Human islet transplantation

Transplante de ilhotas em humanos

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Diabetes is a major burden to healthcare economies despite the use of exogenous insulin injections. Type I diabetes mellitus is a chronic metabolic disorder that currently afflicts 5 million individuals in the world. It results from auto-immune mediated destruction of insulin secreting beta cells in islet of Langerhans of the pancreas.[1] Long-term studies strongly suggest that tight control of blood glucose achieved by conventional or intensive insulin treatment, self blood glucose monitoring, and patient education can significantly prevent developing and retard the progression of chronic complications of this disease.[2] On the other hand, the cost of this benefit was a threefold increase in the number of severe hypoglycemic episodes, a significant increase of body weight and dietary and other lifestyle restrictions affecting the quality of life.[3] The only treatment for Type I diabetes mellitus that achieves insulin-independent, constant normoglycemic state and avoidance of hypoglycemic episodes is the replacement of a patient's islet of Langerhans either by pancreas transplantation or by isolated islet transplantation. The cost of this benefit, however, is the need for immunosupressive treatment of the recipient with all its potential risks.

Currently, only vascularized pancreas transplantation can re-establish long-term normoglycemia however this has been associate with significant morbidity and mortality. Approximately 25.000 patients worldwide underwent this procedure and it has been shown to improve quality of life and even reverse some secondary complications of diabetes.[4] Simultaneous pancreas and kidney transplantation are presently considered the standard of care for selected patients with type I diabetes with end-stage renal failure.[5]

Islet transplantation is an attractive treatment for type I diabetic patients, the procedure itself does not require general anesthesia or major surgery. It is considered a minimally invasive procedure, in which islet can be perfused percutaneously into the liver via the portal vein in local anesthesia and does not require hospitalization.[6] After the initial experience with poor results with islet transplantation in the early 1990s, a detailed review of cumulative world experience in clinical islet transplantation clearly highlighted several factors as being causative for failure in the majority of cases transplanted until 1999[7]: 1. inadequate islet transplant mass; 2. inadequate islet potency; 3. inadequate prophylaxis against allograft rejection or autoimmunity; and 4. routine use of toxic diabetogenic immunosuppression after transplantation.

A new protocol implemented in Edmonton (1999) was designed to systematically address each of the above limitations. Shapiro et al (2000), University of Alberta in Edmonton, Canada, reported successful reversal of diabetes by pancreatic islet transplantation in seven consecutives patients.[8] The major novel approach was to transplant an adequate islet mass through repeated islet implantations on a corticosteroid-free immunosuppressive regimen. Its include harvesting the pancreas before multiorgan retrieval, avoidance of prolonged cold storage of the pancreas (<8 h), avoidance of animal serum products during isolation and a target mass of at least 11.000 islet equivalent (IEQ)/kg of recipient bodyweight, which requires islets from two or three donor preparations. They used an immunosuppressive protocol comprised of induction therapy with a humanized interleukin-2 (IL-2) receptor antibody (daclizumab) and maintenance therapy involving low-dose tacrolimus and sirolimus. Later, a follow-up in more than 50 patients treated at the Edmonton site confirmed 1-year insulin independence rates of 80%.[9] From January 1990 and December 2005 (Islet Transplantation Registry, Giessen) islet allotransplants have been performed in 1.049 patients with type I diabetes mellitus, however, there are only 11 institutions worldwide, four in North America and seven in Europe, to have performed more than 20 cases per center and which have transplanted together more than half of all cases worldwide. Table 1.

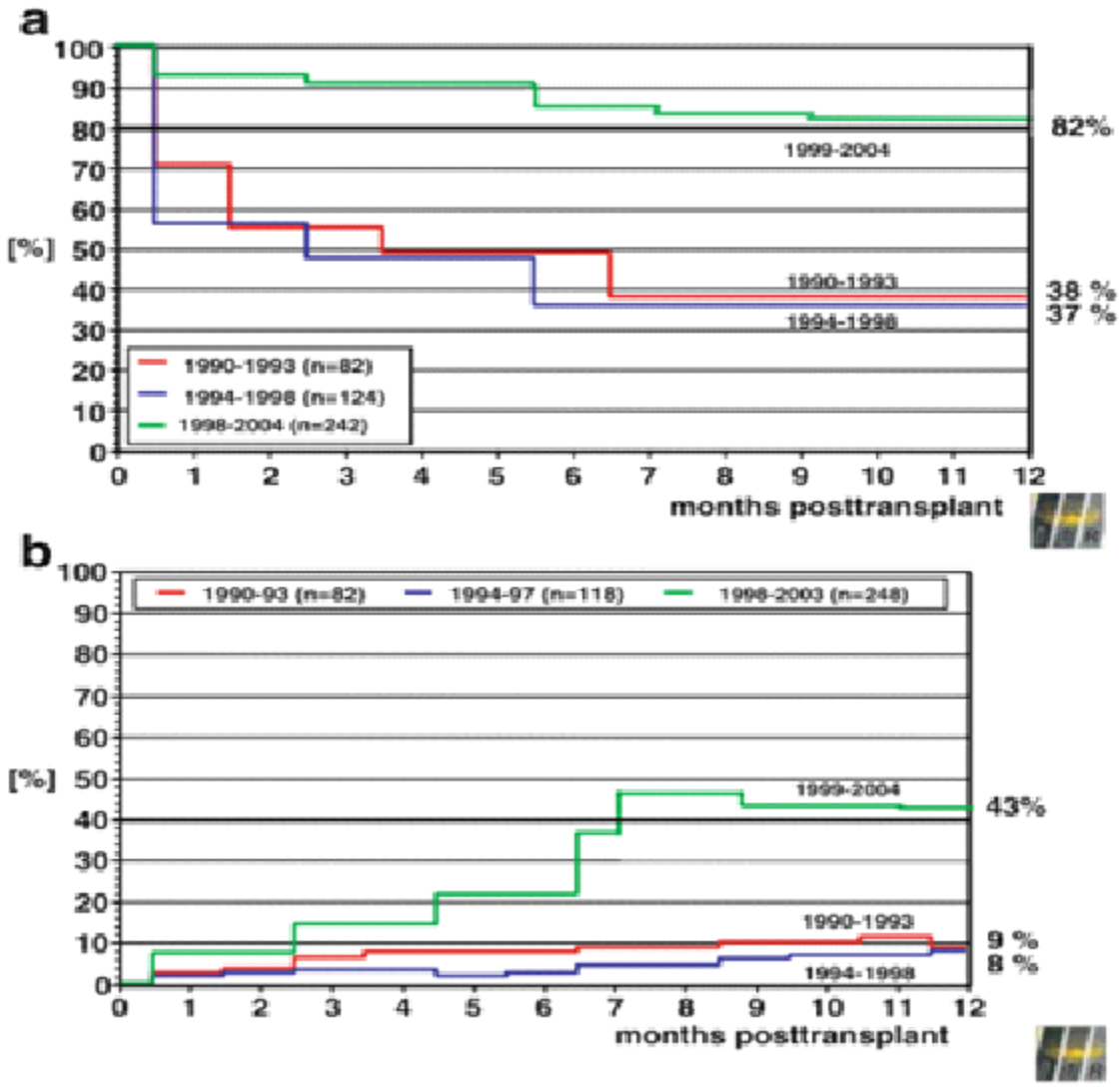
Table 1

Eleven institutions with ≥ 20 adult islet allografs in type 1 diabetic patients 1990-2005

Institution	*Year of TX*	*Nº of cases*
Edmonton	1991-2005	99
Giessen	1992-2005	93
Milan	1991-2005	79
Brussels (Free Univ.)	1994-2005	74
Minneapolis	1991-2005	66
Miami	1991-2005	55
Geneva	1994-2005	39
GRAGIL/Geneva	1999-2005	34
Nordic Network/Uppsala	2001-2005	32
Philadelphia	2001-2005	30
Brussels (Louvain)	2000-2005	24
		591[a]

Data from the International Islet Transplant Registry (ITR), Giessen / Germany
[a] 66% of all adult islet allografts

Cumalative 1-year graft-survival (a) and insulin independence rates (b) in 458 well-documented pre-transplant C-peptide negative type I diabetic recipients era. Data from International Islet Transplant Registry, Giessen, Germany.



Future perspectives

The concept of islet cell transplantation offers many perspectives: **1.** In contrast to pancreas organ transplantation, islet cell aviability could become unlimited, when strategies such as the use of xenogenic islets, engineered beta cell lines, in vitro stem cell expansion and differentiation in insulin-producing cells or transdifferentiation of non-pancreatic cells into beta cells reach the stage of clinical applicability; **2.** Islet cells may be transplanted without chronic immunoisupressive treatment of the recipient by making use of donor-specific tolerance induction strategies or immunoisolation systems. This unique set of characteristics could finally allow adolescents and children with type I diabetes preventing devastating diabetic secondary complications like end-stage renal disease, lower limb ischemia, amputations and blindness.

References

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