Population pharmacokinetics models of sirolimus in renal transplant patients: A systematic review

Modelos farmacocinéticos poblacionales de sírolimus en pacientes trasplantados renales: Revisión sistemática

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Abstract
Objective: Sirolimus is used in the immunosuppressive therapeutic treatment of kidney transplant patients. The high pharmacokinetic variability of sirolimus makes pharmacokinetic monitoring and dosage individualization of immunosuppressive therapy a key process to achieve better efficacy results. The availability of a population pharmacokinetic model can be used to provide better pharmacokinetic adjustment of plasma concentrations of sirolimus and thus achieve greater clinical benefit.

Method: We conducted a systematic review of the literature available in the Medline, Embase, and Scopus databases to identify and subsequently analyze population pharmacokinetic models of orally administered sirolimus in adult patients after kidney transplant. The descriptors used MeSH were kidney transplantation, pharmacokinetics, and sirolimus. The following variables from the selected studies were assessed: study population, immunosuppressive treatment, blood sampling times, covariates analyzed, type of pharmacokinetic model, computer software used, estimated pharmacokinetic parameters, interindividual variability of pharmacokinetic parameters, residual variability and mathematical equations of the pharmacokinetic model.

KEYWORDS
Kidney transplant; Pharmacokinetics; Sirolimus; Drug monitoring; Drug dosage calculations; Population pharmacokinetics.

Resumen
Objetivo: Sirólimus es un fármaco utilizado en los esquemas terapéuticos inmunosupresores en pacientes con trasplante renal. La elevada variabilidad farmacocinética de sirólimus hace que la monitorización farmacocinética y la individualización realizada de la terapia inmunosupresora sea un proceso crucial para conseguir mejores resultados de eficacia. La disponibilidad de un modelo farmacocinético poblacional permite realizar un mejor ajuste farmacocinético de las concentraciones plasmáticas de sirólimus y así conseguir un mayor beneficio clínico.

Método: Se realizó un análisis sistemático de la literatura disponible en las bases de datos Medline, Embase y Scopus para identificar y posteriormente analizar los modelos farmacocinéticos poblacionales de sirolimus administrado actualmente los adultos trasplantados renal. Se utilizaron como descriptors MeSH: trasplante renal, farmacocinética y sirolimus. De cada artículo seleccionado se evaluó la población a estudio, el esquema de tratamiento inmunosupresor, los tiempos de muestreo de las extracciones de sangre, las covariables analizadas, el tipo de modelo farmacocinético, el programa informático utilizado, los parámetros farmacocinéticos estimados, la variabilidad interindividual de...
Results: A total of 548 results were obtained, excluding 175 records that were identified in more than one database. Finally, seven articles that met the inclusion criteria were selected. Most of the pharmacokinetic models found fit a two-compartment model. The interindividual variability of sirolimus was explained by covariates such as age, weight, liver function, cyclosporine exposure and dose, sirolimus doses, CYP3A5 genetic polymorphisms, serum creatinine, and concomitant treatment.

Conclusions: The two-compartment model was the pharmacokinetic model of choice in most of the selected studies. The interindividual variability of the pharmacokinetic parameters of sirolimus is explained by demographic, clinical, genetic, and biochemical variables. The availability of pharmacokinetic models of sirolimus can assist in optimizing therapy in patients after kidney transplant.

Introduction

Renal transplant is the treatment of choice for end-stage renal disease. Patients undergoing renal transplant need treatment with immunosuppressive therapy to prevent acute rejection and allograft loss. After transplantation, immunosuppressive treatment should be closely followed-up because these patients are more susceptible to infections, malignant neoplasms, or cardiovascular disease, comorbidities related to the underlying renal disease should be carefully monitored.

In therapeutic schemes, the main immunosuppressive agents used in combination are glucocorticoids, mycophenolate mofetil, cyclosporine, everolimus, tacrolimus, and sirolimus. Standard pharmacological treatment is based on a combination of immunosuppressive drugs with different mechanisms of action. This strategy minimizes the morbidity and mortality associated with each type of drug while enhancing overall efficacy. Such schemes may vary according to patient characteristics, transplant centre, or geographic area.

Sirolimus has high pharmacokinetic variability, which leads to marked differences in drug exposure in patients receiving the same dose. In this context, a key and necessary process is the individualization of the dosage of immunosuppressive therapy based on pharmacokinetic monitoring to achieve the best results in terms of maximizing efficacy and safety, avoiding acute rejection, minimizing the adverse effects derived from treatment, and controlling other factors that affect the pharmacokinetic profile of the drugs, such as interactions, lack of adherence to treatment, or genetic polymorphisms.

In fact, there is a close association between exposure to sirolimus and efficacy and the appearance of adverse effects. This relationship between the degree of drug exposure and safety and efficacy requires close monitoring of sirolimus plasma concentrations. It is relevant to know the factors that affect the interindividual pharmacokinetic variability of sirolimus in order to achieve the optimal individualization of drug therapy. Thus, the availability of population pharmacokinetic models of sirolimus can be used to estimate individual pharmacokinetic parameters using Bayesian methodology and make individualized pharmacokinetic adjustments to sirolimus dosing regimens, thereby achieving higher efficacy of therapy, lower rejection rates, and the lowest possible toxicity.

The aim of the present study was to conduct a systematic review of the published scientific literature on the available population pharmacokinetic models of sirolimus in renal transplant patients.

Methods

We designed a cross-sectional descriptive study and critical analysis of the scientific articles found through a systematic review. Data were obtained from the following databases: Medline (via Pubmed), Embase, and Scopus.

The bibliographic search terms were defined by consulting thesaurus developed by the U.S. National Library of Medicine. The following descriptors were considered suitable MeSH: kidney transplantation, pharmacokinetics, and sirolimus. The final search equation was designed to be used in the Medline database via Pubmed using Boolean operators: (["sirolimus"[MeSH Terms] OR "sirolimus"[Title/Abstract]) AND (["Pharmacokinetics"[MeSH Terms] OR "Pharmacokinetic"[Title/Abstract]) AND ([Kidney Transplantation"[MeSH Terms] OR "Kidney Transplantation"[Title/Abstract])

This strategy was also designed to be used in the other databases consulted. The search was conducted until May 2021. In addition, we reviewed the scientific articles referenced by the studies selected in the final search to reduce possible publication bias. Any study found by this route was included as a manual search.

Inclusion criteria were as follows: original studies that meet the objectives of the search (i.e., population pharmacokinetic models of oral sirolimus in adult renal transplant patients) that were published in peer-reviewed journals and written in English and Spanish. In addition, we included articles that could be retrieved as full text. We excluded studies that included paediatric patients as the study population and those that were not performed in humans. We also excluded communications to congresses to avoid possible duplication.

The following variables from the selected studies were assessed: study population, immunosuppressive treatment schedule, post-transplant time, and written in English and Spanish. In addition, we included articles that

El modelo bicompartimental fue el modelo farmacocinético de elección en la mayoría de los estudios seleccionados. La variabilidad interindividual de los parámetros farmacocinéticos de sirolimus se explica por variables demográficas, clínicas, genéticas y bioquímicas. La disponibilidad de modelos farmacocinéticos de sirolimus permiten individualizar la terapia en pacientes con trasplante renal.

los parámetros farmacocinéticos, la variabilidad residual y las ecuaciones matemáticas del modelo farmacocinético.
Population pharmacokinetics models of sirolimus in renal transplant patients: A systematic review

Results

The search of the three databases yielded a total of 548 results. A total of 175 records were excluded after being identified in more than one database. Finally, eight were assessed, of which one was excluded because it was a pharmacokinetic model of sirolimus as an intravenous temsirolimus metabolite (Figure 1). No results were obtained from the manual search.

Table 1 shows the characteristics of the studies reviewed. Of the seven studies that met the inclusion criteria, five were retrospective studies (Wang et al.8, Golubovic et al.7, Dansirikul et al.12, Zimmerman et al.9, and Jiao et al.10) and two were prospective. The studies by Jiao et al.10, Wang et al.8, and Ferron et al.13 were multicentre studies and the rest were single-centre studies.

Of the prospective studies, Ferron et al.13 conducted a phase I randomized double-blind placebo-controlled trial which assessed the dose-related pharmacokinetics of sirolimus (single dose of sirolimus 3, 5, 10, and 15 mg/m²). Djebli et al.11 assessed the pharmacokinetics of sirolimus during...

Table 1. Characteristics of the articles selected in the systematic review

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Population IS scheme</th>
<th>Samples</th>
<th>Covariates</th>
<th>Model</th>
<th>Software</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golubovic et al.7</td>
<td>n = 25</td>
<td>Trough</td>
<td>Age, weight, SCR, HTO, TP, TCh, TG, AST, ALT, AP, MM dose, CO dose, gender, DO, pre-tx dialysis</td>
<td>2C Nonmem</td>
<td></td>
</tr>
<tr>
<td>Wang et al.8</td>
<td>n = 22</td>
<td>Tr 6 %</td>
<td>Age, weight, height, BMI, gender, population, doses of CsA, PcCsA, BUN, SCR, ALT, SBR</td>
<td>2C Nonmem</td>
<td></td>
</tr>
<tr>
<td>Zimmerman et al.9</td>
<td>n = 27</td>
<td>Trough</td>
<td>Age, weight, height, BMI, gender, race, 2 1 drug interacting with SIR</td>
<td>2C Nonmem</td>
<td></td>
</tr>
<tr>
<td>Zhen Jiao et al.10</td>
<td>n = 112</td>
<td>Trough</td>
<td>Weight, height, age, BMI, sex, SC, HTO, erythrocytes, Hb, leukocytes, AST, ALT, TCh, TG, platelets, P, CsA, HDL, LDL, TC, TG, erthyrocytes, leucocytes, OHT, Hb, BUN, Cr, GcCl, ALT, AST, SIR, BUN, SCR, CYP3A5, CYP34A and MDR1 genotypes</td>
<td>1C Nonmem</td>
<td></td>
</tr>
<tr>
<td>Djebli et al.11</td>
<td>n = 22</td>
<td>Trough</td>
<td>Age, SBR, Alb, HTO, weight, days posttx, gender</td>
<td>2C Nonmem</td>
<td></td>
</tr>
<tr>
<td>Dansirikul et al.12</td>
<td>n = 25</td>
<td>Trough</td>
<td>Age, SBR, Alb, HTO, weight, days posttx, gender</td>
<td>2C P-Pharm</td>
<td></td>
</tr>
<tr>
<td>Ferron et al.13</td>
<td>n = 36</td>
<td>Trough</td>
<td>Age, weight, height, SC, SIR dose, Pc, CsA on day 1, and study centre</td>
<td>2C P-Pharm</td>
<td></td>
</tr>
</tbody>
</table>

1C one-compartment; 2C two-compartment; Alb: albumin; ALT: alanine transaminase; AP: alkaline phosphatase; AST: aspartate transaminase; AZA: azathioprine; BMI: body mass index; BUN: blood urea nitrogen; CO: corticosteroids; CrCl: creatinine clearance; CsA: cyclosporine; DO: donor origin; HDL: high density lipoproteins; HTO: hematocrit; IS: immunosuppressant; LDL: low density lipoproteins; MM: mycophenolate; Pc: plasma concentration; PRED: prednisone; SBR: serum bilirubin; SCR: serum creatinine; SIR: sirolimus; TA: tacrolimus; TCh: total cholesterol; TG: triglycerides; TP: total proteins; U: urea.

1. Ferron et al. 2005
2. Dansirikul et al. 2005
5. Golubovic et al. 2019
7. Djebli et al. 2006
8. Ferron et al. 2013
9. Zimmerman et al. 2019
10. Wang et al. 2019
11. Djebli et al. 2010
12. Dansirikul et al. 2010
13. Ferron et al. 2013
la etapa inicial de tratamiento. Post-transplante se analizaron los tiempos de lavado de 2 a 10.7 años y en el estudio de Wang et al. se analizaron 49 meses (0-202 meses), respectivamente. Wang et al. incluyeron voluntarios sanos (estudio de bioequivalencia) y recipientes de trasplante renal en los primeros 3 meses post-transplante, mientras que en graphite, 12 meses post-transplante se analizaron 10-20 mg/L y en los estudios de Wang et al. se analizaron 12-20 mg/L o 12-20 mg/L dependiendo de si se utilizó o no la terapéutica de ciclosporina, respectivamente. En el estudio de Wang et al. se utilizó un intervalo terapéutico de 4-10 µg/L y en el estudio de Zimmerman et al. se utilizó un intervalo terapéutico de 0-4 meses post-transplante: 15-25 µg/L; 4-12 meses post-transplante: 25-125 µg/L.

Table 1 muestra el seguimiento para el desarrollo de la farmacocinética de sirolimus. En tres de los estudios, la farmacocinética del sirolimus fue determinada a través de las curvas de concentración-tiempo, mientras que en los demás estudios la farmacocinética del sirolimus fue determinada a través de las curvas de concentración-tiempo irreversibles.

Cuadro 2. Parámetros farmacocinéticos poblacionales estimados en el estudio, interindividual y residual variabilidad
<table>
<thead>
<tr>
<th>Parámetros</th>
<th>Golubovic et al.7</th>
<th>Wang et al.11</th>
<th>Zimmerman et al.7</th>
<th>Jiao et al.8</th>
<th>Djebli et al.11</th>
<th>Dansirkul et al.12</th>
<th>Ferron et al.13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean parameters (RSE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl/F (L/h)</td>
<td>5.07 (48.9)</td>
<td>32.9 (4.5)</td>
<td>27.8 (39)</td>
<td>NR</td>
<td>38.7 (14.99)</td>
<td>20.4 (NR)</td>
<td>25.2 (NR)</td>
</tr>
<tr>
<td>C/F (L/h)</td>
<td>12.2 (20.8)</td>
<td>8.81 (6.4)</td>
<td>7.4 (9)</td>
<td>10.1 (3)</td>
<td>14.1 (7.09)</td>
<td>12.9 (NR)</td>
<td>8.91 (NR)</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>118 (2.15)</td>
<td>676 (38)</td>
<td>128 (29)</td>
<td>3,670 (9.3)</td>
<td>218 (7.06)</td>
<td>117 (NR)</td>
<td>112.9 (NR)</td>
</tr>
<tr>
<td>Vp/F (L)</td>
<td>609 (6.35)</td>
<td>1,380 (10.6)</td>
<td>278 (29)</td>
<td>NR</td>
<td>292 (10.03)</td>
<td>583 (NR)</td>
<td>452 (NR)</td>
</tr>
<tr>
<td>Ka (h-1)</td>
<td>2.19 (0.0022)</td>
<td>0.24 (7.1)</td>
<td>0.24</td>
<td>NR</td>
<td>5.25 (4.76)</td>
<td>2.195 (NR)</td>
<td>2.18 (NR)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>17 (NR)</td>
<td>NR</td>
<td>NR</td>
<td>0.24</td>
<td>NR</td>
<td>NR</td>
<td>0.24 (NR)</td>
</tr>
<tr>
<td>IIV (CV, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl/F</td>
<td>32.09</td>
<td>75.3</td>
<td>NR</td>
<td>NR</td>
<td>78.1</td>
<td>10.1</td>
<td>31.9</td>
</tr>
<tr>
<td>Vc/F</td>
<td>23.39</td>
<td>13.6</td>
<td>22.7</td>
<td>23.8</td>
<td>49.3</td>
<td>43.6</td>
<td>38.2</td>
</tr>
<tr>
<td>Vp/F</td>
<td>55.30</td>
<td>302.1</td>
<td>NR</td>
<td>NR</td>
<td>56.7</td>
<td>52.7</td>
<td>55.2</td>
</tr>
<tr>
<td>Ka</td>
<td>23.63</td>
<td>15.2</td>
<td>NR</td>
<td>NR</td>
<td>20.2</td>
<td>25.6</td>
<td>26.4</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>38.08</td>
<td>NR</td>
<td>NR</td>
<td>42.7</td>
<td>38.1</td>
<td>41.3</td>
<td></td>
</tr>
<tr>
<td>Residual variability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportional (CV, %)</td>
<td>49.9%</td>
<td>65.2%</td>
<td>33.8%</td>
<td>29.9%</td>
<td>242%</td>
<td>61.4%</td>
<td>NR</td>
</tr>
<tr>
<td>Absolute (NG/mL)</td>
<td>1.93 (ng/ml)</td>
<td>NR</td>
<td>NR</td>
<td>3.80 (ng/ml)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Cl/F: aclaramiento; IIV: variabilidad interindividual (coeficiente de variación (CV) %); Ka: constante de absorción; RSE: error estándar relativo; t1/2: tiempo de latencia; Vc/F: volumen de distribución central; Vp/F: volumen de distribución periférico.
sirolimus dose increased CI/F in a non-linear manner. The model of Djebli et al.11 showed an association between CYP3A5*1/*3 polymorphism and an increase in CI/F. Dansirikul et al.12 included age as a covariate inversely proportional to CI/F. Finally, the study by Ferron et al.13 found a correlation between Vp/F and intercompartmental clearance (Q/F) and BSA and weight.

**Discussion**

Sirolimus is a widely used drug in the prophylaxis of solid organ rejection. It has high inter- and intra-patient pharmacokinetic variability, thus requiring periodic pharmacokinetic monitoring to adjust the dosing regimen. In the present review, the search strategy identified seven pharmacokinetic models in the literature. The cutoff for the review was May 31, 2021.

In most of the selected studies, a two-compartment model with linear elimination was the pharmacokinetic model that best fitted the data on plasma concentrations of sirolimus as a function of time. It should be noted that only in the studies by Wang et al.6, Djebli et al.11, and Ferron et al.13 were full concentration-time curves (i.e., multiple concentrations extracted at different times after one dose per patient) available for the development of the pharmacokinetic model. In the studies reviewed, the CI/F values ranged from 7.4 to 14.1 L/h with no relationship in the results obtained between the models developed as a function of the amount of sampling time available in each study (full curves vs troughs alone), the sample size, or the time post-transplant (immediate transplant vs stable patients).

The sirolimus distribution volumes obtained in the seven studies were high, indicating a significant distribution of sirolimus in tissues. The values determined by the authors of the studies differed markedly from each other. Jiao et al.10 observed a Vd/F of 3,670 L with an interindividual variability of 56.7%, which was much higher than that found in other studies (range: 117-676 L). This result may be due to the use of samples taken at trough time points, which are not ideal samples for estimating distribution parameters. However, trough concentrations alone were also the only ones available in the studies by Golubovic et al.7 and Dansirikul et al.12. In these studies, the values of some pharmacokinetic parameters from the study by Ferron et al.13 as “a priori” values using the “PRIOR” function were used in order to determine all the pharmacokinetic parameters of a two-compartment model. This approach would explain the lower Vc/F than that found in the study by Jiao et al.10. On the other hand, the values of the absorption constant (Ka) show that sirolimus has rapid absorption. Some studies9,10,11 fixed the value of this constant based on the value obtained in other studies due to the lack of samples/times in the absorption phase.

In the selected studies, different covariables were identified that explain some of the interindividual variability of the pharmacokinetic parameters of sirolimus. For example, most of the studies showed the clinical relevance of the variable age. Age is a factor usually assessed in pharmacokinetic studies because it affects the physiological and pathophysiological characteristics of the population, which leads to changes in drug pharmacokinetics. Age was assessed as a covariate in all the studies, but only 4 of them9,10,11,13 found an inverse relationship between age and CI/F. This result may be because the age distribution of the population included in the other studies was very homogeneous and therefore this association was not observed.

According to Djebli et al.11, the CYP3A5 genetic polymorphism significantly influences the CI/F of sirolimus because it is a substrate of this enzyme. Thus, homozygous patients with the CYP3A5*3*3 polymorphism have a lower CI/F than patients with the CYP3A5*1*1 and CYP3A5*1*3 polymorphisms, with CI/F being twice as high in the latter (14.1 L/h vs 28.3 L/h). However, given the limited sample size of this study, other studies with a larger sample size would be needed to support its results. Previous authors15,16 have also assessed the influence of CYP3A5 and CYP3A4 isoenzyme polymorphism on sirolimus pharmacokinetics. Both studies found a relationship between the two polymorphisms, although neither of these studies aimed to develop a pharmacokinetic model.

Weight has an influence on distribution parameters because of the lipophilic nature of sirolimus, which has a high partition coefficient and is partly distributed in fatty tissues. Ferron et al.9,10 found a correlation between body weight and BSA and apparent intercompartmental clearance (Q/F) and Vp/F.

In the model developed by Jiao et al.10, the sirolimus dose increased the CI/F of sirolimus in a non-linear manner, which, according to the authors, is explained by the low bioavailability of the drug. Nevertheless, it is inadvisable to model CI/F as a function of dose when the data used are obtained from a targeted monitoring therapy, since the correlation between sirolimus dose and CI/F occurs because the doses are adjusted to obtain concentrations within a target range. Moreover, in the same model, the decrease in the CI/F of sirolimus in patients with elevated total cholesterol levels could be explained by the reduction of the free fraction of sirolimus available to be metabolized.

On the other hand, Jiao et al.10 also found that the administration of silymarin and glycyrrhizin as concomitant treatment reduced the CI/F of sirolimus by 34%. This effect could be explained by the inhibition of CYP3A4 and PGlycoprotein shown by both substances in vitro.17,18

The interaction between cyclosporine and sirolimus has been studied in 2 of the pharmacokinetic models, but with little clinical impact, given that Jiao et al.10 observed a 4.5% decrease in the CI/F of sirolimus for...
every 100 ng/mL increase in the plasma concentration of cyclosporine, and Wang et al. observed a 7.3% decrease in the CL/F of sirolimus for every 100 mg increase in the daily dose of cyclosporine. This association is in line with the results of the study by Zahir et al., in which the clearance of sirolimus decreased by 20.8% per 100 mg increase in cyclosporine dose. Previous authors have observed an interaction between cyclosporine and sirolimus at the level of absorption in healthy volunteers, with the area under the curve of sirolimus increasing by 230%. However, it should be taken into account that current guidelines recommend immunosuppression schemes that include triple therapy with (1) calcineurin inhibitors (tacrolimus being the drug of choice), (2) mycophenolate or mTOR inhibitor, and (3) corticosteroids. Therefore, cyclosporine is little used in renal transplant programs. However, most of the population pharmacokinetic models included in the current review were based on schemes in which cyclosporine was included as an anticalcineurinic, only the model developed by Dansiskul et al. included four patients who were administered sirolimus and tacrolimus in combination.

The inclusion of liver function, expressed as AST > 37 IU/L in the pharmacokinetic model, reached statistical significance only in the study by Golubovic et al., in which the CL/F of sirolimus was reduced by 37% in patients with compromised liver function. This result is in line with previous studies, which have found reductions of 31.8% and 36.0% in patients with mild and moderate hepatic impairment, respectively. In fact, a 50% reduction in the maintenance dose of sirolimus is recommended in patients with severe hepatic impairment.

Sirolimus is widely distributed in blood components, mainly in erythrocytes, but is sparingly distributed in plasma (< 5%). The determining factors for sirolimus to bind to red blood cells are liposolubility, the degree of ionization, molecular size, and capacity for hydrogen bonding. However, in the studies reviewed, no correlation was observed between clearance and hematocrit despite its inclusion as a covariate in most of them. This result is in contrast to that observed in cancer patients treated with sirolimus, in which an inverse relationship was found between hematocrit and sirolimus clearance.

No study assessed concomitant treatment with corticosteroids as a covariate. The metabolism and induction pathways common to immunosuppressants are known, there is little evidence of the clinical impact of the interactions, for this reason, it would have been interesting to include this covariate.

In conclusion, according to the available literature, the two-compartment model was the pharmacokinetic model of choice in most of the selected studies. The interindividual variability of the pharmacokinetic parameters of sirolimus is explained by variables such as age, weight, liver function, cyclosporine exposure and dose, sirolimus dose, CYSP3A5 genetic polymorphisms, serum creatinine, and concomitant treatment. These results provide relevant information to optimize immunosuppressive therapy with sirolimus in renal transplant patients. However, these population pharmacokinetic models need to be validated to assess their suitability and predictive capacity before they are applied in the case of individualized dosage adjustment in specific patient populations.

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Bibliography
