Islet Cell Allo-Transplantation

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Special thanks to Melena Bellin, MD at The University of Minnesota who provided content for this presentation.

Disclosure

- No direct conflicts of interest regarding islet transplantation.
- Dr. Forlenza is a consultant for Abbott Diabetes Care and conducts research sponsored by Medtronic, Animas, Dexcom, Tandem, Bigfoot, Insulet, and Novo Nordisk.

Objectives

- Define Islet Allo-Transplantation
- Describe specific indications for Islet Allo-Transplantation and recent evidence on outcomes.
- Discuss the limitations to islet Allo-Transplantation and the future directions of research
- Audience Discussion: questions asked by patients and families, how we address them and how we may wish to address them differently
Current T1D Control in the US

• Despite >20 years of knowledge of the importance of tight control, patients are still poorly controlled.
  – Evidence from the Type 1 Diabetes Exchange Registry from 2015.
  – Average A1c by age group is too high at all ages and much too high in adolescents.

Islet Transplantation: Definition

• Transplantation of the pancreatic islets to **treat** or **prevent** diabetes mellitus

• Performed for:
  – Labile type 1 diabetes mellitus ("treat")
  – Prevention of surgical diabetes when pancreas is removed to treat pancreatitis ("prevent")

Islet Transplants for Pancreatic Disease

• Autologous islet transplantation (TP-IAT):
  – Patient’s own islets, for treatment of pancreatitis
  – No risk of rejection
  – No immunosuppression
  – An excellent research model for both forms of islet tx!

• Allogenic islet transplantation:
  – Cadaveric donor islets, for treatment of Type 1 DM
  – Risk of rejection and autoimmunity (from T1D)
  – Requires immunosuppression
  – Performed under a FDA IND (for the islet product) in U.S.

• Xenogenic islet transplantation:
  – Use of non-human (e.g. porcine) islets as a source
  – Essentially pre-clinical only and has more issues than allogenic transplant
Background: TPIAT with Auto Transplantation

• Total Pancreatectomy (TP) is successful for improving pain and quality of life.

• Islet auto-transplantation (IAT) may prevent or minimize diabetes.

Background: Islet Engraftment from Auto Transplantation

• After transplant, islets are at high risk for loss.
  – Hyperglycemia causes islet overstimulation in a post-transplant anoxic environment.

• Animal models have demonstrated that hyperglycemia increases beta-cell apoptosis.\(^{14-19}\)
  – Maintenance of narrow-range euglycemia reduces the islets necessary to prevent post-surgical diabetes.
  – Retrospective cohort analysis from UMN supports these findings in humans.

Auto Transplantation Success

• These results from UMN show that long-term insulin independence can occur in \(\sim 25\%\) of patients.
• Insulin dependence can occur in \(\sim 25\%\) of patients.
• Over 50\% of patients have “minimal insulin use”
Auto Transplantation Success

- Larger cohort from UMN of adults and children.
- Shows that over time the rate of insulin independence rises up to 2 years post transplant.
- Also shows that the rate of partial function falls with time.
  - As does insulin independence after 2 years.

Improved Success with use of AP?

- Better BG control after transplant with use of AP.
- In the CL group AP use allowed for significant islet cell rest and thus a lack of variation based on islet cell yield.
- In the control group, islets were not rested and thus avg BG varied with islet yield.

Differences between Auto and Allo Transplant

- Makes Success Less Likely (auto vs. allo)
  - Auto islets are likely to be damaged from the underlying disease state (chronic pancreatitis).
  - Auto islets are less purified making portal infusion more challenging.
  - Allo islets may come from multiple donor sources to increase their number.
- Makes Success More Likely (auto vs. allo)
  - Auto islets undergo less cold ischemia time.
  - Auto islets are less purified and thus may have more islet stem cell mass.
  - Auto islets don’t require immune suppression and patients don’t have underlying auto immunity.
Indications for Islet Allo-Transplantation

- Islet Allo-Transplantation is still under FDA phase 3 clinical trials.
- FDA Recommended Inclusion Criteria:
  - Established T1D for at least 5 years
  - Severe metabolic instability with multiple episodes of severe hypoglycemia, often with hypoglycemia unawareness.
  - Instability has persisted for at least 6 months with intensive management from a qualified diabetes team.
  - Adults (18+ years old).
- FDA Recommended Exclusion Criteria:
  - Subjects with extremes of BMI
  - Subjects with high baseline insulin requirements (>1 U/kg/day)
  - Subjects with complications of chronic hyperglycemia.
  - HbA1c >12%
  - Conditions which place them at risk from immune suppression.

What does an islet allo transplant involve?

- Detailed pre-transplant evaluation
- Eligible participants listed with UNOS (waitlist time ~1y)
- Hospitalized x 5 days
- Minor surgery: percutaneous or minilaparotomy
- Immunosuppression & infection prophylaxis
  - ATG, tacrolimus, and sirolimus/ MMF
- Insulin weaned off gradually after transplant
- Cost is ~$75,000 just for the islets!

Edmonton Protocol

- Published in 2000 (NEJM), it shifted the focus to glucocorticoid-free immunosuppression.
  - Instituted immunosuppression immediately before transplantation with sirolimus (T-cell inhibitor), low-dose tacrolimus (inhibits T-cell activation), daclizumab (IL-2 inhibitor) and avoidance of glucocorticoids.
- Showed that 100% (7 of 7) of allo-islet transplant patients achieved insulin independence.
- Used multiple (2-4) donors to increase islet mass to >5,000 IEQ/kg.
Edmonton Protocol Follow Up Data

- At 2 years post transplant the overall rate of insulin independence is ~30%.
  - Though more recent data puts the rate at almost 50%.
- Rates of insulin independence continue to decline out to 8 years post-transplant.
  - Most (>70%) of patients are still C-Peptide positive with hypoglycemia protection.

Wider Scale Transplantation

- Clinical trials at multiple sites using the Edmonton protocol has been tested via the Immune Tolerance Network.
- Found that there was significant variation in success between sites.
  - Likely due to site-specific experience with islet preparation and possibly dosing of sirolimus.

- Studies have reported improved success with larger islet masses (>11,000 IEQ/kg) over multiple infusions.
  - This limits the total number of potential recipients.
- Exposure to islets from multiple recipients results in sensitization to more HLA antigens.
  - Argument for single donor over multiple pooled donors.
Success is Improving

- Better successes in each era studied.
- Collaborative Islet Transplant Registry (CITR) data from 1999-2010

Improved Immunosuppressive Protocol

- Corticosteroids are incredibly islet-toxic. Their removal in the Edmonton Protocol revolutionized islet transplantation.
- Sirolimus and tacrolimus have been used instead, though they are also somewhat islet-toxic.
- Mycophenolate mofeti has been shown to be less islet-toxic.

Improved Immunosuppressive Protocol

- Bellin, et al. showed the benefit of alternative immunosuppression in single donor allo transplants:
  - Induction with antithymocyte globulin (ATG) plus etanercept (TNF-alpha blocker).
  - Maintenance with cyclosporine and everolimus or mycophenolate mofeti.
  - Found that 5 of 6 recipients with T1D were insulin-independent at 1 year post transplant and 4 were insulin independent at >3 years post-transplant.
- The addition of exenatide and etanercept to the Edmonton protocol has also improved outcomes.
New Immunosuppressive Agents

- Abatacept and belatacept (block T-cell interaction with CD80/CD86) have shown early promise to improve single donor outcomes when combined with ATG.

Future Research: Site Selection

- Islets are traditionally infused into the portal vein to engraft in liver sinusoids.
- Benefits of this site include
  - relative ease of access,
  - good oxygenation and blood flow,
  - physiologic sensing and insulin diffusion environment.
- Drawbacks include
  - instant blood mediated inflammatory reaction after transplant with cell loss,
  - high concentration of immunosuppressive agents due to first pass metabolism,
  - loss of counter regulation compared alternative sites,
  - difficulty in obtaining tissue to assess rejection

- Placement in the an omental pouch shows promise in animal models to provide a rich blood supply with limited IBMIR.
- Other commonly proposed sites include skeletal muscle and the kidney capsule.
Islet Encapsulation

- The concept of providing a secure oxygen and nutrient-rich environment for islets while affording a degree of immune isolation.
  - Idea dates back to 1977.
- This concept is gaining widespread public awareness.
- Patients often ask about this at clinic visits and occasionally during our "new onset" talks.

Macroencapsulation

- Macrocapsules contain a large number of islets within the device.
  - Device may be intravascular or extravascular.
  - Intravascular devices associated with clotting and embolization.
- Most popular design has been a planar device with two composite membranes and a loading port.

Macroencapsulation

- Original planar device the TheraCyte Implant showed promise in the late 1990’s and early 2000’s in pig and monkey models.
  - Original Patent has lapsed.
- New focus on use of a planar macroencapsulation device for use with human embryonic stem cell-derived islets.
  - The macroencapsulation protects the body against possible teratomas formed from the stem cells.
  - Device is also easily retrievable.
Macroencapsulation

- ViaCyte is a commercialization effort of embryonic stem cells and planar macroencapsulation technology.
  - It has received a lot of coverage in the non-medical literature and is a frequent source of questions for me from families.
- Mouse model study of success of function of human embryonic stem cells in macroencapsulation device.

- Pre-clinical trial results showed success reversing hyperglycemia in small animal models.
- ViaCyte has begun Phase 1 clinical trials as of August 2014.
  - [https://clinicaltrials.gov/ct2/show/NCT02239354](https://clinicaltrials.gov/ct2/show/NCT02239354)
  - Current sites are UC San Diego and University of Alberta.
  - Enrolling patients 18-55 years old with T1D for 3+ years
  - Single arm, open label, non-randomized trial with an estimated enrollment of 40 patients and an outcome assessment of August 2017.

Other Encapsulation Trials
Islet Transplantation: What is Success?

- Traditionally defined as insulin independence.
  - Major current indication for experimental allotransplant, however, is hypoglycemia unawareness.
  - Should improvement in severe hypoglycemic events be the measure?

- Many patients achieve what I call chronic honeymoon state whereby they require some small amounts of insulin but control is better (and easier) than prior to transplant.
  - Should presence of C-peptide be the measure?

Islet Transplantation: Discussion

- What questions do your patients ask?
- How do you respond?
  - How may you respond differently after the information discussed today?
- How do you balance providing hope with tempering expectations?
- How broadly would you define “cure?”
- How would you discuss the risks and benefits of islet transplantation?
- At what cost point would you say it would be widely accessible?