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EDITORIAL

Is the near coming xenotransplantation era relieving us from needing to look for more non-living organ donors?

Fernando M Gonzalez, Francisca del Rocío Gonzalez

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Abstract

Despite organ transplantation being the most successful treatment for end-stage organ dysfunction, the number of annual solid organ transplantations is much lower than that required to satisfy the demand of patients on waiting lists. The explanation for this phenomenon is the relative scarcity of non-living organ donors due to several factors, such as: (1) Late arrival of patients with a neurocritical condition to an emergency service; (2) lack of detection of those patients as possible organ donors by health professionals dedicated to procurement or by clinicians at emergency and intensive care units, for instance; (3) late transfer of the patient to an intensive care unit to try to recover their health and to provide hemodynamic, ventilatory, and metabolic support; (4) lack of confirmation of the physiological status of the possible donor; (5) late or incorrect positive diagnosis of the subject's death, either due to brain or cardiac death; (6) difficulty in obtaining legal authorization, either by direct relatives or by the authority, for the extraction of organs; and (7) deficient retrieval surgery of the organs actually donated. The recent reports of relatively successful xenotransplants from genetically modified pigs open the possibility to fix this mismatch between supply and demand, but some technical (organ rejection and opportunistic infections), and economic issues, still remain before accepting a progressive replacement of the organ sources for transplantation. An approximate economic cost analysis suggests that the hypothetical acquisition cost of any genetically modified pig derived organ is high and would not even satisfy the solid organ demand of the wealthiest countries.

Key Words: Organ donation; Xenotransplantation; Procurement; Kidney transplantation; Costs

Core Tip: The recent promising xenotransplants derived from genetically modified pigs (heart and kidneys) will open a new discussion: to maintain and improve human non-living organ procurement or invest in the development of solid xenotransplant clinical services. Issues to be solved before reaching that point will be immunologic (preventing acute and chronic graft rejection), opportunistic infections from pigs (for example, porcine cytomegalovirus) and economic (how to finance and afford those technically complex organs for the population).

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INTRODUCTION

The recent promising xenotransplants derived from genetically modified pigs (heart and kidneys) will open a new discussion: To maintain and improve human non-living organ procurement or invest in the development of solid xenotransplant clinical services. Issues to be solved before reaching that point will be immunologic (preventing acute and chronic graft rejection), opportunistic infections from pigs (for example, porcine cytomegalovirus) and economic (how to finance and afford those technically complex organs for the population).

Solid organ transplantation has clearly improved medical performance in terms of the treatment of end-stage organ failure, as in the case of kidney, liver, or heart failure, among others. Consequently, it has improved the survival and quality of life of patients who suffer from those diseases[1]. Nevertheless, the main limitation in transplanting all patients in need is the availability of donors[2].

For many years it has been suggested that xenotransplantation might provide a solution to the imbalance between the demand and supply of organs for transplantation[3], but it has remained a theoretical option. The recent experiences of heart and kidney implants from genetically modified pigs, however, could mean that solving this imbalance may now be a real possibility and, therefore, it could mean that the activity of searching for and procuring organs, particularly from non-living donors, could decline[4-6].

However, this issue is still a subject of extensive technical considerations.

The prevalence of end-stage kidney, liver, or heart diseases increases as a country's population ages. Age-related chronic diseases appear along with this shift, and the medical treatments in use allow more patients to survive the acute phases of those diseases. As a consequence of this, as well as due to general improvement of road safety measures, potential organ donors no longer come from young subjects who die due to car accidents or trauma, but increasingly older adults and, often, with prevalent chronic diseases that reduce the functionality of the organs to be donated[7]. This could explain, in part, the asymmetries in organ donation rates in different countries, even when they are culturally similar, as occurs, for example, in those countries belonging to Latin America or those belonging to Western Europe[8].

If we analyze the figures of non-living donors in the world, we will see that there are marked differences between countries, ranging from 0.4 donors per million population (pmp) in the Dominican Republic or 4.4 pmp in Greece, to 38 pmp in the United States or Spain[8]. This implies that there are significant growth opportunities in the global procurement activity: Carrying out comparative studies of the realities of the procurement process between different countries and attempting to replicate the "best practices" of the leading countries could, as a conservative estimate, be enough to increase the global donation rate in America and Europe to 15-20 pmp, and could, thinking more ambitiously, be enough to even reach the leading countries[8].

The central question derived from the previous paragraph is why there are so many differences in countries' donation rates. In this regard, the procurement process (framed under a local legislation supportive towards organ donation) can be outlined as a series of stages that include: (1) Arrival of patients with a neurocritical condition (trauma or stroke, for example) to an emergency service; (2) Detection of that patient as a possible organ donor by health professionals dedicated to procurement (organ procurement organizations in the United States or procurement coordinators in Spain), or by clinicians at emergency and intensive care units, for instance; (3) Transfer of the patient to an intensive care unit to try to recover their health and to provide hemodynamic, ventilatory, and metabolic support (if there are critical beds available); (4) Confirmation of the physiological status of the possible donor and the organs to be donated — that is, the ruling out of pathological conditions that contraindicate the

subject as a potential donor (for example metastatic neoplastic disease, encephalitis due to transmissible viruses (rabies), and others); (5) Positive diagnosis of the subject's death, either due to brain or circulatory death; (6) Legal authorization, either by direct relatives or by the authority, for the retrieval of organs; and (7) Procurement surgery of the organs actually donated.

In any of these phases, effective donation is likely to be foiled. During the first year of the severe acute respiratory syndrome coronavirus 2 pandemic, in 2020, we witnessed a natural experiment in which it was possible to observe how the disease associated with the novel coronavirus disease 2019, reduced the arrival of patients with serious trauma or strokes to emergency services[9-11]; how hospitalizations in critical care units were reduced; and how the activity of local procurement units decreased, along with surgical retrieval activities and donation authorizations by family members[12]. These situations together explain why donation and transplant figures plummeted in several countries, including those in the United States and Spain[12,13].

If the failing stages of the process in each country could be improved, it would be feasible to increase their effective donation rates. For example, stage 1 could be improved with the implementation of rescue ambulance systems; stages 2 and 3 could be facilitated with the use of information technology [14]; stages 4 and 5 could benefit from the inclusion of trained professionals; and stage 6 could be improved by including experts in breaking bad news in the procurement team. These are general examples, but performing a careful benchmark analysis of the procurement stages in each country should provide even better improvement opportunities for each country, since the good initiatives observed in some countries could be adapted for other countries.

How much do the proposed improvements cost? Given that the main difficulty is setting up the procurement process and most of the countries have already carried out work to that end, the marginal cost should not be very high, since there would be no significant barriers to implementation of improvements from the economic point of view, and their cost could be easily apportioned by increasing organ implants and the savings that they imply for the health systems of each country.

On the other hand, we have the opportunity to use organs from animals with similarities to humans. Historically, at the beginning of the 20th century, xenotransplantation was conceived as the solution to replace failing organs[15]. However, all the experiences concluded that, although the surgical technique allowed the surgeons to successfully implant the organs, they irremediably did not function as a result of diffuse thrombosis in all the graft vessels. It was not until the second half of the same century when it was described that the cause of thrombosis was mediated by preformed antibodies in the recipients, against vascular antigens from the donor animal. This type of hyperacute rejection was impossible to overcome even with aggressive immunosuppression techniques in non-human models[16]. The second limitation was local thrombosis derived from immune aggression and an exaggerated activation of the complement system[17].

In fact, the cardiac graft implanted in January 2022 came from a transgenic pig with 10 genetic modifications: Three knock-outs of genes associated with cell membrane carbohydrates (galactose alpha-1,3-galactose, Sda blood group antigen and N-glycolylneuraminic acid), a knock-out for the growth hormone receptor, increased expression of CD-46 antigens and "decay accelerating factor" to mitigate the activation of the complement system, expression of thrombomodulin and protein C genes to reduce thrombogenicity, and finally, anti-inflammatory proteins CD-47 and heme-oxygenase-1[5]. The three kidneys implanted on similar dates somewhat later had similar genetic modifications, although in smaller numbers[4,6]. In all these cases, neither hyperacute rejection nor massive intraparenchymal thrombosis occurred, although elements of thrombotic microangiopathy were indeed observed. An additional element which requires cautious is the eventual transmission of infectious agents typical of pigs, such as the porcine-derived retrovirus, or the porcine cytomegalovirus, among others[4-6].

Despite these complications and the disastrous outcome of the recipient with the heart graft, these preliminary experiences are certainly auspicious and appropriate clinical studies will surely elucidate the real usefulness of xenotransplants from genetically modified pigs raised in highly controlled environments.

Assuming that this new xenotransplantation continues to develop favorably, one wonders how much each organ will cost and how many real patients it will benefit, with "real patients" being those who are not part of a clinical trial and who, therefore, must pay (themselves or their insurers) for the xenotransplantation and its associated pharmacological treatments.

One way to calculate the aforementioned cost could be using the economic benefit for society of transplantation with a traditional non-living donor as a reference, and based on these numbers, roughly estimate the value that each heart or kidney could have.

The cost per quality adjusted life year (QALY) of a heart transplant in someone who is on the waiting list receiving exclusive pharmacological therapy is close to US$97000, a figure that increases to US$226000 if the person waiting is connected to a left ventricular assist device[18]. If we consider that in the United States a figure of US$100000/QALY is considered acceptable for a heart transplant, this treatment would be economically viable only in the first group of patients and would therefore force transplant teams to enroll those who suffer from advanced heart failure early. For kidney transplantation, the cost per QALY is slightly less than US$50000[19,20].

Table 1 Organ procurement process and opportunities for improvement

Process	Improving opportunities
(1) Arrival of patients with a neurocritical condition to an emergency service	Implementation and improvement of rescue ambulance systems
(2) Identification as a possible organ donor by health professionals	Training health professionals, use of information technology
(3) Transfer to an intensive care unit to provide full support	Use of information technology, critical care bed selective dedication
(4) Confirmation of suitability to be a donor	Inclusion of trained health professionals
(5) Diagnosis of the subject's death, either due to brain or circulatory death	Availability of on-site neurologists and perfusionist specialists.
(6) Procurement surgery of the organs actually donated	Inclusion of experts in breaking bad news in the procurement team

The problem is, however, that the US$100000/QALY threshold is not necessarily valid for other countries. In fact, the willingness to pay of each country is correlated with its gross domestic product (GDP) per capita and, therefore, the cost-effectiveness analyses and the QALYs improved by a successful transplant should be adjusted for each country. By doing this, it becomes clear that the US$100000 for the United States does not compare fairly with the US$ < 10000 for Thailand or the US$20000-30000 for various South American and European countries which, in turn, also have lower GDP per capita[21].

The implications of the economic data presented are that the price to be paid for a desirable new good correlates with the expected benefit that good is estimated to provide. The price to be paid also correlates with the need for the return on investment demanded by the shareholders who own the companies that develop these improved goods. Finally, these two figures should be adjusted for the risk that such assets have to be successful in the market[22]. If we use the market price of onasemnogene abeparvovec-xioi for spinal muscular atrophy of €1.9 million as a reference, we may find that an independently calculated price would be close to €1.7 million[22]. The €200.000 (10% of €1.9 million) difference between both prices is, in the best of cases, an error in the calculation methodology or, in the worst scenario, an appropriation of "consumer surplus". The latter could imply that the price of an organ from a genetically modified pig would be close to the total QALY gained from the transplant (QALY/year multiplied by additional years of graft or host survival) plus a "consumer surplus" of 10%, which could be no less than US$500000 for a heart or US$250000 for a kidney (assuming that both grafts last only 5 years, which is a very conservative estimate) which, obviously, could be paid by very few people only from the wealthiest countries and certainly even the world strongest public health systems could not finance those transplants[21].

CONCLUSION

So, going back to our initial question: Is the near coming xenotransplantation era relieving us from having to look for more non-living organ donors? Our answer is "not at the moment"; even thinking that xenotransplants will have the same survival as allografts from human donors, their market prices will be prohibitive in many countries, forcing those countries to necessarily continue improving their actual procurement processes from non-living human donors (Table 1). Wealthy countries, however, are likely to be able to improve their transplant rates, at least in the short term, with organs from genetically modified pigs raised in highly controlled environments. Nevertheless, as the xenotransplantation technology and production processes improve, the prices will decrease allowing more consumers to afford a genetically modified xenograft. We did not include a discussion on allografts from living donors as besides the costs, it raises an ethical dilemma that was out of our scope.

FOOTNOTES

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