Tacrolimus de Liberación Prolongada 15 años después:

El valor de las nuevas evidencias en Trasplante Hepático

Evaristo Varo
Catedrático de Cirugía
Jefe Unidad de Trasplante Abdominal
Hospital Clínico de Santiago Compostela

PRESENTACIÓN/ EVENTO EXCLUSIVAMENTE DIRIGIDA A PROFESIONALES SANITARIOS CAPACITADOS PARA PRESCRIBIR O DISPENSAR MEDICAMENTOS.

USO NO PROMOCIONAL

Astellas prohíbe la promoción de indicaciones no aprobadas y cumple con todas las leyes, regulaciones y políticas de compañía.

Astellas vela porque todo el contenido incluido sea acorde a la ficha técnica del producto correspondiente, no obstante, tiene presente que los datos proporcionados por el profesional sanitario se incluyen bajo su estricto criterio médico y tienen exclusivamente fines formativos o informativos científicos.

La siguiente presentación podría incluir, de manera excepcional, información acerca de los productos de otras compañías farmacéuticas que están o pueden ser aprobados por las Agencias Reguladoras para indicaciones específicas. En su caso, esta información se realizaría solo y exclusivamente para labores de formación y en ningún caso debe interpretarse como un intento de promover indicaciones o usos no aprobados.

El contenido de esta presentación no debe utilizarse de ninguna manera para promocionar o vender directa o indirectamente el producto para indicaciones o usos no aprobados.

Asimismo, cualquier opinión o comentario realizado por el profesional sanitario durante su exposición, se realiza bajo su estricta opinión y criterio medico y puede no coincidir con la de Astellas, por lo que la misma no puede ser considerada responsable de dichos comentarios y/u opiniones.

MARCAS REGISTRADAS

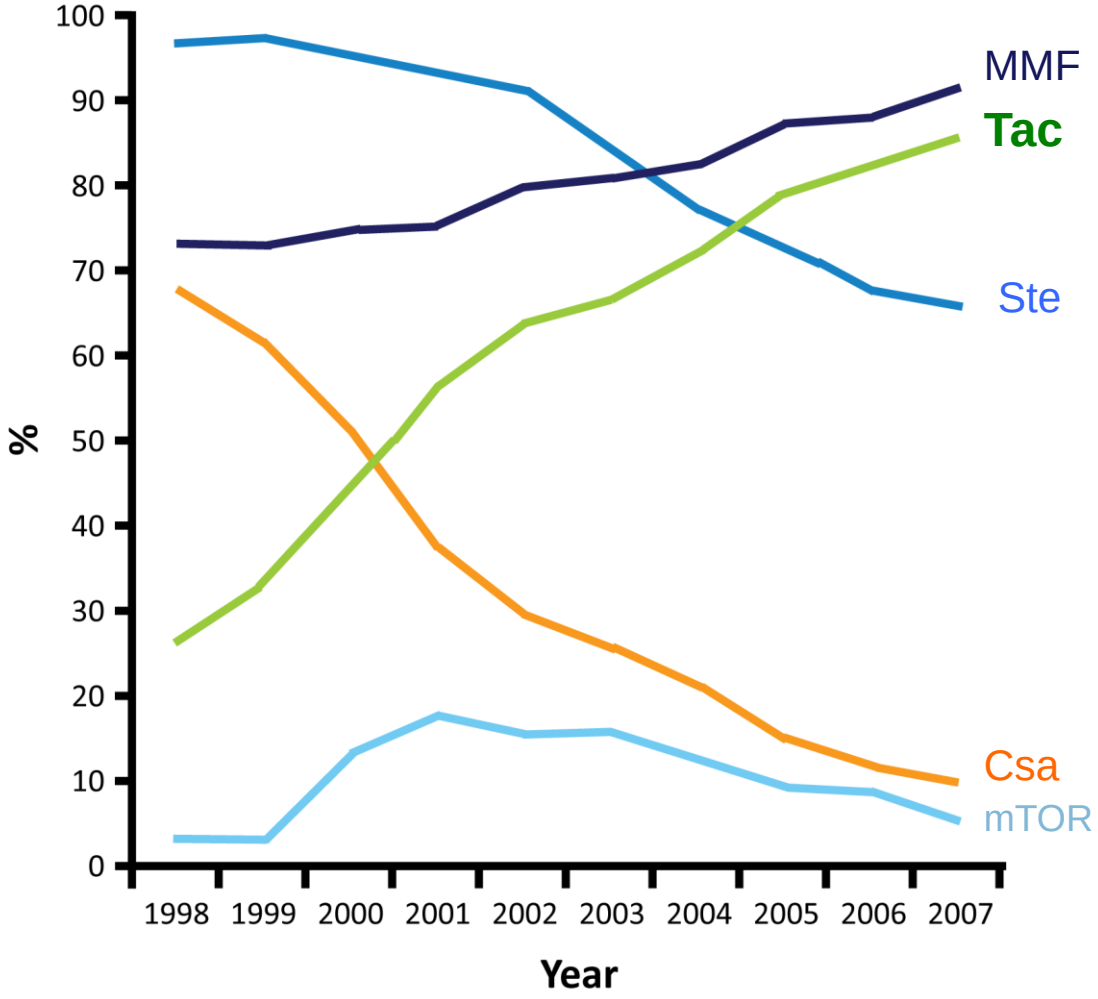
A menos que se indique lo contrario, las Marcas comerciales son propiedad de Astellas Pharma, Inc. y/o sus entidades relacionadas. Las marcas comerciales de terceros son propiedad de la empresa originaria correspondiente y están representadas aquí con el reconocimiento de esa propiedad. Astellas no es responsable de ninguna mala interpretación del uso de la marca.

FORMATOS AUDIOVISUALES

Los videos, audios, imágenes, resultados, conclusiones y opiniones presentados en este material tienen un fin exclusivamente informativo científico y/o formativo. Todo lo expuesto es responsabilidad exclusiva de los autores(as) que lo presentan. Todos los aspectos expuestos se han realizado teniendo en cuenta el conocimiento/ evidencia disponible en el momento de su creación y, por tanto, será necesario verificar su vigencia en el momento en que usted lo esté visualizando/ escuchando.

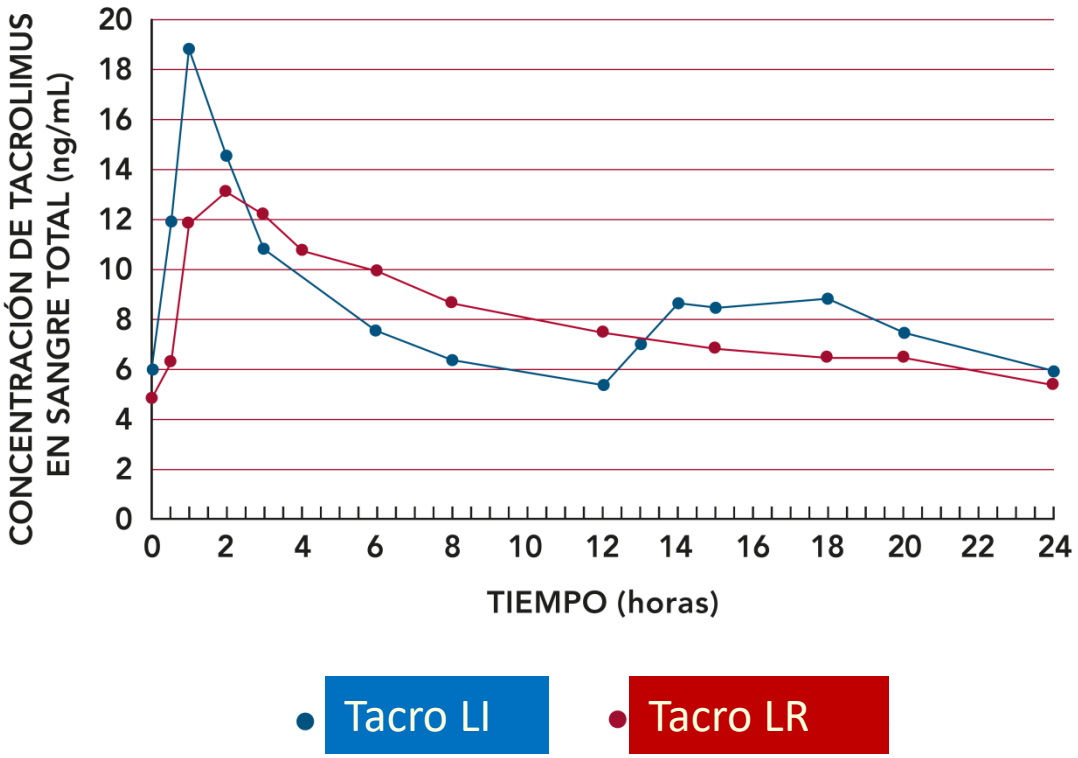
Astellas está comprometida con la formación médica continuada dirigida a profesionales sanitarios y con este objetivo apoya la difusión de estos contenidos, si bien, está exenta de responsabilidad sobre los mismos.

Trends in the Use of Approved Maintenance Immunosuppressive Agents in the Modern Era



Organ Procurement Transplantation Network/Scientific Registry of Transplant Recipients. *OPTN/SRTR Annual Report*

Media de los niveles totales en sangre de 24h



Curva más lineal

Sólo una Cmáx, menor y por la mañana

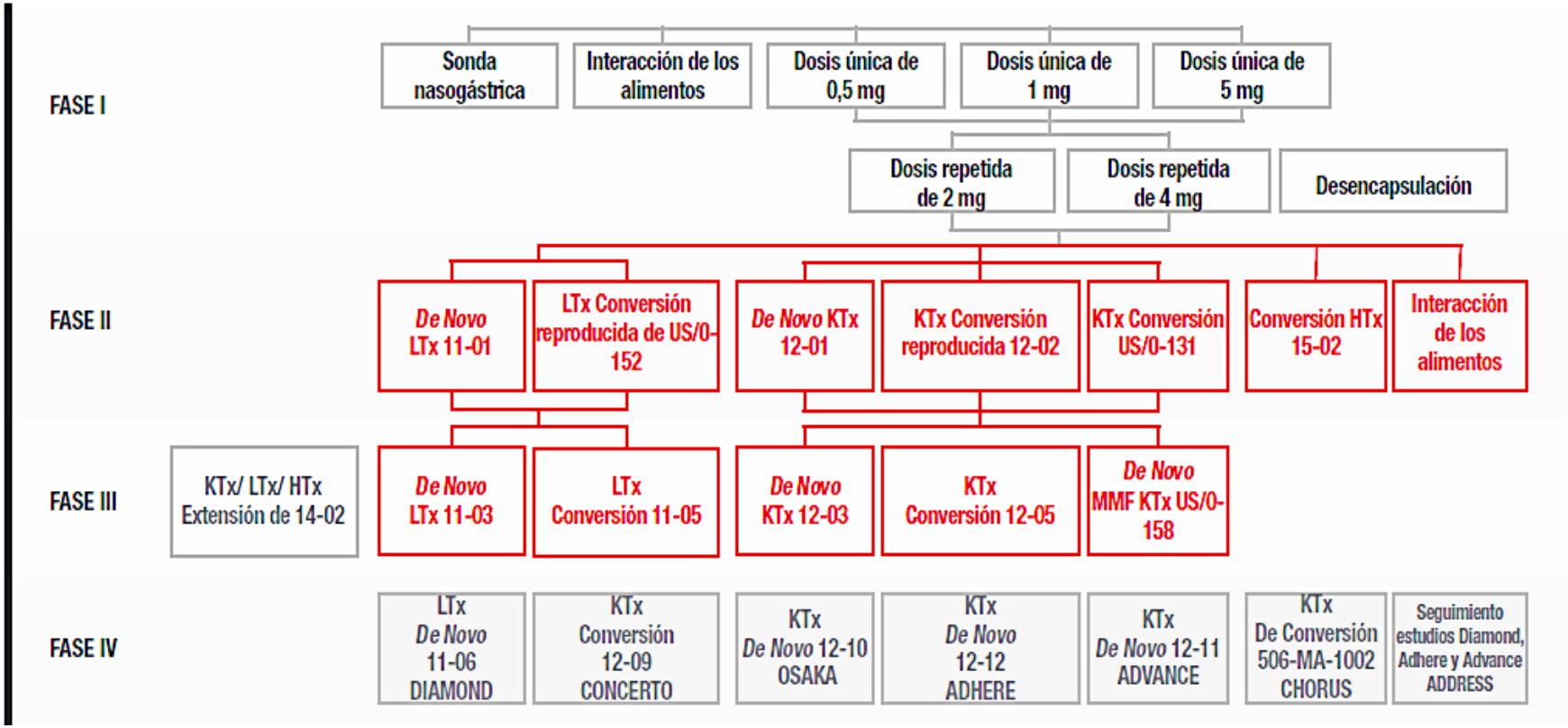
Se evita el pico de la noche

Favorece adherencia

Heffron et al. 2007

Desarrollo Clínico de TAC-LR

(FK-506E- MR4)



Más de 12.000 pacientes incluidos

1. Albano L, et al. Transplantation. 2013;96(10):897-903. **2.** Guirado L, et al. Transplantation Direct. 2015;1(7): e24. **3.** Krämer BK, et al. Am J Transplant. 2010;10(12):2632-43. **4.** European Medicines Agency: Advagraf: EPAR – Scientific Discussion. Disponible en: http://www.ema.europa.eu. **5.** Ficha técnica de Advagraf (tacrolimus en cápsulas duras de liberación prolongada), Astellas Pharma S.A. Disponible en: https://cima.aemps.es/cima/publico/home.html. **6.** First MR, et al. Ther Drug Monit. 2008;30(2):159-66. **7.** van Hooff JP, et al. Clin Transplant. 2011;25(1):E1-12. **8.** Rummo OO, et al. Transplant Int. 2017;30:83–95. **9.** Mourad G, et al. Transplantation. 2017;101(8):1924-1934. **10.** Silva HT Jr, et al. Am J Transplantation. 2007;7(3):595-608. **11.** Rostaing L, et al. Transplant Int. 2012;25(4):391-400. **12.** Trunečka P, et al. Am J Transplantation. 2010;10(10):2313-23. **13.** Wlodarczyka Z, et al. Am J Transplantation. 2009;9(11):2505-13. **14.** Fischer L, et al. Liver Transplantation. 2011;17(2):167-77. **15.** Sańko-Resmer J, et al. Transplant Int. 2012;25(3):283-93. **16.** Trunečka P, et al. Am J Transplantation. 2015;15(7):1843-54. **17.** Rummo O. Transpl Int. 2020;33(2):161-173. **18.** Anaokar S. ATC Congress, Sept 2020. P-18.09. Disponible en: https://virtual.tts.org/virtual/lecture/1218.

ttps://virtual.tts.org/virtual/lecture/1218

Accepted: 6 March 2017

DOI: 10.1111/ctr.12958

ORIGINAL ARTICLE

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Pharmacokinetics of prolonged-release tacrolimus versus immediate-release tacrolimus in de novo liver transplantation: A randomized phase III substudy

Bo-Göran Ericzon[1] | Evaristo Varo[2] | Pavel Trunečka[3] | Lutz Fischer[4] | Michele Colledan[5] | Bruno Gridelli[6] | Andrés Valdivieso[7] | John O'Grady[8] | James Dickinson[9] | Nasrullah Undre[10]

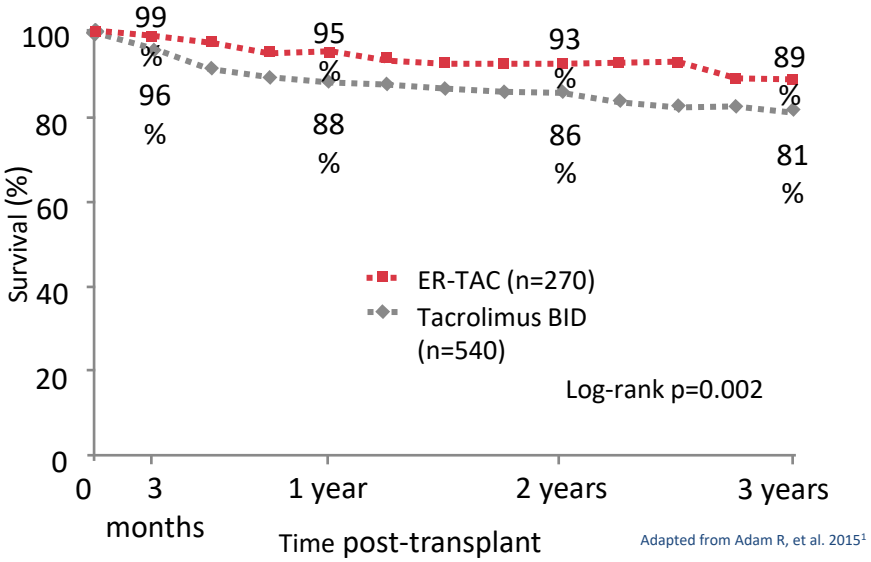
American Journal of Transplantation 2015; 15: 1267–1282
Wiley Periodicals Inc.

doi: 10.1111/ajt.13171

Improved Survival in Liver Transplant Recipients Receiving Prolonged-Release Tacrolimus in the European Liver Transplant Registry

R. Adam[1,*], V. Karam[1], V. Delvart[1], P. Trunečka[2], D. Samuel[1], W. O. Bechstein[3], P. Němec[4], G. Tisone[5], J. Klempnauer[6], M. Rossi[7], O. O. Rummo[8], S. Dokmak[9], M. Krawczyk[10], J. Pratschke[11], O. Kollmar[12,13], K. Boudjema[14], M. Colledan[15], B. G. Ericzon[16], G. Mantion[17], U. Baccarani[18], P. Neuhaus[19], A. Paul[20], P. Bachellier[21], F. Zamboni[22], R. Hanvesakul[23], P. Muiesan[24] and all contributing centers (www.eltr.org) and the European Liver Intestine Transplant Association (ELITA)

Graft survival over 3 years: propensity score-matched cohort



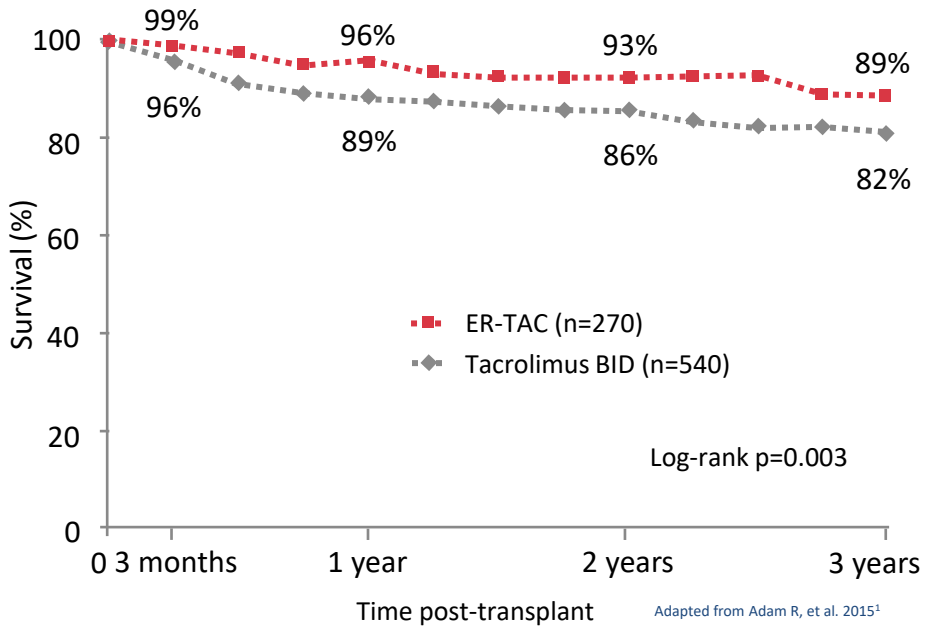
Patients at risk

ER-TAC	260	166	72	39
Tacrolimus BID	503	364	167	58

8% difference in graft survival with ER-TAC vs. tacrolimus BID (p=0.002)

Adam R, et al. Am J Transplant 2015;15(5):1267–82

Graft survival over 3 years: propensity score-matched cohort



Patients at risk

ER-TAC	260	168	73	40
Tacrolimus BID	505	366	169	59

7% difference in patient survival with ER-TAC vs. tacrolimus BID (p=0.003)

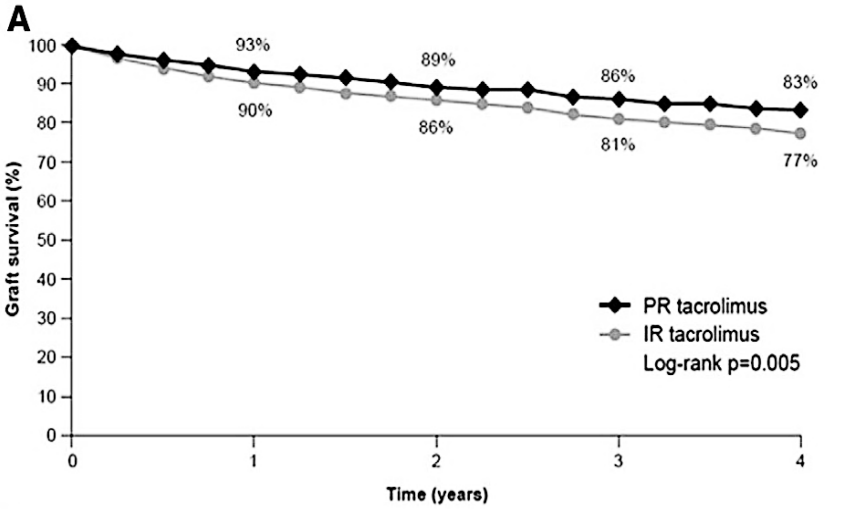
Adam R, et al. Am J Transplant 2015;15(5):1267–82

Original Clinical Science—Liver

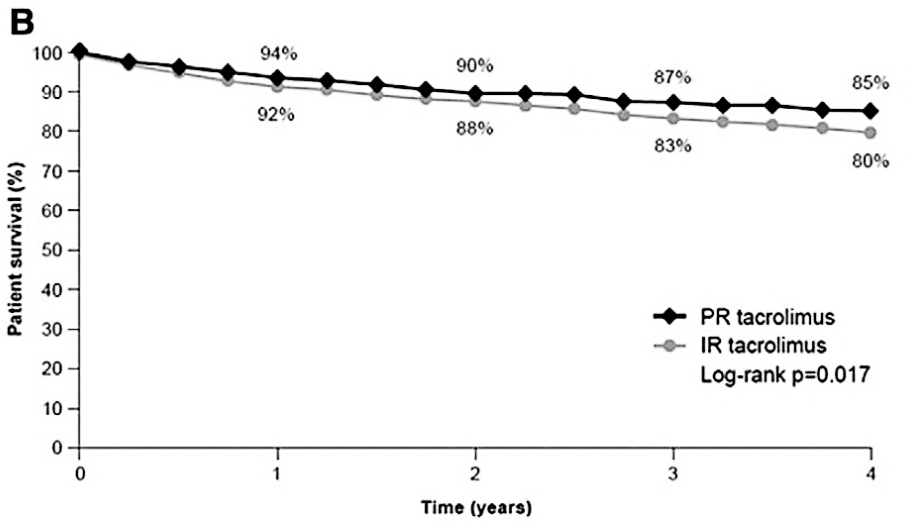
Improved Survival in Liver Transplant Patients Receiving Prolonged-release Tacrolimus-based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension Study

René Adam, MD, PhD,[1] Vincent Karam, PhD,[1] Valérie Cailliez,[1] Pavel Trunečka, MD, PhD,[2] Didier Samuel, MD, PhD,[1] Giuseppe Tisone, MD, PhD,[3] Petr Němec, MD, PhD,[4] Olivier Soubrane, MD, PhD,[5] Stefan Schneeberger, MD, PhD,[6] Bruno Gridelli, MD, PhD,[7] Wolf O. Bechstein, MD, PhD,[8] Andrea Risaliti, MD, PhD,[9] Pal-Dag Line, MD, PhD,[10] Marco Vivarelli, MD, PhD,[11] Massimo Rossi, MD, PhD,[12] Jacques Pirenne, MD, PhD,[13] Jurgen L. Klempnauer, MD, PhD,[14] Aleh Rummo, MD, PhD,[15] Fabrizio Di Benedetto, MD, PhD,[16] Krzysztof Zieniewicz, MD, PhD,[17] Roberto Troisi, MD, PhD,[18] Andreas Paul, MD, PhD,[19] Toomas Vali, MD, PhD,[20] Otto Kollmar, MD, PhD,[21] Karim Boudjema, MD, PhD,[22] Emir Hoti, MD, PhD,[23] Michele Colledan, MD, PhD,[24] Johan Pratschke, MD, PhD,[25] Hauke Lang, MD, PhD,[26] Irinel Popescu, MD, PhD,[27] Bo-Goran Ericzon, MD, PhD,[28] Kestutis Strupas, MD, PhD,[29] Paolo De Simone, MD, PhD,[30] Eberhard Kochs, MD, PhD,[31] Bruno Heyd, MD, PhD,[32] Jean Gugenheim, MD, PhD,[33] Antonio D. Pinna, MD, PhD,[34] William Bennet, MD, PhD,[35] Mirjalal Kazimi, MD, PhD,[36] Philippe Bachellier, MD, PhD,[37] Stephen J. Wigmore, MD, PhD,[38] Allan Rasmussen, MD, PhD,[39] Pierre-Alain Clavien, MD, PhD,[40] Ernest Hidalgo, MD, PhD,[41] John G. O'Grady, MD, PhD,[42] Frausto Zamboni, MD, PhD,[43] Murat Kilic, MD, PhD,[44] and Christophe Duvoux, MD, PhD[45]; all contributing centers (www.eltr.org) and the European Liver and Intestine Transplant Association (ELITA)

(*Transplantation* 2019;103:1844–1862)



Patients at risk	1 year	2 years	3 years	4 years
PR tacrolimus	669	412	241	130
IR tacrolimus	1508	1121	790	559



Patients at risk	1 year	2 years	3 years	4 years
PR tacrolimus	672	415	245	134
IR tacrolimus	1525	1137	803	571

One graft loss could be avoided for each 14 patients treated with prolonged-release tacrolimus instead of bd formulations

ELTR, European Liver Transplant Registry; IR, immediate-release; LT, liver transplant; PR, prolonged-release.

Adam R, et al. *Transplantation*. 2019;103(9):1844–1862.

¿Que factores podriamos cambiar para mejorar los resultados a largo plazo?

¿Podemos reducir algunos factores de riesgo de pérdida de injerto si optimizamos la INMS?

- Nefrotoxicidad
- No adherencia al Tratamiento
- Variabilidad de Exposición al fármaco

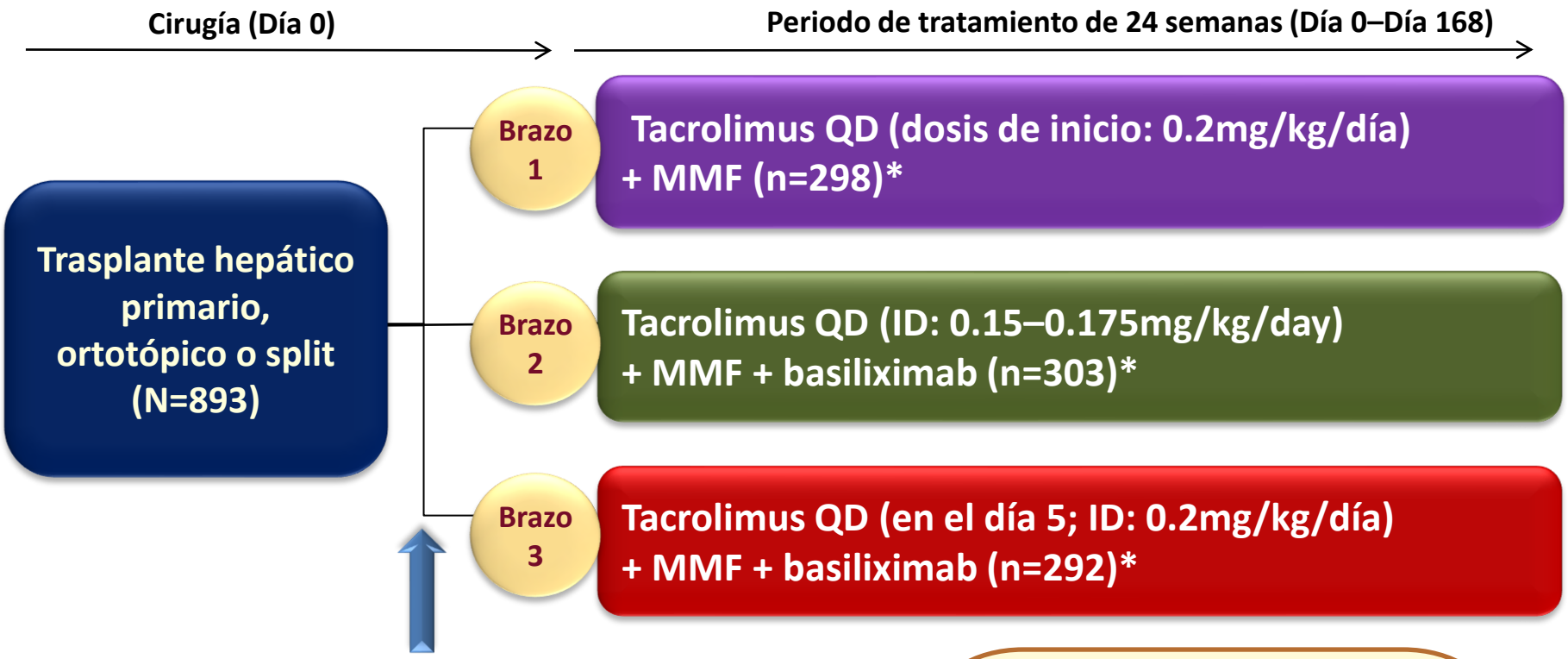
American Journal of Transplantation 2015; 15: 1843–1854
Wiley Periodicals Inc.

doi: 10.1111/ajt.13182

Renal Function in *De Novo* Liver Transplant Recipients Receiving Different Prolonged-Release Tacrolimus Regimens—The DIAMOND Study

DIAMOND diseño del estudio

Fase IIIb, multicéntrico, aleatorio, abierto, comparativo de grupos paralelos



Ninguno de los brazos usa esteroides

*De 0 mg a 1000mg de bolo de corticoide IV (pre-, intra-, or post-op) el Día 0

La FT de advagraf recomienda que su administración debe iniciarse aproximadamente 12-18 horas después de que haya finalizado la cirugía. Para más información, consultar https://cima.aemps.es/cima/publico/home.html

Objetivos del estudio

Variable principal

Función renal valorada por eGFR (MDRD4)

Objetivos secundarios

Eficacia - endpoint compuesto:

- **pérdida de injerto** (retrasplante o muerte)
- **rechazo agudo** (BCAR)

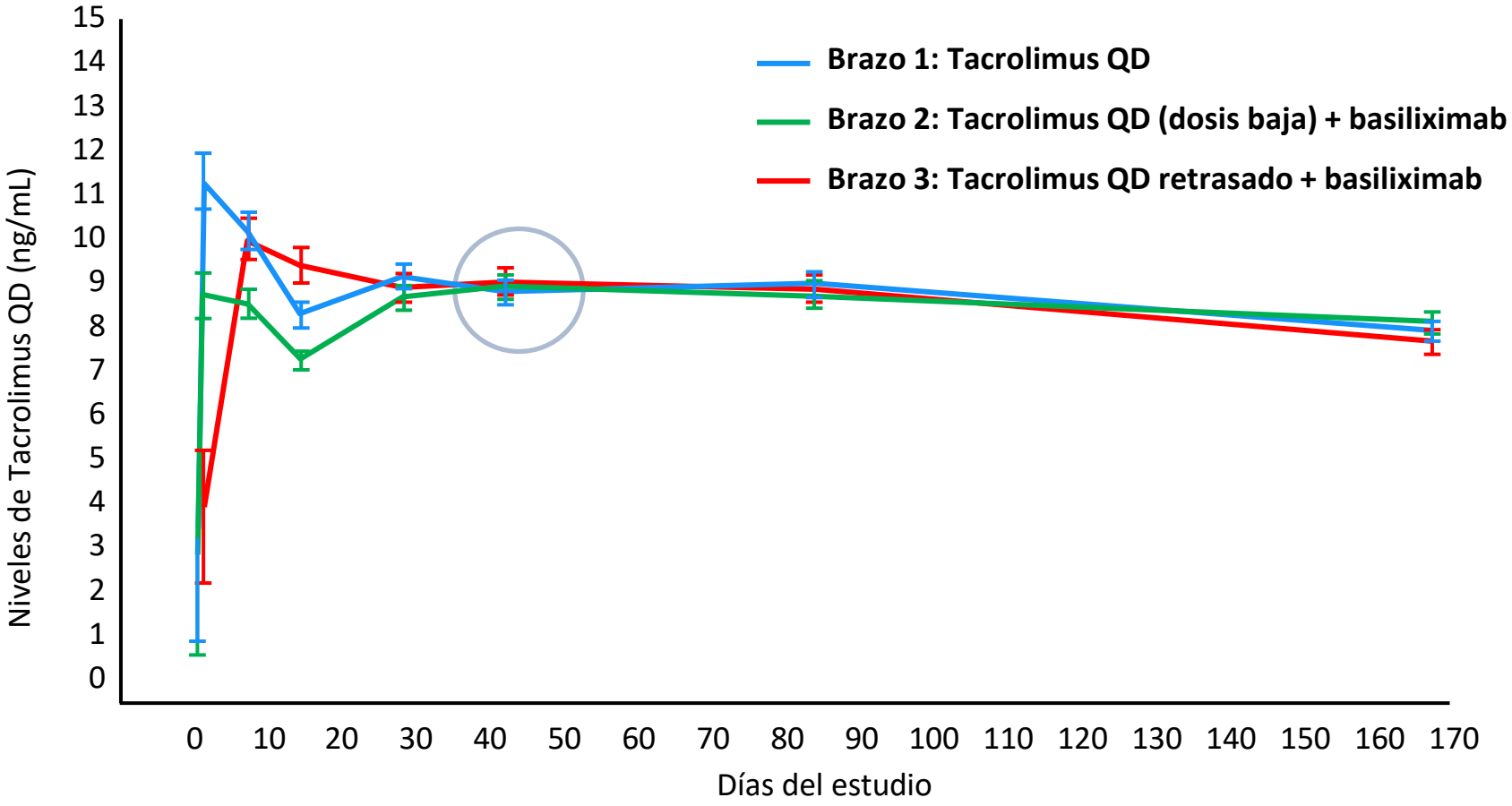
Seguridad

Baseline demographics (recipients)

Characteristics	Arm 1 (n=283)	Arm 2 (n=287)	Arm 3 (n=274)
Sex; male, n (%)	201 (71.3)	203 (70.7)	190 (69.3)
Age; mean (SD), years	54.3 (9.1)	54.0 (9.7)	53.7 (10.6)
<65, n (%)	262 (92.6)	263 (91.6)	246 (89.8)
Race, n (%)			
Caucasian	272 (96.5)	269 (93.7)	257 (93.8)
Other (black/African, Asian, other)	10 (3.5)	18 (6.3)	17 (6.2)
Weight; mean (SD), kg	77.0 (16.6)	78.0 (17.0)	78.1 (16.2)
BMI; mean (SD), kg/m^2	26.2 (4.9)	26.5 (5.4)	26.7 (4.7)
GFR (MDRD4), mean (SD), mL/min/1.73m^2	90.6 (39.1)	89.3 (40.7)	89.9 (34.6)
Renal disorders, n (%)	55 (19.4)	49 (17.1)	47 (17.2)
Arterial hypertension, n (%)	89 (31.4)	73 (25.4)	62 (22.6)
Insulin-dependent diabetes, n (%)	46 (16.3)	40 (13.9)	37 (13.5)
Alcoholic cirrhosis, n (%)	82 (29.0)	109 (38.0)	76 (27.7)
HBV-positive, n (%)	33 (11.7)	42 (14.6)	29 (10.6)
CMV-positive, n (%)	175 (62.1)	188 (65.5)	175 (63.9)
HCV-positive, n (%)	88 (31.2)	77 (26.8)	77 (28.1)
EBV-positive, n (%)	229 (81.2)	218 (76.0)	213 (77.7)

Data are full-analysis set

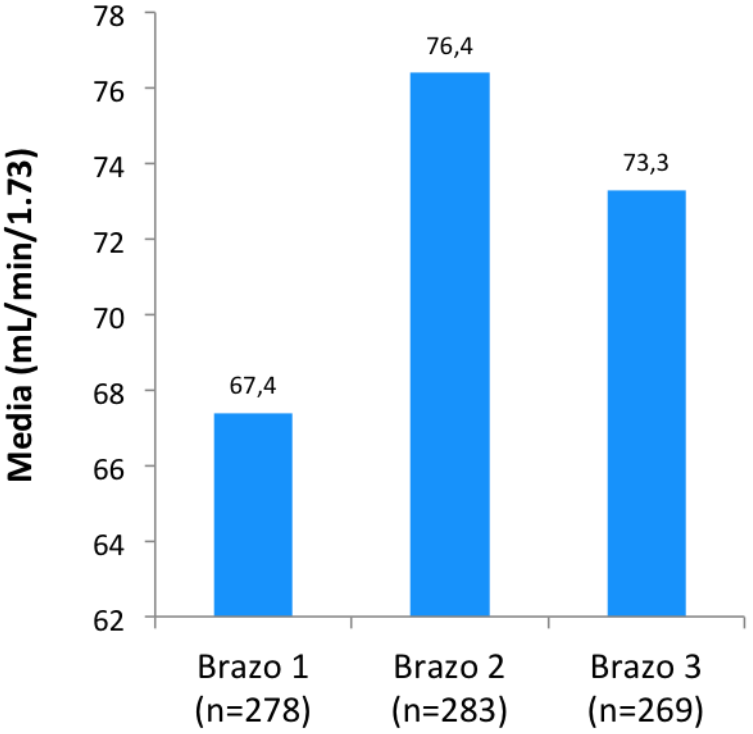
Exposición deTacrolimus QD a lo largo de las 24 semanas de tratamiento

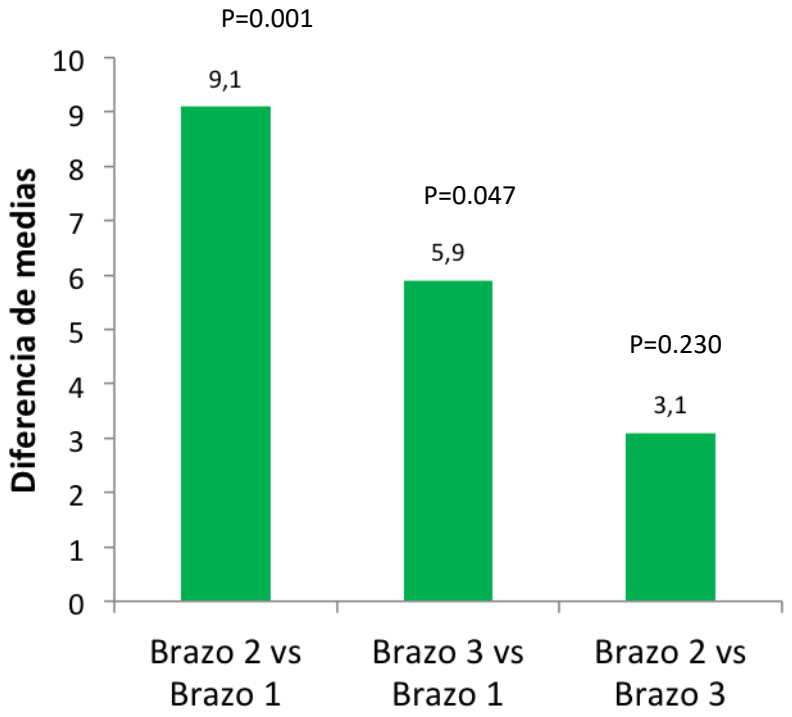


Analisis en población completa (FAS)

Tisone G et al. Abstract LB12 (poster) presented at the American Association for the Study of Liver Disease, Washington, 1-5 November 2013

Variable Principal: eGFR (MDRD4) en la semana 24



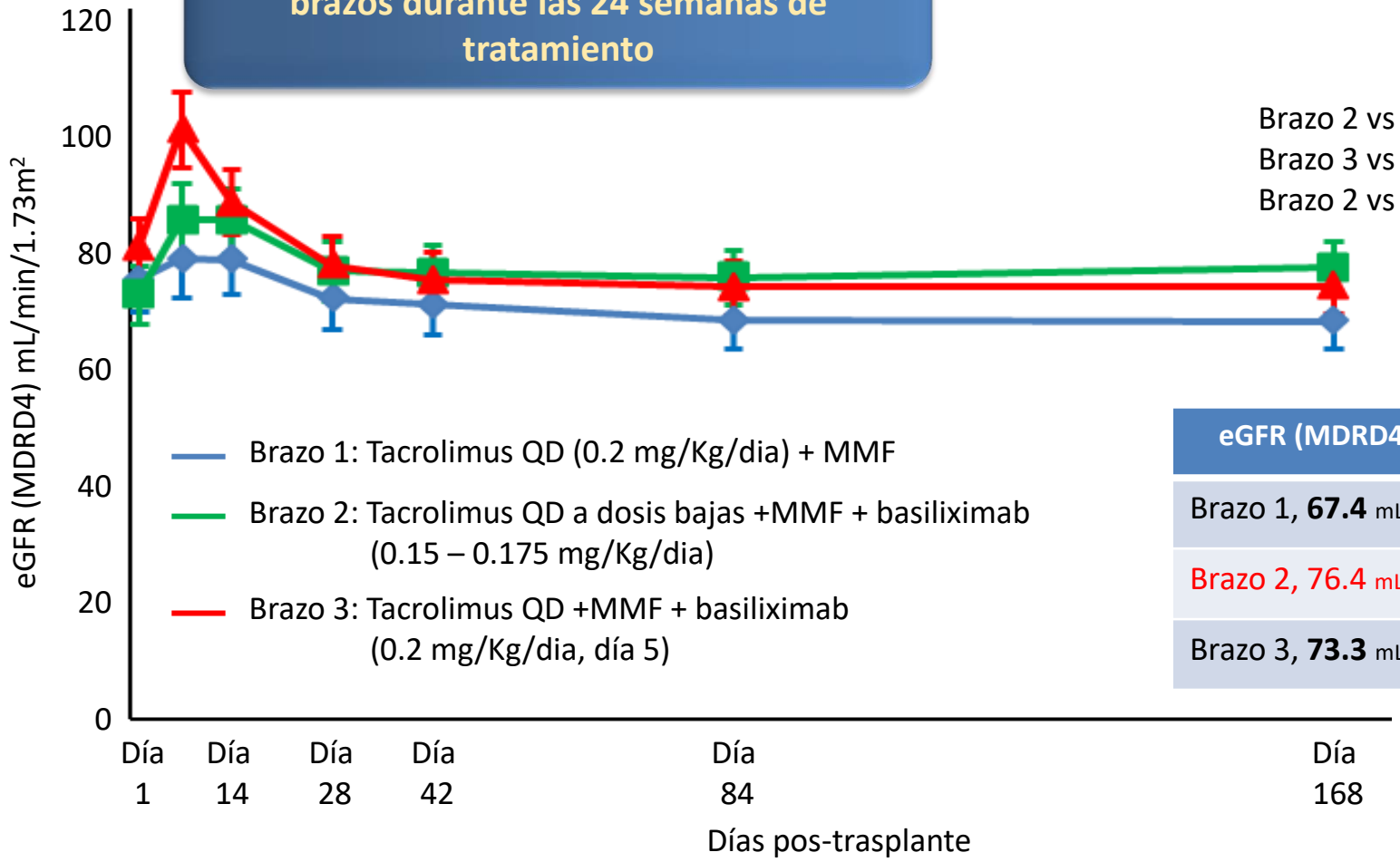


Los brazos 2 y 3 se asociaron con una función renal significativamente mejor en la semana 24 comparados con el brazo 1

Análisis de la muestra completa; valor de P(ANOVA)

Variable Principal: eGFR (MDRD4) en el tiempo

Se preservó la función renal en todos los brazos durante las 24 semanas de tratamiento

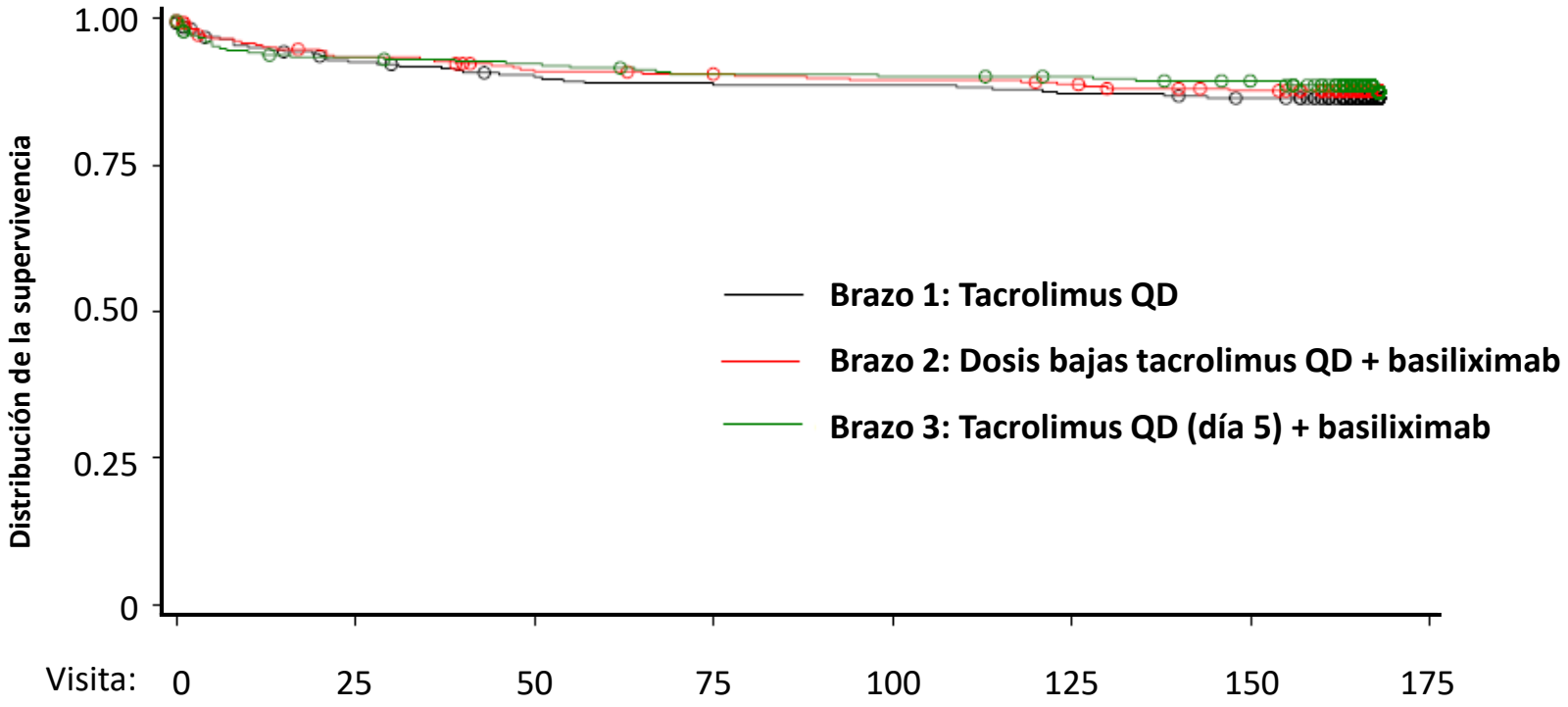


Brazo 2 vs Brazo 1 0.001
Brazo 3 vs Brazo 1 0.047
Brazo 2 vs Brazo 3 0.230

eGFR (MDRD4-sem24)
Brazo 1, **67.4** mL/min/1.73m²
Brazo 2, 76.4 mL/min/1.73m2
Brazo 3, **73.3** mL/min/1.73m2

Análisis de la muestra completa

Variables Secundarias: supervivencia del injerto (análisis Kaplan-Meier) en la semana 24



- **Supervivencia del paciente: 89.3%, 89.1% y 90.4% en Brazos1–3, (p=ns)**
- **Pacientes sin rechazo agudo: 79.9%, 85.7% y 79.6%**
  (Brazo 2 vs 1: p=0.0249, Brazo 3 vs 1: p=ns; Brazo 2 vs 3: p=0.0192)

Datos

Conclusiones:

- La función ***renal se conservó*** en todos los grupos de tratamiento con tacrolimus LR al final del estudio.

- ***La dosis inicial baja de Tacrolimus LR*** o el ***retraso de 5 días después del trasplante más MMF y basiliximab***, mejoró significativamente la función renal (eGFR [MDRD4]) en la semana 24 en comparación con la dosis estándar de Tacrolimus LR más MMF sin basiliximab.

- Una dosis ***más baja de tacrolimus LR 0,15-0,175 mg/kg/día iniciada el día 0 postrasplante + MMF + basiliximab*** fue el régimen óptimo para preservar la función renal manteniendo la eficacia.

1. TruneČka P, Klempnauer J, Bechstein W, Pirenne J, Friman S, Zhao A et al. Renal Function in De Novo Liver Transplant Recipients Receiving Different Prolonged-Release Tacrolimus Regimens—The DIAMOND Study. American Journal of Transplantation. 2015;15(7):1843-1854.

Liver Transplantation

OPEN

Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study

Styrbjörn Friman, MD, PhD,[1] Giuseppe Tisone, MD,[2] Frederik Nevens, MD, PhD,[3] Frank Lehner, MD,[4] Walter Santaniello, MD,[5] Wolf O. Bechstein, MD, PhD,[6] Sergey V. Zhuvarel, MD,[7] Helena Isoniemi, MD, PhD,[8] Oleg O. Rummo, MD,[9] Jürgen Klempnauer, MD,[4] Swapneel Anaokar, MBBS, MD,[10] Martin Hurst, MBBS, FRCP,[10] Gbenga Kazeem, PhD,[10,11] Nasrullah Undre, PhD,[10] and Pavel Trunečka, MD, PhD[12]

Transplantation Direct 2021;7: e722;

DIAMOND Follow-up: Study Design and Endpoints

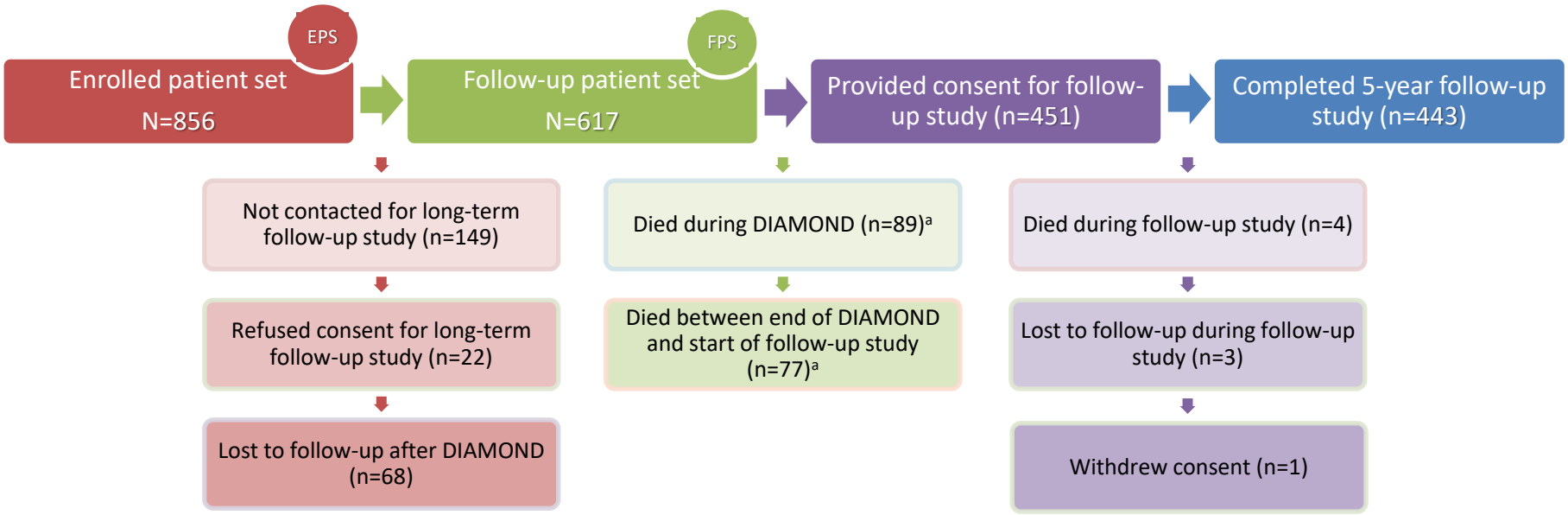
- This study was a **5-years**, non-interventional, prospective follow-up of patients who received a liver transplant and were assigned to treatment with PR-Tac as participants in the ***DIAMOND*** study.
- Patients were grouped according to their ***original randomized treatment arm in the DIAMOND study*** and maintained on their usual immunosuppressive regimen according to standard clinical practice.

Primary endpoint:	**Secondary endpoints:**
Overall graft survival, defined as time from transplantation to graft loss (re-transplantation or death).	Overall patient survival, estimated GFR and AR and BCAR episodes

AR, acute rejection; BCAR, biopsy-confirmed acute rejection;EOS, end of study ; FAS, full-analysis set; QD, once daily; MMF, mycophenolate Mofetil; MDRD4, modification of Diet in Renal Disease

2. Friman S, Tisone G, Nevens F, Lehner F, Santaniello W, Bechstein W et al. Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study. Transplantation Direct. 2021;7(8):e722.

Patient Disposition and Analysis Sets



[a] Patients who died during DIAMOND or between DIAMOND and the start of the follow-up study were included in the FPS but were not considered to have completed the follow-up study.
DIAMOND, ADVAGRAF studied in combination with mycophenolate mofetil and basiliximab in de novo liver transplantation

EPS, enrolled patient set; FPS, follow-up patient set.

Friman S, Tisone G, Nevens F, Lehner F, Santaniello W, Bechstein W et al. Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study. Transplantation Direct. 2021;7(8):e722.

Baseline Demographics and Clinical Characteristics (FPS)

Parameter	Arm 1[a] (n=196)	Arm 2[b] (n=212)	Arm 3[c] (n=209)	Total (N=617)
Age, years, mean (SD)	54.4 (9.1)	54.0 (10.1)	54.4 (10.0)	54.3 (9.8)
Male sex, n (%)	142 (72.4)	155 (73.1)	146 (69.9)	443 (71.8)
Ethnicity, white, n (%)	189 (96.4)	200 (94.3)	201 (96.2)	590 (95.6)
Body mass index, kg/m^2, mean (SD)	26.5 (4.8)	26.9 (5.5)	26.4 (4.4)	26.6 (4.9)
eGFR (MDRD4), mL/min/1.73 m^2, mean (SD)[d]	66.9 (26.7)	73.55 (34.1)	68.5 (28.9)	69.7 (30.2)
Last measured tacrolimus trough level (ng/mL), mean (SD)[d]	8.1 (3.9)	8.5 (4.6)	7.8 (4.0)	8.1 (4.2)
Patients with graft loss prior to start of follow-up study, n (%)	36 (18.4)	34 (16.0)	31 (14.8)	101 (16.4)
Recipient viral status, n (%)				
CMV positive	130 (66.3)	150 (70.8)	140 (67.0)	420 (68.1)
HBV negative	170 (86.7)	180 (84.9)	185 (88.5)	535 (86.7)
HCV negative	134 (68.4)	154 (72.6)	149 (71.3)	437 (70.8)
HIV negative	195 (99.5)	212 (100.0)	206 (98.6)	613 (99.4)
Donor age, years, mean (SD)	51.8 (17.5)	51.3 (18.0)	51.3 (17.9)	51.5 (17.8)
Organ donor type, n (%)				
Deceased	190 (96.9)	207 (97.6)	202 (96.7)	599 (97.1)
Living nonrelated	2 (1.0)	1 (0.5)	2 (1.0)	5 (0.8)
Living related	4 (2.0)	4 (1.9)	5 (2.4)	13 (2.1)

a Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) + MMF.
b Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/day) + MMF + basiliximab.
c Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day delayed until Day 5) + MMF + basiliximab
d Measured at DIAMOND EOS (Day 168 ± 42 days)

CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; EOS, end of study; FPS, follow-up patient set; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MDRD4, 4-variable modification of diet in renal disease; MMF, mycophenolate mofetil; SD, standard deviation.

2. Friman S, Tisone G, Nevens F, Lehner F, Santaniello W, Bechstein W et al. Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study. Transplantation Direct. 2021;7(8):e722.

Total Daily Dose of Prolonged-release Tacrolimus and Whole-blood trough levels over time (FPS)

Visit	Time point	Arm 1[a] (n=196)		Arm 2[b] (n=212)		Arm 3[c] (n=209)		Total (N=617)	
		Total Daily Dose	Whole-blood trough levels	Total Daily Dose	Whole-blood trough levels	Total Daily Dose	Whole-blood trough levels	Total Daily Dose	Whole-blood trough levels
1	DIAMOND EOS (Day 181)	0.09 (0.06)	8.2 (4.0)	0.09 (0.07)	8.5 (4.6)	0.09 (0.06)	7.9 (4.0)	0.09 (0.06)	8.2 (4.2)
	n	190	185	207	205	192	191	589	581
2	1 year (Days 182–547)	0.06 (0.03)	7.4 (3.0)	0.06 (0.04)	7.3 (3.0)	0.07 (0.05)	7.6 (2.6)	0.06 (0.04)	7.4 (2.8)
	n	122	133	125	140	132	135	379	408
3	2 years (Days 548–913)	0.04 (0.03)	6.7 (2.6)	0.05 (0.03)	6.2 (2.4)	0.05 (0.04)	6.8 (3.2)	0.05 (0.03)	6.6 (2.8)
	n	118	126	124	130	125	127	367	383
4	3 years (Days 914–1278)	0.04 (0.02)	5.4 (1.8)	0.04 (0.03)	5.7 (2.7)	0.05 (0.03)	5.7 (2.3)	0.04 (0.03)	5.6 (2.3)
	n	110	120	117	124	120	125	347	369
5	4 years (Days 1279–1643)	0.04 (0.02)	5.1 (1.8)	0.04 (0.03)	5.4 (2.7)	0.04 (0.03)	6.3 (5.3)	0.04 (0.03)	5.6 (3.7)
	n	110	116	115	122	119	127	344	365
6 / EOS	5 years (Days 1644–2009)	0.04 (0.02)	5.4 (1.9)	0.04 (0.03)	4.9 (2.0)	0.04 (0.03)	5.4 (2.4)	0.04 (0.03)	5.2 (2.1)
	n	110	117	113	122	119	121	342	360

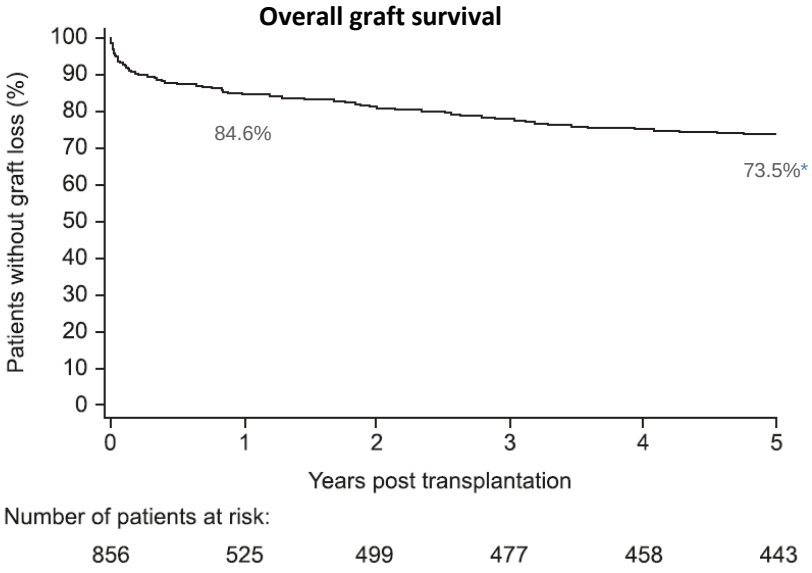
Data are mean (SD) mg/kg/day for Total daily dose
Data are mean (SD) ng/mL for Whole-blood trough levels

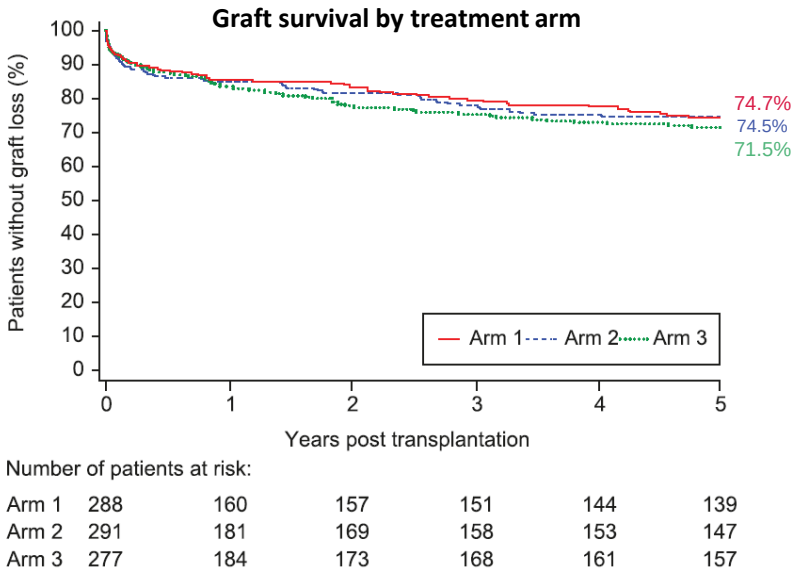
a Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) + MMF.
b Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/day) + MMF + basiliximab.
c Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day delayed until Day 5) + MMF + basiliximab

EOS, end of study; FPS, follow-up patient set; MMF, mycophenolate mofetil; SD, standard deviation.

2. Friman S, Tisone G, Nevens F, Lehner F, Santaniello W, Bechstein W et al. Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study. Transplantation Direct. 2021;7(8):e722.

Results Graft Survival (EPS)





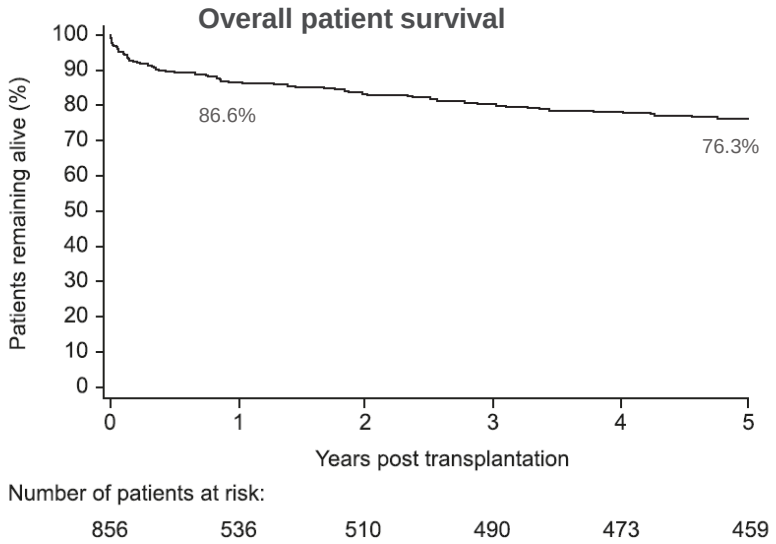
Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF;
Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab;
Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5 post-transplant) + MMF + basiliximab.

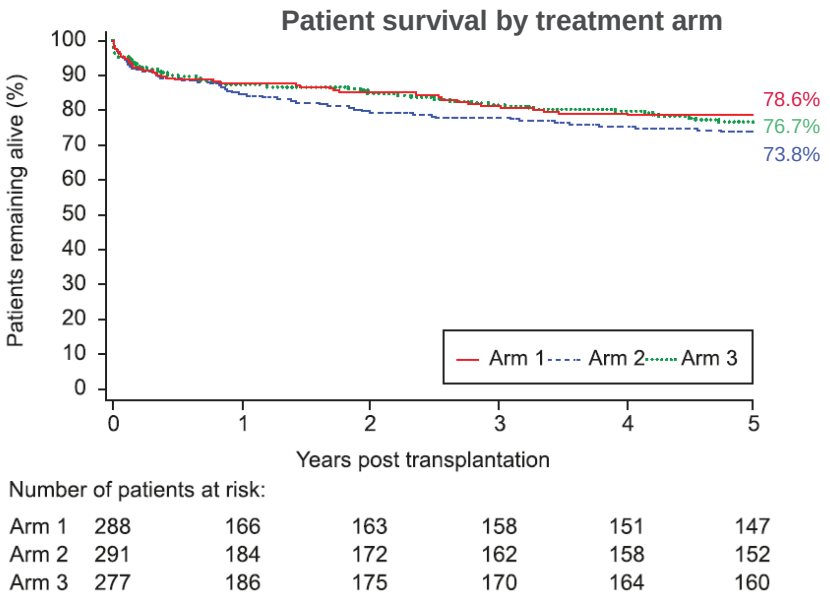
***Graft survival in patients who remained on Prolonged release Tacrolimus at 5 years was 87.3%**

EPS, enrolled patient set; MMF, mycophenolate mofetil.

Friman S, Tisone G, Nevens F, Lehner F, Santaniello W, Bechstein W et al. Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study. Transplantation Direct. 2021;7(8):e722.

Results Patient Survival (EPS)





Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF;
Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab;
Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5 post-transplant) + MMF + basiliximab.

***Patient survival in patients who remained on Prolonged release Tacrolimus at 5 years was 90.6%**

EPS, enrolled patient set; MMF, mycophenolate mofetil.

Friman S, Tisone G, Nevens F, Lehner F, Santaniello W, Bechstein W et al. Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study. Transplantation Direct. 2021;7(8):e722.

Results: eGFR

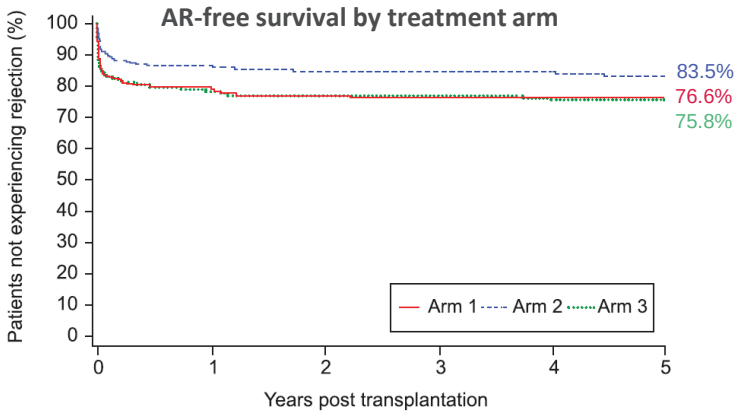
- **eGFR** rate at the end of the 24-week initial study and 5-years post-transplant was 62.1 and 61.5 mL/min/1.73 m^2, respectively, and was similar between the three treatment arms.

- **Graft survival at 5 y** was generally comparable in patients with 12-month eGFR 30–60 mL/min/1.73 m2 or ≥60 mL/min/1.73 m^2, irrespective of treatment arm

- **5-years overall survival** was *numerically lower in patients with baseline eGFR <30 mL/min/1.73 m^2* than in patients with *baseline eGFR ≥60 mL/min/1.73 m^2*, irrespective of treatment arm (EPS).

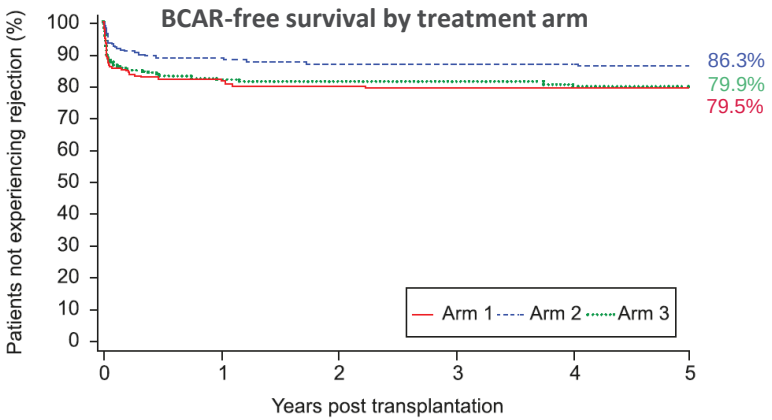
EPS, enrolled patient set; EOS, end of study; eGFR, estimated glomerular filtration rate

Results AR and BCAR (EPS)



Number of patients at risk:

Arm 1	288	119	118	114	113	112
Arm 2	291	136	131	128	128	126
Arm 3	277	128	121	119	119	118



Number of patients at risk:

Arm 1	288	123	122	119	118	117
Arm 2	291	140	135	132	132	130
Arm 3	277	134	127	126	126	125

Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d) + MMF;
Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/d) + MMF + basiliximab;
Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/d delayed until d 5 post-transplant) + MMF + basiliximab.

We found that AR- and BCAR-free survival rates at 6 months in Arm 2 were numerically higher than those in Arm 1 or Arm 3, and the difference was maintained through to 5 years post-Tx

AR, acute rejection; BCAR, biopsy-confirmed acute rejection; EPS, enrolled patient set; MMF, mycophenolate mofetil.

Friman S, Tisone G, Nevens F, Lehner F, Santaniello W, Bechstein W et al. Long-term, Prolonged-release Tacrolimus-based Immunosuppression in De Novo Liver Transplant Recipients: 5-year Prospective Follow-up of Patients in the DIAMOND Study. Transplantation Direct. 2021;7(8):e722.

Eventos adversos y reacciones adversas al fármaco informados durante el período de seguimiento a largo plazo (FPS)

.El ***perfil de seguridad*** de los pacientes en el estudio de seguimiento fue consistente con los del estudio DIAMOND primario.

.Ningún paciente tuvo EA que condujeran a la ***interrupción del tratamiento con tacrolimus.***

.El 1% de pacientes tuvo ***reacciones adversas*** que se consideraron probablemente relacionadas con tacrolimus.

.Solo 22 (3,6%) de los pacientes desarrollaron ***diabetes***, incluidos 21 ,entre el final del estudio DIAMOND y la prestación del consentimiento informado para el estudio de seguimiento. La baja incidencia de diabetes durante el estudio de seguimiento probablemente estuvo relacionada con la ***baja proporción de pacientes (15%) que tomaban esteroides.***

¿Que factores podriamos cambiar para mejorar los resultados a largo plazo?

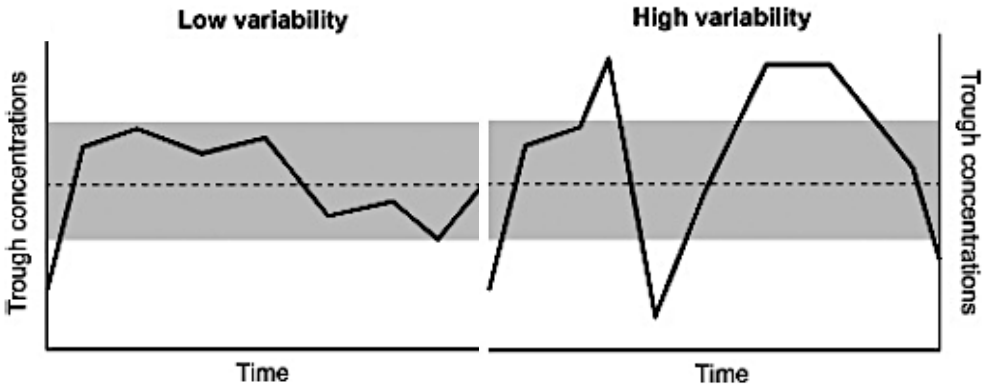
- ¿Podemos reducir algunos factores de riesgo de pérdida de injerto si optimizamos la INMS?

. Nefrotoxicidad

. Variabilidad de Exposición al fármaco

. No adherencia al tratamiento

Tacrolimus intra-patient variability and non-adherence

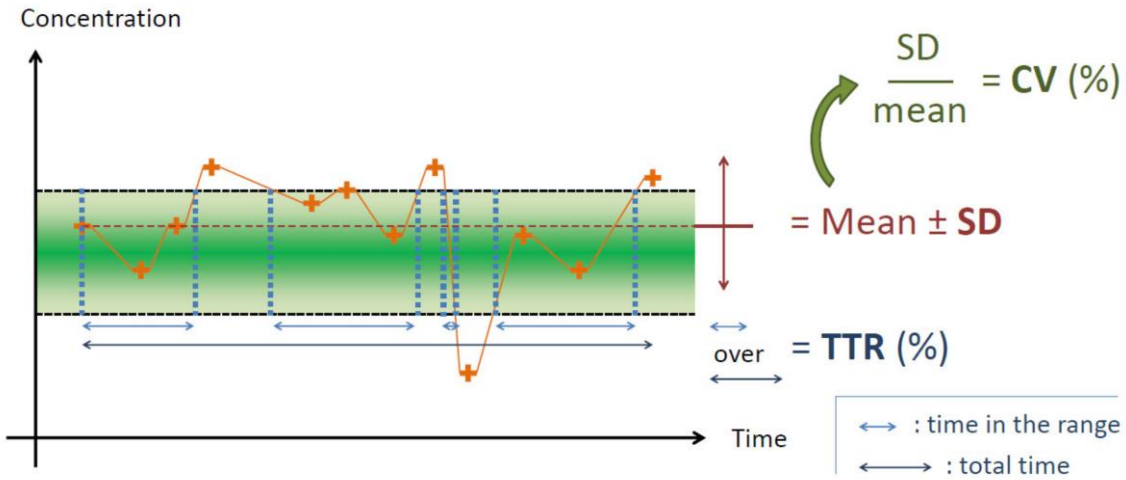


clinically harmful effects

	Factors
Nonmodifiable	• Pharmacogenetics: polymorphisms in CYP3A genes • Circadian rhythm of tacrolimus exposure
Slightly modifiable	• Nonadherence • Gastrointestinal events (diarrhea, vomiting) • Any clinical situation motivating liver graft dysfunction • Low serum proteins (hypoalbuminemia) • Anemia
Highly modifiable	• Food (dietary fat content, grapefruit juice, pomelo) • Drug–drug interactions: antifungals, antivirals, other immunosuppressants, and other drugs • Herbal products • Uncontrolled generic substitution

Neuberger J, et al. *Transplantation*. 2017:101(4S Suppl 2):S1–S56.

TOOLS TO MEASURE tacrolimus intra-patient variability



CV, coefficient of variation; IPV, intra-patient variability; PR, prolonged release; SD, standard deviation; TTR, time in therapeutic range.

Coste G, Lemaitre F. *Pharmaceutics*. 2022:14(2):379.

High tacrolimus intra-patient variability is associated with graft rejection and DSA

Risk factors for a graft-rejection episode						
Variable	**Univariate analyses**			**Multivariate analyses**		
	OR	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
Tacrolimus trough level <5 mg/mL (n=34)	3.00	1.05–8.96	0.02	3.68	1.30–10.41	0.014
CV-IPV tacrolimus (continuous variable)	2.70	1.99–13.45	0.01	1.10	1.01–1.11	0.008
CV-IPV>35%	3.05	1.05–8.96	0.03	3.07	1.14–8.24	0.030
CV>IPV>40%	2.97	0.91–9.30	0.04	4.16	1.38–12.50	0.010

Risk factors for developing *de novo* donor-specific antibodies after liver transplantation						
Variable	**Univariate analyses**			**Multivariate analyses**		
	OR	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
CV-IPV tacrolimus (continuous variable)	1.92	-1.28–21.39	0.08	1.1	1.0–1.12	0.006
CV-IPV>35%	4.66	1.22–19.82	0.02	4.83	1.39–16.72	0.01
CV>IPV>40%	9.10	2.28–40.63	<0.001	9.73	2.65–35.76	0.001

Adapted from Del Bello A, et al 2018[1]

Predictive factors for BPAR:

- Tacrolimus IPV of >35% or >40%
- Tacrolimus trough level of <5 ng/mL

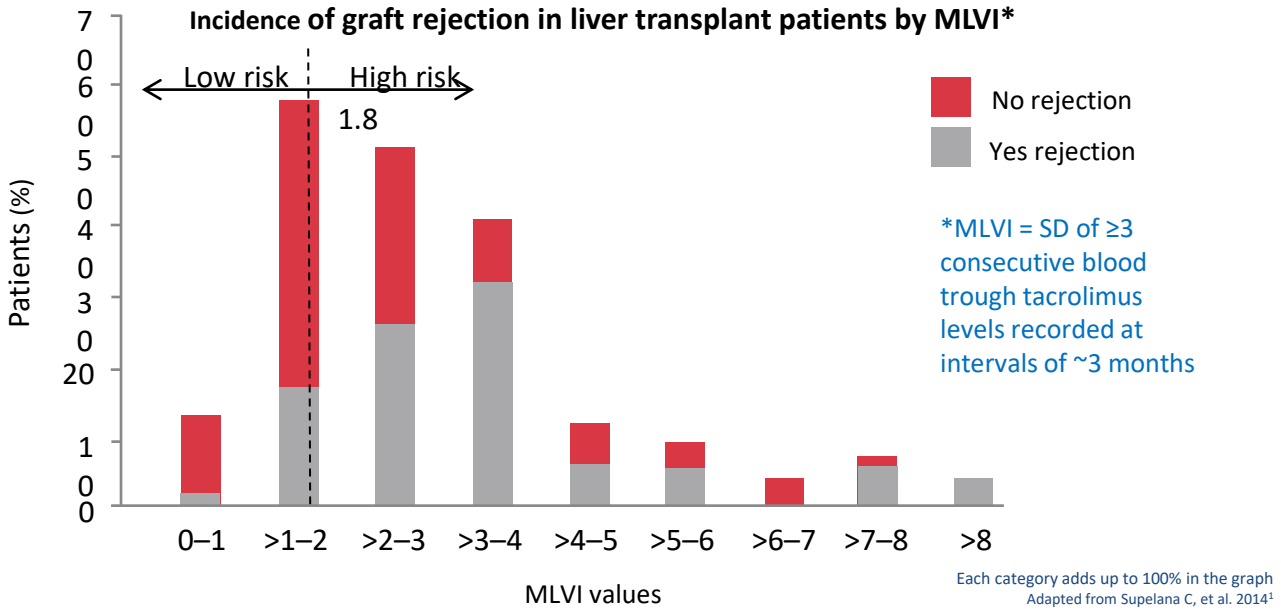
Predictive factors for *de novo* DSA:

- Tacrolimus IPV of >35% or >40%

BPAR, biopsy-proven acute rejection; CV-IPV, Coefficient of variability-intra-patient variability; DSA, donor-specific antibody; IPV, intra-patient variability; OR, odds ratio

1. Del Bello A, et al World J Gastroenterol. 2018 Apr 28;24(16):1795–1802.

High intra-patient variability in tacrolimus level is a risk factor for graft loss in liver transplant patients



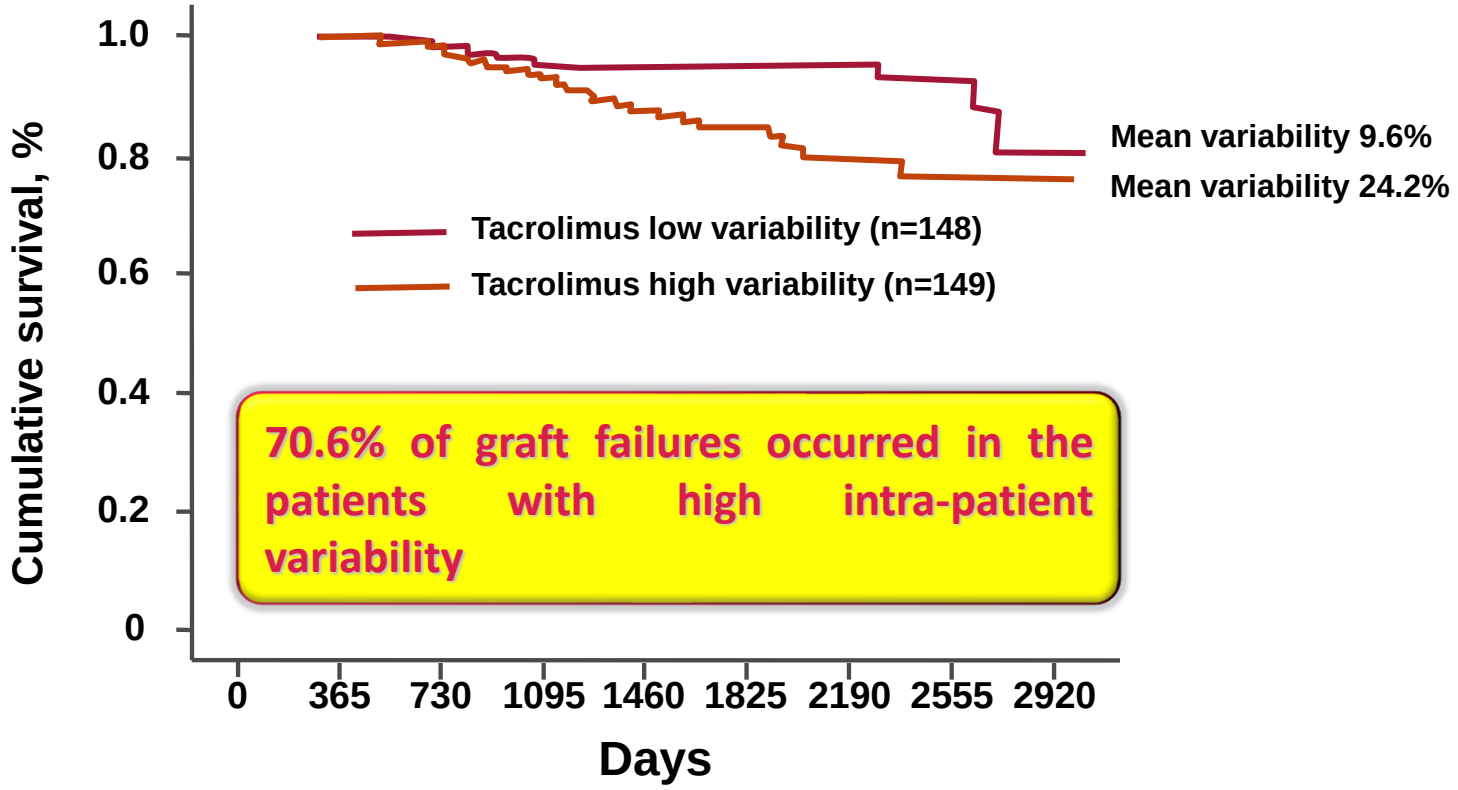
Variability was significantly higher in patients with BPAR vs those without (mean MLVI 3.8 [SD=3.2] vs 2.3 [SD=1.5]; p=0.003)

MLVI, medication level variability index; SD, standard deviation

1. Supelana C, et al. Liver Transpl 2014;20(10):1168–1177

High within-patient variability in tacrolimus exposure is a predictor of graft failure

Graft survival censored for death, p=0.003



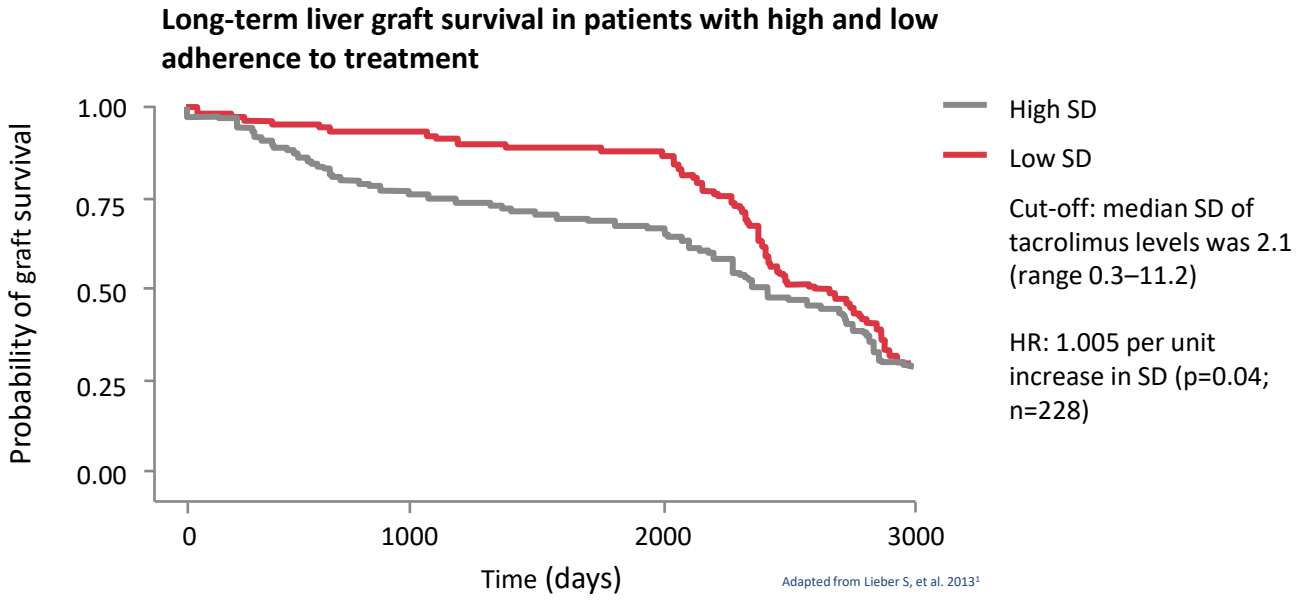
Borra LCP et al. *Nephrol Dial Transplant* 2010;25:2757–2763.

¿Que factores podriamos cambiar para mejorar los resultados a largo plazo?

¿Podemos reducir algunos factores de riesgo de pérdida de injerto si optimizamos la INMS?

- Nefrotoxicidad
- Variabilidad de Exposición al fármaco
- No adherencia al tratamiento

Non-adherence to tacrolimus is a significant risk factor for graft loss in liver transplant patients

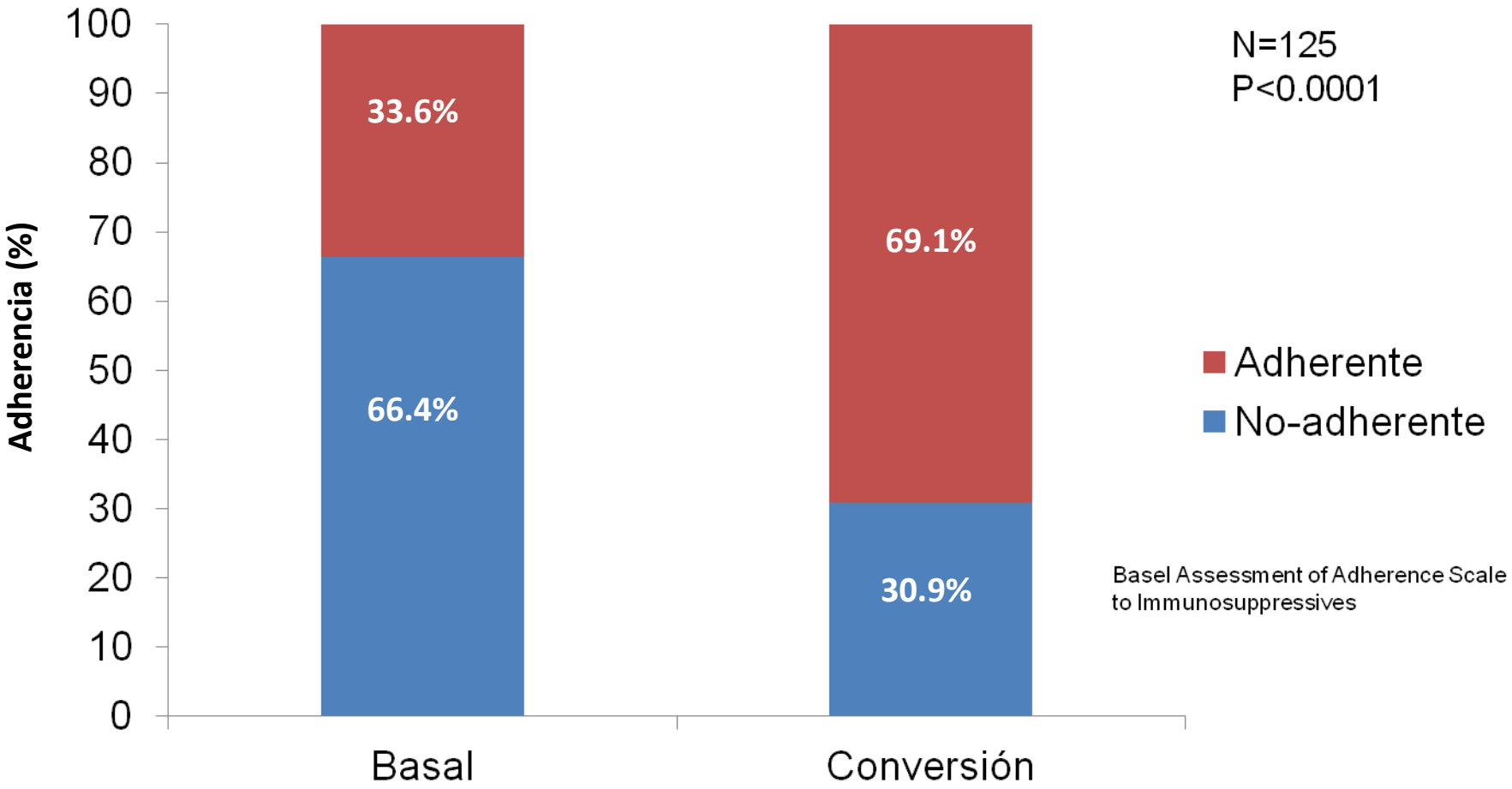


Patients with low adherence to treatment in the first 6–18 months post-transplant were more likely to lose their graft during the first 3000 days (p=0.04)

HR, hazard ratio; SD, standard deviation

1. Lieber S, et al. Dig Dis Sci 2013;58(3):824–834

Effcacia, seguridad y **adherencia** a los inmunosupresores en TxH estables convertidos de ***tacrolimus LI a tacrolimus LR***



Beckebaum S et al. *Transpl Int* 2011:1–10.

Clin Transplant 2012: 26: 369–376 DOI: 10.1111/j.1399-0012.2011.01544.x

Clinical Transplantation

Immunosuppressant treatment adherence, barriers to adherence and quality of life in renal and liver transplant recipients in Spain

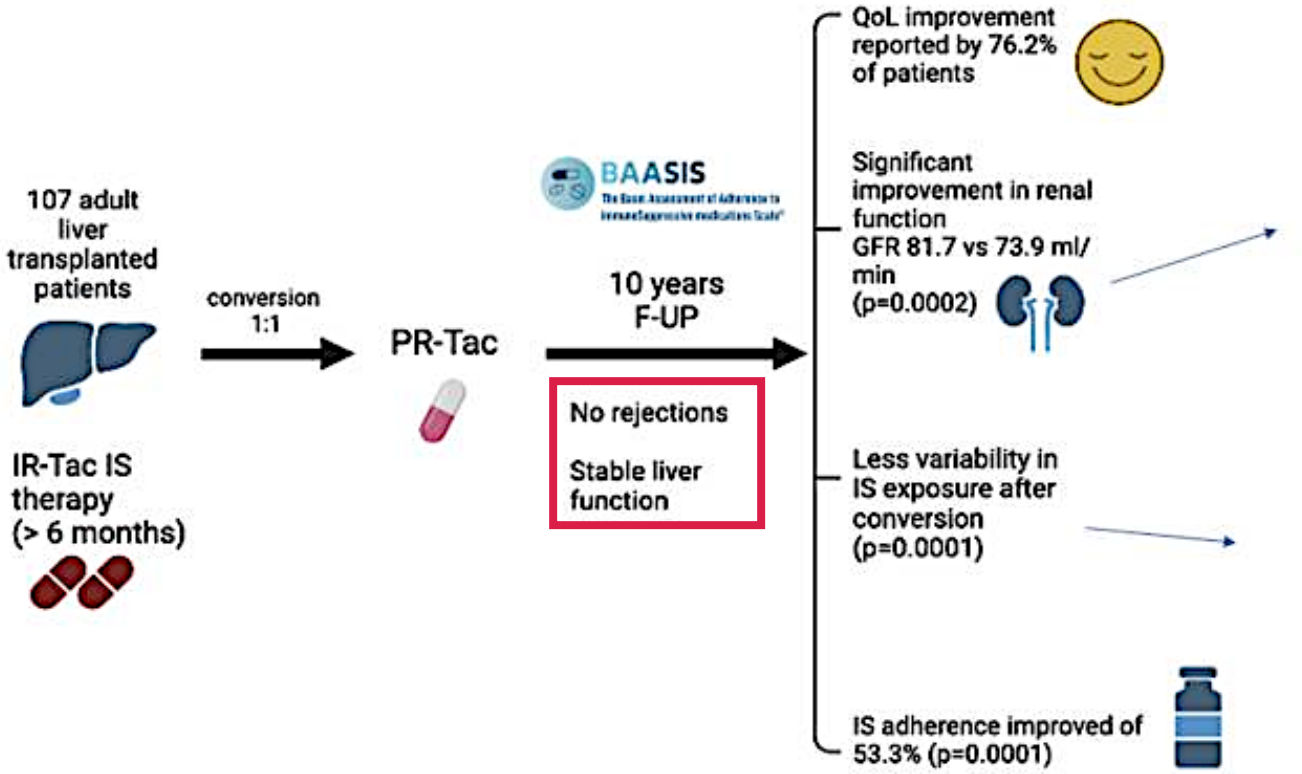
José M. Morales[a], Evaristo Varo[b] and Pablo Lázaro[c]

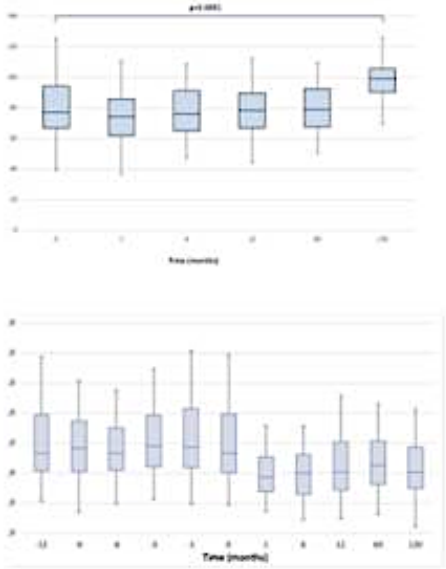
- Data from **1983 RT patients and 1479 LT pati**ents were analyzed

- **High-intensity treatment regimens were associated with poorer QOL (EuroQol <70) compared with low-intensity treatment regimens.**

- **Most RT (71.0%) and LT (61.4%) patients would prefer to suppress the evening dose if they were able to**

10 years follow-up after conversion to prolonged-release tacrolimus after Liver Transplantation





Toti L, et al. *Transpl. Int.* 2022
doi: 10.3389/ti.2022.10384

Balón, Galicia