

## 021 ISLET/CELL TRANSPLANT

O25

**COMBINED PANCREATIC ISLET-LUNG TRANSPLANTATION: A NOVEL APPROACH TO THE TREATMENT OF END-STAGE CYSTIC FIBROSIS**

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**Introduction:** Cystic fibrosis related-diabetes (CFRD) is a major factor of morbi-mortality in lung transplantation. We report the follow-up of five patients with end-stage CF who were treated with combined pancreatic islet-lung transplantation.

**Patients and Method:** All CF patients have an end stage respiratory insufficiency and an uncontrolled diabetes with low C peptide levels (<0.5 ng/ml or absence of response after glucagon stimulation). Bipulmonary bloc and pancreas are procured from the same donor. During the lung transplantation, the pancreas is shipped to the laboratory for islet isolation and culture. One week after lung transplantation, the islets are injected by percutaneous transhepatic catheterization of the portal vein under local anesthesia. Immunosuppression associates steroids and basiliximab, tacrolimus and mycophenolate mofetil.

**Results:** From Oct. 2011 to Oct. 2014, five CF patients (2 F/3M, age: 31 ± 5 years, IMC: 18.8 ± 2 kg/m<sup>2</sup>) with respiratory insufficiency (FEV1: 25.6 ± 4%) and brittle diabetes (HbA1c = 8.6 ± 1%, insulin requirement = 43 ± 14 IU/day) underwent combined pancreatic islet-lung transplantation with an amount of 2940 ± 850 IEQ/kg. The follow up is from 6 to 36 months and 4 patients reached 12 months follow up. Improvement in lung function was observed for all patients with a FEV1 reaching 62 ± 16% and 67 ± 15% respectively 3 and 12 months after lung transplantation. The five patients showed immediately islet graft function with an increase in C peptide plasma levels up to 2.34 ± 1 µg/l and 0.86 ± 0.1 µg/l respectively 3 and 12 months after transplantation. No complications related to the islet injection were observed. All patients presented an improvement in the metabolic control with a decrease in HbA1c to 6.4 ± 0.6% at 12 months in absence of hypoglycemic events and a 30 ± 14% decrease in the exogenous insulin needs.

**Conclusion:** In CF patients, combined transplantation restores both pulmonary and metabolic control without immediate increase in morbidity.

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**ABSENCE OF AMYLOID DEPOSITION IN HUMAN ISLETS TRANSPLANTATION AFTER 13 YEARS INSULIN INDEPENDENCE**

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Long-term insulin independence after islets of Langerhans transplantation is rarely achieved. Amyloid deposition was described around transplanted islets that had lost their function. The aims of this study were to analyze the histological features and the amyloid deposition of transplanted islets in a type 1 diabetic patient who died of a cerebral hemorrhage after >13 years insulin-independence. Insulin-positive islets were found throughout the right and left liver. Two- and three-dimensional analysis showed that islets lost their initial rounded and compact morphology, had a mean diameter of 136 µm and were constituted of an unfolded epithelial band of 39.1 µm. Islets were also present in the pancreas, but were negative for insulin; exceptionally, isolated beta cells could be seen in the pancreatic parenchyma. Glucagon positive cells were present in both organs, and rare somatostatin cells were observed in islets implanted in the liver. Congo red staining revealed near-absent amyloid deposits around the islets in the liver. This data demonstrate that insulin-independence was mediated by the islet graft and not through the regeneration of the native islets favored by chronic immunosuppression. As expected from the literature data, amyloid deposition was only rarely observed in this patient.

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**INFUSION OF THIRD-PARTY MESENCHYMAL STROMAL CELLS AFTER LIVER TRANSPLANTATION: A PHASE I CLINICAL STUDY**

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**Background:** Mesenchymal stromal cells (MSC) are multipotent bone marrow progenitors that have demonstrated significant immunosuppressive effects in various in vivo and in vitro studies. This study aimed to be the first evaluation of the safety and tolerability of MSC infusion after liver transplantation in a prospective, controlled phase-1 study.

**Methods:** 10 liver transplant recipients under standard immunosuppression (TAC-MMF-low dose steroids until day 30) received 1.5-3 × 10<sup>6</sup>/kg third party MSC on post-operative day 3 ± 2. These patients were prospectively compared to a group of 10 control liver recipients. Primary endpoints were MSC infusion toxicity, and incidence of cancer and opportunistic infections at month 6. Secondary endpoints were patient and graft survivals and rejection at month 6, as well as the effects of MSC on recipients' immune function and on immunohistology of at month 6 graft biopsies.

**Results:** No MSC infusional toxicity was observed. Both groups were comparable in terms of donor and recipient characteristics. There was no difference in primary end-points between control and MSC groups. No patient developed de novo cancer. There was no statistical difference in patient and graft survivals or in rejection rates. There was no graft rejection in the MSC group. Month-6 graft biopsies were not different according to Banff and fibrosis scores.

**Discussion:** This phase 1 study showed excellent tolerability and safety of a single infusion of third-party MSC after liver transplantation. There were no graft safety issues and no excess of immunosuppression after MSC injection. Further analyses of consequences of MSC injection on the immune profile are needed. The possibility of avoiding calcineurin-inhibitors with repeated MSC injections as main immunosuppressive therapy and/or tolerance induction by MSC infusion should be investigated by further studies.

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**CHARACTERIZATION AND EFFECTS OF PORCINE ADIPOSE TISSUE MESENCHYMAL STEM CELLS ON KIDNEY GRAFT RECOVERY IN A PRECLINICAL PORCINE MODEL OF RENAL TRANSPLANTATION**

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**Background:** Ischemia reperfusion (IR) is a pathological process involved in acute and chronic renal graft dysfunction. The aim of this study was to characterize mesenchymal stem cells from porcine adipose tissue (pASC) and their role in the graft function recovery in conditions mimicking deceased after cardiac arrest donors.

**Methods:** In vitro, morphology, proliferative capacities, phenotype by flow cytometry and the metabolic profile with Nuclear Magnetic Resonance (NMR) of pASC were determined. Their resistance to a sequence of hypoxia-reoxygenation (HR) was characterized on their viability and metabolic profile in NMR. In vivo, a porcine preclinical model was used with 1 h of renal warm ischemia followed by 24 h of graft storage at 4°C in UW solution and renal auto-transplantation with contralateral nephrectomy. The effects of autologous injection of 106 pASC/kg in the renal artery after cold preservation were determined on renal blood flow, renal graft function and histological outcomes.

**Results:** The cell extraction technique was reproducible and allowed a sufficient extraction rate of pASC characterized by mesenchymal stem cells phenotype. The metabolic profile in NMR of pASC was stable during the first passages. The cell viability after a sequence of HR exceeded 70% underlined the feasibility of a direct injection in the renal artery at reperfusion time. The injection of 106 pASC/kg at passage 2 was practicable 15 days after removal of adipose tissue. The function recovery was significantly improved and the histological lesions were reduced at day 7 in the group treated by pASC.