Manual de rotación del residente por la Unidad de Farmacocinética Clínica

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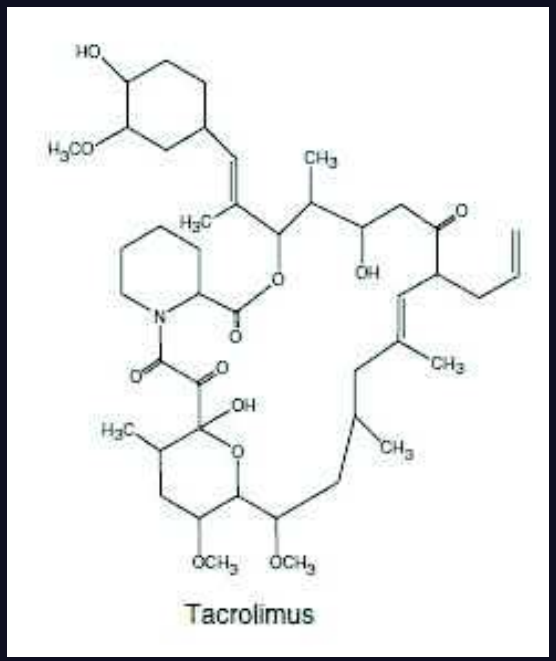
Actividad 11

Monitorización de tacrolimus



Tacrolimus

Generalidades

- Inmunosupresor inhibidor calcineurina
- Estructura macrólida
- Aislado de *Streptomyces tsukubaensis*
- Indicado en Tx hepático y renal
- Perfil toxicidad similar a la ciclosporina
  - Nefrotoxicidad por vasoconstricción renal

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Presentaciones comerciales

- Cápsulas de liberación rápida: Prograf® 0,5, 1 y 5 mg
- Cápsulas de liberación prolongada: Advagraf® 0,5, 1, 3 y 5 mg
- Ampollas iv: Progaf® 5 mg/mL.

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Administración oral

- Advagraf® una sola toma diaria
- Administrar por la mañana
- Tragar enteras con líquido (agua)
- Con el estómago vacío (1 hora antes o 2 horas después de la ingesta de alimentos)

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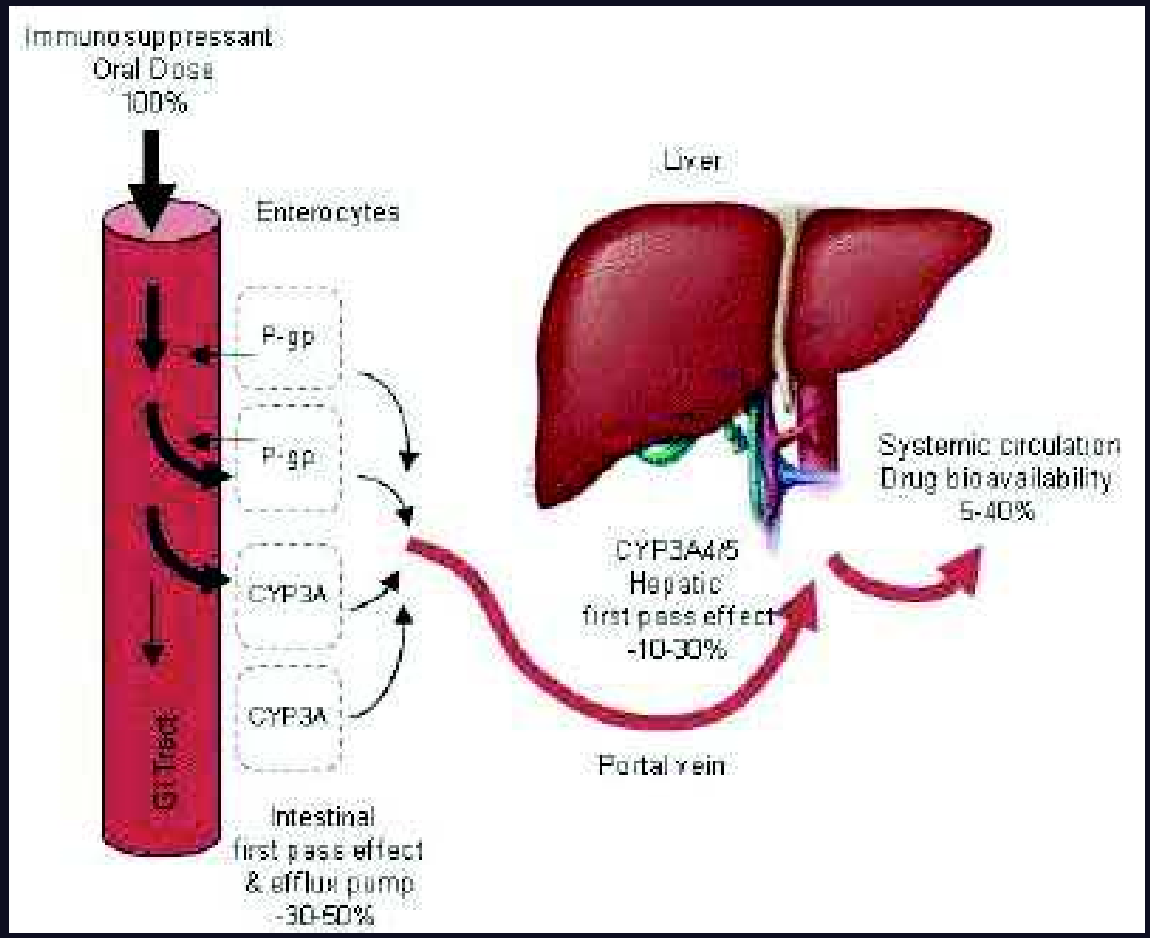
PK del tacrolimus

Absorción

- Errática desde el ID
- BD media: 17-22% (intervalo 4-93%)
- Tmáx: 1.6-2.3 horas
- Alimento: disminuye la BD en magnitud y en velocidad
- El flujo biliar no tiene influencia

Efecto de la P-gp



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Distribución

- Distribución en las células sanguíneas
  - Afinidad por la proteína fijadora de FK de los eritrocitos y linfocitos.
- Ratio sangre/plasma: 15 – 35 /1
- Unión a PP: 98.8% fundamentalmente la alfa-1 acido glicoproteina
- Amplia distribución en tejidos: pulmón, bazo, riñón, corazón, páncreas, cerebro, músculo e hígado

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Metabolismo

- Sufre O-desmetilación, hidroxilación u oxidación → 9 metabolitos
- Metabolito principal: 13-O-desmetil-tacrolimus sin actividad inmunosupresora
- Mediado por el CYP4503A

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Eliminación

- Vía principal de eliminación: Biliar
  - 77,8% y 94,9% de la dosis administrada, respectivamente por vía iv y oral aparece en heces.
  - 0,5% aparece intacta en heces u orina → metabolismo intenso
- Vía secundaria de eliminación: Renal
  - 2,4% de la dosis aparece en orina.

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Destino de los inhibidores de la calcineurina - CNI

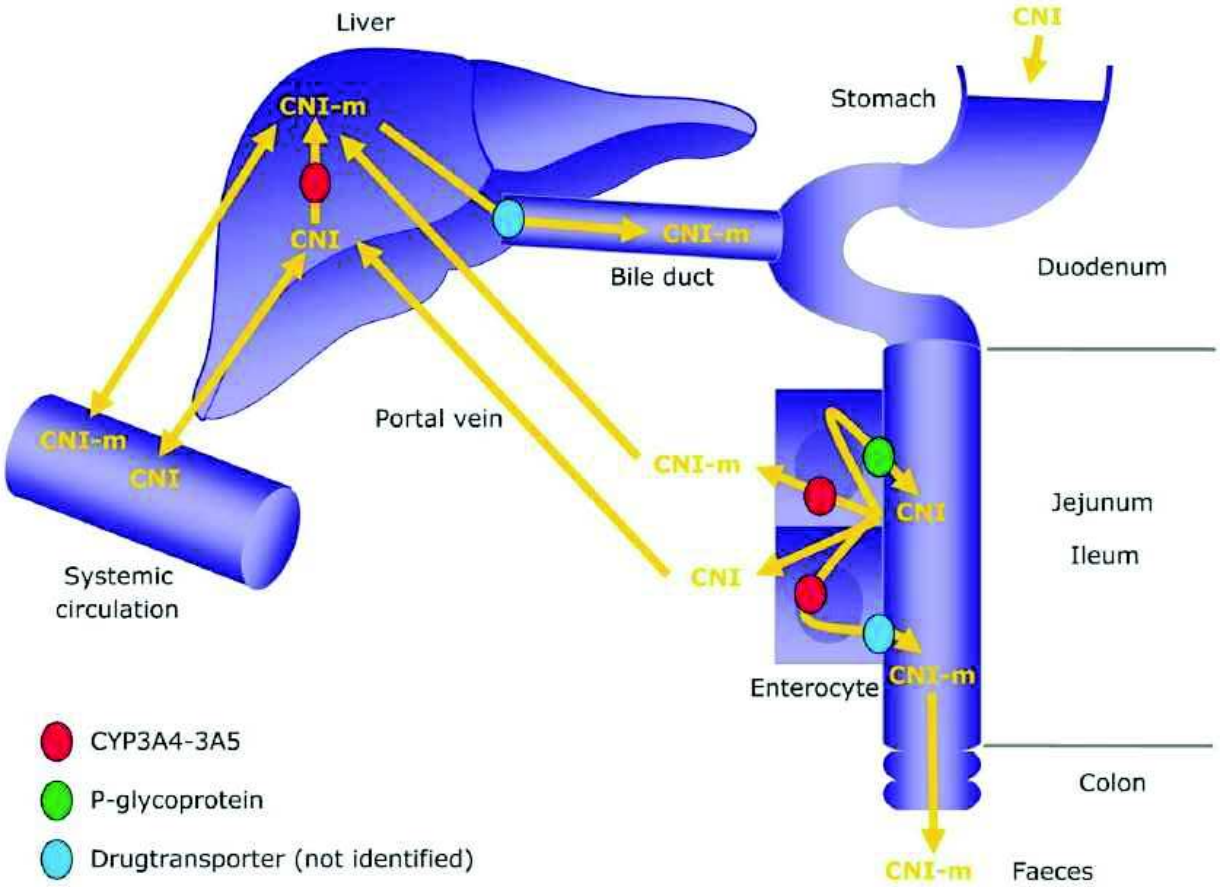

FIGURE 1. Schematic representation of CNI (cyclosporine and tacrolimus) pharmacokinetics. CNI-m, calcineurin inhibitor metabolites; CYP3A4-3A5, cytochrome P450 isoenzymes 3A4 and 3A5.

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Ther Drug Monit 2009;31:416–435

Variabilidad en la PK del tacrolimus

Factores que afectan a la conc. sanguínea de tacrolimus

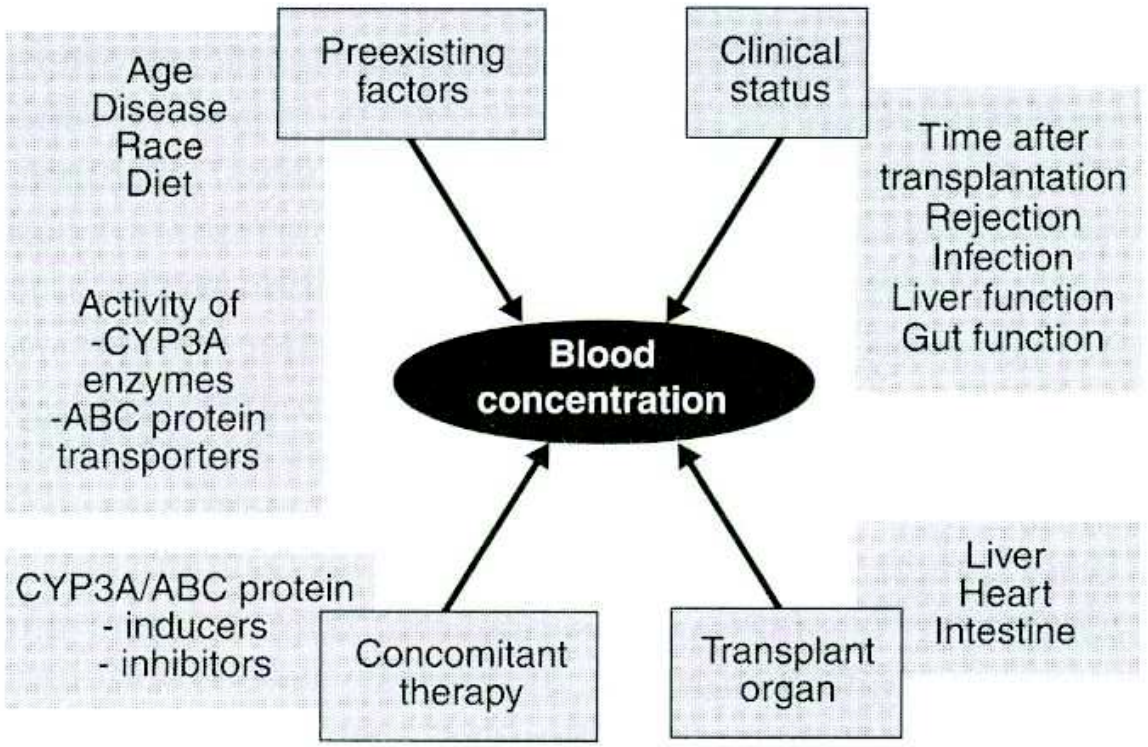

Figure 23-3 Factors affecting tacrolimus blood concentrations. CYP3A, cytochrome P4503A enzyme; ABC, ATP binding cassette.

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Burton ME et al- Applied pharmacokinetics and pharmacodinamics. 2006

Cambios en la PK tacrolimus – Raza, edad y trasplante

- Raza negra: menor BD que caucásica, requieren dosis mayores. Diferencias en la GPP y CYP3A intestinales
- Niños < 6 años: Mayor aclaramiento
- Órgano trasplantado: Cambio en la PK
  - Diferente en Tx renal y hepático y en voluntarios sanos
    - Diferencias en las dosis de esteroides
    - Diferencias en los regímenes inmunosupresores

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Cambios en la PK tacrolimus – Enfermedades concomitantes

- Colestasis: Disminución del aclaramiento tacrolimus → Mayor incidencia de nefrotoxicidad → Ajustar la dosis
- Hepatitis C: Requieren menor dosis de tacrolimus
- No afecta: Ascitis, IR y la IH leve
- Diarrea: aumenta las concentraciones

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Cambios en la PK -Tiempo posttrasplante

- A la larga: Reducción del aclaramiento / Incremento en la BD oral
- Posibles causas
  - Reducción estrés postquirúrgico
  - Estabilización de la función del orgáno
  - Hematocrito
  - Interacciones afectan al CYP3A/GPP
    - Reducción/retirada corticoides inductores → exposición se incrementa un 25%

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Artículo recomendado

Clinical Pharmacokinetics and Pharmacodynamics of Tacrolimus in Solid Organ Transplantation

Christine E. Staatz and *Susan E. Tett*

School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia

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Monitorización PK

Justificación de la monitorización

- Pobre correlación entre dosis y exposición
  - Gran variabilidad intra e interindividual en la PK
  - Gran nº factores que influyen en la PK
- Indice terapéutico estrecho
- Ratio conc/dosis muy variable
- No relación lineal entre la dosis y C0 en el estado estacionario
- Concentraciones bajas asociadas a mayor riesgo de rechazo.
- Concentraciones altas asociadas a mayor riesgo de toxicidad

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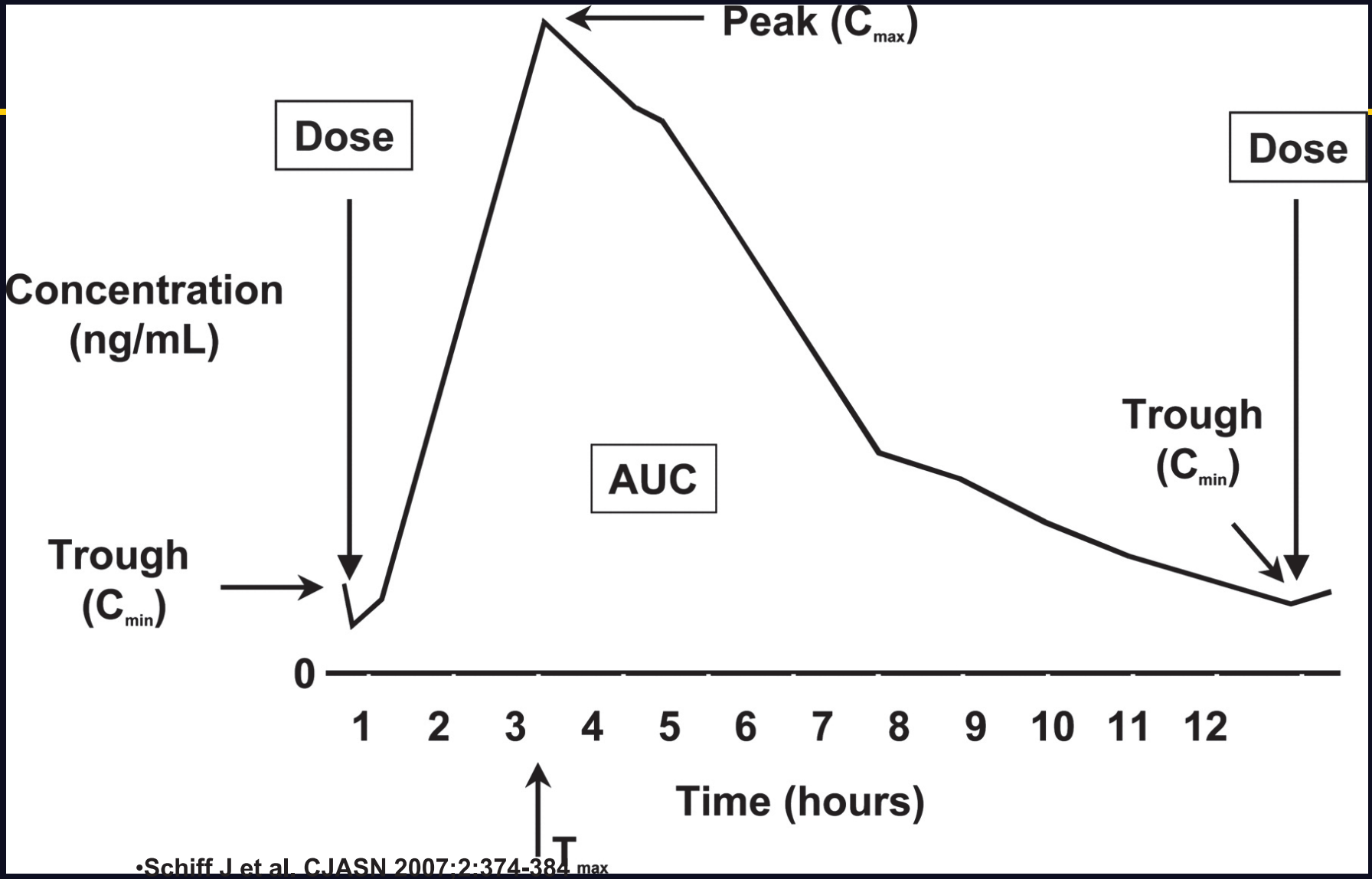
Therapeutic Monitoring of Calcineurin Inhibitors for the Nephrologist



•Schiff J et al. CJASN 2007;2:374-384

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CJASN Clinical Journal of the American Society of Nephrology

Parámetros utilizados en TDM

- AUC_{0-t}
  - Refleja mejor la exposición al fármaco.
  - Potente predictor riesgo de rechazo agudo
    - AUC>200 ng·h/ml →menor riesgo rechazo Tx renal (17 vs 41%) y correlaciona con C_0 de 10 mg/ml
- Cmáx
  - No correlaciona con el riesgo de rechazo
- Cmín: la más utilizada en TDM

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C_0 – concentracion valle o predosis

- Correlación con el AUC
  - 2 estudios correlación baja (r^2=0,11 y 0,362)
  - Otros estudios r^2=0,79-0,86

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Concentración efecto de tacrolimus en Tx hepático

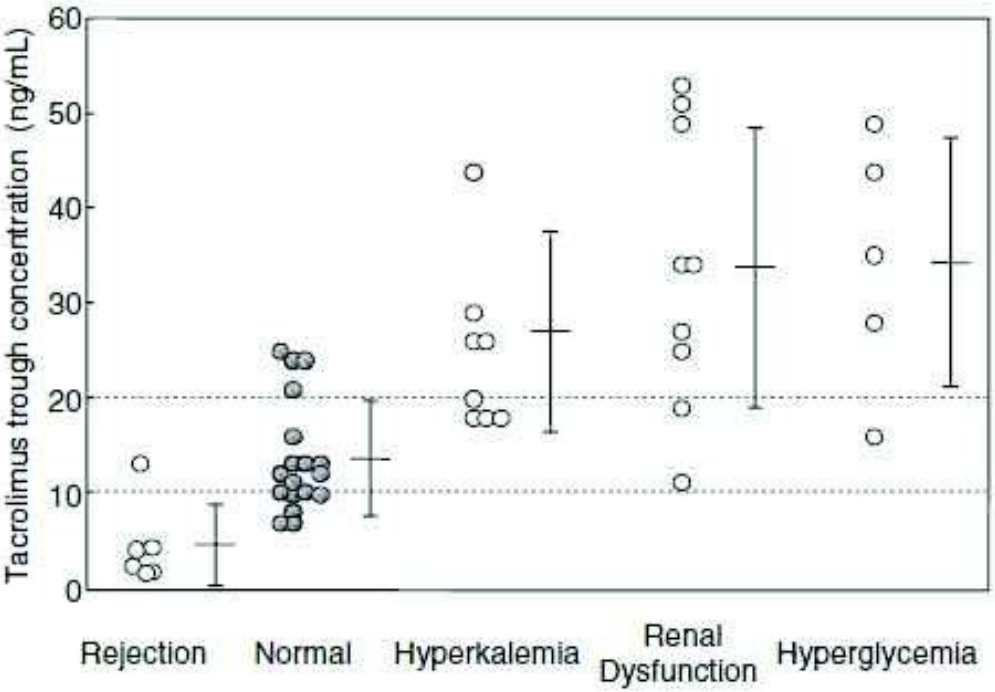

Fig. 2. Blood trough concentration–effect relationships of tacrolimus in pediatric patients after LDLT. Error bars are means±SD. (Reprinted from Yasuhara et al., 1995 with permission from *Elsevier*.)

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Frecuencia de rechazo en Tx hepático con relación al C0

Table 1
Frequency of acute cellular rejection after LDLT with respect to the tacrolimus trough level between postoperative days 2 and 4

Tacrolimus trough concentration between postoperative days 2 and 4 (ng/mL)	Event free	Acute cellular rejection
<5	15	8
5–7	13	15
7–9	21	7
9–11	18	7
>11	15	2

Frequencies of an event-free clinical course and acute cellular rejection are shown. The patients were classified based on the average trough concentration of tacrolimus between postoperative days 2 and 4 during intensive care. The odds ratio of the acute cellular rejection was 2.772 (95% confidence interval, 1.265–6.075) for the patients whose mean trough level of tacrolimus was below 7 ng/mL between postoperative days 2 and 4. (Modified from Masuda et al., 2006 with permission from *American Society for Clinical Pharmacology and Therapeutics*.)

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Intervalo terapéutico

TABLE 1. Proposed Target TAC C_0 Concentration (ng/mL)* Guidelines for Kidney Transplantation[41]

	Without Induction	IL-2R Antibody	Polyclonal Antibodies/HRI	MMF/Steroid	mTOR
Time (mo)		Tritherapy		Minimization	Inhibitors
0–3	10–15	3–7†	5–10/10–15	10–15	3–7
3–12	5–15	3–7†	5–10/10–15	8–12	3–7
>12	5–10	3–7†	5–10/8–12	5–10	3–7

HRI, anti-human rabbit immunoglobulin.
*Proposed concentration range applied for the MEIA assay.
†Three to 7 ng/mL was the target concentration range in the Symphony trial. Actually reached TAC concentrations started at 8 ± 2.2 ng/mL and decreased to 6.4 ± 1.4 ng/mL over 12-month time.[54]

TABLE 2. Proposed Target TAC C_0 Concentration (ng/mL)* Guidelines for Heart and Liver Transplantation[6,44,45]

	Adult Transplant Recipient	
Organ	Time Period†	Target Concentration
Heart	Days 0–60	15–20
	Days 60–180	10–15
	After 6 months	8–10
	>6–9 months in stable patients	5–10
Liver	0–1 month	10–20
	1–3 months	5–15
	>3 months	5–10

*Proposed concentration range applied for the MEIA assay.
†Primary therapy.

Opportunities to Optimize Tacrolimus Therapy in Solid Organ Transplantation: Report of the European Consensus Conference

(*Ther Drug Monit* 2009;31:139–152)

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Otras estrategias

- Un solo punto
  - C2: buena correlación AUC (r^2=0,87)
    - No ha demostrado reducir la tasa de rechazo frente a C0 en Tx renal
  - C4: buena correlación AUC (r^2=0,79-0,81)
- Dos – tres puntos
  - C2 y C3 (y C4)

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Relación entre dosis - conc.

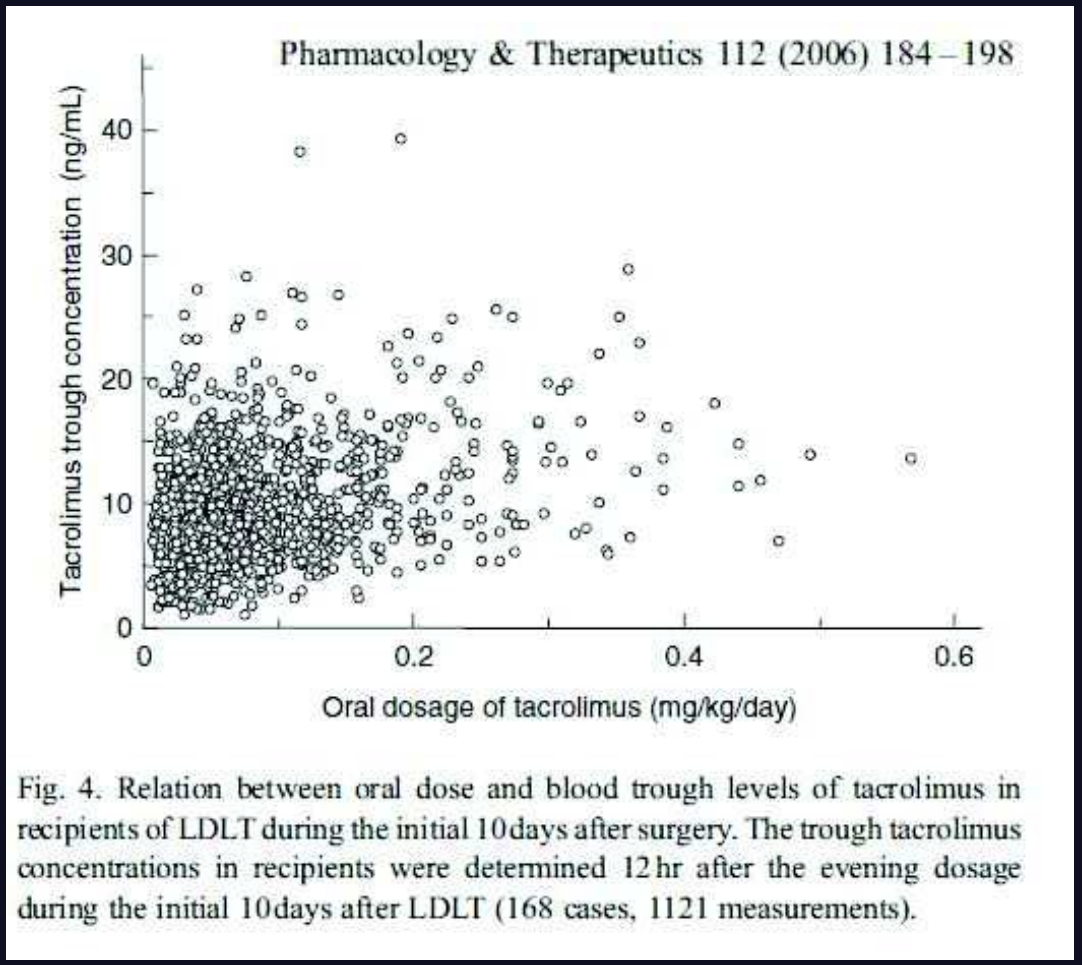

Fig. 4. Relation between oral dose and blood trough levels of tacrolimus in recipients of LDLT during the initial 10 days after surgery. The trough tacrolimus concentrations in recipients were determined 12 hr after the evening dosage during the initial 10 days after LDLT (168 cases, 1121 measurements).

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An up-date review on individualized dosage adjustment of calcineurin inhibitors in organ transplant patients

Frecuencia de la monitorizacion

- 3-7 veces por semana en las dos primeras semanas
- 3 veces por semana en las dos siguientes
- Cada vez que viene a visita ambulatoria

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Incremento de la monitorización

- Sospecha de reacción adversa o rechazo del órgano
- Deterioro de la función hepática
- Tras cambio en la dosis, vía de admon o forma farmacéutica / marca comercial
- Tras añadir o retirar fármacos que actúen sobre el CYP3A4 /GPP o cuando cambien las dosis.
- Enfermedades graves que afecten a la absorción o eliminación tales como reacciones inmunes graves y sepsis
- Sospecha de incumplimiento

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Muestra biológica

- Sangre anticoagulada con EDTA (preferible a la heparina)
  - Mejor correlación entre Csangre y eventos clínicos que con la Cplasmática
  - La Cplasmatica requiere una rigurosa estandarizacion de la centrifugación

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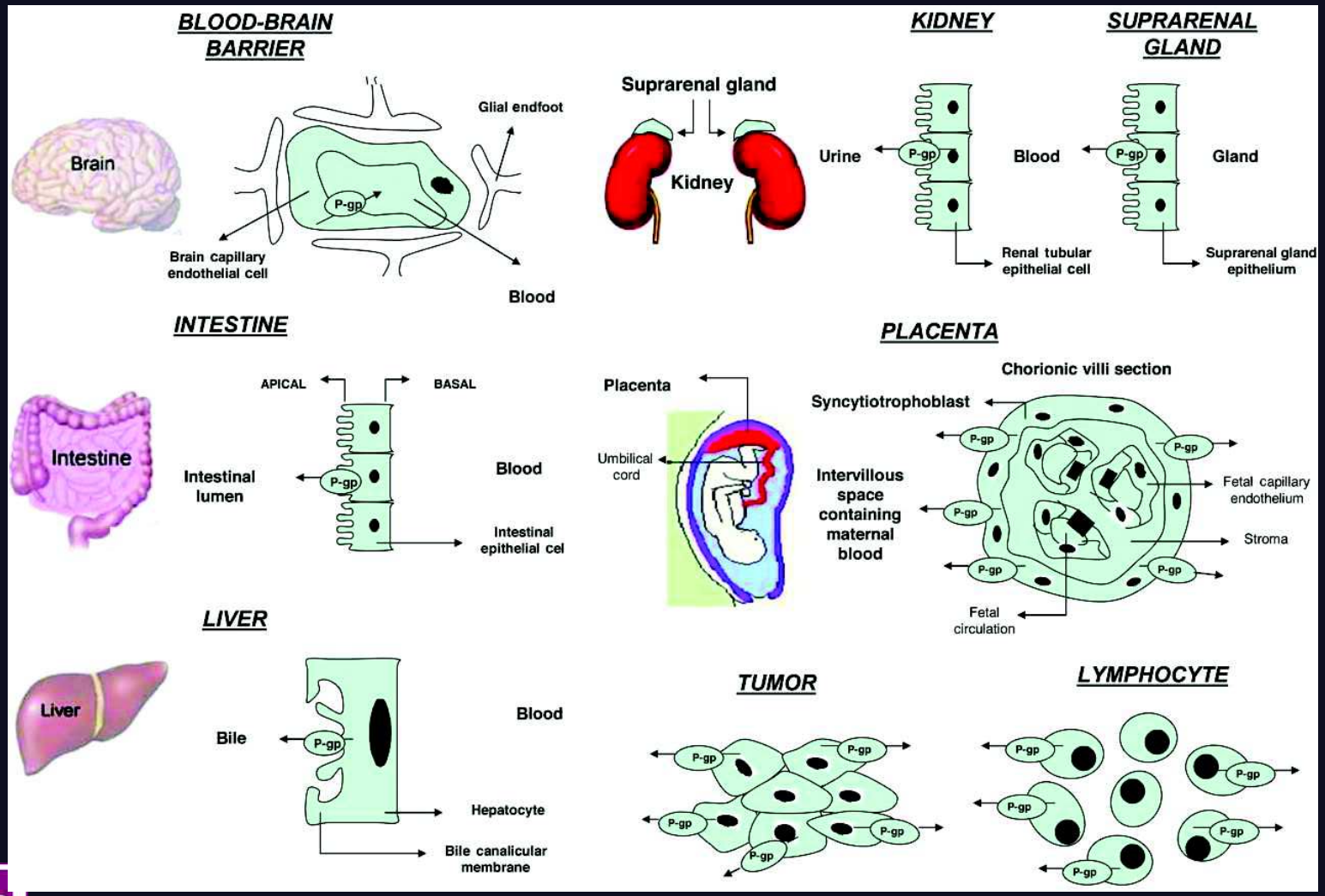
Interacciones del tacrolimus

Localizaciones de la Glicoproteína P en el organismo



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Marchetti, S. et al. Oncologist 2007;12:927-941

Interacciones entre inmunosupresores y transportadores

TABLE 1. Interactions Between the Major Immunosuppressants Used After Transplantation and Active Drug Transporters

Immunosuppressant	P-Glycoprotein (ABCB1)	MRP2 (ABCC2)	OATP	Others
Tacrolimus	Substrate/inhibitor,[22,25] The major metabolite13-O-desmethyl tacrolimus is a substrate/inhibitor[26]	No inhibitor[21]	Inhibitor[24]	

Active Drug Transport of Immunosuppressants: New Insights for Pharmacokinetics and Pharmacodynamics.
Christians, Uwe; Strom, Tobin; Zhang, Yan; Steudel, Wolfgang; Schmitz, Volker; Trump, Saskia; Haschke, Manuel
Therapeutic Drug Monitoring. 28(1):39-44, February 2006.

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Tacrolimus <-->Nefrotóxicos

- Aminoglucosidos, anfotericina B, cisplatino, ciclosporina, etc

Riesgo de nefrotoxicidad

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Tacrolimus <-->Ahorradores K+

- Espironolactona, Amilorida, ciclosporina

Riesgo de Hiperkalemia

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Inductores → Tacrolimus

- Anticonvulsivantes
  - Carbamazepina
  - Fenobarbital
  - Fenitoina
- Corticoesteroides
  - Dexametasona
  - Prednisona
- Ansamicinas
  - Rifabutina
  - Rifampicina
- Hierba de San Juan
- Efavirenz

Disminución concentraciones sanguíneas de tacrolimus: Riesgo de rechazo del órgano

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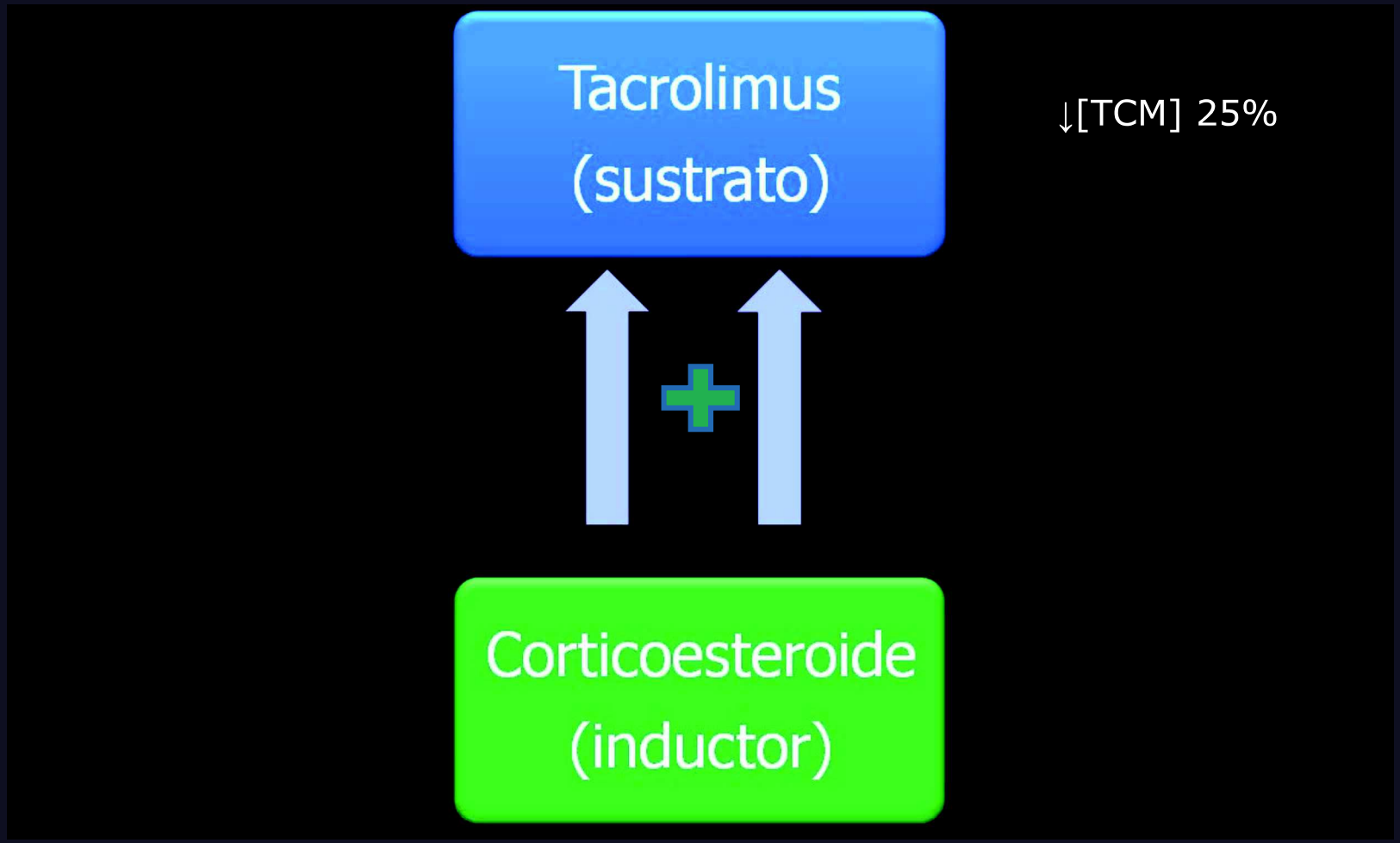
Corticoesteroides → Tacrolimus



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Inhibidores → Tacrolimus

- Macrólidos
  - Claritromicina
  - Eritromicina
  - Troleandomicina
- Inmunosupresores
  - Basiliximab
  - Ciclosporina
- Danazol
- Diltiazem
- Verapamilo
- Nicardipino
- Metilprednisolona
- Nefazodona
- Antifúngicos
  - Fluconazol
  - Itraconazol
  - Ketoconazol
  - Posaconazol
  - Voriconazol
- Inhibidores de proteasa
- Amiodarona

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Mecanismo desconocido

- Caspofungina: ↓ Conc. tacrolimus 20%
- Sirolimus: ↓ Conc. tacrolimus 30%

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Interacciones del TCM con otros inmunosupresores

Inmuno-supresor	F.afectado	Efecto AUC	Mecanismo	Riesgo
Ciclosporina	TCM	↔	Farmacodinámico	Nefrotoxicidad
Micofenolico	TCM	↔	-	-
Sirolimus	TCM	↔↓	CYP3A/GPP	No determinado
Corticoides	TCM	↓	CYP3A/GPP	Mínimo

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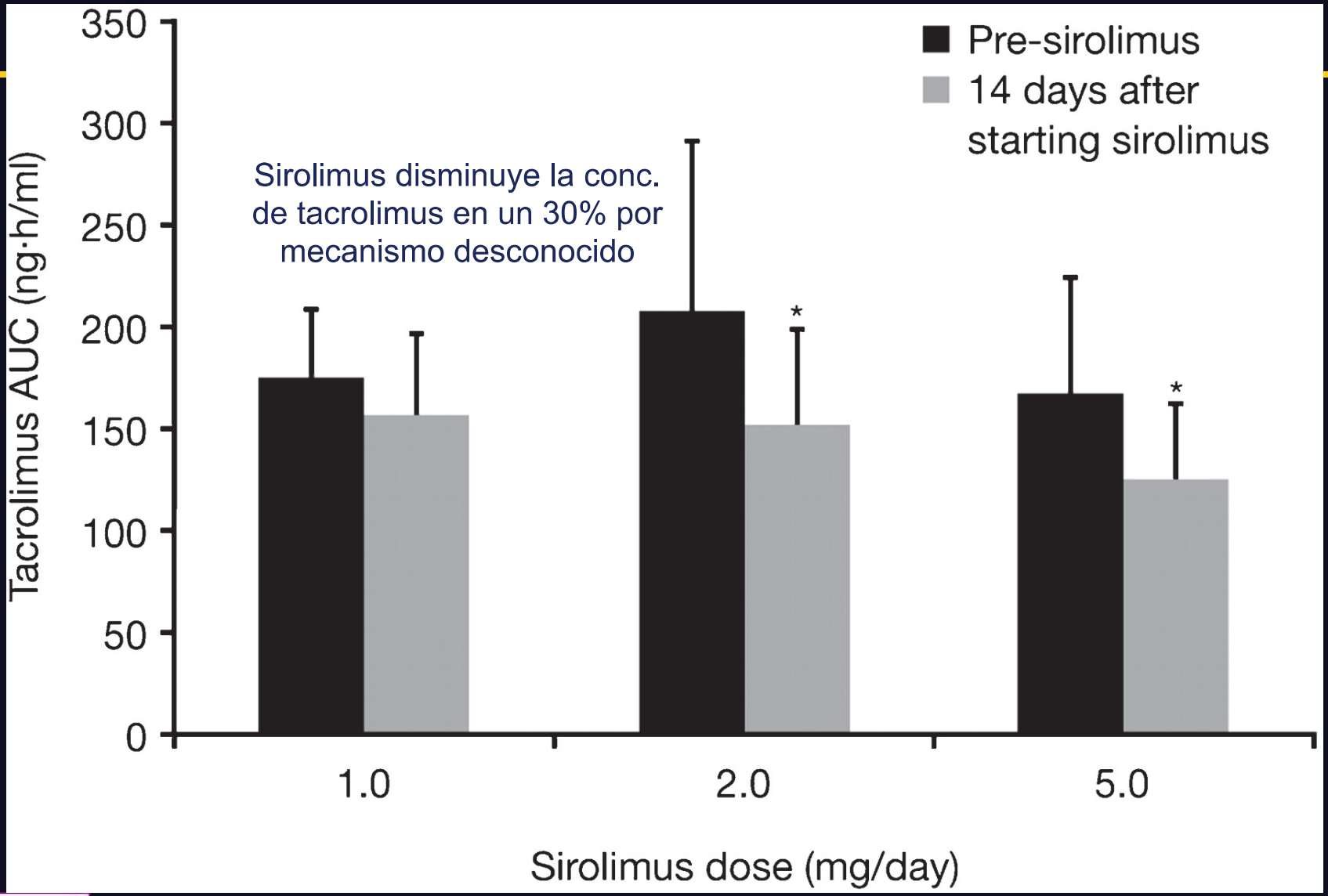
Sirolimus → Tacrolimus



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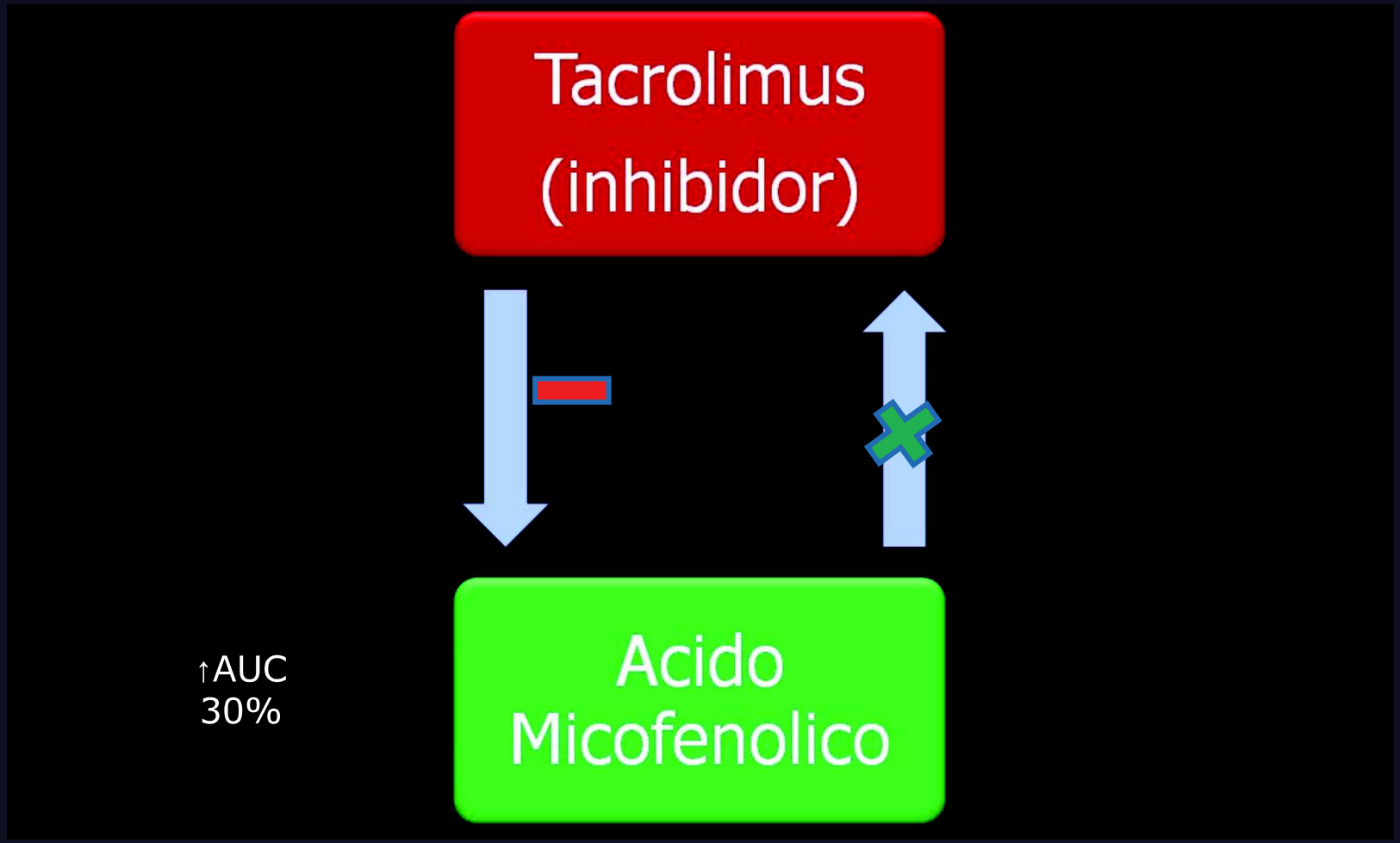
•Undre N A Nephrol. Dial. Transplant. 2003;18:i12-i15

Tacrolimus → Micofenolato



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■ Case 1

The patient is a 32-year-old white woman with a kidney-pancreas transplant. She was admitted to the hospital with low-grade fever, severe headache, and a rise in serum creatinine. The patient has type 1 diabetes mellitus since age 4 with evidence of retinopathy, neuropathy, and recurrent skin infection over the left foot. The transplant was performed about 6 months ago. Her initial immunosuppression consisted of four doses of Thymoglobulin (total of 6 mg/kg) and tacrolimus 2 mg twice daily, a fixed dose of sirolimus 2 mg daily, and prednisone 20 mg every day.

The donor was cytomegalovirus-positive and shared 2 DR matches with the recipient. The surgery was performed without any complication. The patient's postoperative course was unremarkable. Initial graft function was good. The patient required no insulin after the first postoperative day, with normal blood glucose levels. Her creatinine dropped to a level of 0.6 mg/dL by postoperative day 6. At discharge from the hospital, the sirolimus trough blood concentration was 5.2 ng/mL, and the tacrolimus blood trough concentration was 14 ng/mL at a dose of 2 mg twice daily. The tacrolimus dose was lowered to 1 mg twice daily, and the trough blood concentration dropped to 8.9 ng/mL. She was maintained on this tacrolimus dose for the following months and consistently had stable trough concentrations between 8 and 10 ng/mL. Her other medications included Bactrim single-strength, one tablet every day, and valganciclovir (Valcyte) 450 mg every day.

Three days ago, the patient started complaining of headache, nausea, vomiting, and fever. Her immunosuppression included tacrolimus 1 mg twice daily, sirolimus 1 mg twice daily, and prednisone 7.5 mg. On examination she had a blood pressure of 110/70 mm Hg, a pulse of 110 beats/min, and a temperature of 39°C. She had dry mucous membranes and no lymphadenopathy, and the chest was

clear to percussion and auscultation. There was no tenderness over the transplant kidney on the left, no tenderness over the transplant pancreas on the right side of the abdomen, and mild neck rigidity without other central nervous system abnormalities.

Laboratory values were white blood cell count, 3,500/mm^3; hematocrit, 35%; platelet count, 212,000; Na^+, 132 mEq/L; K^+, 3.9 mEq/L; Cl^-, 93 mEq/L; blood urea nitrogen (BUN), 29 mg/dL; creatinine, 1.9 mg/dL; tacrolimus trough blood concentration, 26.2 ng/mL; sirolimus trough blood concentration, 12.7 ng/mL.

A lumbar puncture was performed, and the cerebrospinal fluid virology turned out to be positive for West Nile virus.

Questions

1. What is the most likely explanation for the high tacrolimus concentrations?
2. How would you initially manage this patient?
3. What will be your therapeutic drug monitoring and dosing strategy for the next 4 weeks?

Case 2

A 49-year old, obese African American man with end-stage renal disease secondary to hypertensive nephrosclerosis received a cadaver kidney with 1 DR antigen match. Both the donor and the recipient were cytomegalovirus-positive. There were no technical complications with the operation. However, the allograft failed to produce significant amounts of urine in the first 24 hours after transplant. The patient was induced with basiliximab (Simulect) intravenous 20 mg on day 0 and also on day 4. The patient was started on mycophenolate mofetil (MMF) 1 g twice daily, and prednisone 20 mg every day. No dialysis, however, was needed. Urine output improved on day 2, and serum creatinine concentrations decreased to 3.5 mg/dL from a preoperative value of 9 mg/dL. The patient was then started on tacrolimus (Prograf), 3 mg twice daily, resulting in trough blood concentrations between 6.2 and 9.6 ng/mL. On day 12, owing to poor renal function, he underwent an allograft biopsy. This biopsy revealed recovering acute tubular necrosis without evidence of acute transplant rejection. There was a mild degree of arteriolar sclerosis of donor origin. The patient was continued on MMF 1 g twice daily, tacrolimus 3 mg twice daily, and prednisone 20 mg every day. By the 20th postoperative day the urine output had increased, and the patient's creatinine had fallen to 2.2 mg/dL.

On postoperative day 30, he presented for routine follow-up in the clinic, and the patient's serum creatinine had risen from 2.0 to 3.1 mg/dL. The tacrolimus trough blood concentration was 7.0 ng/mL. A renal transplant biopsy was performed after technical causes of his rising serum creatinine (such as obstruction or urinary leaks) were ruled out. The biopsy revealed moderate acute interstitial rejection. Tacrolimus was discontinued, and the patient was given a 10-day course of OKT3 without good response. Serum creatinine was 2.6 mg/dL and rose to 3.2 mg/dL during OKT3 treatment. Thereafter, tacrolimus was reinstituted (3 mg twice daily). A biopsy of the transplant kidney was performed to assess the response to OKT3. The biopsy revealed changes consistent with acute interstitial nephritis with evidence of some inclusion bodies. Electron microscopy results are pending. The final diagnosis was human polyomavirus BK virus in the transplant kidney. Review of the first biopsy using in-situ hybridization indicated the presence of the virus already in the first biopsy.

Questions

1. Why was tacrolimus treatment delayed after transplantation?
2. In comparison with case 1, the tacrolimus doses required to reach similar trough blood concentrations are significantly higher, e.g., in case 1, 1 mg tacrolimus twice daily resulted in a trough concentration of 8.9 ng/mL; in case 2, 3 mg tacrolimus twice daily resulted in a trough concentration of 7 ng/mL. What are potential reasons?
3. What are the therapeutic options in this patient and which of the above-mentioned facts and events will have a negative effect on long-term graft function and survival?