Department of Surgery

The 31st Annual Charles B. Huggins Research Symposium

March 20, 2024

Center for Care and Discovery (CCD)

Keynote Speaker: Edith Tzeng, MD

THE UNIVERSITY OF CHICAGO

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DEPARTMENT OF SURGERY

presents

The 31st Annual Charles B. Huggins Research Symposium

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Center for Care and Discovery (CCD) Boardroom

11:30-12:30 Buffett Lunch

12:30-12:45 Welcome, Jeffrey Matthews, MD

12:45-1:15 Basic Science Presentations

Elena Jochum, BA (Alexander von Kumberg presenting) — Le Shen Lab
"4NQO Induced Tongue Epidermal Organoid Transformation as a Model for Oral Squamous Cell Carcinoma" (Page 101)

Junsung Kim, BA — Luka Pocivavsek Lab
"Endovascular Aortic Repair Management: A Geometric Comparison between Stable Sac Patients and Endoleak Patients" (Page 88)

1:15-2:00 Clinical Health Services/Implementation Science Presentations

Sarah Gondek, BS — Piotr Witkowski Lab
"Achieving Insulin Independence in Humans through Stem Cell-Derived Islet Cell Transplantation: Preliminary Insights from the VX-880 Multicenter Clinical Trial" (Page 35)

Kimberly Brooke Golisch, MD, MS — Sponsor: Ryan Merkow
"Statewide Quality Improvement Collaborative Initiative to Improve Venous Thromboembolism Prophylaxis after Abdominopelvic Cancer Surgery: A Mixed-Method Study" (Page 29)

Sara Kim, MPH — Lucia Madariaga Lab
"Smartwatch Pilot Study to Facilitate Prehabilitation in Frail and Pre-Frail Thoracic Surgery Patients" (Page 6)

2:00-3:00 Resident Presentations

David Jiang, MD — Luka Pocivavsek Lab
"Fluctuation In Total Curvature as An Imaging Based Quantitative Marker of Aortic Dissection Chronicity" (Page 13)

William Ian McKinley, MD — Sponsor: Susan Rowell
"The Association Between Prehospital TXA and Intracranial Pressure in Patients With TBI" (Page 14)

Alyssa Varsanik, MD — Sponsor: Yalini Vigneswaran
"IDEAL Phase 2a Results on Posterior Rectus Sheath for Hiatal Augmentation (PoRSHA) for Complex Paraesophageal Hernias" (Page 22)

Grace Keegan, BS (Lea Hoefer, MD presenting) — Sponsor: Tanya Zakrison
"Strengths of Women Working in Violence Intervention and Outreach: Providing Space for Emotional Vulnerability and Empathy" (Page 107)

3:00-3:15 **Coffee Break**
Coffee, cookies, and pastries will be served.

3:15-3:30 **Student Presentation**

Raquel dos Santos (BA undergraduate) — Narutoshi Hibino Lab
"Analysis of the Impact of Somatic Growth on Fontan Conduits Over Time" (Page 4)

3:30-3:45 **Poster Oral Presentations (TBA)**

3:45-4:00 **Featured Topic: Education**

Frederick A. Godley IV, MD, MBA, MS
"The Learners in the Room - A Multi-Institutional Study of Needs Assessment of Medical Student Perceptions of Different Operating Room Learning Environments" (Page 23)

4:00-4:15 **Featured Topic: Diversity, Equity, & Inclusion (DEI)**

Devki Shukla, MD — Sponsor: Parth Modi, MD
"Gender Differences in Major and Minor Procedure Volume Among Early-Career Urologists: An Analysis of American Board of Urology Certification Data From 2003 To 2019" (Page 97)

4:15-4:30 **Featured Topic: AI in Health Care**

Darren Bryan, MD
"How Soon Will Surgeons Become Mere Technicians? Chatbot Performance in Managing Clinical Scenarios" (Page 65)

Manish Pathuri, BS (Preetham Kastury, BS presenting)
"Evaluating Artificial Intelligence Chatbot Responses to Patient's Common Sinus Questions" (Page 54) — Sponsor: Christopher Roxbury

4:30-4:40 **Introduction of Keynote Speaker, Jeffrey Matthews, MD**

4:40-5:30 **Keynote Speaker: Edith Tzeng, MD**
UPMC Professor of Surgery
Chief of Vascular Surgery, VA Pittsburgh Healthcare System
"Working Toward Ideal Vascular Conduits: The Role of the Vascular Surgeon"

Customizing Abdominal Incision Based on Patient Age for Minimizing Surgical Wound Complications After Kidney Transplantation

Braden Juengel, Piotr Bachul, Alex Gaffan, Sarah Gondek, Joseph Tomecki, William Lin, Kamila Milejczyk, Linsday Basto, John Fung J. Rolf Barth, Piotr Witkowski

Introduction
This study aimed to prospectively evaluate whether the implementation of a patient-age-specific surgical incision reduces the risk of surgical site complications (SSCs) after unilateral kidney transplantation.

Methods
Initially, we conducted a retrospective analysis comparing the risk of SSCs between the lateral rectus sheath incision (LRS) and the traditional Gibson incision in 144 consecutive kidney transplants performed by the same surgeon. The retrospective data indicated a potential advantage of LRS over Gibson incision for patients under 60 years (SSCs rate 0% vs. 7%), while Gibson incision appeared advantageous for older patients (SSCs 0% vs. 25%, respectively p=0.008). Subsequently, we assessed prospectively SSCs rates in next 104 consecutive kidney transplant recipients, utilizing tailored surgical techniques based on patient age: LRS for those under 60 years and Gibson for those 60 and older.

Results
The majority of patients were on hemodialysis (N=88, 85%), and 37 (36%) had diabetes. Kidney grafts primarily originated from brain-dead donors (86%) and were preserved on the pump (68%). Thymoglobulin served as the immunologic induction agent (85%). LRS incision was applied to 72 patients with a mean age of 48 (range: 19-59) and a BMI of 28 (range: 18-44). Gibson incision was employed in 32 patients with a mean age of 64.5 (range: 60-75) and a BMI of 27 (range: 19-41).

The overall SSC rate after application of prospectively tailored approached was only 3.8% (4/104) in the study cohort compared to 6-15% in historic series. Two wound infections occurred after LRS incision in patients under 60 years old and two after Gibson incision in older patients. Altogether, the application of LRS in younger than 60 years old patients from retrospectively and prospectively assessed cohorts resulted in only 2% rate of SSC (2/92) and the Gibson incision in only 3% SSC rate in patients over 60 years old.

Of note, LRS demonstrated a significant advantage over Gibson incision, particularly in obese (BMI>30) and younger than 60 years old, reducing the risk of SSCs to 0% from 17% (4/23) in the historical control (p=0.007).

Conclusions
Tailoring abdominal incision techniques based on patient age appears effective in reducing the incidence of surgical wound complications after unilateral kidney transplantation. LRS, specifically, exhibits notable benefits in obese patients below 60 years of age.

Achieving Insulin Independence in Humans through Stem Cell-Derived Islet Cell Transplantation: Preliminary Insights from the VX-880 Multicenter Clinical Trial

Sarah Gondek, William Lin, Joseph Tomecki, Braden Joungel, Bachul Piotr, Kamila Milejczyk, Lindsay Basto, Ling-jia Wang, Martin Tibudan, Rolf Barth, John J Fung, Piotr Witkowski

Introduction

VX-880 (Vertex, Boston, MA) marks a groundbreaking allogeneic stem cell-derived pancreatic islet cell replacement therapy, administered intravenously for the first time and assessed in a Phase 1/2 clinical trial involving patients with Type 1 Diabetes (T1D). This report focuses on the outcomes observed in the initial 6 patients who underwent VX-880 dosing.

Methods and Materials

Six participants diagnosed with Type 1 Diabetes Mellitus (T1DM), experiencing impaired hypoglycemic awareness and encountering at least two severe hypoglycemic episodes (SHE) within the last year, were enrolled in this multicenter study. The trial has 3 parts: Part A where 2 patients were enrolled sequentially and received half the target dose, Part B where 4 out of 5 patients to be enrolled sequentially received the target (full) dose, and Part C where 10 patients will be enrolled concurrently and receive the target dose. Following a single VX-880 infusion patients were monitored for safety and tolerability (as assessed by adverse events and clinical laboratory assessments), fasting and stimulated C-peptide, HbA1c, glycemic variability, interstitial glucose by continuous glucose monitoring, and exogenous insulin dose.

The primary efficacy endpoint was the proportion of participants free from SHEs from Day 90 through Month 12 with Hb1Ac < 7% or ≥1% reduction in HbA1c from baseline between Day 180 and Month 12. VX-880 cell product was infused directly into the portal vein via 4F catheter placed percutaneously by an interventional radiologist under the local anesthesia. Patients received a standard continuous immunosuppression consisting of rapamycin, tacrolimus in addition to the anti-thymocyte globulin for induction.

Results

After VX-880 single infusion all six patients presented production of endogenous insulin production based on serum c-peptide, improved blood glucose control based on reduction in HbA1c below 7%, reduction in insulin use, improvement in time-in-range (BG 70-180mg/ml) and the elimination of SHE after initial 90-day period. Importantly, islet cells exhibited physiological function, demonstrating that insulin secretion was effectively regulated in response to blood glucose fluctuations.

Two participants achieved insulin independence. The first individual attained insulin-free status at the 9th month post-transplant and has sustained this state for over 2 years, maintaining an HbA1c of 4.7%. The second patient accomplished insulin independence by the 6th month post-transplant and has successfully maintained it beyond the initial year. The remaining four patients in the study have exhibited progress with partial islet cell function and improved blood glucose control. However, they have not yet reached the 6-month follow-up timepoint required to achieve their full functional potential.

VX-880 has demonstrated a favorable safety profile, being generally safe and well-tolerated at both doses. The majority of adverse events (AEs) reported were mild or moderate in severity, with no serious AEs considered related to VX-880. This safety profile aligns with the immunosuppressive regimen and the perioperative period.

Conclusion

Our findings represent a pioneering milestone, showcasing, for the first time in humans, that a single infusion of stem cell-derived islets (VX-880) can effectively restore insulin production and insulin independence in patients with T1DM. Building on these results, VX-880 emerges as a potential functional cure for patients with diabetes.

Insights From the Initial Patient Cohort: Islet Allotransplantation into Pre-vascularized Sernova Cell Pouch

Joseph Tomecki, Sarah Gondek, William Lin, Braden Juengel, Piotr Bachul, Kamila Milejczyk, Lindsay Basto, Ling-jia Wang, Martin Tibudan, Rolf Barth, John J Fung, Piotr Witkowski

Introduction
The Sernova Cell Pouch (SCP) was designed to enhance islet cell engraftment in extrahepatic tissue, paving the way for potential local immunomodulation and eliminating the necessity for systemic immunosuppression. The study aimed to evaluate the safety, tolerability, and effectiveness of the prevascularized Sernova Cell Pouch (SCP) for pancreatic islet transplantation.

Material
Each of 6 patients with T1DM and problematic hypoglycemia received two cadaveric islet transplants into SCPs pre-implanted onto the muscles of the abdominal wall. Each transplant involved open surgical access and infusion of islets into two 8-channel SCPs and one mini sentinel SCP. Patient received thymoglobulin/basiliximab for induction, tacrolimus and mycophenolate for maintenance immunosuppression.

Results
SCP implants and the combination of SCP with human cadaveric islets were both well tolerated with current durations exceeding 3 years. Wound infection resulting in device removal occurred after only one of 31 (3.2%) surgical procedures. Detectable islet function (≥0.3ng/ml peak serum c-peptide in mixed meal tolerance test) was achieved in 4 patients following islet transplant to SCP. It was correlated with transplanted islet mass of ≥3,000 IEQ/kg per procedure. Transplantation of islet mass < 3,000 IEQ/kg did not lead to detectable c-peptide secretion. C-peptide was detectable for periods ranging from days up to 12 months after the procedure.

Three patients with suboptimal levels of immunosuppression due to non-compliance experienced antibody mediated rejection based on detection of de novo donor specific antibodies (DSAs). One patient with DSAs had detectable stimulated c-peptide at 90 days post-transplant. Histological assessment of sentinel SCPs retrieved ≥90 days post-transplant revealed surviving functional islets within vascularized SCP channels via positive immunofluorescence staining of insulin, c-peptide, glucagon and somatostatin in 5 of 6 patients.

All 6 patients received supplemental intraportal islet transplants (IPITx) and all of them developed insulin independence (>3Y, >2Y, >1M, 5M, 4M, >1M). Safety and dose-response observations from the first cohort of 6 patients led to the implementation of 10-channel SCPs with 50% greater transplant capacity than the 8-channel configuration in a second study cohort. Three patients were recently enrolled in the second cohort and implanted with 10-channel SCPs. Two of them are currently recovering from their first islet transplantation. Belatacept was introduced to maintenance immunosuppression in order to lower dose and toxicity of tacrolimus and myfortic and for improved protection from immunologic rejection.

Conclusions
Interim results confirm long-term safety and tolerability of Cell Pouch for pancreatic islet transplantation with histologically confirmed islet graft survival in five out of six patients.

Early Outcomes of an Innovative Desensitization Protocol Using Proteosome Inhibitors with Co-Stimulation Blockade for Highly Sensitized Kidney Transplant Candidates

William Lin, Sarah Gondek, Joseph Tomecki, Piotr Bachul, Kamila Milejczyk, Lindsay Basto, Yousuf Kyeso, Jerome Weiner, Lisa Potter, Susana Marino, Anita Chong, John Fung, Rolf Barth, Piotr Witkowski

Introduction

A critical gap exists in effective desensitization therapy for highly sensitized patients, limiting their chances of finding a suitable deceased donor for life-saving transplantation. Drawing inspiration from our encouraging outcomes observed in animal models, we introduce a novel desensitization therapy for highly sensitized kidney transplant candidates. Our approach is designed to mitigate anti-HLA antibodies, thereby enhancing the prospect of identifying compatible deceased donors. Grounded in the synergistic effects of proteasome inhibitors and co-stimulation blockade, this innovative strategy holds promise for addressing the current challenges faced by highly sensitized individuals seeking transplantation.

Methods

This pilot study, conducted at the University of Chicago Transplant Center and approved by the Institutional Review Board (IRB), focused on highly sensitized participants with a cPRA of 99-100% and a waiting list duration exceeding 6 years. The intervention involved cycles of carfilzomib or bortezomib, complemented by monthly belatacept therapy.

Results

Three participants, comprising two females and one male, were enrolled in the study, with a median age of 62 (range: 59-66). All patients presented with a class II anti-HLA-Ab PRA of 100%, alongside varying class I HLA antibody (HLA-Ab) PRA. Upon undergoing desensitization therapy with Carfilzomib, the mean fluorescence intensity (MFI) of strong anti-HLA-Ab (>2500) notably decreased. In the first patient, a 57% reduction was observed, resulting in the elimination of two strong HLA-Abs and the conversion of four from strong to moderate. Subsequently, a compatible deceased kidney donor was identified with a negative crossmatch, facilitated by the reduction in strength of two donor-specific antibodies (DSA) during desensitization therapy. This patient successfully underwent a kidney transplant after 22 years on the UNOS waiting list.

In the second patient, the MFI of all 85 strong anti-HLA Abs decreased by 37% (range: 20-70). Following this reduction, the patient received a deceased donor kidney transplant with a negative flow crossmatch. Notably, the MFI of strong donor-specific HLA-Ab A26 decreased after desensitization therapy. Kidney graft function has remained stable in both patients, now one-year post-transplant.For the third patient, the response to belatacept in combination with bortezomib was limited, prompting ongoing exploration of additional plasmapheresis to enhance therapeutic efficacy. Mild leucopenia was observed in all patients, which did not require filgrastim therapy. One patient experienced a viral upper respiratory infection, leading to a temporary interruption of carfilzomib.

Conclusions

The amalgamation of carfilzomib and belatacept exhibited promising efficacy by effectively reducing anti-HLA antibodies, leading to successful kidney transplantation in highly sensitized patients. Preliminary findings indicate manageable short-term side effects. A comprehensive evaluation involving a larger patient cohort is essential for further refining and optimizing this innovative desensitization approach in kidney transplantation.

Aiming for Optimal Immunosuppression in Islet Transplantation: Assessing the Tolerability and Efficacy of Belatacept in Conjunction with Reduced Tacrolimus

Piotr Bachul, Sarah Gondek, Joseph Tomecki, William Lin, Braden Juengel, Kamila Milejczyk, Lindsay Basto, Ling-jia Wang, Martin Tibudan, Alex Gaffan, John J.Fung, Rolf Barth, Piotr Witkowski

Introduction

Belatacept, administered intravenously, offers an advantage, especially in diabetic patients with gastrointestinal disorders. However, its effectiveness in preventing rejection might be insufficient when combined with antimetabolite agents. Conversely, tacrolimus, a potent immunosuppressive agent, is burdened by dose-dependent toxicity. In response, we aimed to evaluate the tolerability and efficacy of a reduced tacrolimus dose when paired with belatacept for maintaining immunosuppression post-islet transplantation in patients with Type 1 Diabetes.

Material and Method

Our study involved a cohort of 14 patients diagnosed with Type 1 Diabetes Mellitus (T1DM) who underwent pancreatic islet transplantation. Induction therapy for all patients included Thymoglobulin. Maintenance immunosuppression consisted of monthly administration of Belatacept at 5mg/kg alongside low-dose tacrolimus (target level 3-5ng/ml). Ten patients (67%) received this combination as de novo therapy at transplantation, while the remaining five (33%) transitioned from tacrolimus/antimetabolite due to complications such as rising creatinine, chronic diarrhea, and increasing donor specific antibodies.

Results

The regimen of Belatacept at 5mg/kg monthly with low-dose tacrolimus effectively prevented de novo donor-specific antibodies (DSA) and antibody mediated rejection (AMR) in all 14 (100%) patients during the 14-month follow-up, contrasting with only 33% (2/6) in a historical cohort treated with tacrolimus and antimetabolite. However, Belatacept required modification in 7 (50%) patients, involving discontinuation in two cases and dose reduction to 2.5mg/kg monthly in five (36%) patients due to adverse events such as chronic neutropenia, mouth ulcers with skin rash, de novo Epstein-Barr virus (EBV) viremia, recurrent norovirus, Clostridium difficile infection, urinary tract, or upper respiratory infections. As a proactive measure to prevent toxic or infectious complications, we also lowered Belatacept to 2.5mg/kg monthly in the remaining 7 patients. Following this adjustment, recurrent infectious complications and toxicity resolved, while islet graft function remained stable in all 12 patients.

Conclusion

Belatacept in combination with low-dose tacrolimus proved effective in preventing de novo DSA, AMR, and islet graft loss. However, the necessity to lower the Belatacept dose to 2.5mg/kg monthly emerged as a crucial strategy to minimize the risk of toxicity and infectious complications, underscoring the delicate balance required for successful long-term immunosuppression in islet transplantation.