apprehension, especially in the United States, which has largely avoided previous pandemic outbreaks. However, there are many differences between zoonosis found in the wild or after xenotransplantation that favor the safety of the latter. Still, these differences, as well as the benefits of xenotransplantation, are not widely understood outside of the field. We must therefore ask what impact the COVID-19 pandemic will have on attitudes toward xenotransplantation.

KEYWORDS

COVID-19, pandemic, PERV, xenotransplantation, zoonosis

Xenotransplantation has long been seen as a logical way to fulfill the promise of transplantation that has been limited by human organ donation.[1] However, concern over potentially infectious zoonotic diseases (crossing from animal to human) is a factor often cited in opposition.[2] While up to 75% of emerging human diseases are of zoonotic origin,[3] including COVID-19,[4] the United States (US) has largely avoided outbreaks until now. However, the United States has recorded over 1.3 million infections and over 84 000 deaths from COVID-19 as of May 14, 2020,[5] figures that will surely rise. Economic and social upheavals, a consequence of the public safety responses to curb the spread of the infection, are as ubiquitous as the disease itself.

A report on the aftermath of H1N1 virus outbreak gives credence that a pandemic could negatively impact societal opinion of xenotransplantation.[6] Those with an interest in xenotransplantation must ask what impact the COVID-19 pandemic may have on public attitudes toward it.

Significant advances have been demonstrated in large animal models of xenotransplantation due to (a) a more complete understanding of underlying causes of graft failure, (b) the advent of

genetic engineering technology to improve pig donor compatibility with primate recipients, and (c) the introduction of novel immunosuppressive agents capable of overcoming the remaining immunological barriers.[7-11] Benchmarks of success in pig-to-non-human primate xenotransplantation may soon justify clinical trials.

However, anxiety felt over COVID-19 may lead many to question the safety of xenotransplantation. The rapid spread of COVID-19 demonstrates the difficulty in controlling a novel pathogen occurring in nature. In China, and even in the United States, with advance warning, COVID-19 quickly spread beyond easy containment. During this time of heightened concern over the ability of zoonotic diseases to spread, it is important to recognize that the deliberate and controlled nature of xenotransplantation provides a level of safety not found in nature.[12]

There will be several differences between clinical xenotransplantation and a natural outbreak of a virus into the community, and these are all in favor of xenotransplantation.

1. The designated pathogen-free organ-source pigs will be bred and housed under strict biosecure isolation conditions and will not be exposed to any animal vector that could transfer a pathologic microorganism to the pigs. The US Food and Drug Administration's (FDA) guidelines require that only the second generation of pigs in the facility can be used as sources of organs for clinical trials.[13] The founder pigs will be born by Cesarean section, immediately transferred into the biosecure facility, and raised under these isolation conditions, but it will only be their offspring (born and raised *entirely* within the facility) that will be able to provide organs for human recipients.
2. The humans caring for the pigs will be regularly tested for the presence of microorganisms and, if necessary, excluded from the facility if they have any symptoms of signs of infection.
3. Members of each cohort of organ-source pigs (sentinel animals) will be tested at regular intervals for the presence of potentially pathologic microorganisms throughout the period they are housed in the facility.
4. The specific organ-source pig will be tested before or at the time of organ transplantation to ensure no transfer of a potentially pathologic microorganism to the recipient.
5. In the initial clinical trials, the number of patients who will be included will be very small, and the trial will be spread over a relatively long period of time. This will provide time to determine whether any infectious (or other) complication has developed before a subsequent patient receives a pig organ graft.
6. The recipient of the pig graft will be monitored by the medical team at regular intervals, and this will include monitoring for novel infectious complications.
7. If relative self-isolation is maintained during the first few weeks after the transplant, any patient that might develop features of infection can be immediately isolated for investigation, and his/her contacts can be readily traced.

When this proposed protocol is compared with the circumstances that the community has been exposed to during the COVID-19 outbreak, and furthermore compared with the usual scenario when an organ from a deceased human donor is transplanted, the differences will be obvious. The risk of a pathologic microorganism, for example, cytomegalovirus and Epstein-Barr virus, being transferred with a deceased human organ is high, and even the transfer of an unusual or rare infectious agent, for example, rabies and West Nile virus, cannot be entirely excluded.[14] Typically, unexpected donor-derived infections are recognized only when identical infections occur among a cluster of recipients of organs from a specific deceased human donor.[15] This will not be the case with the first trials of xenotransplantation.

Porcine endogenous retroviruses (PERVs) represent a special case of potential infection. They can infect human cells in specific laboratory conditions,[16,17] but experts have pointed to several key factors that mitigate this threat.[18,19] (a) There is no evidence of PERV in humans despite millennia of contact with wild or domesticated pigs, or in islet xenotransplantation patients.[20,21] (b) PERV has only been shown to infect human cells in vitro under conditions that are not found in nature.[22] (c) Pigs can be selected from herds in which expression of PERV A and PERV B is minimal, and PERV C is absent (eliminating the potential of a more virulent strain of PERV A/C).[23] (d) PERV can be inactivated[24-26] or deleted[27,28] by genetic manipulation, if this is believed to be necessary (which is not the case at present).[14] (e) PERVs are susceptible to several pharmacologic agents available to us at present.[29,30]

It has been said that adversity provides opportunity. That the current pandemic provides adversity is apparent, and opportunities, though less visible, must be sought. A new respect for researchers seeking vaccines and other solutions to the COVID-19 crisis may also provide credibility for those in xenotransplantation research. As some physicians have advocated treatments for COVID-19 that are unwarranted by scientific evidence or have not undergone adequate testing, it is important that scientists advocating for xenotransplantation stick to a consensus and not risk the credibility of the field in this manner.

The likely immediate aftermath of the pandemic may be a less favorable landscape for xenotransplantation unless supporters present a positive message. As part of its mission, the International Xenotransplantation Association is positioned to play a role in educating the public with consensus opinions backed by solid scientific evidence that mitigates concerns about safety and demonstrates a more balanced risk-to-reward ratio. We have the data and the message, all that remains is to move forward with careful deliberation in these uncertain times.

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