THE UNIVERSITY OF CHICAGO MEDICINE

Durable effect of beta cell replacement therapy on improvement in blood glucose control and prevention of progression of secondary diabetic complications in nonuremic patients with type 1 diabetes mellitus and problematic hypoglycemia

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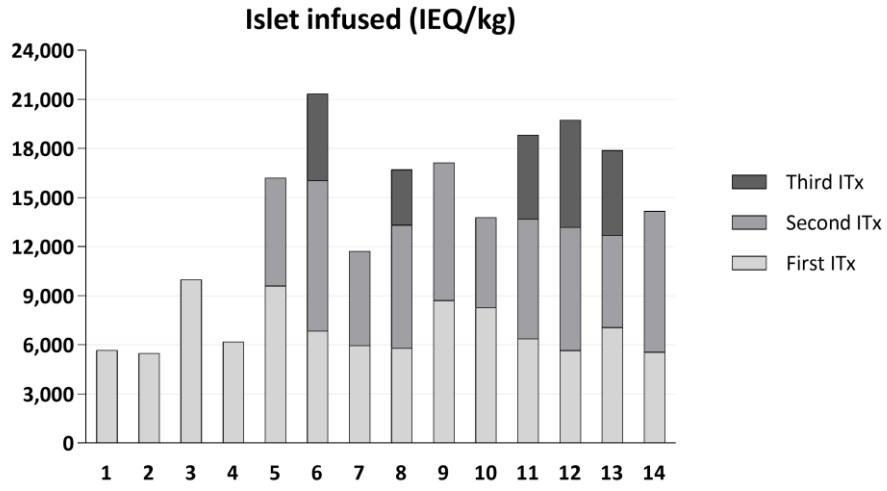
Introduction

- Beta cell replacement therapy in the form of **pancreas** or **islet transplantation** is the only effective treatment for patients with type 1 diabetes mellitus (T1DM) and life-threatening severe hypoglycemic episodes despite intensive insulin treatment.
- Transplantation provides beta cell mass and endogenous insulin secretion with counter-regulation for the optimal blood glucose control.

Methods

- 14 consecutive nonuremic patients with "brittle" T1DM received 30 islet transplants (up to 3 islet infusions) (Figure and Table)
- 4 of them subsequently received pancreas transplant to extend benefit of beta cell replacement and insulin independence (1 SPK, 3 PA).
- Thymoglobulin was used during first islet transplant and basiliximab prior to subsequent islet and pancreas transplants for induction, whereas tacrolimus and mycophenolate for steroid free maintenance immunosuppression.
- Patients received Reparixin (CXCR1/2 blocker), etarnecept or no anti-inflammatory therapy in peritransplant period.

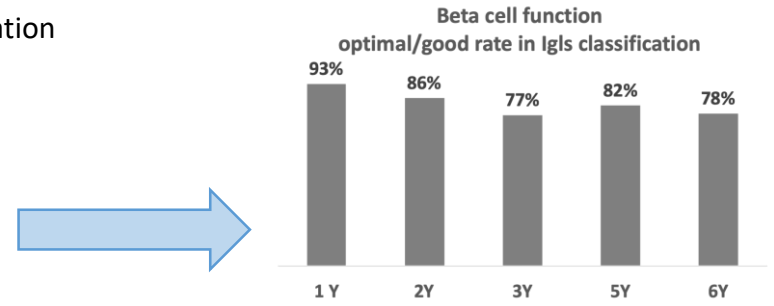


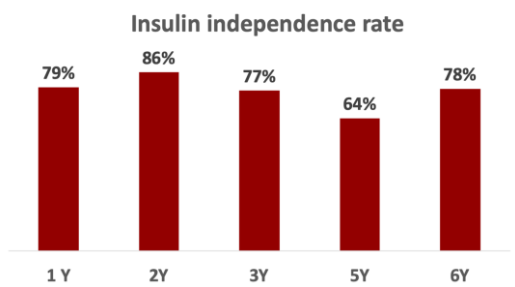
Recipient Characteristics	N = 14
Age at 1st ITx (years)	**43** (28 – 56)
Sex (M/F)	**7M/7F**
Weight at 1st ITx (kg)	**72.1** (42.6 – 93.8)
BMI at 1st ITx (kg/m^2)	**24.3** (18.9 – 29.9)
Pre ITx HbA1c (%)	**7.3** (6.6 – 8.8)
Pre ITx daily insulin	**35.28** (19.74 – 68)
Number of SHEs (last 6 months before 1st ITx)	**11** (3 – 100)
Duration of T1DM (years)	**32** (15 – 47)
Donor Characteristics	**N = 39 donors (30 ITx)**
Age (years)	**43** (17 – 63)
Sex (M/F)	**29M/10F**
Weight (kg)	**99.8** (59 – 179.6)
BMI (kg/m^2)	**32.5** (23.8 – 50.8)
Donor Scoring (NAIDS)	**77** (30 – 100)

Results

❑ **Table.** The IgIs classification of beta-cell graft function after islet allotransplantation

Functional status	HbA1c (%)	Severe Hypo Events (SH)	Insulin requirement (U/kg/d)	C-peptide	Treatment Success
Optimal	≤6.5	None	None	> 50% Baseline	Yes
Good	<7.0	None	<50% Baseline	> 50% Baseline	Yes
Marginal	Baseline	< Baseline	> 50% Baseline	> 50% Baseline	No
Failure	Baseline	Baseline	Baseline	Baseline	No





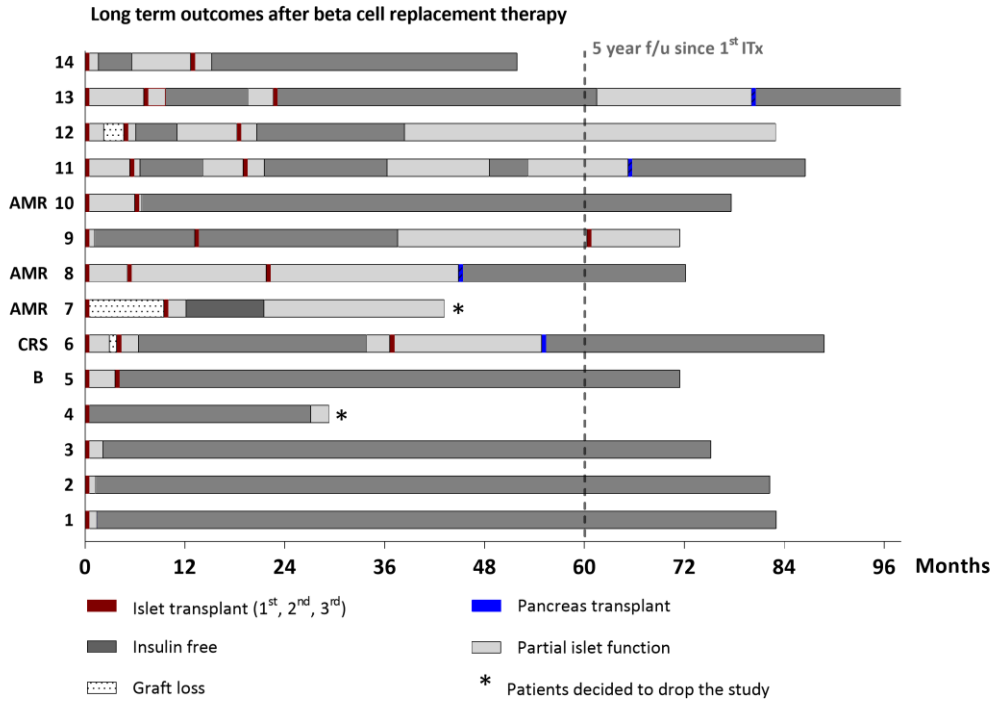
❑ 2 patients dropped the study 2 and 3 years after 1 and 2 islet transplants respectively, with a subsequent islet graft failure.

❑ None of the remaining patients experienced recurrence of severe hypoglycemic episodes during the follow up.

❑ 3 patients developed donor specific antibodies (DSAs) with antibody mediated rejection (AMR), one severe cytokine release syndrome (CRS) and one bleeding (B). All of them were treated with Plasmapheresis and IVIG allowing for PRA decrease below <20% and for a subsequent successful islet and pancreas transplantation.

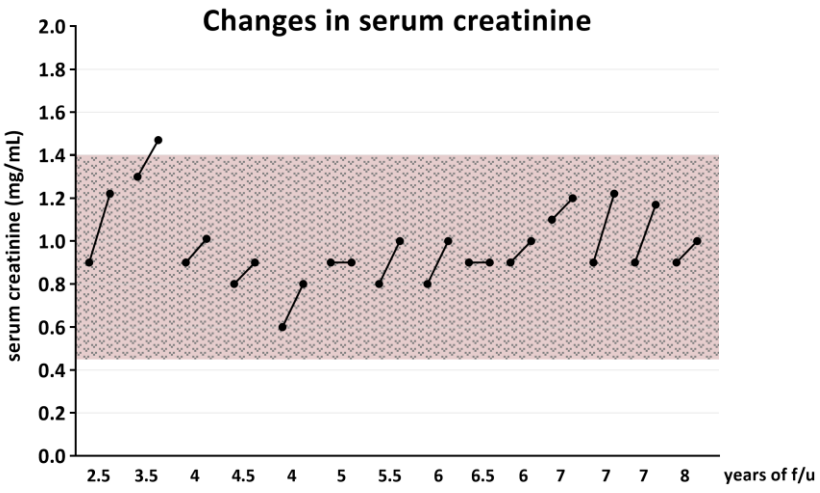
❑ 1 patient (# 5) died due to lung cancer with fully functional graft and insulin independence for 5 and half years after two islet transplantations.

❑ 4 patients after 3 islet transplantations eventually received a subsequent pancreas Tx 4.5 years (3.5-6.5) later increasing insulin independence rate to 64% (7/11) at 5 year and 78% (7/9) at 6 year follow up.



Results cont.

- Secondary diabetic complications such as the diabetic neuropathy remained stable in 12/14 (86%). Retinopathy improved in 4/14 patients (29%).
- None of the patients experienced any of the cardiovascular events.
- Kidney function remained stable during up to 7 years follow up. Changes in serum creatinine is represented by "before (1st ITx) – after (current follow-up)" line graph for each patient separately. None of the patient developed macroalbuminuria.
- One patient with a baseline creatinine of 1.3 mg/dL and microalbuminuria who required pancreas transplantation received simultaneous kidney allograft due to increased creatinine oscillating below 2 mg/dL.



Patient #	F/U years	Time off insulin	Neuropathy	Diabetic Retinopathy
14	4	3 years	Worsen	Stable (no DR)
13	8	5.5 years	Stable	Stable (no DR)
12	6.5	2 years	Worsen	Stable (quiescent PDR)
11	7	4 years	Stable	Stable (quiescent PDR)
10	6	5.5 years	Stable	Stable (no DR)
9	5.5	3 years	Stable	Improved (mild NPDR--- None)
8	5.5	2 years	Improved	Worsened within last year when A1c, quiescent PDR –active OS
7	3.5	9 months	Stable	Improved (from PDR to quiescent)
6	7	5 years	Stable	Stable (mild NPDR)
5	6	5.5 years	Stable	Stable (no DR)
4	2.5	2 years	Stable	Stable (no DR)
3	6	5.5 years	Stable	Stable (no DR)
2	6.5	6.5 years	Stable	Improved (mild NPDR--- No DR)
1	6.5	6.5 years	Stable	Improved (moderate—mild NPDR)

DR – diabetic retinopathy, PDR – proliferative diabetic retinopathy, NPDR – nonproliferative diabetic retinopathy

Conclusions

- Beta cell replacement therapy in form of islet and subsequent pancreas transplantation has proven its long term efficacy in restoring optimal glucose control and hypoglycemic awareness without progression of secondary diabetic complications.