Current status of clinical islet transplantation

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Islet transplantation is a promising therapy for patients with type 1 diabetes and severe hypoglycemia. Several studies have shown that high levels of insulin independence and good control of hypoglycemia can be achieved in the short term. However, long term results are not as good and five year insulin independence rates although improving show progressive loss of function over time. In two recent multicenter trials – one in North America and one in Australia- similar results were achieved. Approximately 85% of patient achieved the primary end point of HbA1c < 7.0% and absence of hypoglycemia in presence of detectable c-peptide. With multiple transplants approximately 60% were insulin independent. Over time there was a progressive deterioration in function. In the North American study graft function had dropped from 87% to 72% by 24 months. Whereas, in the Australian study, graft survival was 64% at 5 years after transplantation. Patients with acceptable graft function have a remarkable improvement in their diabetic control and complete resolution of difficult to control hypoglycemia. As a result there is a profound improvement in quality of life and many recipients are able to return to work. Islet transplantation does come with its own problems particularly regarding complications and tolerability of immunosuppression. In a study where continuous insulin infusion (CSII) was compared with islet transplantation for severe repeated hypoglycemia the data suggested that in subjects with severe hypoglycemia, CSII was an appropriate therapy, which substantially reduced the frequency and severity of hypoglycemia but did not remove the need for islet transplantation in the majority of individuals. CSII reduced duration of time with blood glucose <4 mmol/L and significantly improved glycemic variation as compared with MDI, the latter potentially accounting for reduced frequency of severe hypoglycemia. However, islet transplantation eliminated hypoglycemia regardless of whether insulin independence was achieved. Frequency, severity and risk of hypoglycemia as measured by, respectively, CGM percentage of time in hypoglycemia, HYPOscore, and glycemic variability at 12 months post islet transplantation all returned to levels as good as, or better than, those reported in type 1 diabetes without problems with hypoglycemia. Transplantation reduced HbA1c and mean glucose at 12 months, benefits that were not seen with changing to CSII. The study provided further evidence that in appropriately selected patients with severe hypoglycemia with large glycemic variability, islet transplantation provides superior glycemic control and reduction in hypoglycemia over and above that achieved with CSII.
Clinical islet transplantation from allogeneic toward xenogeneic

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In 2014, opinion leaders of beta cell replacement therapy discussed the current status and future of the therapy at the Oxford University. At the meeting, it was revealed that approximately one-eighth of type 1 diabetic patients with prolonged diabetic history (>20 years) suffered unaware hypoglycemia and 7-10% of cause of death of type 1 diabetes was hypoglycemia. Beta-cell replacement therapy including pancreas and islet transplantation is the best treatment for preventing severe hypoglycemia, however due to donor shortage, only at most only 0.1% of type 1 diabetic patients can receive beta-cell replacement therapy. Donor shortage is the most serious issue.

To alleviate donor shortage, we have conducted islet transplantation using non-heart beating donor, living donor islet transplantation and improving the efficacy of islet transplantation. However, none of them can solve the issue of donor shortage.

Establishment of islet transplantation using non-human pancreas donor (bio-artificial islet transplantation) can solve the donor shortage issue. Three major resources of islets for bio-artificial islets are porcine islet, ES cell derived islet and iPSC cell derived islets. Among them porcine islets have several advantages including previous clinical experiences, clean and healthy islets from healthy designated pathogen free donor, possible gene modification to improve clinical outcomes.

Encapsulated neonatal porcine islet transplantation has been conducted under comprehensive New Zealand regulation. The study had four different dose groups: 5000 IE/kg (n = 4), 10 000 IE/kg (n = 4), 15 000 IE/kg (n = 4), and 20 000 IE/kg (n = 2). There were four serious adverse events related to the procedure, which were resolved without residual effects. Tests for PERV DNA and RNA were negative in the blood of all patients. In terms of efficacy, the number of episodes of unaware hypoglycemia was reduced 1 year after transplantation in all dose groups.

To improve the clinical outcome, the Ricordi isolation method and injection of ETK solution into pancreata were introduced, which resulted in a high islet yield (approximately 180 000 IE/piglet). Next clinical trial was performed in Argentina. Subanalysis of the efficacy dataset demonstrated that when a dose of 10 000 IE/kg was transplanted twice, HbA1c levels <7% for more than 2 years, with a significant reduction of in the number of episodes of unaware hypoglycemia.

Xenogeneic islet transplantation can be a viable option for unstable type 1 diabetes, and the next research target should be curing type 1 diabetes with xenogeneic islet transplantation.
Clinical islet autotransplantation: Beyond simple replacement of islet cell mass

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Islet autotransplantation (IAT) is performed when the pancreas is removed for treatment of benign pancreatic diseases. In chronic pancreatitis with intractable abdominal pain, IAT after total pancreatectomy has been proven to reduce abdominal pain by total pancreatectomy while avoiding brittle diabetes. In contrast to the islet allotransplantation, IAT is not vulnerable to immune rejection, recurrent autoimmunity, or beta-cell toxicity of immunosuppressants. For this reason, IAT represents the maximum functional potential of transplanted islets, with some reported cases of unexpected insulin independence in low-dose autologous islet transplants.

Besides the proven efficacy of IAT in intractable chronic pancreatitis, we have examined the efficacy of IAT after partial pancreatectomy for treatment of benign tumor. We reported the outcome of the 20 patients who underwent IAT after 50% to 60% partial pancreatectomy in this clinical setting. Although the 7-year diabetes-free survival rate was not different between control and IAT groups, prolonged diabetes-free survival was observed in patients who underwent IAT when a high islet yield (>5154 islet equivalents per gram of pancreas) during the islet isolation was achieved. The islet yield and islet function in this clinical setting was superior to those of allogeneic islet transplantation. In addition, we have shown that transplanted islets can promote the regeneration of endogenous beta-cells and differentiation of adult stem cells into beta-cells in experimental models of IAT after partial pancreatectomy.

In conclusion, IAT after partial pancreatectomy for benign tumors could be a promising indication of IAT. IAT in this setting may improve the metabolic milieu after the pancreatic resection, and is a unique opportunity for understanding the biologic effect of intraportal islet transplantation beyond the simple replacement of islet cell mass.