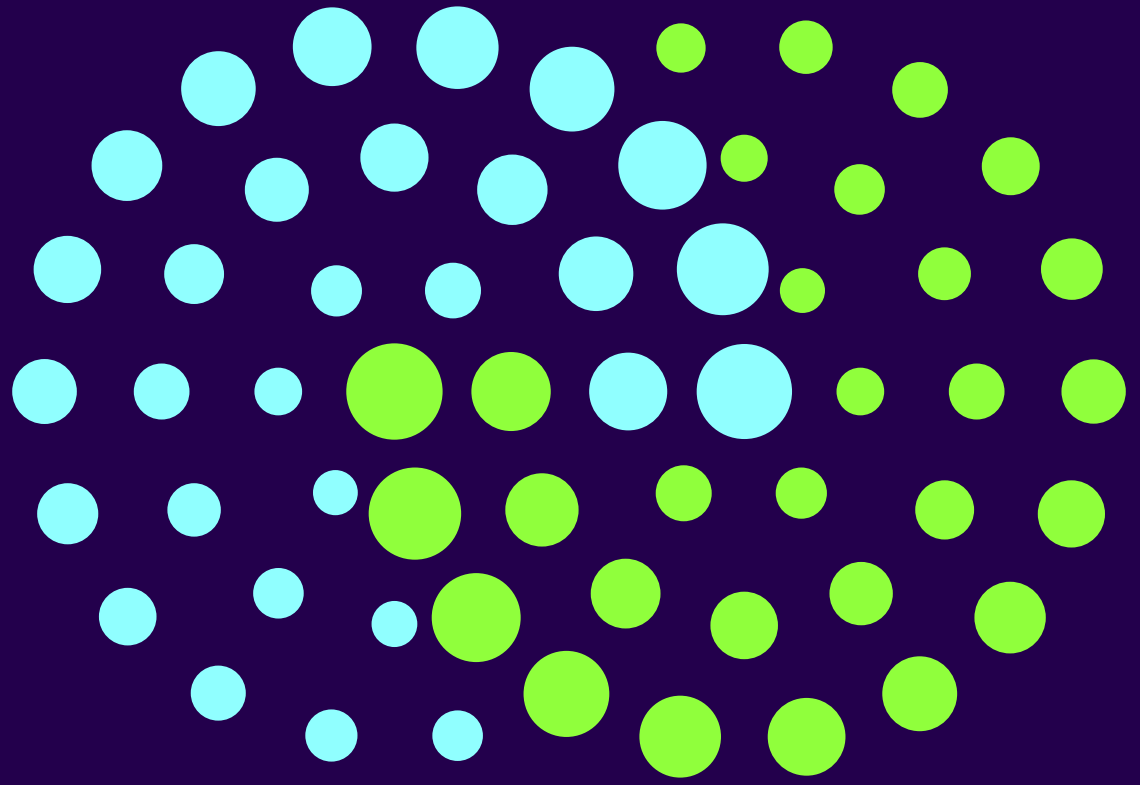
sanofi

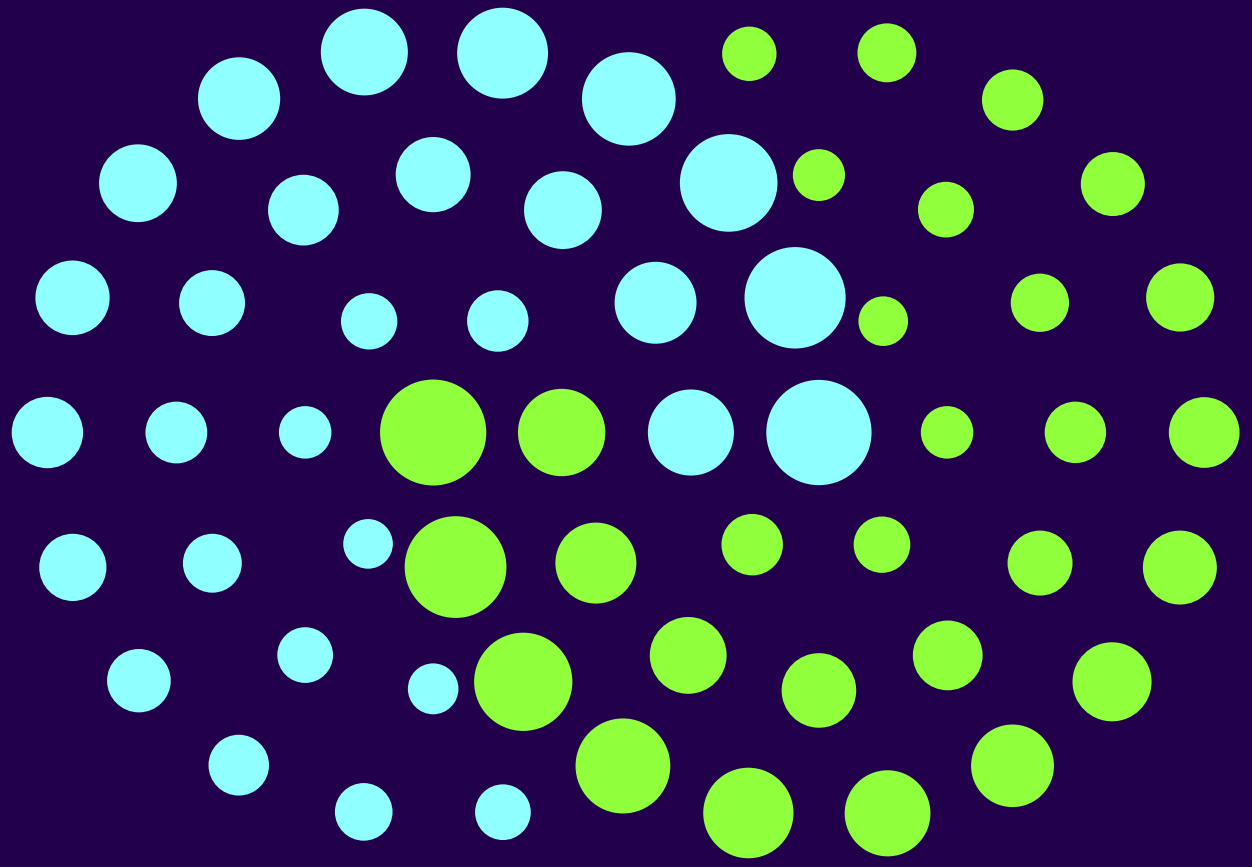


Explorando terapias inmunomoduladoras en Trasplante Renal Perspectivas actuales y avanzando hacia el futuro

MAT-ES-2401453-1.0-05/24

Agenda

Timing	Session	Faculty
15 min	Ponencia: State of the art en terapia de inducción	Dra. Inza
15 min	Ponencia: Nuevas dianas biológicas en trasplante	Dr. Bestard
15 min	Preguntas y cierre	Dra. Mazuecos



State of the art en terapia de inducción

Dra. Inza San Salvador del Valle

Servicio de Nefrología
Hospital de Cruces
Bilbao

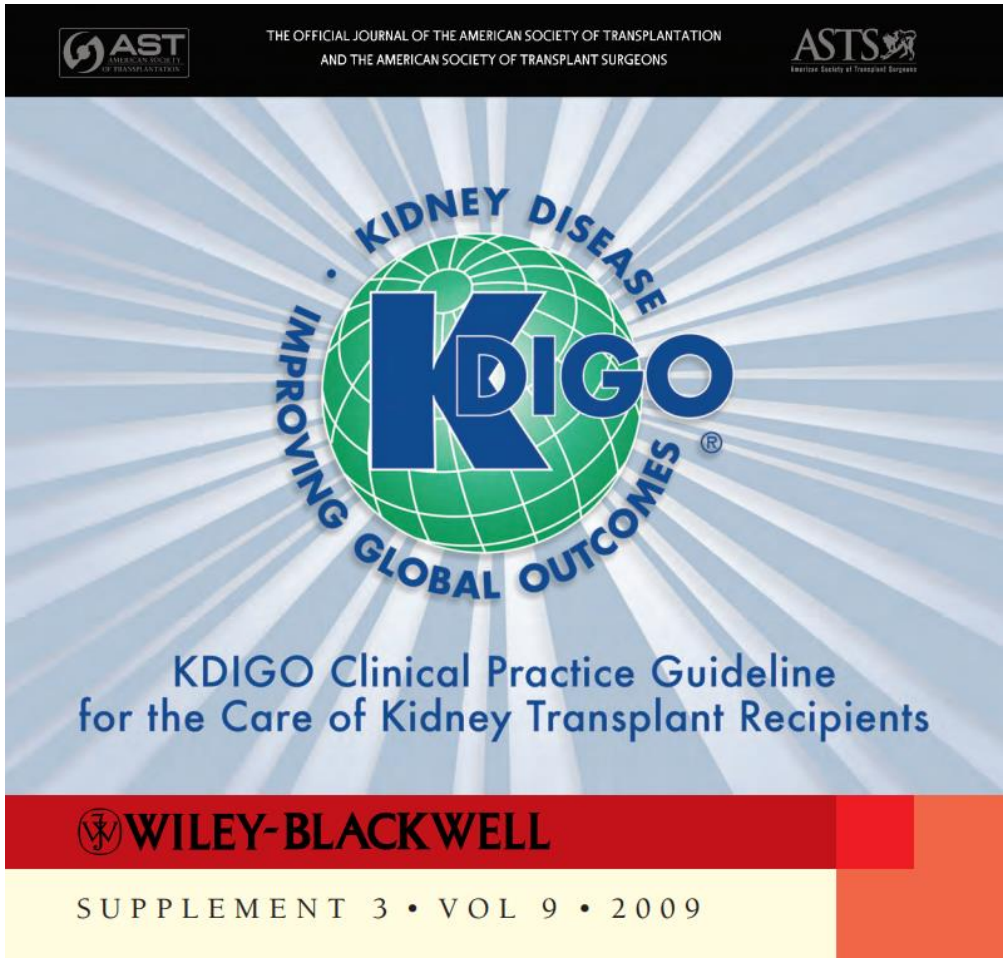
MAT-ES-2401453-1.0-05/24

sanofi

Conflictos de interés

- Fees for this presentation from Sanofi
- Participated in a Talk sponsored by Astellas Pharma

Terapia de inducción



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation

Daniel C. Brennan, M.D., John A. Daller, M.D., Ph.D., Kathleen D. Lake, Pharm.D., Diane Cibrik, M.D., and Domingo Del Castillo, M.D., for the Thymoglobulin Induction Study Group*

Terapia de inducción

- **Esteroides intravenosos: 250-500 mg iv el día del trasplante**
- **Anticuerpos monoclonales**:
  - Anti CD-25
  - Anti CD-52
  - Anti CD-23
  - Anti CD-20
  - Anti C5
  - Otros

- **Anticuerpos policlonales** (timoglobulinas antitimocíticas [ATG]):
  - ATG conejo
  - ATG equina

Crespo M, Diekmann F, Redondo-Pachon D et al. Inmunosupresión en el Trasplante Renal.En: Lorenzo V., López Gómez JM (Eds). Nefrología al día. ISSN: 2659-2606. Disponible en: https://www.nefrologiaaldia.org/602

PERFILES DE RECEPTOR. Terapia de inducción: ¿a quién? ¿Dosis?

Table 1 Risk stratification for selection of immunosuppression in kidney transplantation

Risk Type	Low	Medium	High	Possible Strategy
Immunological	0-DR mismatch First graft Unsensitised Recipient >60	1-DR mismatch Afro-Caribbean recipient Historical DSAs NDSAs DGF Older donor [45]	2-DR mismatch Previous early immunological graft loss DSAs ABO-incompatible Sensitised (high CRF/PRA) Preoperative anti-ATIIR Abs [117]	Increase total immunosuppressive load
Metabolic	Low BMI Age <40 Normal pre-Tx GTT	Positive family history ADPKD	Impaired GT BMI >35 HCV positive Age >60 Previous CVD Race	Avoid/minimise steroids and tacrolimus
Neoplastic	Age <40	Pre-malignant lesion	Previous cancer Hereditary syndrome e.g. VHL	Consider low immunosuppression load or sirolimus
Ischaemia-reperfusion injury	Living donor Deceased donor <40	CIT >12 h Donor aged 50–60	DCD CIT > 24 h Extended criteria donor	Reduce CNI exposure
Non-adherence			Poor RRT compliance Age <20 Transition from paediatric to adult	Education Simple drug regime alemtuzumab or belatacept

Baker RJ, Mark PB, Patel RK, Stevens KK, Palmer N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. BMC Nephrol. 2017;18(1):174. Published 2017 Jun 2. doi:10.1186/s12882-017-0553-2

Alto riesgo rechazo agudo

Factores de riesgo de rechazo agudo:

- Receptor:
  - Número de incompatibilidades HLA
  - Receptores jóvenes
  - Etnia afro-americana
  - Presencia de anticuerpos antiHLA (donante específicos o no)
  - Incompatibilidad grupo sanguíneo

- Donante (favorecen retraso función injerto):
  - Isquemia fría superior a 24 horas
  - Criterios expandidos
  - Edad avanzada
  - Donante asistolia controlada/no controlada

kdigo am j transplant 2009 s1-s155

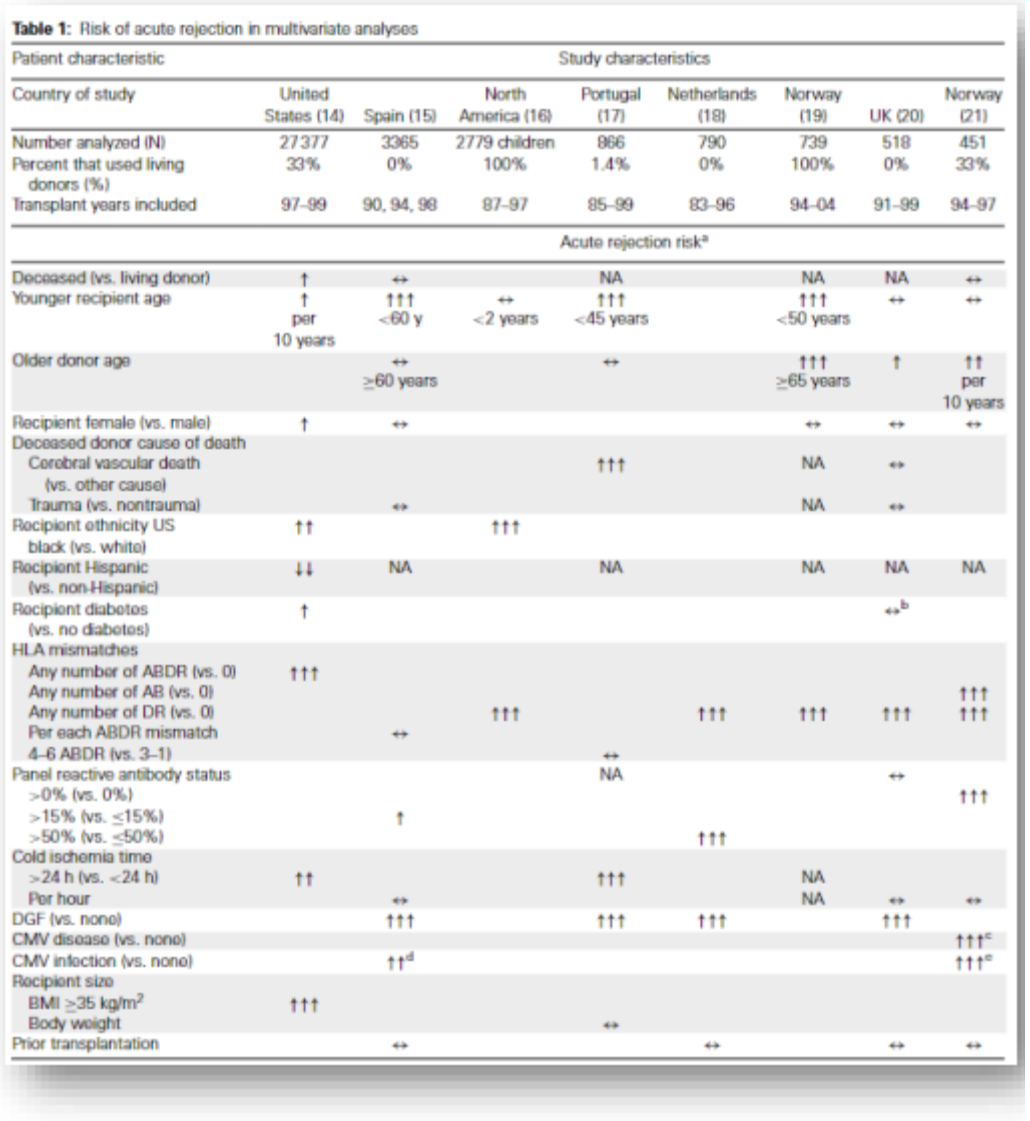


Table 1: Risk of acute rejection in multivariate analyses

Patient characteristic	Study characteristics							
Country of study	United States (14)	Spain (15)	North America (16)	Portugal (17)	Netherlands (18)	Norway (19)	UK (20)	Norway (21)
Number analyzed (N)	27 377	3365	2779 children	866	790	739	518	451
Percent that used living donors (%)	33%	0%	100%	1.4%	0%	100%	0%	33%
Transplant years included	97–99	90, 94, 98	87–97	85–99	83–96	94–04	91–99	94–97
	Acute rejection risk[a]							
Deceased (vs. living donor)	↑	↔		NA		NA	NA	↔
Younger recipient age	↑ per 10 years	↑↑↑ <60 y	↔ <2 years	↑↑↑ <45 years		↑↑↑ <50 years	↔	↔
Older donor age		↔ ≥60 years		↔		↑↑↑ ≥65 years	↑	↑↑ per 10 years
Recipient female (vs. male)	↑	↔				↔	↔	↔
Deceased donor cause of death								
Cerebral vascular death (vs. other cause)				↑↑↑		NA	↔	
Trauma (vs. nontrauma)		↔				NA	↔	
Recipient ethnicity US black (vs. white)	↑↑		↑↑↑					
Recipient Hispanic (vs. non-Hispanic)	↓↓	NA		NA		NA	NA	NA
Recipient diabetes (vs. no diabetes)	↑						↔[b]	
HLA mismatches								
Any number of ABDR (vs. 0)	↑↑↑							
Any number of AB (vs. 0)								↑↑↑
Any number of DR (vs. 0)			↑↑↑		↑↑↑	↑↑↑	↑↑↑	↑↑↑
Per each ABDR mismatch		↔						
4–6 ABDR (vs. 3–1)				↔				
Panel reactive antibody status				NA			↔	
>0% (vs. 0%)								↑↑↑
>15% (vs. ≤15%)		↑						
>50% (vs. ≤50%)					↑↑↑			
Cold ischemia time								
>24 h (vs. <24 h)	↑↑			↑↑↑		NA		
Per hour		↔				NA	↔	↔
DGF (vs. none)		↑↑↑		↑↑↑	↑↑↑		↑↑↑	
CMV disease (vs. none)								↑↑↑[c]
CMV infection (vs. none)		↑↑[d]						↑↑↑[e]
Recipient size								
BMI ≥35 kg/m^2	↑↑↑							
Body weight				↔				
Prior transplantation		↔			↔		↔	↔

Alto riesgo de rechazo agudo o de DGF

Table 1. Eligibility Criteria According to Allograft Cold-Ischemia Time.*

Duration of Cold Ischemia	Required Risk Factors
<16 Hr, or ≤30 hr and any machine perfusion	If donor had a heartbeat, the donor had to be older than 50 yr or have a serum creatinine level >2.5 mg/dl (220 μmol/liter); if donor did not have a heartbeat, no further recipient risk factors required†
16–24 Hr	One donor or recipient risk factor†
>24 Hr	No additional risk factors required
>30 Hr and some machine perfusion	No additional risk factors required

* All information available before transplantation was considered.
† Donor risk factors were cold ischemia for more than 24 hours, donor age older than 50 years, donor without a heartbeat, donor with acute tubular necrosis, and donor requiring high-dose inotropic support. Recipient risk factors were repeated transplantation, panel-reactive antibody value exceeding 20% before transplantation, black race, and one or more HLA antigen mismatches with the donor.

- Seguimiento 12 meses
- Pacientes USA (N=183) y Europa (N=95)
- Anti CD25 *vs* rATG (1,5 mg/Kg/día * 5 días)

Brennan DC, et al. New England Journal of Medicine. 2006 Nov 9;355(19):1967–77.

Alto riesgo de rechazo agudo o de DGF

Table 3. Efficacy End Points 12 Months after Transplantation.

End Point	Antithymocyte Globulin (N=141)	Basiliximab (N=137)	P Value
	no. of patients (%)		
Composite of acute rejection, delayed graft function, graft loss, and death	71 (50.4)	77 (56.2)	0.34
Biopsy-proven acute rejection	22 (15.6)	35 (25.5)	0.02
No. of black recipients/total no. of such recipients	8/41 (19.5)	13/39 (33.3)	0.14
No. of nonblack recipients/total no. of such recipients	14/100 (14.0)	22/98 (22.4)	0.07
No. of recipients in United States/total no. of such recipients	13/91 (14.3)	21/92 (22.8)	0.07
No. of recipients in Europe/total no. of such recipients	9/50 (18.0)	14/45 (31.1)	0.12
Antibody-treated acute rejection	2 (1.4)	11 (8.0)	0.005
Delayed graft function	57 (40.4)	61 (44.5)	0.54
Graft loss	13 (9.2)	14 (10.2)	0.68
From death	4 (2.8)	3 (2.2)	
From acute rejection	1 (0.7)	1 (0.7)	
From primary nonfunction	1 (0.7)	4 (2.9)	
From graft thrombosis	0	4 (2.9)	
From chronic rejection	2 (1.4)	1 (0.7)	
From infection	1 (0.7)	1 (0.7)	
From toxic effects of cyclosporine	1 (0.7)	0	
From recurrent disease	1 (0.7)	0	
From hypertension	1 (0.7)	0	
From urinary fistula	1 (0.7)	0	
Death	6 (4.3)	6 (4.4)	0.90
From cardiovascular disease	2 (1.4)	5 (3.6)	
From pulmonary disease	1 (0.7)	1 (0.7)	
From gastrointestinal disease	2 (1.4)	0	
From unknown cause	1 (0.7)	0	

Table 4. Frequency of Adverse Events at 12 Months.*

Adverse Event	Antithymocyte Globulin (N=141)	Basiliximab (N=137)	P Value
	no. of patients (%)		
Total events	140 (99.3)	135 (98.5)	0.62
Serious events	103 (73.0)	99 (72.3)	0.89
Leukopenia	47 (33.3)	20 (14.6)	<0.001
Thrombocytopenia	15 (10.6)	8 (5.8)	0.19
All infections	121 (85.8)	103 (75.2)	0.03
Urinary tract	55 (39.0)	37 (27.0)	0.04
Probable bacterial or other	87 (61.7)	70 (51.1)	0.09
Confirmed bacterial	74 (52.5)	51 (37.2)	0.01
Cytomegalovirus	11 (7.8)	24 (17.5)	0.02
Viral other than cytomegalovirus	30 (21.3)	16 (11.7)	0.04
Fungal	20 (14.2)	20 (14.6)	1.00
Protozoal	0	1 (0.7)	0.49
Cancer	5 (3.5)	1 (0.7)	0.21
Post-transplantation lymphoproliferative disease	3 (2.1)	0	0.13
Renal-cell carcinoma in native kidney	1 (0.7)	1 (0.7)	1.00
Cutaneous squamous-cell carcinoma	1 (0.7)	0	1.00

CONCLUSIONS

Among patients at high risk for acute rejection or delayed graft function who received a renal transplant from a deceased donor, induction therapy consisting of a 5-day course of antithymocyte globulin, as compared with basiliximab, reduced the incidence and severity of acute rejection but not the incidence of delayed graft function. Patient and graft survival were similar in the two groups. (ClinicalTrials.gov number, NCT00235300.)

Brennan DC, et al. New England Journal of Medicine. 2006 Nov 9;355(19):1967–77.

Continuación a 10 años (NEJM)

Seguimiento a largo plazo de pacientes de USA (N=183)

RESEARCH Open Access

Long-term safety and efficacy of antithymocyte globulin induction: use of integrated national registry data to achieve ten-year follow-up of 10-10 Study participants

Krista L. Lentine[1,2,4*], Mark A. Schnitzler[2], Huiling Xiao[1,2] and Daniel C. Brennan[3]

	rATG %	Basiliximab %	*P*
Outcomes at 1 year			
Acute rejection	14.3 %	22.8 %	0.08
Patient survival	94.5 %	95.7 %	0.74
All-cause graft survival	89.0 %	85.9 %	0.47
Freedom from acute rejection, graft failure or death	80.0 %	68.5 %	0.04
Any malignancy	1.1 %	1.1 %	0.99
Post-transplant lymphoproliferative disorder	0	0	1.00
Non-melanoma skin cancer	1.1 %	0	0.31
Non-skin cancer	0	1.1 %	0.32

Outcomes at 5 years			
Acute rejection	21.0 %	32.8 %	0.07
Patient survival	72.5 %	75.0 %	0.64
All-cause graft survival	67.5 %	60.6 %	0.32
Freedom from acute rejection, graft failure, or death	57.6 %	44.2 %	0.04
Any malignancy	4.5 %	4.5 %	0.97
Post-transplant lymphoproliferative disorder	1.1 %	0	0.31
Non-melanoma skin cancer	2.3 %	1.1 %	0.54
Non-skin cancer	2.3 %	3.3 %	0.67

Outcomes at 10 years			
Acute rejection	21.0 %	32.8 %	0.07
Patient survival	52.8 %	52.2 %	0.92
All-cause graft survival	34.3 %	30.9 %	0.56
Freedom from acute rejection, graft failure, or death	32.6 %	24.0 %	0.09
Any malignancy	9.5 %	8.1 %	0.75
Post-transplant lymphoproliferative disorder	2.2 %	0	0.15
Non-melanoma skin cancer	3.6 %	1.1 %	0.30
Non-skin cancer	6.0 %	6.9 %	0.79

La inducción con rATG es superior a Basiliximab a los 5 años postrasplante para el triple objetivo de rechazo agudo, fallo del injerto o muerte. A los 10 años postrasplante la inducción con rATG es comparable en eficacia y seguridad a Basiliximab (no inferioridad).

Lentine KL, et al. Trials. 2015 Aug 19;16(1).

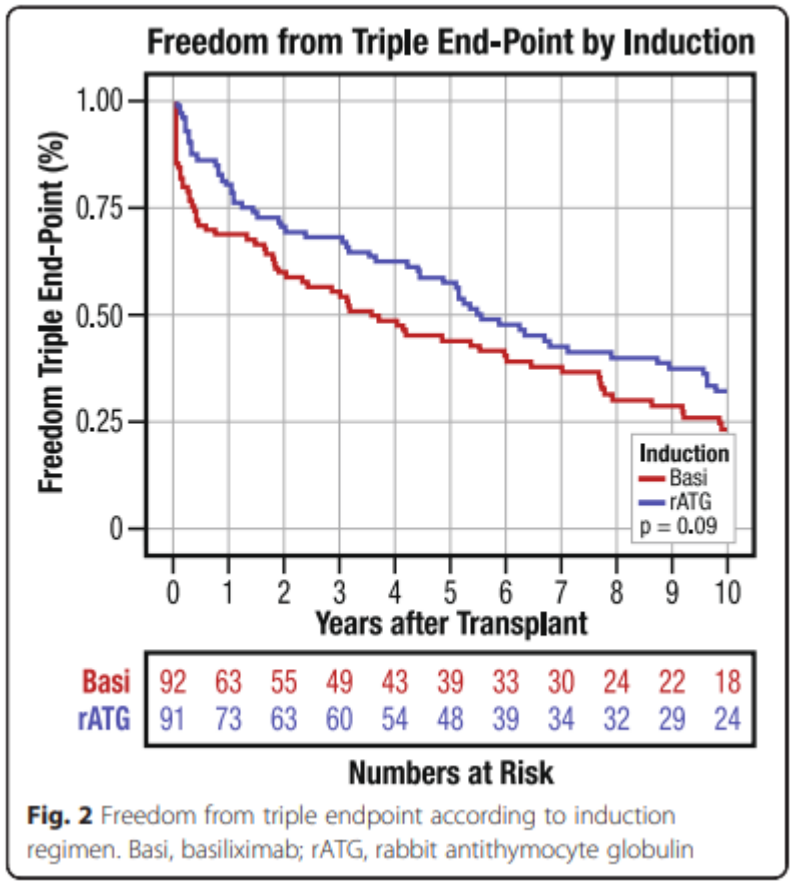
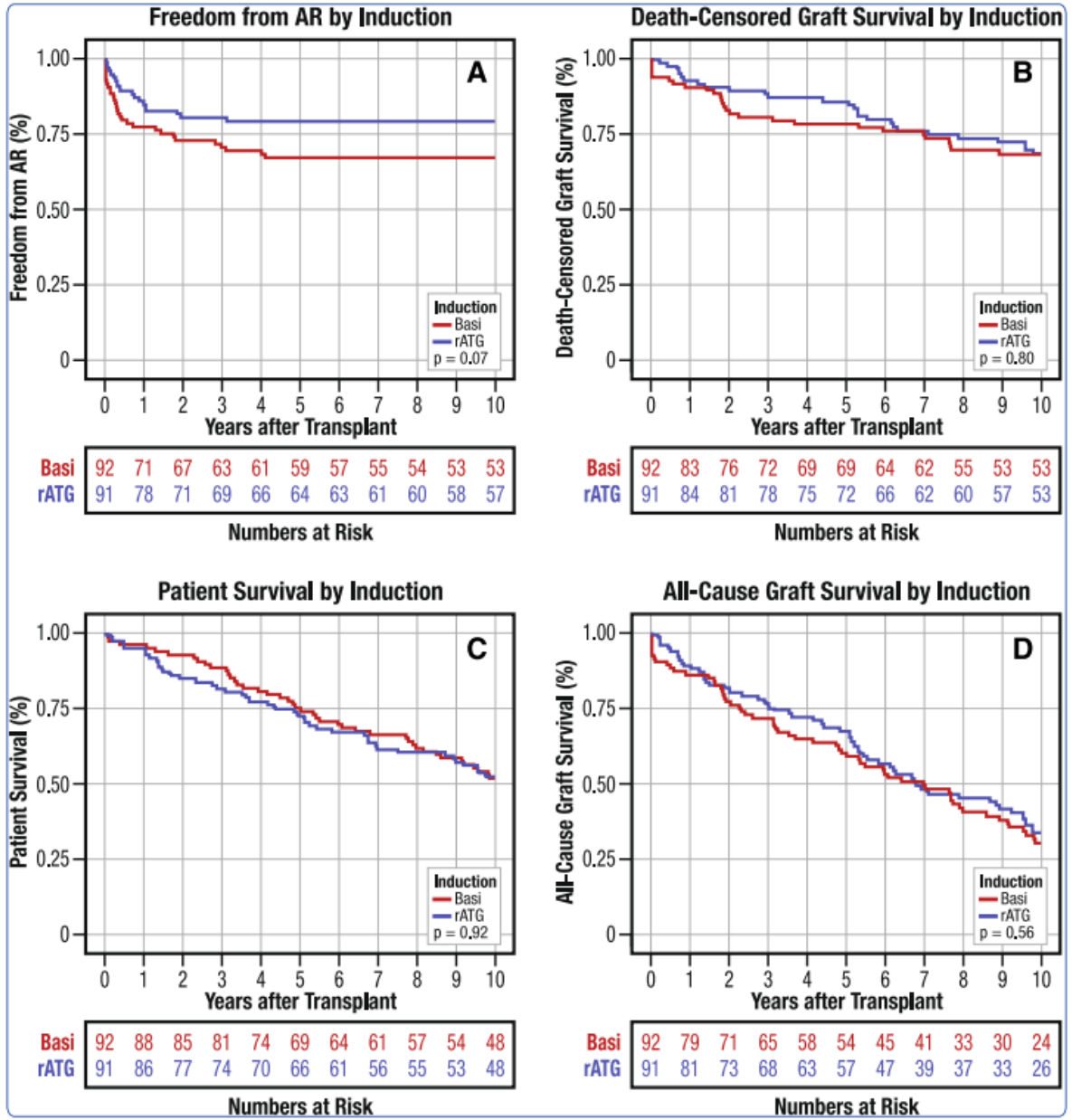


Fig. 2 Freedom from triple endpoint according to induction regimen. Basi, basiliximab; rATG, rabbit antithymocyte globulin



Lentine KL, Schnitzler MA, Xiao H, Brennan DC. Long-term safety and efficacy of antithymocyte globulin induction: use of integrated national registry data to achieve ten-year follow-up of 10-10 Study participants [published correction appears in Trials. 2015;16:412]. Trials. 2015;16:365.

Donantes con criterios expandidos

ELSEVIER

Safety and Efficacy of Induction Treatment with Low Thymoglobulin Doses in Kidney Transplantation from Expanded-Criteria Donors

A. Sancho Calabuig*, E. Gavela Martínez, J. Kanter Berga, S. Beltrán Calatán, A.I. Avila Bernabeu, and L.M. Pallardó Mateu

Hospital Universitario Dr Peset, Valencia, Spain

Estudio retrospectivo:

- Dosis timo = 1-3 dosis de 1,25 mg/kg por protocolo
- Profilaxis CMV 3 meses ambos brazos
- Resultados:
  - menos rechazos agudos con ATG
  - Mayor incidencia CMV con ATG
  - Incidencia similar de neoplasias
  - No diferencias en supervivencia de paciente e injerto a los 2 años

Table 1. Demographics Characteristics of Studied Groups

	Thymoglobulin (n = 162)	Basiliximab (n = 159)	P Value
Follow-up (mo)	76.6 ± 41.34	70.02 ± 43.45	.131
Recipient age (y)	56.7 ± 11.94	54.8 ± 11.55	.479
Recipient sex (male)	103 (64.8)	86 (53.1)	.033
Donor age (y)	58.4 ± 14.05	56.8 ± 13.41	.284
Donor sex (male)	85 (54.5)	94 (58)	.525
Cerebrovascular donor death	113 (72.4)	105 (65.6)	.191
Donor >70 y	44 (25.3)	22 (13.8)	.010
Donor serum creatinine (mg/dL)	1.01 ± 0.62	0.86 ± 0.28	.006
HLA mismatches	3.8 ± 1.05	3.5 ± 0.99	.022
Retransplantation	2 (1.3)	7 (4.6)	.100
Cold ischemia time (h)	19.7 ± 8.43	19.8 ± 8.20	.929
Main immunosuppressant drug			.015
Tacrolimus	129 (76.2)	133 (87.1)	
Cyclosporine	39 (23.8)	20 (12.9)	
Delayed graft function	62 (40)	81 (48.8)	.308
Acute rejection	19 (11.4)	34 (22.1)	.010
Neoplasia	35 (22)	42 (25.9)	.412
Non-skin cancer and melanoma	17 (10.7)	18 (11.1)	.904
CMV infection	42 (29.2)	59 (40.4)	.044
Infectious hospitalizations	57 (39)	68 (48.2)	.117

Note. Values are presented as mean ± SD or n (%).

Conclusions. Induction with low doses of antithymocyte globulin resulted in a lower incidence of acute rejection with graft and patient survivals similar to that obtained with basiliximab induction, in spite of a worse donor profile. CMV disease was more frequent with antithymocyte globulin, without an increase of infectious hospitalizations or cancer development, in long-term follow-up.

Sancho Calabuig A, et al. Transplantation Proceedings. 2015 Jan;47(1):50–3.

Donantes de edad avanzada

ELSEVIER

Induction Treatment With Low-Dose Thymoglobulin or Basiliximab in Renal Transplants From Older Donors

E. Gavela Martínez, A. Sancho Calabuig, V. Escudero Quesada, A.I. Ávila Bernabeu, S. Beltrán Catalán, A.I. Morales García, J.F. Crespo Albiach, and L.M. Pallardó Mateu

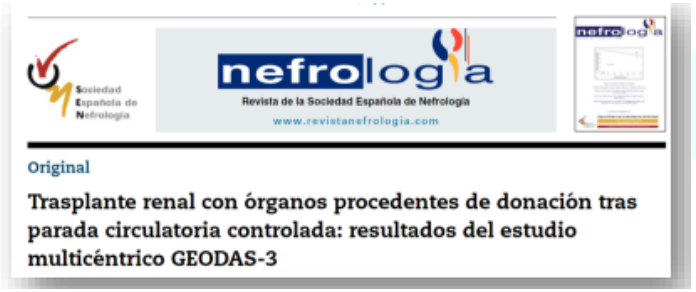
Estudio retrospectivo:

- N=63 (27 ATG vs 36 BSX) con edad media donantes 63 años y receptores 61 años.
- Dosis timo = 1,25 mg/kg en D0 y D2
- **Resultados** a 3 años:
  - Tendencia a menor DGF con timoglobulina → 33% vs 55,6% (P = 0.08)
  - 0% rechazo agudo con timoglobulina vs 30,6% con basiliximab
  - Similar incidencia de CMV (15% vs 14,3%), neoplasias o readmisiones por infecciones
  - Menor estancia hospitalaria tras trasplante con timoglobulina (13 vs 16 días)

<u>Conclusiones</u>: Bajas dosis de timoglobulina son más efectivas que Basiliximab evitando rechazo agudo y, probablemente el DGF, sin diferencias en complicaciones infecciosas o supervivencia del injeto y del paciente

Gavela Martínez E, et al. Transplantation Proceedings. 2008 Nov;40(9):2900–2.

Donante en asistolia controlada



- Análisis retrospectivo multicéntrico (N=335)
- Inducción 99,7%. 67,4% timoglobulina y 32,6% basiliximab
- Incidencia de 3,4% de fallo primario del injerto, y 48,8% de DGF (a pesar de inducción e introducción retrasada de ICN)
- Se asocian a DGF: tiempo isquemia caliente > 14h, hemodiálisis frente a diálisis peritoneal, edad del donante

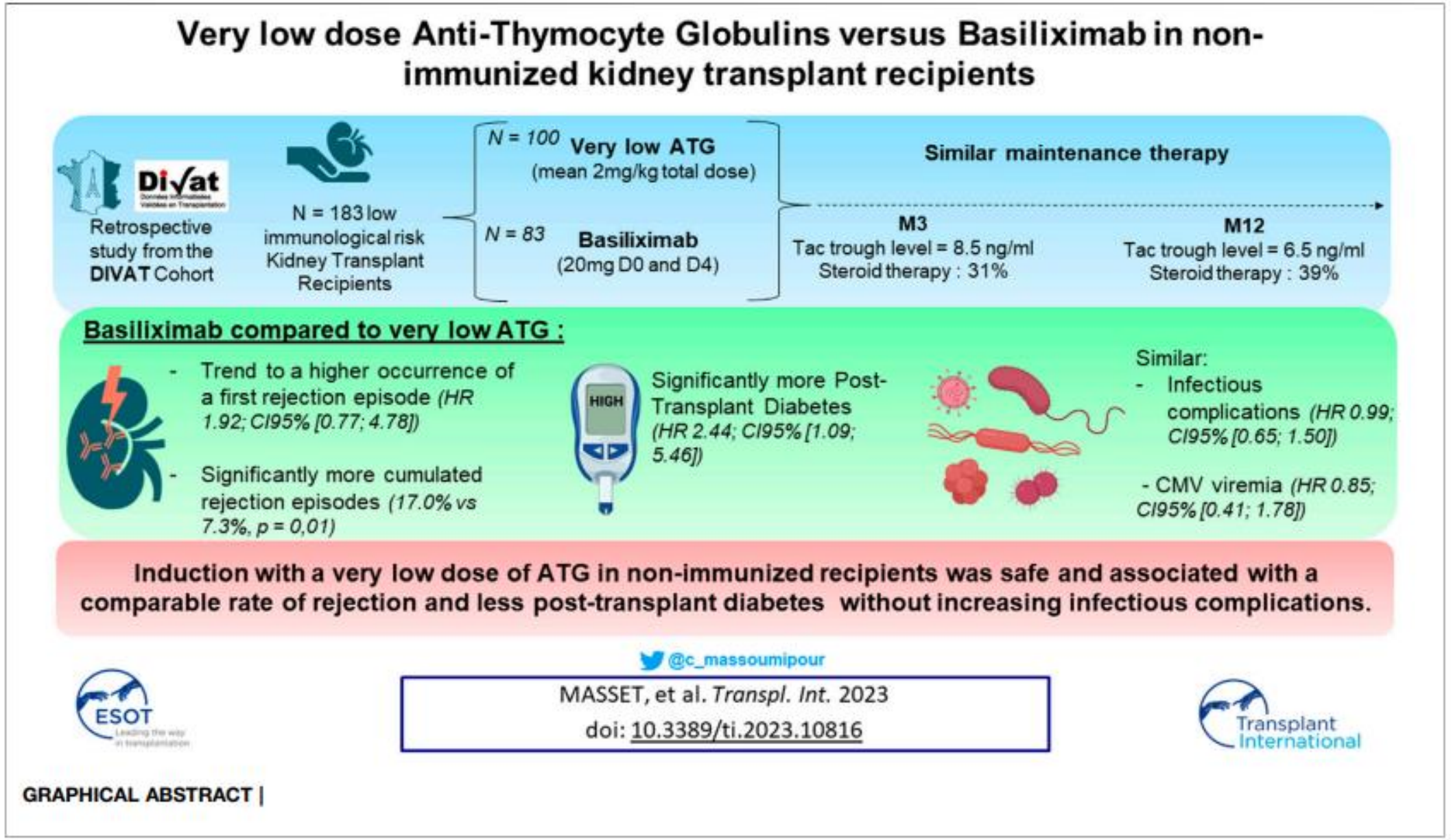
Tabla 1 – Características basales de los donantes, receptores y datos relevantes del proceso del trasplante

Donantes	n = 335
Edad en años, media (DE)	57,2 (12,0)
Hombre (%)	69,1
Donante con criterios expandidos (%)	45,9
Causa de muerte cardiovascular (%)	55,3
Receptores	**n = 566**
Edad en años, media (DE)	56,5 (12,0)
Edad > 65 años (%)	24,1
Hombres (%)	68,4
Diabetes mellitus (%)	32,1
Evento cardiovascular previo (%)	10,8
Etiología de la ERC (%)	
Glomerulonefritis	17,5
Nefropatía hipertensiva	12,2
Nefropatía diabética	13,8
Intersticial	11,1
Poliquistosis	14,5
Otras	10,3
Desconocida	20,7
Terapia renal previa (%)	
Hemodiálisis/diálisis peritoneal	75,4 / 19,7
Trasplante en prediálisis	4,9
Tiempo previo en diálisis en años, mediana (IQR)	2,02 (1,19-3,57
Pacientes sin trasplante previo (%)	91,9
Características del trasplante	
Número de incompatibilidades HLA, media (DE)	3,9 (1,3)
Isquemia fría en horas, media (DE)	12,3 (6,5)
Isquemia caliente en minutos, media (DE)	26,5 (15,6)
Inducción (timoglobulina/basiliximab) en %	67,4/32,6
Seguimiento en años, media	1,9

DE: desviación estándar; DM: diabetes mellitus; DP: diálisis peritoneal; ERC: enfermedad renal crónica; HD: hemodiálisis; HLA: antígeno leucocitario humano; IQR: intervalo intercuartílico.

Portolés JM, Pérez-Sáez MJ, López-Sánchez P, et al. Kidney transplant from controlled donors following circulatory death: Results from the GEODAS-3 multicentre study. Trasplante renal con órganos procedentes de donación tras parada circulatoria controlada: resultados del estudio multicéntrico GEODAS-3. Nefrologia (Engl Ed). 2019;39(2):151-159.

Receptores de bajo riesgo inmunológico



Masset C, et al. Transplant International. 2023 Feb 3;36.

Revisión sistemática y metaanálisis

- **<u>Trasplante estándar</u>**:
  - ATG reduce el rechazo agudo
  - Mejor supervivencia del injerto a 3-5 años con ATG
  - ATG aumenta incidencia CMV.
  - No diferencias en dosis estándar de ATG 6 mg/Kg frente a dosis más bajas (1,5-5 mg/Kg). No diferencias en administración fraccionada frente a dosis única.

- **<u>Trasplante alto riesgo rechazo</u>**:
  - ATG reduce riesgo rechazo agudo
  - No diferencia en DGF.
  - No se precisa dosis acumulativa timoglobulina >7 mg/Kg

- **<u>Trasplante alto riesgo DGF</u>**:
  - No diferencias de DGF entre ambos tratamientos (ATG vs IL2RA).
  - ATG permite introducción retrasada de ICN

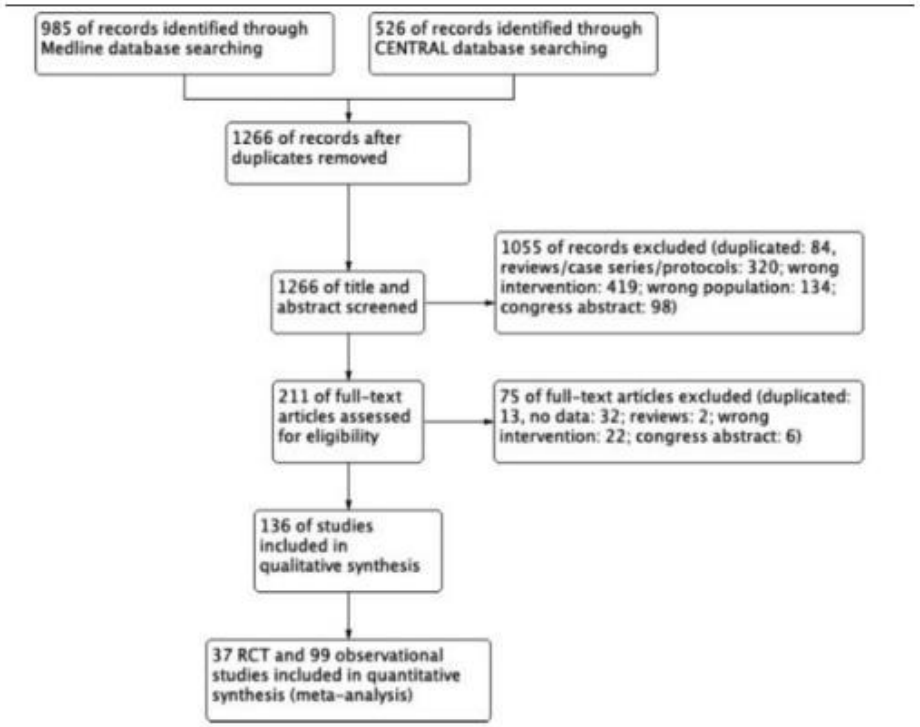
- **<u>Trasplante donante vivo</u>**:
  - Tendencia a menor rechazo agudo con timoglobulina (p=0.19).
  - No diferencias en DGF, función renal, nefropatía BK o DSA de novo.

- **<u>Trasplante receptor añoso</u>**: no datos concluyentes sobre mejor opción de terapia de inducción.


Transplantation Reviews

Review article

The use of lymphocyte-depleting antibodies in specific populations of kidney transplant recipients: A systematic review and meta-analysis



Montero N et al. Transplantation Reviews. 2023 Dec;37(4):100795.

PERFILES DE RECEPTOR. Terapia de inducción: ¿a quién?

Table 1 Risk stratification for selection of immunosuppression in kidney transplantation

Risk Type	Low	Medium	High	Possible Strategy
Immunological	0-DR mismatch First graft Unsensitised Recipient >60	1-DR mismatch Afro-Caribbean recipient Historical DSAs NDSAs DGF Older donor [45]	2-DR mismatch Previous early immunological graft loss DSAs ABO-incompatible Sensitised (high CRF/PRA) Preoperative anti-ATIIR Abs [117]	Increase total immunosuppressive load
Metabolic	Low BMI Age <40 Normal pre-Tx GTT	Positive family history ADPKD	Impaired GT BMI >35 HCV positive Age >60 Previous CVD Race	Avoid/minimise steroids and tacrolimus
Neoplastic	Age <40	Pre-malignant lesion	Previous cancer Hereditary syndrome e.g. VHL	Consider low immunosuppression load or sirolimus
Ischaemia-reperfusion injury	Living donor Deceased donor <40	CIT >12 h Donor aged 50–60	DCD CIT > 24 h Extended criteria donor	Reduce CNI exposure
Non-adherence			Poor RRT compliance Age <20 Transition from paediatric to adult	Education Simple drug regime alemtuzumab or belatacept

Baker RJ, Mark PB, Patel RK, Stevens KK, Palmer N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. BMC Nephrol. 2017;18(1):174. Published 2017 Jun 2. doi:10.1186/s12882-017-0553-2

Riesgo cardiometabólico

TABLA 1. Definición de las alteraciones del metabolismo de la glucosa y su frecuencia [4] [30].
SOG: Sobrecarga oral de glucosa.

Criterios Diagnósticos	Frecuencia
Diabetes Mellitus Postrasplante:	
• Glucemia en ayunas ≥126 mg/dl en más de una ocasión	28% a los 3 meses
• Glucemia al azar ≥200 mg/dl con síntomas	19% al año
• Glucemia a las 2 horas de una SOG ≥200 mg/dl	30% a los 3 años
Intolerancia a la Glucosa:	
• Glucemia 2h tras test TOG ≥140 y <200 mg/dl	18% al año y 19% a 3 años
Glucemia basal alterada: Glucemia en ayunas ≥100 y <126 mg/dl	11% (aislada o combinada con intolerancia a la glucosa)
Síndrome Metabólico: Obesidad central, disminución de HDL-c, hipertrigliceridemia, glucemia basal alterada, hipertensión arterial (3 de 5 criterios)	38% a los 3 años

Figura 1. Incidencia de Diabetes Postrasplante renal [4]

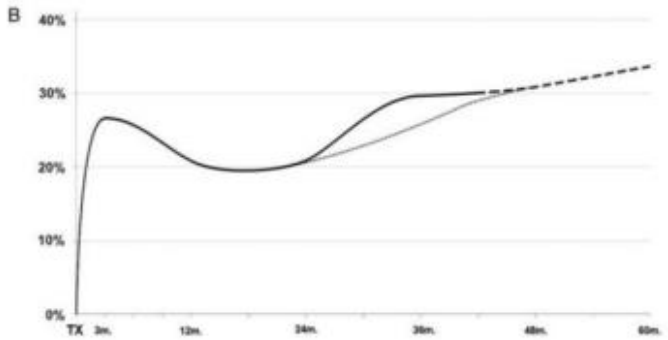


Figura 1.

Figura 2. Patogénesis de la Diabetes Postrasplante Renal.
ACN: Anticalineurínicos. Tacro: Tacrolimus; CsA: Ciclosporina A

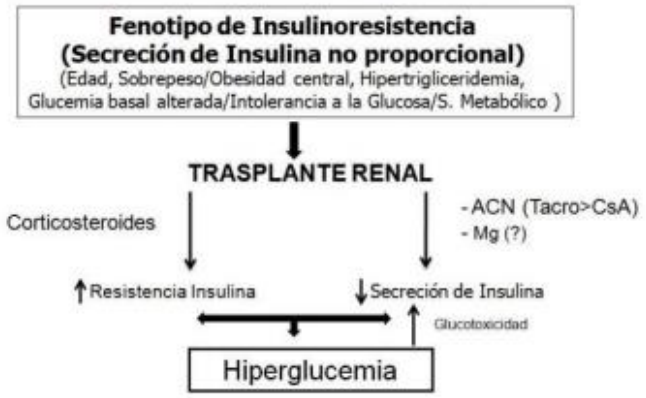


TABLA 2. Factores de riesgo de Diabetes Postrasplante Renal.
*** Comunes a la Diabetes tipo 2.**

PRETRASPLANTE	POSTRASPLANTE
Edad*	Inmunosupresión:
Sobrepeso/Obesidad central*	• Dosis acumulada de corticosteroides
Historia familiar*	• Anticalcineurínicos (Tacrolimus > CsA)
Hipertrigliceridemia*	• Inhibidores mTOR.
Glucemia basal alterada*	Hipomagnesemia
Intolerancia a la glucosa*	Infección por CMV (otras infecciones)
Síndrome Metabólico*	
Infección por Virus C*	
Raza (negra, hispana)*	
Poliquistosis renal	
Hipomagnesemia	
Polimorfismos genéticos relacionados	

La inmunosupresión explica el 75% del riesgo de desarrollar DPT → buscar equilibrio entre riesgo de desarrollarla y aumento riesgo de rechazo

Torres Ramírez A, Rodríguez Rodríguez AE, Porrini E. Diabetes tras el Trasplante Renal.En: Lorenzo V., López Gómez JM (Eds). Nefrología al día. ISSN: 2659-2606. Disponible en: https://www.nefrologiaaldia.org/298

Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial

Oliver Thomusch, Michael Wiesener, Mirian Opgenoorth, Andreas Pascher, Rainer Peter Woitas, Oliver Witzke, Bernd Jaenigen, Markus Rentsch, Heiner Wolters, Thomas Rath, Tülay Cingöz, Urs Benck, Bernhard Banas, Christian Hugo†

- Pacientes de "bajo riesgo inmunológico": compatibilidad AB0, CDC, no DSA, y PRA como mucho del 30%
- 3 brazos, timo (1,5 mg/Kg x 4 días) o BSX + Tac + MMF + prednisolona
- Brazo estándar: prednisolona el día de la cirugía (día 0) y disminución gradual según el estándar institucional con el requisito de alcanzar una dosis de 10 mg de prednisolona por día después de 4 semanas y una dosis de mantenimiento de 2,5 a 5,0 mg por día después 3 meses.
- Brazos retirada rápida: se retiraron los corticosteroides a partir del día 8. Por lo tanto, 500 mg de prednisolona el día 0 fueron seguidos por 100 mg el día 1, 75 mg el día 2, 50 mg el día 3 y 25 mg por día los días 4 a 7

	Arm A: basiliximab plus steroids (n=206)	Arm B: basiliximab plus rapid steroid withdrawal (n=189)	Arm C: rabbit ATG plus rapid steroid withdrawal (n=192)	Total (n=587)
Age (years)	54·5 (1·0)	54·0 (12·8)	53·6 (11·9)	54·1 (1·2)
Men	141 (68%)	122 (65%)	124 (65%)	387 (66%)
Caucasian	205 (100%)	186 (98%)	188 (98%)	579 (99%)
Cause of end-stage renal disease				
Hypertension or large vessel disease	77 (37%)	71 (38%)	69 (36%)	217 (37%)
Glomerulonephritis	57 (28%)	56 (30%)	48 (25%)	161 (27%)
Polycystic kidney disease (adult type, dominant)	43 (21%)	34 (18%)	36 (19%)	113 (19%)
Diabetes	27 (13%)	16 (8%)	19 (10%)	62 (11%)
Interstitial nephritis or pyelonephritis	16 (8%)	15 (8%)	13 (7%)	44 (7%)
Secondary glomerulonephritis or vasculitis	3 (1%)	7 (4%)	1 (1%)	11 (2%)
Other hereditary or congenital diseases	14 (7%)	4 (2%)	6 (3%)	24 (4%)
Neoplasms or tumours	3 (1%)	1 (1%)	3 (2%)	7 (1%)
Other	61 (30%)	59 (31%)	69 (36%)	189 (32%)
Undefined cause	10 (5%)	25 (13%)	18 (9%)	53 (9%)
Type of donor				
Deceased	174 (84%)	169 (89%)	168 (88%)	511 (87%)
Living	32 (16%)	20 (11%)	24 (13%)	76 (13%)
Donors with expanded criteria†	90 (44%)	86 (46%)	84 (44%)	260 (44%)
Donor age (years)	54·0 (14·6)	55·0 (14·4)	53·1 (15·1)	54·0 (14·7)
Antigen mismatches: A, B, and DR‡	0·8, 1·0, 0·9	0·8, 1·0, 0·8	0·8, 1·0, 0·9	0·8, 1·0, 0·9
No panel-reactive antibodies before transplantation	177 (86%)	168 (89%)	172 (90%)	517 (88%)
Previous transplants	11 (5%)	6 (3%)	6 (3%)	23 (4%)
Cold-ischaemia time: deceased donors only (min)	699 (269)	702 (295)	732 (303)	710 (289)
Cytomegalovirus serologic status: donor positive, recipient negative	51 (25%)	47 (25%)	50 (26%)	148 (25%)
Epstein-Barr virus serological status: donor positive, recipient negative	10 (5%)	11 (6%)	8 (4%)	29 (5%)

Thomusch O, et al. The Lancet. 2016 Dec;388(10063):3006–16.

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	Arm A: basiliximab plus steroids (n=206)	Arm B: basiliximab plus rapid steroid withdrawal (n=189)	Arm C: rabbit ATG plus rapid steroid withdrawal (n=192)	p value
Primary endpoint				
Acute rejection at 12 months				
Biopsy proven (excluding borderline rejection)	23 (11%)	20 (11%)	19 (10%)	..
Arm A versus arm C	..	..	..	0·75
Arm B versus arm C	..	..	..	0·87
Steroid-resistant rejection*	4 (2%)	5 (3%)	4 (2%)	0·88
Banff classification 2005				
Acute T-cell-mediated 1A	8 (4%)	9 (5%)	5 (3%)	
Acute T-cell-mediated 1B	1 (<1%)	1 (1%)	1 (1%)	..
Acute T-cell-mediated 2A	7 (3%)	7 (4%)	2 (1%)	..
Acute T-cell-mediated 2B	..	1 (1%)	1 (1%)	..
Acute antibody-mediated 1	2 (1%)	1 (1%)	2 (1%)	..
Acute antibody-mediated 2	1 (<1%)	1 (1%)	1 (1%)	..
Acute antibody-mediated 3	..	..	..	..
Secondary endpoints				
Patient survival at year 1*	195 (95%)	184 (97%)	186 (97%)	0·32
Death censored allograft survival at year 1*	198 (96%)	183 (97%)	184 (96%)	0·87
Graft loss or death at year 1*	18 (9%)	11 (6%)	13 (7%)	0·52
Malignancies*	5 (2%)	2 (1%)	5 (3%)	0·58
Post-transplant lymphoproliferative disease*	..	..	1 (1%)	0·65
Steroids at 1 year†	185 (90%)	31 (16%)	33 (17%)	0·87
Mean glomerular filtration rate (mL/min)				
Cockcroft-Gault‡	57·3 (22·5)	58·0 (22·6)	62·9 (23·5)	0·10
CKD-EPI equation‡	46·3 (19·5)	47·4 (19·8)	50·2 (20·4)	0·25
Cardiovascular risk factors				
Cholesterol (mmol/L)§	5·2	4·9	5·0	0·13
HDL cholesterol (mmol/L)§	1·3	1·2	1·2	0·0155
LDL cholesterol(mmol/L)§	3·1	2·9	3·0	0·06
Triglycerides (mmol/L) §	2·1	1·9	2·2	0·49
Body-mass index change from baseline (kg/m²)§	+0·1	−0·2	−0·2	0·25
Bodyweight change from baseline (kg)§	+0·3	−0·6	−0·4	0·27
Mean systolic blood pressure (mmHg)§	134·6	134·7	135·8	0·80
Mean diastolic blood pressure (mmHg)§	77·8	76·9	78·9	0·95
Anaemia*	55 (27%)	73 (39%)	67 (35%)	0·0164
ESA drug (erypoetin) *	76 (37%)	88 (47%)	92 (48%)	0·0185
Anaemia and ESA drug*	22 (11%)	44 (23%)	41 (21%)	0·0005
Cataract*	2 (1%)	3 (2%)	..	1·00
Osteoporosis*	24 (12%)	10 (5%)	12 (6%)	0·0220
Fractures*	2 (1%)	..	..	0·12
Avascular necrosis*	..	..	1 (1%)	1·00
Wound-healing disorder*	14 (7%)	6 (3%)	9 (5%)	0·16

(Table 2 continues on next page)

	Arm A: basiliximab plus steroids (n=206)	Arm B: basiliximab plus rapid steroid withdrawal (n=189)	Arm C: rabbit ATG plus rapid steroid withdrawal (n=192)	p value
(Continued from previous page)				
Infections				
Infections*	106 (51%)	108 (57%)	104 (54%)	0·53
Opportunistic infection*	71 (34%)	59 (31%)	59 (31%)	0·69
Non-opportunistic infection*	61 (30%)	71 (38%)	69 (36%)	0·20
Cytomegalovirus infection*	43 (21%)	39 (21%)	38 (20%)	0·96
BK virus infection*	26 (13%)	14 (7%)	21 (11%)	0·21
Epstein-Barr virus infection*	6 (3%)	2 (1%)	7 (4%)	0·25

Data are n (%) or mean (SD), unless otherwise stated. The intention-to-treat population consists of all patients who received at least one dose of a study drug. The calculated GFR was determined from the serum creatinine level with the use of the Cockcroft-Gault formula or the CKD-EPI equation to calculate the creatinine clearance. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. ESA=erythropoiesis-stimulating agent. *Fisher´s exact test: p value calculated for study arm A vs B vs C. †Fisher´s exact test: p value calculated for study arm B vs C. ‡Student's t test: p value calculated for study arm A vs B vs C. §Student's t test: p values calculated for study arm A vs B and C.

Table 2: **Primary endpoint and selected secondary endpoints at 1 year**

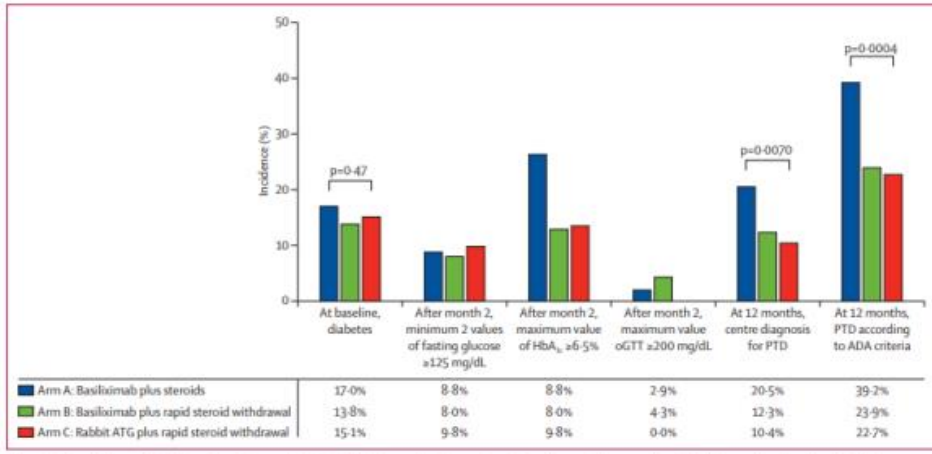

Figure 3: **Cumulative probability of post-transplantation diabetes mellitus from two to twelve months according to all diagnostic criteria and study group**
Excluding renal transplant recipients with the diagnosis of diabetes at baseline (left column), the cumulative incidence of the diagnosis of post-transplantation diabetes according to all criteria (fasting glucose, oGTT, HbA_{1c} value) starting 2 months after transplantation and ending at 12 months is reported. Interestingly,

- **No se observaron diferencias en el rechazo agudo, supervivencia del injerto y del receptor entre las 3 ramas.**
- **Menor desarrollo de diabetes y osteoporosis con la retirada precoz de esteroides.**

Thomusch O, et al. The Lancet. 2016 Dec;388(10063):3006–16.

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Advance access publication date: 30 June 2023

Excellent efficacy and beneficial safety during observational 5-year follow-up of rapid steroid withdrawal after renal transplantation (Harmony FU study)

Table 3: Efficacy endpoints at 3 and 5 years after transplantation.

Variable groups	Category	3 year rates[a] Arm A: basiliximab/ steroids	3 year rates[a] Arm B: basiliximab/ RSWD	3 year rates[a] Arm C: rATG/ RSWD	5 year rates[a] Arm A: basiliximab/ steroids	5 year rates[a] Arm B: basiliximab/ RSWD	5 year rates[a] Arm C: rATG/ RSWD	P-value[b]
BPAR	% (*N* + new events)[c]	14.7 (23 + 3)	12.4 (20 + 1)	13.2 (19 + 2)	14.7 (26)	14.5 (21 + 2)	13.2 (21)	.932
BPAR including borderlines	% (*N* + new events)[c]	19.4 (34 + 2)	17.8 (28 + 2)	19.6 (27 + 5)	19.4 (36)	20.8 (30 + 3)	20.7 (32 + 1)	.987
Patient survival	% (*N* + new events)	89.2 (11 + 7)	95.1 (4 + 3)	93.4 (6 + 3)	84.7 (18 + 7)	89.4 (7 + 6)	90.4 (9 + 5)	.178
Death-censored graft survival	% (*N* + new events)	95.8 (8 + 0)	96.6 (6 + 0)	95.3 (8 + 0)	94.9 (8 + 1)	93.0 (6 + 3)	91.4 (8 + 5)	.477
Patient and graft survival	% (*N* + new events)	85.8 (18 + 7)	92.7 (10 + 2)	89.5 (13 + 3)	80.7 (25 + 8)	84.0 (12 + 9)	83.2 (16 + 10)	.448

[a]Estimated by Kaplan–Meier method.

Table 4: Cox regression analysis for time to death from any cause.

Risk factor		Unadjusted models HR	95% CI	P-value	Adjusted model[a] HR	95% CI	P-value
Age (per 10 years)		3.143	(2.163–4.567)	<.001	3.296	(2.094–5.187)	<.001
Sex	Female vs male	1.099	(0.617–1.958)	.750			
Rapid steroid withdrawal	Yes vs no	0.575	(0.330–1.003)	.051	0.554	(0.314–0.976)	.041
Induction therapy	rATG vs basilix.	0.773	(0.411–1.456)	.426			
Time on dialysis (per 6 month)		0.999	(0.958–1.043)	.981	1.047	(1.000–1.095)	.048
Donor with expanded criteria	Yes vs no	2.757	(1.529–4.970)	<.001			
Diabetes mellitus at transplant	Yes vs no	4.818	(2.731–8.498)	<.001	2.968	(1.617–5.447)	<.001
Cardiovascular disease at transplant[b]	Yes vs no	3.391	(1.922–5.981)	<.001	1.876	(1.028–3.426)	.041
Renal anemia at transplant[b]	Yes vs no	0.913	(0.484–1.720)	.778			
Arterial Hypertension at transplant[b]	Yes vs no	0.994	(0.358–2.764)	.991	0.461	(0.159–1.339)	.155
Hyperlipidemia at transplant[b]	Yes vs no	1.792	(1.027–3.129)	.040			
Elevated cholesterol at transplant[b]	Yes vs no	1.333	(0.746–2.381)	.332			
Elevated triglycerides at transplant[b]	Yes vs no	1.363	(0.749–2.482)	.311			

[a]Effect selection by forward selection. Significance level for entering a predictor into the model is 0.20.
[b]According to centre definition and local laboratory references.

Table 2: Safety endpoints at 5 years after transplantation[a].

Variable	Arm A: basiliximab/ steroids *n* = 113	Arm B: basiliximab/ RSWD *n* = 101	Arm C: rATG/ RSWD *n* = 98	FU-ITT[a] *n* = 312	P-value[e]
Infections					
Severe bacterial infections, hospitalization required	29/112 (25.9)	35/101 (34.7)	14/98 (14.3)	78/311 (25.1)	.004
More than one severe bacterial infection	14/112 (12.5)	19/101 (18.8)	8/98 (8.2)	41/311 (13.2)	.086
Invasive opportunistic infection	4/112 (3.6)	7/101 (6.9)	8/98 (8.2)	19/311 (6.1)	.366
Any CMV infection	9/112 (8.0)	10/101 (9.9)	14/98 (14.3)	33/311 (10.6)	.348
Any BKV infection	3/112 (2.7)	2/100 (2.0)	5/98 (5.1)	10/310 (3.2)	.476
BKV viremia	3/112 (2.7)	2/100 (2.0)	5/98 (5.1)	10/310 (3.2)	.476
BKV nephropathy	1/112 (0.9)	0/100 (0.0)	3/98 (3.1)	4/310 (1.3)	.164
Anti-HLA antibodies[b]					
Screening performed	54/113 (47.8)	44/101 (43.6)	45/98 (45.9)	143/312 (45.8)	
All anti-HLA antibodies	7/54 (13.0)	11/44 (25.0)	15/45 (33.3)	33/143 (23.1)	.049
De novo Anti-HLA antibodies	3/54 (5.6)	6/44 (13.6)	9/45 (20.0)	18/143 (12.6)	.087
Donor-specific anti-HLA antibodies	4/54 (7.4)	5/44 (11.4)	5/45 (11.1)	14/143 (9.8)	.825
De novo DSA	0/54 (0.0)	3/44 (6.8)	1/45 (2.2)	4/143 (2.8)	.072
Diverse					
Any cardio- or cerebrovascular event	11/109 (9.7)	14/97 (13.9)	7/96 (7.1)	32/302 (10.3)	.281
Anemia	14/110 (12.7)	16/97 (16.5)	16/96 (16.7)	46/303 (15.2)	.671
Anemia requiring ESA	3/110 (2.7)	10/97 (10.3)	10/96 (10.4)	23/303 (7.6)	.041
Any fracture event	3/109 (2.7)	2/97 (2.0)	3/96 (3.1)	8/302 (2.6)	.910
Weight, relative change[c] (mean ± SD)	1.0 ± 0.13	1.0 ± 0.13	1.0 ± 0.11	1.0 ± 0.13	.190
BMI, relative change[c] (mean ± SD)	1.0 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	.203
PTDM[d]	5/58 (8.6%)	7/76 (9.2%)	4/67 (6.0%)	16/201 (8.0%)	.802
Current immunosuppressive medication					
Corticosteroids	42/109 (38.5)	23/101 (22.8)	21/96 (21.9)	86/306 (28.1)	.012
Tacrolimus	87/109 (79.8)	85/101 (84.2)	81/96 (84.4)	253/306 (82.7)	.626
MMF/MPA	87/109 (79.8)	82/101 (81.2)	83/96 (86.5)	252/306 (82.4)	.444
mTOR inhibitors	7/109 (6.4)	5/101 (5.0)	3/96 (3.1)	15/306 (4.9)	.602
Cyclosporine	4/109 (3.7)	3/101 (3.0)	5/96 (5.1)	12/306 (3.9)	.760

[a]Safety endpoints during FU reported for patients who gave informed consent for FU study and did not experience death by the first FU visit. Data presented as absolute and relative frequencies, mean ± SD or median and IQR.
[b]Anit-HLA antibodies were considered positive with detectability.
[c]Computed as value at 5-year visit divided by value at baseline (value 1 means constant weight).
[d]Among patients without diabetes mellitus at baseline and without PTDM during original Harmony study (203 patients in total; Arm A 59 patients, Arm B 76 patients, Arm C 68 patients).
[e]P-values calculated for comparison of Arm A vs B vs C. Fisher's exact test, analysis of variance or Kruskal–Wallis H test, as appropriate.
rATG: rabbit ATG; ITT: intention-to-treat; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; SD: standard deviation; IQR: interquartile range; RSWD: Rapid steroid withdrawal; CMV: Cytomegalovirus; BKV: BK polyomavirus; PTLD: Post-transplant lymphoproliferative disorder; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; DSA: Donor-specific antibody; ESA: Erythropoiesis-stimulating agents; BMI: Body mass index; PTDM: Post-transplant diabetes mellitus; MMF/MPA: Mycophenolates.

Stumpf J, et al. Nephrology Dialysis Transplantation. 2023 Jun 30;39(1):141–50.

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Immunosuppression Regimen Use and Outcomes in Older and Younger Adult Kidney Transplant Recipients: A National Registry Analysis

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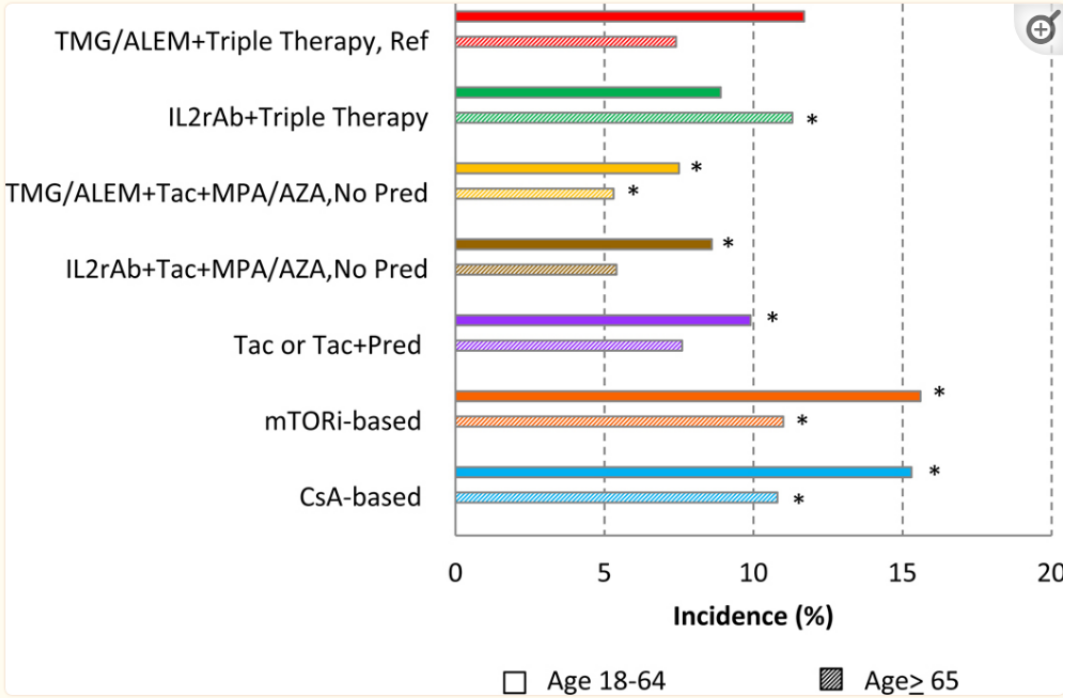

Figure 1.

Acute rejection incidence >6 months to 3 years after kidney transplant, by early ISx regimen and recipient age. * P<0.05 for comparison to reference regimen, within each age group. ALEM, alemtuzumab; AZA, azathioprine; CsA, cyclosporine; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; Pred, prednisone; Tac, tacrolimus; TMG, anti-thymocyte globulin

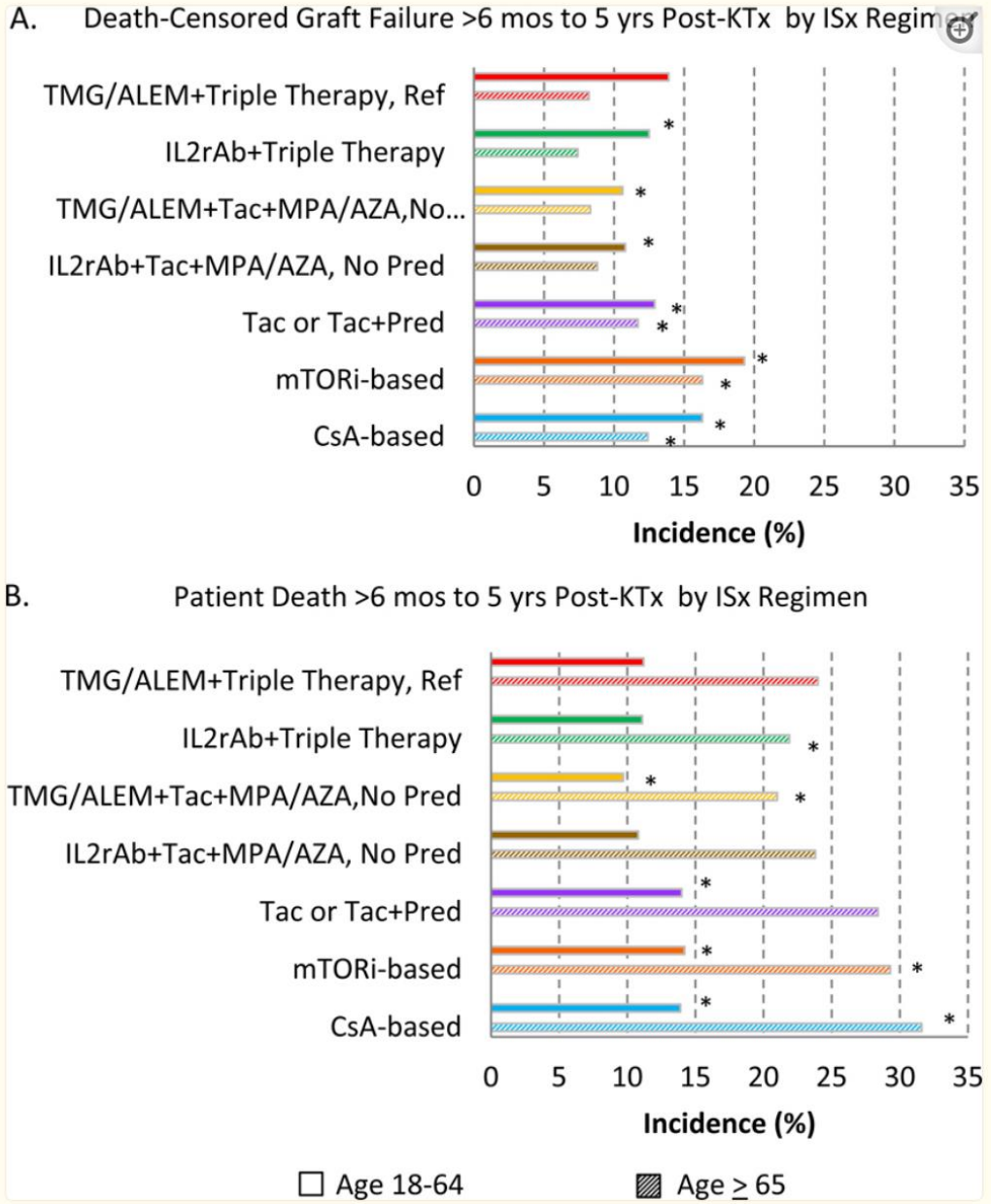

Figure 3.

Death-censored draft failure (A) and death (B) incidence >6 months to 5 years after transplant, according to early ISx regimen and recipient age.

Conclusiones y reflexiones

- ¿Qué consideramos alto riesgo inmunológico? Siguen sin estar bien definidos los criterios.

- En donante en asistolia se produce un daño por isquemia-reperfusión y puede ser interesante retrasar la introducción de CNI para evitar nefrotoxicidad.

- En donante mayor y donante de criterios expandidos se recomienda individualizar la dosis de ATG. El uso de ATG a dosis bajas es eficaz en la prevención del rechazo y se asocia a buen perfil de seguridad.

- ¿Debemos considerar únicamente riesgo inmunológico o también cardiometabólico? En el paciente cardiometabólico, la elección de la terapia de inducción podría permitir reducir dosis de corticoides sin riesgo de aumentar el rechazo y con ello reducir la incidencia de la diabetes mellitus post-trasplante.

- Se precisan más estudios para saber qué grupos se beneficiarían más de inducción con ATG, cuál es el régimen óptimo y cómo monitorizar la ATG para optimizar la respuesta y limitar su toxicidad.