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ORIGINAL ARTICLE

INTERNATIONAL HUMAN XENOTRANSPLANTATION INVENTORY: THE ADVENT OF CLINICAL TRIALS

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Summary

Objective. Xenotransplantation is a potential solution for the current organ shortage in organ transplantation. An online international inventory (www.humanxenotransplant.org) has been documenting human xenotransplantation cases since 2006. Previous publications have covered activities over the periods of 1995 to 2010 and 2010 to 2020. Here, we present recent updates that demonstrate major breakthroughs with long-term outcomes.

Methods. Information was gathered from different sources, including scientific publications, press releases and news articles from January 2021 to December 2022.

Results. During the aforementioned timeframe, four applications of human xenotransplantation involving 6 patients were identified: two trials of heart transplant (involving 3 patients) and two trials of kidney transplant (also involving 3 patients). All cases were performed in the USA and used genetically modified pigs with 1 genetic modification (2 patients) or 10 modifications (4 patients). In total, 5 patients were in a state of brain death during the transplant.

Conclusions. Transplantation of life-sustaining solid organs (hearts and kidneys) signifies a major breakthrough in the field of xenotransplantation. The use of organs from genetically modified animals and the broad adoption of the brain-dead deceased donor model also show a paradigm shift in clinical studies of human xenotransplantation. With growing public interest in this field, this information can be used to better inform officials, media, and the public in order to encourage best practice based on internationally harmonized guidelines, following the initiative of the Changsha Communiqués.

Key words: transplantation, heterologous, kidney failure, chronic, heart failure, public health surveillance

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INTRODUCTION

Demand for organ transplantation is increasing around the world and, despite a growing number of transplantations performed, the shortage of organs is still the limiting factor in the treatment of patients with end-stage organ failures. In Europe, an average of 20 patients die every day while waiting for a transplant [1]. This mismatch between donor supply and demand for organs

is also exacerbated by the rising prevalence of chronic diseases, which increases demand even more while reducing the donor pool [2].

Xenotransplantation, the process of using organs from animals, could represent a reliable solution for a steady supply in this organ shortage crisis. A more widely available organ source could allow transplantations to be performed at earlier stages of organ failure, which would likely improve the quality of life and the general outcomes of patients. However, the clinical application of xenotransplantation faces many challenges, notably related to major immunologic differences between species. The potential risk of zoonosis, the transfer of infectious animal diseases to humans, is also particularly relevant considering the immunosuppressive regimen currently required to avoid graft rejection.

In order to make recommendations of good practice in this growing field of transplant research, a panel of experts in the field of xenotransplantation was gathered by the World Health Organization (WHO) in 2005 for an advisory consultation, during which the creation of an international inventory for practices of human xenotransplantation was suggested [3]. In collaboration with the International Xenotransplantation Association (IXA) and the WHO, an online inventory (www.humanxenotransplant.org) was created in 2006 and curated by the Geneva University Hospital until a redesign in 2020 and the transfer of its management and hosting to the Sichuan Provincial People's Hospital in Chengdu, China. This inventory lists the various procedures of xenotransplantation performed on human, from the year 1995, and is regularly kept up to date. A first article published in 2010 introduced the inventory and presented all registered clinical practices of xenotransplantation on human between 1995 and 2010 [4]. A recent update was made and published in 2021, presenting applications performed between 2010 and 2020 [5]. Starting at the end of 2021, a series of successive breakthroughs put the practice of xenotransplantation under the spotlight and brought major media and popular attention to the field, after the first transplant of a gene-edited porcine kidney into a brain-dead patient [6], followed by the first successful transplant of a genetically modified porcine heart [7].

This article aims to present the recent practices of human xenotransplantation, as considerable advances has been made.

MATERIALS AND METHODS

The inventory contains information collected from various sources, including but not limited to scientific publications, press releases, presentations at academic congresses, news articles and declarations of IXA members. An electronic form is also available online for submitting new data. In this article, the information is mainly provided by scientific publications, press releases and news articles, as most of the new research projects are still ongoing.

RESULTS

From January 2021 to December 2022, a total of 4 applications of human xenotransplantation involving 6 patients were identified (Tab. I). The source animal was the pig in all cases, including practices of heart transplant (n = 2 trials, involving a total of 3 patients) and kidney transplant (n = 2 trials, involving a total of 3 patients). All cases were performed in the USA and used genetically modified pigs with either 1 modification (n = 1 trial, involving 2 patients) or 10 (n = 3 trials, involving 4 patients). All practices were approved by institutional ethic boards and related state departments of health.

Kidney

On September 25, 2021, Montgomery and colleagues from New York University (NYU) Langone performed the first porcine kidney xenotransplantation in a brain-dead recipient. A second case was then repeated on November 22, 2021 [8]. Both recipients received a genetically modified porcine kidney from an animal provided by Revivicor, Inc., (Virginia, USA). The source animal presented a knockout of the alpha-1,3-galactosyltransferase gene responsible for forming alpha-Gal, a major porcine xenoantigen. Subcapsular autologous thymic tissue was also fused with the graft for immunologic purposes (as a composite called thymokidney). The grafts' vessels were anastomosed to the femoral circulation and the graft was placed outside of the body for easier observation. Over 54 hours, neither grafts showed any signs of hyperacute rejection and both were able to produce urine shortly after reperfusion. The serum creatinine level also decreased significantly in both recipients after the transplant. The immunosuppressive regimen consisted of methylprednisolone and mycophenolate mofetil [9].

Locke's group at the University of Alabama at Birmingham (UAB) reported a case of bilateral porcine kidney xenotransplantation on a brain-dead patient, on September 30, 2021 [10]. The patient received two genetically modified porcine kidneys after bilateral native nephrectomies, using conventional heterotopic allotransplantation techniques. The source animals were also provided by Revivicor, Inc., and exhibited ten genetic modifications (10-GE pigs), including knockout of three immunodominant xenoantigens and the pig growth hormone receptor gene, and the insertion of six human transgenes for immunologic and anticoagulatory

Table I. List of human xenotransplantation practices from January 2021 to December 2022.

Type of cells, tissue, or organ	Primary author	Number of patients	Date of event	Therapeutic purpose	Source of information	Genetic modifications
Kidney	Montgomery et al., New York University Langone	2	Sept 25, 2021 Nov 22, 2021	Kidney failure	Press release, publication [9]	*1-GE; (GGTA1-KO)*
Kidney	Porrett et al., University of Alabama at Birmingham	1	Sept 30, 2021	Kidney failure	Press release, publication [11]	*10-GE; (GGTA1-KO, CMAH-KO, B4GALNT2-KO, GHR-KO, hDAF, hCD46, hTBM, hEPCR, hCD47, hHO1)*
Heart	Griffith et al., University of Maryland Medical Center	1	Jan 7, 2022	Heart failure	Press release, publication [7]	*10-GE; (GGTA1-KO, CMAH-KO, B4GALNT2-KO, GHR-KO, hDAF, hCD46, hTBM, hEPCR, hCD47, hHO1)*
Heart	Moazami et al., New York University Langone	2	June 16, 2022 July 6, 2022	Heart failure	Press release	*10-GE; (GGTA1-KO, CMAH-KO, B4GALNT2-KO, GHR-KO, hDAF, hCD46, hTBM, hEPCR, hCD47, hHO1)*

purposes. No hyperacute rejection was observed during the 74 hours of observation, and the vascular integrity of the xenograft was maintained against human blood pressures. The grafts were able to produce urine but were unable to clear creatinine from the circulation. Immunosuppression consisted of methylprednisolone, anti-thymocyte globulin, and anti-CD20 for induction, whereas mycophenolate mofetil, tacrolimus and prednisone were used for maintenance [11]. The same group of researchers are planning a phase I clinical trial with the intention to perform 10-GE porcine kidney xenotransplantation into 20 dialysis dependant patients with risk factors for high waitlist mortality, prolonged wait time or inability to access a suitable organ offer. The estimated study start date is planned in 2023 [12].

Heart

On January 7, 2022, the first successful cardiac xenotransplant of a genetically modified porcine heart was achieved by Griffith and colleagues, led by Mohiuddin from the University of Maryland Medical Center (UMMC). In this first-of-its-kind surgery, a 57-year-old patient with severe heart failure, dependant on extracorporeal membrane oxygenation (ECMO) and ineligible for any other standard treatments, including allograft, received a "compassionate use" permission from the US Food and Drug Administration for a heart xenotransplant. The source animal was the 10-GE pig from Revivicor, Inc., and various molecules were used for an immunosuppression based on CD40 blockade, including anti-CD40 monoclonal antibody, rituximab, anti-thymocyte globulin, C1 esterase inhibitor, methylprednisolone, and mycophenolate mofetil. The patient was successfully weaned off ECMO, and the xenograft provided life supporting function for 7 weeks, when signs of graft failure necessitated the reintroduction of ECMO. Life support was withdrawn on day 60 after conclusion of irreversible graft injury. The biopsies did not show any typical signs of acute or antibody-mediated rejection, but increasing evidence of porcine cytomegalovirus (pCMV) was detected after day 20, despite pathogen screening and specific husbandry practices [7]. The exact mechanisms involved in the failure of the xenograft are still being investigated.

A press release by NYU Langone announced the success of two cases of pig-to-human cardiac xenotransplantation performed on brain-dead patients by Moazami and colleagues in summer 2022 [13]. The xenografts were collected from 10-GE pigs provided by Revivicor, Inc., and were observed for 3 days. They showed no signs of early rejection while presenting normal cardiac function without additional mechanical support. The immunosuppressive regimen was not specified. After the pCMV incident that occurred during the UMMC case, more sensitive screening methods were introduced to detect traces of pCMV. These cases are part of a larger study that is still ongoing, with plans to study xenograft function in brain-dead patients for over 72 hours, ideally up to "two-to-four weeks" [14].

DISCUSSION

The two groups involved in kidney transplantation addressed the problem of feasibility and safety in a pre-clinical human model for kidney xenotransplantation. Both trials showed no signs of hyperacute rejection during a follow-up duration of a few days in brain-dead patients and explored the logistical aspects of a human xenotransplantation. However, this model suffers from essential differences compared with a living recipient, as brain death is associated with organ damage due to haemodynamic consequences, hormonal changes, coagulopathy, and inflammatory reactions [15]. The procedure described by Montgomery and colleagues and many previous works on non-human primates confirmed the ability of a xenokidney to clear creatinine, although this was not observed in the UAB case. Moreover, the short follow-up duration does not address many of the challenges that a successful long-term kidney transplantation needs to overcome. Ultimately, the transplantation of a genetically modified porcine kidney in a living patient is therefore necessary to constitute a real proof of function and to determine the long-term viability of kidney xenotransplantation as a reliable alternative to dialysis.

In contrast, the group from UMMC performed a life-sustaining porcine heart transplant in a living patient with end-stage heart disease, as no alternative option was available. The patient survived for two months before life support was compassionately withdrawn after the conclusion of irreversible graft injury. The xenograft was life-sustaining for seven weeks before presenting acute signs of failure, in a context of increasing pCMV development. Although the patient presented severe deconditioning prior to the procedure and digestive complications following the transplantation, the involvement of pCMV in the loss of the xenograft and the patient remains unclear, as the biopsies did not show typical graft infection. In studies with non-human primates, the presence of pCMV is associated with reduced survival time of the transplant and its elimination is likely essential for a long-term graft survival [16]. However, the virus was not detected pre-transplant despite rigorous husbandry protocols, including early weaning and regular screening every three months for relevant pathogens, including pCMV. Techniques used for raising and monitoring source animals may be insufficient for safe clinical practice, as polymerase chain reaction (PCR) tests may be falsely negative when used as routine test in a context of viral latency, a state in which pCMV is often found before reactivation in instances such as allogeneic stimulation [17,18] (and possibly xenogeneic stimulation as well, by extension). Therefore, the use of immunological testing for pCMV antibodies might be necessary to detect the presence of the virus in future practice, combined with appropriate use of PCR techniques [19].

Moreover, intravenous immunoglobulin (IVIG) was used twice after the xenotransplantation procedure, including after detecting evidence of infection on day 43, as it is often used in the treatment of infections or of antibody-mediated rejection in allotransplantation. However, its polyclonal content could have a potential cytotoxic effect on porcine cells [20] and the use of IVIG should be evaluated carefully in future clinical trials [21].

During future clinical trials, the use of sensitive methods and strategies to exclude specific infections in source animals will be a core concern, especially in the case of latent viruses [22,23]. The successful implementation of protocols and techniques leading to "designated pathogen free" breeding colonies could make the source animals a safer choice from an infectious point of view than allograft donors, in which the absence of relevant infectious pathogens cannot always be confirmed [24].

CONCLUSIONS

Recent trials of human xenotransplantation contribute to a great advance in the field and confirm the applicability of many previous observations made from non-human primate studies. They also underline the necessity of further investigation with rigorous elimination of potential infection sources through meticulous methods of testing. Upcoming trials on kidney xenotransplantation are expected to involve living dialysis-dependent patients with no hope of allotransplantation, while studies of heart xenotransplantation might continue to develop through brain-dead recipient models for now, as the xenoheart's life-sustaining role imposes a more cautious approach. As recent trials have attracted considerable media and public attention, it becomes even more important to develop and conduct future trials with particular regard to social and ethical aspects. This information can be used to better inform officials, media, and the public in order to encourage good practices based on internationally harmonized guidelines, following the initiative of the Changsha Communiqués [25].

Conflict of interest statement

All authors declare no conflict of interest.

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Author contributions

XH, LB: designed the study; XH, ZG: collected the data and contributed equally; CGG, WY, WH, BE, SD: interpreted the data; XH, LB: wrote the manuscript.

Ethical consideration

No ethical approval is required for this article.

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