Diagnosis of Antibody-mediated Rejection: complement-binding DSA vs. DSA MFI intensity

M. Crespo, D Redondo-Pachón, MJ Pérez-Sáez, J Gimeno[1], C García, M Mir, J Hernández, J Pascual.

Departments of Nephrology, Immunology and Pathology[1], Hospital del Mar, Barcelona, Spain.

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BACKGROUND

HLA DSA detected early or late after kidney transplantation (KT) correlate with graft outcomes, but not all DSA are equal and produce the same functional consequences. Early complement-binding DSA have been associated with ABMR and loss, but there is scarce information of the value of detecting complement-binding DSA late after KT. (1-4).

AIMS

Analyze if the ability of late DSA to bind complement «on Luminex» with 2 different assays (C3d & C1q) & dynamic testing correlates with **clinical outcomes**:

- Kidney transplant survival
- Graft function
- Tissue damage

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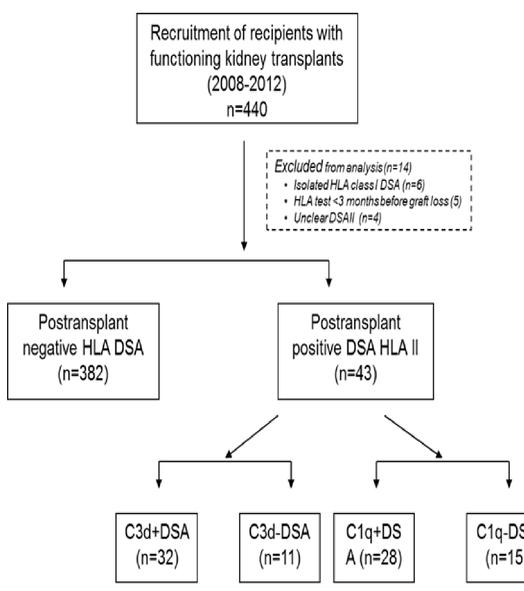
METHODS

- Prospective study of 440 active KT (1979-2012).
- HLA ab tests from 2008 to V/2016 or graft-loss (1382 samples).
- Screening beads, and SAB when needed (Immucor®).
- C3d (provided by Immucor®) and C1q tests for DSA.
- For analysis, we selected the 1st time point when the patient showed a C3d+DSA, 1st DSA when C3d- or 1st time tested if no DSA.

RESULTS

I. Patient flow chart :



II. Baseline characteristics:

	No DSA n=382	C3d+DSA n=32	C3d-DSA n=11	p C3d+ vs. C3d-
Recipient age at transplant (years)	50±14	45±15	41±9	0.4
Female recipient (%)	35.6%	50.0%	54.5%	0,79
Deceased donor (%)	91.1%	93.8%	100%	1
Retransplantation (%)	13.1%	43.8%	36.4%	0.73
Peak PRA CDC (%)	3±10	17±28	13±27	0.64
Pretransplant PRA CDC (%)	2.1%	5.3±12	0.6±2.1	0.047
Pretransplant SAB DSA (n=285) (%)	8.1% (21)/258)	55% (11/20)	85.7% (6/7)	0.2
- C3d+pretransplant DSA	31.8%	100,0%	71,4%	0.35
Antilymphocyte induction (%)	28,6%	50,0%	18,2%	0,08
Delayed Graft Function (%)	38.5%	46.9%	27.3%	0.31
Biopsy proven Acute rejection (%)	5%	15,6%	36.4%	0.2

III. Clinical data at index sample:

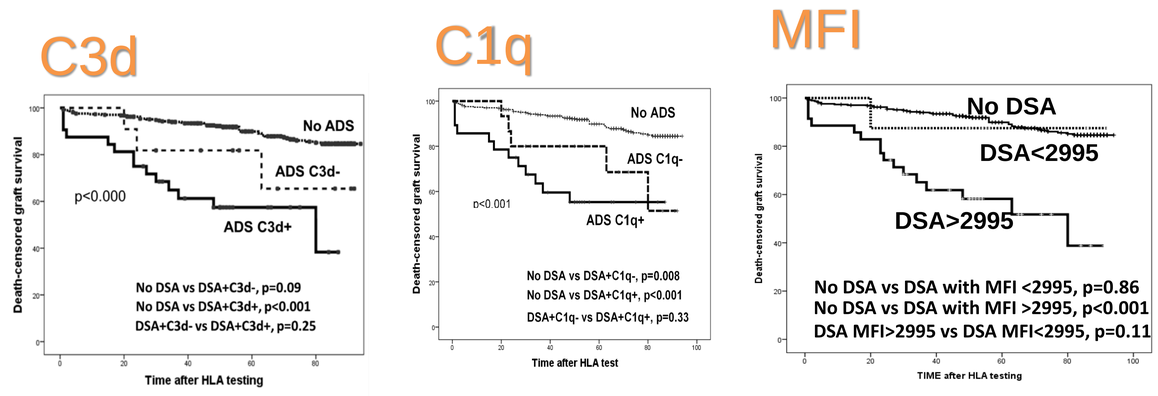
	No DSA n=382	C3d+DSA n=32	C3d-DSA n=11	p for C3d+ vs. C3d-
PostKT time at sample, months (median, IQR)	29 (10-92)	55 (13-152)	45 (20-118)	0.9
Creatinine (mg/dl) (mean±SD)	1.71±0.65	1.74±0.76	1.51±0.67	0.38
MDRD-4 eGFR (ml/min) (mean±SD)	45.8±16.2	47.2±23.3	50±17.5	0.67
Urinary Protein/creatinine (mg/mg) (median, IQR)	181 (114.5-310)	267 (160-632)	146 (70.2-420)	0.11
Steroid treatment (%)	59.4%	59.4%	54.5%	0.78
Tacrolimus treatment (%)	62.8%	25%	63.6%	**0.03**
Cyclosporine treatment (%)	28.3%	53.1%	18.2%	0.08
mTOR inhibitors (%)	6%	18.8%	9.1%	0.65
Mycophenolic treatment (%)	79.7%	81.3%	90.9%	0.65

IV. Characteristics of DSA:

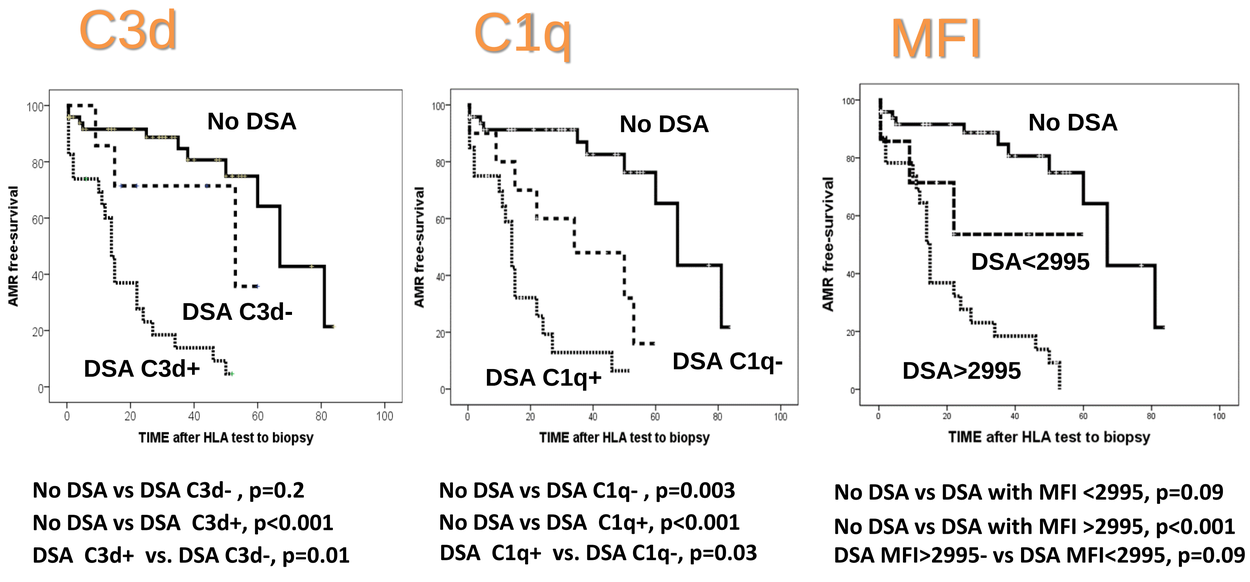
	C3d+DSA n=32	C3d-DSA n=11	p
More than ONE DSA	15 (46.9%)	1(9.1%)	0.03
DQ DSA included	21 (65.6%)	7 (63.6%)	1
MFI of highest DSA	13910±5647	4644±4425	0.000
SUM of raw MFI of DSA	19300±11319	4787±4728	
MFI of highest DSA > 8000	26 (81.3%)	2 (18.6%)	0.001
MFI of highest DSA < 3500	2 (6.3%)	8 (72.7%)	0.001
Clearance of DSA in follow-up	0/22 (0%)	7/8 (87.5%)	0.001

(in 30 patients with more tests after DSA detected)

V. Outcomes: graft -survival:



VI. Outcomes: AMR free -survival:



No DSA vs DSA C3d- , p=0.2
No DSA vs DSA C3d+, p<0.001
DSA C3d+ vs. DSA C3d-, p=0.01

No DSA vs DSA C1q- , p=0.003
No DSA vs DSA C1q+, p<0.001
DSA C1q+ vs. DSA C1q-, p=0.03

No DSA vs DSA with MFI <2995, p=0.09
No DSA vs DSA with MFI >2995, p<0.001
DSA MFI>2995- vs DSA MFI<2995, p=0.09

VII. Outcomes: biopsy findings

%	C3d+DSA n=23	C3d-DSA n=7	p	C1q+DSA n=20	C1q-DSA n=10	p	MFI> 2995 n=23	MFI<2995 n=7	p
AMR diagnosis	95.7	42.9	**0.006**	90	70	**0.37**	95.7	42.9	**0.006**
Glomerulitis	78.3	42.9	0.15	75	60	0.43	82.6	28.6	**0.014**
Peritubular capillaritis	91.3	14.3	**0.001**	90	40	**0.007**	87	28.6	**0.007**
Microvascular inflammation	78.3	42.9	**0.15**	75	60	0.43	82.6	28.6	**0.014**
C4d >0	47.8	28.6	0.427	55	20	0.12	52.2	14.3	0.09
CTG 2013	54.5	42.9	0.68	45	66.7	0.43	54.5	42.9	0.68
EM CTG or PTCML	52.4	42.9	1	42.1	66.7	0.42	52.4	42.9	0.5
DC Graft Loss	30,4	14,3	0.63	30	20	0.68	45.7	12.5	**0.088**
DSA persistence	100	12.5	**0.001**	94.7	45.6	**0.004**	91.3	8.7	**0.003**

CONCLUSIONS

- Detection of complement-binding DSAII after transplantation identifies KT recipients at higher risk of ABMR.
- C1q lacked to categorize adequately a significant number of DSA patients compared with C3d, based on outcomes and histology.
- Complement binding ability is significantly associated with the strength of DSA, so it is uncertain if it provides additional independent prognostic aid in the asessment of a patient with DSA.

REFERENCES: ***1.*** *Crespo et al. Tr Immunol 2013****. 2.*** *Loupy et al. NEJM 2013.* ***3****. Sicard et al. JASN 2014.* ***4.*** *Kalp-Inal et al. Kidney Int 2015* ***5.*** *Eskandary et al. Transpl 2016*

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Marta Crespo

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