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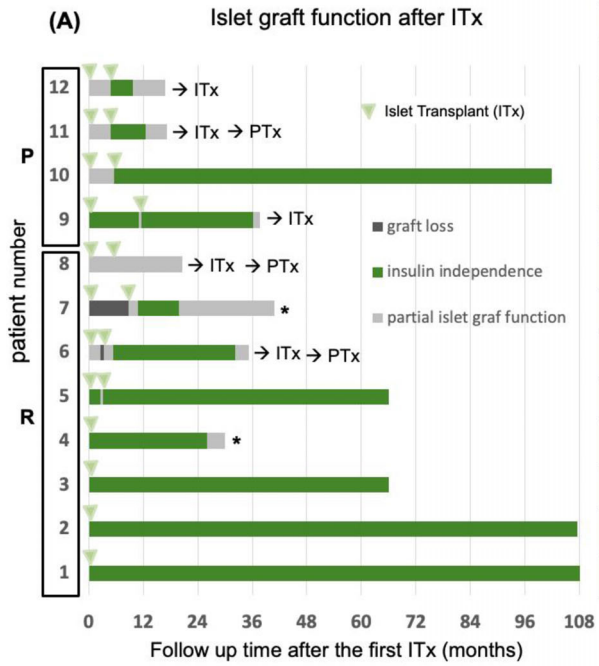
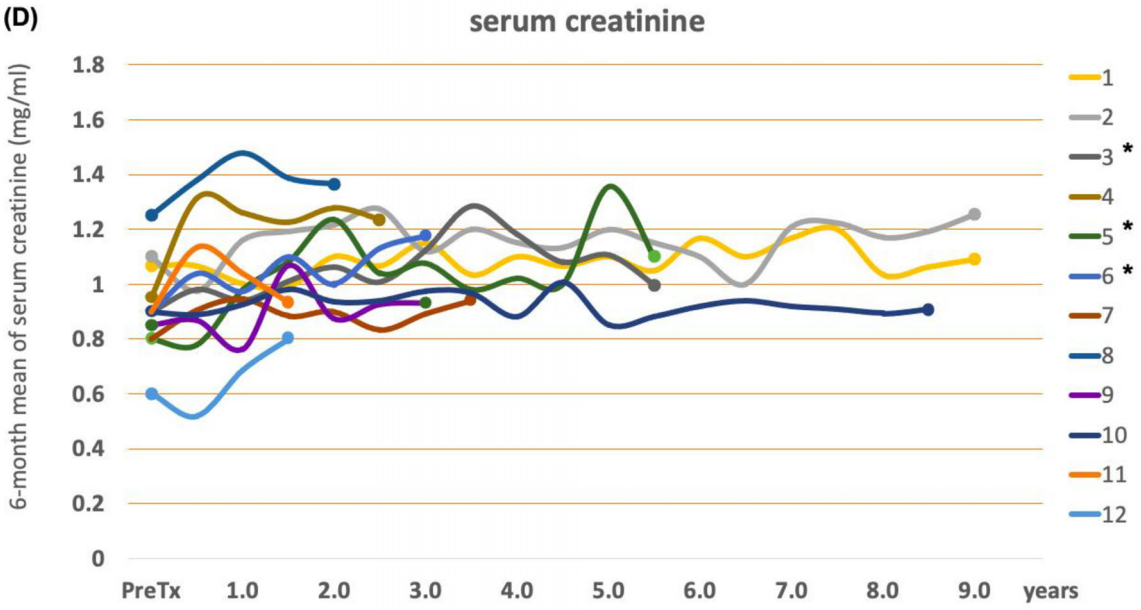
LETTER TO THE EDITOR

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

We report a 5-year follow-up study of the multicenter Reparixin trial involving 12 patients who provided informed consent and underwent islets transplantation (ITx) at the University of Chicago between June 2013 and October 2015.[1,2] All patients received anti-thymocyte



(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



globulin for induction and tacrolimus and mycophenolate (sodium or mofetil) for maintenance immunosuppression. Patients in the Reparixin group ($N = 8$) also received a new leukocyte migration inhibitor (CXCR1/2 antagonist), Reparixin (Dompe Pharmaceutical, Italy) perioperatively 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 versus 1/4 (25%) in placebo remained insulin independent at 5-year follow-up ($p = .58$, Fischer exact test) (Figure 1A). The 50% 5-year insulin independence rate in the Reparixin group is higher than that reported in multicenter trials and is comparable to those achieved in the most experienced individual centers.[2–4] Our insulin independent patients also achieved 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 following ITx. 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 2 (17%) while it remained stable in 9 (75%) patients (Figure 1B). Prior to ITx most patients suffered from diabetic neuropathy: four polyneuropathies and three ulnar mononeuropathies in the baseline nerve conduction study (Figure 1C). 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 a potentially nephrotoxic immunosuppressive medication such as tacrolimus, serum creatinine remained stable (Figure 1D). Only one patient developed new microalbuminuria 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 ITx.[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 ITx. 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 the outcomes.[2]

In summary, 50% of patients who received Reparixin maintained insulin independence beyond 5 years after 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.

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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 maintain such a long-time insulin independence in three patients from reparixin group (Nos. 1,2,3), while two subsequent ITx were required in one 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 >.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 next three 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 nine 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. LOF, loss of follow-up; no DR, no diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; quiescent PDR, quiescent proliferative diabetic retinopathy. (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; 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 (D). 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 ($R = .61$, $p = .036$), No. 5 ($R = .58$, $p = .048$), and No. 6 ($R = .82$, $p = .023$). Statistical difference in (D) was marked with *. However, the difference between preTx and last observed 6-month mean of the serum creatinine did not have clinical significance. PreTx versus last post Tx observed 6-month mean of the serum creatinine for patient No. 3 was .9 versus 1.17 mg/mL, for patient No. 5 was .8 versus 1.1 mg/mL, for patient No. 6 was .9 versus 1.0 mg/mL, respectively.

CONFLICT OF INTEREST STATEMENT

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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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