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Kidney, pancreas, and pancreatic islet transplantation

Many patients with end-stage renal disease are now being helped with improved transplantation techniques and immunosuppressive regimens.

ABSTRACT: Kidney transplantation is the treatment of choice for many patients with kidney failure, and outcomes in BC are excellent. Because donor organ shortage remains a major challenge, BC has developed innovative programs to expand the pool of both living and deceased donors, and allocation policies for deceased donor kidneys have evolved to improve utility while maintaining equity. Other improvements in kidney transplantation have been made by individualizing immunosuppressive therapy to maximize efficacy while minimizing toxicity.

Pancreas and pancreatic islet transplantation are reserved for those with type 1 diabetes. Because of the very limited number of suitable organ donors, whole pancreas transplantation is restricted to individuals with end-stage renal disease who have otherwise limited comorbidities and who are already on immunosuppressive medication. Successful pancreas transplantation can significantly improve both quality and quantity of life. Islet transplantation is still in its infancy, but has been shown to improve glycemic control and stabilize retinopathy and nephropathy.

Kidney transplantation

The first kidney transplant in BC was performed in 1968. With the dramatic improvement in graft and patient survival, transplantation has become the treatment of choice for many patients with end-stage kidney disease. However, significant challenges remain. Although immunosuppressive agents are effective, they have significant toxicity and individualized therapy is required to optimize function while limiting complications. There are also too few deceased donor kidneys to meet patient needs, and waiting times are in excess of 5 years after starting dialysis. This leads to morbidity in patients waiting for transplantation and affects survival after transplantation. More living kidney donation and expansion of the deceased donor pool are needed to address the deceased donor kidney shortage. It is critical with deceased donor kidneys to maximize their utility by appropriate allocation so that potential kidney life years are not lost when patients die with functioning kidneys.

Individualizing immunosuppressive therapy

Graft survival rates (**Figure 1**) and patient survival rates (**Figure 2**) for BC recipients of deceased donor and living donor kidneys have steadily improved. This is mainly due to refinements in immunosuppressive therapies. Today tacrolimus has largely replaced cyclosporine; mycophenolate mofetil has replaced azathioprine; and the use of steroids is no longer routine. Biological agents such as basiliximab (an interleukin-2 receptor blocker) or antithymocyte globulin (ATG) are now commonly used at the time of transplant.[1,2] The immunosuppressive regimen is determined by a patient's immunological risk of experiencing rejection. Low-risk patients are recipients of first transplants without evidence of antibodies to HLA antigens. Patients with detectable anti-HLA antibodies and those who have previously rejected a transplant are high-risk and receive more aggressive immunosuppression. Low-risk

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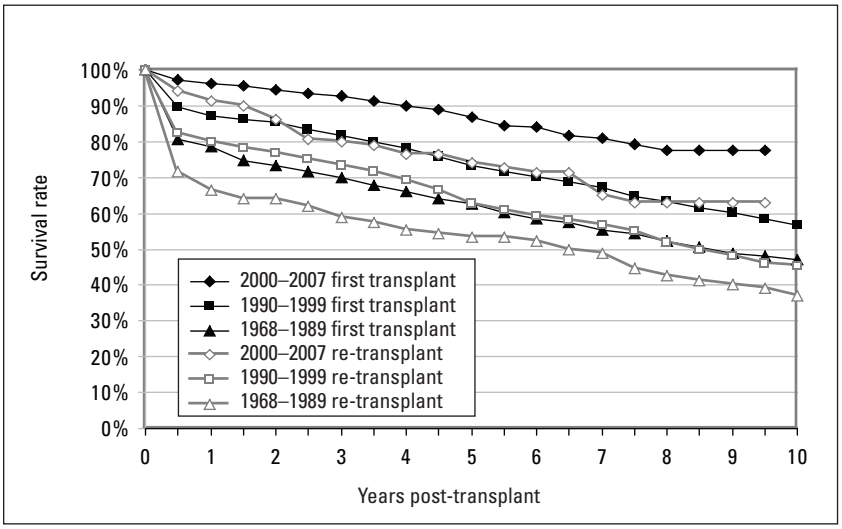

Figure 1. Graft survival for kidney transplants by graft number and year of transplant, 1968–2007.

Source: BC Transplant

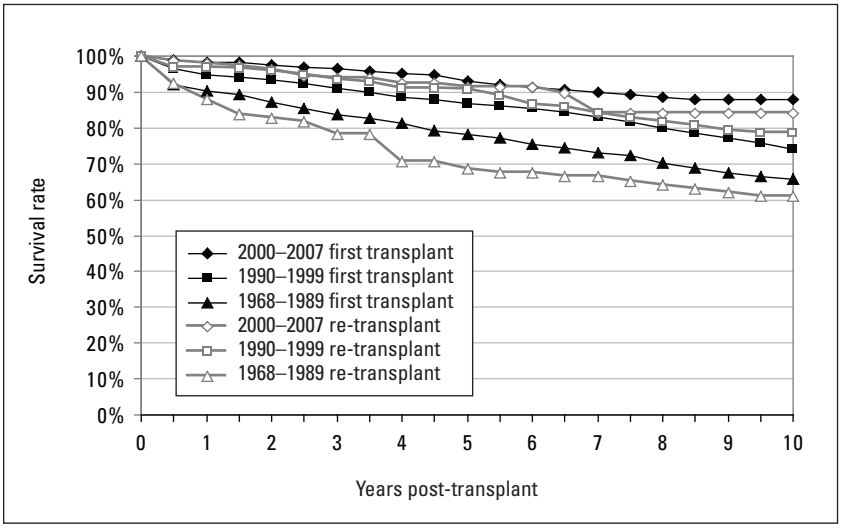

Figure 2. Patient survival for kidney transplants by graft number and year of transplant, 1968–2007.

Source: BC Transplant

patients receive a protocol consisting of basiliximab, tacrolimus, mycophenolate, and rapid steroid elimination, while high-risk patients receive ATG, tacrolimus, mycophenolate, and steroids.

In BC approximately 80% of transplant recipients are low-risk and thus receive minimal corticosteroid exposure. Of these low-risk patients, only those who experience acute rejection episodes are treated with steroids, and less than 20% of low-risk patients required steroids over the past 5 years. The steroid-free regimen has contributed to reduced morbidity and weight gain, better bone density, and improved patient satisfaction. The BC protocols were derived from our local experience and confirmed by results of international large-scale trials.[3] Results in low-risk patients have been excellent, with 1- and 10-year graft survival at 96.4% and 77.7%.

Results in high-risk patients have also improved. This is in part through laboratory tests that can detect anti-donor antibodies and hence avoid situations in which the likelihood of rejection is very high.[4,5] In addition to the introduction of potent antirejection drugs, there has been improvement in the use of antiviral agents and screening for viral infections, reducing the risk of severe or even fatal complications.[6]

Promoting and expanding living donation

In BC there has been a decrease in the number of deceased donor kidney transplants performed since 1990, but this has been offset by an increase in the number of living donor transplants (**Figure 3**). Today the BC program promotes pre-emptive living donor kidney transplant, whereby transplantation occurs before the initiation of dialysis, as the treatment of choice for most patients with kidney failure. This approach allows for better outcomes.[7]

Living donation has grown because of a number of factors. These include the development of programs that help recipients reach out to identify and request living donors, the acceptance of genetically unrelated living donors, the anonymous living donor program, the donor exchange program, and protocols to desensitize recipients to their living donors. It should be emphasized that living donors undergo rigorous medical and psychological testing before being accepted into the program, and are followed lifelong.

Historically, living donors were close family members, such as parents, children, or siblings. With improved

immunosuppressive therapy, HLA matching is less important and transplants from living unrelated donors are as successful as those from living related donors.[8] Today in BC more than 50% of transplants come from ABO compatible living unrelated donors, such as spouses, friends, in-laws, and coworkers. Part of our pretransplant assessment involves counseling patients on ways to reach out for living donors.

The BC Transplant kidney transplantation program was the first in Canada to utilize living anonymous donors (LAD). After initial research probing societal views on this issue,[9] the first LAD transplant was performed in 2005. In this program, individuals who have undergone rigorous medical and psychological testing donate their kidney to a recipient who is unknown to them. This is done anonymously to protect both the recipient and the donor. LAD kidneys may be given to a patient at the top of the wait list, or used in the donor exchange program.

Up to 30% of donor and recipient pairs may be incompatible because of ABO blood group mismatch or the presence of donor-specific anti-HLA antibodies. In paired exchange, approved donor and recipient pairs are registered into a database where suitable combinations are identified. In the simplest example, pair 1 has a donor who is blood group A and a recipient who is blood group B. Pair 2 has a blood group B donor and a blood group A recipient. The exchange occurs by the A donor from pair 1 donating to the A recipient from pair 2, and vice versa. In more complicated situations, chains are established to allow multiple transplants. The success of the paired donor exchange program is based on the number of donor and recipient pairs who are entered into the exchange. There is now a national paired donor exchange registry, which will facilitate matches. The use of LADs in the exchange program greatly enhances the number of possible matches, as the LAD is not tied to a recipient who must receive a transplant and thus can act as a key to unlock a chain of transplants. In the example shown in **Figure 4**, the use of the LAD kidney allows a four-way exchange to take place and still generates a kidney for the deceased donor wait list.

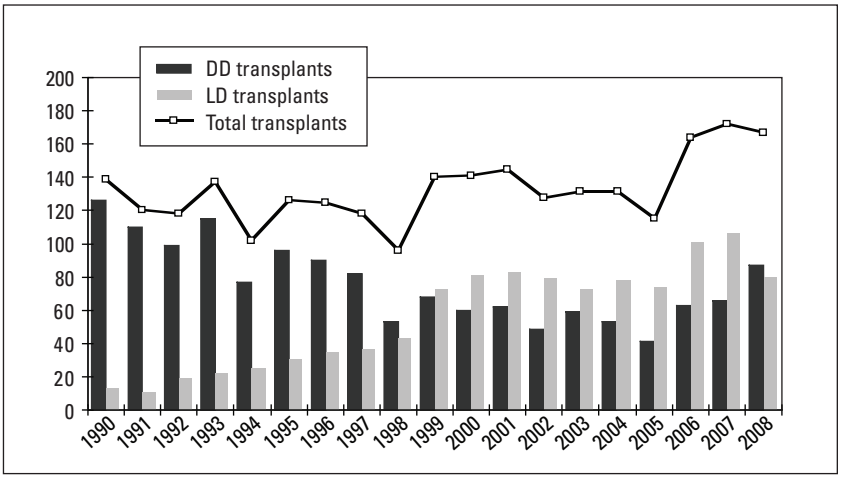

Figure 3: Living (LD) and deceased (DD) donor transplants in BC by year, 1990–2008.

Source: BC Transplant

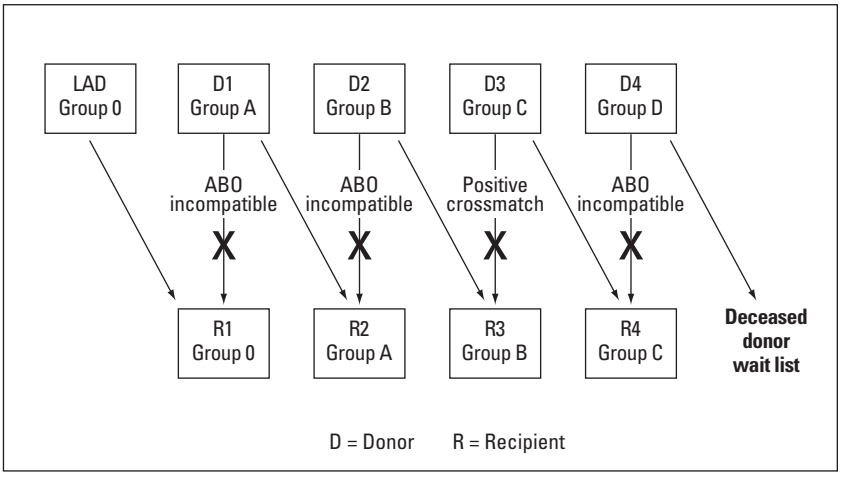

Figure 4. Four-pair transplant chain triggered by a living anonymous donor (LAD) and resulting in one kidney going to a recipient on the deceased donor wait list.

Expanding the deceased donor pool

Historically, organ donation has occurred when donors have been declared brain dead but have maintained circulation and hence organ perfusion. Until recently, donors who suffered cardiac death have not been used because of concerns that irreversible organ damage will have followed circulatory collapse. However, in controlled situations, organ damage, especially kidney damage, can be

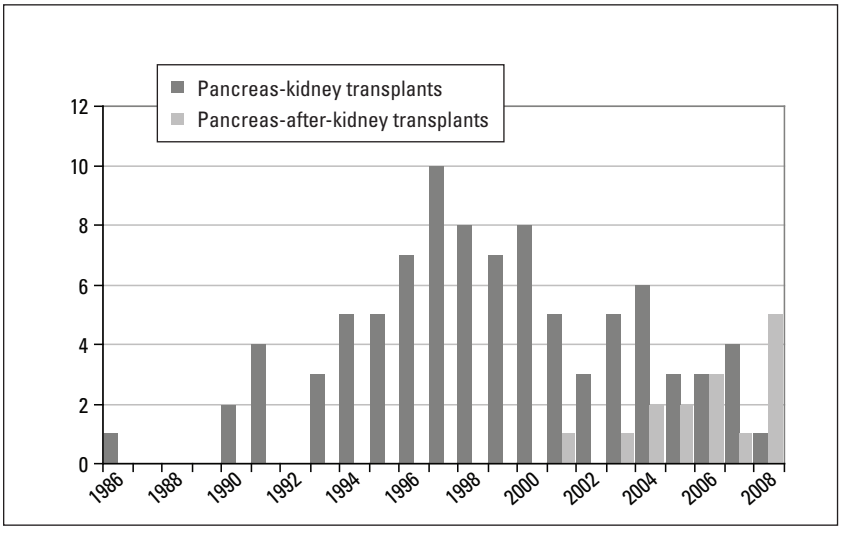

Figure 5. Simultaneous pancreas-kidney (SPK) and pancreas-after-kidney (PAK) transplants in BC, 1986–2008.

Source: BC Transplant

reduced to the point where the organs can be effectively utilized for transplantation. This process is referred to as donation after cardiac death (DCD). In this case family may consent or request that organ retrieval occur after the heart has stopped and death has been declared. Withdrawal of life support occurs in the operating room or an adjacent area, with the retrieval team on standby. The patient is monitored but there are no interventions. If cardiac standstill ensues quickly without a prolonged period of hypotension, the organs are still viable and organ retrieval commences 5 minutes after the heart stops. If cardiac arrest does not occur within 2 hours of removal of life support, organ donation does not occur and the patient receives the same palliative care that would have occurred after life support withdrawal. The first DCD in BC occurred in November 2008. We believe that this donor source will increase the donor pool by 20%.

Donors over the age of 60 or younger donors with risk factors for kidney damage, such as hypertension, have traditionally not been used for transplantation. However, there has been increased utilization of such donors, termed expanded criteria donors (ECD), as long as renal function is adequate. Older recipients who receive ECD kidneys benefit because of reduced time on the wait list.[10,11,12] In BC the ECD program allows recipients who have received the appropriate information and consented to this procedure to receive these kidneys.

Kidney allocation

Transplant recipients may die with their transplant still functioning well, an event termed "death with a functioning graft." It would be optimal to direct kidneys with shorter expected duration of function into older recipients who have shorter life expectancies, and kidneys from younger donors into younger recipients.[12] In BC a system preferentially allocating kidneys from donors under the age of 35 to recipients under 55, and kidneys from donors over the age of 60 to recipients over the age of 60 has recently been implemented and will be carefully monitored to ensure that it is achieving the desired results and maintaining fairness for all patient groups.

Pancreas transplantation

As is the case for kidney transplantation, demand is far greater than supply for pancreas transplantation and this disparity appears to be increasing.[13] The goals of pancreas transplantation are to provide sustained normoglycemia without insulin and, over time, to reverse or minimize microvascular and macrovascular complications. With whole pancreas transplantation, unlike pancreatic islet transplantation, the counter-regulatory axes are also restored. Most centres have found that successful pancreas transplantation significantly improves both quality and quantity of life.[14,15]

Pancreas transplantation is reserved for those with insulinopenic type 1 diabetes. There are only six to eight suitable pancreas donors annually in BC, and hence eligibility criteria are fairly strict to maximize the likelihood of successful outcomes. Individuals being considered for simultaneous pancreas-kidney transplantation (SPK) must have end-stage renal disease, good cardiac function, minimal peripheral vascular disease, be nonsmoking, and have few other significant comorbidities. SPK in BC did not really begin to flourish until the mid-1990s (**Figure 5**).[15] SPK with both grafts from a common deceased donor was the usual form of transplantation. However, because the waiting time for SPK is now so prolonged, prospective recipients are encouraged to identify potential live kidney donors, and wait for pancreas-after-kidney transplantation (PAK). The usual waiting time between kidney transplantation and PAK is in the order of several years, with blood groups O and B waiting

the longest. Candidates for PAK, in addition to the requirements for SPK, must have achieved good renal graft function and be free of severe immunological or infectious disease risk. Recipients opting for PAK have significantly enhanced long-term patient survival compared with those who wait for deceased donor kidneys.[14] This has been attributed to lessening the morbidity and mortality from excessive amounts of urea, which accumulates while the recipient waits. Recipients with good kidney function at the time of PAK experience fewer perioperative complications and shorter hospital stays compared with those with renal failure. Pancreas transplant alone (PTA) is an option that has been offered to individuals with brittle diabetes but no end-stage renal disease. However, patient selection is problematic, and there are higher than expected rates of graft failure and development of renal failure.[15]

Initial surgical approaches in the 1970s and 1980s utilizing a form of enteric drainage were abandoned because of surgical complications. Exocrine pancreas drainage was redirected to the bladder, which allowed monitoring of pancreas rejection by urinary amylase. However, bladder drainage posed its own problems, mainly from the exocrine secretions (metabolic acidosis from loss of urinary bicarbonate, chronic bladder inflammation, bladder stones) and in the mid-1990s most pancreas programs switched back to a simplified version of enteric drainage. In this operation, the donor duodenum with the attached pancreas is anastomosed end-to-side to the recipient small bowel and placed in the pelvis in a way similar to kidney transplantation. The arterial anastomosis is to the recipient's iliac artery and either systemic or portal venous drainage can be used.

Pancreas transplantation requires more intensive immunosuppression than kidney transplantation alone. For SPK, patients receive induction therapy with an interleukin-2 receptor antibody and methylprednisolone; maintenance therapy consists of mycophenolate, tacrolimus, and steroids. The standard protocol differs from that in renal transplant recipients in that steroids are continued. For those undergoing PAK, the induction regimen consists of a T-cell depleting agent (antithymocyte globulin) and methylprednisolone, with maintenance treatment the same as for SPK. It is controversial whether the two grafts are independent in terms of developing rejection or if rejection in one graft is always concordant with simultaneous rejection in the other graft.[16] Acute pancreas rejection rates are difficult to quantify, as pancreatic biopsies are not performed as routinely as kidney biopsies. Deteriorating renal function, reflected by a rise in serum creatinine, is sometimes used as an indicator of pancreas rejection, although it is recognized that this is an insensitive marker. Rising serum amylase is a more reliable indicator of acute rejection and should prompt pancreas biopsy. By the time impaired glucose levels are established, pancreatic rejection has probably been present for some time, and the pancreatic allograft may be difficult to salvage. Loss of pancreas function can also occur from recurrence of type 1 diabetes (autoimmune loss versus alloimmune loss). These two entities can be reliably distinguished by pancreas biopsy.[17]

Active pancreas rejection rates are difficult to quantify, as pancreatic biopsies are not performed as routinely as kidney biopsies.

For patients with type 1 diabetes and end-stage renal disease, timely transplantation is particularly important. Death on the wait list for SPK candidates is very common, with a reported 4-year mortality of 41.3% compared with 18.3% for those waiting for PAK.[14,18] This underscores the significant mortality attached to uremia and highlights the reason we advise patients to seek live donor kidney transplant while they wait for a pancreas.

Patient and graft survival for pancreas transplantation in BC are good. In patients with SPK, cumulative 5-year kidney graft survival in BC over several different transplant eras is

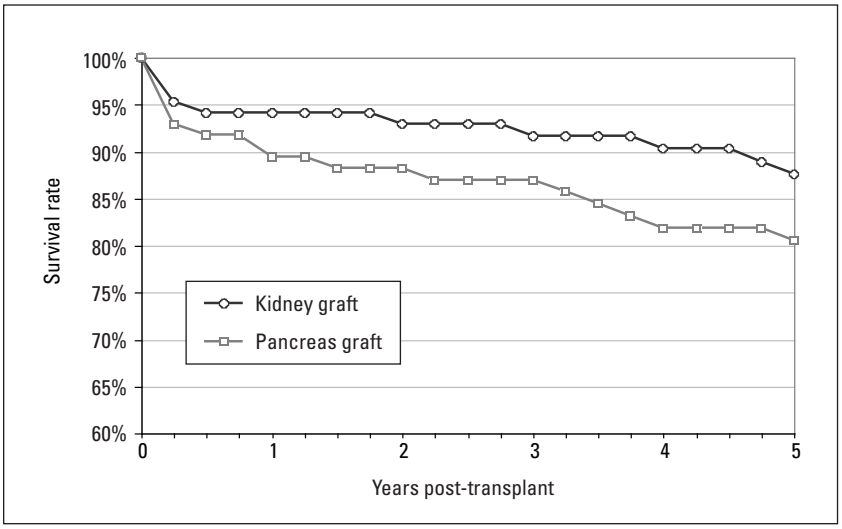

Figure 6. Graft survival for the first simultaneous pancreas-kidney (SPK) transplants in BC by organ, 1986–2008.

Source: BC Transplant

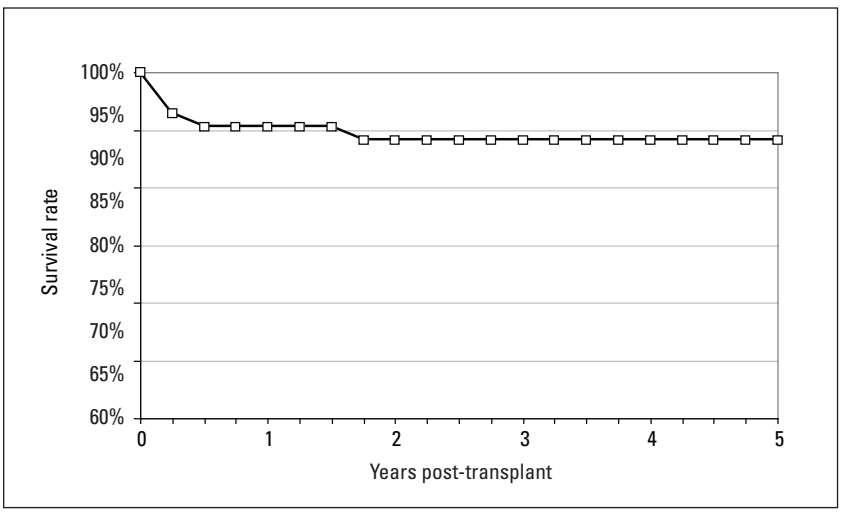

Figure 7. Patient survival for the first simultaneous pancreas-kidney (SPK) transplants in BC, 1986–2008.

Source: BC Transplant

87.5%, while the rate for pancreas graft survival is 80.5% (**Figure 6**). Patient survival for this same time span is 94.5% (**Figure 7**), comparable to US registry data with 5-year patient survival reported at 83% to 87% for SPK[13,14] and pancreas graft survival at 73%.[13] While there is an initial excess mortality in the first 90 days following SPK,[14,18] successful SPK confers a significant survival advantage, with more than 20 life years gained over those on a wait list.[14] Failure of the pancreatic graft leads to increased mortality,[18] the most important contributor being cardiovascular disease.[14,15,18]

Islet transplantation

Despite the initial success of islet transplantation reported from Edmonton in 2000,[19] this therapy is still considered experimental and offered only to those who have refractory hypoglycemia or who are being treated in experienced centres undertaking research.[20,21] The goals of islet transplantation are to decrease or eliminate the need for insulin, to improve HbA1c readings, and to minimize or prevent diabetes complications in patients with type 1 diabetes.

There are significant technical and medical challenges with islet transplantation. Islet isolation requires expertise, and the quality and quantity of islets must be assessed before being deemed suitable for donation. Most individuals require multiple islet transplants in order to achieve sufficient functioning islet mass. Placement of islets is also problematic, and although current practice relies on portal venous embolization, this site is probably not optimal.[22] At the time of transplantation, the immediate problems include an acute intrahepatic coagulation reaction, and promotion of cell viability and engraftment. Over time, the potential for alloimmune and autoimmune destruction becomes apparent.

In BC the islet program began in the context of research, comparing islet transplantation with intensive insulin therapy. Candidates had to have normal renal function, minimal albuminuria, and minimal retinopathy. The first islet transplantation occurred in 2003, and since then 70 islet transplantations have been performed in 31 patients.[23] Our results have demonstrated stable and improved metabolic control, with significantly lower HbA1c values in islet transplant recipients compared with those on intensive medical therapy. As well, renal function has not declined, and ret-

inopathy has stabilized in transplant recipients compared with medical controls.[23]

Immunosuppressive regimens continue to be refined. The original Edmonton protocol relied on a combination of sirolimus and tacrolimus, but this combination proved more nephrotoxic than anticipated. In BC we use induction with antithymocyte globulin for the first transplant and maintenance with tacrolimus and mycophenolate in a steroid-free regimen. For subsequent transplants, induction is with basiliximab. Other centres use a variety of induction agents and maintenance regimens.[24] There is also a nonimmunological component in the therapy of islet transplantation, with drugs directed at the coagulation cascade, and antiapoptotic strategies utilizing incretin-based therapies.[25,26]

The advantages and disadvantages of islet transplantation are summarized in the accompanying **Table**. A sufficient functioning islet mass must be obtained to achieve the principal advantages—freedom from or reduction in insulin requirements, improved metabolic profile, and stabilization of diabetic complications. However, these benefits come with the cost of lifelong immunosuppression and its attendant risks, including infection and malignancy. In addition, there is also the risk of immune sensitization, particularly as multiple donors are required, which may significantly limit access to future renal transplantation should that be required.[21,27] Unlike whole pancreas transplantation, islet transplantation does not have a durable response, with less than 50% of patients remaining insulin-independent at 3 years.[28]

Renal transplant recipients in BC enjoy excellent success rates, but there remains the ongoing challenge of the shortage of donor organs for transplantation.

Conclusions

Kidney transplantation has been one of the true medical miracles of the past 50 years. Renal transplant recipients in BC enjoy excellent success rates, but there remains the ongoing challenge of the shortage of donor organs for transplantation. The BC renal transplant program has developed and implemented innovative strategies to deal with these issues.

For those with type 1 diabetes, successful simultaneous pancreas-kidney transplantation or pancreas-after-kidney transplantation with preceding live donor kidney transplantation offers superior long-term graft and patient survival compared with either kidney transplant alone from a deceased donor or remaining on the wait list.[14]

Pancreatic islet transplantation holds promise for individuals with type 1 diabetes. However, there are still significant technical and medical hurdles to overcome. Newer treatment strategies include refining immunosuppressive protocols and developing agents that will improve islet viability and function.

Table. Advantages and disadvantages of pancreatic islet transplantation.

Advantages	Disadvantages
Freedom from insulin injections over the short term	Not a durable transplant, with more than 50% returning to some insulin use after 3 years
Improved glycemic control, with less hypoglycemia, better HbA1c, measurable C-peptide	Requires lifelong immunosuppression with attendant risks (infection and malignancy)
Stability or improvement in nephropathy, retinopathy	May need multiple classes of drugs: oral hypoglycemic agents; glucagon-like peptide-1 agonists (exenatide) or dipeptidyl-4 inhibitors (januvia) for successful long-term results
	Risk of sensitization, jeopardizing future renal transplant opportunities

Competing interests

None declared.

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