CLINICAL UPDATE

Islet transplantation in type 1 diabetes mellitus

Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000;343:230-8.

Background: Results of islet transplantation in patients with type 1 diabetes mellitus have been disappointing, with only 12.4% of the allografts transplanted since 1990 resulting in insulin independence for more than 1 week.[1] Part of the difficulty relates to the glucocorticoid-containing immunosuppressive regimen used, which may damage β cells or induce peripheral insulin resistance.[2]

Question: Will a glucocorticoid-free immunosuppressive regimen of sirolimus, low-dose tacrolimus and daclizumab be more effective in islet transplantation in patients with brittle type 1 diabetes?

Design: In a nonrandomized, uncontrolled study 7 patients with type 1 diabetes for at least 5 years and a history of recurrent severe hypoglycemia or severe metabolic instability underwent islet transplantation in conjunction with an immunosuppressive regimen of sirolimus, tacrolimus and daclizumab. Prophylactic antibiotics and vitamins were also given. Following transplantation, inhaled pentamidine was administered monthly, and oral ganciclovir treatment was prescribed for 14 weeks. Islets were isolated by means of ductal perfusion with cold, purified collagenase, digested and purified in xenoprotein-free medium, and transplanted immediately by means of percutaneous transhepatic portal embolization. Islet preparations were matched to the recipient's blood type and cross-matched for lymphocytotoxic antibodies, with no attempt at matching histocompatibility leukocyte antigens. Insulin therapy was stopped after transplantation and only resumed if blood glucose levels rose above 11.1 mmol/L, at which time another transplantation was performed. Capillary glucose levels were measured at least 7 times daily, and oral glucose tolerance testing and mixed-meal testing were also performed. Glycosylated hemoglobin, C-peptide, lipid and creatinine levels were also monitored.

Results: After a median duration of follow-up of 11.9 months (range 4.4–14.9) all 7 patients remained free of the need for exogenous insulin under basal conditions. Two patients briefly required small amounts of insulin during intercurrent illness. Six of the 7 patients required a second transplantation within 14-70 days after the first procedure, and 1 patient required 3 transplantations, to achieve sustained insulin independence. The first 2 patients had problems with bleeding at the puncture site, a complication that was subsequently averted by injecting a Gelfoam plug and reducing the intraportal dose of heparin.

After transplantation none of the 7 patients met current criteria for diagnosis of diabetes on oral glucose tolerance testing, although in some the response showed impaired glucose tolerance. No subject had any episodes of severe hypoglycemia, cytopenia or cytomegalovirus infection. The mean glycosylated hemoglobin value was 5.7% at 3 and 6 months. Although there appeared to be a minor increase in total cholesterol and triglyceride levels after treatment, this difference was not statistically significant.

Commentary: The results of this small series renews optimism regarding a potential cure for type 1 diabetes mellitus. Enthusiasm is tempered by the short duration of follow-up and the need for more information about the long-term risks of the new immunosuppressive regimen used and the durability of the islet grafts. Also, pancreata are in very limited supply, and public awareness about the need for organ donation will need to be increased.

Practice implications: Until more information is available about the long-term risks, benefits and costs of islet transplantation, this procedure will remain experimental. Currently it is offered only to patients at very high risk of complications from diabetes mellitus. Patients interested in being considered as candidates for future studies can self-refer at the authors' Web site (**www.med.ualberta.ca/research/groups/islet/cand.html**). Physicians may refer high-risk patients who fulfil the current study criteria by means of a covering letter (more details available at Web site). — *Katherine A. Kovacs*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

References

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2. Zeng Y, Ricordi C, Lendoire J, Carroll PB, Alejandro R, Bereiter DR, et al. The effect of prednisone on pancreatic islet autografts in dogs. *Surgery* 1993;113:98-102.