C1q-fixing donor-specific antibodies detected before kidney transplantation do not predict rejection or early graft loss, but HLA class I do

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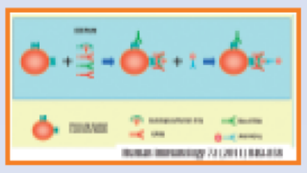
Introduction



Anti-HLA donor-specific antibodies (DSA) identified by single antigen bead array are questioned for their excess in sensitivity and lack of event prediction after transplantation.
New developed tests try to discriminate which HLA antibodies detected with SAB can fix complement (C4d, C1q or C3d)despite not doing it in CDC assays.

Aims

Primary we performed a retrospective study in kidney transplants to evaluate if a specific type of preformed DSA, whether class I or II or C1q fixing, has a clearer impact on graft survival.

Secondary:

To analyze characteristics of C1q+ DSA.
To evaluate their impact on graft function.
To evaluate impact on acute rejection.
To analyze postransplant behavior of ADS.

Population

Kidney transplant recipients (2006-2011) performed across prospective negative **CDC-XM**.

355 kidney transplant recipients:

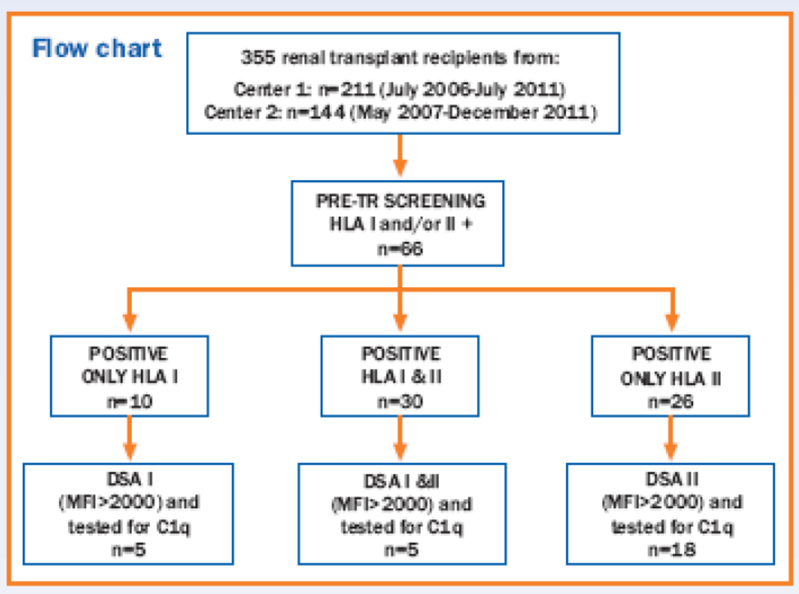
H Mar: n=211 (7/06-7/11)
Las Palmas: n=144 (5/07-12/11)

Methods

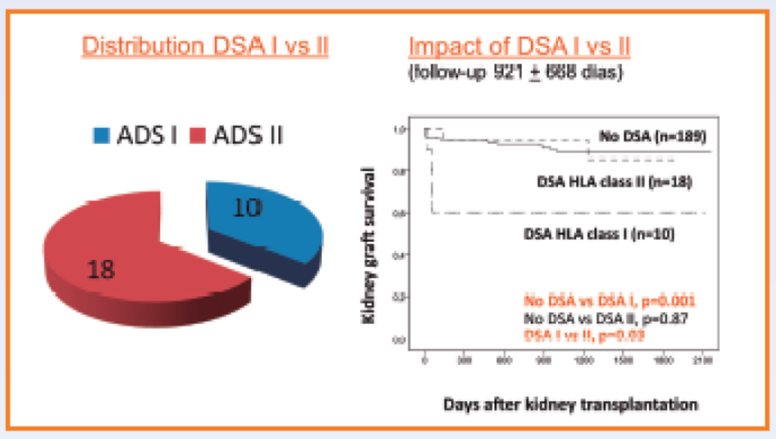
1. Data base with transplant information on (SPSS 18):
   - Demographics of donor and recipients
   - Immunological
   - Clinical
2. Serum samples:
   - Prospective: pre % postransplant samples.
   - Storage at -80º until C1q tests.
3. Anti-HLA antibody tests in pre & post-TR samples:
   - Lifecodes G-P kits on Luminex platform
     - Screening
     - Single antigen
   - Donor specificity: antibodies with raw MFI> 2000 against:
     - Donor's HLA A, B or DR antigens.
     - Most DQ considering linkage disequilibrium with DR.
4. Detection of antibodies able to fix C1q in samples pre-TR:
   - One Lambda single antigen kits on Luminex.
   - DSA C1q+ were considered when MFI>500.

Results

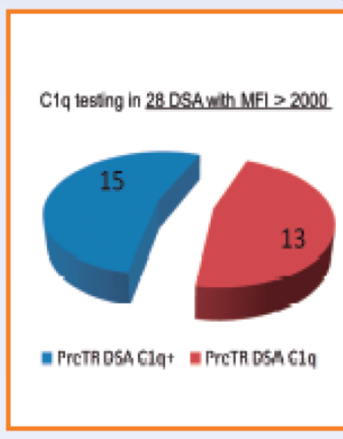
Prevalence of DSA



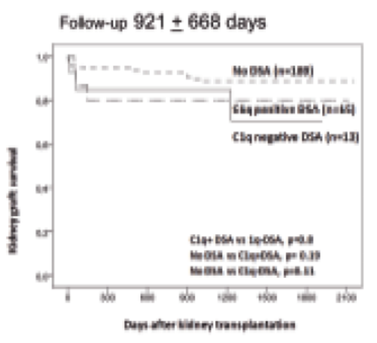
DSA I vs II



Distribution of DSA C1q+



Survival



Features of DSA Ivsll and C1q+ vs C1q-

Demographics, clinical and immunological data for patients with preformed DSA I and DSA II

	DSA HLA I (n=10)	DSA HLA II (n=18)	p
Female recipients	70%	77.8%	0.67
Recipient Age at transplant (years, mean ± SD)	48.9 ± 11.6	54.8 ± 12.4	0.23
Previous transplants	60%	66.7%	1
Induction treatment: Thymoglobulin	60%	38.9%	0.54
Delayed Graft Function	60%	50%	0.7
Days of Delayed Graft Function [median (IQR)]	11 (5, 60)	13 (12, 16)	0.68
Biopsy Proven Acute Rejection	50%	33.3%	1
Acute cellular rejection	0%	16.7%	0.53
Acute antibody-mediated rejection	50%	16.7%	0.06
C4d in early biopsy (<3 months), n=11	50%	16.7%	0.1
6 month creatinine (mg/dl, median IQR), n=24	1.4 (1.3, 1.8)	1.48 (1.16, 1.77)	0.58
Last creatinine (mg/dl, median IQR), n=22	1.6 (1.2, 1.9)	1.23 (1.08, 1.39)	0.20
Last urine protein/creatinine (median IQR), n=22	247 (120, 660)	223 (167, 989)	0.97
Follow-up (months, median IQR),)	15 (1, 39)	39 (14, 51)	0.09
Peak PRA>5%	80%	38.9%	0.055
Pretransplant PRA>5%	30%	27.7%	1
Pretransplant HLA I screening (% positive)	100%	50%	0.01
Pretransplant HLA II screening (% positive)	100%	100%	
AB Mismatches: > 0 MM	100%	83.3%	0.5
DR Mismatches > 0	80%	100	0.14
Immunodominant DSA MFI pretransplant	4069 ± 1844	11963 ± 7083	0.0001
C1q positive DSA	20%	61.1%	0.19
Last Original DSA status (% positive >3mo)	16.7%	66.7%	0.06

DSA: Donor specific antibodies.SD: Standard deviation. IQR: Interquartilic range. PRA: Panel reactive antibodies. KT: Kidney transplantation

Demographics, clinical and immunological data for patients with preformed C1q+DSA and C1q-DSA

	C1q DSA positive (n=15)	C1q DSA negative (n=13)	p
Female recipients	80%	69.2%	0.67
Recipient Age at transplant (years, mean ± SD)	53.2 ± 14.7	52.1 ± 9.1	0.65
Previous transplants	73.3%	53.8%	0.43
Induction treatment: Thymoglobulin	40%	53.8%	0.73
Delayed Graft Function	66.7%	38.5%	0.25
Days of Delayed Graft Function [median (IQR)]	12.5 (10, 26)	13 (12, 16)	0.76
Biopsy Proven Acute Rejection	33.3%	46.2%	0.70
Acute cellular rejection	6.7%	15.4%	0.58
Acute antibody-mediated rejection	26.7%	30.8%	0.67
C4d in early biopsy (<3 months), n=11	26.7%	30.8%	1
6 month creatinine (mg/dl), n=24	1.4 (1.3, 1.7)	1.43 (1.02, 1.8)	0.86
Last creatinine (mg/dl), n=22	1.2 (1.1, 1.3)	1.63 (1.12, 1.98)	0.09
Last urine protein/creatinine, n=22	190 (141, 619)	523 (207, 980)	0.23
Follow-up (months)	35 (8, 51)	15 (9, 41)	0.62
Peak PRA>5%	66.7%	38.5%	0.25
Pretransplant PRA>5%	40%	15.4%	0.22
Pretransplant HLA I screening (% positive)	60%	76.9%	0.43
Pretransplant HLA II screening (% positive)	100%	100%	
AB Mismatches >0	6.7%	15.4%	0.14
DR Mismatches >0	93.3%	92.3%	0.06
DSA I pretransplant	26.7%	46.2%	0.43
DSA II pretransplant	93.3%	69.2%	0.15
Immunodominant DSA MFI	14681 ± 5899	6726 ± 4870	0.001
Last DSA I after KT (% positive > 3mo)	0%	20%	0.53
Last DSA II status after KT (% positive >3mo)	81.8%	42.86%	0.23
Last Original DSA status (% positive >3mo)	69.2%	36.4%	0.21

DSA: Donor specific antibodies. SD: Standard deviation. IQR: Interquartilic range. PRA: Panel reactive antibodies.

Conclusions

- C1q testing in pretransplant sera with DSA was unable to predict antibody-mediated rejection or graft loss, but the presence of DSA class I compared to class II did.
- Patients with C1q-fixing DSA had higher MFI of their immunodominant DSA.
- Despite lack of capacity to fix complement in vitro, pretransplant C1q-negative DSA I can mediate rejection and graft loss.

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