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Editorial

Liver xenotransplantation: Time to make the leap to the clinic

Xenotrasplante hepático. Momento de dar el salto a la clínica

A little over a year ago, news about the first xenotransplantations of polytransgenic pig organs to humans (kidney and heart) hit the news. The media impact was comparable to the first heart transplantation performed in Cape Town in 1964 by surgeon Christian Barnard. These xenotransplants were used in the USA, after prior authorization from the FDA.[1–3] The 2 renal xenotransplantations (one at the University of New York and the other in Alabama) were performed on 2 brain-dead persons; subsequently, no hyperacute rejection was observed, and the renal grafts functioned adequately for 3 days.[1,2]

But without a doubt, what had the greatest media impact was the news of the first pig heart xenotransplantation performed in January 2022 (University of Maryland) in a 57-year-old man with heart failure and no other therapeutic options.[3] The patient survived for 2 months (much longer than Barnard's first transplant), and during that time there was no sign of rejection of the porcine heart. The patient was even discharged to his home but later died of CMV infection. These examples of xenotransplantation described were performed with polytransgenic pig organs (Revivicor) that included at least 10 human genetic modifications. The scientific publications of these clinical trials[1–3] explain the genetic modifications in more detail, as well as the regimen and management of the immunosuppression used.

Why this jump to clinical practice, and why now?

The most important determining factor has been the spectacular progress observed over the last 3 years in survival results of preclinical xenotransplantation models using polytransgenic pig organs in non-human primates. Specifically, normally functioning renal xenografts have been reported up to 9 months after xenotransplantation, more than 2 years in the case of the heart grafts, and almost one month in the case of liver xenotransplantation. Another decisive factor that has made these results possible has been the application of CRISPR technology for the gene editing and production of these polytransgenic pigs. With this technique, it is possible to obtain in a few months, and not in years, the polytransgenic pigs used in these first clinical xenotransplantations. The main aim of the genetic modifications that were included is to avoid hyperacute rejection as well as the thrombotic phenomena associated with acute vascular rejection, which characterize xenorejection. In addition to the immunosuppressants commonly used in non-human primate preclinical programs, a new immunosuppressant has been used for the first time, KPL-40, an anti-CD40 monoclonal antibody that inactivates the interaction between T lymphocytes and B lymphocytes. In this way, it minimizes the activation of acute vascular rejection, achieving an acceptable clinical biosafety profile.[1–3]

Is it reasonable to consider liver xenotransplantation?

Although the maximum survival achieved in baboons with liver xenotransplantation is more modest than in cases of kidney or heart transplants, genetically modified pig livers avoid xenorejection and remain functional for at least one month. If we accept the premise that xenotransplantation should currently be considered the last therapeutic option, we believe that there is a place for it as temporary life support (liver xenotransplantation as a bridge therapy) for patients with fulminant hepatic failure awaiting a suitable human organ. Our group has been defending this precise position for more than 20 years. Even then, the preclinical xenotransplantation program at the Hospital Universitario Virgen de la Arrixaca, using a transgenic pig-to-baboon model,[4] achieved functioning pig graft survival rates of up to 8 days, with no rejection. In this pioneering preclinical trial, the donor liver came from the first monotransgenic pig, which had been generated and provided by the University of Cambridge,

designed to inhibit hyperacute rejection (human DAF). During these 20 years, biosafety conditions regarding xenozoonosis have improved with the development of farms and animals free of specific pathogens by means of gene-editing techniques also applied to the control of the remote risk of infections by endogenous porcine retroviruses.

Indeed, the time has come. The possibility of performing liver xenotransplantation is clinically and ethically justified in patients with fulminant liver failure, risk of imminent death, and no human donor available. These patients cannot wait, and we can offer them an alternative. We do not have devices for these clinical situations, hemodynamic support, or hemodialysis, as in the case of patients with heart or kidney failure, respectively. Furthermore, several studies in our setting have shown the social acceptance, at different levels, of this therapy with animal involvement.[5–7]

In May 2023, the National Transplant Organization established the Clinical Xenotransplant Advisory Council, promoted by the ISCIII, which has begun to evaluate clinical xenotransplantation proposals in Spain.

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