CURRENT OPINION

Drugs 2001; 61 (14): 2017-2020
0012-6667/01/0014-2017/$27.50/0

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Pancreatic Islet Cell Transplantation

Likely Impact on Current Therapeutics for Type 1 Diabetes Mellitus

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Abstract

Pancreatic islet transplantation as a cell-based treatment for diabetes mellitus has been pursued for over quarter of a century, ever since the first successful use of this approach to cure diabetes mellitus in rodents in the 1970s. However, even though autoislet intrahepatic transplantation in patients with chronic pancreatitis who did not have diabetes mellitus was successful in the 1980s, reliable success with alloislet transplantation in patients with diabetes mellitus remained elusive until the year 2000.

The reasons for previous failures appear to include use of corticosteroids as an immunosuppressive agent, a drug that both interferes with islet β-cell function and promotes resistance to insulin action. Corticosteroid-free immunosuppressive regimens in one recent series have permitted much greater success for over 1 year. Benefits accrued in this series include normal fasting glucose levels, normal levels of glycosylated haemoglobin, and total independence from exogenous insulin or other therapy for hyperglycaemia.

These dramatic results have presented the research community with the challenges of replicating these results and, ultimately, with providing solutions to the serious supply and demand issues that will inevitably follow.

Management of hyperglycaemia for patients with type 1 (insulin-dependent) diabetes mellitus has recently undergone the beginnings of a therapeutic revolution. The seeds of this revolution were planted over quarter of a century ago when diabetes was successfully cured in rodents by pancreatic islet transplantation.[1] Since that initial promise, attempts to successfully transplant pancreatic islets donated by one human into another human with diabetes has been met largely with failure with few notable exceptions.

All this dramatically changed recently when Shapiro et al.[2] reported that seven of seven patients with type 1 diabetes who received alloislet transplantation achieved normal fasting glucose levels without using exogenous insulin or any other treatment for hyperglycaemia. This highly acclaimed report brings cell-based replacement therapy for patients with diabetes much closer to reality. However, as with any new potent therapy, there are potential problems that require close attention.

1. Brief History of Cell Transplantation

The mass of the pancreas is comprised of approximately 3% pancreatic islets and 97% exocrine tissue. Approximately 1 million pancreatic islets are present in the healthy human pancreas. Each islet is comprised of four cell types; α, β, δ and PP cells. The α-cell synthesises and releases glucagon, a hormone with the primary function of stimulating hepatic glycogenolysis and thereby release glucose from the liver. The β-cell produces insulin, the pri-

mary functions of which are to diminish glucose production by the liver and to promote glucose uptake by peripheral tissues such as muscle and fat. The δ-cell produces somatostatin, the primary function of which is to dampen the release of glucagon and insulin secretion. The PP-cell produces pancreatic polypeptide, the function of which remains an enigma in humans.[3]

In 1894, Williams[4] appears to have generated the first report of an attempt to transplant islet tissue as a treatment for a patient with diabetes. This unsuccessful venture utilised a glycerine extract of sheep pancreas. In 1967, Lacy and Kostianovsky[5] established a methodology to isolate pancreatic islets. This was followed in 1972 by a report from Ballinger and Lacy[1] that transplantation of rodent islets could partially correct hyperglycaemia and glycosuria in rats with diabetes. Between 1972 and 1990 many unsuccessful attempts were made to adapt this procedure as a treatment for humans with type 1 diabetes. Finally, beginning in 1990, several reports of successful islet transplantation appeared that stimulated an increased interest in this procedure. However, a high rate of success was not experienced until the report of Shapiro et al.[2] in 2000.

In marked contrast to the struggle with allotransplantation with islets, striking success was being experienced with islet autografts. Sutherland et al.[6] reported the first success with this procedure in 1978, and in 1980 Najarian et al.[7] reported results of total or nearly total pancreatectomy in ten patients with chronic pancreatitis who did not have diabetes followed by intraportal infusions of crude preparations of their own islets. Seven of these ten patients had variable degrees of insulin independence for as long as 38 months. Two others returned to insulin dependence and one died of a perforated colon post-operatively. In 1995, Wahoff et al.[8] reported a series of 48 patients with autoislet transplants. Overall, the success rate for insulin independence and normal glycaemia for >2 years was 74% for 14 patients who received >300 000 islets. The potential lethality of this procedure was reinforced by Froberg et al.[9] who published a case report of fatal disseminated intravascular coagulation immediately after autoislet transplantation.

Other notable events occurring concurrently with these developments include the first successful whole pancreas transplantation in 1966.[10] Although this procedure met with low success rates initially, the advent of modern immunosuppressive therapy and improved surgical techniques allowed combined kidney and pancreas transplantation in patients with diabetes to achieve 1- and 3-year post-transplant graft success rates of approximately 80 and 70%, respectively, by 1997.[11] These rates are comparable to those encountered for other solid organ transplantation. In 1993 the highly cited Diabetes Control and Complications Trial (DCCT) established that intensive management of hyperglycaemia in patients with diabetes achieved a marked decline in rates of secondary complications.[12] Hence, the DCCT established once and for all that optimal management of hyperglycaemia was mandatory for the prevention of devastating consequences of this disease such as retinopathy, nephropathy and neuropathy. This made the prospect of successful islet transplantation even more enticing.

2. Current Status of Islet Cell Transplantation

The Edmonton group[2] reported on intrahepatic transplantation of approximately 800 000 islet equivalents in two separate stages. Since islet preparations are never 100% pure, the actual number islets transplanted was <800 000. Nonetheless, the procedure achieved total independence from exogenous insulin therapy, normal fasting glucose levels and normal levels of glycosylated haemoglobin (HbA_{1c}) in seven of seven patients for an average of 12 months. In an updated series of 12 patients, four have normal glucose intolerance, five have impaired glucose tolerance and three have post-transplant diabetes.[13] This was in marked contrast to the 5 to 6% success rate recorded by the Islet Transplant Registry for the years 1990 to 1995.[14] The major change in strategy followed by the Edmonton group was the elimination of glucocortico-

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steroids from the immunosuppressive regimen. However, other variables included maximum measures to insure transplantation of fresh, pure islet tissue and immunosuppression using low dose tacrolimus, sirolimus and daclizumab.

This alteration in immunosuppressive strategy has begun to unravel a pharmacological conundrum. Why was it that the same immunosuppressive regimen (corticosteroids, cyclosporin and azathioprine) that allowed successful pancreas transplantation could not support islet transplantation? The answer could not be simply one of islet survival after transplantation into the liver because intrahepatic transplantation of autoislets had been successful since 1980.[7] A very real possibility was that one or more of the immunosuppressive drugs were harmful to isolated pancreatic islets but not to the intact pancreas. Elimination of corticosteroids made sense because they are known to be toxic for islets *in vitro* and to increase insulin resistance *in vivo*. In general, the potential deleterious effects of immunosuppressive drugs are made all the worse when islets are placed in the liver because these drugs are taken orally. Consequently, the intrahepatic concentrations of the drugs are much higher than those found in peripheral blood. Adjustment of immunosuppressive drug doses to achieve an acceptable systemic circulating concentration underestimates the higher intrahepatic levels. It now appears that the high concentrations of intrahepatic corticosteroids were responsible for islet transplantation failure rates in the past, although the additional protection provided by daclizumab needs to be taken into account.

The remarkable success of the Edmonton group has prompted other researchers throughout the United States, Canada and Europe to evaluate their protocol. Under the leadership of the Immune Tolerance Network, jointly funded by the National Institutes of Health and the Juvenile Diabetes Foundation International, ten clinical centres will attempt to replicate the Edmonton protocol. Each centre will transplant four patients over the next 2 years. By the year 2003, the initial success rate of these 40 patients will be reported as well as the 3-year follow up data from the Edmonton patients. At that time, the scientific community should be in an ideal position to decide whether or not islet cell transplantation is a therapy that can be considered as a sound clinical approach to normalising glucose levels in patients with diabetes.

3. The Future

To the extent we can look into the future beyond the year 2003, it is easy to identify the next major problem. If islet transplantation achieves a success rate similar to or better than that now being experienced by pancreas transplantation, the demand for islet transplantation will be huge. The central problem will be one of supply. To put this in perspective, it is estimated that 5000 pancreases are harvested annually in the United States from donors who have died. On the other hand, it is estimated that 16 million people in the United States have diabetes. Approximately 7 to 10% of these have type 1 diabetes. Obviously, the rate of organ donation, which is at a relatively low rate in the United States, needs to increase greatly to make islet transplantation a viable therapeutic option on any kind of reasonable scale. One can envision gradually switching over from whole organ pancreas transplantation to the use of organs for islet transplantation if the efficiency of islet isolation improves so that one pancreas is sufficient. According to the Edmonton results, two pancreases are needed to harvest sufficient islets to achieve successful islet transplantation and normalisation of HbA_{1c} levels.[2]

Other critical issues that will need to be settled are the inclusion criteria for patients selected to receive islet transplantation. In this latter consideration, severity of diabetes and its complications, especially metabolic instability with a high risk of severe, recurrent hypoglycaemia, will probably be among the criteria. However, the case can also be made that the most effective use of islet transplants would be to provide them to patients who do not yet have significant complications since normalisation of their glucose levels should provide a

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powerful preventive effect. Another issue will be the assumption that this therapy should be provided primarily to patients with type 1 diabetes. There is no defensible *a priori* reason to exclude patients with type 2 (noninsulin-dependent) diabetes mellitus. Even though type 2 diabetes is associated with obesity and insulin resistance, 20% of patients with type 2 diabetes are lean and have a lesser degree of insulin resistance. Moreover, the complications for patients with type 2 diabetes can be every bit as severe as those with type 1 diabetes when clinical courses are matched for duration and severity of hyperglycaemia.

A final consideration for cell-based therapy is implantation of engineered β-cells. This is an exciting frontier currently being investigated by many groups throughout the world. The goal is to genetically engineer cells so they will synthesise and release insulin in a glucose-regulated manner. Preferably, the cells would be from the patient's own body so that immunosuppressive drugs would not be required. This goal is clearly a very ambitious one that must overcome the challenge of creating a cell that can mimic the complicated intracellular sensing and delivery machinery of an islet β-cell and, at the same time, avoid the potential dangers of introducing viruses and oncogenes via the engineered cell into humans. Another approach that is being used in answering the supply and demand question is pancreatic islet cell expansion, using either mature β-cells or embryonic stem cells. This area of research is also exciting to think about, but it is still in its infancy. It seems doubtful that engineered β-cells or islet expansion will be used as routine treatment for diabetes in the near future, which emphasises the need to optimise methods of obtaining donated pancreases to support islet transplantation.

Acknowledgements

This work was supported in part by NIH RO1 DK39994.

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