RISK FACTORS FOR ACUTE ALLOGRAFT REJECTION IN HIV+ KIDNEY TRANSPLANT RECIPIENTS

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BACKGROUND

Kidney transplantation (KT) of HIV positive patients has transformed the management of end-stage kidney disease in this population. Although favourable outcomes have been reported, patients experience high rates of acute allograft rejection (AR) (1, 2).

AIMS

The aims of the study were:

- To examine if the choice of calcineurin inhibitor (CNI) immunosuppressive therapy had an impact on AR in the first year post-KT
- To examine factors associated with AR in the first year post-KT

METHODS

- The UK HIV/Kidney Transplant Study is an on-going observational cohort study collecting data from 40 Transplant and HIV treatment centres in the UK (1).
- The study was approved by the National Health Service multicentre research committee (MREC).
- Case ascertainment
  - Patients were included if HIV+ and ≥18 years of age at time of KT and KT was performed in the UK between 01/01/2005 and 31/12/2013
- For all analyses, patients were *a priori* stratified by the type of CNI (ciclosporin, CsA or tacrolimus, Tac) received immediately post-KT
- Statistical analysis
  - Overall patient and graft survival and cumulative incidence of AR were estimated using Kaplan-Meier methods, patients were censored at the first episode of AR or CNI switch. Log-rank test was used to compare groups..
  - Univariable and multivariable Cox proportional hazard regression analyses were used to identify factors associated with acute allograft rejection
  - A sensitivity analysis was conducted which examined factors associated with AR during weeks 1-2 and weeks 3-52 post-KT.

RESULTS

- Between January 2005 and December 2013, 78 HIV positive adults underwent KT at the participating centres, with a median follow up of 44.6 (38.5, 51.4) years
- The median age was 45 years, 74% of black ethnicity with a median (IQR) CD4 cell count of 366 (277, 516) cells/mm^3 and HIV Viral Load <50cps/mL (Table 1).
- Immunosuppression consisted of induction therapy plus maintenance therapy including CNI + mycophenolate or azathioprine + corticosteroids.

RESULTS (Cont.)

Table 1 Baseline Patient Characteristics

		All Patients	Ciclosporin	Tacrolimus	P
N		**78**	**31**	**47**	
Age, median (IQR)	Years	44.6 (38.5, 51.4)	39.5 (36.6, 49.6)	47.3 (42.0, 52.6)	**0.01**
Gender, n (%)	Male	52 (67)	24 (77)	28 (60)	0.10
Ethnicity, n (%)	Black	58 (74)	24 (77)	34 (72)	0.62
Cause of ESKD, n (%) **	HIVAN	40 (52)	18 (58)	22 (48)	0.38
Duration of pRRT, median(IQR) ǂ	Years	4.9 (2.6, 7.1)	4.5 (2.2, 6.4)	6.1 (3.3,7.3)	0.27
Mode of acquisition§, n (%)	HTS	54 (75)	22 (71)	32 (78)	0.46
CD4 count at KT, median (IQR)**	cells/mm^3	92 (40, 171)	92 (38, 160)	95 (41, 179)	0.93
Viral load at KT, median (IQR)	$\log_{10}$ copies/ml	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.6 (1.6, 1.7)	0.07
PI/r-Containing ART, n(%)		30 (38)	15 (48)	15 (32)	0.14
Hepatitis B co-infection, n (%)**		10 (13)	5 (16)	5 (11)	0.50
Hepatitis C co-infection, n (%) ¶		4 (5)	3 (10)	1 (2)	0.16
Allograft type, n (%)**	Cadaveric	51 (66)	18 (58)	33 (72)	0.21
Donor/Recipient CMV mismatch status, n (%)	D+/R-	4 (5)	2 (6)	2 (4)	0.67
Induction IS therapy, n(%)[a] Anti-CD25 monoclonal antibody		68 (93)	29 (94)	36 (92)	0.90

*Comparing medians, Wilcoxon rank-sum (Mann-Whitney) test; comparing proportions (%), chi-squared test and two-sample test of proportions. Statistically significant (p < 0.05); Missing values - **n=1, ¶ n=3, ϟ n=6, ǂ n=7, a Tacrolimus n=8.
Key: IS – immunosuppression, KT – Kidney transplantation, HTS – heterosexual, PI/r – Ritonavir boosted protease inhibitors, CMV – Cytomegalovirus, pRRT – Permanent renal replacement therapy, ESKD – End-stage kidney disease

Allograft Outcomes

- Overall 1 year patient and graft survival rates were 96.8% and 95.3% respectively.
- Delayed graft function occurred in 16 patients (21%; ciclosporin 7, tacrolimus 9).
- Biopsy proven acute allograft rejection was diagnosed in 28 (36%) patients. The median time to AR was 2.6 (0.5, 5.9) months from allograft insertion.
- At 1-year post KT, the cumulative incidence of acute rejection was 60% in the ciclosporin group compared with 20% in the tacrolimus group (p=0.0003, Fig 1).

Fig 1: Cumulative Incidence of Acute Allograft Rejection

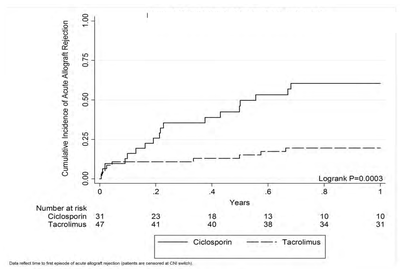
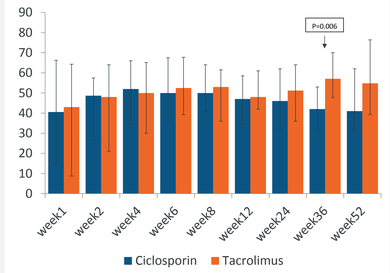


Fig 2: Graft Function (eGFR)



Graft function

- The median eGFR at 52 weeks was 41 (IQR 31, 62) and 55 (IQR 40, 78) mL/min/1.73 m^2 ciclosporin vs tacrolimus, respectively (Fig 2).
- The median eGFR for recipients who experienced AR vs no AR at 1 year (38 [IQR 27, 48] vs. 60 [IQR 47, 83] mL/min per 1.73 m^2 (p=0.0002).

RESULTS (Cont.)

Table 2 Factors Associated with Acute Allograft Rejection

	Entire follow up (n=78)		Excludes follow up during the first 2 weeks post-KT (n=72)			
	Univariable		Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at KT (per year older)	1.00 (0.95, 1.04)	0.84	0.99 (0.94, 1.05)	0.71		
Gender (Male)	1.49 (0.63, 3.53)	0.36	1.58 (0.57, 4.34)	0.38		
Ethnicity (Black)	1.36 (0.55, 3.37)	0.51	0.92 (0.36, 2.41)	0.87		
Mode of acquisitionΨ (Other)	1.24 (0.55, 2.85)	0.60	1.61 (0.64, 4.05)	0.31		
Transplant year	1.04 (0.89, 1.21)	0.59	1.00 (0.84, 1.18)	0.97		
CD4 count at KT (per 50 cell increase)**	0.98 (0.89, 1.08)	0.71	0.98 (0.89, 1.08)	0.71		
HBV Co-infection (Yes)**	1.71 (0.65, 4.56)	0.28	1.97 (0.65, 5.93)	0.23		
HCV Co-infection¶ (Yes)	2.80 (0.84, 9.38)	0.09	2.60 (0.60, 11.31)	0.20		
Donor/Recipient CMV IgG mismatch (D+R-)	0.88 (0.12, 6.46)	0.90	excluded			
CMV Prophylaxis (Yes)	1.35 (0.63, 2.9)	0.44	0.80 (0.31, 2.03)	0.64		
Allograft type¶ (Cadaveric)	0.98 (0.44, 2.19)	0.96	0.72 (0.30, 1.77)	0.48		
Delayed graft function (Yes)	1.83 (0.80, 4.18)	0.15	1.50 (0.54, 4.13)	0.43		
cART regimen (PI/r containing)	1.57 (0.74, 3.35)	0.24	2.63 (1.08, 6.44)	**0.03**	1.06 (0.47, 2.39)	0.89
Abacavir containing cART (Yes)	0.62 (0.29, 1.33)	0.22	0.39 (0.16, 0.94)	**0.04**	0.74 (0.33, 1.67)	0.47
CNI Choice at KT (Tacrolimus)	0.25 (0.11, 0.57)	**0.001**	0.16 (0.06, 0.43)	**0.000**	0.27 (0.12, 0.61)	**0.002**

HR=Hazard ratio estimated from Cox proportional hazard regression model with 95CI of the estimated HR. Model adjusted for CNI switch; CI=Confidence Interval; P=p-value;
Missing values - **n=1, ¶ n=3, ◻ n=6, b Tacrolimus n=8

Factors Associated with Acute Allograft Rejection

- In univariable analyses, the only factor that was significantly associated with AR was choice of CNI (HR for Tac vs, CsA 0.25 [95% CI 0.11, 0.57], p=0.001).
- In sensitivity analysis which excluded 8 patients with AR in the first two weeks post KT, use of Tac (HR 0.16 [0.06, 0.43]), abacavir (0.39 [0.16, 0.94]) and PI/r (2.63 [1.08, 6.44]) were associated with AR in univariable analysis; only use of Tac (HR 0.27 [0.12, 0.61]) was associated with AR in multivariable analysis (Table 2).

DISCUSSION

Summary

- Use of Tac was associated with a significantly reduced incidence of AR in the first year post KT.
- Our data suggest that Tac may be the preferred CNI for KT in HIV infection.
- Use of protease inhibitor-sparing antiretroviral therapy may facilitate the safe administration of Tac.

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