Narrative Review Article

The Current Landscape and Progress of Xenotransplantation

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ABSTRACT

Several studies have suggested that xenotransplantation on humans may successfully serve as an alternative organ supply for patients; however, due to differences in genomes and the addition of porcine endogenous retroviruses (PERVs), a long-term solution remains unclear. From the animal organs that have been tested on humans, many pig organs fail almost immediately upon implantation due to T-cell immune system response in the human body. Analysis from three case studies on brain dead patients show the effects of using xenotransplantation as a replacement for human organs, with the body's immune system reacting violently in some cases. Throughout the reported studies, the patients used a variety of immunosuppressants, attempting to integrate the new organ. In addition to scientific challenges, xenotransplantation also raises important ethical concerns regarding animal welfare, public health risks, and access to treatments. Despite these limitations, current research suggests that xenotransplantation could potentially change many lives and give people more flexibility and freedom. However, this research can still cause many ethical and scientific challenges.

Keywords: Xenotransplantation; immunosuppressants; immune system response; organ integration; pig to human transplant

INTRODUCTION

Organ transplantation is a prominent issue in the healthcare system. Many issues arise throughout the process of finding a donor, choosing a patient to receive the organ, keeping the organ functioning, and many other things. Each year 100,000 people in America suffer from organ failure, stemming from kidneys, lungs, and hearts. However, not only are many in need of organ transplants, but more than 28,000 donated organs, due to issues like transportation or matching with a patient, are unused every year (1). The lack of donors and organs has caused over 300 patients on the waiting list to die every day in the United States (2). Additionally, there are many requirements needed in order to have a successful transplant for patients and donors alike. Waiting for an organ that matches the same constitution and structure as the patient could take as long as 5 years and in some cases more (3).

Recent studies have sparked ideas about xenotransplantation, a process of transplantation, implantation, or infusion of organs or tissues from an animal source into a human. This method would allow animals, usually pigs, to be able to transplant organs into humans without having to wait for a human organ with the exact blood match. In order for the body not to immediately reject the organ, they have to be genetically modified to match

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systems in the human body. Genetic engineering (GE) is necessary for the human body to take in the organ and not attack it, making it less immunogenic (4). Many pig antigens are recognized as foreign by the human immune system and can trigger immune rejection, but with GE, modifying and replacing the dangerous antigens with the expression for human regulatory proteins can lessen the reactions. It would lessen the damage to the body as well as allow the organ to integrate into the body easier. One method used to create GE donor pigs is somatic cell nuclear transfer (SCNT), in which a nucleus of a GE somatic cell containing desired mutations is inserted into an enucleated egg cell to produce cloned organisms. By creating a desired somatic cell, SCNT allows for the production of transgenic pigs to reduce organ rejection or infectious disease in recipients (5). However, the method still does not solve all complications during the integration into the human genome.

One of the main issues of xenotransplantation is the presence of PERVs within pig genomes. Some of these viruses are able to infect human cells and will cause the pig organs to not be compatible with the human body, reacting negatively in xenotransplantation (5). The lethal effects of PERVs need to be considered when modifying the somatic cells. Typically, these are integrated into the genome and become hereditary in pigs, so they must be inactivated through gene knockout (KO) approaches (6). After deoxyribonucleic acid (DNA) has been modified into a desired form, it is then introduced during the SCNT procedure to the cultured somatic cells. These cells are then altered to perform DNA integration before being fused or inserted into the egg cell. Once the reconstructed embryo begins to divide, it evolves into a blastocyst in vitro and implanted into a surrogate mother, causing the piglets to carry the wanted genes (5).

This narrative review examines recent developments in xenotransplantation research, focusing on immune rejection, GE strategies, and outcomes from pig to human organ and tissue transplantation studies. By comparing findings from published case studies and experimental reports, this review evaluates the current progress, limitations, and future potential of xenotransplantation.

ORGAN REJECTION AND EFFECTS IN XENOTRANSPLANTATION

To test the effectiveness of xenotransplantation in this era, the reviewed studies were first compared to lung transplantation effects on a brain-dead patient to the effects of a regular functioning immune system and organ function.

Due to the anatomical and physiologic differences between pig and human organs, researchers hypothesized that the body would have a negative reaction to the transplanted organ due to the genomic differences as well as the overall structural difference of a pig organ. Researchers predicated that transplantation would trigger hyperacute rejection (HAR) because of immunologic differences between pig and human tissues.

Pig to Human Lung Transplantation

The left lung was extracted from a pig with six genes, GTKO, B4GalNT2KO, CMAHKO, CD55, CD46, and TBM before being transplanted into the brain-dead patient. However, within 24 hours of transplantation, severe swelling was visible and continued to show progressive signs of rejection from days three and six. There was a large increase in cytokines in the response to the transplantation with B and T cells flooding into the left lung, degrading and attacking it. The patient was put on immunosuppressants in order to prevent further degradation of the rejected organ, including rabbit anti-thymocyte globulin (rATG), basiliximab, rituximab, eculizumab, tofacitinib, tacrolimus, mycophenolate, mofetil and other steroids. On day nine the lung seemed to experience partial recovery with the lack of immune response. One of the measurements researchers used to evaluate the results was the left-to-right lung ratio, a measurement comparing the volume and fluid accumulation of the transplanted left lung to the right lung. Throughout the nine-day study, the ratio from the left to right lung slowly decreased from the lowest at 0.31 at the third day mark after only 48 hours, deviating from the initial ratio of 0.8. A decreasing ratio indicated that inflammation and progressive swelling occurred in the transplanted lung, suggesting a decline in graft function (7).

However, immunohistochemistry rates of membrane cofactor protein (CD46), decay-accelerating factor (CD55) and thrombomodulin (TBM) that were originally not expressed in the pig's lung tissue, appeared successfully with a consistent presence of the transgenes during post and pretransplant (8, 9). Immunoglobulin M (IgM), on the other hand is minimal, seen as a delayed response, allowing the lung to survive for longer. Its presence starts the buildup of C3 and C5 convertases, building the Membrane Attack Complex (MAC) which would result in the faster deterioration of the vessels (7).

Pig to Human Kidney Transplantation

Alternatively, the xenotransplantation of the kidney only required one gene edit of the GTKO gene to survive in the body. For this xenograft, the scientists incorporated thymic transplant along with SCNT to promote immune tolerance in the recipient. To promote tolerance, the thymic tissue from the donor pig was transplanted together with the kidney. Exposure to the donor tissue helps recipient T-cells to recognize pig antigens as less foreign, reducing cellular rejection response and improved graft acceptance. The donor kidney and vascularized thymic tissue were prepared prior to transplantation and were implanted into the brain-dead recipient. Researchers monitored graft function, immune responses and signs of rejection over the time of observation. The kidney was able to last 61 days in the body and showed evidence of antibody-mediated rejection (AMR) around day 33. In the first few days, IgM was observed to increase rapidly in association to the kidney's glomeruli with early complement activation. However, the kidney was still functioning well at this point and no prominent protein loss was discovered. T-cells began rebounding during day 20 and continued to increase up to day 33 (10).

Creatinine levels also started to increase, showing a worsening kidney function as well as an increase in donor-specific IgG antibodies. From here, the brain-dead patient was put on rATG and complement inhibitors for immunosuppression which efficiently suppressed the rejection reaction in the body. This quickly caused creatinine levels to stabilize again, improved inflammation, and aided in the decrease of antibody levels. Even with thymic grafting and immunosuppressants, pre-existing human T-cell populations were still capable of recognizing the antigens post-transplantation. This study showcases the sustainability and effectiveness of organs with little gene edits that can maintain physiologic function while paving a way for longer lasting organs (10).

Lung and Kidney Transplantation Differences

Compared to lung xenografts, kidney xenotransplants demonstrated longer graft survival and reduced immediate rejection responses. This difference may be associated with the use of thymic transplantation and reduced complement activation in kidney models (10). While the pig-to-human lung xenograft survived for nine days before severe immune rejection and inflammation caused rapid deterioration, the kidney xenograft was able to remain functioning for 61 days in comparison (7, 10).

In the lung transplantation study, researchers observed early cytokine release, causing B-cells and T-cells to attack and flood the organ, resulting in severe swelling within 24 hours of the transplant. HAR and complement activation continued to rapidly damage the lung tissue, only experiencing a slight recovery, despite the use of multiple immunosuppressive therapies (7). In contrast, the kidney xenograft displayed a slower progression of immune rejection and more stable organ function during the early stages of the transplantation. However, AMR eventually developed around day 33, but the transplanted kidney was able to continue functioning for several weeks after. The use of thymic transplantation may have helped contribute to a partial immune tolerance by reducing T-cell mediated responses against the pig's composition (10). Additionally, immunosuppressive therapies and complement inhibitors helped stabilize creatinine levels and temporarily reduce inflammation and donor-specific antibody formation, allowing for better recovery than the lung organ (7, 10).

The amount of GE required also differed significantly between the lung and kidney organs. The lung xenograft required six gene edits in an effort to reduce HAR and complement activation. These edits targeted major xenoantigens and added human complement regulatory proteins to limit immune-mediated destruction of the organ (7). Comparatively, the kidney xenograft primarily relied on a single edit in combination with thymic transplantation and immunosuppressive therapies (10). Although the lung transplant received more gene edits, it demonstrated significantly shorter survival compared to the kidney transplant. This suggests that successful xenotransplantation may depend not only on the quantity of genetic edits, but also on other factors like complexity, immune sensitivity, and compatibility of the transplanted organ.

The differences between lung and kidney xenotransplantation also highlight the varying levels of compatibility between organ systems. Depending on their physiologic compatibility and susceptibility to immune injury, they can survive better and maintain function despite immune-mediated challenges. Kidneys appear to tolerate xenogeneic transplantation in the short term compared to lungs, suggesting that some organs may be more successful for early xenotransplantation applications than others (10). To compare these models, Table 1 summarizes the donor genetic modifications, immune barriers, immunosuppressive strategies, and major outcomes across the xenotransplantation studies.

Table 1. *Comparison of Recent Xenotransplantation Studies Involving Lung, Kidney, and Corneal Grafts. Abbreviations: GTKO, α-1,3-galactosyltransferase gene knockout; B4GALNT2KO, β-1,4-N-acetyl-galactosaminyltransferase 2 gene knockout; CMAHKO, cytidine monophosphate-N-acetylneuraminic acid hydroxylase gene knockout; GGTA1 KO, α-1,3-galactosyltransferase gene knockout; CD46, membrane cofactor protein; CD55, decay-accelerating factor; TBM, thrombomodulin; hCRPs, human complement regulatory proteins; HAR, hyperacute rejection; AMR, antibody-mediated rejection; rATG, rabbit anti-thymocyte globulin; IVIG, intravenous immunoglobulin.*

Organ/ Tissue	Donor Modifications	Recipient	Survival Duration	Rejection Mechanisms	Immunosuppressive Strategies	Major Outcomes
Lung	GTKO, B4GALNT2KO, CMAHKO, CD46, CD55, TBM	Brain-dead human recipient	9 days	HAR, cytokine release, complement activation, T-cell, B-cell infiltration	rATG, basiliximab, rituximab, eculizumab, tofacitinib, tacrolimus, mycophenolate, mofetil, steroids	Severe swelling and progressive rejection
Kidney	GTKO	Brain-dead human recipient	61 days	Complement activation, AMR, donor-specific antibodies	rATG, complement inhibitors	Maintained function, rejection controlled with immunosuppression
Cornea	GGTA1 KO, hCRPs	Non-human primates	Up to 511 days	Cell-mediated rejection, neovascularization, AMR	IVIG, tacrolimus, basiliximab, corticosteroids, local steroids	Long survival due to immune privilege and lower physiologic incompatibility

TISSUE SPECIFIC XENOTRANSPLANTATION OUTCOMES

Corneal Xenotransplantation Trials

Xenotransplantation is not limited to organs. Corneal xenotransplantation represents a unique opportunity because of its natural immune privileges. The absence of blood and lymphatic vessels limits exposure to immune cells and antibodies. As a result, HAR, which is commonly pushed by IgM antibodies and is often seen in other xenografts, is rarely seen in corneal xenotransplantation, providing an advantage for graft integration (11, 12).

The porcine cornea's physical properties also allow it to be compatible with human corneas. With a thickness of 659 to 995 μm, it is similar to the human thickness of around 527 μm. In one study, non-human primates (NHPs) were used because their immune systems, corneal anatomy, and rejection pathways most resembled humans. During the time period of corneal transplant, the graft was able to stay clear and functional for 6 months in 16 out of the 22 studies conducted at the time. In other NHPs, the grafts were able to survival for longer than six months while maintaining structure and functionality. This survival period was substantially longer than that observed in rabbit models which only lasting for 16 to 29 days. With longer lasting tissues, however, high counts of T and B cells were present at the rejected graft and an increase of cytokines in that area (11).

Immunosuppressive Strategies in Immune Privilege in Corneal Xenotransplantation

Alternatively, corneal tissue transplantation does not require the usual methods due to the composition and immune privileges of the cornea. There is an absence of blood and lymphatic vessels, expression of immunomodulatory molecules, and induction of anterior chamber-associated immune deviation (ACAID), making the tissue have multiple mechanisms of immune privileges (12). Although corneal tissue possesses immune-privileged properties, rejection can still occur when inflammatory conditions disrupt this protective environment. Consequently, immunosuppressive therapies remain important for prolonging graft survival and reducing AMR.

Several immunosuppressive agents have been investigated to improve corneal xenograft survival. Drugs like IVIG target the Fc receptor of the B cell and the complement. While other drugs, like Tacrolimus and Basiliximab and corticosteroids (CS) are catered towards T-cell regulation and activation. Without advanced immunosuppression, donor tissues were seen to only last

12 to 20 days. However, just with local steroids, survival was able to be extended up to four to nine months, with one graft reaching 276 days. However, with these immunosuppressants mentioned above, grafts were able to survive for longer with the longest time being 511 days (11).

Cell-mediated rejection had also been observed, with macrophage and neutrophil recruitment contributing to graft opacity and structural damage. Despite immune privilege, cell-mediated rejection involving macrophages and neutrophils continues to contribute to graft failure in some studies (11, 12).

Organ Specific Differences in Xenotransplantation Outcome

Compared to lung and kidney xenografts, corneal xenotransplants experience significantly lower immune exposure due to the cornea's lack of direct blood and lymphatic vessel networks (12). This reduced vascularization limits rapid buildup of antibodies and immune cells that contribute to a strong immune reaction that is usually seen in more vascularized organs like the kidneys and lungs. Corneal xenotransplantation may also require less extensive GE compared to whole organ transplantations due to reduced complexity. While lung xenografts required multiple genetic edits and modifications to reduce complement activation and inflammation (7), corneal grafts were able to achieve prolonged survival with fewer physiologic compatibility barriers (12). Table 1 summarizes the major findings across lung, kidney, and corneal xenotransplantation studies, allowing for direct comparison of donor modifications, rejection mechanisms, and overall outcomes and challenges.

The prolonged survival seen in corneal xenografts also contrasts with the significantly shorter survival periods seen in the lung xenotransplantation studies. While the lung xenograft survived for only nine days before it experienced severe inflammation (10), several corneal grafts remained functional for months, and in some cases, longer than 500 days with immunosuppressive therapy assistance (7). These differences suggest that the tissue-specific immune privilege may play a major role in the survival of xenografts compared to organs that are surrounded by immune cells and are more prone to experience attacks from antibodies.

These findings suggest that corneal and other tissue xenotransplants may become more clinically feasible earlier than complex organs, such as the lungs and kidneys. This could help facilitate future transplantation applications with immune advantages to be used as xenotransplantation continues to grow. It can also provide a safer experimental model for testing gene edits and immunosuppressive strategies. Successful approaches from these experiments could be applied to other organs, too, displaying the advantages of tissue transplantation. They may be easier to implement than whole-organ transfers because of their lower need for full integration with the body and can eventually address the growing demand for tissue grafts.

Their lower immune sensitivity and reduced demands may provide safer models for refining immunosuppressive therapies and GE technologies before opening up to broader organ transplantation applications.

GENETIC ENGINEERING STRATEGIES

In these sections, PERVs are the central challenge to the feasibility and adaptability of xenotransplantation. Advances in GE and CRISPR technologies have enabled researchers to modify pig genomes to improve compatibility with human recipients.

Immune Rejection and Physiologic Incompatibility

One of the main barriers for successful xeno-transplantation is immune rejection caused by incompatibilities between pig and human tissues. Since pig tissues contain different surface antigens, proteins, and cellular structures than human tissues, the immune system recognizes xenografts as foreign material and attacks it. This triggers an inflammatory response and cytokine release, causing the organ to be attacked and can start to degrade in the human body shortly after transplantation (6).

HAR is one of the earliest and most severe immune responses observed in xenotransplantation. It is commonly driven by preexisting human antibodies, including IgM and IgG, that bind to the pig's antigens. Once these antibodies bind to the donor organ, the complement cascade becomes active leading to rapid graft deterioration, inflammation, and tissue swelling in the body. This process promotes rapid vascular injury, inflammation, and graft dysfunction. In addition to these responses, T-cell activation also plays a major role in xenograft rejection with immune cells infiltrating and stimulating inflammatory signaling, contributing to the AMR (6). However, the severity of these responses varies among organ types, with lung xenografts exhibiting more rapid inflammation and more severe immune response injury than kidney or corneal xenografts (7).

Deficiencies in protein CD55 reduce the ability of the graft to regulate complement activation, increasing the graft's susceptibility to damage and disease to its composition (8). These hCRPs also inhibit C3 and C5 convertase, preventing a cascade from completing. C3 and C5 convertase activation are one of the primary causes of immediate organ rejection in the body. Usually, the presence of enzymes causes the formation of MAC, causing the donor organ's blood vessels to be destroyed causing rapid graft failure as well as severe inflammation in the body (6). In the cases of the lung xenograft, the formation of MAC was observed, likely contributing to deterioration and progressive dysfunction.

The different physiologic incompatibility greatly affects the long-term survival of the donor organs. Differences in structure and inflammatory signaling may prevent normal function of the organs and deteriorate the organs at difference speeds. As a result, current xenotransplantation research and development has increased focus on reducing immune incompatibilities through GE and immunosuppressive therapies in order to control the organs from experiencing worsening conditions.

Thymic Transplantation and Immune Tolerance

One possible explanation for the differences in immune responses is the thymic transplantation methods to improve immune tolerance. Unlike standard xenotransplantation approaches that rely primarily on GE and immunosuppressive therapies alone, thymic transplantation is designed to improve tolerance within a patient's body (13). In the kidney xenotransplant study, the thymic tissue from the donor pig was transplanted with the kidney to help regulate the patient's T-cell immune response and promoted partial immune tolerance (10).

This additional immune tolerance strategy may have contributed to the longer graft survival seen in the kidney xenograft compared to the lung xenograft. Although AMR eventually developed with increasing IgG levels, immunosuppressive therapy and complement inhibitors were able to temporarily stabilize organ function and reduce portions of rejection response (10). However, in contrast, the lung xenograft experienced rapid inflammation and complement activation. Even with the help of more GE and immunosuppressive therapy than the kidney, the lung still experienced tissue degradation (7).

Exposure to the tissue allowed the developing T-cells to become partially tolerant to the pig's antigens and helped reduce cellular rejection compared to organs transplanted with the SCNT technique (5, 13). However, thymic transplantation alone isn't enough to completely prevent AMR since donor-specific IgG antibodies and T-cell responses will still develop with time as shown in the study (10).

Genetic Engineering and CRISPR Strategies

The data from all three case studies demonstrate the development and increasing feasibility of xenotransplantation. The case of the kidney organ primary highlights the possibility of minimal gene editing to still have an organ maintain its function for an extended period of time compared to the six-gene edited lung (10). While the lung transplant required extensive modification, inflammation and rapid graft deterioration still developed shortly after the transplantation (7).

However, the possibility of adding more gene edits may further reduce cytokine release, complement activation, and inflammatory responses that became more prominent near day 33 of transplantation (10). Additional knockout (KO) genes targeting xenoantigens such as GGTA1 may help further decrease AMR and donor-specific immune responses as seen in current studies (7). At the same time, excessive genetic modification may also introduce unintended physiologic consequences. Nonsense or missense mutations caused during GE could potentially alter important cellular pathways or diminish the necessary function of the organ. With further development of CRISPR/Cas9, researchers may be able to produce more precise and stable genetic modifications while also minimizing unintended mutations all while preserving organ functionality. Future developments could allow xenografts to better regulate immune compatibility and improve long-term graft integrations in the human body.

ETHICAL AND CLINICAL CONSIDERATIONS

Although xenotransplantation could heavily change the tide in the need of donor organs, many ethical issues are present. It raises questions pertaining to human subject research, animal welfare, disease risk, and societal implications to our communities.

Brain-Dead Human Recipient Models and Research Ethics

The studies conducted on brain-dead recipients represent a step towards living human trials and animal research, but yet remain ethically neutral. Because the

procedures did not aim at restoring life, but instead to generate data on xenotransplantation, transparency and strict oversight and regulations were necessary to keep ethical legitimacy. Braindead patients are used for these studies due to the ability to safely test the effectiveness of GE pig organs in a body without risking a living, conscious patient. It also allows their immune response, rejections, or organ function to be monitored in a controlled clinical environment. Brain-death patients are defined as having irreversible loss of their brain functions, translating to legal death. Researchers also received consent from the administration in their areas and the families of the brain-dead patients before procedures (14).

However, the ethical use of brain-dead recipients in xenotransplantation research remains controversial. Although brain-dead individuals are legally deceased, some might argue that maintaining bodily support for experimental purposes challenge beliefs on human dignity after death. In most cases, brain death also changes human physiology and causes major disruptions in systems, such as the endocrine, immune and nervous system. Data might be different from how it would occur in living patients and could over or underestimate what is achievable in living patients (14).

Some also question if family consent is enough highly experimental procedures involving genetically engineered animal organs. This is also emphasized when long-term outcomes and public health risks are still uncertain. Since xenotransplantation research is still in early stages, concerns also exist regarding whether brain-dead recipients are being used as research models instead of as patients receiving therapeutic care. Additionally, these studies bring into question the line between clinical treatment and experimental testing. While the procedures provide valuable scientific data, they also raise concerns about how far experimental procedures should be allowed to proceed on humans.

Xenogeneic Infections and Public Health Risks

Not only does the use of human life factor heavily in research ethics, but also the risk of transmitting PERVs or other pig pathogens into humans could exacerbate danger to research subjects. During transplantation, cross-species disease transmission remains a concern as pathogens and PERVs present in donor pigs may be transmitted to human recipients as well as pose broader public health concerns. Unlike traditional organ transplantation, xenotransplantation has the possibility of cross species disease transmission, also known as xenozoonoses (15). Not only can the transplantation affect the chances of infection, but the immunosuppressants used during the procedure can also increase a patient's susceptibility to the infection.

One of the major risks of xenozoonoses are latent infections since the animal tissues can harbor viruses or parasites that can become active while using immunosuppressants (15). In recent studies, transplants, like the kidney xenograft, still need the assistance of immunosuppressants in order to function and to not be attacked by immune defenses (10). Some viruses may also reactivate within the transplanted organ, directly damaging the organ without infecting human cells. Concerns for this risk could be reduced if source animals are raised in a controlled, germ-free environment, however it has caused issues for the pig's size and waste production. It leaves pigs to be more vulnerable and does not fully eliminate the risk of transmission. PERVs can also affect a person's health in regards to human exposure. Their involvement with pig's genomes guaranteed contact with human cells and can potentially infect human cells, while also being an unavoidable category of xenozoonoses (15).

Xenozoonoses cannot be fully eliminated and are difficult to detect in donor animals. Their unpredictable behavior can pose a risk for ongoing xenotransplantation research, while also raising ethical concerns for the health of the public (15). These donor organs from pigs have the risk of spreading to not only the recipient, but also healthcare providers, workers, and the broader public, expanding the issue from individual health to the public health of society. Even before the transplantation occurs, many screenings and long-term protocols were required for pathogens and other deadly spreading diseases before clinical application was allowed in each study (14).

Animal Welfare and Genetic Modification

Similarly, not only are human ethics at risk, but also the lives and welfare of the donor pigs come into question. Some concerns include the genetic modification of sentient animals and the resulting experiences due to the likely unsustainable lifestyle that it would cause. One of the primary concerns surround the extensive and necessary genetic modifications needed to be performed on the donor animals before their organs are able to be more compatible with the human body. Repeatedly altering pig genomes and breeding the animals specifically for organ procurement may negatively affect the animals' quality of life and overall wellbeing (16). The long-term and physical effects of GE and cloning on

donor animals have also remained a prominent issue in animal welfare.

In addition, the concept of breeding animals only for organ harvesting continues to generate ethical concern with the xenotransplantation process. Some may view it as a necessary and important medical intervention to save patients currently waiting on transplant waitlists and require organ transplants. However, the question of animal life as a primarily resource for the human benefit should be considered regarding animal ethics. The large-scale production of GE pigs for transplantation raises additional societal and environmental questions on the industrialization of organ production (16). Strict animal welfare regulations and humane treatment standards could help reduce some ethical concerns while still allowing for research to further progress.

Accessibility and Future Clinical Applications

However, the potential to save many patients and the possibility of strict animal welfare standards could alleviate these concerns as studies expand. As xenotransplantation advances towards clinical availability, questions of justice, accessibility, and healthcare equity also emerge. The cost or first testers of xenografts may come into play on the ethical and human health risks that might come with the grafts. It may also initially limit treatment availability to only a small portion of the population and as a result could majorly cause socioeconomic gaps in healthcare to widen with only the wealthy being able to access and benefit from the accessibility of the organs.

The current organ transplantation system in the United States follows strict allocation guidelines through organizations like the Organ Procurement and Transplantation Network (OPTN). Some factors include waiting time, medical urgency, and proximity to the location of the organ to determine which patient receives the available donor organ. For example, a lung graft prioritizes the survival benefit, medical urgency, waiting time, and distance from the donor hospital. These systems allow fairer consideration of circumstances instead of wealth aspects while also increasing the number of transplants performed (17). These regulations could also be applied to future xenotransplantation development in order to create a fairer system due to the limited supply of current human donor organs.

With GE slowly becoming more clinically accessible and available, unethical and unregulated organ distribution may also be used outside of approved methods. The growing accessibility of GE technologies may further complicate oversight and increase concerns on ethics. These risks would make future xenotransplantation development to face certain strict regulation, international oversight, and transparent clinical guidelines in order to be performed safely and ethically.

CONCLUSION

Xenotransplantation represents a promising solution to the continuous and increasing shortage of donor organs and tissues as seen through recent studies involving transplantation of pig to human kidneys, lungs, and corneal tissues. These products demonstrate that genetically engineered organs can temporarily support physiologic function, such as blood filtration in kidney xenograft and gas exchange in lung xenografts, in human recipients. However, as research moves on, so will the evolution and progress of further organs survive for longer periods of time. The success of each transplantation depended on the biological characteristics of the organs, the differences between the pig and human organs, and the interactions and effects it had on the human immune system. Across lung, kidney, and corneal xenografts, advances in gene editing and immunosuppressive therapies have reduced immediate rejection as well as improve short-term survival.

Despite these advancements, HAR, AMR, T-cell activation and complement cascade has remained limitations to long term xenograft survival. Additionally, issues surrounding PERVs, chronic immune suppression, and other physiological incompatibilities remain unsolved. While GE techniques like gene knockouts and hCRPs have greatly helped reduce immediate rejection, they are not enough alone to ensure long term success. Additional strategies, including thymic transplantation and SCNT have helped promote immune tolerance by reducing rejection and increasing graft survival.

Despite these challenges, xenotransplantation has advanced substantially and is moving closer to clinical application. Corneal and other tissue xenotransplants may serve as early applications, helping provide a foundation for organ transplants in the future. Future research should focus on improving long-term immune tolerance allowing the organs to survive longer and function more effectively within the recipient. Refining CRISPR and GE strategies can also close up danger of PERVs and will be a fundamental target to focus on to overcome the current limitations as well as reducing zoonotic disease risk. Although xenotransplantation

remains experimental, current advances suggest that it may play an important role in addressing organ shortages, reducing waiting times for transplantation, and improving patient outcomes in the future.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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