NOVEL MANAGEMENT OF DIABETIC NEPHROPATHY WITH CHRONIC RENAL FAILURE IN TYPE-2 DIABETES MELLITUS BY LIVING DONOR RENAL TRANSPLANTATION USING PRE-TRANSPLANT INSULIN-SECRETING CELLS WITH STEM CELL THERAPY AND REGULATORY T-CELL THERAPY POSTTRANSPLANT

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INTRODUCTION

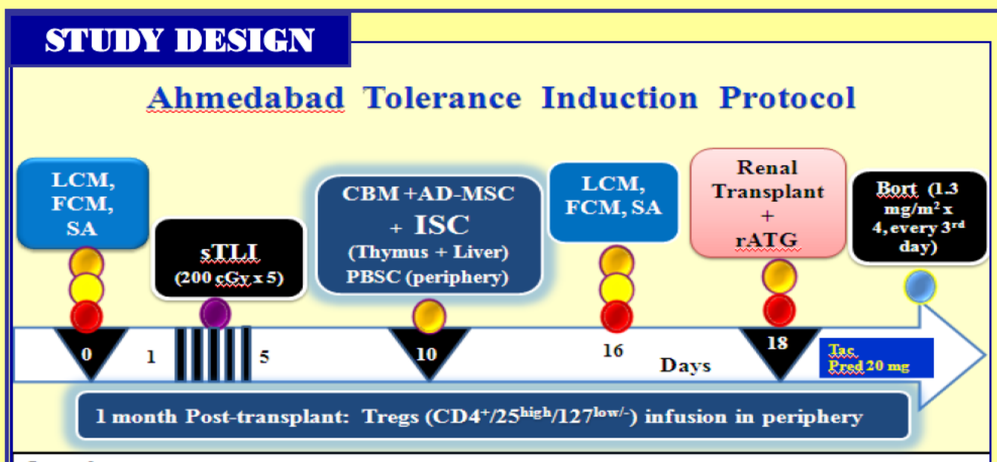
- Type-2 DM (T2DM) is a metabolic disorder leading to diabetic nephropathy (DN) responsible for ≈ 35% chronic renal failure (CRF) on waiting list of renal transplantation (RT).
- RT although well accepted, requires life-long immunosuppression (IS) mandatory to prevent allograft rejection exposing the patients to high risk of recurrence of DM, toxicity, infections and malignancy.
- Stem cell therapy (SCT) holds promise of minimizing IS, diabetogenicity and immune injuries.

OBJECTIVE:

We present early experience of pre-transplant SCT with insulin-secreting cells (ISC) and post-transplant T-regulatory cell (Treg) therapy in T2DM patients with DN-CRF subjected to living donor RT (LDRT).

MATERIAL AND METHODS

STUDY DESIGN



Legends:
LCM : Lymphocytotoxicity cross-match
SA : Single antigen
r-ATG : rabbit Anti-thymocyte globulin (1.5 mg/ kg BW)
CBM : Cultured donor bone marrow
AD-MSC : (Donor) adipose tissue derived mesenchymal stem cells
PBSC : Donor-derived peripheral blood stem cell infusion
FCM : Flow cross-match
Bort : Bortezomib
sTLI : Sub total lymphoid irradiation
ISC : Insulin secreting cells

IRB Approved

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Established T2DM with DN - CRF • Age > 40 Years	•HIV/HBsAg/ HCV Reactive patients

PATIENT DETAILS

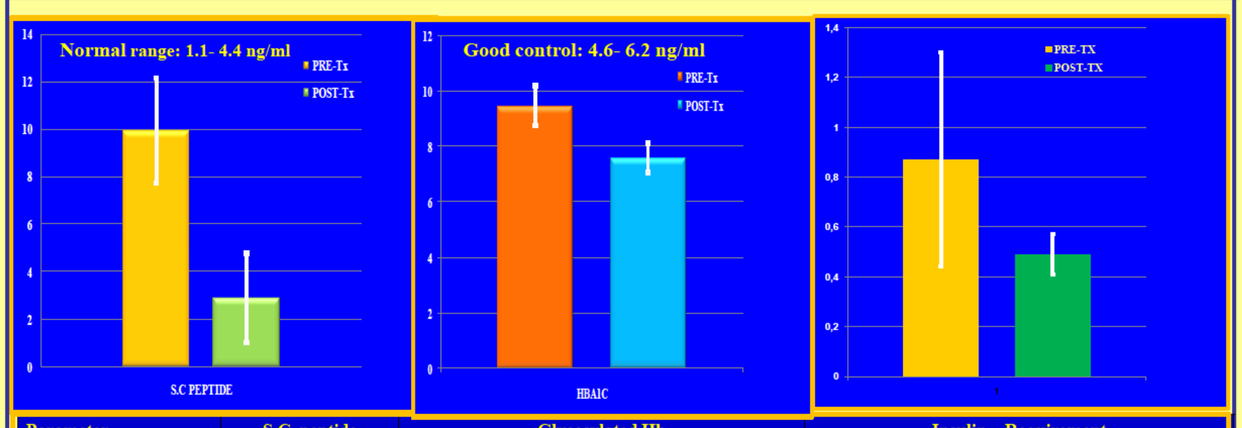
Single armed open labeled prospective study
N=7
Mean age: 44.4 6.5 years
Sex : M = 7, F = 0
Duration of T2DM: 12.4 2.15 years
Donors: Wife-5, Brother-1, Mother-1 Mean age: 44 8.2 years
Mean HLA match: 2.3 1.25

CELL INFUSION DETAILS (Mean number of cells / Kg BW)

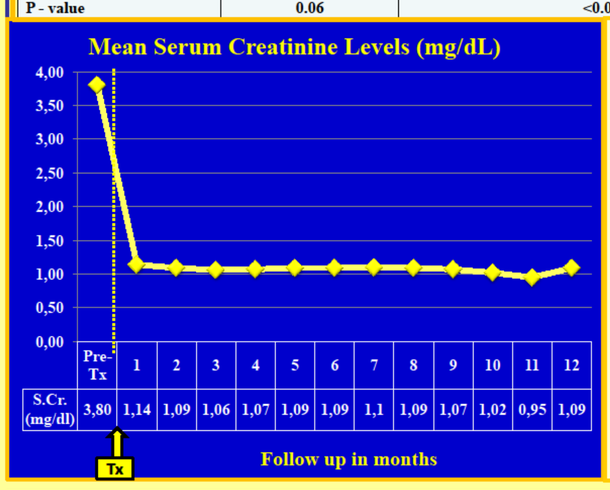
HSC (CD34+)	0.8 0.75 X 10^6
AD-MSC (CD45-90+ 73+)	1.47 1.24 X 10^4
Insulin Secreting Cells	1.73 0.99 X 10^4
Tregs ($CD4^+/25^{high}/127^{low/-}$)	55.13 82.96 X 10^4

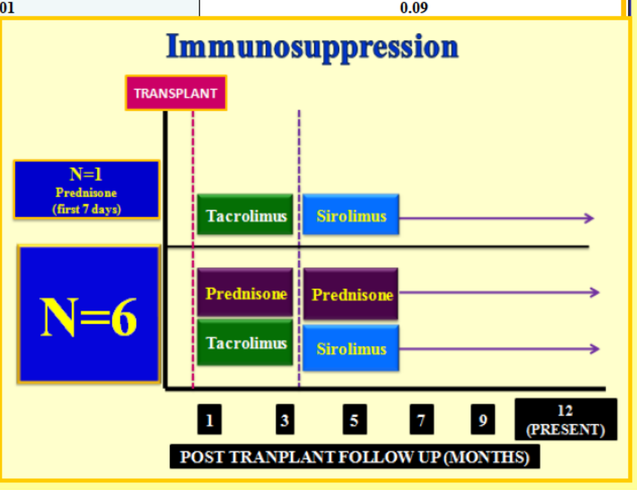
No adverse effects

EFFECT OF SCT INCLUDING ISC AND Tregs ON GLYCEMIC CONTROL AND GRAFT FUNCTION STATUS AFTER RENAL TRANSPLANTATION



Parameter	S.C. peptide (ng/ml)	Glycosylated Hb (HbA1C) %	Insulin Requirement (IU /kg/day)
Before transplantation	9.96 2.21	9.46 0.72	0.43
1 year post-transplantation	2.87 1.89	7.1 0.86	0.08
P - value	0.06	<0.01	0.09





DISCUSSION

Review of RT in DM-CRF patients

Study	Patients	Immunosuppression	Patient Survival	Graft Survival
Boucek P et al, NDT, 2002, 17 (9): 1678-1683.(1)	64	CsA, Aza, Pred	1yr- 85% 5 yr- 74%	1 yr- 84% 5 yr- 77%
Bittar J, et al. Transplant Proc. 2006, 38(3):895-8.(2)	35	CsA/Tac, MMF, Pred	5 yr- 90.5%	1yr- 82.7% 5 yr- 63%
Veroux M, et al, Urol Int. 2010;84(3): 301-4.(3)	24	13- Tac, Siro, Pred 11-Siro, MMF, Pred	100% at 29 months	100% at 29 months
Kute VB et al, Int Urol Nephrol. 2012;44(1):269-74.(4)	35	CsA/Tac, MMF/ Aza, Pred	2.3 yrs- 68.5%	2.3 yrs-88.5%

- No report on use of SCT with RT in DN-CRF patients is available.
- We generated ISC in vitro and then we treated 11 IDDM patients with IS-AD-MSC+CBM successfully. (5) Over mean follow-up of 23 months, they had a decreased mean exogenous insulin requirement to approx. 50% , fall in HbA1c and raised S.c-peptide levels from 0.1 to 0.38 ng/mL, and became free of diabetic ketoacidosis.(6)
- T2DM is an autoimmune disease, hence we used stem cell therapy.(7)
- Why T-regs?- Immunomodulators. (8)
- Why liver?- most tolerogenic organ.(9)
- Why infusion in thymus ?- for inducing central tolerance.(10)

CONCLUSIONS

- Thymic and portal co-infusion of donor AD-MSC, HSC, ISC pre- transplant and thymic infusion of T-regs post-transplant in T2DM with DN-CRF subjected to LDRT is safe.
- It offers graft protection from immune injury with acceptable glycemic control and normal renal allograft function.

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51ERA-EDTA 273--MP

N) Renal Transplantation. N1) Transplantation basic science and immune-tolerance of allogenic and xenogenic transplants.
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DOI: 10.3252/pso.eu.51era.2014

Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM 2014

PosterSessionOnline.com