MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Trasplante Hepático

“¿Qué debe saber un hepatólogo no trasplantador del tratamiento inmunosupresor? INMUNOSUPRESIÓN PERSONALIZADA”

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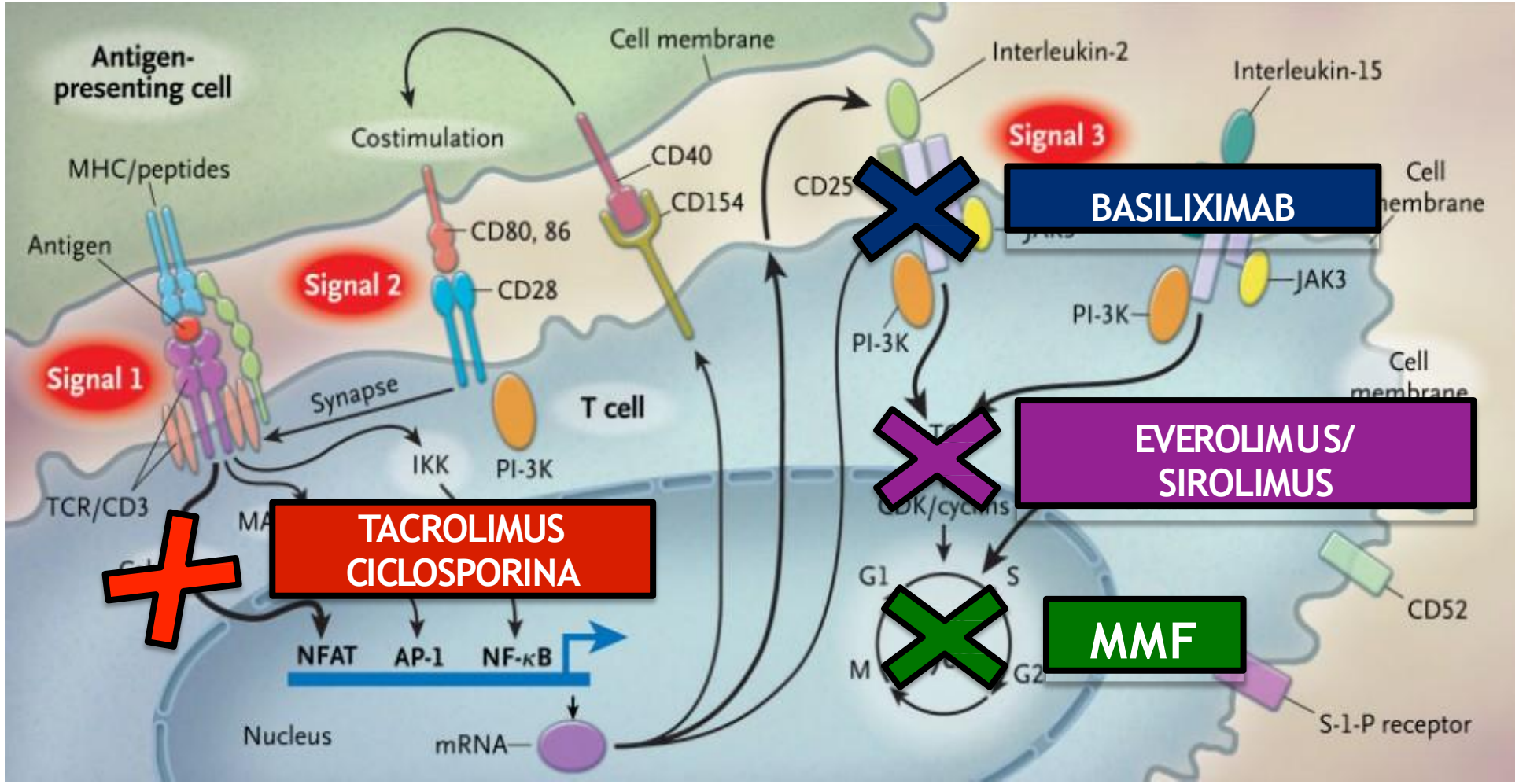
Formas clínicas de rechazo del injerto

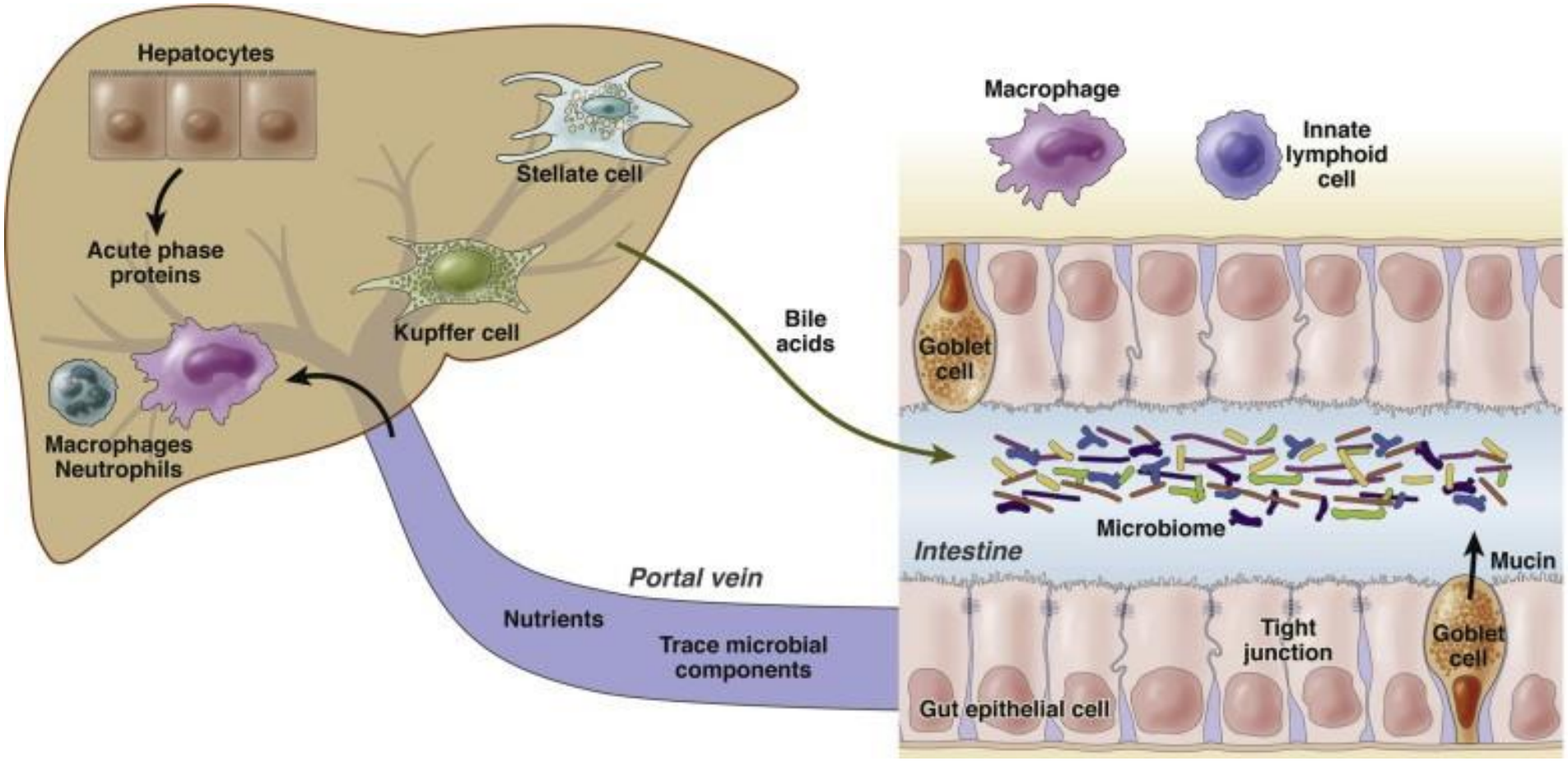
	HIPERAGUDO	CELULAR AGUDO	HUMORAL AGUDO	CRÓNICO
Prevalencia	--	20%-60%	¿?	<5%
Sospecha clínica	ABO incomp Disfx injerto grave	Disfx injerto (< 6 meses)	Aparición DSA tipo II Disfx injerto	Disfx injerto (>12 meses)
Diagnóstico	Biopsia	Biopsia	Biopsia	Biopsia
Tratamiento	Retrasplante	Bolos esteroides	¿?	Incremento IMS
Pronóstico	Grave	Leve	Desconocido	Grave

Inmunosupresores en trasplante



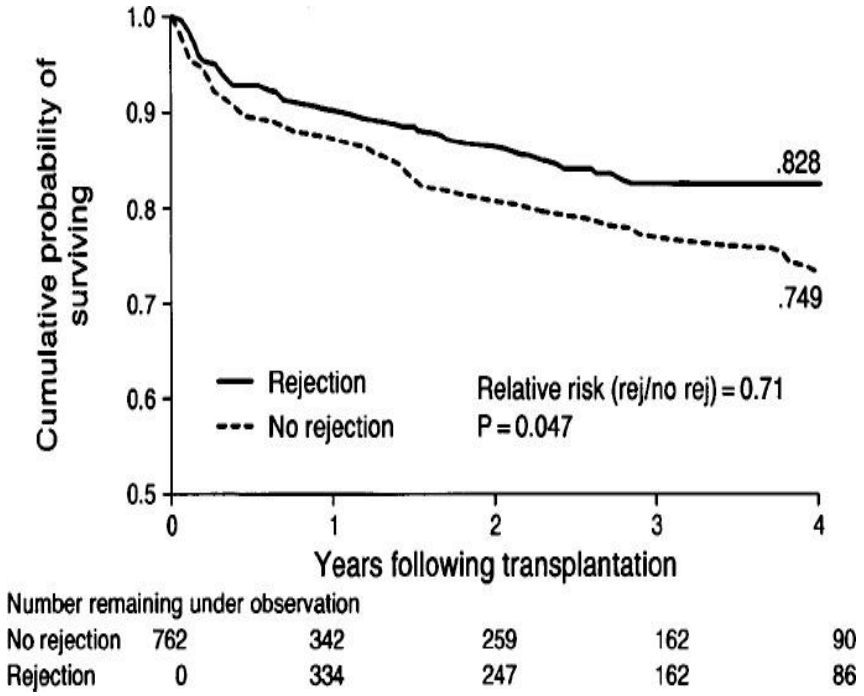
Halloran P. Et al, *New Engl J Med* (2003)

El Hígado es un órgano privilegiado

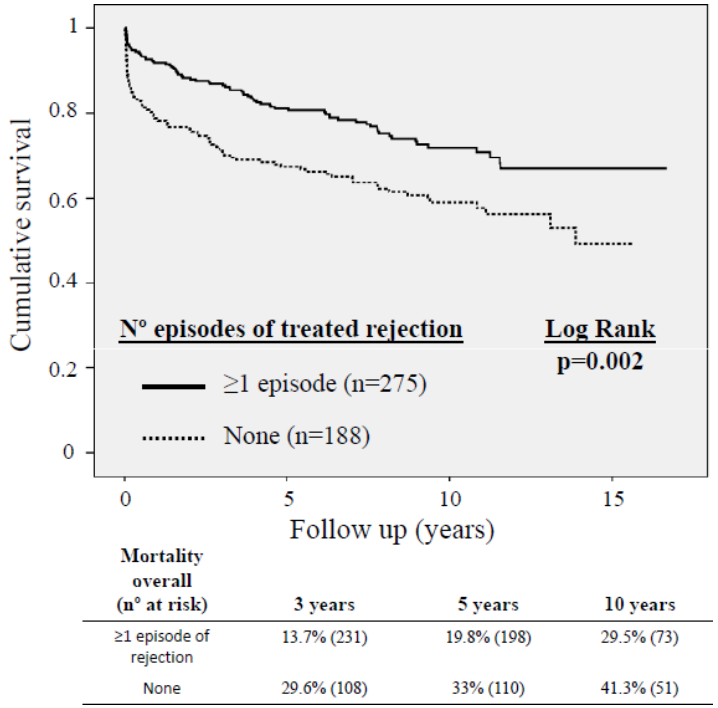


Error interpretativo frecuente

RECHAZO AGUDO ≠ PÉRDIDA INJERTO



Wiesner, Hepatology (1998)

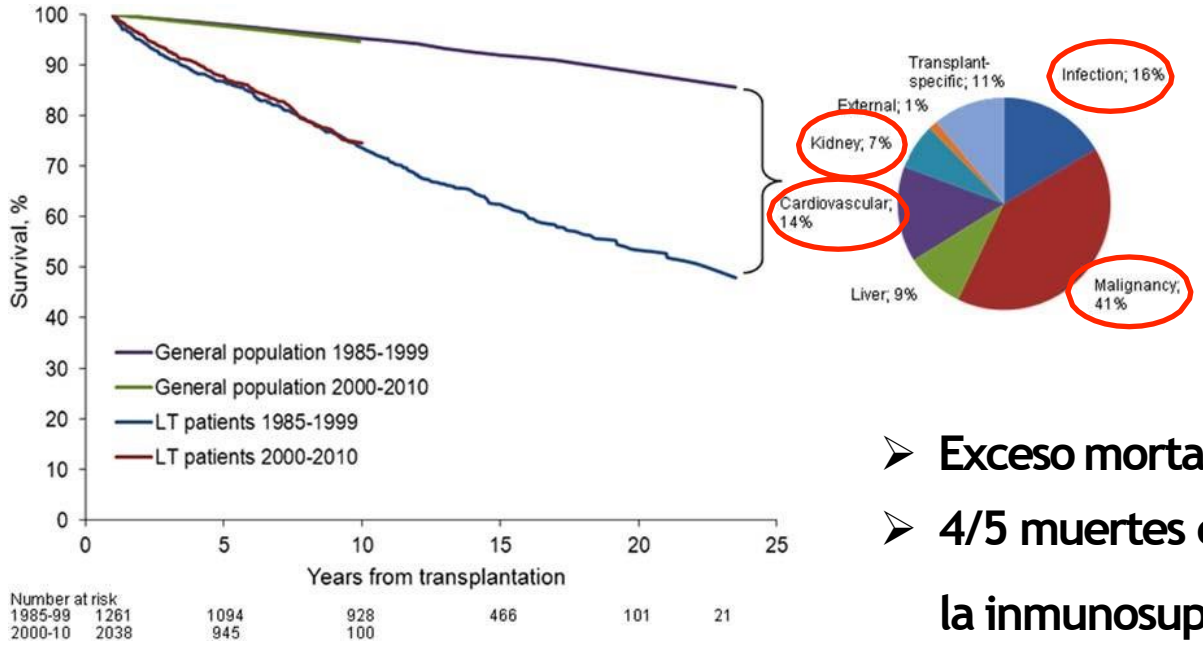


Mortality overall (n° at risk)	3 years	5 years	10 years
≥1 episode of rejection	13.7% (231)	19.8% (198)	29.5% (73)
None	29.6% (108)	33% (110)	41.3% (51)

Rodríguez-Perálvarez, J Hepatol (2013)

Causas de mortalidad post-trasplante

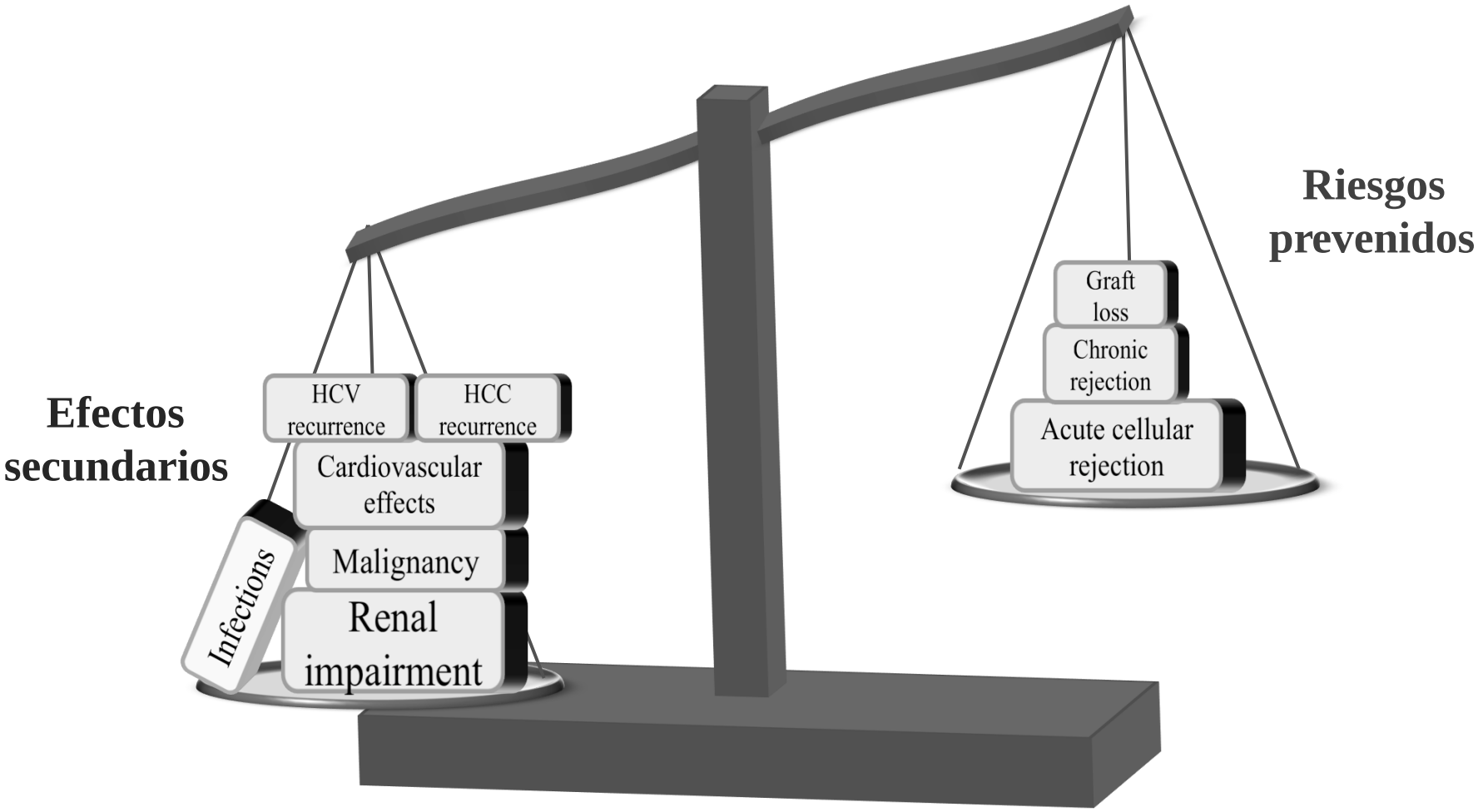
Differences in Long-Term Survival Among Liver Transplant Recipients and the General Population: A Population-Based Nordic Study



- Exceso mortalidad a 10 años: 20%
- 4/5 muertes evitables tienen relación con la inmunosupresión

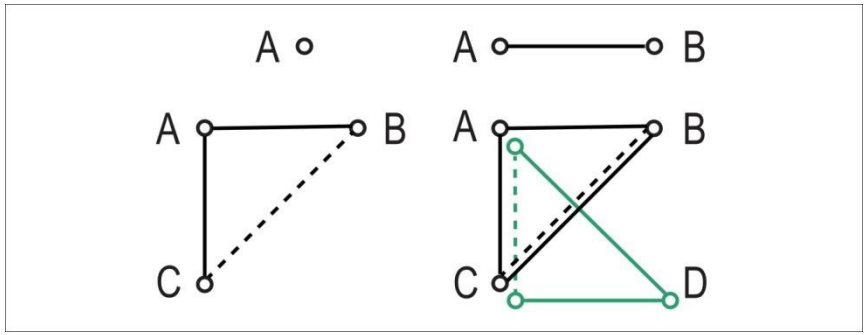
Aberg, Hepatology (2015)

Balancear los riesgos y beneficios del tratamiento inmunosupresor

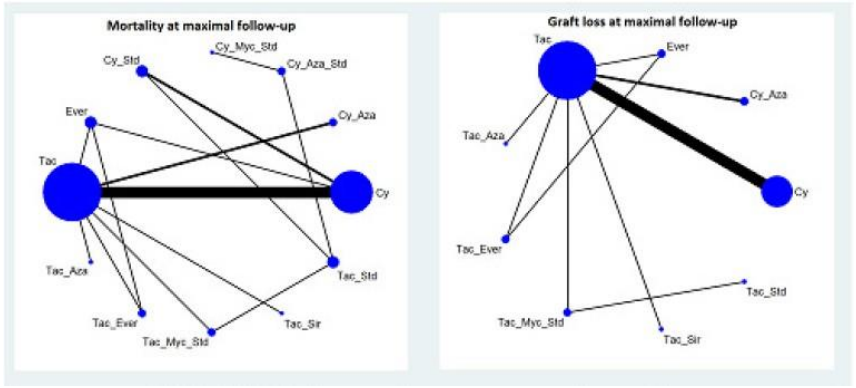


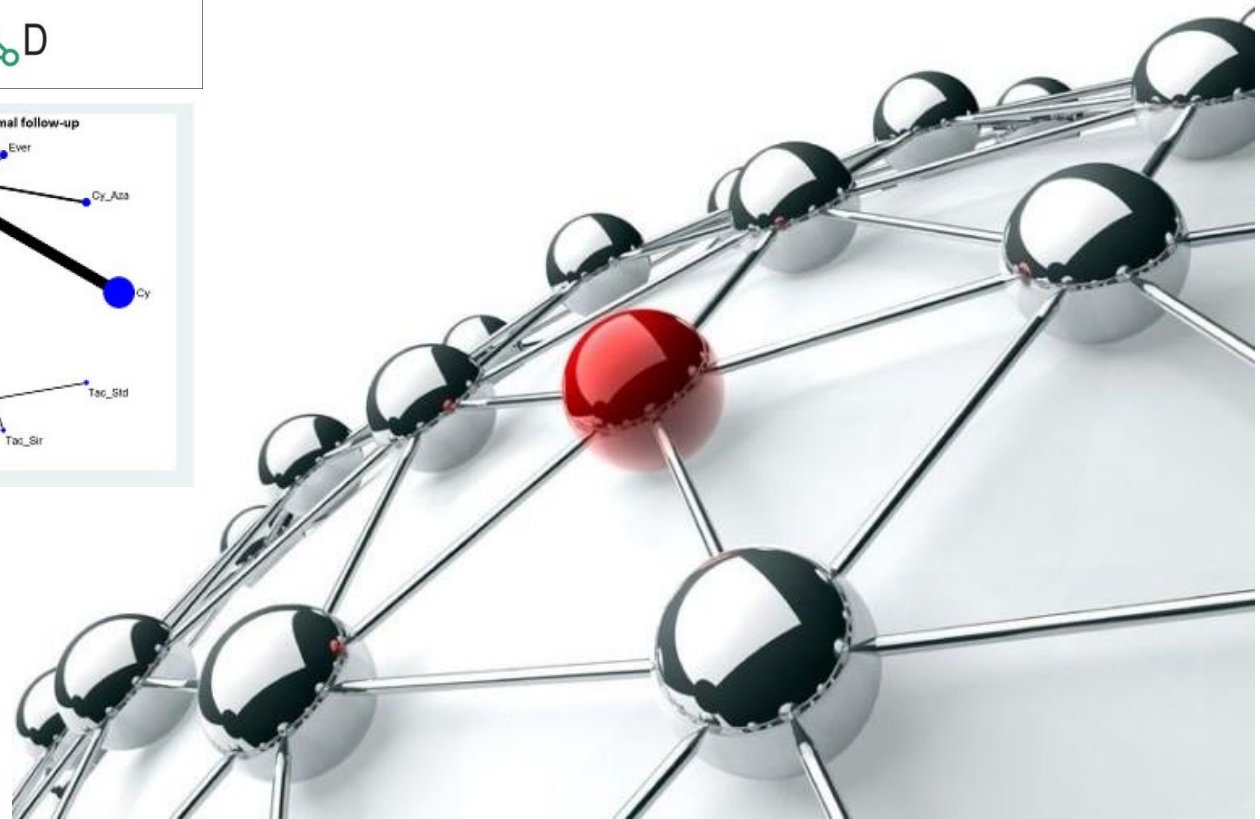
Rodríguez-Perálvarez, Am J Transplant (2012)

¿Existe un régimen imunosupresor ideal?



META-ANÁLISIS EN RED



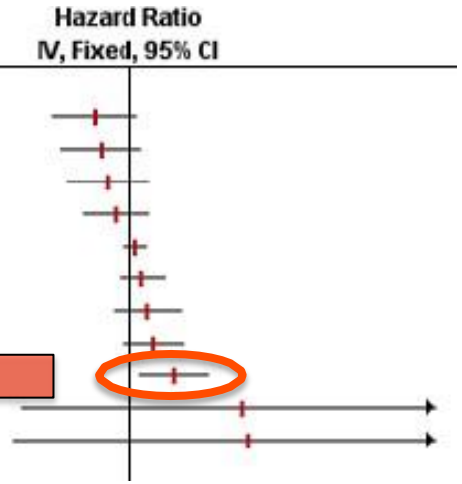


Meta-análisis en red

Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis (Review)

Sirolimus containing regimes were associated with increased mortality

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Network meta-analysis (fixed-effect model)			
Tac_Aza vs Tac	-0.7823	0.479949	0.46 [0.18, 1.17]
Tac_Myc_Std vs Tac	-0.6684	0.455051	0.51 [0.21, 1.25]
Tac_Std vs Tac	-0.5149	0.469311	0.60 [0.24, 1.50]
Cy_Std vsTac	-0.3356	0.371327	0.71 [0.35, 1.48]
Cy vs Tac	0.1094	0.127985	1.12 [0.87, 1.43]
Cy_Aza vs Tac	0.26	0.25648	1.30 [0.78, 2.14]
Tac_Ever vs Tac	0.3995	0.37977	1.49 [0.71, 3.14]
Ever vs Tac	0.531	0.331554	1.70 [0.89, 3.26]
Tac_Sir vs Tac	0.997	0.394311	2.71 [1.25, 5.87]
Cy_Aza_Std vs Tac	2.543	2.565816	12.72 [0.08, 1942.84]
Cy_Myc_Std vs Tac	2.697	2.723469	14.84 [0.07, 3086.83]



Rodríguez-Perálvarez, Cochrane Database Syst Rev (2017)

Cochrane Library

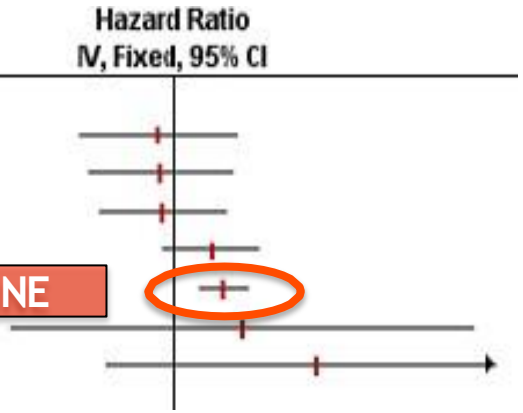
Cochrane Database of Systematic Reviews

Meta-análisis en red

Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis (Review)

Cyclosporine based regimes were associated with increased need for retransplantation

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
1.6.1 Network meta-analysis (fixed-effect model)			
Tac_Std vs Tac	-0.3717	0.861735	0.69 [0.13, 3.73]
Tac_Myc_Std vs Tac	-0.3163	0.782908	0.73 [0.16, 3.38]
Tac_Aza vs Tac	-0.2726	0.689796	0.76 [0.20, 2.94]
Cy_Aza vs Tac	0.7954	0.540842	2.22 [0.77, 6.39]
Cy vs Tac	1.05	0.263112	2.86 [1.71, 4.78]
Cy_Aza_Std vs Tac	1.475	2.544643	4.37 [0.03, 640.60]
Tac_Myc vs Tac	3.057	2.306319	21.26 [0.23, 1953.35]



Rodríguez-Perálvarez, Cochrane Database Syst Rev (2017)

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Meta-análisis en red

Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis (Review)

- Se deben evitar protocolos de inmunosupresión basados en sirolimus y en ciclosporina ya que ocasionan mayor mortalidad y retrasplante.
- Los protocolos basados en tacrolimus parecen ser más eficaces y seguros.
- Se precisan estudios con mayor calidad metodológica.

Rodríguez-Perálvarez, Cochrane Database Syst Rev (2017)

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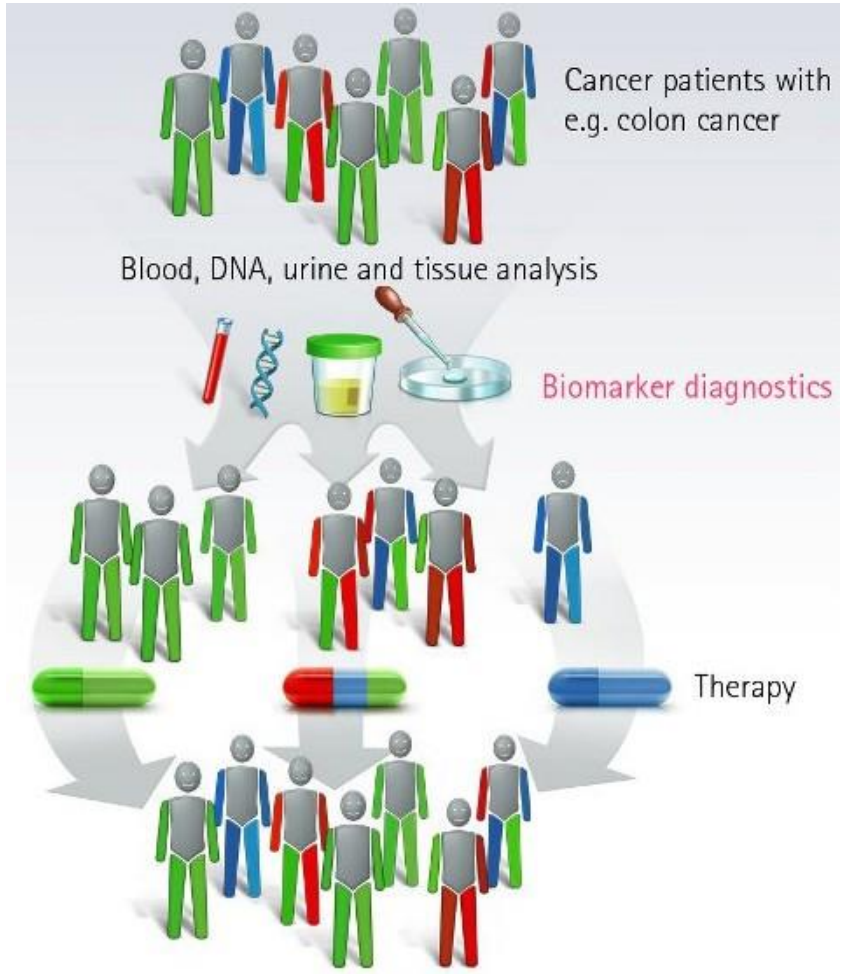
TACROLIMUS
Standard of care

MEDICINA PERSONALIZADA

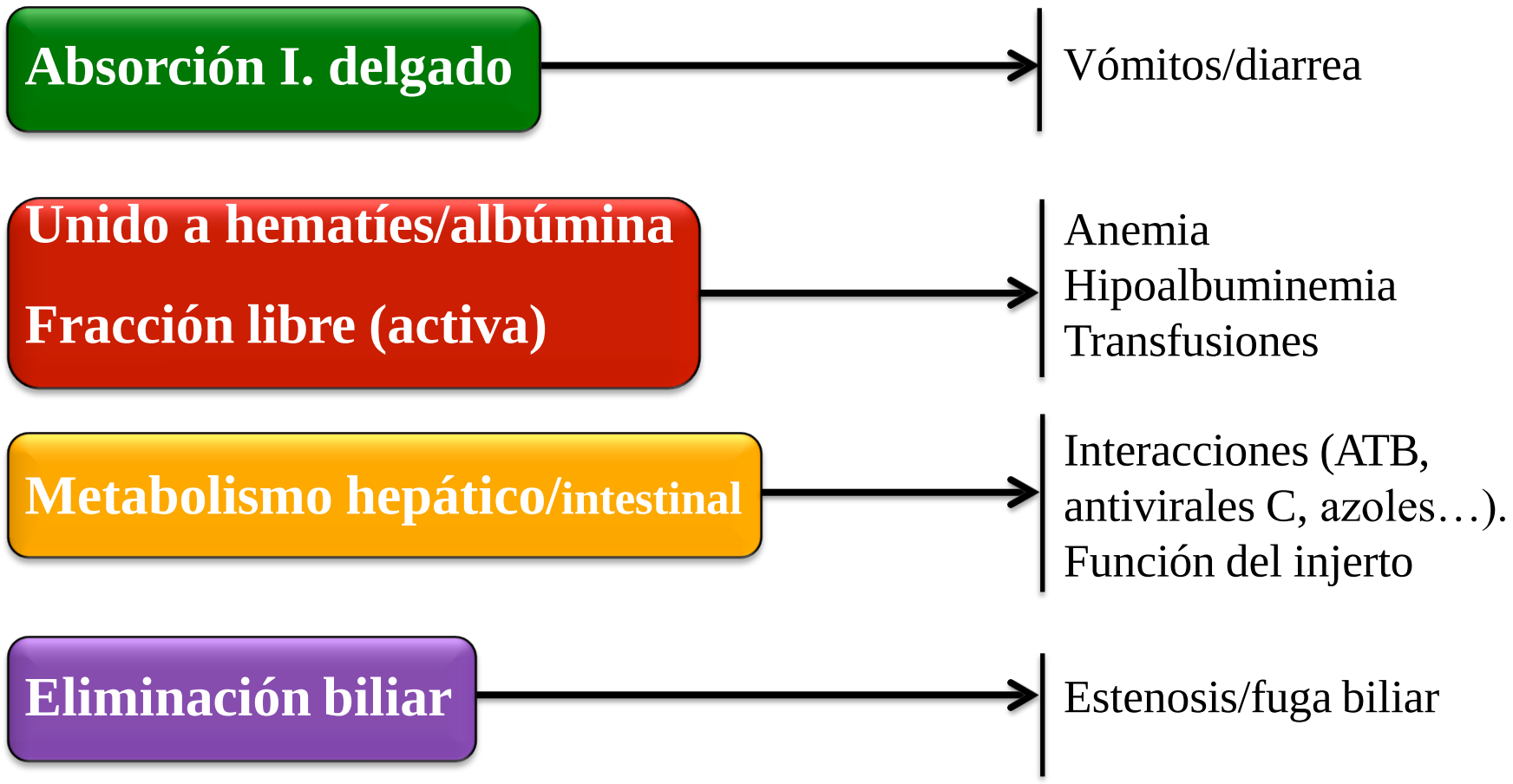


DIFERENTES OPCIONES DE TRATAMIENTO

SUBGRUPOS CON DIFERENTES NECESIDADES

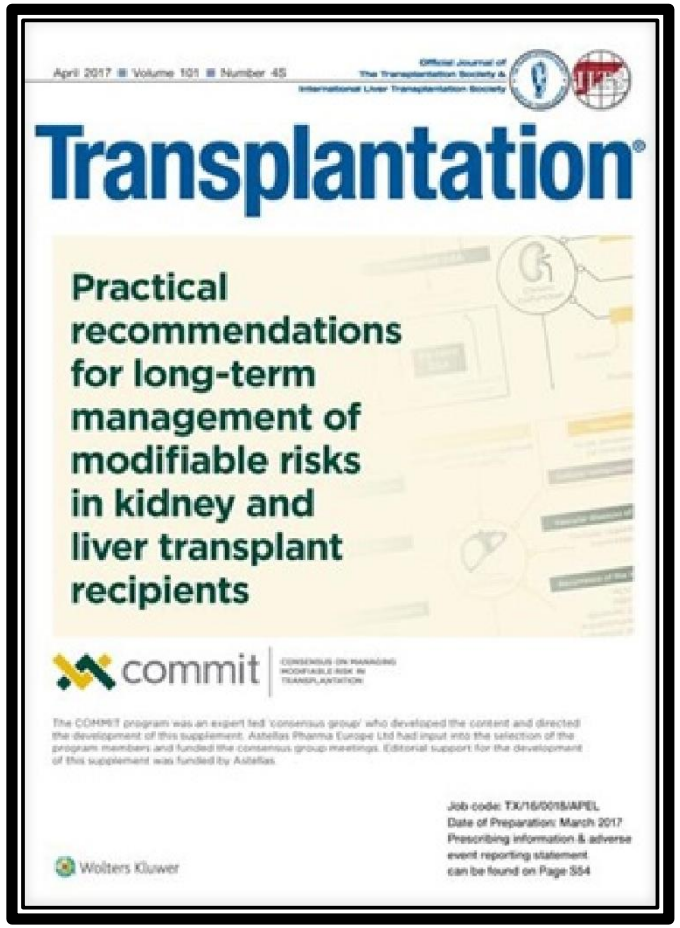
~~INDIVIDUALIZADA~~

El ingrediente principal:Tacrolimus



Shuker N, Van Gelder T, Hesselink DA. Transplant Rev (Orlando) (2015)

Monitorización de niveles de tacrolimus



- Cada 48 horas hasta el alta, semanal hasta el mes, mensualmente hasta los 6 meses y cada 3 meses en adelante.
- Se pueden considerar intervalos más prolongados a largo plazo.
- Monitorización intensiva en situaciones de alto riesgo de variabilidad o interacciones farmacológicas.
- Ajustar niveles entre 6-10 ng/mL en el primer mes y entre 4-8 ng/mL en adelante.
- Niveles más reducidos pueden ser aceptables en casos seleccionados y bajo seguimiento estrecho.

Neuberger et al. Transplantation (2017)

commit CONSENSUS ON MANAGING MODIFIABLE RISK IN TRANSPLANTATION

Línea Roja>10ng/mL

Mantener niveles de tacrolimus<10ng/mL...

1. Reduce la tasa de disfunción renal

Study or Subgroup

Boudjema 2011

Neuberger 2009

Total (95% CI)

Total events

Heterogeneity: Tau² = 0.00;

Test for overall effect: Z = 4.

Figure 8: Forest plot diagr
using reduced (< 10 ng/m

Rodr

2. Prolonga la supervivencia del injerto

R

3. Previene la recidiva del CHC

R

4. Previene los tumores de novo

Day after LT	Overall population n=247	No solid cancer n=204	Solid cancer n=43	p-Value Wilcoxon
3	12.4	11.8	14.8	0.04
7	10.2	9.8	12	0.03
14	10.5	10.1	12.8	0.001
28	10.7	10.3	12.6	0.001
60	9.6	9.1	11.9	<0.0001
90	9.2	8.9	10.8	0.01
120	8.9	8.6	10.4	0.002
150	8.4	8.3	9.2	0.1
180	8.2	7.9	10	0.001
270	7.6	7	10.5	<0.0001
365	7	6.7	8.6	<0.0001

Carenco et al, Am J Transplant (2014)

Opciones de combinación en función del perfil de riesgo

1 BAJO RIESGO DE RECHAZO

- Edad >60 años
- MELD muy elevado
- Desnutrido
- Mala situación clínica

2 DISFUNCIÓN RENAL

- Disfunción renal pretrasplante.
- DM, HTA
- MELD elevado

3 COMPLIC. METABÓLICAS

- Indicación por NASH
- DM, HTA mal control
- Dislipemia, obesidad

4 RIESGO TUMORES

- Hepatocarcinoma
- Cirrosis etílica
- Fumador activo

5 ALTO RIESGO DE RECHAZO

- CEP, CBP o HAI
- Retrasplante por rechazo crónico
- Jóvenes con buena función hepática

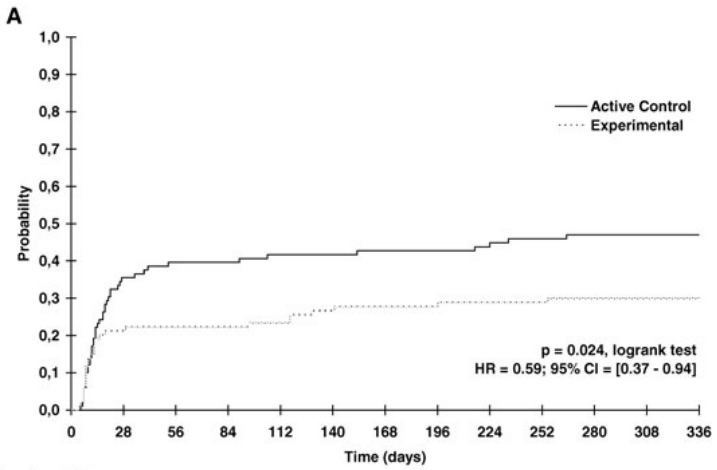
1 Bajo riesgo de rechazo

TACROLIMUS + MMF +/-STDS

6-8 ng/mL <1 month

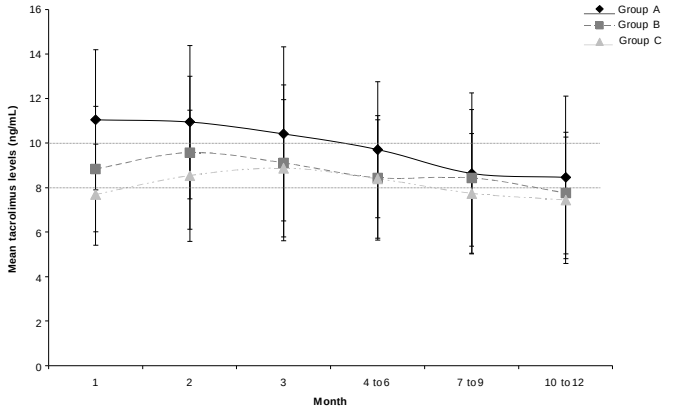
3-5 ng/ml >1 month

Reduced-Dose Tacrolimus with Mycophenolate Mofetil vs. Standard-Dose Tacrolimus in Liver Transplantation: A Randomized Study



Boudjema et al, Am J Transplant (2011)

Delayed Introduction of Reduced-Dose Tacrolimus, and Renal Function in Liver Transplantation: The 'ReSpECT' Study



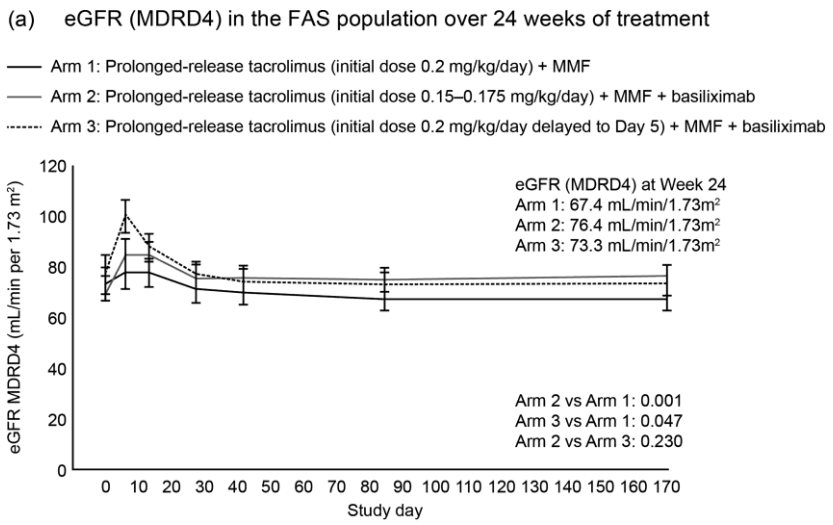
Neuberger et al, Am J Transplant (2009)

2 Riesgo de disfunción renal (Opción A)

(BASILIXIMAB) TAC INICIO TARDÍO + MMF +/- STDS

No tacro: días 1-5
6-8 ng/mL <1 mes
3-5 ng/ml >1 mes

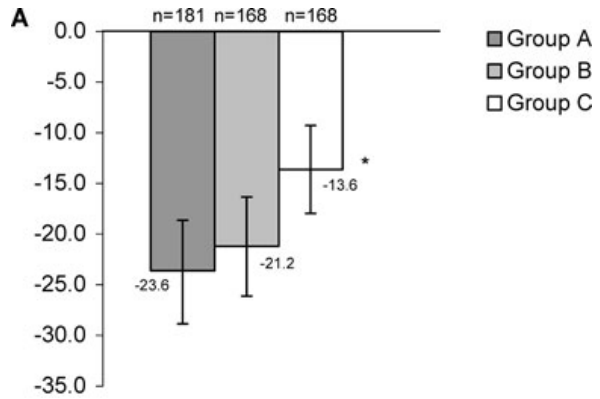
Renal Function in *De Novo* Liver Transplant Recipients Receiving Different Prolonged-Release Tacrolimus Regimens—The DIAMOND Study



Trunecka et al, Am J Transplant (2015)

Delayed Introduction of Reduced-Dose Tacrolimus, and Renal Function in Liver Transplantation: The 'ReSpECT' Study

Standard-dose tacrolimus, corticosteroids (group A) (N = 181)	*MMF, reduced-dose tacrolimus corticosteroids (group B) (N = 168)*	*Daclizumab induction, MMF, delayed reduced-dose tacrolimus and corticosteroids (group C) (N = 168)*



Neuberger et al, Am J Transplant (2009)

2 Riesgo de disfunción renal (Opción B)

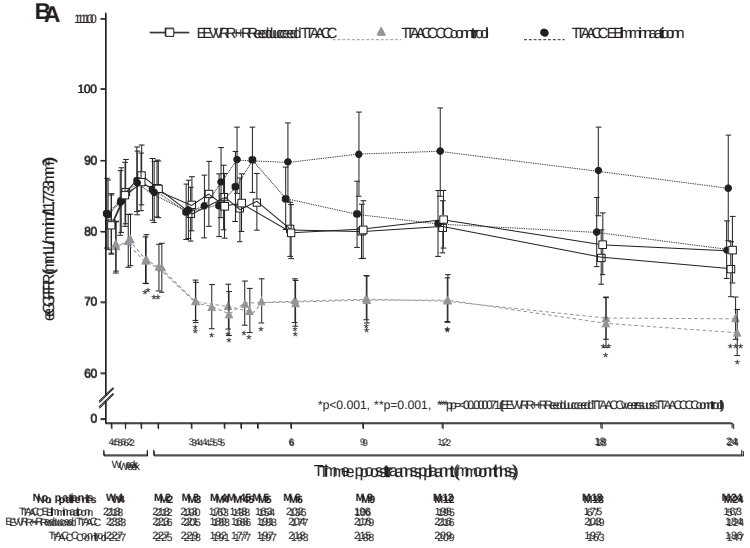
TACROLIMUS + EVEROLIMUS + STDS

4-8 ng/mL <1 mes

3-5 ng/ml >1 mes

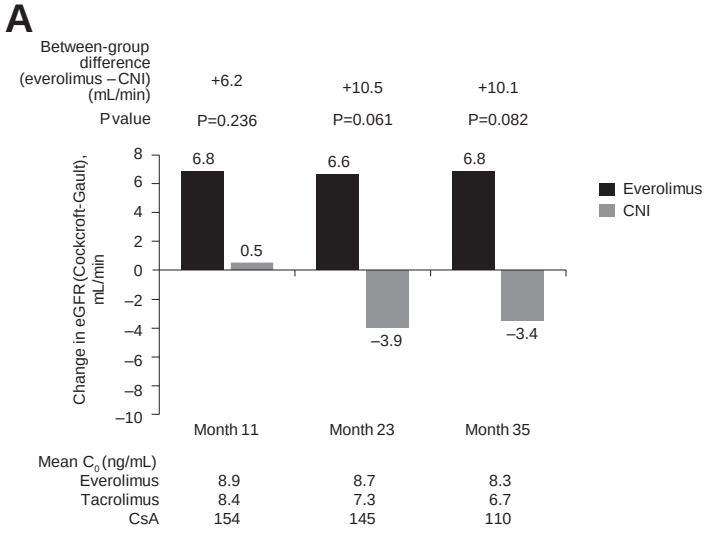
3-8 ng/mL

Everolimus With Reduced Tacrolimus Improves Renal Function in *De Novo* Liver Transplant Recipients: A Randomized Controlled Trial



De Simone et al, AJT (2012); Saliba et al, AJT (2013)

A Randomized, Controlled Study to Assess the Conversion From Calcineurin-Inhibitors to Everolimus After Liver Transplantation—PROTECT



Fischer et al, AJT (2012); Sterneck et al, AJT (2014)

3

Complicaciones metabólicas

PAUTAS LIBRES DE ESTEROIDES

HIPERTENSIÓN

Study or subgroup	Gluc avoid n/N	Gluc cont n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Glucocorticosteroid avoidance					
Ju 2012	2/43	9/44		4.3 %	0.23 [0.05, 0.99]
Lerut 2008	6/78	10/78		4.8 %	0.60 [0.23, 1.57]
Llado 2006	48/96	60/102		28.0 %	0.85 [0.66, 1.10]
Margarit 2005	4/30	9/33		4.1 %	0.49 [0.17, 1.42]
Pelletier 2013	28/50	24/50		11.6 %	1.17 [0.80, 1.70]
Reggiani 2005	2/12	5/18		1.9 %	0.60 [0.14, 2.60]
Subtotal (95% CI)	**309**	**325**		**54.7 %**	**0.81 [0.66, 1.00]**

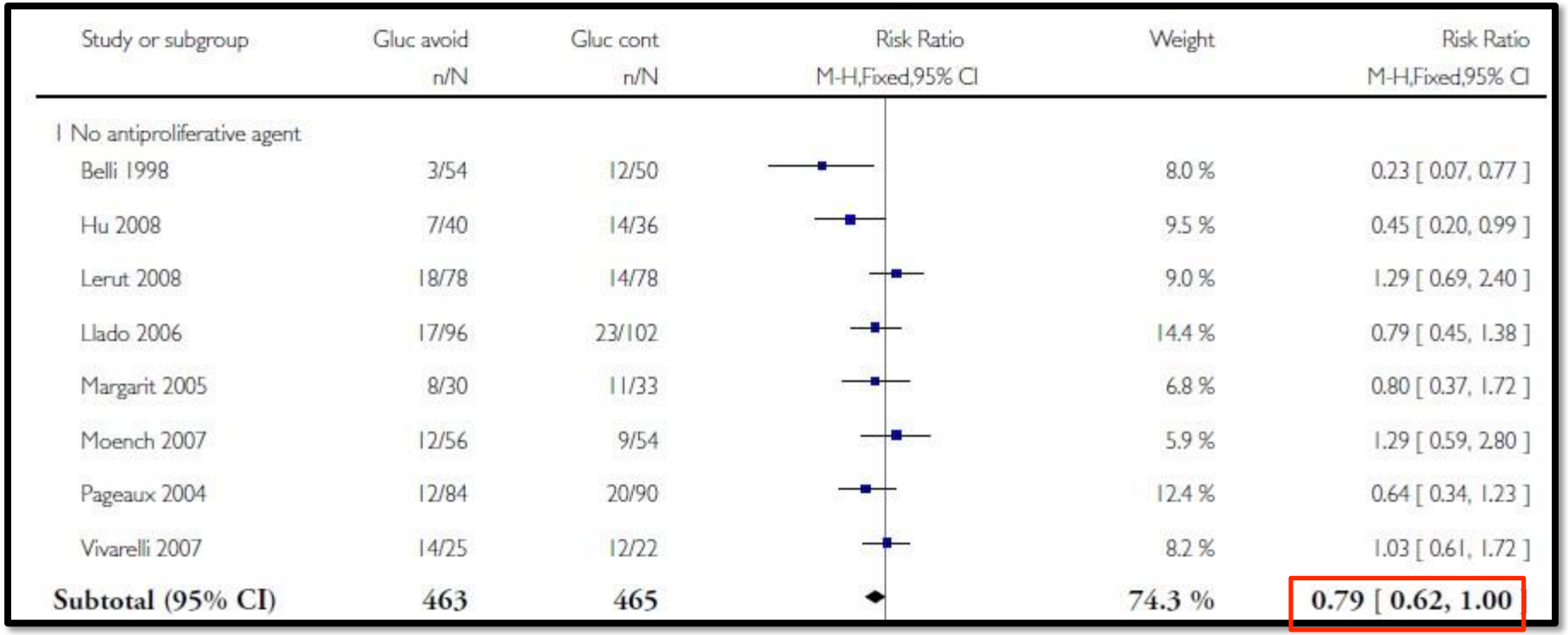
Fairfield et al, Cochrane Syst Rev (2018)

3

Complicaciones metabólicas

PAUTAS LIBRES DE ESTEROIDES

DIABETES



Study or subgroup	Gluc avoid n/N	Gluc cont n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 No antiproliferative agent					
Belli 1998	3/54	12/50		8.0 %	0.23 [0.07, 0.77]
Hu 2008	7/40	14/36		9.5 %	0.45 [0.20, 0.99]
Lerut 2008	18/78	14/78		9.0 %	1.29 [0.69, 2.40]
Llado 2006	17/96	23/102		14.4 %	0.79 [0.45, 1.38]
Margarit 2005	8/30	11/33		6.8 %	0.80 [0.37, 1.72]
Moench 2007	12/56	9/54		5.9 %	1.29 [0.59, 2.80]
Pageaux 2004	12/84	20/90		12.4 %	0.64 [0.34, 1.23]
Vivarelli 2007	14/25	12/22		8.2 %	1.03 [0.61, 1.72]
Subtotal (95% CI)	**463**	**465**		**74.3 %**	**0.79 [0.62, 1.00]**

Fairfield et al, Cochrane Syst Rev (2018)

4 Riesgo de tumores-hepatocarcinoma

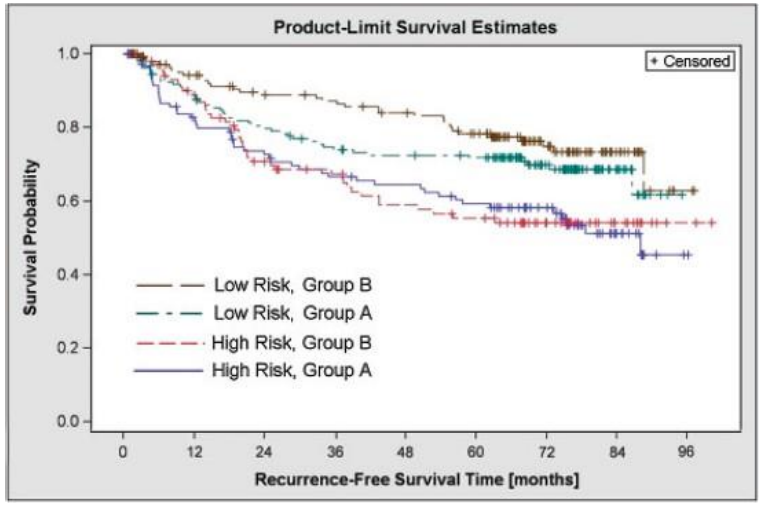
¿ **TACROLIMUS → EVEROLIMUS + STDS** ?

6-8 ng/mL <1 mes

3-5 ng/ml >1 mes

3-8 ng/mL

Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial



Time point after LTx	Group A (N=146)	Group B (N=146)	P-value (log-rank test)
1 year	128 (87.7%)	138 (94.5%)	0.0566
2 years	117 (80.1%)	131 (89.7%)	0.0383
3 years	109 (74.7%)	128 (87.7%)	0.0106
4 years	107 (73.3%)	124 (84.9%)	0.0280
5 years	106 (72.6%)	118 (80.8%)	0.1393
7 years	102 (69.9%)	114 (78.1%)	0.1668

Geissler et al, Transplantation (2015)

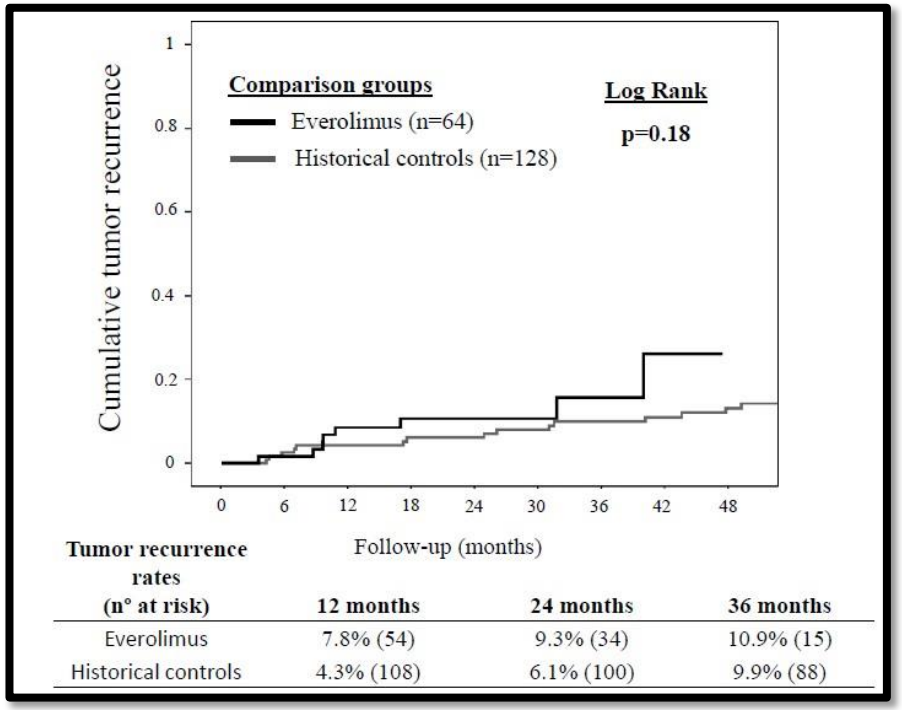
4 Riesgo de tumores-hepatocarcinoma

¿ TACROLIMUS → EVEROLIMUS + STDS ?

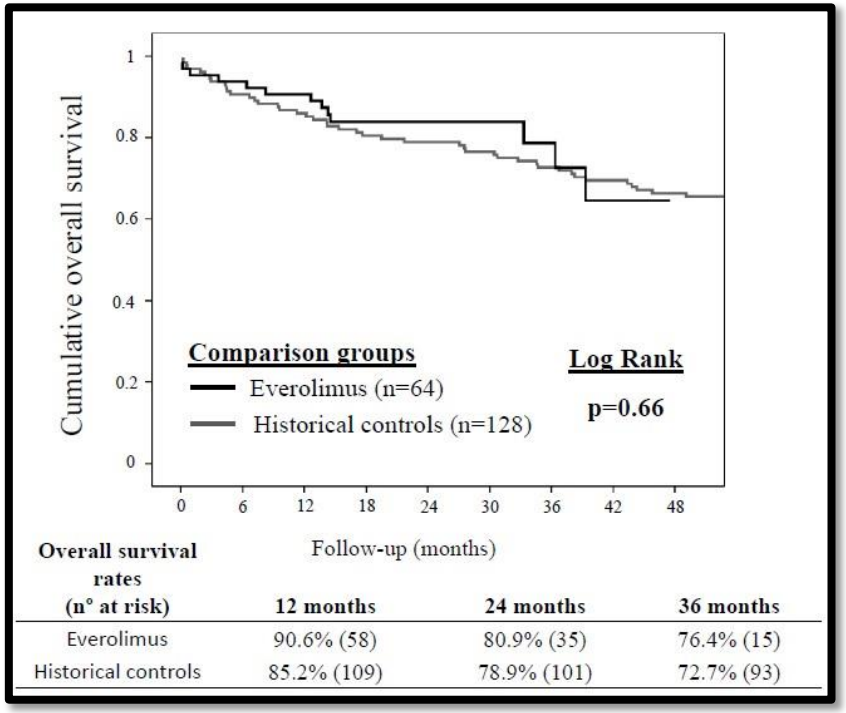
6-8 ng/mL <1 mes

3-5 ng/ml >1 mes

3-8 ng/mL



Tumor recurrence rates (n° at risk)	12 months	24 months	36 months
Everolimus	7.8% (54)	9.3% (34)	10.9% (15)
Historical controls	4.3% (108)	6.1% (100)	9.9% (88)



Overall survival rates (n° at risk)	12 months	24 months	36 months
Everolimus	90.6% (58)	80.9% (35)	76.4% (15)
Historical controls	85.2% (109)	78.9% (101)	72.7% (93)

Rodríguez-Perálvarez et al, Transplantation (2018)

5 Alto riesgo de rechazo

(BASILIXIMAB) TACROLIMUS+ EVEROLIMUS + STDS

7-10 ng/mL <1 mes
4-8 ng/ml >1 mes

+

Screening and preemptive management of opportunistic infections

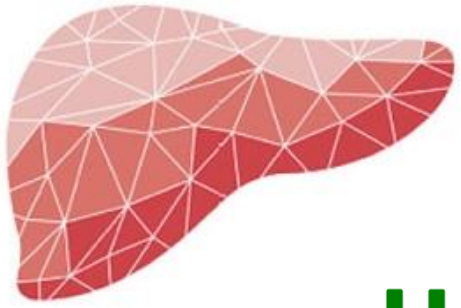
Careful cardiovascular assessment and dedicated follow-up

Adherence to cancer screening programs

CONCLUSIONES

1. El **objetivo** de la inmunosupresión primaria es **evitar** episodios de rechazo grave y **pérdida del injerto**.
2. **Ante un deterioro de la función del injerto** no justificado por complicaciones vasculares/biliares, debe indicarse una **biopsia hepática**.
3. El uso de **bolos de esteroides** debe restringirse a pacientes con **rechazo agudo histológico moderado-grave.**
4. **El protocolo de inmunosupresión** debe adaptarse a cada paciente, priorizándose las combinaciones con **perfil de seguridad** más favorable.

MÁSTER EN HEPATOLOGÍA



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