Editorial

Unraveling the Secrets of Single Donor Success in Islet Transplantation

A. M. James Shapiro and Camillo Ricordi

Clinical Islet Transplant Program, University of Alberta, Edmonton AB, Canada
Diabetes Research Institute, University of Miami, Miami, FL
Corresponding author: James Shapiro, shapiro@islet.ca

Received 10 November 2003, revised and accepted for publication 21 November 2003

Islet transplantation is emerging as an attractive alternative to solitary pancreas transplantation for a highly select group of patients with severe, labile forms of Type 1 diabetes that had previously tried and failed on intensive insulin therapy. The year 2000 marked a dramatic shift in clinical success with the introduction of the so-called ‘Edmonton Protocol’, which built upon many years of intensive research and extensive collaborations between islet groups worldwide (1,2).

With cumulative combined data in more than 75 islet recipients from Edmonton, Miami and Minnesota since 1999, 99% of patients have demonstrated primary graft function, and 96% remained C-peptide positive at 1 year (3). Rates of insulin independence were 85% at 1 year, and approximately 70% remained insulin free at 2 years. This combined series of more than 75 cases was associated with a 0% patient mortality, with no cases of malignancy, cytomegaloviral disease or Epstein-Barr-related post-transplant lymphoproliferative disorder to date (3). In most of the cases at the Edmonton and Miami sites, islets were transplanted from usually two (or rarely, three) donors (4). There were no reports of main portal vein thrombosis in this series, but 4% of the 75 patients developed a segmental thrombus of a branch portal vein associated with infusion of less pure islet preparations (Edmonton site only) (5). These excellent outcomes match the current success rate for solitary pancreas transplantation in the United States (6).

Preliminary data from the Immune Tolerance Network’s (ITN) international nine site trial indicates that Edmonton’s success has indeed been replicated elsewhere at selected international centers, with a 90% insulin-free rate noted in three of the centers with long-standing expertise in islet preparation and clinical use of this immunosuppressive protocol (7). Furthermore, by restricting donor pancreas cold ischemia to less than 8 h (from up to 20 h in the original Edmonton series), combined with more restrictive maximal candidate body weight and insulin requirement cut-offs (from upwards of 90 kg and >1.0 U/kg/day in the Edmonton series, down to 70 kg and 0.7 U/kg/day in the ITN trial), five of the first 13 ITN patients (38%) attained insulin independence with a single donor islet transplant, and single donor success was as high as 75% at one of the centers (8). Preliminary analysis suggests that the two most significant factors affecting clinical success are: (a) the center’s skills in preparation of high-quality, high-yield islets following an identical isolation protocol; and (b) the center’s ability to maintain the recipient’s immunosuppressant levels within a specified target range after transplantation.

The degree of glycemic control provided by successful islet transplantation is far superior to all forms of exogenous insulin therapy available presently, and HbA1C is routinely maintained in the normal range after discontinuation of insulin (4,9). Islet transplantation has thus far proven to be highly effective in completely reversing both hypoglycemic episodes and lability even in those with partially functioning grafts, despite the fact that counter-regulatory glucagon responses are not fully restored (10). These findings recently led the Food and Drug Administration’s (FDA) Biological Response Modifier’s Advisory Committee to propose an alternative definition of islet transplant success as ‘Restoration of sustained euglycemia, either without exogenous insulin or with reduced insulin requirements’, as the FDA begins to explore the possibility of moving forward with a Biologics License for islet manufacture (3).

Over the past 4 years since the introduction of the ‘Edmonton Protocol’, extensive progress has continued, and currently more than 300 new islet recipients have received treatment on a worldwide basis since 1999 (11,12). This expanded experience has not only confirmed the initial Edmonton findings, but has highlighted important limitations that must be overcome if islet transplantation is to be more broadly applied as a potential cure for diabetes (4,13,14). The results of islet after kidney transplants appear to match the success of islet alone transplants under sirolimus-based immunosuppression (15–17). The Milan group have recently shown that long-term islet graft function (with persistent C-peptide secretion) can not only prolong the half-life of a kidney transplant, but may be...
associated with a reduced incidence of diabetic vascular complications and enhanced patient survival (11,18–20).

Notable progress includes the introduction of the perfluorodecalin (PFC) ‘two-layer’ method for pancreas protection during transportation and rescue of marginal donors (21–25), successful single-donor islet transplants from obese, nonheart-beating donors (26,27), and the routine use of islet culture rather than immediate transplantation to further improve the purity, practicality and safety of the procedure (22,28–31). The risk of acute bleeding following percutaneous transhepatic access to the portal vein has been reduced substantially by physical and mechanical ablation of the catheter tract using combinations of coils, thrombotic static agents or a coagulative laser (30,32). The use of a bag rather than a syringe for islet delivery has further improved the sterility and safety of the procedure (33).

The most notable recent progress however, has been the emergence of routine, single donor islet transplant success at the University of Minnesota (31). In the current issue of the American Journal of Transplantation, Hering and colleagues describe their unprecedented pilot experience with an innovative series of strategies designed to optimize the success with single donor islet transplantation. The authors are to be congratulated both on the quality and potency of their islet preparations. Donor pancreas organs were shipped in ‘two-layer’ oxygenated PFCs, and islets were dissociated using the automated Ricordi method (2), purified on non-Ficoll-based iodixanol gradients and cultured for 2 days in insulin-transferrin-selenium supplemented media (28,29). The use of the hOKT3g1 (Ala-Ala) antibody was associated with the documented emergence of increased peripheral CD4 + CD25 + ‘regulatory’ T-cell populations (31). A substantial body of evidence suggests that this antibody may effectively regulate autoimmunity in Type 1 diabetes, and is therefore a particularly attractive agent to test in islet transplantation (34–37). These strategies were associated with improved outcome, with four of six patients achieving and maintaining insulin independence beyond 1 year after single donor islet transplantation (31). Hering’s paper is also the first to demonstrate a clear predictive association between outcome of marginal mass islet transplants in diabetic nude mice and functional outcome after clinical transplantation of islets from the same human donor (31).

As others try to unravel the secrets of the single donor islet success reported by Hering and colleagues, it is not easy to define whether the dominant factors lie in the optimal selection of initial quality pancreas organs, in the islet process itself, in the immunosuppressant protocol or in the recruitment of optimal, insulin-sensitive recipients. Some might argue that the careful selection of young, stable, obese pancreas donors (donor weight range 90–159 kg, donor age range 16–39) coupled with a limited duration of cold ischemic storage ensured a more potent islet product. Careful selection of low-weight, relatively insulin-sensitive recipients may have further contributed to the single donor success. The answer likely lies in the combination of these factors. Indeed, single donor islet success has been achieved by a number of other groups using variants of the ‘Edmonton Protocol’, but not to this consistent level of success. To go beyond speculation, it would take a large, randomized, stratified, controlled trial to robustly define the relative importance of each factor. The islet field would likely be better served however, by a continued series of iterative pilot trials, all aimed at trying to further improve the safety, efficacy and availability of islet transplantation.

One of the biggest limitations to advancement in islet transplantation presently is access to high-quality donor pancreas organs. Greater than 70% of cadaveric pancreas organs are never recovered in the US, and of the 30% that are, the few that are offered for islet transplantation typically only become available after being offered and declined by whole pancreas transplant programs across the country. The problem with this approach is that it frequently exceeds the 6–8-h ‘shelf-life’ required to optimize the islet isolation process. The immediate challenges ahead in islet transplantation are clear. Accruing data at the major islet transplant institutions may soon be sufficient to justify a Biologics License with the FDA (3). This would facilitate the transition from research to insured clinical care in the US, thereby preserving valuable research funds to take islet transplantation to the next stage. This would also facilitate a parallel shift in organ allocation policy to allow more ideal pancreas donor organs to be used for islet isolation, rather than the ‘left-over’ organs that are available currently. There is a need for reliable, practical, predictive assays of islet function that will consistently define the potency of an islet preparation before transplantation. With more than 45 separate IND applications for islet research protocols registered with the FDA in the US, and with an estimated 75 islet start-up programs worldwide, perhaps it is time to re-examine the concept of regionalized islet isolation centers, with shipment of a high-quality final islet product to a number of recipient centers (30,38). This would clearly improve both the safety and the efficiency of the challenging process required for islet manufacture, thereby making more islets available to a broader recipient base. Meanwhile, additional studies are needed to define whether the improved outcome in the Minnesota study was indeed the result of any, or a combination, of the several strategies selected, or whether the real determining factors could have been related to the selection of pancreases from donors with a high BMI, which yield higher numbers of islets, in combination with careful selection of lean and insulin-sensitive recipients.

In the longer term, further improvements in antirejection therapies that do not have ‘nonimmunosuppressive side-effects’, strategies designed to induce immunological tolerance, and a means to supply an unlimited cell source for controlled insulin delivery will be the key steps to
define an ultimate cure for diabetes. With a potential 300 million people worldwide currently at risk of developing diabetes, and an annual diabetes healthcare cost worldwide of at least $153 billion (US), it is clear that new solutions must be found. Ultimately, an alternative stem cell or xenogeneic source may perhaps address these needs, but until such time, advances in islet transplantation continue to offer enormous hope to countless thousands of prospective candidates.

References


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