
Regular Article

Temporal Decline in Sirolimus Elimination Immediately After Pancreatic Islet Transplantation

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Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

Summary: Pancreatic islet transplantation is a curable treatment for type 1 diabetes and has been put into practice in various countries. In this study, we analyzed the pharmacokinetic characteristics of sirolimus and tacrolimus in six Japanese patients with pancreatic islet transplants immediately after surgery, and monitored efficacy and toxicity. The patients were treated with immunosuppressive therapy based on the Edmonton protocol, that is, sirolimus and low-dose tacrolimus. Pharmacokinetic analyses were performed using the nonlinear mixed-effects modeling program NONMEM. Large inter- and intra-individual variability was observed in the pharmacokinetics of both drugs. A model with increased apparent clearance in the postoperative period explained well the intra-individual variability in the pharmacokinetics of both drugs. The most frequent drug-induced toxicity was a decrease in the white blood cell count, and two of six patients required the administration of granulocyte colony-stimulating factor. Clinical laboratory tests immediately before the transplantation and cytochrome P450 3A5 genotype were not related to the high blood concentrations of sirolimus after the loading dose. From these results, the apparent clearance of sirolimus and tacrolimus might temporally decline immediately after pancreatic islet transplantation. A high trough concentration of sirolimus might increase the risk of hematological toxicity, and adjustment of the dosage for immunosuppressive treatment will be necessary in Japanese patients.

Key words: tacrolimus; pharmacokinetics; CYP3A5; HPLC/UV; LC/MS/MS; diabetes

Introduction

Pancreatic islet transplantation is a curable treatment for type 1 diabetes and has been put into practice in various countries. The Manual for Clinical Islet Transplantation in Japan was released in May 2002, and revised in April 2004. Because the procurement of pancreas for islet transplantation from brain-dead donors is not approved in Japan, it is only possible to prepare islets from non-heart-beating donors. Therefore, the report of success with non-heart-beating donors by Markmann et al.1) was highly useful. Using an improved islet-preparation method,2) the first case of pancreatic islet transplantation in a Japanese type 1 diabetic patient was successfully performed at Kyoto University Hospital in April 2004. Since the supply of pancreas from cadaveric donors is especially limited in Japan, transplantation from a living-donor was planned.3) In January 2005, our group succeeded in a living-donor islet transplantation for the first time anywhere in the world.4) It is difficult to diagnose cellular and humoral rejection in the transplanted islet, and successful immunosuppressive therapy is critical. Glucocorticoid, which is widely used for organ transplant patients, is unsuitable for pancreatic islet transplantation, because it has the effect of increasing the blood glucose level.5) Calcineurin inhibitors are also undesirable as a main
immunosuppressant because of their pancreatic toxicity. In 2000, Shapiro et al. reported outstanding results in seven patients using a glucocorticoid-free immunosuppressive regimen, that is, sirolimus (rapamycin), low-dose tacrolimus and a monoclonal antibody against the interleukin-2 receptor. After that, the outcome of pancreatic islet transplantation improved remarkably. Sirolimus binds to an immunophilin, the 12-kDa FK506-binding protein (FKBP12), and the complex inhibits the mammalian target of rapamycin (mTOR), and blocks T-cell proliferation stimulated by interleukin 2 and other cytokines. It has been reported that sirolimus suppresses rejection effectively in liver, kidney, and pancreas transplantations when combined with low-dose tacrolimus. On the other hand, sirolimus has hematological toxicity and decreases the white blood cell (WBC) and platelet count, and increases serum cholesterol values.

Both sirolimus and tacrolimus are mainly metabolized by cytochrome P450 (CYP) 3A4 in the liver and small intestine, and liver function may affect elimination of these drugs from the body. The pancreatic islet is infused into the portal vein in the transplantation, and Rafael et al. reported a temporal ascension in the biochemical parameters of liver function after pancreatic islet transplantation. Therefore, we hypothesized that a transient loss of hepatic function immediately after islet transplantation may cause the intra-individual variability in the pharmacokinetics of sirolimus as well as tacrolimus. It is reported that CYP3A5 is also involved in the metabolism of both sirolimus and tacrolimus. We previously reported that patients engrafted with a CYP3A5*1 allele to achieve adequate blood concentrations of sirolimus after living-donor liver transplantation than those with a CYP3A5*3/3-carrying graft liver. In addition, high-dose sirolimus was needed in renal transplant patients carrying the CYP3A5*1 allele to achieve adequate blood trough concentrations. In the present study, we attempted a pharmacokinetic and toxicodynamic analysis of sirolimus and tacrolimus in patients with pancreatic islet transplants immediately after surgery, and also examined the effect of CYP3A5 genotype on blood level profiles of these two drugs.

**Patients and Methods**

**Patients:** Six patients were enrolled in this study. They had had type 1 diabetes for more than 5 years, their fasting and glucagon loading serum C-peptide concentrations were less than 0.3 and 0.5 ng/mL, respectively, and they had poorly controlled blood glucose concentrations despite an optimal insulin regimen. Each patient received a pancreatic islet transplantation from a non-heart-beating donor at Kyoto University Hospital between April and November 2004. All protocols followed the Manual for Clinical Islet Transplantation in Japan, the 2nd Edition. The genetic analysis was performed in accordance with the Declaration of Helsinki and its amendments, and approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee. Written informed consent was obtained from each patient. Characteristics of patients are listed in Table 1.

**Immunosuppressive therapy:** Immunosuppressive therapy was performed based on the Edmonton protocol with some modifications. Sirolimus (Rapamune®, Wyeth-Ayerst, New York, NY) was given orally at 0.2 mg/kg immediately before transplantation, and 0.1 mg/kg on the following day. Subsequently, the dose of sirolimus was adjusted to control the trough drug concentration in the range of 12–15 ng/mL and given once daily. Tacrolimus (Prograf®, Astellas Pharm Inc., Tokyo, Japan) was given orally at an initial dose of 1 mg twice daily, and the dose was adjusted to maintain a trough concentration of 3–6 ng/mL after that. Basiliximab (anti-CD25 monoclonal antibody, Simulect®, Novartis Pharma KK, Tokyo, Japan) was administered intravenously immediately before the transplantation and on the 4th day after the transplantation.

**Therapeutic drug monitoring of immunosuppressants:** Blood sampling was performed once a day in the morning before the administration of sirolimus and tacrolimus. Sirolimus (purity >99.0%) and 32-desmethoxyrapamycin (internal standard, purity >99.0%) were kindly provided by Wyeth-Ayerst. The extraction of sirolimus from the whole blood sample was performed by the method of Campanero et al. with some modifications. Whole blood sample (1 mL) and internal standard (40 μL, 1000 ng/mL in blood) were transferred to a grass tube, then 1 mL of acetone was added. After vortex-mixed well for 1 min, 1 mL of 6.25% zinc sulphate was added to the tube. After vortex-mixed for 1 min, the tube was centrifuged at 2600 × g and 1°C for 10 min. The supernatant was decanted to clean grass tube and 2 mL of t-butyl methyl ether was added. After vortex-mixed for 1 min, the tube was centrifuged at 2600 × g and 1°C for 10 min. Afterwards, the supernatant was transferred to clean grass tube and dried up. The dried extract was reconstituted in 200 μL of 50% methanol. The concentration of sirolimus was quantified by reverse-phase high performance liquid chromatography in combination with ultraviolet detector (HPLC/UV). Briefly, the HPLC/UV system comprised two pumps (LC-10AS, Shimadzu Corporation, Kyoto, Japan), an analytical column (ZORBAX® ODS 5 μm, 250 × 4.6 mm i.d., Agilent Technologies, Inc., Palo Alto, CA) and a spectrophotometric ultraviolet detector (SPD-10AV, Shimadzu Corporation). The mobile phase consisted of a multiple gradient of solvent A (water:methanol = 1:2) and solvent B (acetonitrile): 0

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**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CYP3A5 Genotype</th>
<th>Sirolimus Trough Concentration</th>
<th>Tacrolimus Trough Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>CYP3A5*1</td>
<td>2.5 ng/mL</td>
<td>6 ng/mL</td>
</tr>
<tr>
<td>P2</td>
<td>CYP3A5*1</td>
<td>3 ng/mL</td>
<td>8 ng/mL</td>
</tr>
<tr>
<td>P3</td>
<td>CYP3A5*3/3</td>
<td>1 ng/mL</td>
<td>5 ng/mL</td>
</tr>
<tr>
<td>P4</td>
<td>CYP3A5*3</td>
<td>5 ng/mL</td>
<td>9 ng/mL</td>
</tr>
<tr>
<td>P5</td>
<td>CYP3A5*3</td>
<td>4 ng/mL</td>
<td>6 ng/mL</td>
</tr>
<tr>
<td>P6</td>
<td>CYP3A5*3/3</td>
<td>2 ng/mL</td>
<td>3 ng/mL</td>
</tr>
</tbody>
</table>
min, 60% (A); 25 min, 70%; 30 min, 60%. The column temperature was kept at 50°C, and the flow rate was set at 1 mL/min. Chromatographic peaks of sirolimus and an internal standard were monitored with the UV detector at 278 nm. The retention times of sirolimus and internal standard were 12 min and 14 min, respectively. The lower limit of quantification was 5 ng/mL. The whole blood concentration of tacrolimus was quantified by semiautomated microparticle enzyme immunoassay (IMx®, Abbott Japan Co., Ltd., Tokyo, Japan).

Pharmacokinetic analysis: Pharmacokinetic analyses were performed using the nonlinear mixed-effects modeling program NONMEM version V18® approximating the behavior of sirolimus and tacrolimus delivered as multiple intravenous doses with a one-compartment model. We first analyzed the population data by the first-order conditional estimation (FOCE) method to examine which model better fit the pharmacokinetics of sirolimus and tacrolimus. We designed two typical models, namely the Basic model and the POD-model. While the Basic model has a fixed apparent clearance, the apparent clearance in the POD-model increases linearly in the postoperative period up to some point and is fixed after that as shown in the following equations:

Basic model: \[ CL/F = \theta_1 \times WT \]

\[ V/F = \theta_2 \times WT \]

POD-model: \[ CL/F = (\theta_1 + \theta_3 \times POD/X) \times WT \]

\[ X \leq \text{POD} \]

\[ CL/F = (\theta_1 + \theta_3) \times WT \]

\[ \text{POD} > X \]

\[ V/F = \theta_2 \times WT \]

Where POD is the postoperative day, CL is total body clearance (L/hr), V is the volume of distribution (L), F is oral bioavailability, and WT is body weight (kg). \( \theta_1, \theta_2 \) and \( \theta_3 \) are parameters to be estimated. In the POD-model, X is an optional integer from 2 to 14. A model with minimal objective function was concluded to be optimal.

Next, pharmacokinetic parameters of sirolimus and tacrolimus in each patient were estimated by the ordinary nonlinear least squares method using the optimal model obtained in the analysis of the population data. The elimination half-life (\( T_{1/2} \)) was calculated as \( \ln 2 \times (V/F)/(CL/F) \).

Identification of CYP3A45 genotype: Genomic DNA from whole blood was isolated with a MagNAPure LC DNA isolation kit (Roche, Mannheim, Germany). Genotyping of the CYP3A45 gene was performed by the polymerase chain reaction-restriction fragment length polymorphism method according to the method of van Shaik et al. 20

Determination of sirolimus blood concentration by high performance liquid chromatography with tandem mass spectrometry (LC/MS/MS): The method of sample preparation for LC/MS/MS was similar to that for HPLC/UV, except that 150 µL of whole blood and 10 µL of 150 ng/mL internal standard in blood were needed, and dried extract was reconstituted in 150 µL of 1 mM ammonium acetate in 80% methanol. The HPLC system for LC/MS/MS consisted of two pumps (LC-20AS, Shimadzu Corporation), a column oven (CTO-20AC, Shimadzu Corporation) and an analytical column (Chemopak, Chemosorb 5-ODS-H, 150 × 4.6 mm i.d., Chemo Scientific Co. Ltd., Osaka, Japan). The mobile phase consisted of a multiple gradient of solvent A (1 mM ammonium acetate in water) and solvent B (1 mM ammonium acetate in methanol): 0 min, 10% (A); 8 min, 0%; 10 min, 0%; 10.1 min, 10%. The separation by liquid chromatography was carried out at 60°C with a flow rate of 0.6 mL/min. The mass analysis was performed using a triple quadrupole mass spectrometer (API4000TM, Applied Biosystems Japan Ltd., Tokyo, Japan) equipped with an electrospray ionization interface and operated in the positive ion mode. The ion transitions monitored were mass-to-charge ratio (m/z) 931.6 → 864.7 for sirolimus and m/z 901.5 → 834.7 for the internal standard. The retention times of sirolimus and internal standard were 4.6 min and 4.8 min, respectively. The lower limit of quantification was 0.5 ng/mL.

Statistical analysis: Values are presented as the mean ± S.D. or median with range, depending on the type of data. For the estimation of pharmacokinetic parameters, the statistical significance of the parameters was evaluated with the likelihood ratio test. A difference in the objective function (−2 log likelihood difference, −2LLD) of more than 3.84, with 1 degree of freedom, was considered statistically significant (p<0.05). A comparison of sirolimus blood concentrations obtained by HPLC/UV and LC/MS/MS was made using the simple linear regression. Statistical analysis was performed with the program StatView 5.0 (Abacus Concepts, Berkeley, CA).

Results

Figures 1A and 1B show the trough concentration per dose (C/D) ratio profiles of sirolimus and tacrolimus for two weeks after the transplantation. The inter- and intra-individual variability in the C/D ratio of both drugs was rather large. No influence of the polymorphism CYP3A45*1 or *3 on either drug was apparent in this period. As shown in Table 1, all patients had normal liver function before transplantation. During the first two weeks after the transplantation, biochemical parameters of liver function, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), changed dynamically in some patients (Figs. 1C, D).

We attempted pharmacokinetic analyses of sirolimus and tacrolimus immediately after transplantation. A
Fig. 1. Individual trough concentration per dose (C/W) ratios of sirolimus and tacrolimus, and results of liver function tests. Profiles of C/W ratios of sirolimus (A) and tacrolimus (B), and aspartate aminotransferase (AST) (C) and alanine aminotransferase (ALT) values (D) for two weeks immediately after pancreatic islet transplantation are plotted. In panels A and B, dotted and solid lines show carriers of the CYP3A5*1/W*3 and *3/W*3 genotype, respectively.

Table 1. Demographics and clinical data before the transplantation in pancreatic islet transplant recipients

| Age (year)  | 39 (35–58) |
| Male/Female| 2/4        |
| Weight (kg) | 57 (37–70) |
| Aspartate aminotransferase (U/L) | 20 (15–32) |
| Alanine aminotransferase (U/L) | 18 (16–26) |
| Serum creatinine (mg/dL) | 0.75 (0.4–2.1) |

Values are presented as the median (range)

patient had kept low blood concentrations of tacrolimus after about 10 days of surgery, and started the administration of mycophenolate mofetil 23 days after. Therefore, we examined the pharmacokinetics of both drugs in patients with a similar background. In the pharmacokinetic analysis of sirolimus using the population data, the POD-model was significantly superior to the Basic model (p < 0.05), and the objective function value was minimized in the POD-model when X was 12. The estimated apparent clearance of sirolimus following the transplantation is shown in Fig. 2A. Figure 3 shows the simulation curves of the sirolimus concentration in each patient obtained with the Basic and POD-models. The fitting between the simulation curve and measured concentrations was significantly better in the POD-model except Pts 1 and 4 (p < 0.05). Similar results were obtained in the tacrolimus pharmacokinetic analysis. The POD-model with X = 4 for tacrolimus (Fig. 2B) had the smallest objective function value, and was significantly better than the Basic-model (p < 0.05). Table 2 shows pharmacokinetic parameters of sirolimus and tacrolimus using the POD-model. Extensive inter-individual variability in each pharmacokinetic parameter for both drugs was indicated.

Figure 4 shows the daily blood trough concentrations of sirolimus and tacrolimus, and WBC counts. A decrease in the WBC count of more than 30...
Fig. 3. Pharmacokinetic analysis of sirolimus in each patient applying the Basic model or POD-model. Open circles show measured blood trough concentrations of sirolimus, and the dotted area shows daily dosages. Chain and solid lines are simulation curves applied to the Basic model and POD-model, respectively. POD, postoperative day.

Table 2. Pharmacokinetic parameters of sirolimus and tacrolimus in pancreatic islet transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$</td>
<td>0.0776±0.0620</td>
<td>0.0803±0.0953</td>
</tr>
<tr>
<td>$\theta_3$</td>
<td>0.167±0.131</td>
<td>0.241±0.160</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>14.1±7.1a</td>
<td>17.0±5.1b</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>790±659</td>
<td>469±393</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>37.3±27.9c</td>
<td>17.1±14.4b</td>
</tr>
</tbody>
</table>

Values represent the mean±S.D. for 6 patients.

If POD≤X, CL/F = $(\theta_1 + \theta_3^*\text{POD})^*\text{WT}$, otherwise CL/F = $(\theta_1 + \theta_3)^*\text{WT}$. CL, total body clearance; V, volume of distribution; F, oral bioavailability; $T_{1/2}$, half-life; POD, postoperative day.

aConstant value 12 days after transplantation
bConstant value 4 days after transplantation
cX is 12 for sirolimus, 4 for tacrolimus.

during the first 10 days after the pancreatic islet transplantation (Fig. 4C). Two of six patients received an administration of granulocyte colony-stimulating factor (G-CSF) because of remarkable decreases. The average blood trough concentrations of sirolimus during the initial 5 days after transplantation were higher in these patients than in other patients (27.2 vs. 18.0±7.2 ng/mL) (Fig. 4A). Tacrolimus blood concentrations were kept within a low range in all patients (Fig. 4B). No laboratory test results immediately before the transplantation correlated with the high blood concentration of sirolimus after the first administration. The polymorphism CYP3A5*1/*3 did not affect the trough concentration of sirolimus (Fig. 4A). In addition, one patient showed a decrease in the platelet count, and no patient had
increased cholesterol levels within one month after the transplantation. No patient showed a distinct rejection.

We tried to establish an analytical system using LC/MS/MS, because the target range of sirolimus was gradually lowered a few months after transplantation, and because the lower limit of quantification was 5 ng/mL and a relatively large volume of sample was needed for HPLC/UV. Figure 5 shows the sirolimus concentration measured by the two methods, HPLC/UV and LC/MS/MS, for pancreatic islet transplanted patients. A linear regression analysis of the data yielded the following equation: HPLC/UV = 0.284 + 1.06 × LC/MS/MS (r² = 0.907, p < 0.0001).

Discussion

Since the publication of the Edmonton protocol, the results of pancreatic islet transplantation have shown a dramatic improvement.8) In our study, all patients showed an improvement of diabetes mellitus; stabilized blood glucose levels, presence of C-peptide in blood, normalization of glycosylated hemoglobin (HbA1c) and so on.2) In this study, we characterized the pharmacokinetics of sirolimus and tacrolimus in pancreatic islet transplant recipients during the first two weeks after the transplantation. In addition, we investigated the relationships between the pharmacokinetics and toxicity of sirolimus.

As shown in Figs. 1A and 1B, both sirolimus and tacrolimus showed remarkable inter- and intra-individual variability in the C/D ratio. In most subjects, the C/D ratio of sirolimus increased for several days after the transplantation, probably because the steady state had not been attained yet due to the long half-life of this drug (Table 2). Since the pancreatic islet was infused into the portal vein in the transplanted procedure, liver function was expected to be affected (Figs. 1C, D), which was consistent with a report by Rafael et al.14) It is considered that the infused islet blocks the portal capillary and causes hypoxic damage to the hepatocytes. Otherwise, the inflammatory cytokines might relate to the decreased hepatic function.20) Based on these findings, we considered that the hepatic clearance of sirolimus and tacrolimus decreased for a few days after the transplantation, and gradually recovered with time. While the results of AST or other liver function tests did not directly correlate with the apparent clearance of sirolimus, the POD-model, in which the apparent clearance linearly increased up to postoperative day 12, well expressed the changes in the trough concentration of sirolimus immediately after the transplantation (Fig. 3). We also investigated a model which assumes that the apparent clearance gradually decreased after transplantation and increased thereafter, but the resulting objective function value was larger than that of the POD model (data not shown). Therefore, the postoper-
ative day was suggested to be a primary factor explaining the intra-individual variation in the pharmacokinetics of sirolimus.

As shown in Table 2, the apparent clearance of sirolimus after postoperative day 12 was estimated as 14.0 L/hr. This value is about 1.5-fold as large as the values in renal transplant patients who received sirolimus and cyclosporine.\textsuperscript{21,22} We considered that this discrepancy may be caused by the difference in concomitantly used drugs such as tacrolimus and cyclosporine. Since sirolimus and calcineurin inhibitors (tacrolimus and cyclosporine) are substrates of CYP3A and P-glycoprotein,\textsuperscript{12,13,23} both calcineurin inhibitors can affect the pharmacokinetics of sirolimus. However, cyclosporine, but not tacrolimus, was reported to significantly increase the blood concentration of sirolimus in humans.\textsuperscript{24–26} The therapeutic window and dose of cyclosporine was about 10-fold that of tacrolimus, and tacrolimus with a lower blood concentration in this study (3–6 ng/mL) may not have had any influence on the pharmacokinetics of sirolimus. While, the apparent clearance of tacrolimus after postoperative day 4 was calculated as 17.0 L/hr (Table 2), this was larger than the values in renal transplant recipients.\textsuperscript{27} We considered this observation was due to the difference in the target therapeutic concentration. Since tacrolimus was maintained at a lower blood concentration in this study than that in renal transplant patients, the first pass effect of tacrolimus at the intestine and liver might be relatively greater than that in renal transplant patients.

Since the living-donor islet transplantation is carried out on a scheduled date, it is possible to start the administration of immunosuppressants several days before the transplantation to achieve targets.\textsuperscript{41} However, patients who receive islets from a dead-donor need a loading dose because the transplantation is performed without notice. The present loading dose might be too great for Japanese patients since the trough concentration of sirolimus in 3 of 6 patients was over the target range immediately after transplantation (Fig. 4A). Besides, Hong \textit{et al.}\textsuperscript{28} reported that the frequency of leucopenia was increased when the trough concentration of sirolimus was over 15 ng/mL. Dansirikul \textit{et al.}\textsuperscript{29} described a significantly lower WBC count when the sirolimus trough concentration was greater than 12 ng/mL. In the present study, all of 6 patients had a blood concentration of sirolimus of more than 15 ng/mL within 5 days after the transplantation, and the WBC count was decreased in 5 of 6 patients (Fig. 4). Two patients, who showed a higher trough concentration of sirolimus than the others immediately after the operation, required an administration of G-CSF to prevent infectious diseases. To reduce the risk of hematological toxicity, it is necessary to find out the desirable loading dose of sirolimus for pancreatic islet transplant recipients based on the pharmacokinetic analysis of a large population in a future study. Anglicheau \textit{et al.}\textsuperscript{16} reported that carriers of the CYP3A5*1 allele required significantly more sirolimus to achieve an adequate blood trough concentration in steady-state renal transplant recipients. So we expected carriers of the CYP3A5*3/*3 genotype to show a higher C/D ratio of sirolimus, but no effect of the polymorphism was apparent in the present study (Fig. 1A). Although the CYP3A5 genetic polymorphism may affect the variability of sirolimus pharmacokinetics, this effect was not obvious immediately after transplantation mainly because of the hepatic damage caused by the portal infusion of the transplanted islet.

Additionally, we measured the blood concentration of sirolimus by two methods, HPLC/UV and LC/MS. HPLC/UV was used for therapeutic drug monitoring of sirolimus at first in our institution. However, the target blood concentration of sirolimus was lowered a few months after transplantation, and measurements using HPLC/UV became difficult. Therefore, we established a more sensitive and quantitative method of analysis using LC/MS/MS. As shown in Fig. 5, the values dispersed in a range of low concentrations, while the values measured with the two methods correlated statistically as a whole. Although we carried out a pharmacokinetic analysis of sirolimus using the values measured by HPLC/UV in this study, similar results should be obtained even if values quantified by LC/MS/MS are used.

In conclusion, we clarified the decreased apparent clearance of sirolimus and tacrolimus in the early phase after a pancreatic islet transplantation. The dosage of both drugs in the Edmonton protocol can be modified in Japanese patients to avoid an abrupt rise in the blood concentration immediately after the transplantation.

Acknowledgments: This work was supported in part by a Grant-in-Aid from the Japan Health Sciences Foundation, by a Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by the 21st Century COE Program ‘Knowledge Information Infrastructure for Genome Science’.

References


Sirolimus PK Immediately After Islet Transplantation


