Multiple Options for Insulin Independence in Type 1 Diabetic Patients with a Functioning Kidney Transplant

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Many patients with diabetic nephropathy who have received a successful kidney transplant continue to live with Type 1 diabetes. Type 1 diabetes can be ameliorated with successful transplants of either the whole pancreas or just the isolated/purified islets. Because renal transplant recipients already are taking anti-rejection medicines, the transplantation of functional insulin-producing beta cells via the whole organ or through an infusion of purified islets is an attractive option to further enhance well-being.

There are many similarities and differences between pancreas and islet transplants. Candidates for either type of transplant have Type 1 diabetes (no C-peptide production), and good kidney transplant function and are tolerating the anti-rejection medicine. The typical patient who receives a pancreas-after-kidney transplant is 42 years old, has had diabetes for 35 years, has a body mass index (BMI) of 25 (39 percent have a BMI greater than 25 and 10 percent have a BMI greater than 30) and has had a transplanted kidney for 30 months from a deceased donor, or 12 months from a living donor. The typical anti-rejection protocol includes tacrolimus (Prograf®) and mycophenolate (CellCept®) and prednisone immunosuppression. Approximately 350 to 400 pancreas-after-kidney transplants are performed annually in the United States. The most recent analysis by the International Pancreas Transplant Registry for a cohort of more than 1,100 individuals transplanted between 2000 and 2004 shows that the one-year pancreas graft survival rate resulting in complete insulin independence and normal HgbA1c levels is between 79 and 85 percent, with the higher success rate seen in patients who received a T-cell depleting induction agent with tacrolimus and MMF maintenance. At five years the pancreas survival rate is approximately 60 percent.

For the islet-after-kidney transplant recipient, the Collaborative Islet Transplant Registry report shows that the average recipient is approximately 45 years old, has had diabetes for 31.5 years and has a BMI of 23 (maximum 27). The most common immunosuppressive combination includes tacrolimus and sirolimus (Rapamune®), and is steroid free. Most recipients require at least two infusions of islet cells. Approximately 50 percent of recipients achieve insulin independence within one year following the first infusion, and in those who are not insulin independent there is an approximate 70 percent reduction in insulin requirements compared to the pre-transplant baseline level. There also is a decrease in HgbA1c level, and a sharp decrease in the number of hypoglycemic events compared to the pre-transplant level. The immunosuppression is virtually the same for both transplants.

The differences between the patient populations for pancreas versus islet transplant relate to the more inclusive criteria for candidacy in the former. Specifically, there are more liberal criteria for body weight, BMI and the amount of insulin required. Also, in the pancreas-after-kidney transplant population, the rate of insulin independence is higher. The advantage of the islet cell transplant is that for select patients it is a less invasive procedure. The islet infusion typically is done in the radiology suite with the transplant surgeon and radiologist working together. The patient is awake and receives lidocaine to numb the skin. The islets are infused through a catheter that goes through the skin on the anterior abdominal wall and into the liver. The islets are infused though the catheter into the portal venous circulation to imbed in the liver.

The National Institutes for Health-supported Clinical Islet Transplantation Consortium is conducting a pivotal licensing study comparing islet transplantation to intensive insulin therapy in Type 1 diabetic kidney recipients in order to examine the efficacy of islet-after-kidney transplants. Northwestern Memorial Hospital and Northwestern University are partners in this study and comprise one of six U.S. centers, and the only one in Illinois, involved in this prospective, multi-center randomized trial. The experimental treatment group of patients will receive an infusion of islets with a (Continued on Page 4)
Immunosuppression is now manageable in the short term but it remains a major hurdle for long-term outcomes in renal transplantation. Specifically, current combinations of immunosuppressive agents have markedly reduced acute rejection rates in transplantation but they have not provided a related increase in long-term graft survival. The reasons for this include cardiovascular disease, cancer, infections, bone fractures and other toxicities related to the immunosuppressant agents themselves. Efforts to maintain low acute rejection rates while minimizing longer-term toxicity focus not only on creation and use of novel immunosuppressant agents but also on improved employment of existing agents.

The adverse effects of corticosteroids are well known, but the historical data strongly suggest that withdrawal of steroids in the months after renal transplant increases the rate of rejection. Based on further scrutiny of that historical data and also based on growing use of induction protocols (e.g., with lymphocyte-depleting agents or interleukin-2 receptor antagonists) and newer immunosuppressive agents, several investigators have recently explored new strategies to limit steroids as a maintenance agent.

In one retrospective analysis, results with a rapid discontinuation protocol were compared with those from a more typical slow tapering of steroids over months. In the rapid elimination group, thymoglobulin in five doses was the standard induction and prednisone was completely eliminated by day five after surgery. In this study, there were no significant differences in patient survival, graft survival or creatinine clearance over 48 months.

Similarly, at Northwestern Memorial Hospital and Northwestern University we recently performed a retrospective analysis of 212 kidney transplant patients either with or without prednisone as part of the maintenance immunosuppression. All patients were managed with induction, including IL-2-RA (days zero and three) and methylprednisolone (days zero and two), followed by maintenance with tacrolimus and MMF either with or without prednisone. The Kaplan-Meier analyses of patient and graft survival at seven years after transplantation were not statistically different between the groups (Figure 1). Neither were there significant differences in acute rejection rates (P=0.12), severity of rejection or GFR (P=0.19). As reported at this year’s American Transplant Congress, histological evaluation of the allografts indicates a lack of differences between groups in terms of fibrosis, inflammation or transplant glomerulopathy. The prednisone-treated patients had a significantly higher incidence of hyperlipidemia (50 percent versus 30 percent, P=0.001) and post-transplantation diabetes (15 percent versus 5 percent, P=0.001).

Several investigators have recently reported on early steroid withdrawal in special transplant populations. In African-Americans (AA), a retrospective analysis showed that one group of AA patients without steroid maintenance had one-year graft survival and function and acute rejection rates that were essentially similar to AA patients with steroid maintenance. A larger and longer (three years) comparison has now confirmed that kidney function and graft survival are comparable in AA patients with or without early steroid withdrawal. The same author has reported comparable five-year patient and graft outcomes, but higher five-year serum creatinine and early (one month) subclinical acute rejection, in AA recipients compared to non-AA recipients. Experience with early steroid withdrawal also has been

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Laparoscopic Resection of Polycystic Kidney Disease (PCKD): The Northwestern Memorial Hospital Experience

Talia Baker, MD

Autosomal dominant polycystic kidney disease (ADPKD) affects 4 to 6 million people worldwide, including 600,000 Americans. Not only is PKD one of the most common heritable diseases in the United States but also, in 60 percent of cases, sufferers develop end-stage renal disease ultimately requiring dialysis.

Pathologically, ADPKD is characterized by multiple expanding cysts on both kidneys that destroy renal parenchyma, eventually leading to renal failure. Patients are able to retain renal function until 40 to 60 years of age because the cysts initially affect only a portion of the nephron.

The etiology of ADPKD is still unknown but it is known to involve mutations in genes on 16p13.3 (PKD1) and 4q21 (PKD2), which code for polycystin integral membrane proteins; polycystin proteins are thought to be important in cell-to-cell and cell-to-matrix interactions in tubular epithelium.

The cysts are filled with electrolytes, water, growth hormones, rennin, amino acids, urea, glucose, erythropoietin, albumin and many other substances. They are not passive structures and have various active absorptive and secretory mechanisms. Furthermore, they have proliferation and apoptosis control mechanisms. Due to its complex etiology, ADPKD presents with numerous problems, which include back and flank pain, hypertension, UTIs (occurring in 60 to 70 percent of women and 20 percent of men), renal colic, shortness of breath and gastrointestinal problems. Patients also experience pain caused by stretching of the kidney capsule, cyst ruptures, pyelonephritis, urolithiasis (occurring in 20 to 30 percent of patients), kidney subcapsular hematoma, nephrolithiasis (occurring in 20 to 36 percent of patients) abdominal wall hernias (occurring in 45 percent of patients) and/or pressure created by the enlarged kidneys against the abdominal wall.

In order to address all of these problems, native nephrectomy has emerged as a viable treatment option. This procedure can be done pre- or post-transplantation and often is indicated simply to create enough space for safe transplantation. Traditional methods to remove cystic kidneys weighing up to 38 pounds each, such as trans-abdominal incisions, often leave patients debilitated. Although laparoscopy has been difficult to perform because patients suffer from multi-system problems such as liver cysts, renal failure and physical obstructive difficulties, laparoscopic nephrectomies for PKD patients have been performed since 1996. Laparoscopy certainly provides a shorter post-operative course and better wound healing as compared to traditional open procedures.

At Northwestern Memorial Hospital we offer laparoscopic unilateral or bilateral nephrectomy. A review of the literature suggests that ours is the largest series of bilateral laparoscopic nephrectomies for ADPKD by any one surgical team. We feel this series also shows the best outcomes among comparative studies and demonstrates the best option for ADPKD sufferers. In our series, a total of 11 patients underwent 20 nephrectomies (10 left and 10 right kidneys); nine patients had bilateral nephrectomies and two had unilateral nephrectomies. Patients came from a multitude of backgrounds and had a variety of other health issues, such as diabetes, smoking and others. The average patient age was 49.9 years (with a range of 33 to 62 years) and average weight was 218.8 pounds (with a range of 148 to 317 pounds). Five patients also had pre-existing liver cyst involvement. The average operative time was 4.24 hours (with a range of 2.03 to 7.63 hours and a median of 4.1 hours) with an average blood loss of 160mL (with a range of 50mL to 300mL). The average pathological dry weight of the removed kidney was 1,418.3 grams (with a range of 466 grams to 3,702 grams). There were no intra-operative surgical complications. The average time until discharge was 4.9 days (with a range of one to 12 days and a median of 4.5 days) with an average subjective pain rating of 3.89 out of 10 (with a range of zero to 10). The average patient reached a pain level of zero in two days (with a range of one to three days).

In our procedure, we used hand-assisted laparoscopic techniques, as we believe the benefits they provide in making the surgery easier and decreasing complication risks outweigh the downsides of creating a hand port. Lee and Clayman investigated this in their study and concluded that hand-assisted nephrectomy tends to show benefits over non-hand-assisted laparoscopic methods such as decreased morbidity as well as significant drops in operative time. Tactile feedback is helpful in situations where renal and abdominal architecture is abnormal. The hand-assisted laparoscopic method provides additional control that can prevent problems such as vena cava or cecal lacerations. We believe this is one of the main contributing factors that led to our zero-percent intraoperative complication rate.

In conclusion, we believe that in experienced hands bilateral hand-assisted nephrectomy is not only as safe and as feasible as open trans-abdominal surgery for sufferers of ADPKD, but also that it renders better post-operative outcomes with regard to blood loss, surgical complications, subjective pain rating in the ICU and days until discharge.
Patients with a Functioning Kidney Transplant
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goal of achieving insulin independence. The primary endpoint is the proportion of subjects with both a hemoglobin A1C of less than 6.5 percent and an absence of severe hypoglycemic events at one year after the first islet transplant.
The study will include male and female subjects between 18 and 65 years old.
Subjects also must meet the following inclusion criteria:
• history compatible with Type 1 diabetes
• disease onset less than 40 years of age
• insulin dependence for at least five years, absent stimulated C-peptide

A Review of Recent Clinical Trials
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reported in ABO-incompatible patients, cross-match positive patients and re-transplanted patients.
In summary, induction therapy with IL-2-RA or a T-cell depleting agent allows safe elimination of steroids in many patients without increasing the risk of acute rejection or long-term allograft problems. A steroid-free maintenance regimen has been shown to have significant health benefits in terms of fewer adverse events. In terms of a combination maintenance regimen in a steroid-free protocol, tacrolimus plus MMF may provide better graft survival and function than tacrolimus plus sirolimus. In AA patients, steroid-free immunosuppression can be safe but increased rates of subclinical rejection suggest the need for an early biopsy. In patients with high levels of anti-blood group antibodies, steroid therapy may need to continue for a longer period to avoid acute humoral rejection.

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