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Extracorporeal liver support with a porcine liver: The United States Food and Drug Administration approves the first trial

In April, the US Food and Drug Administration (FDA) approved the Investigational New Drug (IND) application for a human-compatible, genetically engineered porcine liver, used in combination with an extracorporeal liver (ECL) cross-circulation system, for patients with acute-on-chronic liver failure (ACLF) who suffer from decompensated liver function and are critically ill.¹ The approval and the clinical trial represent a tremendous potential advancement for the 35 000 patients in the US hospitalized each year for acute liver failure (ALF) or ACLF. These patients have limited treatment options and face high mortality rates.

1. MULTIPLE SOLUTIONS TO THE PROBLEM

While the livers of patients with ALF may still have regenerative capacity, clinicians lack the mechanical support options available for patients with heart or kidney failure to allow for adequate regeneration to take place. Instead, today, plasma exchange is the only therapy that has been shown via randomized controlled trials to have any survival benefit in ALF.² However, multiple solutions are in development.

Researchers separate ECL support into 2 broad categories: nonbiological artificial liver support (NBAL) and biological artificial liver support (BAL).³ NBALs target detoxifying functions and focus on mechanical approaches to filtration and adsorption. BALs incorporate active hepatocytes and offer the theoretical advantage of providing additional functions such as metabolite synthesis and biotransformation.

Some bioartificial devices utilize human liver cells (see sidebar), while others employ porcine liver cells. Such hepatocyte-based systems, however, can be limited by the cost of hepatocyte isolation and preservation, as well as the large number of viable hepatocytes required to provide liver support. Moreover, such devices have a significantly smaller number of liver cells compared with those found in a whole liver.

Despite advances in the field of ECL support regarding biochemistry and hemodynamics, researchers have yet to document a consistent correlation between these factors and improved survival rates. A systematic review of the safety and efficacy of artificial liver support systems revealed that studies evaluating NBAL/BAL systems were heterogeneous, particularly in terms of reported outcomes and the timing of assessment. Perhaps due to this heterogeneity, the review found no statistically significant pooled effect of NBAL/BAL devices compared with standard medical care. In one glimmer of hope, NBAL did appear to provide some reduction in overall mortality (pooled relative risk = 0.77; $P = .076$).³ Robert S. Brown, Jr., MD, MPH, Chief, Division of Gastroenterology and Hepatology, Weill Cornell Medicine in New York City, has made significant contributions to this body of work. “As someone who did the original extracorporeal device trials 20 years ago, back then we thought we would be way ahead of where we are right now,” he says.

2. XENOTRANSPLANTATION

As some researchers continue to advance NBALs/BALs, others have turned their attention to xenotransplantation. The

KEY POINTS

- *The US Food and Drug Administration has approved the first clinical trial using a genetically engineered porcine liver to treat critically ill patients with no option for liver transplantation.*
- *While the livers of patients with acute liver failure may still have regenerative potential, clinicians lack a liver support system that can allow that regeneration, which takes time, to take place.*
- *The ability to genetically modify pigs has reduced the risk of rejection and advanced xenotransplantation.*
- *Last year, researchers at the University of Pennsylvania completed the first successful extracorporeal perfusion of a decedent's blood through a genetically engineered pig liver.*

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ability to genetically modify pigs has had a tremendous effect on xenotransplantation. Such modifications reduce the risk of rejection and possibly modulate the immune response.⁴

“The logical approach to moving into xenotransplantation is to start with the kidney and heart,” says Dr Brown. He explains that, in the case of xenotransplantation, there are 2 main challenges: immunology and physiology. While immunology is a problem shared by all organs, physiology differs for each. Because the heart is primarily a muscle, it is the simplest. The kidney is more complex because of its role in fluid management and maintaining electrolyte balance. The liver is the most complex of the 3 because it is metabolically active and pig proteins must work in humans. Many years ago, before the era of genetic modification, Dr Brown says, researchers attempted cross-perfusion using pig livers. Unfortunately, complement activation was swift and severe. Genetic modification to humanize the pigs should remove this reaction.

3. XENOTRANSPLANTATION ADVANCES TOWARD CLINICAL TRIALS

In 2021, surgeons attached a pig kidney to the blood vessels of a brain-dead patient’s upper leg. Later that same year, surgeons performed a second pig kidney transplant into a human, gathering data for 5 days. The decedent models paved the way for the first cases of human xenotransplantation.

In 2022, the day after receiving emergency use authorization from the US FDA, surgeons transplanted the heart of a genetically modified pig into a patient, and another patient followed soon afterward.⁵ Unfortunately, the first 2 living human recipients of pig hearts died unexpectedly within 2 months, suggesting that there are still many unknowns about human xenotransplantation.

“There had been an increasing acceptance by the regulatory authorities of exploring xenotransplantation,” says Dr Brown, explaining that he now feels that successful xenotransplantation will occur within his career. In January 2024, Abraham Shaked, MD, PhD, Eldridge L. Eliason Professor of Surgery at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, and colleagues completed the first successful extracorporeal perfusion of a decedent’s blood through a genetically engineered pig liver outside of the body using an ECL cross-circulation device made by OrganOx, Inc.⁶ “What we’re doing is in line with what has been done recently for kidneys and heart,” says Dr Shaked.

4. APPROVAL OF THE FIRST TRIAL

The PERFUSE-2 study, led by Dr Shaked and conducted at the University of Pennsylvania, utilizes pig livers (EGEN-5784) genetically engineered by eGenesis to deter rejection and enhance compatibility with humans. The study includes 4 perfusions with decedent recipients and demonstrates the feasibility of using EGEN-5784 with the OrganOx ELC system to support patients suffering from liver failure. In November 2024, OrganOx and eGenesis began an exclusive clinical codevelopment agreement

to advance the technology. Dr Brown consults for eGenesis, the company that performs the genetic modifications of the pigs.

“There has been a lot of excitement in the past years about the development of xenotransplantation,” says Dr Shaked. While these advances in xenotransplantation have been significant, the transplant community has found it challenging to design the clinical trials necessary for FDA approval of xenografts. “With the decedent model, it is hard to demonstrate true efficacy,” acknowledges Dr Brown. However, the results from PERFUSE-2, in combination with the documented limitations of NBAL/BAL, led eGenesis and OrganOx to propose that whole-organ ECL perfusion may be a promising treatment for ACLF. The FDA appears to agree, as it has approved the recent IND application.

“The FDA has finally decided that the time has come,” says Dr Brown, adding that “the decedent model gave everybody enough confidence to then take the next step... The decedent model was critical to show, at least in the short term, that nothing horrible would happen. When the FDA said that they were ready to do it, I was amazed... When they said yes so quickly, I was astonished but excited.”

The new clinical trial will utilize pig livers to provide temporary support for patients with ACLF and allow for the collection of necessary data to pave the way for whole-organ transplantation of xenolivers. “For those of us in the artificial liver support business, this feels like it was a long time coming,” says Dr Brown, adding, “I can’t wait to see where this goes,” says Dr Brown.

In the phase 1 trial, as many as 20 patients with ACLF (grades 2 and 3) and hepatic encephalopathy ($\leq$ grade 3) and ineligible for transplant will be enrolled across multiple US centers. “Many of us feel this is overdue,” says Dr Brown, adding that “the technology has come far enough along that there are enough potential benefits to justify doing a clinical trial... We have enough confidence from the decedent model that we can take this next logical step. The good thing about doing this as a perfusion instead of implanting the organ is if there are clotting or other safety concerns, we can turn it off.” He explains that the fact that the livers are extracorporeal means that they can be disconnected from the circuit at a moment’s notice.

5. PATIENT CARE

Dr Brown points out, however, that even if EGEN-5784 is tremendously successful, there will likely still be room for NBALs/BALs in patient care. It may be, for example, that EGEN-5784 is best for patients who require more liver function over a short time. Patients who need less support for a more extended period may benefit more from the cellular solution.

“We are going to generate an enormous amount of data in a short amount of time,” says Dr Brown, acknowledging that the data may reveal the need to do further genetic modifications of the pigs. “We were all happy and surprised to see that the FDA was willing to take it seriously,” says Dr Shaked. “It’s pretty amazing how fast things are going.”

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Miromatrix: An example of a bioartificial liver support system

This year, Miromatrix began recruiting for its phase 1, open, single-arm clinical trial to assess the safety of miroliverELAP for the treatment of acute liver failure without underlying chronic liver disease (NCT06285253).¹ Their bioartificial liver support system consists of a recellularized liver placed on a circuit with a Baxter dialysis machine. The single-use external liver assist combination product is created by first using a safe washing process to remove cells from a pig organ, leaving a noncellular matrix with the appropriate organ architecture. Human cells are then introduced into the matrix to create a new human organ.

Bioengineers developed the microliverELAP to support the native (failed) liver for up to 48 hours of continuous treatment, thereby allowing time for liver recovery or to bridge to liver transplantation. In the study, 15 subjects will be treated with miroliverELAP continuously for 48 hours and evaluated for the ability of the bioartificial liver support system to support liver function. Safety will be characterized by survival throughout therapy, the presence of microliverELAP-related adverse events, and the proportion of subjects surviving 21 days posttreatment initiation. The hope is that, if the phase 1 trial is successful, the bioengineered organ can ultimately be implanted into patients using standard transplantation techniques and equipment.

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