




POINT OF VIEW

US food and drug administration (FDA) panel endorses islet cell treatment for type 1 diabetes: A pyrrhic victory?

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SUMMARY

Allogeneic islet transplantation is a standard of care treatment for patients with labile type 1 diabetes in many countries around the world, including Japan, the United Kingdom, Australia, much of continental Europe, and parts of Canada. The United States is now endorsing islet cell treatment for type 1 diabetes, but the FDA has chosen to consider islets as a biologic that requires licensure, making the universal implementation of the procedure in the clinic very challenging and opening the manufacture of islet grafts to private companies. The commercialization of human tissues raises significant legal and ethical issues and ironically leads to a situation where treatments developed as a result of the scientific and economic efforts of academia over several decades become exploited exclusively by for-profit entities.

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On April 15, the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee voted 12 to 4 in favour of approval of the biologics license application (BLA) 125734 seeking to market 'donislecel', under the commercial trade name Lantidra, a cell therapy product composed of allogeneic islets of Langerhans for the treatment of 'brittle type I diabetes mellitus (T1D) in adults whose symptoms are not well controlled despite intensive insulin therapy'. Donislecel development at the University of Illinois Hospital and Health Sciences Center (UI Health) began in 2004. The BLA applicant, CellTrans, a for-profit faculty start-up company of UI Health, acquired the rights to the donislecel development programme with the purpose of supporting a BLA, while product manufacturing remains at the UI Health facility. Donislecel was granted Orphan Drug Designation, and UI Health transferred all rights and responsibilities to CellTrans. Donislecel is nothing more than a new name for pancreatic islet allotransplantation. The FDA endorsement of islet transplantation for the treatment of 'brittle' T1D is in itself very good news, and it adds to the list of national agencies in Europe, such as the Federal Office of Public Health in Switzerland, the National Health Service (NHS) in the UK, the Swedish Local Authorities and Regions, the Ministry of Health in Poland and Belgium or, more recently, the French National Authority for Health (HAS) in France that have approved islet transplantation as a reimbursed standard-of-care procedure. It is also a decision consistent with the results obtained by four successful multicentre phase 3 clinical trials in islet transplantation recently published: CIT-07 (multicentre, single-arm) [1], CIT06 (pivotal trial) [2], TRIMECO (multicentre, open-label, randomized) [3] and REP0211 (multicentre, Double blind, randomized) [4].

Despite this, as usual, the devil is in the details. This approval comes after a long journey of basic and clinical research over several decades by academia, sustained by

public funding and charities. In 2000, the Edmonton group published in the *New England Journal of Medicine* a series of seven T1D patients all of whom remained insulin-free one year after islet transplantation [5]. To test the efficacy and safety of the Edmonton protocol, the National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation (JDRF) supported a network of seven US clinical centres (Clinical Islet Transplantation Consortium, CIT), which successfully completed phase 1/2 and subsequent phase 3 multicentre CIT trials between 2005 and 2015. In the last 6 years, orphan drug designation for allogeneic islets of Langerhans for the treatment of brittle T1D has been granted to 6 CIT sponsors: University of Illinois Hospital and Health Sciences Center (UI Health, 01/02/2017, then transferred to CellTrans), Hospital of the University of Pennsylvania (Penn Medicine; 26/03/2018), University of Miami (01/05/2019), University of Chicago (01/05/2019), University of California, San Francisco (04/06/2019) and University of Minnesota (09/03/2020). The orphan drug designation programme provides orphan status to drugs and biologics, which are defined as those intended for the treatment, prevention or diagnosis of a rare disease or condition, that is one that affects less than 200,000 persons in the United States. Orphan drug designation qualifies the sponsor of the drug for various development incentives, including tax credits for qualified clinical testing. The granting of an orphan drug designation does not alter the standard regulatory requirements and process for obtaining marketing approval. Surprisingly, FDA has regulated human allogeneic islets (isolated from deceased donors) as a 'biologic'. As such, allogeneic islet transplantation in the United States requires FDA premarket review and approval (i.e. clinical trials followed by submission of Biologics License Application (BLA) to FDA; a BLA can be submitted by any legal person or entity who is engaged in manufacturing or an applicant for a license

who takes responsibility for compliance with product and establishment standards). Up until now, none of the academic centres participating in the US federally funded clinical trials (a total expenditure of over \$100 M over a span of 15 years) have been able to submit their own BLA because of logistical, financial and legal challenges [6]. In 2018, leaders in the islet transplantation field in the United States and investigators of the NIH-sponsored trial requested that human allogeneic islets be re-classified for exemption from premarket review and approval, as is the case elsewhere in the world, as well as for autologous islets. The FDA did not grant this exemption and the situation has not changed to date, despite attempts to mobilize the physician and patient communities [7, 8]. One of the key tenets of the FDA position is that preservation of human allogeneic islets in an incubator for 72 hours constitutes cell culture, and therefore exceeds the 'minimal manipulation' standards. However, the same point of view is not shared by the European Medicines Agency (EMA) and its Committee for Advanced Therapies (CAT). In the EU, products consisting of cells or tissues may scientifically be on the border between the Tissue and Cell directives (Directive 2004/23/EC)[9] and the Advanced Therapy Medicinal Product (ATMP) regulation. The EMA recognizes that cells/tissues harvested and separated by a simple selection method (that does not result in a substantial manipulation of the cells/tissue) and re-administered to fulfil their same essential function will generally be regarded as non-ATMPs. Accordingly, the CAT recommended that both autologous and allogeneic preparation of human pancreatic islets of Langerhans should not be classified as an ATMP [10]. The CAT considered that, for the manufacture of islet grafts, the described process steps do not constitute substantial manipulations for the intended use so that there is no change in the biological characteristics of the islets. In addition, the product is intended to be used for the same essential function in the recipients as in the donor, be it allogeneic or autologous in origin. This position appears more consistent with current knowledge on pancreatic islets, as we know that short-term human islet culture does not change relevant biological characteristics (islets do not divide or proliferate and their qualities are comparable to the islet products obtained before culture). More generally, more than 4,000 islet transplantation procedures all over the world have already been performed without the BLA rules and have proven the safety and efficacy of human islet processing and transplantation under regulations applicable to tissue or whole organ transplant.

However, the problem is not only to understand what is justified from a scientific point of view, but also to understand how some regulatory positions result in significant consequences affecting future development of the field. Before 15 April 2021, no BLA had been approved consequently, no allogeneic islets have been transplanted in the United States outside clinical trials nor are they generally reimbursed by third-party healthcare coverage, leaving patients in the United States at a considerable disadvantage compared with the rest of the world. April 15th marks the date of CellTrans' BLA approval; a for-profit company is now the only entity authorized to produce human islets for treatment of brittle diabetes, making availability and equity of treatment a challenge.

FDA's decision produces a number of potential risks and concerns. First, in accordance with the FDA rules pertaining to BLAs for orphan drug designation, CellTrans can have exclusive rights to manufacture human islets as a biologic product for the next 7 years in the United States. Even if there is an assurance by CellTrans to waive the exclusivity rights, the cost of the regulatory burden in a relatively small market will discourage others competitors. Second, the price of the islet product and islet transplant procedure could increase because of the cost of the biologics license application, the implementation of additional levels of regulation and the lack of competition. If private payers will provide coverage, rather than the public healthcare system, this will particularly be a disadvantage for patients of low socio-economic status. Third, CellTrans is currently a small company with a single isolation facility and it could foreseeably be difficult to meet the demands of the entire United States. Strategies like building a network of islet isolation facilities or shipping islets between the islet isolation facility and transplantation sites should be considered and implemented, which will take time, investment, additional costs, and process validation according to the regulatory standards of the BLA. Fourth, conferring to a private, for-profit company the marketing rights for the isolation of allogeneic islets could foreshadow the commercialization of human organs and their subparts [7]. The manufacturing on an 'industrial' scale and commercialization of human tissues raises significant legal and ethical issues, since these products are obtained based on 'a philosophy of voluntary and unpaid donation, altruism of the donor and solidarity between donor and recipient'. This is spelled out in the EU Cell and Tissue Directive, which further 'urges ... Member States are urged to take steps to encourage a strong public and non-profit sector

involvement in the provision of tissue and cell application services [9].

What is happening in the United States demonstrates that, despite good intentions, some regulatory choices that are initially aimed at defending the patient and ensuring the best benefit-risk balance can cause a boomerang effect. Islet transplantation in many countries has already been implemented as a standard-of-care procedure and a minimally invasive alternative to whole pancreas transplantation for patients with 'brittle' T1D. It is performed only at accredited transplant centres, after meeting all required standards for islet processing and clinical transplantation. Excessive regulatory burden, unjustified by scientific evidence, could irreversibly block its application and further development by increasing the costs and limiting the accessibility. We hope that the situation in the United States can be quickly changed to a more rational, inclusive and equitable direction as is currently the case for islet autografts. In fact, islet autotransplants (e.g. islets obtained from surgical pancreatectomy of the patient's own pancreas for chronic pancreatitis or trauma) are already approved and reimbursable in the United States outside the BLA rules. The manufacturing process is comparable to that used for allogeneic islet transplants (using enzymatic digestion and purification steps to reduce the volume of the tissue infused) with the exception that islets are used without 48-72 hours of low temperature *in vitro* tissue culture. Indeed, the problem discussed herein is not limited to the field of islet transplantation or to the United States. In the EU, some products previously considered as non-ATMP because of a minimal manipulation or maintenance of the initial biological properties have been classified as ATMP because of their intended use (i.e. different essential function(s) of the cells/tissues in the recipient and in the donor). An example is the use of bone marrow mononuclear cells for the treatment of ischaemic syndromes. As hematopoietic stem-cell preparations undergo non-substantial manipulations, cell processing can be performed in hospital facilities termed tissue establishments (TEs) under the EU Tissue and Cell Directives. On the contrary, the same cells used for the treatment of ischaemic syndromes are classified as ATMP and cell processing must follow the most stringent GMP requirements in facilities qualified for ATMP production. This creates contradictions that are hard to justify. The same cell

processing procedure will be managed and regulated differently depending on the clinical indication. Academic centres are allowed to process cells for bone marrow transplantation in immune-compromised patients who receive an allogeneic product, while they are obliged to send them to a (private or third party) facility for the treatment of ischaemia in immunocompetent patients receiving their own cells. Additional costs will be paid for a process they routinely perform, using the same technology, for higher risk recipients, with a significant economic impact that cannot be justified in terms of patient safety [11].

Today, we know that cell and gene therapies, tissue-engineered products and biologicalization of medical devices are no longer science fiction, and that they can change the therapeutic horizon for many diseases [12]. The development of these innovative approaches is a result of the extensive work of multiple academic and research centres. The clinical success of these approaches depends on the ability of clinicians and their teams to perform such treatments and their economical sustainability. Increasing the costs and the regulatory burden without objective evidence of improved patient safety risks the possibility that after years of scientific and economic investment by academia to pioneer and develop novel treatments, those academic centres will be unable to implement these treatments in their facilities or further improve them for optimal outcomes. A new development and integration model that genuinely puts the patient at the centre of all regulatory decisions, whatever their background, location or financial status, is not only desirable, but also essential for the ongoing credibility of modern science and medicine.

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Conflicts of interest

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