ACADÉMIE NATIONALE DE MÉDECINE

The heart works again. A major scientific breakthrough... and crucial medically?

Press release of the French National Academy of Medicine [1]

January 19, 2022

A surgical team from Baltimore (University of Maryland, USA) has just performed a heart transplant in a 57- old patient, using a genetically modified pig heart. The patient, in terminal heart failure, was not eligible to receive an allograft due to significant comorbidities. In end-stage heart failure, a possible modality for functional replacement is xenotransplantation, the Carmat artificial heart being another option.

This xenograft followed an intense research activity in the laboratory in various fields: production of pigs having undergone multiple genetic modifications; development of new immunosuppressive approaches; prevention of transmissible infections; prolonged survivals after pig heart xenograft in baboons and, recently, survival of a pig kidney implanted for a few days in the elbow bend of a brain-dead woman. This team, which was ready to move to the clinical stage, had received, 48 hours before, FDA authorization to perform this xenograft.

This is not the first time that a xenograft has been performed in humans. Indeed, if we disregard the few "last chance operations" that were carried out in the first half of the 20th century using organs taken from pigs, sheep or chimpanzees, two structured xenotransplantation programs had been undertaken from baboon organs, in Loma Linda (California) in 1984, where the little "Baby Fae" had a heart transplant, then in Pittsburgh (Pennsylvania) in 1992, where a patient with terminal viral cirrhosis B had a liver transplant. In both cases, the grafts had worked several weeks before the recipients died of nosocomial infection.

This new xenograft implicitly lifts the international moratorium on interspecies transplants decreed in 1999, which effectively suspended the authorization of xenotransplants due to the risk of transmission of endogenous retroviruses to humans, that could lead to uncontrollable pandemics. This risk was controlled, in this case, by one of the genetic modifications of the pig. In this context the FDA has requested a monitoring of this specific risk. This approach shows that in medicine, "transgression" can still drive innovation, provided it is based on a solid experimental research program, conducted in this case by a company specialized in the breeding of transgenic animals, and on risk-taking authorities capable of overcoming the precautionary principle.

If the success of this heart xenograft is confirmed, attempts will rapidly multiply with a view to reducing the permanent imbalance, in adults and children, between the needs and the number of grafts. Rich ethical debates can be expected on the use of animal organs, particularly from pigs, but also on the risk of transmission of viral pathologies, especially in the context of the current pandemic. Although the problems of an hyper-acute rejection seem to be in the way of

being resolved, caution is required due to the need to highlight the uncertainties that remain regarding the control of acute cellular and humoral rejection phenomena, and chronic rejection.

Following its previous press release, dated April 15, 2021, on "**New developments in transplantation: the challenge of surgical performance versus alternatives**", the French National Academy of Medicine:

1) welcomes this new scientific advance and recalls that the transgenic modifications of animal species used for xenografts are intended to improve the tolerance of the transplanted tissues without altering the DNA (the genome) of the recipients;

2) stresses that, while early humoral rejection and cellular rejection appear to be under control, the avoidance of chronic rejection and the maintenance of graft function remain major challenges to overcome;

3) urges French teams to develop such an interventional research, whose nature requires prior authorization from the Biomedicine Agency, the National Drug Safety Agency, the Protection of Persons Committee, and the Ethics National Advisory Committee.

[1] Press release from the Academy's Rapid Communication Platform validated by the members of the Board of Directors on 18 January 2022.