Pancreatic Islet Transplantation: Is the Glass Half-Empty or Half-Full?

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In this Forum, we are fortunate to have contributions addressing this question from six leading authorities in the field, including the three major centers for clinical islet transplantation. The authors describe where they feel pancreatic islet transplantation is today, what the current problems to be resolved are, and how this might be accomplished to achieve insulin independence in patients with Type 1 diabetes (insulin dependent) using islets from a single donor pancreas.

In the first paper in this Forum, Korsgren and his colleagues from Uppsala state quite firmly that for islet transplantation to be considered clinically successful then the islets from one pancreas have to be sufficient to achieve insulin independence reliably, and that is not the case today. They maintain that the instant blood mediated inflammatory reaction (IBMIR), which is induced by inflammatory mediators such as tissue factor (TF) and MCP-1 following contact of the islets with ABO-compatible blood, is a key factor in the failure of islets from a single donor to achieve insulin independence after implantation in the portal vein of the recipient liver.

This is but one reason that, in general, islets from at least two donors are required to render diabetic patients insulin independent. Although a good preparation of approximately 500,000 islet equivalents (IEQ; i.e., islets with a diameter of 150 microns) can be obtained from a single pancreas, which is not far off the number of IEQs present in a normal pancreas, both the poor quality of the islets obtained and the IBMIR after implantation represent critical barriers to success both in the short term and the long term. There is little evidence of B cell replication and no evidence of an increase in islet volume, so the functional capacity of transplanted islets is far below that of islets in a normal person. He also raises another potential problem with using multiple organ donors to achieve insulin independence: patients may be sensitized against HLA, making a successful kidney transplant more difficult if that becomes required later.

Derek Gray agrees that the numbers of IEQs suggested by Korsgren that are required to render diabetic patients insulin independent is probably correct. He also agrees that IBMIR is a significant problem in islet allografts in the primate and man, but goes on to pose an interesting question as to why IBMIR does not occur after autologous grafts but only after allografts! He wonders if there is an MHC allospecificity to this reaction because although no alloantibody is demonstrable in the recipient, the reaction is instant and indeed has some of the characteristics of the response to xenotransplanted islets in primates. Of relevance to the long-term survival of islets is his reminder of the primate experiments carried out in Oxford quite a few years ago with autologous islet transplants in a totally pancreatectomized model. The recipients were rendered insulin independent but all became diabetic again in times ranging from several months to three years after transplantation. These islets were implanted in the liver and at the time the question was raised as to whether this was the most appropriate place for islets to be implanted—a question also raised by Bernhard Hering in his article.

Bernhard Hering agrees that improvement in the quality of islets must be a top priority and he argues that an extra vascular site of islet implantation to avoid IBMIR might be more appropriate than the portal vein. He goes on to suggest the possible use of an omental pouch for the implanted islets. He also proposes that the avoidance of corticosteroids and calcineurin inhibitors would be an appropriate regimen, which also seems to be effective in primates. His recent clinical experience in Minneapolis is impressive in that 13 out of 15 single pancreas islet transplants have been successful. He attributes this success to a number of factors including the use of younger donors (under 50 years of age), restriction of ischemia to less than 8 hr, two layer preservation, avoidance of toxic agents during preparation, prophylactic use of anticoagulation, and the culture of the islets for two days before implantation. Again he points out that the maintenance of insulin independence in the medium and longer term after transplantation is another major problem and wonders whether the neogenesis of beta cells in the transplanted islets might be stimulated in some way.

Ricordi and his team have now achieved insulin independence in 90% of 31 patients at one year in patients receiving islets alone or islets after a kidney transplant. Indeed, 6 of the 31 successful islet transplants resulted from the use of islets from one donor only. He does make the point strongly that if a single pancreas islet donation is to be successful then the pancreas must be of a high quality, which seemed to be the message arising from Hering’s paper. Unfortunately, this is unusual in the U.S. (and elsewhere) where the best pancreases go to the vascularized pancreatic organ transplant programs. He does outline the areas of research required in the coming years. These include selection of the donor and improved processing of the pancreas, resulting in better preparations and better viability of the islets, the achievement of tolerance and the production of other sources of insulin-producing cells. He feels that the final phase of development in this area will see a restoration of tolerance to B cell autoantigens with regeneration of islet tissue from the patients’ own cells,
making islet transplantation a redundant procedure. How far away the final target is unknown, but it will probably be quite some time.

Smith and Gale agree that IBMIR is an important problem but emphasized that there are other important factors in determining a successful outcome. They remind us that islet preparations that are clinically satisfactory for transplantation are achieved in only 50% of pancreases. They do feel that the adoption of the two-layer method of pancreatic preservation has had a significant impact on the quality of islet preparations. The prevention of apoptosis that is produced by inflammatory cytokines under metabolic stress and hypoxia is also considered important by these authors. They also discuss the indications for islet transplantation and wonder how common is severe recurrent hypoglycemia in the diabetic population, as this is considered the main indication for islet transplantation today. They also point out that of 250,000 patients with Type 1 diabetes in the U.K., there may be as many as 7,500 with severe recurrent hypoglycemia but in only a small minority would islet transplantation be justified. With respect to islet transplantation after kidney transplantation, some 250 patients in the U.K. are potentially suitable each year, emphasizing that however successful islet transplantation becomes the demand will not be met. In countries where the incidence of Type 1 diabetes is higher, then the discrepancy between supply and demand will be even higher.

Finally, James Shapiro and his team from Edmonton, who have been responsible for the resurgence of interest in islet transplantation with their initial report of successful islet transplantation in seven patients in 2000, review a large experience over the last decade and in particular the excellent result of the three major centers in Edmonton, Miami, and Minneapolis. He does emphasize that the loss of insulin independence over time is of great concern and that only one of their five patients transplanted over 5 years ago was still insulin independent at 5 years. However, he does point out that a patient who becomes insulin dependent again but is C-peptide positive (i.e., still producing some insulin) remains far more stable in terms of diabetic control. He outlines the areas of development that are required and are similar to those suggested by others in this forum. However, he does raise the controversial issue of live islet donor transplantation, which he feels will become possible and acceptable in due course and which would provide an approach applicable to children and contribute to the reduction in the shortfall between supply and demand.

All in all, the reader might ask whether that much progress in human islet transplantation from a clinical point of view really has been made over the last 20 years. To some extent this depends on whether you see the glass as being half-full or half-empty. However, from our perspective, having been involved in islet transplantation from its earliest days but now looking at it from the outside, so to speak, we do feel that enormous progress has been made. And with a sustained effort to solve the problems pointed out by the contributors to this forum, successful islet transplantation with islets from a single donor and with acceptable immunosuppression will be achieved. Thus we feel that the glass is more than half-full!