PAPER

Excellent Short-term Results With Steroid-Free Maintenance Immunosuppression in Low-Risk Simultaneous Pancreas-Kidney Transplantation

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Hypothesis: Steroid avoidance is possible in simultaneous pancreas-kidney transplantation with the use of newer immunosuppressive agents and induction therapy.

Design: A retrospective consecutive case review.

Setting: A university tertiary referral center.

Patients: Medical records of 40 consecutive patients who underwent pancreas-kidney transplantation from November 2000 to July 2002 were reviewed.

Intervention: The immunosuppression protocol used in this series of patients consisted of Thymoglobulin induction combined with mycophenolate mofetil, tacrolimus, and sirolimus for maintenance immunosuppression. Steroids were used as pretreatment only, given with Thymoglobulin, and were typically discontinued by postoperative week 1.

Main Outcome Measures: Graft and patient survival rates, rejection rates of the kidney or pancreas, infection rates, and surgical complication rates.

Results: Patient, kidney, and pancreas survival rates were 95.0%, 92.5%, and 87.5%, respectively. Biopsy-proven pancreas rejection rates at 1 and 3 months' posttransplantation were 2.5%. Kidney rejection rates at 1 and 3 months were 2.5%. Steroids were given only to patients with documented transplant rejection. Surgical and medical complications were no different from earlier protocols.

Conclusions: Immunosuppression protocols that do not include maintenance steroids have shown minimal rejection in the first 3 months and equivalent patient and graft survival rates compared with protocols that use steroids. The potential beneficial long-term impact of steroid avoidance will require further study.

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SIMULTANEOUS pancreas-kidney transplantation is a well-accepted procedure for patients with type I diabetes mellitus and renal failure. Historically, rejection rates of the pancreas in this type of dual transplantation have been as high as 80%, typically requiring antibody therapy, with an accompanying high rate of graft dysfunction or graft loss due to a failed response.[1] With the introduction of both tacrolimus and mycophenolate mofetil (MMF) in the later part of the last decade, rejection rates of the pancreas have dropped considerably.[2] This has led several groups to alter both induction immunosuppression as well as maintenance immunosuppression.[3-5] With the introduction of sirolimus in the last 2 years, the potential for a protocol that avoids steroid use has been suggested. It is well known that steroids have diabetogenic potential. Additionally, protocols that avoid steroid use in islet cell transplantation have enjoyed good early results, with no obvious problems with rejection.[6] Given these concepts, our center embarked on a steroid-free immunosuppression protocol for maintenance immunosuppression. The first 40 patients treated with this regimen are the subjects of this report.

METHODS

This is a retrospective, single-center review of our experience with a steroid-avoidance immunosuppression protocol in recipients of simultaneous pancreas-kidney transplants at the University of California–San Francisco. The study was approved by the committee on human research at the University of California–San Francisco. Forty consecutive patients who underwent first-time simultaneous pancreas-kidney transplantation from November 2000 to July 2002 were included. Patients who underwent retransplantation or patients who were sensitized (panel reactive antibody >30%) were excluded from the protocol and were not included in this analysis. Patient records and clinic flow sheets, as well as pathology re-

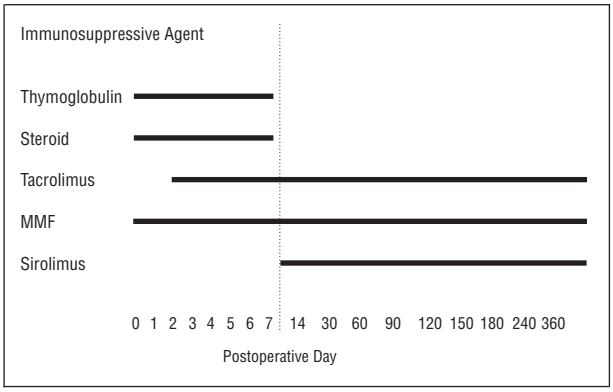

Figure 1. Overview of immunosuppression regimen. Treatment with steroids was discontinued by 1 week posttransplantation. Tacrolimus and sirolimus doses were adjusted to target levels as outlined in the text. MMF indicates mycophenolate mofetil.

ports, microbiology reports, and immunosuppression doses, for a minimum follow-up of 6 months, were reviewed.

All patients underwent simultaneous pancreas-kidney transplantation through a midline incision. The pancreas was prepared as previously described and implanted in the right iliac fossa, with venous drainage to the external iliac vein and exocrine drainage to the terminal ileum.[7] The kidney transplant was then placed in the left iliac fossa with an extravessicular bladder anastomosis. Patients were monitored postoperatively in the intensive care unit for 24 hours and then transferred to the regular care floor. Nasogastric tubes were removed with the first sign of bowel activity, typically on postoperative day (POD) 3 to 4, and an oral diet was started. Bladder catheters were routinely removed by POD 4. Perioperative broad-spectrum antibiotics were given until POD 5 and only continued if the donor duodenal culture grew an identified organism. Routine infection prophylaxis consisted of oral ganciclovir, trimethoprim-sulfamethoxazole, and weekly fluconazole. Oral ganciclovir was continued for 6 months posttransplantation, fluconazole for 3 months, and trimethoprim-sulfamethoxazole for life.

The immunosuppression protocol is summarized in **Figure 1**. All patients began receiving Thymoglobulin (SangStat, Fremont, Calif) at a dose of 1.5 mg/kg at the time of the incision, and it was infused for 6 hours. A dose of 1 mg/kg was then given daily, adjusted for white blood cell count. The Thymoglobulin was discontinued when an adequate tacrolimus level was reached, typically by POD 7. Solumedrol (500 mg) was given intravenously with the first Thymoglobulin dose, followed by 250 mg with the second dose, 2 mg/kg with the third dose, and 0.5 mg/kg with subsequent doses. The steroid was stopped as soon as the course of Thymoglobulin was discontinued. In patients who experienced profound leukopenia (white blood cell count $<1.5\times10^3/\mu L$), the MMF dose was cut in half. If this did not improve the counts, the Thymoglobulin dose was held for 1 day and then restarted. This occurred in less than 20% of patients.

All patients with initial renal function started receiving oral tacrolimus when their creatinine levels began to fall, usually by POD 2. The dose was adjusted to achieve a target trough level of 12 to 15 ng/mL. When this level was achieved, the Thymoglobulin and steroids were discontinued. Levels were measured daily while patients were hospitalized. Patients with initial slow graft function or delayed graft function did not receive tacrolimus until there was evidence of improving renal function, and Thymoglobulin was continued during this period. This occurred in 2 patients.

Mycophenolate mofetil was administered preoperatively at an oral dose of 1000 mg, and then continued postoperatively at a dose of 500 mg twice daily, adjusted for leukopenia. Sirolimus was started on the day following discontinuation of Thymoglobulin at an oral loading dose of 6 mg and then continued at a maintenance dose of 3 mg/d, adjusted for leukopenia or anemia. Levels were obtained after 3 doses, and target trough levels were 8 to 10 ng/mL.

For outpatient management, laboratory values were measured twice weekly for the first 6 weeks, then weekly for another 6 weeks, then every other week for another month, and then monthly, assuming that the patient was stable. Total cholesterol levels were measured every 3 months. Drugs with the potential for causing leukopenia (MMF, sirolimus) were adjusted if white blood cell and hematocrit counts were low ($<2.5\times10^3/\mu L$ and $<28\%$, respectively). Target trough levels for tacrolimus remained at 12 to 15 ng/mL for the first 3 months, then were lowered to 8 to 10 ng/mL until 6 months, and then maintained at 5 to 8 ng/mL. Sirolimus target levels remained at 8 to 10 ng/mL for the first 3 months, then fell to 6 to 8 ng/mL. Further adjustment in drug dosing was guided by specific toxic reactions, most commonly diarrhea, necessitating a lowering of MMF initially, and then sirolimus if the symptoms continued. Data are given as mean±SD unless otherwise indicated.

RESULTS

The cohort consisted of 40 patients with a mean age of 39±6 years and a male-female ratio of 24:16. All 40 patients had a minimum follow-up of 6 months. The mean follow-up time for the entire group was 474 days.

There were 2 early patient deaths, one of which occurred in a patient who had lost the pancreas to an early thrombosis. The other patient had lost the pancreas graft to infection after an attempt to repair a bowel anastomotic leak. Both patient deaths were attributed to uncontrollable sepsis. The 1-year patient survival rate was 95%. This is equivalent to our patient survival rate in a historic control group receiving steroids, MMF, and tacrolimus.

A total of 3 patients lost their pancreas grafts to an early thrombosis within 5 days of surgery, before sirolimus was started. The other pancreas graft loss was due to a mild rejection that occurred while the patient was still receiving Thymoglobulin. Because of ongoing fevers, the patient underwent exploration, and the decision was made to remove the graft based on its appearance. Pathologic analysis of the explant identified mild rejection. Therefore, the 1-year pancreas graft survival was 87.5%, which is also equivalent to pancreas survival rates in our earlier experience.

The reasons for loss of kidney grafts included death in 2 patients and a microangiopathy similar to hemolytic uremic syndrome in a third patient. No kidney grafts were lost to rejection. The 1-year kidney survival rate was 92.5%—also no different from graft survival of historic controls. The reasons for all graft losses are presented in **Table 1**.

Biopsies of the kidney were performed to detect any elevation in creatinine level that was not explained by a technical problem or drug toxicity. A total of 19 kidney biopsies were performed. Rejection of the kidney was seen only once in the first 6 months. Rejection was diagnosed on POD 27 in the same patient who had lost the

pancreas to an early rejection; this was treated with a steroid pulse and maintenance steroids. Another patient had a biopsy-proven rejection at POD 393, also treated with a steroid pulse. Therefore, the kidney rejection rate at 3 and 6 months was 2.5%.

Pancreas biopsies were performed to detect a persistent rise in serum amylase. The one biopsy performed revealed rejection, which was treated with Thymoglobulin and prednisone. Treatment of this patient had already deviated from the protocol because of her intolerance to calcineurin inhibitors due to hemolytic uremic syndrome. Her maintenance immunosuppression consisted of prednisone, sirolimus, and MMF at the time of the rejection. The only other pancreas rejection occurred on POD 27 as described above, leading to graft loss. Therefore, the pancreas rejection rate was 2.5% at 3 months and 5% at 6 months. A summary of the rejection rates is shown in **Figure 2**.

All patients who were free of rejection continued to receive the steroid-avoidance protocol with the exception of 1 patient. Because of the patient's fever and elevated blood glucose level, and our inability to perform a biopsy of the pancreas secondary to the overlying bowel, this patient was treated empirically with Thymoglobulin and a steroid pulse. Of note, a kidney biopsy performed at the same time showed no rejection. There was no improvement in blood glucose level, and the patient was given cyclosporine on the chance that the elevated blood glucose level was related to tacrolimus toxicity. This resulted in normalization of blood glucose, but the patient continued to receive steroids at a dose of 10 mg/d. The 3 other patients with rejection had low-dose prednisone added to their maintenance regimen and were considered for eventual weaning of the prednisone at the time of this review.

In general, the combination of tacrolimus, sirolimus, and MMF was well tolerated. In addition to the patient previously described, one other patient was given cyclosporine as a replacement for tacrolimus because of hair loss. Over time, MMF was reduced in most patients, owing to either leukopenia or gastrointestinal distress. The mean MMF dose at 6 months posttransplantation was 242 ± 283 mg twice daily. In 14 patients (38%), MMF was stopped completely by 6 months. Sirolimus was well tolerated; the mean dose at 6 months was 3.3 ± 1 mg daily.

This immunosuppression regimen did not appear to have an increased surgical complication rate. The pancreas graft thrombosis rate was 7.5%, there were 2 peripancreatic abscesses that responded to percutaneous drainage, and there were 3 incisional hernias and 1 bowel anastomotic breakdown. The mean length of stay for the entire cohort for the initial transplantation was 13.9 ± 7 days (range, 8-36 days). There was an average of 0.94 readmissions per patient, but 17 patients never required another hospitalization after discharge.

In terms of infection-related complications, both deaths were related to sepsis. The first death occurred on POD 70 after the patient had been through emergency coronary artery bypass grafting for new-onset ischemia, and was related to overwhelming *Aspergillus* infection. The second patient died of overwhelming sepsis, likely related to peritonitis from vancomycin-resistant *Enterococcus* species, also in the setting of a perioperative myocardial infarction. Other infections included the 2 peripancreatic abscesses, successfully treated, and a renal abscess that occurred 10 months' posttransplantation. This was also treated successfully with percutaneous drainage. There was 1 mild cytomegaloviral infection, treated with valganciclovir. Of greatest concern were 2 polyoma infections in the transplanted kidney, both occurring more than 1 year after transplantation. At the time of this review, 1 patient was close to resuming dialysis, and the other patient had a marked decrease in immunosuppression and treatment with cidofivir, with some stabilization of renal function.

Table 1. Reasons for Patient and Graft Loss

Patient loss (n = 2)
Aspergillus sepsis
VRE sepsis
Pancreas loss (n = 5)
Thrombosis (n = 3)
Infection due to enteric leak
Mild rejection
Kidney loss (n = 3)
Patient death (n = 2)
Microangiopathy

Abbreviation: VRE, vancomycim-resistant enterococci.

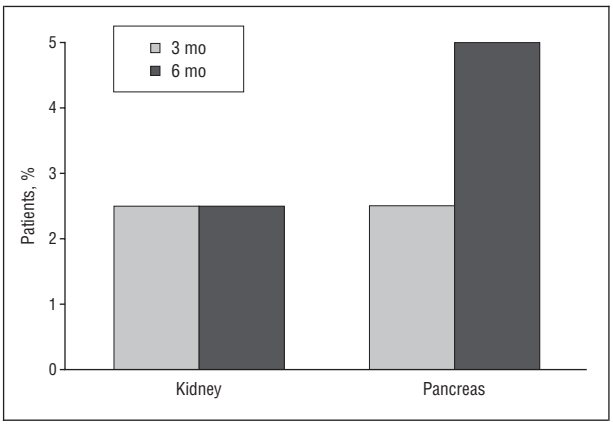

Figure 2. Kidney and pancreas rejection rates at 3 and 6 months. All rejections were biopsy proven.

One patient was diagnosed as having posttransplantation lymphoproliferative disorder at 8 months' posttransplantation. He was taking tacrolimus and sirolimus at the time, and had symptoms of ongoing diarrhea. A colonoscopy and biopsies revealed monomorphic B-cell lymphoma consistent with posttransplantation lymphoproliferative disorder. He had no evidence of transplant dysfunction. Sirolimus treatment was discontinued, tacrolimus was decreased, and anti-CD20 monoclonal antibody (rituximab) therapy was started in this patient and continued to the present.

Another measure of the success of this protocol would be evidence that the classic adverse effects of steroids were diminished. We followed cholesterol levels, weight changes, and the need for antihypertensive medications. The mean cholesterol levels at 3 and 6 months

Table 2. Outcomes at 6 Months

Patient survival	95
Kidney survival	92.5
Pancreas survival	87.5
Kidney rejection	2.5
Pancreas rejection	5
No. of readmissions	0.94 episodes/patient
Mean sirolimus dose (daily), mean ± SD, mg	3.3 ± 1
Mean MMF dose (daily), mean ± SD, mg	484 ± 283
Mean weight change, mean ± SD, kg	0.7 ± 4.1
Mean cholesterol, mean ± SD, mg/dL	191 ± 44
Hypertension drugs	
0	47
1	38.2
2	14.8

Abbreviation: MMF, mycophenolate mofetil.
*Data are given as percentage of patients unless otherwise indicated.

were 188±36 mg/dL (4.85±0.93 mmol/L) and 191±44 mg/dL (4.93±1.14 mmol/L), respectively. Only 3 patients required the initiation of cholesterol-lowering agents, and statins were used in each case. The average weight gain at 6 months was 0.7±4.1 kg. In patients who had a weight measurement at 1 year, the average gain was 3.5±5 kg. At 6 months posttransplantation, there was an average of 0.68 antihypertensive medications per patient, with 16 patients requiring no antihypertensive treatment. The overall outcome data at 6 months are presented in **Table 2**.

COMMENT

This report summarizes our experience with a steroid-sparing protocol, which appears to be efficacious in terms of graft survival rates and rejection rates. The introduction of newer and more potent immunosuppressive agents, such as tacrolimus and sirolimus, has expanded the options for maintenance immunosuppression and allowed for steroid-avoidance protocols. The ultimate benefit of these strategies remains to be seen, although this series suggests favorable metabolic benefits in terms of lipid profiles, hypertension, and weight changes.

In any report claiming low rejection rates, one must be concerned about overimmunosuppression. While there was not an obvious increased problem with infection, the 2 patient deaths due to infection early in the postoperative period are of great concern. Both of these patients had perioperative cardiac events, which prolonged their hospitalization and complicated their course. Whether the potent combination of immunosuppression contributed to their death could be debated. Similarly, the increased incidence of polyoma seen in many centers seems to correlate with the introduction of these newer agents and may ultimately be responsible for more kidney graft loss than rejection. The polyoma infection rate of 5% seen in this series is higher than we have previously seen.

The problem of posttransplantation lymphoproliferative disorder is also a possible sign of overimmunosuppression. While we have seen cases of posttransplantation lymphoproliferative disorder in patients who have undergone simultaneous pancreas and kidney transplantation previously, longer-term follow-up will be needed with this cohort to determine if the incidence is increased.

The rational for eliminating steroids is sensible. Trials to eliminate steroid use in kidney transplantation or liver transplantation have demonstrated positive effects.[8,9] However, with any new agent that fills the gap created by a steroid-free protocol comes a potential penalty. With the current protocol, tacrolimus levels were typically kept high during the first year. The potential toxic effects on renal function may outweigh the benefits of steroid avoidance. Tacrolimus has also been associated with abnormal lipid profiles, although less so than cyclosporine. Likewise, sirolimus has been shown to have its own negative effect on lipid profiles.[10] We did not see any problem with triglyceride levels, and the measured total cholesterol levels were acceptable in this cohort. Of course, long-term experience with sirolimus is limited, and other potential risks, such as malignancy, have not been determined. The advantage of a regimen that uses a combination of these newer agents is the potential dosing of each agent at a level that may avoid its inherent toxicity. This also pertains to the potential toxic effect of tacrolimus on beta cells, which appears to be dose-dependent.

It is clear from our experience that patients are pleased to have an immunosuppression regimen that avoids steroids. However, it is not hassle free. Many patients required constant early adjustment of MMF and sirolimus to address their toxicity in gastrointestinal functioning. The average dose of MMF at 6 months was only 250 mg twice daily, and MMF was discontinued in 14 patients. As experience with this protocol evolves, discontinuation of MMF at 3 to 6 months in all patients may result in a more acceptable adverse effect profile and may potentially avoid infections, such as polyoma. An alternative is to simply use dual therapy with either sirolimus or MMF in combination with tacrolimus from the time of transplantation. This has been shown by other investigators to have excellent early results.[11]

One other consideration with these newer protocols is cost. Although it was not specifically analyzed, yearly drug costs will certainly be higher in a protocol that avoids the inexpensive prednisone and substitutes newer agents that are not available in generic forms. This increased drug cost may be offset by the decreased need for treatment related to rejection. The rehospitalization rate was quite low in this cohort. Other cost savings may result from decreased complications related to cardiovascular disease if steroid avoidance is able to alter this comorbidity.[12]

As newer agents are introduced into our armamentarium, we face the challenge of finding the combination of drugs that is well tolerated with good efficacy and reasonable cost. This will certainly lead to many variations in protocols, none of which will be easily validated in a controlled trial, since rejection rates have plummeted. However, focusing on different end points may yield information to elevate one protocol over another. Longer-term follow-up data on cardiovascular problems, toxicity to renal functioning, and the effect on beta cell function will likely become discriminating measures for these new drugs. This protocol appears to have

excellent early results, and longer follow-up information will be forthcoming.

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DISCUSSION

Richard V. Perez, MD, Sacramento, Calif: Dr Freise and his coauthors have described a retrospective, single-center review of 40 consecutive patients undergoing kidney and pancreas transplantation. The problem that they face is essentially the general challenge of pancreas transplantation. This is a high-risk group of patients with advanced complications of diabetes and increased cardiovascular morbidity. As they mentioned, they traditionally have a higher incidence of rejection when compared to other transplant patients, and for this reason, they receive more immunosuppression. This and other factors leads in general to a higher incidence of infectious complications, especially in the setting of enteric drainage of the pancreas, a technique which was utilized in this series of patients.

So, the challenge that they face, and we as transplant physicians face in general, is the development of an immunosuppressive protocol which is potent enough to suppress rejection, tailored to minimize toxicity of immunosuppressive drugs, and yet gentle enough to avoid the complications of overimmunosuppression. To achieve these goals, they chose a protocol which they term *steroid avoidance*, patterned after recent protocols developed in kidney transplantation, and he mentioned the 5 different agents used: Thymoglobulin, tacrolimus, sirolimus, mycophenolate, and then a rapid steroid taper over 1 week. They reported excellent patient and graft outcomes, and they are to be commended for this.

Did they achieve the secondary goals as mentioned—that of efficacy, avoiding toxicity, and avoiding the complications of immunosuppression? In terms of efficacy, there is no question that the rejection rates that they report are amongst the lowest if not the lowest that has been reported in the literature—2.5% in kidney and 5% in the pancreas. So, it is a very potent drug therapy.

Did they minimize the adverse effects of the steroids? They mentioned the improvements in cholesterol, weight gain, and hypertension. I guess what we would have to ask is, and my first question is, are they really seeing improvements in the metabolic profile, and have they compared cholesterol, weight, and hypertension to their previous experience using their old immunosuppressive regimen?

We do know that with regard to bone changes, that the adverse effect of steroids on bone occurs during the first week, in large part due to the high doses of steroids, and so are they really benefiting the patients with regards to the bone disease? So, the second question I would ask is: are the steroids actually necessary in this protocol? The ideal protocol would be complete avoidance of steroids, which would not only have the metabolic benefits, but possibly, immunologic benefits as well because we know that steroids impede the development of tolerance and suppressor networks in some experimental models.

The third goal in terms of the immunosuppressive regimen is avoidance of the complications of overimmunosuppression. This area, as Dr Freise mentioned, is his biggest concern, and it would be mine as well if you are going to embrace such a protocol. The signs of overimmunosuppression as mentioned would be sepsis, and it is concerning that 2 of his patients died of overwhelming sepsis. Two very serious polyoma viral infections will probably lead to kidney graft loss in 2 other patients. He mentioned that bone marrow suppression was noted in a significant number of patients, so this may reflect that these patients may be overimmunosuppressed. As surgeons, we, of course, deal with wound healing issues and some complications may be a sign of overimmunosuppression. There were 3 hernias, 2 abscesses, and an anastomotic leak during the short term, possibly due to overimmunosuppression. Those of us that have used sirolimus have had the unpleasant experience of having late wound complications of having the patient come to clinic a month or 6 weeks posttransplant with a wound that is falling apart. I would ask, did you see any late wound problems that occurred on an outpatient basis?

Additionally, the mean hospital stay of 2 weeks would be a touch long in most series today, and especially, in the setting of these patients who had no rejection and kidneys that are working fine. I would ask, why was the length of stay so long? How does that compare to your previous length of stay?

Additionally, most of the readmissions for pancreas transplantation in the past have been secondary to metabolic and fluid problems related to bladder drainage of the pancreas. I am wondering what his readmissions in your enteric drained patients were for.

So, lastly, I would really commend the group for developing a strategy to deal with this difficult problem. The proof of the pudding though would be, and my last question is, what is your present standard of therapy? In other words, how would

you treat your next 40 patients? Would you make any changes in your immunosuppression based on what you have learned with these patients?

Chris Shackleton, MD, Los Angeles, Calif: Again, I would like to commend the authors for an incremental contribution to immunosuppression in organ transplantation because most of our advances nowadays do have to be made incrementally. I wonder if the authors could just summarize the actual protocol that was used because I wasn't quite clear on the slide whether all of these patients received serolimus or whether it was introduced sequentially following use of tacrolimus in the induction therapy with immunoglobulin.

Dr Perez asked the question regarding the hernia issue with serolimus. But that is an emerging issue with this agent in addition to its potent immunosuppressive capabilities. There is increasing evidence that it does impair wound healing significantly. Although the trial in the United States with the use of serolimus in liver transplantation was halted, we probably had the greatest single-center experience in liver transplantation with serolimus of over 70 patients, and when we analyzed our own data, the only significant thing that we noted compared to retrospective, historical controls as treated with FK-based immunosuppression was an increased incidence of incisional hernias.

That leads me into my third comment, pertaining to the issue of vascular complications. As Dr Freise mentioned that they had 3 episodes of thrombosis in 40 patients for about an 8% incidence of thrombosis, I would submit that that is somewhat high. I don't think it is related to the use of serolimus, and in all forms of organ transplantation, my own mantra whenever these issues arise is that vascular thrombosis is always a technical issue except in the rare instance where the patient actually has a coagulopathy of some sort.

Dr Freise: I agree totally with what you had to say, Rick, in terms of metabolic parameters. It would be great if we had a good control group and good data to compare our current lipid profiles, too. Unfortunately, there are a lot of holes in the data when we look retrospectively at our previous experience. If one looks at the literature, certainly, the cholesterol levels that we are seeing in our patients in this series appear to be better than what has been reported, at least for kidney transplant alone patients who are on steroid in combination with calconeurin inhibitor.

In terms of the issue of bone disease and early prednisone, you are absolutely correct that there is good evidence that just a week's worth of prednisone may have its own set of complications. The use of prednisone in our protocol is mainly to decrease the potential side effects of Thymoglobulin when that agent is given over the first week's time. There are investigators who have used Thymoglobulin without steroid pretreatment and have actually had good results. The only potential issue is that those patients typically have very high fevers, and, as you well know, these pancreas patients are already a setup for infection. I would be nervous to watch fevers of 40° for the first 3 or 4 days postoperatively. So, that's our rationale behind the steroids. It may be that we could get by with a much lower dose during that induction time and avoid the Thymoglobulin complications.

In terms of overimmunosuppression, which is really the biggest issue with this type of protocol using 3 very potent drugs over a long period of time, there is no question that we have concerns about infection complications. And as I alluded to, this polyoma viral infection, I believe, is going to be the real problem for us in the next decade as we start to learn more how to use these drugs. In the 80s, of course, cytomegalovirus (CMV) was a big problem, and many patients died from overwhelming CMV infections. Of course, now, with good antiviral prophylaxis for CMV, it really isn't as much of an issue and has allowed us to make advances in how we use these even more potent drugs. But with any new drug regimen, there will be penalties, and infection such as polyoma is something that we are going to have to watch for.

In terms of the 2 early deaths from sepsis, that's an unusual occurrence in our overall program experience, and, certainly, it is possible that those early deaths were related to overimmunosuppression. I would also emphasize that those patients had complicated courses related primarily to cardiac problems. Of course, once a patient who has had diabetes for many years undergoes this complex operation and begins to have other complications related to their heart, their postoperative course always becomes much more difficult.

In terms of surgical complications, and this gets at Dr Shackleton's question as well, the 3 hernias that we saw were all picked up in the outpatient follow-up. Generally, early on in the experience, we used absorbable suture for wound closure and have now gone to prolene exclusively in a 2-layered closure of the midline incision. There is no question in my mind that this early regimen has had a slightly higher rate of hernia formation. Whether that will be resolved with switching to nonabsorbable suture remains to be seen.

In terms of length of stay, this series has a slightly longer length of stay than our earlier experience by about 1 day. I did calculate mean length of stay. The median might have been a little bit more appealing number since about 25% of the patients were actually able to go home between 8 and 10 days rather than the mean stay of about 14 days.

Dr Perez' final question is a very important one. We now have this series of 40 patients that we have had an opportunity to learn from, and what are we going to do in the future? These patients, to a certain degree, were slightly overimmunosuppressed, and a future protocol will start out exactly as we are doing here, which is to use Thymoglobulin induction with prednisone followed by maintenance with sirolimus, tacrolimus, and MMF in all patients, and then weaning the MMF by 3 to 6 months posttransplant. Of note, about half the patients were able to come down to very low doses or no dose of MMF by 6 months and maintained a very low rejection rate. So, variation in the regimen will work for us.

Lastly, in terms of Dr Shackleton's question about thrombosis, I agree with you. Our thrombosis rate of about 8% in this series is higher than one would expect in most modern series, and I also agree that every graft thrombosis should be considered technical unless proven otherwise. When those 3 patients were explored for their graft pancreatectomy, one was clearly technical. There was a kink in the vein. The other 2 I don't have an obvious technical explanation for, but I would consider technical. I also do not believe that this particular regimen will be associated with a higher graft thrombosis rate.