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Islet cell autotransplantation update

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Autologous Islet Transplantation (AIT) is increasingly performed to preserve insulin secretory function in patients with chronic pancreatitis (CP) undergoing total pancreatectomy (TP). Outcomes of diabetes-free survival differ across patients undergoing AIT. Studies have shown that at 28 to 36 months following transplantation, one third of patients were insulin independent, one third attained partial insulin independence, and one third were fully dependent on insulin therapy[1,2]. These results were consistently reported between centers with local islet isolation facilities and those with remote processing sites[3]. A critical factor in predicting superior metabolic outcomes which translate into insulin independence is the mass of islets transplanted, often expressed as the islet equivalent (IEQ), or IEQ adjusted for body weight [IEQ/kg]. Rates of insulin independence range from 12% in those receiving <2,500 IEQ/kg to 72% in subjects transfused >5,000 IEQ/kg. Therefore, forecasting the islet yield or IEQ/kg pre-AIT is key. However, accurate assessment of the latter mandates elaborative work-up with mixed meal tolerance testing (MMTT), in addition to hemoglobin A1c measurement. Fasting plasma glucose of <100 mg/dL and stimulated plasma C-peptide of ≥4 ng/mL during MMTT independently predicted higher IEQ/kg yield (often ≥2,500 IEQ/kg), whilst total glucose area under the curve and hemoglobin A1c measurements both correlated inversely with the islet yield[4]. Considering the cost of a labor intensive MMTT, we amongst others have investigated the use of alternative, more feasible indices for assessment of beta cell function pre-and post-AIT. Amongst the many scores assessed, the BETA-2 score showed the strongest positive correlation to beta cell measurements (fasting and peak glucose)[5]. The BETA-2 score computes a fasting plasma glucose, fasting C-peptide and hemoglobin A1c, all obtained through a single fasting blood sample[6]. With a score of 16 or above, BETA-2 assessment accurately predicted insulin independence post-AIT[5]. Additionally, an annual 6-point decline in BETA-2 score was seen in the first 24 months post-AIT[7].

Following autologous transplantation, loss of islet mass and subsequent decline in beta cell functionality are inevitable[8–10]. Although AIT is not significantly affected by the stress of cellular rejection classically encountered in allotransplantation, increasing evidence suggests that islet survival and function are largely governed by the degree of cellular damage inflicted during the isolation and transplantation processes. Pro-coagulatory and pro-inflammatory cascades of inflammatory cytokines such as IL-1Ra, IL-6, IL-8 and IL-10 are activated within minutes of islet infusion into the host, and actively accelerate injury to

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CONFLICT OF INTEREST

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transplanted islets[11]. Therefore, there has been general consensus that providing anti-inflammatory agents in the peri-transplant period should protect the graft from the initial inflammatory challenge and preserve beta cell function[12,13]. Recent studies have proposed the use of TNF-α inhibitors to short-circuit the innate inflammation known to be detrimental to beta cell function and survival[14]. In our institution, we have initiated a collaborative, phase II, randomized placebo-controlled clinical trial investigating the effects of an immunomodulatory and anti-inflammatory agent, hydroxychloroquine, in improving islet engraftment efficiency leading to sustained beta cell working capacity. We are currently assessing the effects of hydroxychloroquine on islet functionality on several clinical, molecular and genomic levels[15].

Transplanted patients are monitored lifelong for metabolic complications of AIT, mainly the development of hyperglycemia. Recent evidence suggests increased rates of attrition of insulin independence with time, necessitating annual in-office screening with fasting plasma glucose and hemoglobin A1c, complemented by patient self-monitoring of capillary glucose. More elaborative metabolic testing with oral glucose tolerance tests and/or MMTT may supplement the annual screen for a more accurate assessment of beta cell reserve[16]. Metabolic complications following AIT have not only been limited to hyperglycemia. Hypoglycemia has been increasingly recognized and reported in up to 50% of insulin independent subjects post-AIT[17]. Glucose homeostasis in fasting, post-prandial and exercise-induced states changes significantly after AIT. Most notably, impairment in the hypoglycemia counterregulatory mechanisms manifested by deficiencies in endogenous glucose and glucagon reflex production, has been documented[17–20]. Of interest, glucagon response to hypoglycemia is dependent on islet implantation site. Patients receiving both intrahepatic and non-intrahepatic islets were able to mount sufficient alpha-cell response to hypoglycemia comparable to that of controls, whereas a lack of response was seen in those with intrahepatic islets only[18]. It has been theorized that in intrahepatic environments, islets are bathed in free glucose present at higher concentrations than that of systematic blood. Therefore, islets may inaccurately sense, and therefore adjust glucagon and insulin secretion during episodes of systematic hypoglycemia[18]. Whilst such complications may not be entirely preventable, amelioration of hypoglycemia may be achieved through implementing small, frequent meals and snacks, facilitating shorter fasting intervals, as we have previously demonstrated[17].

Autologous islet transplantation has become an increasingly acceptable approach to prevent or mitigate surgical diabetes in CP patients undergoing TP. Significant advances have been made thus far in the field of autologous transplantation. However, long-term preservation of islet function remains amongst many others a challenge, with much needed to be elucidated.

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