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Islet cell transplantation hits a milestone

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Abstract

This month's installment of "The *AJT* Report" discusses the controversy behind pending regulation of allogeneic pancreatic islet cells as a treatment for brittle type 1 diabetes, and provides an update on a recent governmental hearing concerning organ procurement organizations.

As regulation of allogeneic islet cells as a biologic awaits final FDA approval

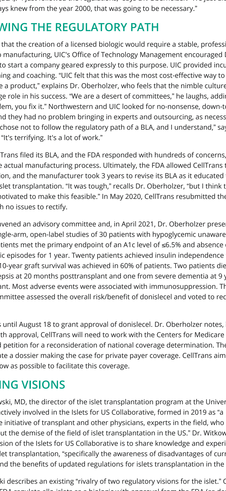

Figure 1 Open in figure viewer | PowerPoint

Key Points

- The FDA has voted to endorse a pancreatic islet cell transplant product for the treatment of people with brittle type 1 diabetes who cannot be managed with current therapies.
- The FDA made the decision to regulate allogeneic islet cells as a biologic in 1993.
- Researchers from the University of Illinois in Chicago formed a company to file a Biologics License Application (BLA) to bring allo-islets to market.
- Some in the transplant community feel that allo-islets should be FDA regulated as solid organs in lieu of granting BLA approval.

On April 15, the Cellular, Tissue, and Gene Therapies Advisory Committee of the U.S. Food and Drug Administration (FDA) voted to endorse a pancreatic islet cell transplant therapy for the treatment of people with brittle type 1 diabetes that cannot be managed with current therapies. In a 12-to-4 decision (with one abstention), the panel concluded that the biologic donsilecel (Lantidra), a product consisting of purified allogeneic pancreatic islets of Langerhans derived from deceased donors, had "an overall favorable benefit-risk profile," for some patients with type 1 diabetes. The FDA panel's decision is the culmination of a journey filled with controversy that began nearly 30 years ago.

EARLY PROMISE OF ISLET TRANSPLANTATION

In 1993, the FDA set forth the regulatory principles of Somatic Cellular Therapy, thus regulating allo-islets (but not autologous islets) as a new biologic. In 2000, researchers in Edmonton, Canada reported on the successful transplantation of seven patients with type 1 diabetes who remained insulin free for 1 year post procedure.[1] That same year, the FDA sent a "dear colleague" letter to transplant surgeons to remind them that allo-islets are considered a biological drug.[2] Together, the published study and the FDA letter "led to a reorganization of the field," says Jose Oberholzer, MD, founder and president of CellTrans, the manufacturer of donsilecel.

In 2003, Dr. Oberholzer joined the faculty of the University of Illinois in Chicago (UIC) and began phase 1/2 trials in allo-islet transplantation using his startup funds, philanthropic donations and private family grants. In 2004, a network of clinical centers and a data coordinating center formed the Clinical Islet Transplant Consortium (CITC) to conduct studies of islet transplantation in patients with type 1 diabetes. UIC joined the CITC in 2007, following approval for a phase 3 trial. Chicago-based Northwestern University also joined and going forward, the universities worked with the larger consortium, sharing data and strategizing ways to advance the field of allogeneic islet transplantations.

The 1993 FDA decision to regulate deceased donor allo-islets as a biologic meant that any transition from clinical trial to a standard patient offering would require its approval. Therefore, while the CITC could work to create a new drug application and perform clinical trials, per FDA requirements each institution would have to file its own Biologics License Application (BLA). "I just followed the regulations," says Dr. Oberholzer. "We just did the work that we always knew from the year 2000, that was going to be necessary."

FOLLOWING THE REGULATORY PATH

Recognizing that the creation of a licensed biologic would require a stable, professional staff dedicated to manufacturing, UIC's Office of Technology Management encouraged Dr. Oberholzer to start a company geared expressly to this purpose. UIC provided incubator space, teaching and coaching. "UIC felt that this was the most cost-effective way to consistently manufacture a product," explains Dr. Oberholzer, who feels that the nimble culture at UIC played a large role in his success. "We are a desert of committees," he laughs, adding, "You have a problem, you fix it." Northwestern and UIC looked for no-nonsense, down-to-earth solutions, and they had no problem bringing in experts and outsourcing, as necessary. "Other universities chose not to follow the regulatory path of a BLA, and I understand," says Dr. Oberholzer. "It's terrifying. It's a lot of work."

In 2017, CellTrans filed its BLA, and the FDA responded with hundreds of concerns, mostly involving the actual manufacturing process. Ultimately, the FDA allowed CellTrans to withdraw the application, and the manufacturer took 3 years to revise its BLA as it educated the FDA on the field of islet transplantation. "It was tough," recalls Dr. Oberholzer, "but I think they were extremely motivated to make this feasible." In May 2020, CellTrans resubmitted the BLA and was met with no issues to rectify.

The FDA convened an advisory committee and, in April 2021, Dr. Oberholzer presented data from two single-arm, open-label studies of 30 patients with hypoglycemic unawareness. Nineteen patients met the primary endpoint of an A1c level of ≤6.5% and absence of severe hypoglycemic episodes for 1 year. Twenty patients achieved insulin independence for at least 1 year, and 10-year graft survival was achieved in 60% of patients. Two patients died, one from fulminant sepsis at 20 months posttransplant and one from severe dementia at 9 years posttransplant. Most adverse events were associated with immunosuppression. The FDA's advisory committee assessed the overall risk/benefit of donsilecel and voted to recommend approval.

The FDA has until August 18 to grant approval of donsilecel. Dr. Oberholzer notes, however, that even with approval, CellTrans will need to work with the Centers for Medicare & Medicaid Services and petition for a reconsideration of national coverage determination. They will also need to create a dossier making the case for private payer coverage. CellTrans aims to keep the cost as low as possible to facilitate this coverage.

DIFFERING VISIONS

Piotr Witkowski, MD, the director of the islet transplantation program at the University of Chicago, is actively involved in the Islets for US Collaborative, formed in 2019 as "a collaborative initiative of transplant and other physicians, experts in the field, who have been worried about the demise of the field of islet transplantation in the US." Dr. Witkowski states that the mission of the Islets for US Collaborative is to share knowledge and experience related to islet transplantation, "specifically the awareness of disadvantages of current regulation and the benefits of updated regulations for islets transplantation in the US."

Dr. Witkowski describes an existing "rivalry of two regulatory visions for the islet." One vision is to have the FDA regulate allo-islets as a biologic with approval from the FDA (as described above). The other regulatory vision, supported by Dr. Witkowski, is to regulate islets as an organ as is done in many countries worldwide, and thus "provide allo-islet transplantation to patients under appropriate regulation under the US Department of Health and Human Resources Organ Procurement and Transplantation Network and United Network for Organ Sharing." He and others in the transplant community have written numerous papers seeking to inform the community and the administration.[3, 4]

Dr. Witkowski cites a statement made by Sukhanya Jayachandra, PhD, of the FDA as a critical point. During the hearing, Dr. Jayachandra stated that "variability in quality attributes makes it difficult to correlate product attributes to clinical outcomes." Dr. Witkowski says, "Practically, it means that the quality of the islets which provide a therapeutic effect cannot be determined and verified prior to transplantation, so the main goal of the BLA implementation was not achieved."

Not surprisingly, words exchanged within the transplant community have been heated. Some people are concerned that the commercialization of allogenic islets opens the door for unseemly profiteering. "We waived any exclusivity to rights the moment we filed our application," reports Dr. Oberholzer, noting that he welcomes other universities and companies to follow CellTrans' example and file a BLA.

THE FUTURE?

The future of allogeneic islet presentation will no doubt be influenced by the FDA decision to grant a BLA to CellTrans. On one side is a concern that authorizing a private company to provide human islets when there is a known variability in quality will, as Dr. Witkowski describes it, "jeopardize patient safety and public interest, and lead to the demise of the field." On the other side, Dr. Oberholzer sees a future when what is now an experimental procedure becomes an insurance-covered option for those who desperately need it.

REFERENCES

PRESSURE BUILDS FOR OPO OVERSIGHT

The call for greater oversight of organ procurement organizations (OPOs) is gaining momentum. Recently the Centers for Medicare & Medicaid Services finalized an OPO reform rule, to be enforced in 2026.[1] On May 4, the U.S. House Committee on Oversight and Reform held a hearing entitled "The Urgent Need to Reform the Organ Transplantation System to Secure More Organs for Waiting, Ailing, and Dying Patients." The virtual meeting examined the nation's system for securing organs for transplant. Witnesses included patients waiting for transplant, a living donor and mother of a transplant recipient, and the chief executive officer of the Association for Organ Procurement Organizations. In her testimony, Donna R. Cryer, JD, liver transplant recipient and president and CEO of the Global Liver Institute, said, "The OPO final rule is a critical first step toward reducing waiting lists that are much longer than necessary. But as no OPO will currently face decertification until 2026, I ask the Committee to do all that it can to usher in urgent accountability sooner."

REFERENCE