Protocolos de inmunosupresión de inducción según grupos de riesgo

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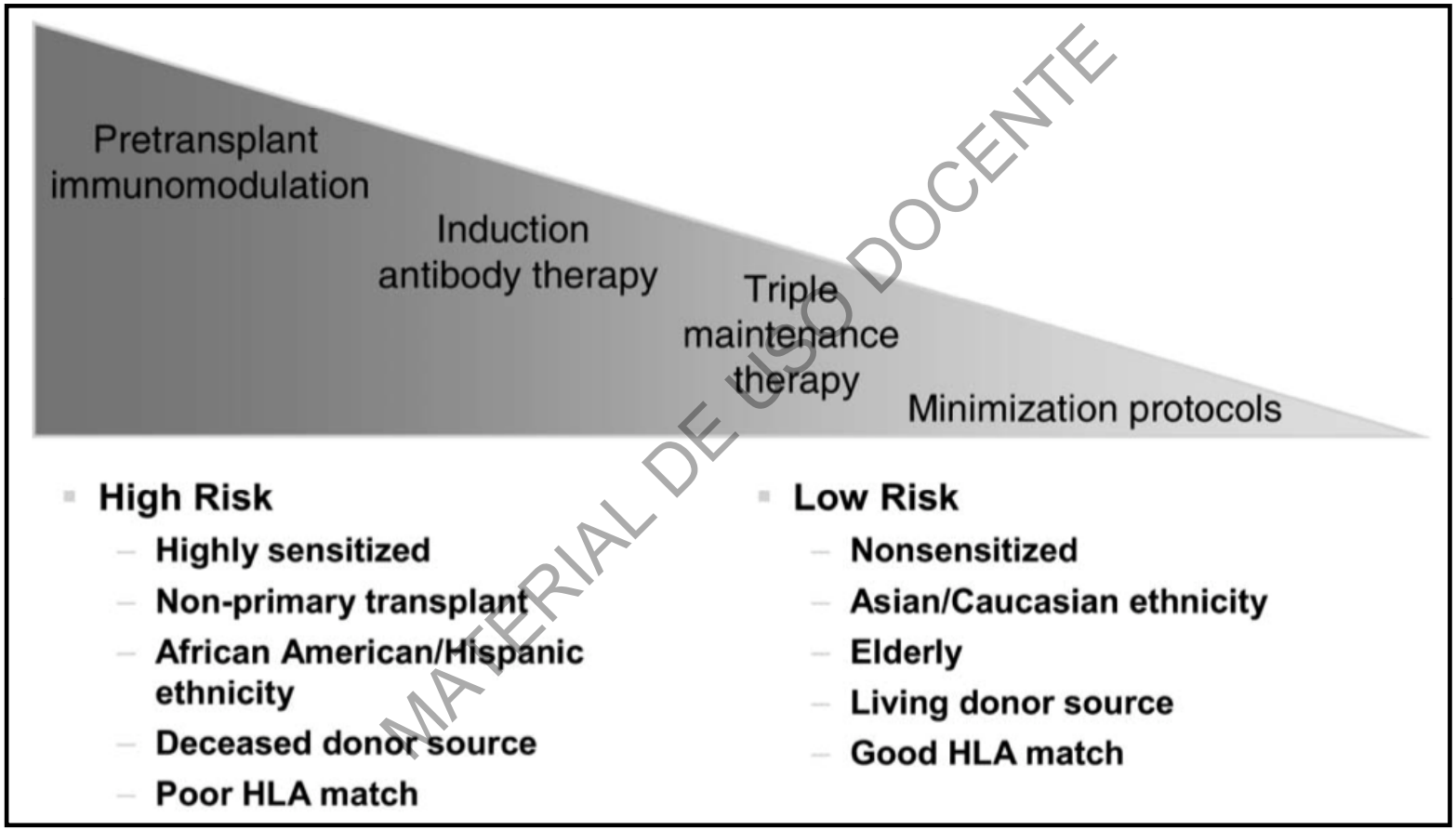
Challenges in kidney transplantation

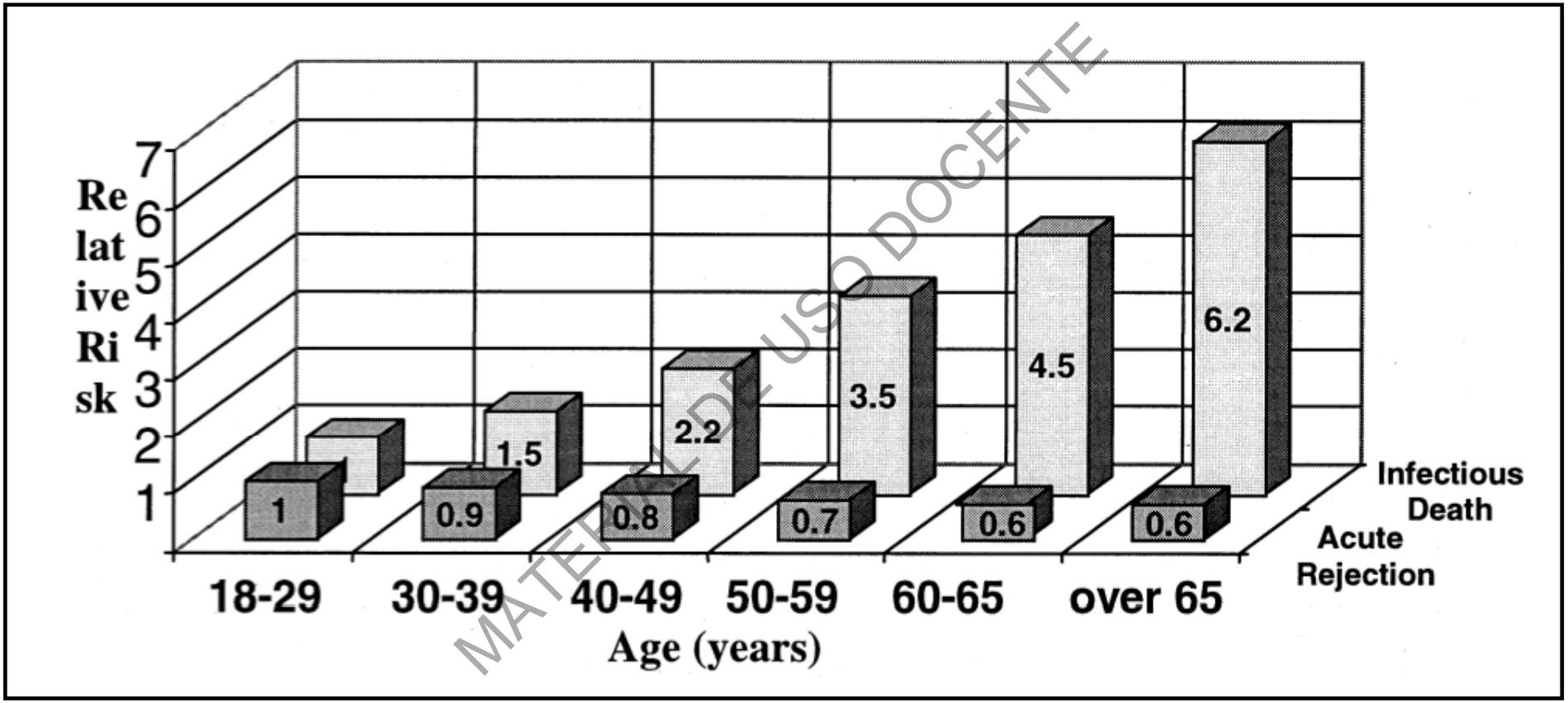
- Expanded criteria for donors and recipients
  - Non primary function
  - Delayed graft function
  - Increased immunogenicity of the ECD grafts
  - Nephrotoxicity
  - Cardiovascular risk factors and diabetes
  - Incidental cancer in the donor or in the recipient
  - Donation after cardiac death
- Chronic subclinical oncoviral infections and malignancies
  - EBV, CMV, Papilloma, HCV
- Acute and chronic antibody-mediated rejection
- Desensitization strategies (anti-HLA or/and anti-ABO)

Immunosuppression moving toward individualization based on immunologic risk



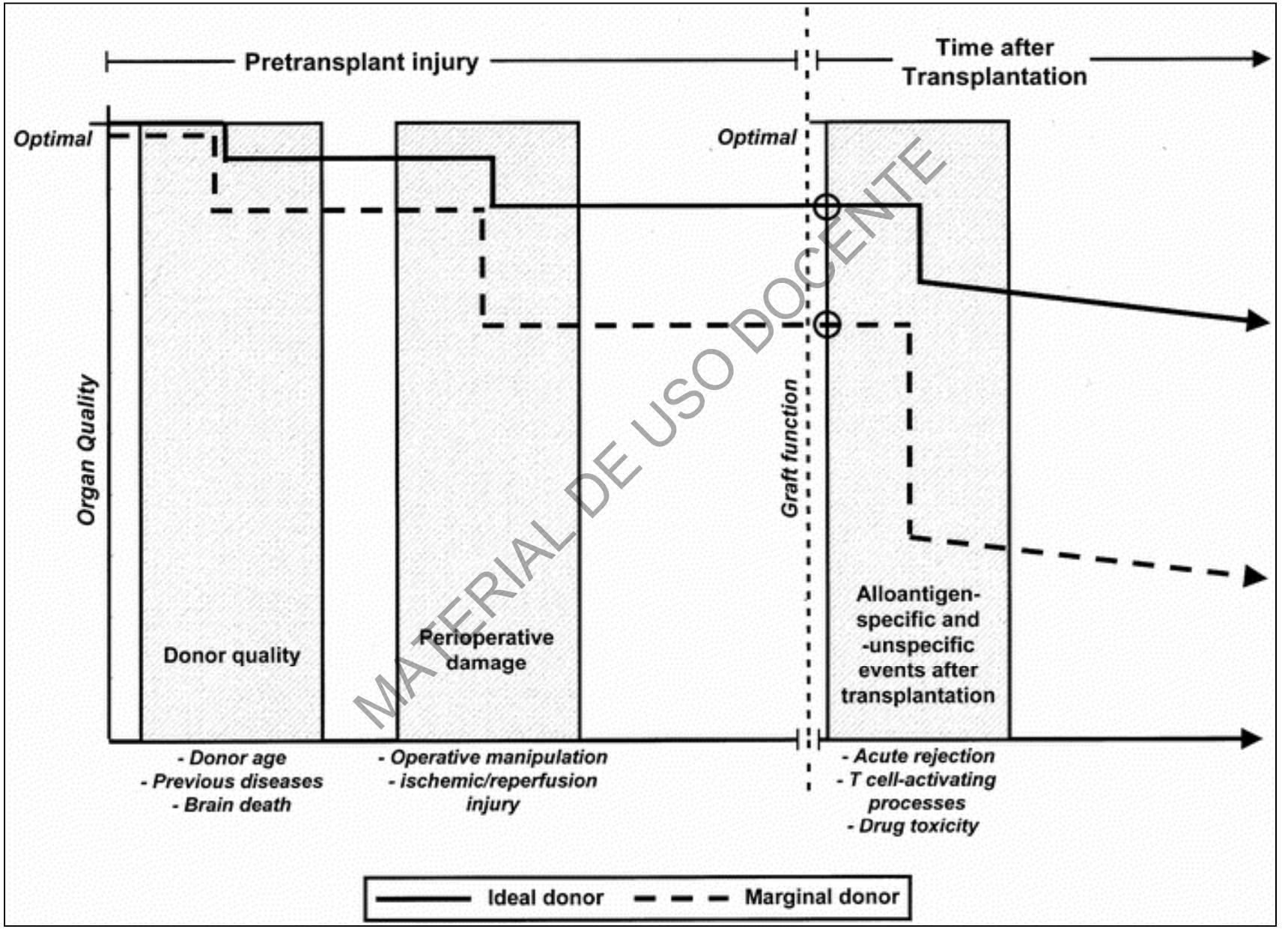
Levy GA, Ther Drug Monit, 2010, 32, 3:246-249

Relative risk of infectious death versus acute rejection by recipient age



Meier-Kriesche HU et al, Transplant Proc 2001, 33: 1190-1191

The postulate of an increased sensitivity of grafts from marginal donors towards additional injuries



Tullius SG et al, Transplantation 2001, 72:1341-1349

Clinical variables with interest for the individualization of the immunosuppression

Variable	Individualization factor
Immunological risk	High PRA, reTX, +ve Xmatch
Original disease	HUS, FSGS
Patient age	Pediatric, Elderly
Donor age	Elderly
Donor source and matching	HLA-identical siblings
Donor cause of death	Brain death vs. cardiac arrest
Chronic viral hepatitis	HCV, HBV
Malignancies	Tx in patients with cancer
Diabetes	Tx in diabetics or pre-diabetics

Individualization of the immunosuppression

At transplantation	After transplantation
Immunological risk	Graft dysfunction
Nephrological risk (donor and/or recipient)	New onset diabetes mellitus
HCV+ recipients	Side effects
Risk of disease recurrence	Cancer

Individualization of the immunosuppression

Immunological risk	
Retransplantation after immunological failure Low anti-HLA sensitization	Induction with basiliximab and CsA or Tac, MPA, Steroids
High anti-HLA sensitization	Induction with rATG and Tac, MPA, Steroids
Positive cross-match	Plasma exchange + IvIg ± Rituximab and rATG, Tac, MPA, Steroids

Individualization of the immunosuppression

Nephrological risk	
Expanded criteria brain-death donors Donors with acute renal failure	Induction with basiliximab and minimize or delay CNI
Donor death after cardiac arrest	Induction with rATG and minimize and delay CNI

Individualization of the immunosuppression

Risk of disease recurrence	
FSGS with risk of recurrence (genetic studies and / or high plasma levels of soluble podocyte urokinase receptor (suPAR)	High dose of CsA Plasma exchange ± Rituximab No stop steroids
Primary Membranous GMN (special caution if high anti-PLA2R levels)	Rituximab ACE-inhibitors
IgA nephropathy	Induction with rATG
Atypical haemolytic uraemic syndrome	Avoid CNI: rATG + mTORi + MPA + steroids

Individualization of the immunosuppression

HCV positive patients

CNI: Cyclosporine A
Induction: none or basiliximab
Minimize steroids

Immunosuppression regimens in Hospital Clinic Historical perspective 1984 - 2013

	Standard population	Immunological risk	Elderly patients, ECD & DCD
1984	CsA monotherapy CsA + Aza ALG + CsA + Aza +Pred (ATN) ATGAM+CsA + Aza + Pred (ATN)	CsA monotherapy / CsA + Aza OKT3 + CsA + Aza + Pred	CsA monotherapy CsA + Aza
1996	CsA + MMF + Pred		MMF – Pred
1998	Tacro + MMF + Pred	Basilix + Tacro + MMF + Pred rATG+ Tacro + MMF + Pred	Basilix + MMF + Pred
2002	Basilix + Tacro + MMF + Pred (LRD)		rATG+ MMF + Pred + SRL (NHBD) Basilix + MMF + Pred + SRL (Old)
2005	Basilix + Tacro + MPS + Pred	rATG+ Tacro + MPS + Pred	Basilix + MPS + Pred + (EVE)
2013	Tacro + EVE + Pred Basilix + Tacro + EVE + Pred	rATG+ Tacro + EVE + Pred	Basilix + Tacro + EVE + Pred (Old) rATG+ Tacro + SRL+ Pred

mTOR *de novo*:
541

Immunosuppression regimens in Hospital Clinic Historical perspective 1984 - 2013

	Standard population	Immunological risk	Elderly patients, ECD & DCD
1984	CsA monotherapy CsA + Aza ALG + CsA + Aza +Pred (ATN) ATG+CsA + Aza + Pred (ATN)	CsA monotherapy / CsA + Aza OKT3 + CsA + Aza + Pred	CsA monotherapy CsA + Aza
1996	CsA + MMF + Pred		MMF – Pred
1998	Tacro + MMF + Pred	Basilix + Tacro + MMF + Pred rATG+ Tacro + MMF + Pred	Basilix + MMF + Pred
2002	Basilix + Tacro + MMF + Pred (LRD)		rATG+ MMF + Pred + SRL (NHBD) Basilix + MMF + Pred + SRL (Old)
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2013	Tacro + EVE + Pred Basilix + Tacro + EVE + Pred	rATG+ Tacro + EVE + Pred	Basilix + Tacro + EVE + Pred (Old) rATG+ Tacro + SRL+ Pred

Immunosuppression protocol

	Basiliximab	rATG	Tacrolimus	Everolimus	Prednisone
Low immunological & Nepgrological risk			✔	✔	✔
High immunological risk		✔	✔	✔	✔
ECD	✔		✔	✔	✔

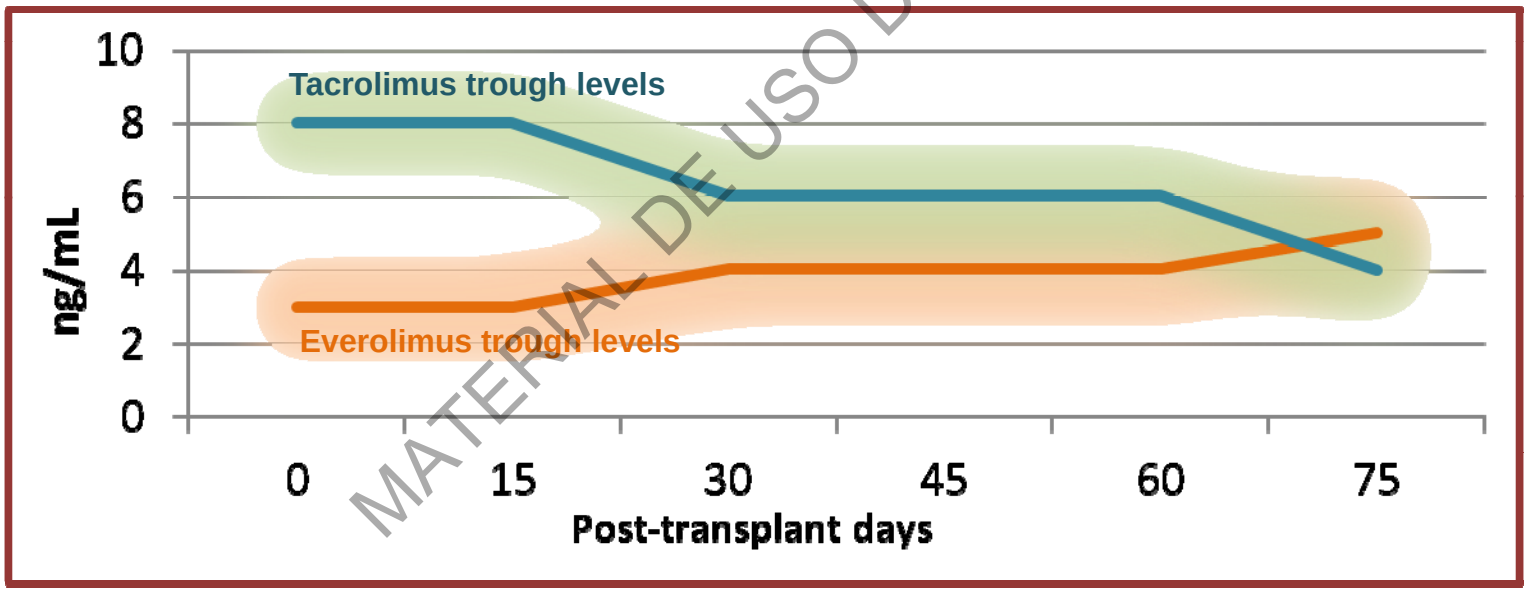
	Basiliximab	rATG	Tacrolimus	Sirolimus	Prednisone
DCD (controled and uncontroled)		✔	✔	✔	✔

Contraindications of *de novo* use of mTORi

- Obesity (BMI > 32)
- Aggressive surgery
- FSGS
- Severe dyslipidemia
- Chronic pulmonary disease

Current Immunosuppression Protocol Hospital Clinic Barcelona

Day 0		Post-transplant	
Basiliximab	20 mg	Basiliximab	20 mg (D4)
Tacrolimus	0.15 mg/kg	Prednisone	100mg -> 0.5 mg/kg -> 20 mg (D7) -> 10 mg (M1)
Prednisolone	500 mg	Tacrolimus	0.15 mg/kg/day -> through levels
		Everolimus	1 mg bid (D1) -> through levels



Tacrolimus + Everolimus trough levels : 8 - 12

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Kidney Transplants with *de novo* mTORi
June 2013 – June 2015

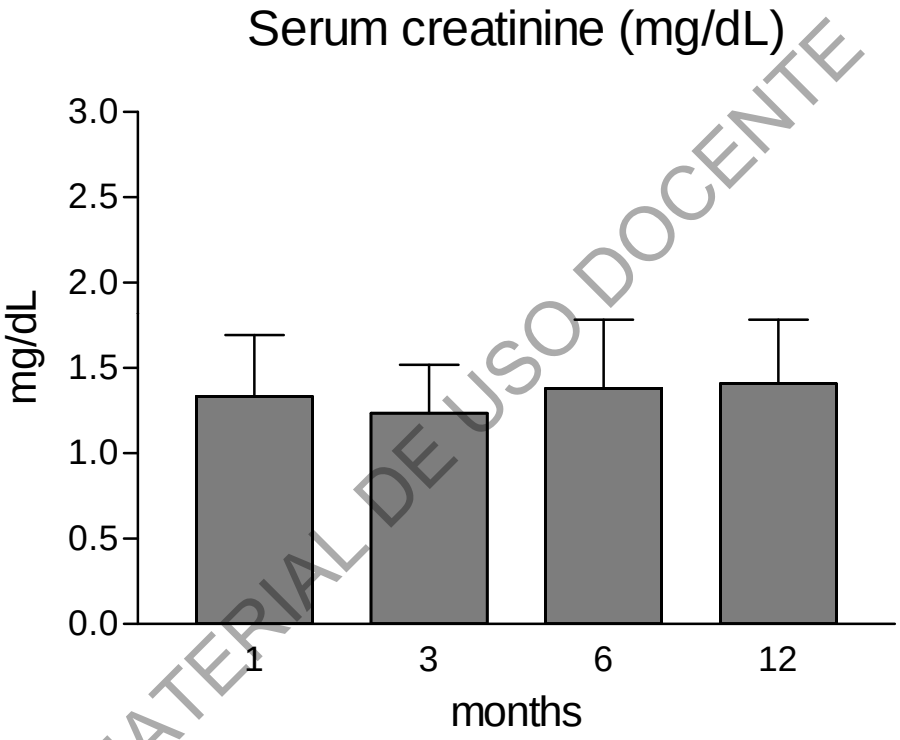
	N	Patient age	Donor age	2º KTx	3rd KTx	4th KTx
Living donors	31	53.0 (23 - 76)	55,8 (34 -72)	3	3	0
Brain-death donors	58	63.0 (31 - 80)	64.1 (20 - 82)	9	2	1
DCD donors	38	57.2 (35 - 75)	52.2 (21 -78)	3	0	0
Total	127	58.8 (23-80)	58.5 (20-82)	15	5	1

	TAC + EVEROL	BASIL + TAC + EVEROL	ATG + TAC + EVEROL	ATG + TAC + SIROL
Living donors	7	10	14	0
Brain-death donors	9	34	15	0
DCD donors	0	0	0	38
Total	16	44	29	38

Renal function recovery

	N	NPF n	DGF n (%)	DGF length days (range)
LD	31	0	0	
BDD	58	1	10 (17.5)	12.7 ± 11.2 (2 – 40)
DCD	38	2	21 (58.4)	12.2 ± 11.8 (1 – 35)
Maastricht 2 Maastricht 3	23 15	2 0	15 (71.4) 6 (40)	16.0 ± 11, (1 – 35) 2.8 ± 3.1 (1 – 9)

Renal function – Living donors



months	1	3	6	12
mean	1,27	1,25	1,35	1,31
std	0,37	0,37	0,43	0,38

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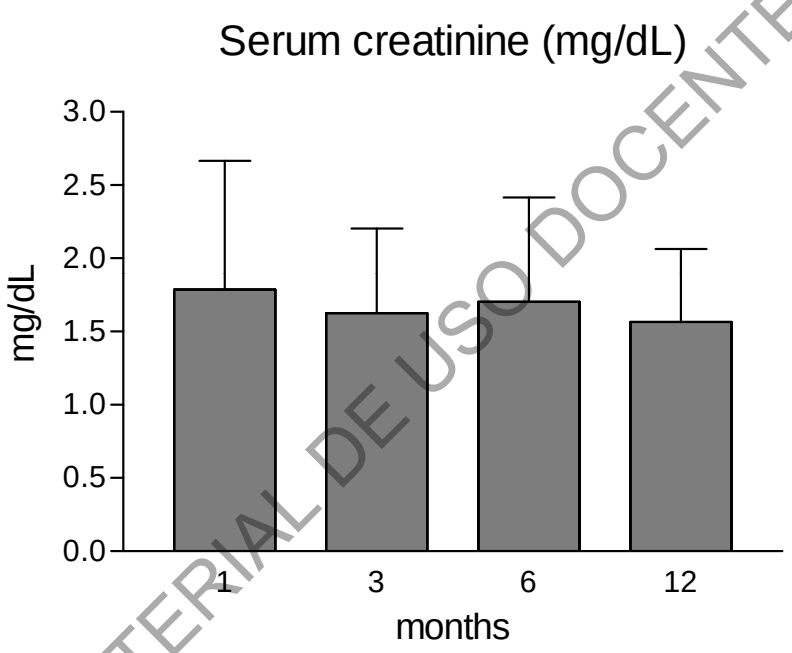
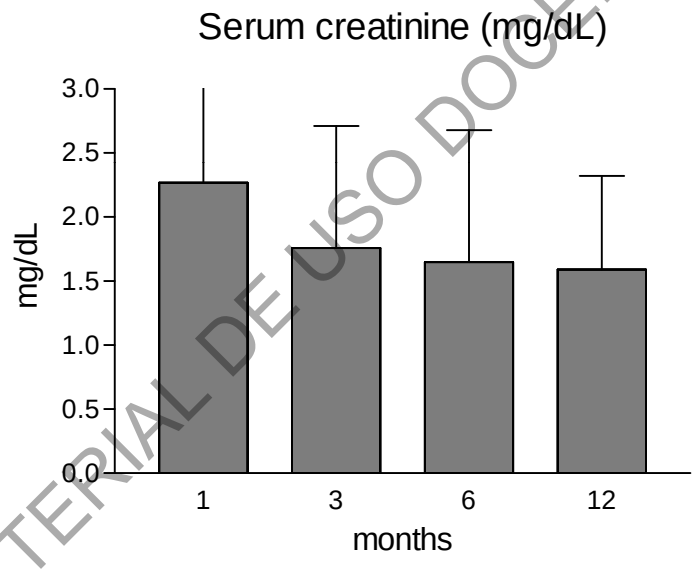
Renal function – BDD



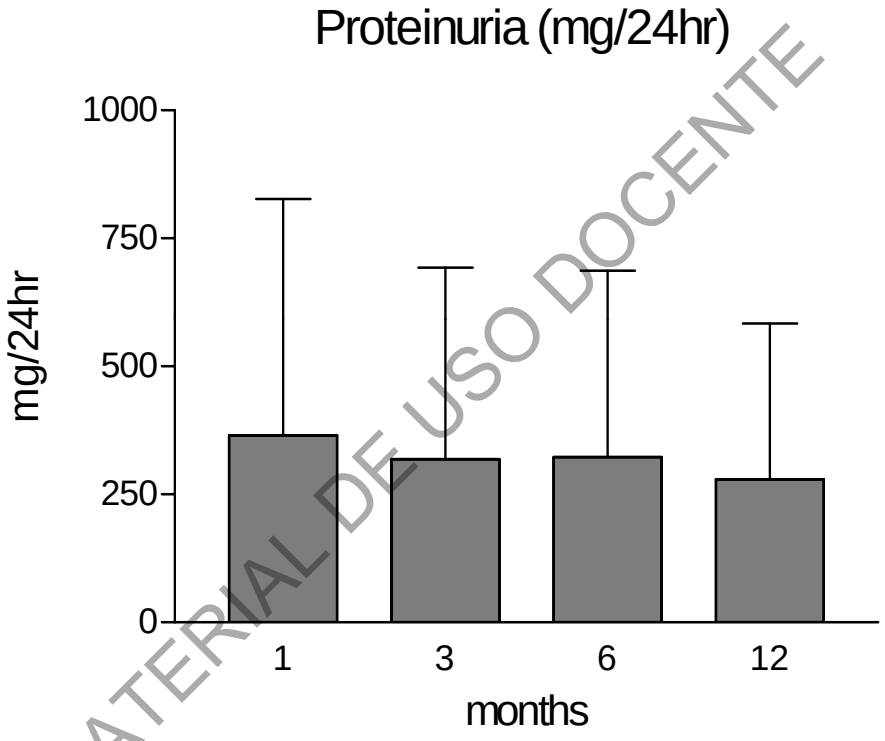
months	1	3	6	12
mean	1,79	1,63	1,70	1,57
std	0,88	0,58	0,71	0,50

Renal function – DBD



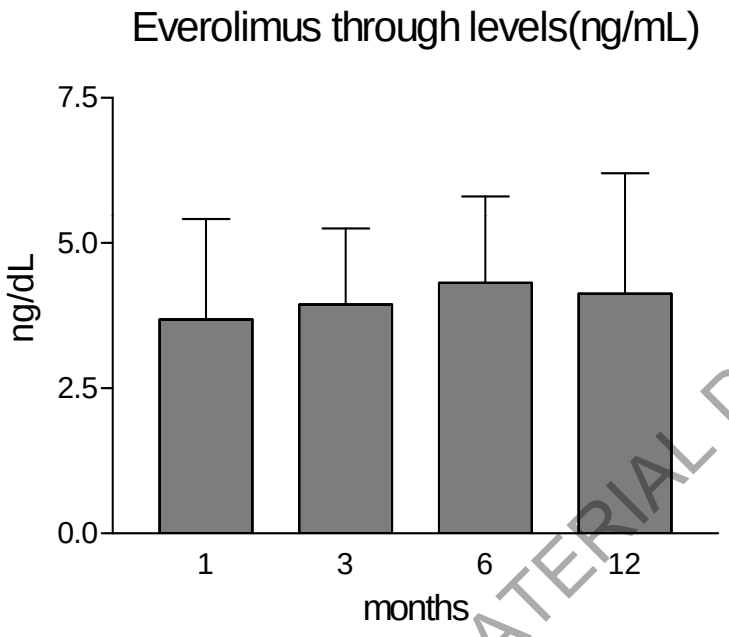
months	1	3	6	12
mean	2,27	1,76	1,65	1,59
std	1,68	0,95	1,03	0,73

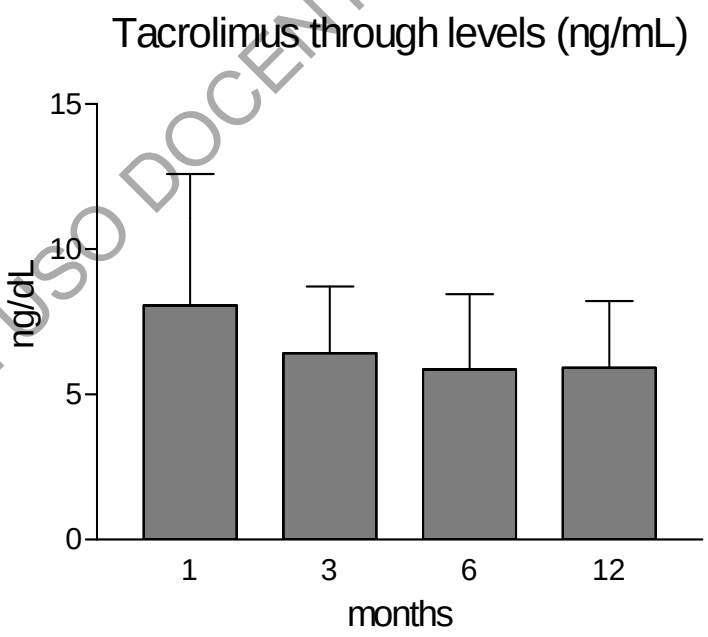
Proteinuria



months	1	3	6	12
mean	390	362	304	362
std	414	431	320	530

Everolimus and Tacrolimus Blood Levels





months	1	3	6	12
mean	4,00	4,20	4,82	5,76
std	1,65	1,31	1,75	2,64

months	1	3	6	12
mean	9,38	7,15	6,25	7,01
std	10,40	2,40	2,42	2,97

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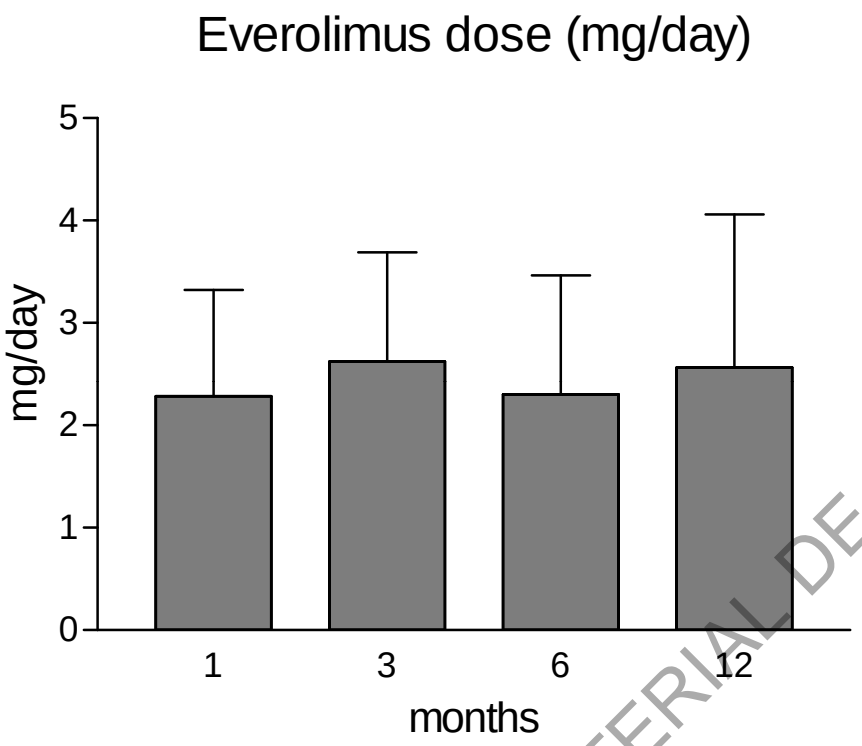
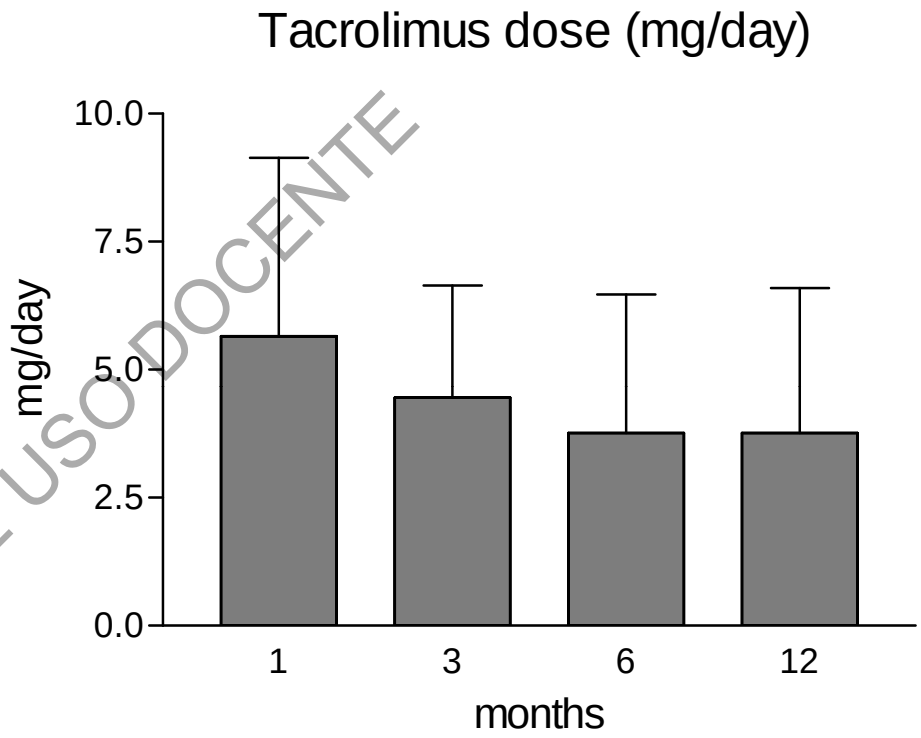
Everolimus and Tacrolimus Mean Daily Doses





months	1	3	6	12
mean	2,61	2,86	2,66	2,90
std	1,10	1,07	1,08	1,14

months	1	3	6	12
mean	6,70	5,64	4,89	4,42
std	3,34	3,39	3,42	2,95

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Survival

- 6 patients died:
  - D4: myocardial infarction in a diabetic patients
  - D47: sepsis due to bronco-aspiration pneumonia
  - D62: undetermined (at home, one day after discharge)
  - D87: peritonitis due to perforated diverticulitis
  - D 242: bacterial pneumonia (Legionella + P. Aeruginosa)
  - D337: acute lymphoblastic leukemia

- 4 grafts lost
  - 2 thrombosis
  - 2 non primary functioning

Acute Rejection

21/125 (16.8%) (Basiliximab + Tacro + Everolimus: 6/44; 13.6%)

4 Banff 1A

1 Banff 1B

1 Banff 2A

1 Banff 2B

6 Humoral type 1

2 ATN + C4d or DSA without inflamación

6 Borderline with graft dysfunction (steroids pulses)

14/125 (11.2%) Borderline w/o dysfunction

mTORi withdrawal: 28/125 (22.4%)

Surgical and/or wound healing problems: 7/88 (10.6%)

- 2 Lymphocele
- 1 Urinary leak
- 3 Wound dehiscence
- 1 Wound infection

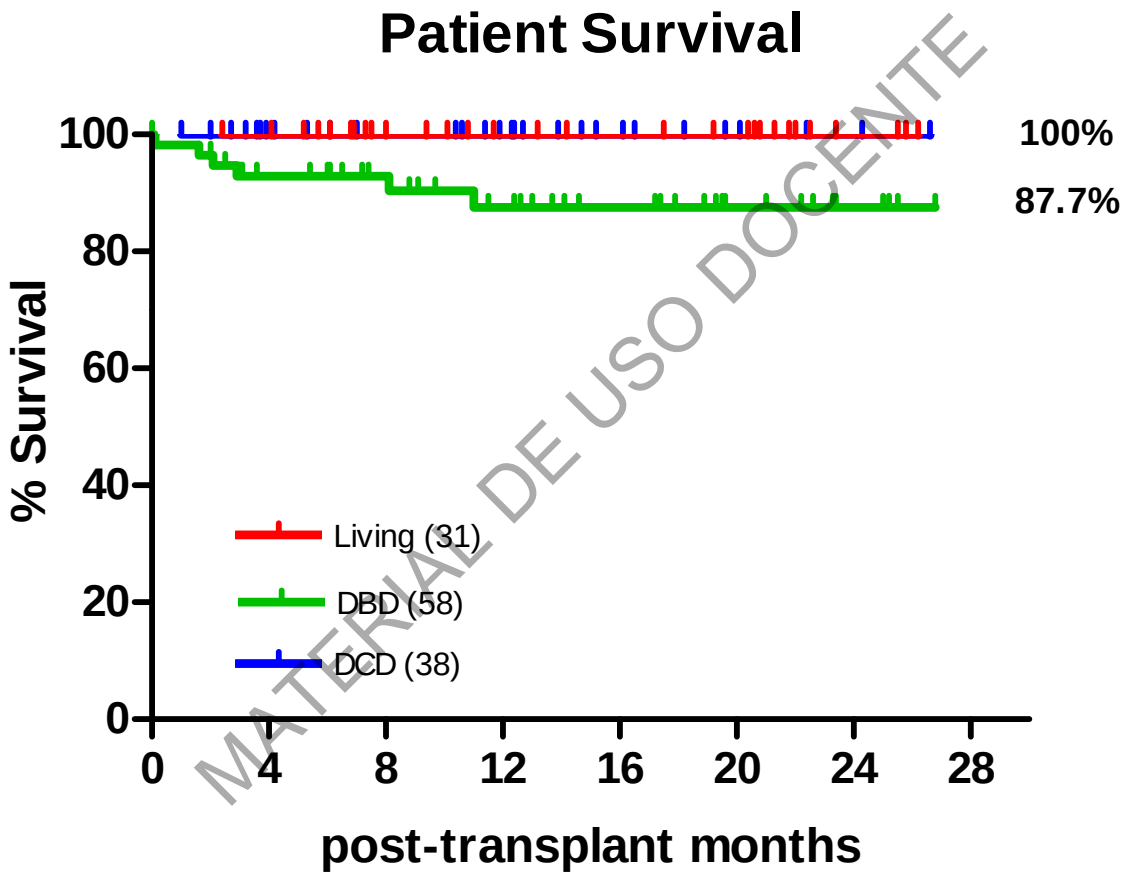
Other reasons for conversion:

- 5 planned surgery
- 6 acute rejection
- 1 proteinuria
- 1 diarrhoea
- 1 oedema
- 1 reflex sympathetic dystrophy
- 1 repeated bacterial pneumonia
- 5 no clear reasons

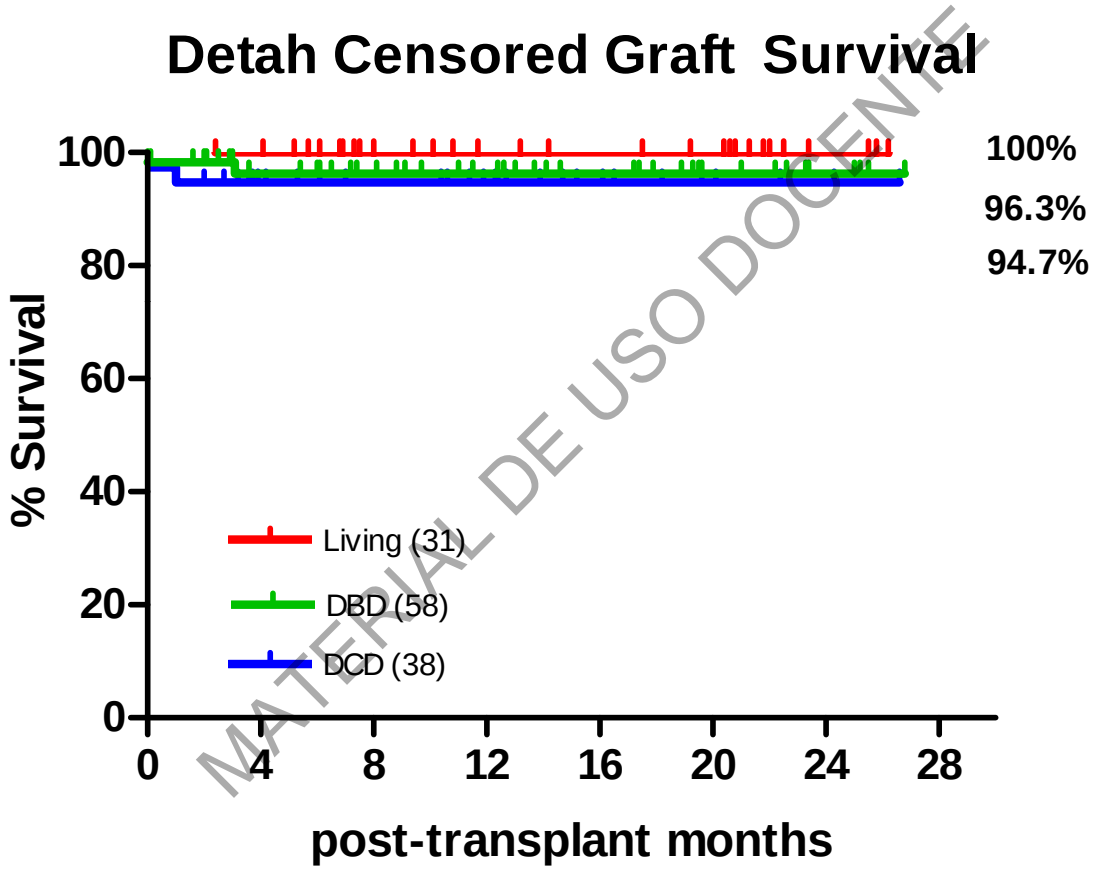
Luminex Screening

	Pre – Tx	3 months				
	n	Negative	I	II	I+II	Pending / NA
I + II negative	107	70	3	3	1	30
I positive	2	0	2	0	0	0
II positive	5	1	0	3	0	1
I + II positive	13	1	6	0	5	1

Kaplan-Meier Survival Rate



Kaplan-Meier Survival Rate



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Clinical Case
4th KTx (BDD)

Immunological characteristics

- Donor
  - Blood group: AB
  - HLA A*11/A*33 B*35/B*51 C*08/C*15 DQB1*03:01/05:01 DRB1*01/DRB1*11

- Recipient
  - Blood group: AB+
  - HLA A*03/*32, B*18/*35, DRB1*03/-
  - DSA (actual) : DQB*03:01 MFI 19.000
    DRB1*11:01 MFI 13.317

- CDC Crossmatch: negative
- FC Crossmatch: positive for B cells (450)
  negative for T cells

Clinical Case

Post-transplant period:

- Immediate recovery of renal function (sCr 0.9 mg/dL)
- No rejection
- Protocol biopsy a POD 9: no inflammation. C4d positive +++
- Luminex screening Class I negative, Class II positive

MICROSCÓPICO / MICROSCÒPIC
Calidad de la muestra: Insuficiente
Número de glomérulos 5 Glomérulos con esclerosis global 0
Número de arterias 1

C4d (C) 3 (C: Congelado, P: parafina)

Descripción: Muestra constituida en su mayor parte por médula. Pequeño fragmento de parénquima cortical sin alteraciones.

DIAGNÓSTICO / DIAGNÒSTIC
BIOPSIA RENAL:
- MUESTRA POCO REPRESENTATIVA. C4d POSITIVO SIN EVIDENCIA MORFOLOGICA DE RECHAZO.

Clinical Case

3 Months follow up

- Protocol biopsy at 3 months: no inflammation. C4d negative
- Luminex screening Class I negative, Class II negative

MICROSCÓPICO / MICROSCÒPIC
Calidad de la muestra: Insuficiente
Número de glomérulos 5 Glomérulos con esclerosis global 0
Número de arterias 2

C4d (C) 0 (C: Congelado, P: parafina)

Descripción: Muestra constituida en su mayor parte por médula. Parénquima cortical con focos mínimos de fibrosis. Ausencia de infiltrado inflamatorio. Ausencia de alteracione en glomérulos y vasos.

DIAGNÓSTICO / DIAGNÒSTIC
BIOPSIA RENAL:
- MUESTRA POCO REPRESENTATIVA. PARENQUIMA RENAL SIN ALTERACIONES PATOLOGICAS SIGNIFICATIVAS. NO EVIDENCIA DE RECHAZO.

Fecha de validación\Data validació: 24/01/2014 15:32:04

Clinical Case

1 year follow up

- Protocol biopsy at 1 year: no inflammation. C4d negative
- Luminex screening Class I negative, Class II negative

MICROSCÓPICO / MICROSCÒPIC
Calidad de la muestra: M (A: Adecuada, M: Marginal)
Número de glomérulos 10 Glomérulos con esclerosis global 0
Número de arterias 1

i 0 t 0 v0 g 0 ah 0 ptc 0 ti 0 aah 0

ci 0 ct 0 cv 0 cg 0 mm 0

C4d (C) 0 (C: Congelado, P: parafina)

DIAGNÓSTICO / DIAGNÒSTIC
BIOPSIA RENAL:
- PARENQUIMA RENAL SINALTERACIONES PATOLÓGICAS SIGNIFICATIVAS.
- NO EVIDENCIA DE RECHAZO.

Fecha de validación\Data validació: 02/02/2015 13:05:25

Strategies for an optimal use of mTOR inhibitors in *de novo* kidney transplantation

To be administered as soon as possible, preferably from the first day after transplant, associated to reduced dose CNI

A proactive use of mTOR inhibitors expands the benefit of the drug to a larger number of patients, while reducing the number and severity of side effects

The vast majority of patients do not have a contraindication for an early use, avoiding the need of subsequent protocolized switches

Accurate adjustment of CNI & everolimus levels

Exclusion criteria:

- Morbid obesity
- Severe dyslipidemia
- Chronic pulmonary disease
- Vascular anastomosis to artificial by-passes or other technical issues
- FSGS

¡Muchas gracias !