Clinical Islet Transplantation
Islet transplantation

Thierry Berney, Geneva, Switzerland
Subject with TID

Glucose - mmol/L

Time Of Day

Click sensor plot line to read data value
Subject with T1D: 5 years after islet transplantation

Sensor Modal Day

MiniMed Solutions: CGMS Sensor
MMT-7310 3.0A

Glucose - mmol/L

<table>
<thead>
<tr>
<th>Time Of Day</th>
<th>Sunday</th>
<th>Tuesday</th>
<th>Thursday</th>
<th>Saturday</th>
</tr>
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<tbody>
<tr>
<td>03:00</td>
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<tr>
<td>06:00</td>
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<td>09:00</td>
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<td>12:00</td>
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<td>18:00</td>
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<tr>
<td>21:00</td>
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</tbody>
</table>

Legend

- Sunday
- Tuesday
- Thursday
- Saturday
- Monday
- Wednesday
- Friday

Report Printed: 05/09 2008 12:07
This problem has not abated over the 15 years since it was highlighted by the report of the DCCT in the NEJM in 1993

Iatrogenic hypoglycemia continues to cause recurrent physical and psychosocial morbidity (incl. coma, seizures, and significant social embarrassment)

7% to 10% of deaths of people with T1D are the result of hypoglycemia

(Feltbower RG et al., 2008; Skrivarhaug T et al., Diabetologia 2006)
ASSOCIATION BETWEEN SEVERE HYPOGLYCEMIA AND MOST RECENT HbA1c: INTENSIVE THERAPY

COMBINED COHORT

Rates per 100 Person Years at Risk

HbA1c

<6.5   6.5-7.0   7.0-7.5   7.5-8.0   8.0-8.5   8.5-9.0   9.0+

0     20     40     60     80
Clinical Islet Transplantation Consortium

Current Status and Future Directions
Islet Mfg Sites and Clinical Centers

- U. of Miami
- U. of Illinois-Chicago
- U. of Minnesota
- Northwestern Univ.
- UC San Francisco
- U. of Pennsylvania
- Emory Univ.
- Massachusetts General Hospital
- U. of Wisconsin
- U. of Alberta-Edmonton
- Uppsala Univ.
  - Karolinska Univ – Stockholm*
  - Oslo Univ.*

*clinical centers only
CIT Clinical Trials

- Phase III licensure trials of human islets
  - Islet Transplant Alone (CIT-07)
  - Islet After Kidney Transplant (CIT-06)
- Five additional Phase II trials (CIT-01 to -05)
- Long-term follow-up study (CIT-08)
CIT-07 (Islet Alone Licensure Study)

ISLET TRANSPLANTATION IN SUBJECTS W/ TYPE 1 DIABETES
CIT-07 Study Population

- Age 18 to 65 yrs
- Type 1 diabetes for $\geq 5$ years
- Absent ($<0.3$ng/ml) stimulated C-peptide
- $\geq 1$ episode of severe hypoglycemia in previous yr
  AND
  documented reduced awareness of hypoglycemia and/or marked glycemic lability
- 32 exclusion criteria (e.g., BMI$>30$; GFR$<80$, pos PRA)
CIT-07: Study Design

- Prospective, single-arm, multi-center Phase III study testing human islets in T1D
- Subjects will receive up to 3 separate infusions of islets within 8 months
- Accrual objective: 48 transplanted subjects followed for at least 24 months
- Primary endpoint at 1 year after initial transplant
Subjects will receive up to 3 separate infusions of islets

Basiliximab instead of ATG for 2nd and 3rd transplants
CIT-07: Primary Endpoint

- Proportion of subjects with HbA1c < 7.0% at day 365 and free of severe hypoglycemic events from Day 28 to Day 365 inclusive following the first islet transplant

- Multiple secondary endpoints for safety and efficacy
Because study results have not been published yet, no primary outcome measure or any of its components will be presented.

In particular,
- HbA1c is not reported
- The rate of occurrence of severe hypoglycemic events after the initial transplant is not reported.
CIT-07 Enrollment

- All subjects have completed follow-up in CIT-07 and many have enrolled in a long-term follow-up study within the CIT consortium.
- Out of 48 subjects, 26 received a second transplant. 1 subject received 3 transplants.
- Awaiting primary endpoint publication.
Islet Dose

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (N=48)</th>
<th>Subjects with 1 Txp only (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IEQ</td>
<td>IEQ/Kg*</td>
</tr>
<tr>
<td>Mean</td>
<td>806,587</td>
<td>11,476</td>
</tr>
<tr>
<td>St. Dev.</td>
<td>290,340</td>
<td>4,023</td>
</tr>
<tr>
<td>Minimum</td>
<td>286,566</td>
<td>5,233</td>
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<tr>
<td>Maximum</td>
<td>1,562,774</td>
<td>25,553</td>
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</tbody>
</table>

* Weight of recipient

Approximately 50% of initiated isolations were ultimately released for transplant
DEFINITION OF INSULIN INDEPENDENCE:

- No insulin usage in last week
- AND
- HbA1c < 7.0% or ≥ 2.5% decrease from baseline
- Fasting capillary glucose ≥ 140 mg/dL no more than 3 times in past week
- Post-prandial glucose ≤ 180 mg/dL at 90 minutes during MMTT
- Fasting serum glucose ≤ 126 mg/dL (confirmed)
- At least one MMTT (fasting or stimulated) C-peptide ≥ 0.5 ng/mL
Insulin Use and C-Peptide Levels (CIT-07)
Insulin Independence: CIT-07

- Baseline
- Day 75
- Day 365
- Day 730

Time Point

Insulin Independent (%)

0 20 40 60 80 100

Chart showing the progression of insulin independence over time.
Glycemic Lability Index: CIT-07
Hypoglycemia (Hypo) Score: CIT-07
Quality of Life: Diabetes Distress Scale
Quality of Life: Hypoglycemia Fear Scale
CIT-07 (Islet Alone Licensure Study)

SAFETY PROFILE
Serious Adverse Events

- Y1 of follow-up: 21/48 subjects experienced 30 SAEs
- Y2 of follow-up: 7/45 subjects experienced 8 SAEs
- No SAE resulted in death, disability or permanent sequelae, and none required expedited reporting to the FDA
Serious Adverse Events: CIT-07

- The Y1 SAEs were attributed to:
  - the transplant procedure and/or immunosuppression (n = 25/30); the rest non-study causes.

- The Y2 SAEs were attributed to:
  - Immunosuppression (n = 2/8); the rest non-study causes.
Renal Function: CIT-07

- Renal function was monitored closely due to potential nephrotoxicity from IS
- Average GFR at study entrance was 102 mL/min (range: 79 – 130 mL/min)
- Small but non-significant drops in GFR at Day 75 (98 mL/min) and Day 365 (93 mL/min).
1 patient (GFR of 82 ml/min at study entry) developed acute kidney injury of unclear etiology after Txp with a fall in GFR to 31 mL/min at day 75.

By day 365 he had substantial recovery with an GFR of 63 ml/min.
Development of Alloantibody: CIT-07

- Development of anti-HLA antibody was an additional safety outcome. Presence or history of panel-reactive anti-HLA antibodies was a study exclusion criterion.
- At two years, 6 patients had developed non-zero cPRAs of 2, 14, 29, 64, 74, and 98%; only the last two subjects had DSA.
Comments on Adverse Experiences

- Preliminary data suggests a favorable safety profile
- No deaths, protocol-related malignancies, or opportunistic infections
- Very few serious adverse events observed – all resolved w/o sequelae
- Non-serious adverse events mostly transient and related to immunosuppression
Preliminary Conclusions: CIT-07

- Islet products meeting all release criteria can be prepared at multiple manufacturing centers using a standardized protocol.
- Subjects enrolled in CIT-07 experienced substantially reduced insulin use and glycemic lability post-transplant.
- To date, the CIT-07 protocol shows a favorable safety profile.
Thank you!

- NIH Program Officers, Medical Monitors, Regulatory Experts, and Project Managers
- CTSDMC (DCC) Staff at Univ. of Iowa (Biostatisticians, Protocol Coordinators, etc.)
- Manufacturing and Clinical Centers (Investigators, RNs, Islet Isolation and QC Staff, Data Entry Staff, etc.)

More information available at: www.clinicaltrials.gov and www.citisletstudy.org
The future

“next 1-2 years”
The ‘β-Air’ Device – The O₂ Refueling Process

Oxygen Tank

Cross-section of the implantable device

The Implantable BAP Subunit

The Injectable Subunit

Injectable Subunit

Skin

Subcutis

External O₂ refueling (every 24 hours)
Daily averages of non-fasting blood glucose of 18 isogeneic and 7 allogeneic diabetic rats were adjusted to near normal levels following implantation of the devices and returned to the disease state after their removal.
Clinical islet encapsulation

Screening to determine eligibility

Primary endpoint
No adverse or serious adverse effects after device implantation

- MRI, CGM, MMTT, IVGTT, QoL, DTSQ
- 5-HTP PET/CT

Explantation: IHC (inflammation, fibrosis, islet survival, retrieval of islets for in vitro functional assays.)

Wait to implant

Device implantation

Insulin titration phase (Fasting P-glucose <6.0 mmol/L)

Daily oxygen refueling exogenous insulin according to metabolic needs

Days
0 90 180 210 360

Observation point

Observation point
Reversal of diabetes with insulin-producing cells derived \textit{in vitro} from human pluripotent stem cells

Alireza Rezania$^1$, Jennifer E Bruin$^2$, Payal Arora$^1$, Allison Rubin$^1$, Irina Batushansky$^1$, Ali Asadi$^2$, Shannon O’Dwyer$^2$, Nina Quiskamp$^2$, Majid Mojibian$^2$, Tobias Albrecht$^2$, Yu Hsuan Carol Yang$^2$, James D Johnson$^{2,3}$ & Timothy J Kieffer$^{2,3}$

Generation of Functional Human Pancreatic $\beta$ Cells In Vitro

Felicia W. Pagliuca$^{1,3}$, Jeffrey R. Millman$^{1,3}$, Mads Gürtler$^{1,3}$, Michael Segel$^1$, Alana Van Dervort$^1$, Jennifer Hyoe Ryu$^1$, Quinn P. Peterson$^1$, Dale Greiner$^2$, and Douglas A. Melton$^1$,*

$^1$Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138, USA
$^2$Diabetes Center of Excellence, University of Massachusetts Medical School, 368 Plantation Street, AS7-2051, Worcester, MA 01605, USA
$^3$Co-first author
*Correspondence: dmelton@harvard.edu
http://dx.doi.org/10.1016/j.cell.2014.09.040
Clusters of human embryonic stem cells that express a green fluorescent protein, under the regulation of the transcription factor NANOG.
“Roadmap” to clinical application using insulin producing cells generated from hESC. A collaborative study with Prof Henrik Semb

Encapsulation of human islets “establishment of the encapsulation device”

Creation of a master cell bank

Functional characterization

Regulatory approval hESC -> insulin producing cells

Clinical study with encapsulated hESC derived insulin producing cells (safety)

Clinical study with encapsulated hESC derived insulin producing cells (efficacy)

Clinical study with non-encapsulated hESC derived insulin producing cells in subjects with systemic immunosuppression (efficacy)
The Nordic Network for Clinical Islet Transplantation
All national and international colleagues and friends
UU, UAS, VR, JDRF & NIH