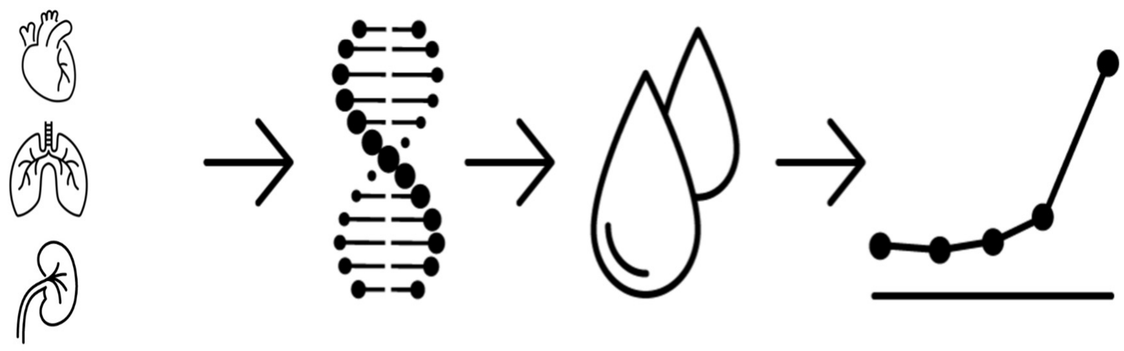
Donor-derived cell-free DNA among Allograft Protocol Biopsy at University Malaya Medical Centre

Jalalonmuhali M[1], Ng KP[1], Mohamad M[2], Mohamed Yusoff N[2], Syed Sultan MK[2], Lee YW[1], Lim SK[1].
1.Division of Nephrology, Department of Medicine, Faculty of Medicine, University Malaya.
2.Molecular and Genetic Analysis Laboratory, Division of Laboratory Medicine, Department of Pathology, University Malaya Medical Centre.

Background

Donor-derived cell-free DNA (cfDNA) is a non-invasive test of allograft injury that is growing in the pipeline. Diagnosing active rejection in kidney transplant recipients (DART) group demonstrated that dd-cfDNA more than 1% is significantly associated with rejection and the results were higher in patients with ABMR[1]. While in a study divided into cfDNA ≥ 0.5% and < 0.5% among borderline and TCMR 1A demonstrated that cf-DNA ≥ 0.5% revealed declining in eGFR[2], formation of de novo HLA-DSA and persistent rejection.



Cell injury (Donor organ) → DNA is released (Recipient's plasma) → Measures → A high dd-cfDNA (Potential organ injury)

Objective

To evaluate the value of cfDNA comparing no rejection, borderline rejection, chronic TCMR and chronic ABMR in all transplant recipients undergoing protocol kidney allograft biopsy with stable renal function

Methodology

All patient's post kidney transplantation at University Malaya Medical Centre (UMMC) that is scheduled for protocol renal allograft biopsy were recruited. A blood sample for cfDNA was collected in the morning before the scheduled procedure. Patients' demographic data, induction and maintenance immunosuppression and biopsy reports were obtained from the electronic medical report.

Results

A total of 24 transplant recipients were recruited in our study. Mean age of our transplant cohort was 45.38 + 11.55 with 58.3% were male. Their mean duration post transplantation was 39.21 ± 54.02 months. Out of those 45.8% (11/24) had allograft biopsy reported as no rejection, 37.5% (9/24) borderline changes, 4.2% (1/24) chronic active TCMR, 8.3% (2/24) chronic active ABMR and 4.2% (1/24) interstitial nephritis. The mean value of dd-cfDNA were **0.19% ± 0.11 in no rejection**, **0.20% ± 0.09 in borderline**, **0.09% in chronic active TCMR**, **1.7% ± 0.57 in chronic active ABMR** and 0.51% in interstitial nephritis.

* 2 patients were excluded from subsequent analysis (1 borderline-developed AKI secondary to COVID-19, 1 interstitial nephritis)

Lessons learned

Low level of dd-cfDNA (<0.5%) was found in no rejection and borderline rejection cohorts.

Higher level of dd-cfDNA was found in patients with transplant glomerulopathy. Indicate ongoing tissue injury?

Characteristic (n=23)	No rejection (n=11)	Borderline (n=8)	Rejection (n=3)	P value
Duration post transplant (months)	40.73 ±73.27	26.12 ± 20.14	76.33 ± 43.50	0.436
Recipient				
Age	42.45 ± 13.73	45.25 ± 10.25	47.00 ± 7.21	0.798
Gender (Male)	63.6%	62.5%	66.7%	0.650
Primary disease (GN)	36.4%	50.0%	0	0.465
DM	27.3%	25.0%	33.3%	0.930
HPT	72.7%	100%	100%	0.288
Immunological risk				
ABO compatible	72.7%	75.0%	66.7%	0.482
HLA-DSA (positive)	45.5%	12.5%	33.3%	0.605
History of rejection (ABMR)	9.1%	0.0%	100%	0.001*
Induction regime				
ATG	55.6%	25.0%	50.0%	0.710
Low dose ATG	22.2%	25.0%	0	
Basiliximab	22.2%	50.0%	50.0%	
Systolic BP (mmHg)	130.73 ±15.97	149.00 ± 15.57	153.33 ± 4.51	0.022*
Diastolic BP (mmHg)	81.09 ± 12.86	83.13 ± 7.81	90.67 ± 2.08	0.393

Table 1: Demographic, immunological, induction therapy and clinical characteristics among no rejection, borderline and rejection groups.

Characteristic (n=22)	No rejection (n=11)	Borderline (n=8)	Rejection (n=3)	P value
cfDNA (%)	0.19 + 0.11	0.18 + 0.07	1.16 + 1.01	0.001*
Baseline creatinine (umol/L)	105.82 ± 30.76	116.50 ± 32.94	170.33 ± 66.77	0.047*
Baseline tacrolimus (ng/mL)	7.04 ± 1.77	8.73 ± 5.18	7.65 ± 2.19	0.623
Baseline urinalysis (negative proteinuria)	77.7%	100.0%	0	0.024*
Creatinine at 3-months (umol/L)	107.45 ± 36.09	107.13 ± 25.90	175.00 ± 62.86	0.027*
Tacrolimus level at 3-months (ng/mL)	5.68 ± 1.84	6.16 ± 1.51	6.73 ± 1.86	0.634
Urinalysis at 3 month (negative proteinuria)	81.8%	87.5%	0	0.147

Table 2: Clinical parameters at baseline and 3-months after cfDNA analysis among no rejection, borderline and rejection groups.

Conclusions

Our cohort demonstrated that the dd-cfDNA results < 0.5% were consistent with allograft biopsy reported as no rejection or borderline changes. Higher dd-cfDNA was reported in patients with a previous history of ABMR, and biopsy was reported as transplant glomerulopathy.

References

1. Bloom RD et al. J Am Soc Nephrol. 2017.
2. Stites E, et al. Am J Transplant. 2020.

Things forward

dd-cfDNA monitoring is useful in monitoring allograft injury after an appropriate therapy (respond to treatment).

AlloSeq® cfDNA CareDx®