Risk factors of acute organ rejection after liver transplantation in HIV+/HCV+ patients

Poster #541

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Background

With the improvement of HIV therapies, the number of HIV-HCV co-infected patients that require liver transplant (LT) has increased significantly over the past years. HIV co-infected HCV+ LT recipients show a markedly increased rate of organ rejection when compared to LT in HIV-negative patients (Manzardo C et al. CROI 2016. Poster #572). However, the risk factors for rejection of LT in coinfected patients have been poorly studied. Here, we investigated the contribution of clinical and genetic, patient and donor variables that may predict LT outcome, with special focus on acute organ rejection.

Methods

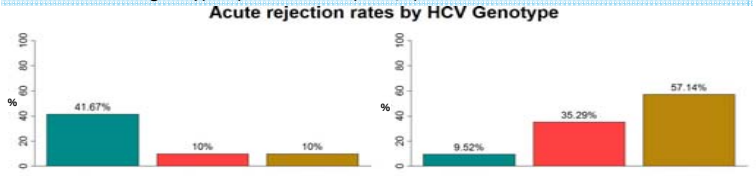
We studied 45 consecutive HIV/HCV co-infected patients that underwent LT between 2006-2012 in 9 referral centers across Spain. For 33 of the 45 recipients, organ donor samples or at least some genetic donor information were available. Samples were stored in the Spanish HIV HGU Biobank, of Hospital GU Gregorio Marañón, Madrid (Spain), integrated in the Spanish AIDS Research Network (RIS). Recipient and donor gender and age as well as patient's pre- and post OLT HCV viral loads, CD4+ cell count, MELD score, immune suppressive treatment and HCV genotype were recorded. In addition, donor and recipient genetic markers were determined, including HLA-A, -B and DR genotype and IL28B single nucleotide polymorphisms (SNPs: rs12979860, rs8099917 and ss469415590). All acute rejections were biopsy-proven.

Results

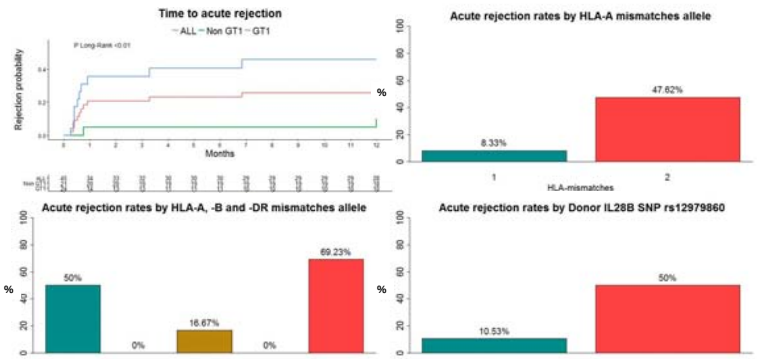
1) Demographics

	ALL N=45	Non-acute rejection N=33 (73,3%)	Acute rejection N=12 (12,7%)	p-value
Pre-trasplant recipient variables				
Age (years)	47.9 (4.93)	47.8 (4.66)	47.9 (5.84)	0.971
Male gender	38 (84.4%)	28 (84.8%)	10 (83.3%)	1
HIV-1 RNA <50 copies/ml at listing	39 (90.7%)	28 (87.5%)	11 (100%)	0.558
cART: PI-based at LT	15 (33.3%)	13 (40.6%)	5 (45.5%)	1
MELD score at LT	16 (6)	15 (6)	17 (8)	0.464
CD4+ T-cell counts<200 at LT		13 (39.4%)	2 (16.7%)	0.283
Plasma HCV RNA viral load at LT	266520	339312	152224	0.385
	[40652;1932164]	[50882;1932164]	[3964;1592240]	
HVC genotype				0.185
1a	17 (38.6%)	11 (34.4%)	6 (50.0%)	
1b	7 (15.9%)	3 (9.38%)	4 (33.3%)	
3a	10 (22.7%)	9 (28.1%)	1 (8.33%)	
4a	2 (4.55%)	2 (6.25%)	0 (0.00%)	
4d	8 (18.2%)	7 (21.9%)	1 (8.33%)	
Hepatocellular carcinoma	14 (31.1%)	11 (33.3%)	3 (25.0%)	0.725
Donor variables				
Age (years)	62.8 (18.0)	60.2 (17.3)	70.2 (18.6)	0.120
Male gender	24 (53.3%)	16 (48.5%)	8 (66.7%)	0.457
Donor Risk Index (DRI)	1.69 (0.38)	1.71 (0.40)	1.65 (0.30)	0.605
Immunosuppression variables				
Induction (Basiliximab®)	10 (22.2%)	9 (27.3%)	1 (8.33%)	0.246
Cyclosporin A based regimens	15 (33.3%)	12 (36.4%)	3 (25.0%)	0.722
Tacrolimus based regimens	23 (51.1%)	17 (51.5%)	6 (50.0%)	1

2) Of the 45 patients, more than a quarter (n=12, 27%) had a histology-proven episode of acute rejection within the first year after transplant. Independent risk factors for an acute rejection was infection with HCV genotype 1 (GT1 vs non-GT1 p=0.036).



3) Acute rejection was associated with mismatches in the HLA class I and II loci, especially with a complete mismatch across HLA-A, -B and DR alleles (p=0.001). This risk was driven particularly by the HLA-A locus (p=0.027). In addition, patients receiving organs carrying the interferon-λ3 gene (IFNL3, also named IL28B) SNP rs12979860 -CC alleles had a higher risk for organ rejection (p-value=0.030)



4) Summary of univariate analyses

	Non-acute rejection N=33	Acute rejection N=12	p-value
HCV genotype 1	14 (42.4%)	10 (83.3%)	0.036
HLA mismatches			
HLA-A: 1	11 (50.0%)	1 (9.09%)	0.027
2	11 (50.0%)	10 (90.9%)	
HLA-B:0	1 (4.00%)	0 (0.00%)	0.608
1	9 (36.0%)	2 (18.2%)	
2	15 (60.0%)	9 (81.8%)	
HLA-C: 0	2 (11.1%)	0 (0.00%)	0.096
1	4 (22.2%)	5 (71.4%)	
2	12 (66.7%)	2 (28.6%)	
HLA-E: 0	5 (83.3%)	5 (71.4%)	0.462
1	1 (16.7%)	0 (0.00%)	
2	0 (0.00%)	2 (28.6%)	
HLA-DRB: 0	1 (4.35%)	1 (9.09%)	1
1	4 (17.4%)	1 (9.09%)	
2	18 (78.3%)	9 (81.8%)	
HLA-A+B: 2	4 (18.2%)	1 (9.09%)	0.010
3	12 (54.5%)	1 (9.09%)	
4	6 (27.3%)	9 (81.8%)	
HLA-A+B+DRB: 2	1 (5.00%)	1 (9.09%)	0.002
3	1 (5.00%)	0 (0.00%)	
4	5 (25.0%)	1 (9.09%)	
5	9 (45.0%)	0 (0.00%)	
6	4 (20.0%)	9 (81.8%)	
SNP-Polymorphisms			
Donor SNP rs8099917: GT/TT	2 (8.70%)	0 (0.00%)	1.000
GG	21 (91.3%)	7 (100%)	
Donor SNP rs12979860: CT/TT	5 (22.7%)	5 (71.4%)	0.030
CC	17 (77.3%)	2 (28.6%)	
Donor SNP ss469415590: dG	2 (8.70%)	0 (0.00%)	0.227
TT	8 (34.8%)	5 (71.4%)	
TT/dG	13 (56.5%)	2 (28.6%)	

Conclusions

1) HCV genotype 1 was associated with acute rejection. Further studies are needed to confirm this finding due to the small sample size of our study.
2) We have identified other additional host and donor genetic markers that may potentially increase the risk of organ rejection and which may help in the clinical management and organ allocation in liver transplantation in the HIV/HCV co-infected population.

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