FARMACOGENÉTICA de los Inmunosupresores (tacrolimus) en el TxRenal

Congreso Sociedad Gallega Nefrología
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Trasplante Renal: tratamiento inmunosupresor.

Tratamiento inmunosupresor → Evitar el **rechazo** del injerto

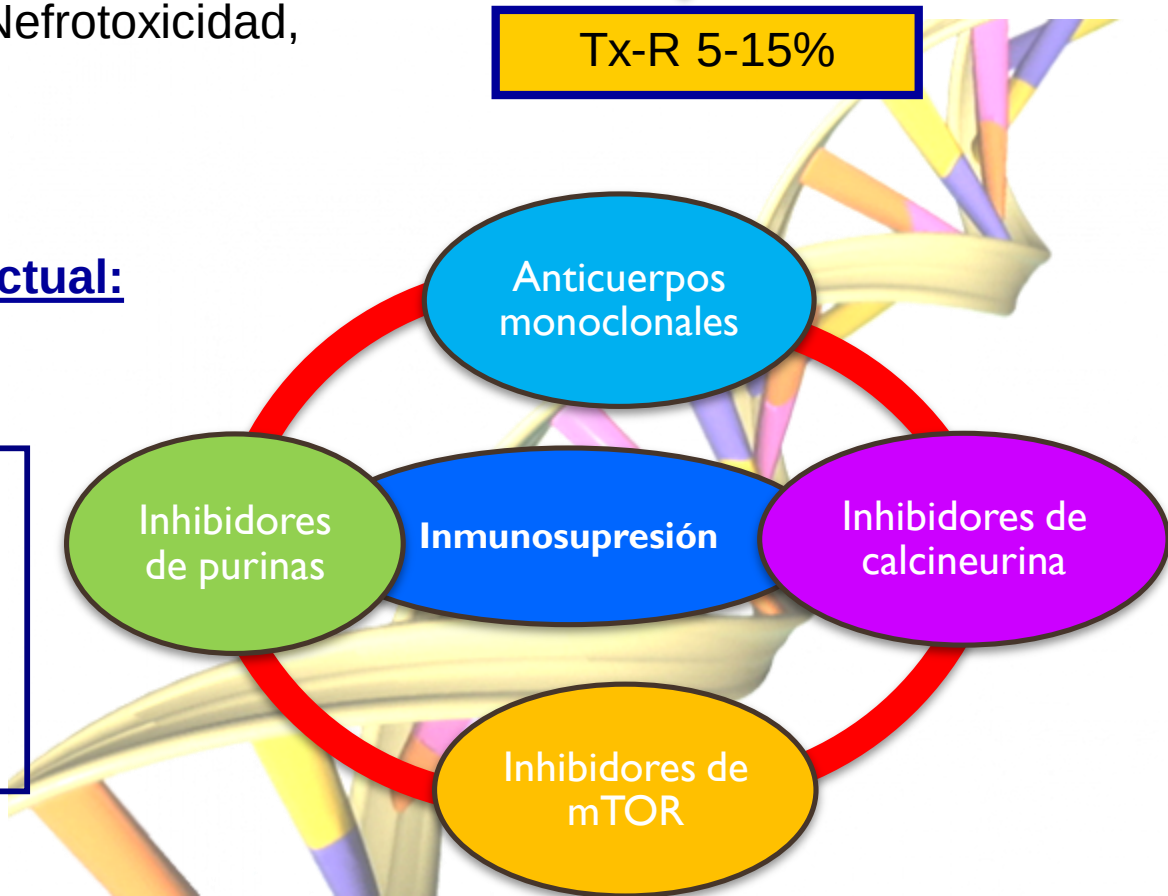
Efectos secundarios: Diabetes, Nefrotoxicidad, neurotoxicidad…

Tx-R 5-15%

Estrategia inmunosupresora actual:

Combinación de fármacos

- Búsqueda de sinergia
- Reducción de toxicidad
- Evitar efectos adversos

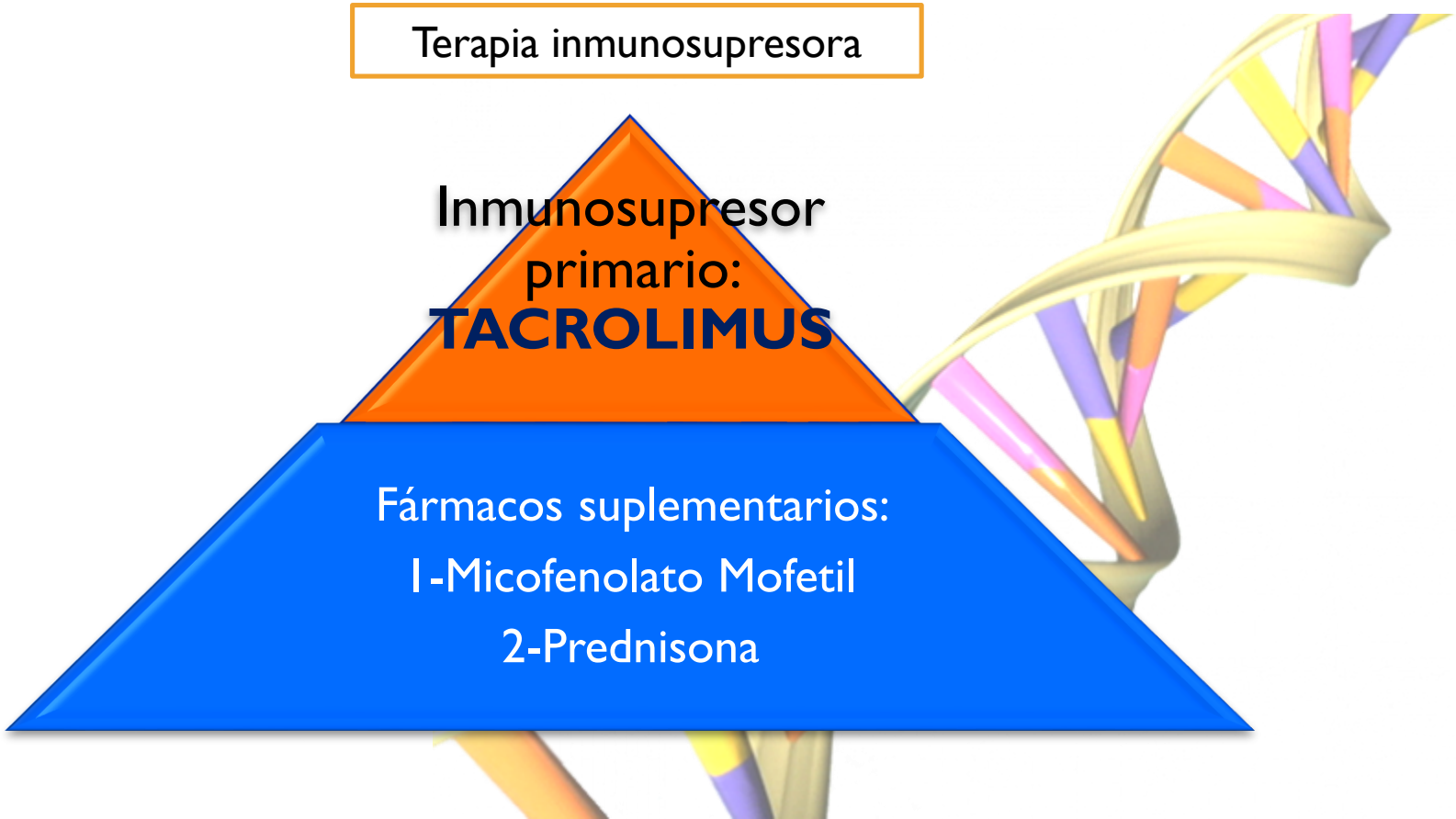


Trasplante Renal: tratamiento inmunosupresor

Terapia de inducción (anticuerpos mono/policlonales) → Timoglobulina

+

Terapia inmunosupresora



Tratamiento inmunosupresor

Puntos clave: determinación de las dosis adecuadas

→ Farmacocinética variable

Monitorización de las dosis → inmunoensayos

Introducción a la farmacogenética: terapia individualizada

Terapia común → Terapia individualizada

FARMACOGENÉTICA

Farmacogenética:
de la terapia común a la terapia individualizada

Aplicación en diferentes campos

Clin Pharmacol Ther. 2011 Aug;90(2):328-32. doi: 10.1038/clpt.2011.132. Epub 2011 Jun 29.

Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy.

Scott SA, Sangkuhl K, Gardner EE, Stein CM, Hulot JS, Johnson JA, Roden DM, Klein TE, Shuldiner AR; Clinical Pharmacogenetics Implementation Consortium.

Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, New York, USA.

ANTIPLAQUETARIOS

PLoS One. 2011;6(11):e27808. Epub 2011 Nov 16.

Clinical and genetic determinants of warfarin pharmacokinetics and pharmacodynamics during treatment initiation.

Gong IY, Schwarz UI, Crown N, Dresser GK, Lazo-Langner A, Zou G, Roden DM, Stein CM, Rodger M, Wells PS, Kim RB, Tirona RG.

Department of Physiology & Pharmacology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

ANTICOAGULANTES ORALES

Cancer Genomics Proteomics. 2011 Sep-Oct;8(5):255-9.

Gemcitabine and platinum pathway pharmacogenetics in Asian breast cancer patients.

Wong AL, Yap HL, Yeo WL, Soong R, Ng SS, Wang LZ, Cordero MT, Yong WP, Goh BC, Lee SC.

Department of Hematology-Oncology, National University Cancer Institute of Singapore.

CÁNCER

Mol Psychiatry. 2004 May;9(5):442-73.

Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response.

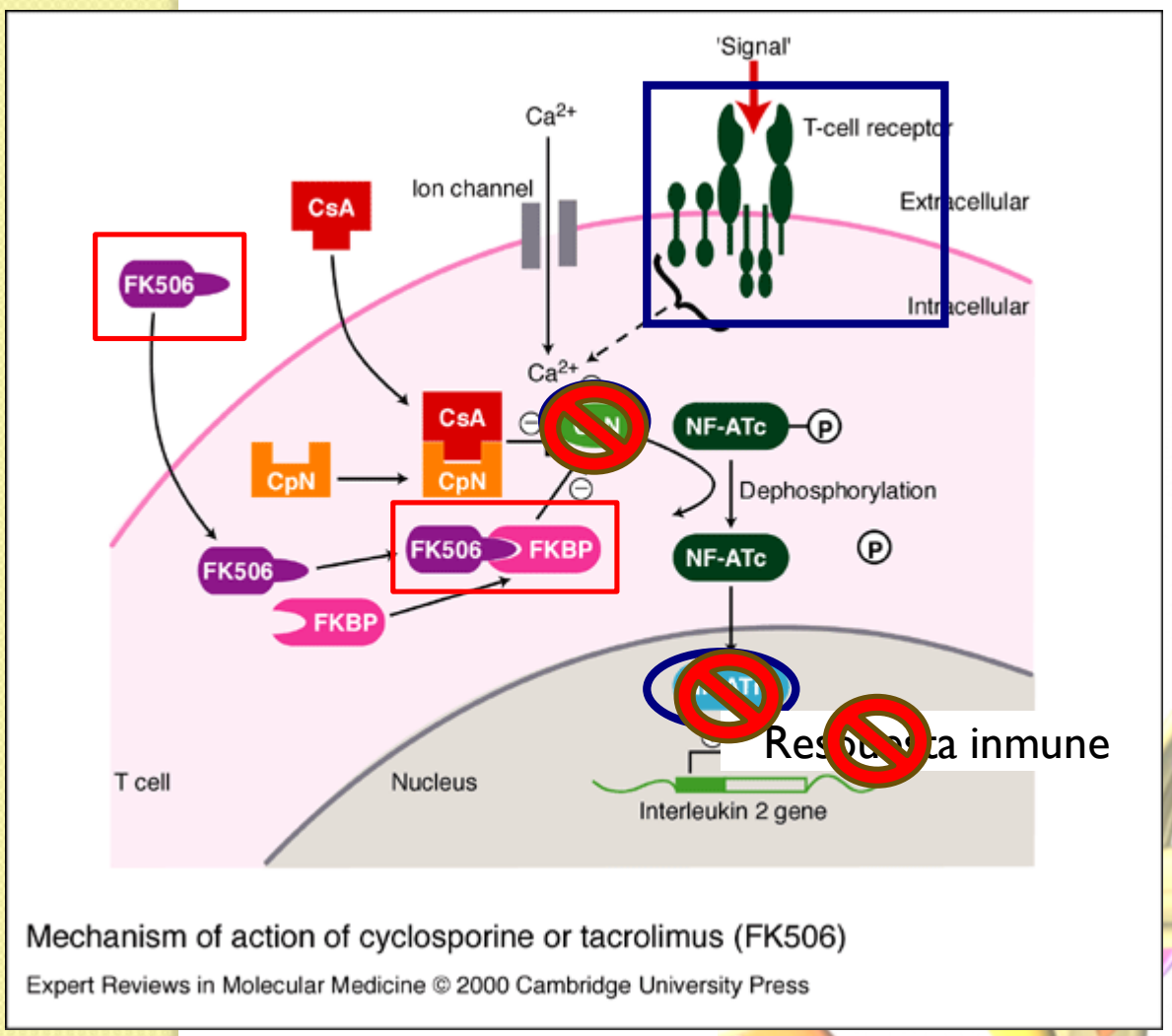
Kirchheiner J, Nickchen K, Bauer M, Wong ML, Licinio J, Roots I, Brockmöller J.

Institute of Clinical Pharmacology, Campus Charité Mitte, University Medicine Berlin, Berlin, Germany. julia.kirchheiner@gmx.de

ANTIDEPRESIVOS Y ANTIPSICOTICOS

Farmacogenética de Tacrolimus

Farmacocinética y mecanismo de acción de Tacrolimus



Mechanism of action of cyclosporine or tacrolimus (FK506)

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press

Farmacocinética variable

Estrecho margen terapeutico

Monitorización de las dosis

1-Absorción variable

2-Distribución unido a:

- Eritrocitos
- Albúmina

3-Metabolismo hepático

Citocromo P-450 reductasa

- CYP3A5*3
- CYP3A4*1

4-Metabolismo intestinal

- MDR-1

5-Excrecion biliar

6-Eliminación heces

Farmacogenética de Tacrolimus

Superfamilia P-450 reductasa

Biotransformación de sustancias xenobioticas

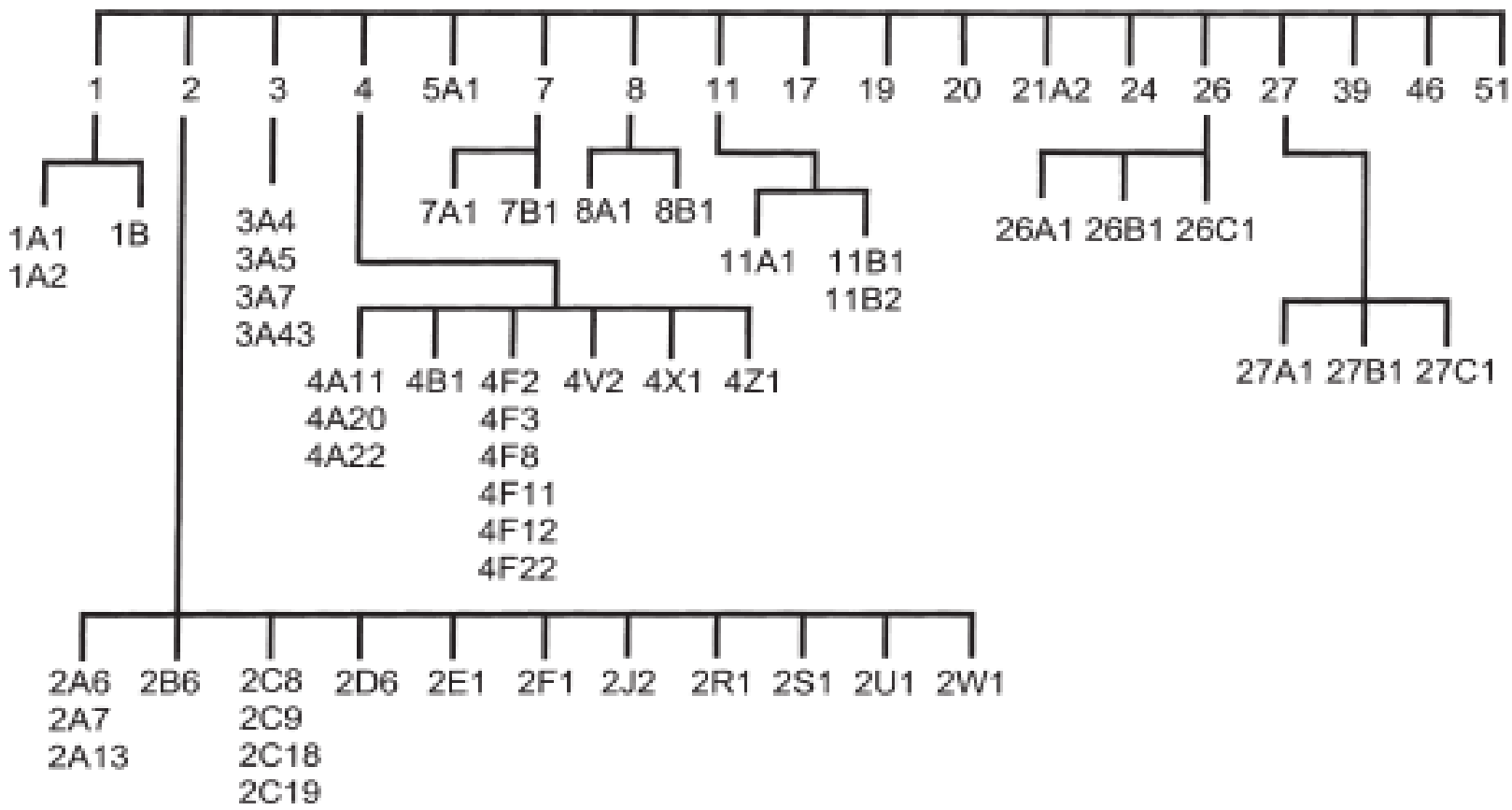


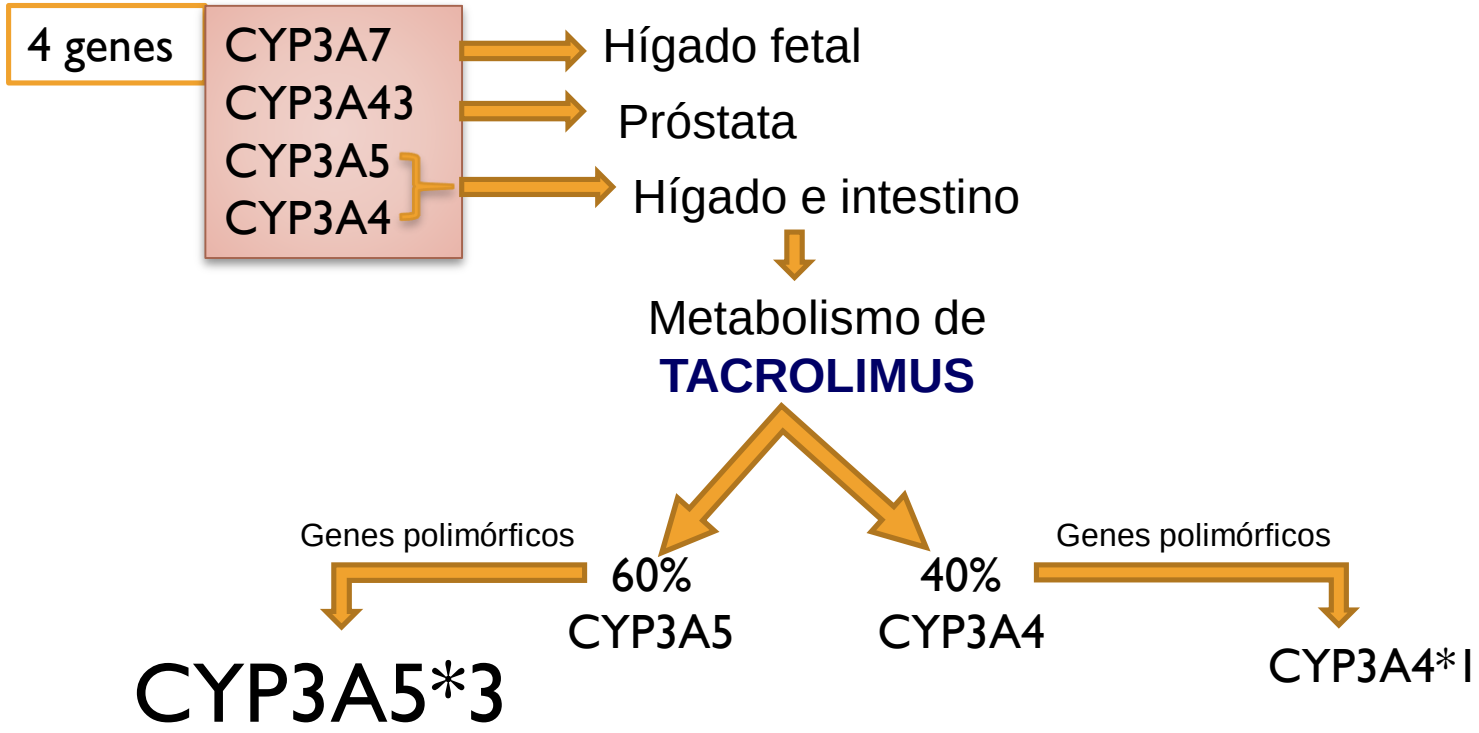
FIGURA 5. *Los enzimas P-450 identificados en la especie humana*

Farmacogenética de Tacrolimus

Superfamilia P-450 reductasa

Subfamilia : CYP3A

• Se trata del grupo de enzimas con mayor importancia en el metabolismo de agentes terapéuticos



Farmacogenética de Tacrolimus

Genotipos de polimorfismos CYP3A: fenotipos metabolizadores

Dosis de Tacrolimus

Genotipo **CYP3A5*1/*3-CYP3A5*1/*1**

(20% población Caucásica)

Fenotipo **METABOLIZADOR**

Dosis de Tacrolimus

Genotipo **CYP3A4*1/*1B-CYP3A4*1/*1**

(5% población Caucásica)

Fenotipo **ALTO METABOLIZADOR**

Dosis de Tacrolimus

Genotipo CYP3A5*3/*3

(80% población Caucásica)

Fenotipo **BAJO METABOLIZADOR**

Dosis de Tacrolimus

Genotipo CYP3A4*1/*1

(95% población Caucásica)

Fenotipo **BAJO METABOLIZADOR**

MDR-1 (C3435T) en la dosis > controversia

Farmacogenética de Tacrolimus

Estudio Tx-Renal: Objetivos

Estudio multicéntrico

Objetivo principal: Determinar la influencia de los polimorfismos de los genes CYP3A5, CYP3A4 y MDR-1 en la dosis de Tacrolimus.

Centros participantes

Elaboración de un protocolo farmacogenético como herramienta de ayuda en la determinación de la dosis óptima (pre TrX).

Farmacogenética de Tacrolimus

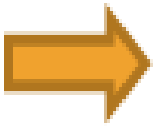
Variables clínicas de estudio

Edad paciente
Sexo
Desarrollo de diabetes post-trasplante (NODAT)
IMC

Variables de seguimiento (alta, 6 y 12 meses)

Dosis de Tacrolimus
- mg/dia
- mg/kg/dia
- normalizadas (ng/ml por mg/kg/dia)

Niveles de Tacrolimus (ng/ml)



Dosis normalizadas

$$\frac{\text{ng/ml}}{\text{mg/kg/dia}}$$

Farmacogenética de Tacrolimus

Estudio Tx-Renal: Características de la población

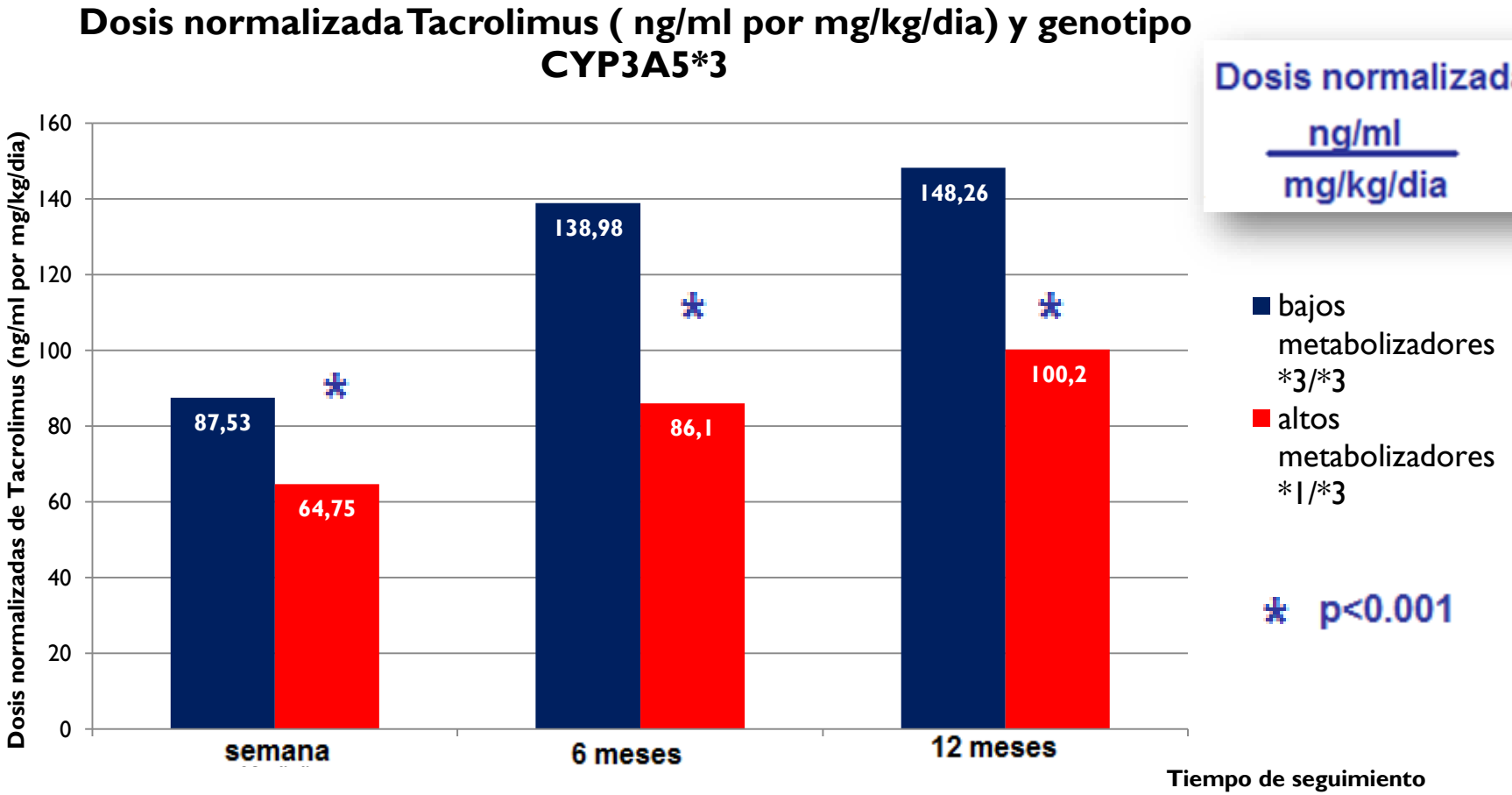
Table 1 Main characteristics and Tac values in the total (n=400) patients.

	Mean ± SD, range
Age, years	48.02 ± 13.29, 15–70
Male, %	60.5%
Non-diabetics (new-onset diabetes)	72.7%
Weight, kg	
1 week	68.75 ± 13.06, 37.3–112
6 months	71.35 ± 13.28, 40–113.5
12 months	73.02 ± 14.00, 41.2–125

	Median	Range
BMI, kg/m^2		
1 week	24.61	16.79–42.45
6 months	25.51	17.20–43.70
12 months	25.49	17.66–43.16
Total tacrolimus, mg/day		
1 week	8	1–30
6 months	5	0.5–55
12 months	4	0.5–30
Tacrolimus blood levels, ng/mL		
1 week	11.4	1.6–38.1
6 months	8.4	1.5–23.6
12 months	7.9	2.4–18
Tacrolimus dose, mg/kg/day		
1 week	0.12	0.014–0.446
6 months	0.07	0.013–0.873
12 months	0.06	0.010–0.880
Normalized dose, ng/mL per mg/kg		
1 week	81.72	14.31–700
6 months	127.75	14.08–1300
12 months	138.13	12.15–1528.8
Blood concentrations, ng/μL		

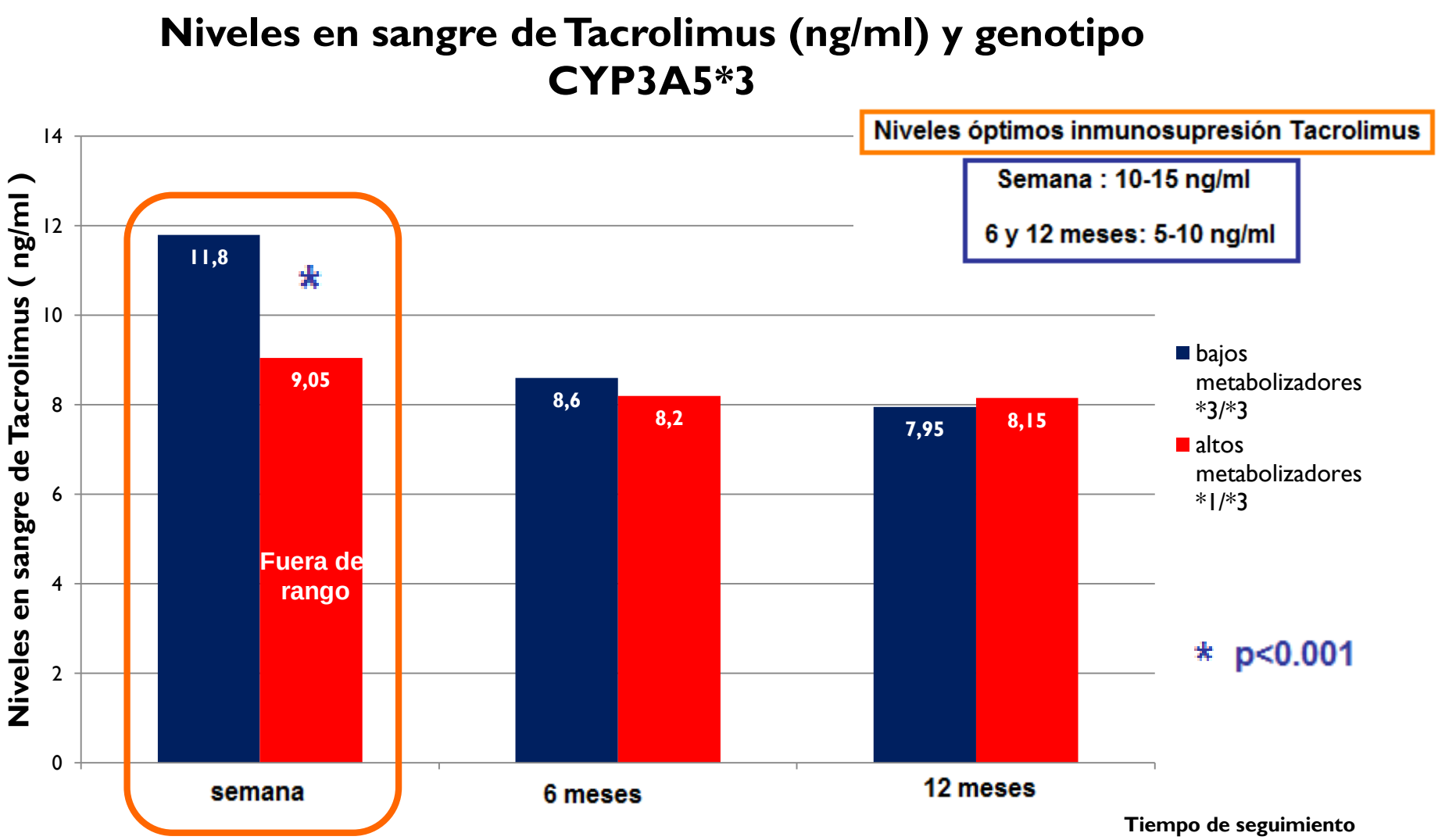
Farmacogenética de Tacrolimus

Estudio Tx-Renal: Resultados CYP3A5



Farmacogenética de Tacrolimus

Estudio Tx-Renal: Resultados CYP3A5

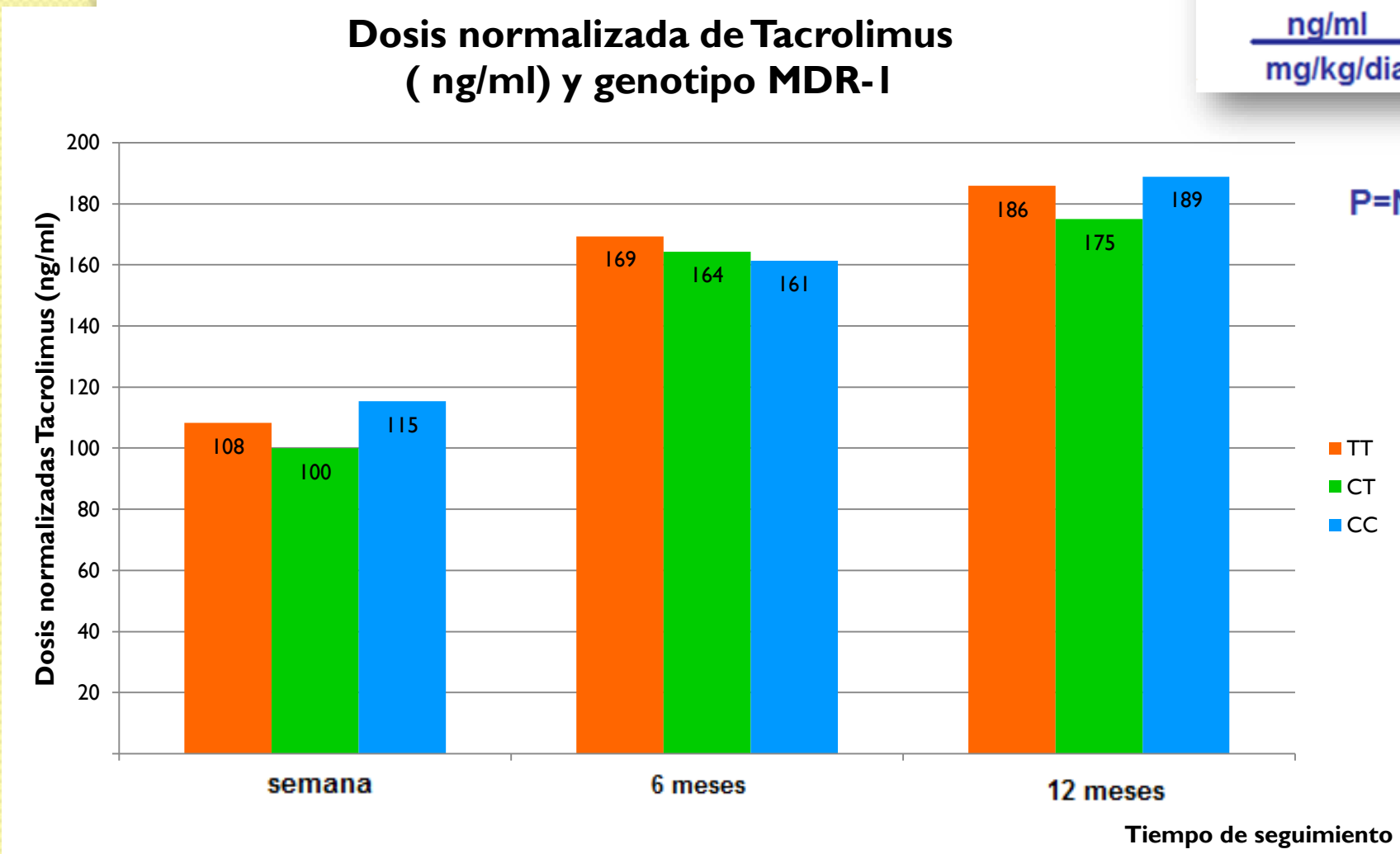


Farmacogenética de Tacrolimus

Estudio Tx-Renal: Resultados MDR-1

Dosis normalizadas

$$\frac{\text{ng/ml}}{\text{mg/kg/dia}}$$



Farmacogenética de Tacrolimus

Estudio Tx-Renal: Resultados

Pharmacogenetics of tacrolimus after renal transplantation: analysis of polymorphisms in genes encoding 16 drug metabolizing enzymes.

Tavira B, Coto E, Díaz-Corte C, Ortega F, Arias M, Torres A, Díaz JM, Selgas R, López-Larrea C, Campistol JM, Alvarez V; REDINREN Pharmacogenetics group.

Clin Chem Lab Med. 2011 May;49(5):825-33.

PMID: 21480817 [PubMed - indexed for MEDLINE]

Related citations

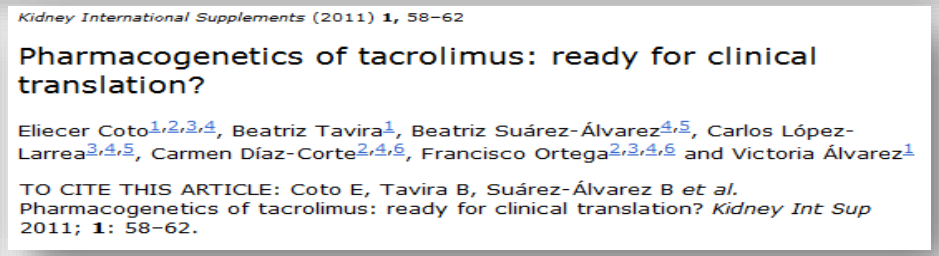
Pharmacogenetics of calcineurin inhibitors in renal transplantation.

Coto E, **Tavira** B.

Transplantation. 2009 Aug 15;88(3 Suppl):S62-7.

PMID: 19667964 [PubMed - indexed for MEDLINE]

Related citations



Kidney International Supplements (2011) **1**, 58–62

Pharmacogenetics of tacrolimus: ready for clinical translation?

Eliecer Coto[1,2,3,4], Beatriz Tavira[1], Beatriz Suárez-Álvarez[4,5], Carlos López-Larrea[3,4,5], Carmen Díaz-Corte[2,4,6], Francisco Ortega[2,3,4,6] and Victoria Álvarez[1]

TO CITE THIS ARTICLE: Coto E, Tavira B, Suárez-Álvarez B *et al.* Pharmacogenetics of tacrolimus: ready for clinical translation? *Kidney Int Sup* 2011; **1**: 58–62.

ABCB1 (MDR-1) pharmacogenetics of tacrolimus in renal transplanted patients: a Next Generation Sequencing approach.

Tavira B, Gómez J, Diaz-Corte C, Suarez B, Coronel D, Arias M, López-Larrea C, Iglesias S, Alonso B, Rodrigo E, **Coto E**.

Clin Chem Lab Med. 2015 Sep 1;53(10):1515-9. doi: 10.1515/cclm-2014-1195.

PMID: 25781547

A search for new CYP3A4 variants as determinants of tacrolimus dose requirements in renal-transplanted patients.

Tavira B, **Coto E**, Diaz-Corte C, Alvarez V, López-Larrea C, Ortega F.

Pharmacogenet Genomics. 2013 Aug;23(8):445-8. doi: 10.1097/FPC.0b013e3283636856.

PMID:23778326

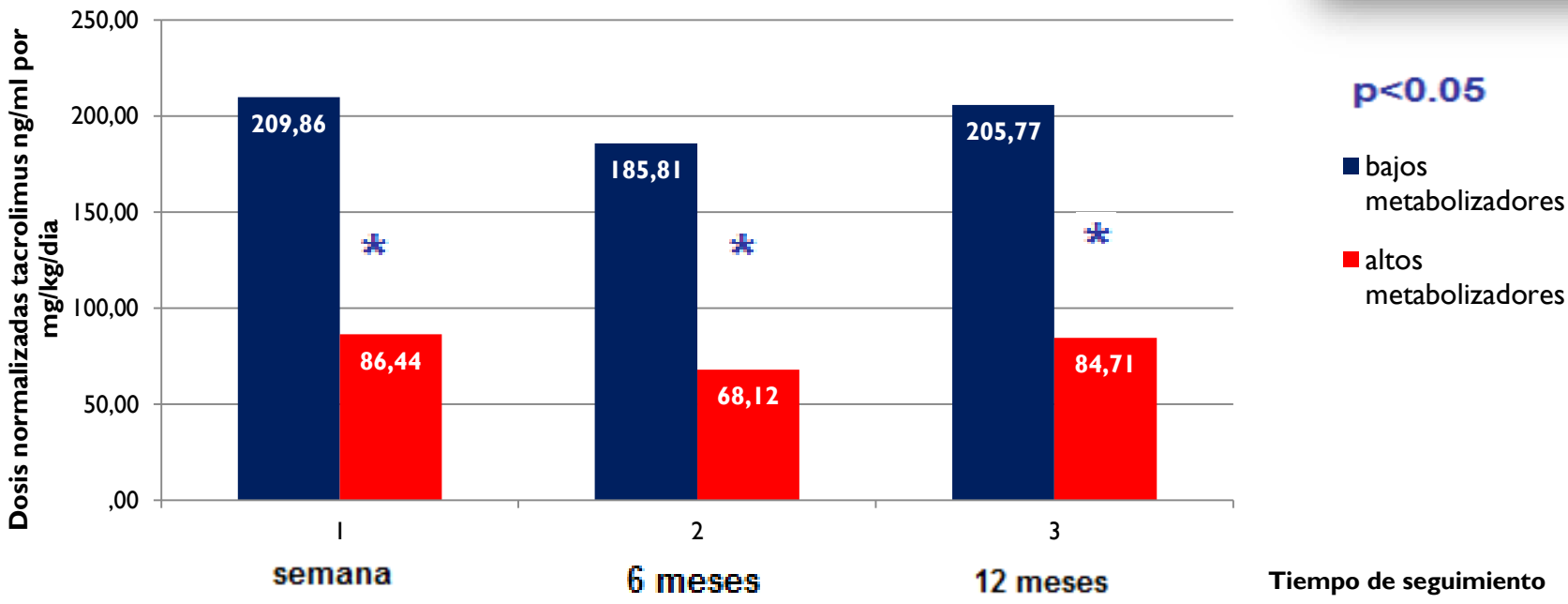
Farmacogenética de Tacrolimus

Tx-Cardiaco: Resultados CYP3A5*3

Dosis normalizadas

$$\frac{\text{ng/ml}}{\text{mg/kg/dia}}$$

Dosis normalizadas de Tacrolimus y genotipo CYP3A5



ELSEVIER

Effect of *CYP3A5, CYP3A4,* and *ABCB1* Genotypes as Determinants of Tacrolimus Dose and Clinical Outcomes After Heart Transplantation

B. Díaz-Molina, B. Tavira, J.L. Lambert, M.J. Bernardo, V. Álvarez, and E. Coto

Transplantation Proceedings, 44, 2635–2638 (2012)

Farmacogenética de Tacrolimus

Estudio prospectivo, Thervet et al.

Clin Pharmacol Ther. 2010 Jun;87(6):721-6. Epub 2010 Apr 14.

Optimization of initial tacrolimus dose using pharmacogenetic testing.

Thervet E, Loriot MA, Barbier S, Buchler M, Ficheux M, Choukroun G, Toupance O, Touchard G, Alberti C, Le Pogamp P, Moulin B, Le Meur Y, Heng AE, Subra JF, Beaune P, Legendre C.

Department of Renal Transplantation, Assistance Publique-Hôpitaux de Paris, Necker-Enfants Malades Hospital, Paris, France. eric.thervet@nck.aphp.fr

236 pacientes Tx-R

Dosis según régimen estándar de inmunosupresor, N=120

0,2 mg/kg/day

29%

C_0 en rango a los 3 días

Dosis inicial según genotipo CYP3A5 N=116

Expressors: 0.30 mg/kg/day

Non-expressors: 0.15

43%

En los que reciben dosis según genotipo:

1- Menos modificaciones en el ajuste de la dosis

2- 75% pacientes alcanzaron el C_0 más rápido

Table 3 Study end points

End point	Control group ($n = 120$)	Adapted-dose group ($n = 116$)	*P* value
Primary end point			
Proportion of patients with TAC C_0 in target range after six oral doses, % (95% CI)	29.1% (22.8–35.5)	43.2% (36.0–51.2)	0.030
Secondary end points			
TAC C_0 at day 10, ng/ml (median (1st–3rd quartiles))	15.4 (10.6–21.2)	12.1 (9.1–15.2)	0.001
*CYP3A5*1/*1*	5.6 (4.4–9.7)	14.0 (11.5–18.3)	0.035
*CYP3A5*1/*3*	10.1 (6.8–14.6)	12.3 (8.6–17.9)	0.26
*CYP3A5*3/*3*	16.6 (12.5–21.7)	12.0 (9.1–14.9)	<0.001
Time to achieve target TAC C_0, days (median (1st–3rd quartiles))	7 (3–25)	6 (3–8)	0.001
*CYP3A5*1/*1*	23 (6–24)	3 (3–27)	
*CYP3A5*1/*3*	7 (6–23)	6 (3–7)	
*CYP3A5*3/*3*	7 (3–25)	7 (3–8)	
Number of tacrolimus dose adaptations per group	420	281	0.004
Delayed graft function			
Incidence	18 (15.0%)	17 (14.7%)	
Number of dialysis sessions per patient, (median (1st–3rd quartiles))	2.0 (1.0–4.5)	2.0 (1.0–3.0)	
Acute rejection (number of patients (%), number of episodes)	8 (6.7%), 9	10 (8.6%), 11	
Graft function			
GFR at day 14, ml/min (median (1st–3rd quartiles))	48 (35–63)	48 (35–65)	
*CYP3A5*1/*1*	50 (26–60)	37 (22–45)	
*CYP3A5*1/*3*	47 (31–63)	54 (25–76)	
*CYP3A5*3/*3*	48 (37–63)	49 (37–63)	
GFR at day 90, ml/min (median (1st–3rd quartiles))	56 (47–73)	61 (45–73)	
*CYP3A5*1/*1*	53 (47–56)	82 (71–90)	
*CYP3A5*1/*3*	63 (48–81)	63 (35–66)	
*CYP3A5*3/*3*	58 (46–73)	58 (44–74)	
Patient survival, *n* (%)	120 (100.0%)	115 (99.1%)	
Graft survival censored for death	2[a] (98.2%)	116 (100.0%)	

Y el donante???

JOURNAL OF SURGICAL RESEARCH 178 (2012) 988–995

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Donor age and *ABCB1* 1199G>A genetic polymorphism are independent factors affecting long-term renal function after kidney transplantation

Martine De Meyer, MD,[a] Vincent Haufroid, PhD,[b,c] Laure Elens, PhD,[c] Fabio Fusaro, MD,[a] Damiano Patrono, MD,[a] Luc De Pauw, MD,[a] Nada Kanaan, MD,[d] Eric Goffin, MD,[d] and Michel Mourad, MD, PhD[a,]*

J Hum Genet. 2015 May;60(5):273-6.

The donor ABCB1 (MDR-1) C3435T polymorphism is a determinant of the graft glomerular filtration rate among tacrolimus treated kidney transplanted patients.

Tavira B[1], Gómez J[1], Díaz-Corte C[2], Coronel D[3], Lopez-Larrea C[4], Suarez B[5], Coto E[6].

Pharmacogenomics. 2016 Feb;17(3):249-57.

Donor ABCB1 3435 C>T genetic polymorphisms influence early renal function in kidney transplant recipients treated with tacrolimus.

Yan L[1], Li Y[1], Tang JT[1], An YF[1], Wang LL[1], Shi YY[2].

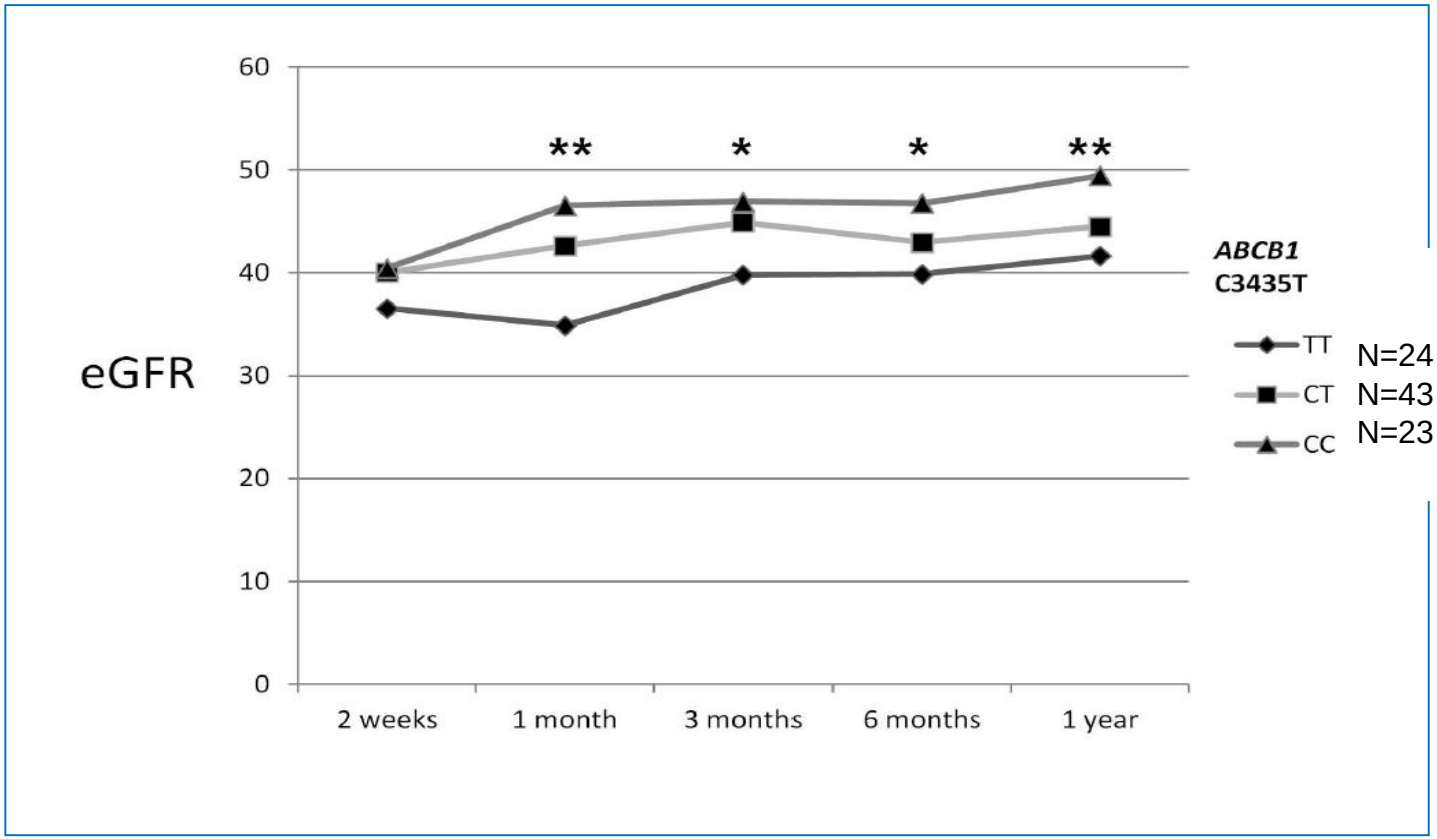
J Hum Genet. 2015 May;60(5):273-6.

The donor ABCB1 (MDR-1) C3435T polymorphism is a determinant of the graft glomerular filtration rate among tacrolimus treated kidney transplanted patients.

Tavira B[1], Gómez J[1], Díaz-Corte C[2], Coronel D[3], Lopez-Larrea C[4], Suarez B[5], Coto E[6].

Figure 1. Mean eGFR at five post-transplant times according to the three *ABCB1* donor genotypes. We show the mean reduced eGFR among the patients who received a kidney from 3435 T-donors.

* p<0.05; **p<0.01



MUCHAS GRACIAS

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