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췌장이식환자에서 Tacrolimus와 Cyclosporine이 급성거부반응과 신장장애에 미치는 영향

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The Effects of Tacrolimus versus Cyclosporine on Acute Graft Rejection Episode and Acute Renal Dysfunction Following Pancreas Transplantation

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췌장이식의 성공률은 지난 10년 동안 상당히 상승되었다. International Pancreas Transplant Registry에 따르면 1995년 이래 미국에서만 매년 1,000건 이상의 췌장이식이 실시되고 있다. 장기이식후 나타나는 급성 거부반응은 이식 후 6개월 이내에 가장 높은 빈도수로 나타난다. 췌장이식환자에서는 신장을 이식한 것보다 두배나 높은 거부반응을 나타나며 이로 인한 입원율의 증가, 항림프제(antilymphocyte)의 사용과 감염의 증가로 이환율이 높다. 더구나 Cyclosporine (CsA)을 기초로 한 면역억제제요법의 사용은 높은 급성 거부반응률(acute graft rejection)을 초래하여 이식한 장기의 조직손실이 문제가 되고 있다. 새로운 면역억제제인 Tacrolimus (FK506)의 사용은 이식환자에서의 거부반응을 감소시켜 생존율을 증가시키는 것으로 알려져 있다. Tacrolimus는 neutral macrolide로 cyclic peptide인 CsA과는 화학구조는 매우 다르나 비슷한 면역억제 효과를 보인다. 하지만 Tacrolimus의 사용시 신경독성, 신독성, 특히 고혈당증의 발생률이 높아 일부 이식센터에서는 장기이식 후에 사용하기를 꺼리기도 한다. 하지만 여러 연구논문에서 간과 신장 이식 후 급성 거부반응 예방에 Tacrolimus는 CsA에 비해 이점이 있는 결과를 발표하였다. 결과적으로, 현재 췌장이식 후 Tacrolimus를 기초로 한 면역억제의 효과에 대한 연구가 활발히 진행중이다. 따라서 본 연구에서는 1994-1996년 사이에 Tacrolimus 또는 CsA를 기초로 한 면역억제요법을 투여 받은 췌장이식환자 101명을 후향적으로 조사하여 Tacrolimus (n=54)와 CsA(n=57)의 급성 거부반응 예방 효과와 신부전 발생률을 비교하였다. 모든 환자는 항림프구 약물, Azathioprine, Prednisone을 이식 후 면역억제제로 투여 받았다. 기준선으로부터 20% 이상의 혈청 creatinine의 상승이 있는 환자에서는 급성 신부전으로 정의하였고 신장생검법으로 거부반응을 진단하였다. Matched-pair analysis에 따르면 췌장이식환자의 6개월 생존율은 CsA군에서 97%, Tacrolimus군에서 96%로 별다른 차이가 없었으며(p=0.57), 6개월간의 이식한 췌장의 보존율은 CsA군에서는 88%, Tacrolimus군에서 91%로 유의한 차이는 없었다(p=0.29). 췌장이식 후 6개월 동안 Tacrolimus의 사용은 생검으로 증명되는(biopsy-proven) 급성 거부반응의 발생빈도는 CsA보다 유의하게 낮았을 뿐만 아니라 ($p<0.05$) 거부반응 증상의 심각도 또한 감소시켰다 (p=0.03). 급성거부반응 발생빈도의 감소로 Tacrolimus군에서 antilymphocyte의 치료가 유의하게 줄어들었다(p=0.01). CsA군에서 Tacrolimus군보다 신부전의 발생률이 높았으나 통계학적 차이는 없었다. 췌장이식후의 최적의 면역억제요법의 결정하기 위해서는 향후 Tacrolimus와 CsA을 비교하는 전향적 무작위 연구가 필요하다.

□ Key words – Pancreas transplantation, Tacrolimus, Cyclosporine, Acute rejection, Renal failure

Diabetes mellitus is the one of the most common disease and the primary cause of blindness, renal failure, lower-limb amputation, and impotence.[1,2,3] Long-term complications in patients with diabetes account for decreased quality of life and an increased death rate.[2,3] As demonstrated in the Diabetes Control and Complications

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Trial (DCCT), tight glycemic control dramatically decreases the likelihood of developing retinopathy, nephropathy and neuropathy associated with poorly controlled diabetes.[4] For patients with diabetes successful pancreatic transplantation is currently the most effective therapy that establishes an insulin-independent euglycemic state, and prevents or reverses many of the devastating long-term complications that arise from disordered glucose control.[5-12]

Transplantation of cadaveric, immediately vascularized pancreas grafts has been carried out either simultaneous with kidney (SPK) or after kidney transplantation (PAK) in uremic type I diabetic patients.[8-10] Pancreas transplant alone (PTA) in nonuremic type I diabetics has also been performed in an attempts to prevent the progression of complications related to chronic hyperglycemia.[8-10]

It has been shown that rejection episodes occur twice as frequently after pancreas-kidney transplantation compared to kidney transplantation alone causing an increased in the rate of hospitalization, the use of antilymphocyte agents, and in infection-related morbidity.[13,14] According to the information provided by the International Pancreas Transplantation Registry (IPTR), the 1-year function rates achieved after pancreas-kidney transplants (SPK) are approximately 81% (pancreas) and 86% (kidney).[14] These improvements are mainly due to the development of surgical technique (pancreasduodenal transplantation) and to the standardization of the perioperative management.[15,16] However, acute graft rejection (between 55% and 83.5%) occurring within the first 6 months with Cyclosporine (CsA) combined with corticosteroid, and often with Azathioprine (AZA) the-rapy despite of induction therapy with monoclonal or polyclonal antibodies, remains the most important barrier to the success and safety of organ transplantation.[17] The search for more effective and safer antirejection agents has led to the development of Tacrolimus. The introduction of Tacrolimus has yielded a new era for immunosuppression of solid organ recipients. Its use is associated with a lower incidence of acute rejection in kidney transplantation compared with CsA in both US and European multicenter trials.[18,19] In addition, data suggests that Tacrolimus may also yield longer half-lives for kidney transplant than standard CsA-based regimens.[20] These reports have encouraged our center to evaluate the safety and efficacy of Tacrolimus as primary therapy for pancreas transplantation.

The principles guiding immunosuppressive management for pancreas transplant recipients are similar to those employed for recipients of other solid organ transplantation. Tacrolimus, a neutral macrolide, is an immunosuppressive agent that has completely different chemical structure from that of CsA, but has similar immunosuppressive effects as CsA. Clinical trials and outcomes in Tacrolimus treated recipients of liver, kidney, heart, lung, intestinal, and islet transplants have been reported,[21-26] but its use as maintenance therapy in pancreas transplantation has not been fully evaluated. Furthermore, since Tacrolimus is associated with a high incidence of neurotoxicity, nephrotoxicity, and diabetogenic including new-onset of insulin-dependent diabetes mellitus, some transplant centers have been hesitant to use Tacrolimus as the primary immunosuppresant after pancreas transplantation.

The purpose of this study is to evaluate the effects of Tacrolimus based immunosuppression on acute graft rejection and renal dysfunction and compare it to the outcomes with CsA based regimen.

METHOD

Data Selection

To compare outcomes of treatment efficacy and acute renal dysfunction in Cyclosporine versus Tacrolimus recipients, a matched-pair analysis of two different but comparable periods was performed between CsA and Tacrolimus based immunosuppression within the first 6 months after SPK, PAK, or PTA pancreas transplantation. Male and female patients who had received pancreas transplantation (first or second transplantation) from September 1994 to September 1996 were retrospectively evaluated for the treatment efficacy and acute renal dysfunction.

Starting on August 1995 Tacrolimus instead of CsA were employed as immunosuppressive agent for patients undergoing pancreas transplantation at University of Maryland Medical System. Therefore, patients who received pancreas transplantation from July of 1994 through July of 1995 were included in CsA-analysis group and patients who received pancreas transplantation from August of 1995 through August of 1996 were included in Tacro-limus-analysis group. A matched-pair analysis cannot replace a randomized study, but it does provide a relevant comparison.

All patients were reviewed with respect to demographics, transplant characteristics, diagnosis, management, and outcomes (treatment efficacy and acute renal

dysfunction).

Patient and Graft Survival

The primary measures of treatment efficacy were patient and graft survival at 6 month. Actual 6-month patient and graft survival rates were determined for the 101 recipients of pancreas transplant from the time of transplantation. Graft survival was defined as those patients who were alive at 6 months after transplantation with a functioning graft not requiring chronic exogenous insulin therapy. Secondary efficacy measures were acute rejection episodes defined as the occurrence of biopsy proven graft rejections and the use of antilymphocyte preparations for rejection within the first 6 months of pancreas transplantation. Most pancreas graft rejections and losses, according to the IPTR, occur within the first 6 months posttranplant.[27] Thus, this data allows for a meaningful assessment of early graft function.

Acute Rejection

All rejection episodes in this study were biopsy proven rejection. The severity of graft rejection was graded using Banff grading system; grade I (mild), grade II (moderate), and grade III (severe).[28] When biopsy grades were intermediate, for the purpose of this analysis, the higher grade was utilized (i.e., moderately severe was upgraded to severe). The serum creatinine was used as the index of rejection. Any elevation of serum creatinine from baseline greater than 0.2 mg/dl was usually indicated for biopsy. If rejection was suspected, patients received one dose of 500 mg of methylpred-nisolone IV empirically. If the biopsy showed mild rejection patient was continued to receive methylpredni-solone for 3-5 doses. If the biopsy showed moderate to severe rejection, the patient was treated with antilymphocyte therapy as either OKT3 or ATGAM for 7-14 days.

Acute Renal Dysfunction

Kidney dysfunction was assessed by serum creatinine elevation with kidney loss defined as return to dialysis. Acute renal dysfunction was defined as (20%) increase in serum creatinine from baseline.

Immunosuppression

In general, all patients received antilymphocyte induction therapy as either OKT3 or ATGAM for the first 7-10 days (range 5-15 days) after transplantation. Corticosteroids were administered as methylprednisolone 500 mg intraoperative and at postoperative day 1 and then the dose was gradually tapered to baseline oral prednisone dose (0.3 mg/kg). When serum creatinine level decreased to less than 2.5 mg/dl, patients were started on either Tacrolimus or CsA with a 2-3 days overlap with either OKT_3 or ATGAM to assure therapeutic levels. Patients either received Tacrolimus 0.1 mg/kg orally twice daily, or CsA 10 mg/kg/day orally in divided doses. Dosage modifica-tions of CsA and Tacrolimus were made according to the therapeutic range per protocol. Patients also received azathioprine as part of triple immunosuppressive regimen.

Concomitant Medicines and Infection Prophylaxis

Viral prophylaxis included IV Ganciclovir (5 mg/kg in

Table 1. Baseline Characteristics of pancreas transplant patients[a]

Characteristic	CsA (n=57)	Tacrolimus (n=54)
Recipient age (yr)	39±13.1	37±12.7
Sex		
Male	36	28
Female	21	26
Race		
Caucasian	51	51
African American	6	3
Type of Transplant		
SPK[b]	38	27
PAK[c]	17	20
PTA[d]	2	7
Number of previous transplants		
0	50	47
1	6	5
2	1	2
CMV serologic status (recipient/donor)[e]		
P/P	26	25
P/N	17	13
N/P	7	8
N/N	6	7
Missing	1	1

[a]Data are expressed as number of patients
[b]Simultaneous pancreas and kidney
[c]Pancreas after kidney
[d]Pancreas transplant alone
[e]P=positive, N=negative

two divided doses) during induction and rejection treatment followed by oral Acyclovir (1,200 mg/day in four divided doses) for 3 months. Other concomitant medicines for infection prophylaxis included clotrimazole (10 mg QID) and Bactrim® orally (1 single-strength tablet QD) for 3 months. Patients also received H_2 receptor antagonist adjusted for renal function or sucralfate for ulcer prophylaxis.

Statistical Analysis

Differences of means of parametric data were performed using *t* test. Descriptive summaries for the time-to-event data for patient and graft survival were prepared by using the Kaplan-Meier method. Multivariate Cox regression models was used to assess the consistency of the overall result.

RESULTS

Characteristics of the Treatment Groups

A total of 101 patients who had received pancreas transplantation were reviewed. 57 patients were evaluated for CsA-based efficacy and 54 patients were evaluated for Tacrolimus-based efficacy. CsA-treated group and Tacrolimus-treated group were comparable with respect to patient demographic characteristics (Table 1), and there were no differences in donor and recipient characteristics (Table 2). There were no significant differences between groups in the mean dose of antilymphocyte antibody preparations (OKT_3 or ATGAM) used for induction therapy. Both groups were comparable for azathioprine and oral steroid dose throughout the comparison period.

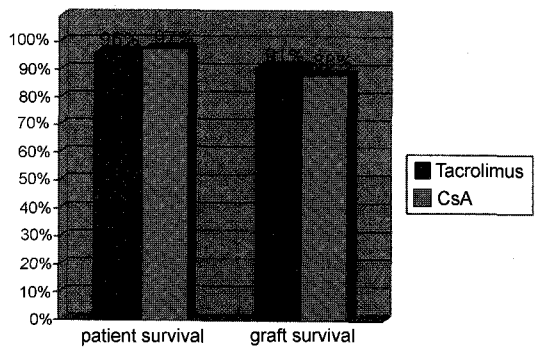

Fig. 1. Patient and graft survival rate 6 months after transplant.

Table 2. Transplant donor and recipient characteristics[a]

Characteristic	CsA (n=57)	Tacrolimus (n=54)
Donor sex		
Male	39	30
Female	18	24
Donor age (yr)	49±15.1	47±13.2
Number of HLA mismatch		
HLA-B mismatch		
0	11	7
1	27	28
2	19	19
HLA-A,B,DR mismatch		
0	5	3
1	4	5
2	8	7
3	13	14
4	17	16
5	9	7
6	1	2
CMV serologic status (recipient/donor)		
P/P	26	25
P/N	17	13
N/P	7	8
N/N	6	7
Missing	1	1

[a]Data are expressed as number of patients

EFFICACY

Patient and Graft Survival

No significance was demonstrated when comparing CsA versus Tacrolimus in regards to patient or graft survival at 6 months post-transplantation. The 6-month patient survival rate was 96% with Tacrolimus-treated group versus 97% with CsA treated-group (p=0.57) (Fig. 1). The 6-month pancreas graft survival rate was 91% with Tacrolimus-treated group versus 88% with CsA-treated group (p=0.29) (Fig. 1). Covariate analysis indicated that, regardless of treatment, the number of histo-compatibility antigen (HLA) mismatches, panel-reactive antigen grade, and the number of previous transplants had no effect on patient or graft survival.

Rejection Episodes

The incidence of biopsy proven rejection episodes at 6

Table 3. Incidence and severity of acute rejection[a]

Acute rejection	CsA (n=57)	Tacrolimus (n=54)	P
Biopsy-proven	37 (69)	24 (46)	<0.05
Severity			
Mild	5 (9)	8 (15)	
Moderate	17 (30)	12 (22)	
Severe	15 (26)	4 (7)	
Antilymphocyte antibody treatment for rejection	32 (56)	16 (30)	<0.01

[a]Data are expressed as number of patients, with percentage in parenthesis

Table 4. Incidence of acute renal dysfunction[a]

Acute rejection	CsA (n=57)	Tacrolimus (n=54)	P
Total acute renal dysfunction	291	189	NS
Mean events/patient	5.1	3.5	NS
Mean baseline serum creatinine (mg/dl)	1.7	1.8	NS
Mean acute renal dysfunction serum creatinine (mg/dl)	2.2	2.5	NS
Mean % increase in serum creatinine	41	43	NS

[a]Data are expressed as number of patients
N=not significant, p>0.05

months for all pancreas transplant patients was 57%. The median time to first rejection for all patients with rejection episodes was 25 days. There was a significant reduction in the incidence of biopsy confirmed acute rejection in the Tacrolimus-treated group (46%) compared with the CsA-treated patients (69%) (p<0.05) (Table 3). Classification of acute rejection episodes according to severity indicated significantly more CsA treated patients had moderated or severe acute rejections compared with Tacrolimus-treated patients (p=0.03) (Table 3) (Fig. 2).

Use of Antilymphocyte Treatment

The use of antilymphocyte antibody therapy for rejection in each group was consistent with the incidence and severity of acute rejection. The CsA-treated group required more antilymphocyte treatment for rejection (56% of the CsA-treated group compared with 30% of the Tacrolimus-treated group) (Table 3) (p<0.01).

Acute Renal Dysfunction

A total of 101 pancreas transplant patients had 497 acute renal dysfunction episodes (mean of 4.9 events/patient). A summary of acute renal dysfunction episode characteristics between the two treatment groups is given in Table 4. Only 3% of patients had no acute renal dysfunction, 37% had 1-5 events, and 29% had 5-10 events. The main causes of acute renal dysfunction in all patients were drug toxicity (39%), graft rejection (31%), and dehydration (11%). There was a higher incidence of acute renal dysfunction in the CsA-treated group versus Tacrolimus-treated group, but it was not statistically significant (5.1 vs 3.5 events/patient).

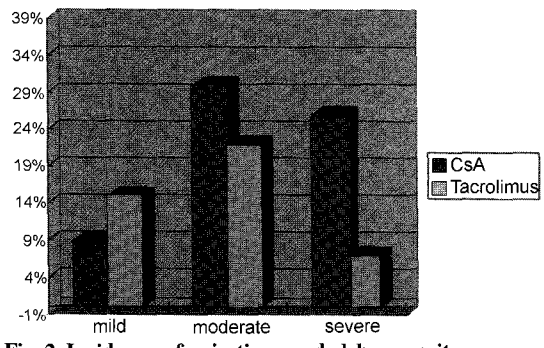

Fig. 2. Incidence of rejection graded by severity

DISCUSSION

The introduction of CsA in the early 1980's was associated with an improvement in patient and graft survival rates in organ transplant patients. Neoral® the recently developed microemulsion formulation of Cyclosporin has further improved the success of organ transplantation.[29,30] As a result, the success of pancreas transplant in diabetes patients increased, particularly in conjunction with kidney transplant.[31] However, the incidence

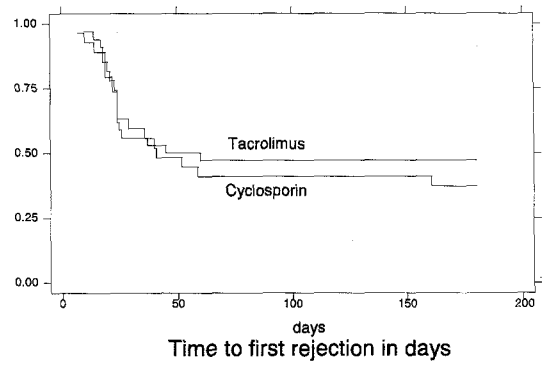

Fig. 3. Kaplan-Meier pancreas graft survival estimate

of graft rejection with Cyclosporine has remained high in pancreas transplantation.[32] Tacrolimus has been an effective immunosuppressive agent after liver, kidney, and heart transplantation for other transplantation. Recently, Tacrolimus has been used in the pancreas transplantation and has proven to be an effective agent in preventing graft rejection.[33-35] However, since Tacrolimus has been associated with hyperglycemia in other organ transplantation, certain centers have been hesitant to use it as a primary immunosuppressive agent in pancreas transplantation.[36] Other centers have safely converted pancreas transplant recipients to Tacrolimus from CsA and have reported only a minor incidence of hyperglycemia and superior patient and pancreas survival.[37] Our study showed that there was no significant difference between CsA and Tacrolimus in regards to patient and graft survival at 6-months post-transplantation. However, patients receiving Tacrolimus after pancreas trans-plantation showed a significantly lower incidence and severity of biopsy proven rejection requiring less antily-mphocyte treatment for rejection.

The overall incidence of acute renal dysfunction was also examined in this study. Even though the difference was not statistically significant the study demonstrated a lower incidence of acute renal dysfunction in pancreas patients on a Tacrolimus-based immunosuppressive regimen when compared to CsA treated patients. This difference in renal dysfunction may have been primarily due to the higher incidence of graft rejection with a greater severity of rejection in the CsA versus the Tacrolimus patients. The advantage utilizing a Tacrolimus based immunosuppressive regimen compared to CsA was unaccompanied by an increase in nephrotoxicity in pancreas transplant patients.

CONCLUSION

In conclusion, no significance was demonstrated when comparing CsA versus Tacrolimus in regards to patient and graft survival at 6-months post-transplantation. However, the use of Tacrolimus in pancreas transplant recipients was associated with a significant lower incidence and severity of biopsy proven rejection requiring less antilymphocyte treatment for rejection. There was a higher incidence of acute renal dysfunction in the CsA-treated group versus Tacrolimus-treated group, but it was not statistically significant.

All these factors may contribute to a superior patient and graft survival in long-term outcomes of pancreas recipients and to potential cost benefits with Tacrolimus based immunosuppression.

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