Peri-operative Reparixin therapy resulted in 50% 5-year insulin independence rate: The University of Chicago Experience

Mateusz Ogledzinski[1], Piotr J. Bachul[1], Kourosh Rezania[2], Seenu M. Hariprasad[3], Sarah Gondek[1], William Lin[1], Braden Juengel[1], Kamila Milejczyk[1], Lindsay Basto[1], Ling-Jia Wang[1], Laurencia Perea[1], Martin Tibudan[1], Rolf Barth[1], John Fung[1], Piotr Witkowski[1]

[1] Transplantation Institute, Department of Surgery, University of Chicago, Chicago, IL, USA

[2] Department of Neurology, University of Chicago, Chicago, IL, USA

[3] Department of Ophthalmology and Visual Science, University of Chicago, Chicago, IL, USA

Corresponding author: Piotr Witkowski MD, PhD, pwitkowski@surgery.bsd.uchicago.edu

ORCIDs: Mateusz Ogledzinski - https://orcid.org/0000-0002-1500-793X, Piotr J. Bachul - https://orcid.org/0000-0002-7694-1793;; Kourosh Rezania - https://orcid.org/0000-0003-3986-5709; Seenu M. Hariprasad - https://orcid.org/0000-0003-0985-9551; Sarah Gondek https://orcid.org/0000-0003-0771-3217; Lindsay Basto - https://orcid.org/0000-0003-2168-2269, Braden Juengel - https://orcid.org/0000-0002-5673-9344; Ling-Jia Wang - https://orcid.org/0000-0003-4536-8805; Laurencia Perea - https://orcid.org/0000-0002-5936-8067; Martin Tibudan - https://orcid.org/0000-0002-7674-4634;; Rolf Barth - https://orcid.org/0000-0002-6770-5473; John Fung - https://orcid.org/0000-0002-3038-0441; Piotr Witkowski - https://orcid.org/0000-0002-4459-6673

Abbreviations: CXCR1/2 blocker- C-X-C Motif Chemokine Receptor 1/2, ITx - islet transplant, m-

TOR inhibitor- mammalian (mechanistic) target of rapamycin, T1DM - type 1 diabetes mellitus,

Abstract

We report that 50% of patients who received intraportal islet transplantation and peri-operative Reparixin in addition to the standard immunosuppressive therapy remained insulin-independent at 5 years. Diabetic end-organ complications did not progress in mean follow-up of 4.54± 2.89 years in eleven patients who achieved insulin independence at any time point during the follow-up.

Text

Here we report a 5-year follow-up study of the multicenter Reparixin trial involving 12 patients who provided the informed consent and underwent an islet cell transplantation at the University of Chicago between June 2013 and October 2015 (1,2). All patients received anti-thymocyte globulin for induction and tacrolimus and mycophenolate (sodium or mofetil) for maintenance immunosuppression. Patients in Reparixin group (N=8) also received a new leukocyte migration inhibitor (CXCR1/2 antagonist), Reparixin (Dompe Pharmaceutical, Italy) peri-operatively for eight days, while four other patients received placebo. Patient characteristics and transplant islet mass were comparable in both groups (1). Four of eight (50%) patients in the Reparixin group vs. 1/4 (25%) in placebo remained insulin independent at 5-year follow-up (p=0.58, Fischer exact test) (Figure 1A). Fifty percent 5-year insulin independence rate in Reparixin group is higher than those reported in multicenter trials and is comparable to those achieved in the most experienced individual centers (2-4). Our all insulin independent patients achieved also optimal functional outcome based on the Igls Classification and BETA-2 score: median 21.8 (20.8-27.8).

Eleven out of 12 (92%) patients achieved insulin-independence at some time point of the follow-up post-islet cell transplant. They all regained hypoglycemic awareness, experienced no severe hypoglycemic episodes and reported a significantly improved quality of life. Additionally, they showed

no progression of secondary diabetic complications. Diabetic retinopathy improved in two (17%) while it remained stable in nine (75%) patients (Figure 1B). Prior to islet cell transplant, most patients suffered from diabetic neuropathy: four polyneuropathies and three ulnar mononeuropathies in the baseline nerve conduction study (Figure C). Neuropathy remained stable in all 10 patients who had a conduction follow-up study, which is consistent with other reports (5).

As for renal function, despite being on potentially nephrotoxic immunosuppressive medication such as tacrolimus, serum creatinine remained stable (Figure 1D). Only one patient developed new micro-albuminuria but no macroalbuminuria. Similar results were reported in the crossover study, where the rise in serum creatinine was diminished during the post-transplant follow-up compared to prior to islet cell transplant (5). Nevertheless, nephrotoxicity is of concern in the long term, and there remains a need for an effective calcineurin inhibitor-free immunosuppression.

No *de novo* donor-specific antibodies were observed at a 5 year follow-up. No patients developed a post-transplant lymphoproliferative disease, recurring infections, or cardiovascular events. One patient with a 25-year history of heavy smoking developed a lung adenocarcinoma 4 years after the islet cell transplant . Her insulin independence persisted for over 5 years.

Small sample size is a main limitation of our study. The benefit of Reparixin over placebo was not confirmed in a multicenter study, however the variability of the immunosuppression protocols used in participating centers might have affected combined outcomes (2).

In summary, fifty percent of patients who received Reparixin maintained insulin independence beyond 5 years after the islet transplantation. Secondary diabetic complications did not progress once insulin independence was achieved. Our results confirmed long-term benefits of islet transplantation in patients with T1DM and problematic hypoglycemia.

Acknowledgments

We acknowledge support from the NIDDK P30 DK020595 and the Kovler Family Fund. We also acknowledge the generosity and support of the Gift of Hope Organ & Tissue Donor Network in Chicago as well as the New Jersey Sharing Network for providing the human pancreas tissues used in the study.

Disclosure

The study was supported by the Dompe´ Farmaceutici S.p.A.

The authors of this manuscript have no conflicts of interest to disclose as described by the Journal of Clinical Transplantation. PW served as a consultant for Dompe Farmaceutici S.p.A. in regards to another study involving liver transplantation.

Supporting Information

Supplementary Material is available on request

Figure Legend

Figure 1. Outcomes after ITx in the cohort of 12 patients.

Reparixin group: patients No. 1 thought No. 8, placebo group: patients No. 9 though No. 12.

A) Islet graft function over time. Dark green bar represents duration of insulin independence, light gray- partial islet graft function, dark gray- islet graft failure (no detectable serum c-peptide). Four (50%) patients from Reparixin group (No. 1, 2, 3, 5) and one from placebo group (No. 10) maintained insulin independence over 5 years after last ITx. Of note, single transplant was sufficient to achieve such outcome in three patients from reparixin group (No. 1,2,3), while two

subsequent ITx were required in a patient from placebo group (No. 10). Green triangle was used to mark the time point of ITx procedure.

Seven (58%) patients had left our long-term follow-up study with partial islet graft function (serum c-peptide > 0.5 ng/mL). Five (71%) of them proceeded with a supplemental intraportal islet transplant according to different protocols (->ITx). Subsequently, three patients received a pancreas transplantation (→ PTx) and continued to be insulin independent beyond 3 years. Two remaining subjects did not proceed with subsequent transplants due to social reasons (*). Their islet graft function gradually declined with deterioration of glucose control (HbA1c > 7.0 %), and recurrence of severe hypoglycemic episodes.

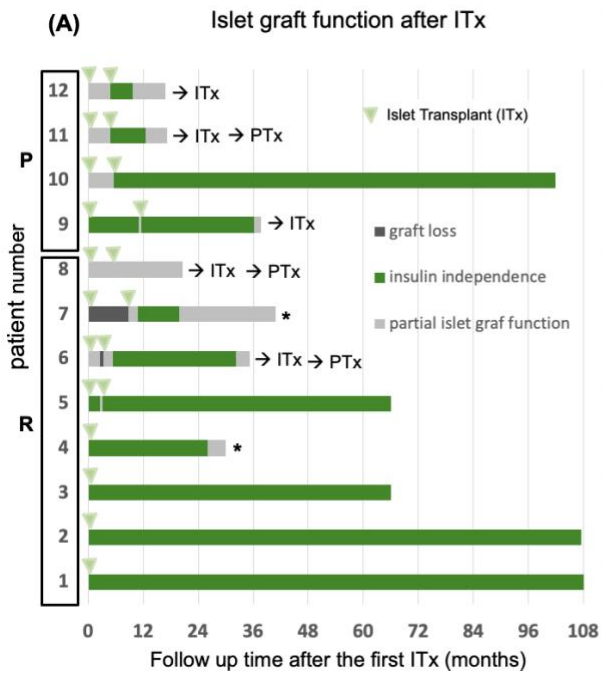
B) Status of retinopathy during the study. Diabetic Retinopathy (DR) improved in two (17%) patients (No. 1 and 2), worsened in one (No. 8) and remained stable in the rest of the patients (75%).

A dilated retina fundus examination was performed in each eye prior to first ITx and yearly afterwards by a fellowship trained retina specialist. Uncontrolled proliferative diabetic retinopathy precluded participation in this study. Diabetic retinopathy was assessed using the following scale: no diabetic retinopathy, non-proliferative diabetic retinopathy (mild, moderate, or severe), or proliferative diabetic retinopathy.

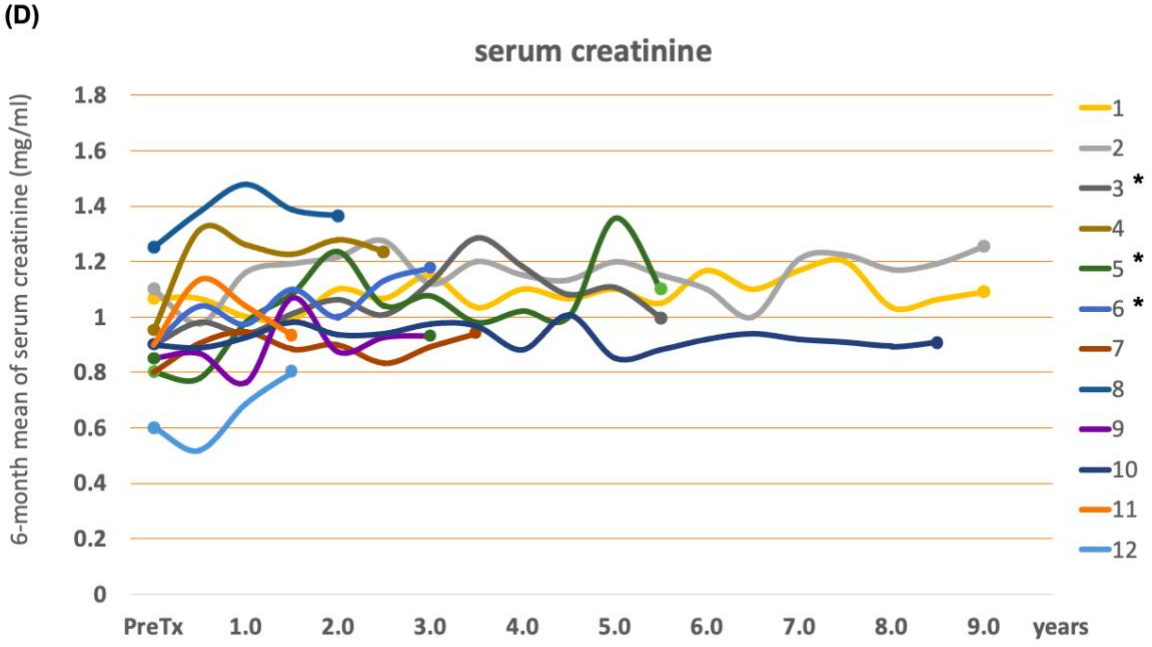
- no DR- no diabetic retinopathy.
- quiescent PDR- quiescent proliferative diabetic retinopathy;
- NPDR- nonproliferative diabetic retinopathy;
- LOF- loss of follow up

C) Status of neuropathy during the study. Neuropathy did not progress in 10 patients (83%), while remaining two subjects did not proceed with neurological evaluation after ITx (loss of follow-up, LOF). Neurological evaluation was based on clinical evidence for neuropathy, including calculation of Utah Neuropathy Scale;[11] and a limited nerve conduction study, which consisted of bilateral sural, right radial, and right ulnar sensory responses, right peroneal and ulnar motor responses, and F wave latencies. The neurological evaluation was done prior to first ITx and yearly afterwards.

D) Changes of renal function in individual patients during the follow after islet transplantation based on changes in serum creatinine. All serum creatinine measurements were aggregated for each patient into means from each 6-month period following the first islet transplant. Those means were connected with a line and are presented for each patient separately on the figure 1D. Based on Spearman`s rank correlation between pre-Tx and post- transplant subsequent 6-month means. Statistically significant elevation in serum creatine was observed in patient No. 3 (R=0.61, p=0.036), No. 5 (R=0.58, p=0.048) and No. 6 (R=0.82, p=0.023). Statistical difference in figure 1D was marked with *. However, the difference between preTx and last observed 6-month mean of the serum creatinine did not have clinical significance. PreTx vs. last post Tx observed 6-month mean of the serum creatinine for patient No. 3 was 0.9 vs 1.17mg/ml, for patient No. 5 0.8 vs 1.1mg/ml, for patient No. 6 0.9 vs 1.0mg/ml, respectively.



(B) EYE exam	(C) EMG study
Diabetic Retinopathy (DR) over the time	Neuropathy over the time
stable- quiescent PDR	stable- severe polyneuropathy
stable- no DR	stable- mild mononeuropathy
stable – no DR	stable- normal study
stable – no DR	normal study- loss of f/u
progression- quiescent to active PDR	stable- severe polyneuropathy
stable- PDR	mild polyneuropathy-loss of f/u
stable- NPDR	stable- normal study
stable – no DR	stable- mild mononeuropathy
stable – no DR	stable- normal study
stable – no DR	stable- normal study
Improved - mild NPDR to no DR	stable- mild polyneuropathy
Improved- moderate to mild NPDR	stable- mild mononeuropathy



References

1. Bachul PJ, Golab K, Basto L, et al. Post-Hoc Analysis of a Randomized, Double Blind, Prospective Study at the University of Chicago: Additional Standardizations of Trial Protocol are Needed to Evaluate the Effect of a CXCR1/2 Inhibitor in Islet Allotransplantation. *Cell Transplant*. 2021;30:096368972110017.
2. Maffi P, Lundgren T, Tufveson G, et al. Targeting CXCR1/2 Does Not Improve Insulin Secretion After Pancreatic Islet Transplantation: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial in Type 1 Diabetes. *Diabetes Care*. 2020;43(4):710-718.
3. Shapiro AMJ Islet Transplantation in Type 1 Diabetes: Ongoing Challenges, Refined Procedures, and Long-Term Outcome. Rev Diabet Stud 2019; 385-406.
4. Hering BJ, Clarke WR, Bridges ND et al. Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia. Diabetes Care 2016;39:1230–1240.
5. Reid L, Baxter F, Forbes S. Effects of islet transplantation on microvascular and macrovascular complications in type 1 diabetes. *Diabet Med*. 2021;38(7):e14570.