P-44

Liver transplantation in HIV-HCV co-infected patients

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ABSTRACT

Background:

End stage liver disease in HIV_HCV co-infected patients is an emerging problem requiring to assess the benefit risk ratio of liver transplantation (LT). We started a prospective evaluation of LT in co-infected patients in December 1999 assessing several parameters: impact on the immune system and HIV replication, drug interactions, mitochondrial toxicity and incidence of HCV relapse.

Methods:

Up to June 2003, eleven HIV-HCV co-infected patients without history of opportunistic infection, were transplanted. At time of LT all patients were exposed to HAART, HIV plasma viral load was < 400 copies/mL and the median CD4 lymphocyte count was 350 cells/mm3 (range: 103-659). Immunosuppression therapy consisted of steroids and Tacrolimus. Anti HCV viral therapy was used when necessary and its benefit risk ratio was prospectively evaluated. Lastly, mitochondrial toxicity on the graft was studied by spectrophotometric analyses of the respiratory chain complexes and molecular analysis of mitochondrial DNA (mtDNA).

Results:

At time of evaluation, the median follow-up is 18 months (range: 3-45): three patients died, four, eleven and nineteen months after LT. Seven patients are in good condition and one patient is in poor condition. None on the patients developed opportunistic infection. Drug interaction was under control, only one patient developed a transient renal insufficiency. HCV replication started promptly after LT in all patients. Seven patients began pegylated interferon (PEG-IFN) and ribavirin therapy. This treatment was stopped in three patients because of intolerance. One patient showed a virological response and another a biochemical response and a decrease of liver fibrosis. At last biopsy, METAVIR score was staged F4 in two patients, F3 in one, F2 in two. Microvesicular steatosis was observed in nearly all patients. The ratio mtDNA nuclear DNA was low in four patients. A significant defect on the activities of respiratory chain was noted in five patients.

Conclusion:

Liver transplantation in HIV -HCV co-infected patients is feasible in a very selected population. Our experience do not suggest a deterioration of immune deficiency. Drug interaction is not a limiting problem. The early and severe relapse of hepatitis C suggest to start promptly an association of PEG-IFN and ribavirin. LT requires a multidisciplinary partnership.

INTRODUCTION

Life expectancy in HIV infected patients has dramatically increased due to the efficacy of highly active antiretroviral therapy (HAART). Liver disease progression to cirrhosis is much faster in HIV-HCV co-infected patients than in HCV mono-infected patients. End stage liver disease is an emerging problem that requires to asses the benefit risk ratio of liver transplantation (LT). We started a prospective appraisal of LT in HIV-HCV co-infected patients in December 1999. This study addresses morbidity, mortality, impact on the immune system, HIV replication, drug interactions, mitochondrial toxicity and incidence of HCV relapse.

METHODOLOGY

Till June 2003, eleven HIV-HCV co-infected patients had a liver transplantation in our institution. At time of LT (see Table 1):

> All patients were exposed to HAART.

> HIV plasma viral load was < 400 copies/ml and the CD4 lymphocyte count was >100 cells/ml average: 350 cells/ml, (range: 103-659].

> None of the patients had experienced any opportunistic infection.

> Liver grafts were obtained from cadaveric or living donors or from patients with familial amyloidotic polyneuropathy (domino program).

> Immunosuppression therapy consisted of steroids and Tacrolimus; single rejection episodes were treated with a bolus of methylprednisolone.

> Prophylaxis therapy of opportunistic infections consisted of Fluconazole, Cotrimoxazole and Ganciclovir.

> Clinical examination and liver biochemical test were performed daily during 14 days post LT, three times a week during the first month, once a week during three months and once a month afterwards.

> Liver biopsies were performed: after 1 month (post LT), after 6 months and then every year.

> HCV and HIV RNA levels and CD4 cell counts were monitored every week during the first month post-LT and monthly afterwards.

> Anti HCV viral therapy was used when necessary and its benefit risk ratio was prospectively evaluated.

> Monitoring of residual plasma concentration of antiretroviral treatment (PI and NNRTI) was made post LT and one week after re-introduction of treatment.

> Mitochondrial toxicity on the graft was studied by spectrophotometric analyses of the respiratory chain complexes and molecular analysis of mitochondrial DNA (mtDNA).

Patient	1	2	3	4	5	6	7	8	9	10	11
Age at LT*	29	37	43	40	43	41	49	40	63	42	46
Sex**	F	M	M	M	M	M	M	M	M	M	M
Cirrhosis*	1.5	5	1.5	1	1.5	1	3	2	9	1	4
HIV infection*	7	13	15	16	14	16	12	15	14	18	15
Prothrom(%) V fact. (%)	25 32	26 30	33 55	18 15	64 57	48 56	54 50	30 29	35 55	73 65	60 62
Albumin (g/L) Bilirubin (μM)	42 258	24 70	27 50	39 201	29 39	32 99	25 36	27 109	25 46	30 48	36 18
Creatinine (μM)	59	96	97	69	69	71	84	70	132	90	125
Ascites Encephalop.	Yes No	Yes No	No No	Yes Yes	Yes No	No No	Yes No	Yes No	Yes No	Yes No	No No
HCV genotype	1b	4c,4d	1a	1a	3a	1b	1a	1a	1	1a	3a
HCV RNA (log IU/mL)	5.9	5.3	6.8	4.6	5.9	5.6	6.2	5,8	4	5,7	4,3
HIV RNA (copies/mL)	294	<50	<50	210	<50	<50	134	<50	<50	<50	<50
CD4 (cells/mm3)	341	103	510	320	180	240	430	980	659	488	320
HAART***	d4T NVP NFV	d4T 3TC	AZT 3TC IDV	d4T DDI	NFV EFV DDI	AZT 3TC EFV	AZT 3TC DDI	3TC ABC TNF	D4T 3TC TNF	ABC EFV 3TC	TNF NFV 3TC
LT protocol§	Total D.	split D. + Cad. d.	total D.	Liv. d.	Cad. d.	Cad. d.	total D.	Cad.d	Liv.d	Cad.d	Total D.

Table 1: Clinical and laboratory features of HIV-HCV coinfected patients before LT
LT: Liver Transplantation ;* age, duration of cirrhosis and duration of HIV infection are given in years, **M:
Male, F: Female; Prothrom = prothrombin time; Total D=. Domino protocol, Cad. d. = Cadaveric donor, Liv.
d. = living donor, patient 2 was transplanted twice because of rapid dysfunction of the first graft.

RESULTS

The median follow-up is 18 months (range 3-45). At time of evaluation (see table 2):

> Three patients died after LT (mortality: 28%):

- **Patient 3 died 22 months after LT with HAART hepatotoxicity and severe recurrence of HVC infection on the liver graft.**
- **Patient 6 died 4 months after LT with HAART hepatotoxicity and acute recurrence of HCV infection on the liver graft.**
- **Patient 8 died 11 months after LT with Carcinoma de pancreas**

> Seven patients are in good condition and one patient is in poor condition.

> None of the patients develop ed opportunistic infection.

> Drug interaction was under control, only one patient developed a transient (?) renal insufficiency.

> HCV replication started between day 12 and month 2 post LT in all patients. Nine patients started pegylated interferon (PEG-IFN) and ribavirin therapy. This treatment was stopped in four patients due to a poor tolerance.

> The ratio mtDNA nuclear DNA was low in four patients. A significant defect on the activities of respiratory chain was noticed in five patients. Other evaluations are underway (see table 3).

Patient	1	2	4	5	7	9	10	11
Delay after LT (months)	45	34	26	24	18	7	5	3
Karnovsky score (%)	80	80	80	50	80	80	80	70
ALAT (IU/L)	16	35	83	18	26	49	99	89
Bilirubine level (μM)	6	18	19	70	10	7	28	28
Prothrombin time (%)	86	78	100	52	100	100	96	100
HIV RNA (copies/mL)	nd	nd	nd	nd	nd	nd	Nd	Nd
HCV RNA (log IU/mL)	nd	6	6.6	6.5	6.7	6.7	6.1	6.6
CD4 (cells/mm3)	420	190	300	160	250	310	200	480
HAART*	d4T EFV NFV	ABC TDF LPV RTV	NFV EFV 3TC	NFV EFV 3TC	ABC TDF LPV RTV	EFV TDF 3TC	ABC EFV 3TC	TDF 3TC NFV

Table 2: Clinical and laboratory features of HIV-HCV co-infected patients after LT
Patient 3 died 22 months after LT with HAART hepatotoxicity and severe recurrence of HVC infection on the liver graft. Patient 6 died 4 months after LT with HAART hepatotoxicity and acute recurrence of HCV infection on the liver graft. Patient 8 died 11 months after LT with Carcinoma de pancreas
nd = not detectable; * abbreviations of HAART therapy: d4T: stavudine EFV: efavirenz NFV: nelfinavir ABC: abacavir TDF: tenofovir LPV: lopinavir; RTV: ritonavir 3TC:lamivudine.

Patient	histological lesions *	mitochondrial activities **	mtDNA	HAART therapy *
2	centrilobular necrosis (M7)	I 10, IV 4, CS170 (M18)	0.2 (M18)	d4T-3TC-EFV (M8) d4T-DDI-LPV-RTV (M18) ABC-TNF-LPV/RTV
3	moderate microvesicular steatosis (M10)	I 20, IV 0, CS 164 (M18)	0.3 (M18)	ZDV-3TC-IDV (M10) ZDV-3TC-NFV
4	moderate microvesicular steatosis (M6)	I 26, IV 9, CS 89 (M6) I 31, IV 14, CS 108 (M12) I 16, IV 3, CS 68 (M18)	1.4 (M12)	DDI-d4T-3TC (M6) EFV-NFV-3TC
5	diffuse microvesicular steatosis (M2)	I 22, IV 12, CS 110 (M6)	5.2 (M6)	EFV-NFV-DDI
7	moderate microvesicular steatosis (M4)	I 6, IV 12, CS 83 (M1) I 30, IV 21, CS 142 (M3) I 11, IV 0, CS 86 (M8) I 20, IV 11, CS 114 (M12) I 24, IV 17, CS 66 (M15)	4,7 (M1) 0.1 (M3)	AZT-3TC-DDI (M4) AZT-3TC-NFV (M6) DDI-TNF-LPV/RTV (M9) ABC-TNF-LPV/RTV
10	Lobulaire hepatitis (M6)	I 1, IV 14,CS 122(M5)		ABC-EFV-3TC
11	Lobulaire hepatitis Microvesicular steatosis (M3)	I 27, IV 26, CS 81 (M1) I 14, IV 66, CS 36 (M3)		TNF-NFV-3TC

Table 3: Description of mitochondrial toxicity on the liver graft. Management of HAART
* The time from LT at disclosure of each of the anomalies or at therapeutic change is given in months after LT (M).
** Activities of the mitochondrial enzymes are expressed as nanomoles substrate utilized per minute and milligram protein of the post-nuclear supernatant obtained from frozen liver fragments (nmoles/min/mg). Normal values range from 13 to 31, 20 to 56 and 21 to 55 nmoles/min/mg for NADH ubiquinone oxido-reductase (I: complex I of the respiratory chain, cytochrome c oxidase (IV: complex IV of the respiratory chain) and citrate synthase (CS, a Krebs cycle enzyme, which is used to measure the mitochondrial content in the sample) respectively. § mtDNA quantity is expressed as a ratio of mtDNA to nuclear DNA. A ratio >1 is considered normal for liver mtDNA.

CONCLUSION

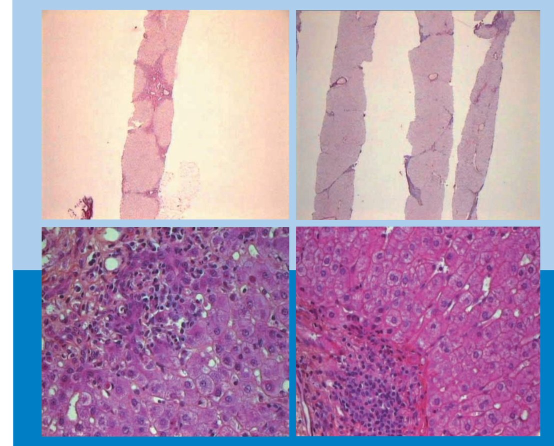
Liver transplantation in HIV-HCV co-infected patients is feasible in a very selected population. The management "a la carte" is the only way to ensure a favorable benefit risk ratio in grafted HIV-HCV co infected patients. This management depends on careful monitoring of all clinical, biochemical, virological and pathological parameters characterizing the post-LT period.

The early and severe relapse of hepatitis C suggests starting promptly an association of PEG-IFN and ribavirin.

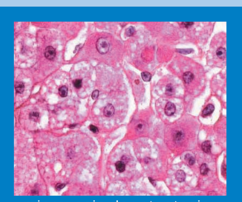
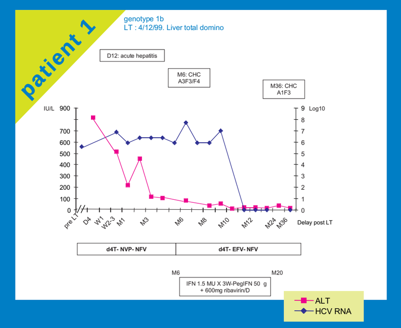
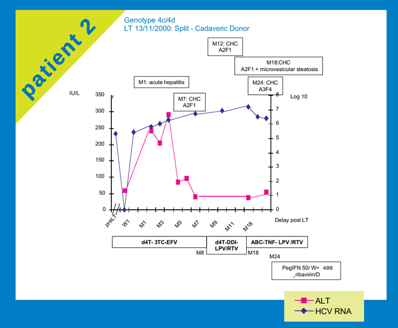
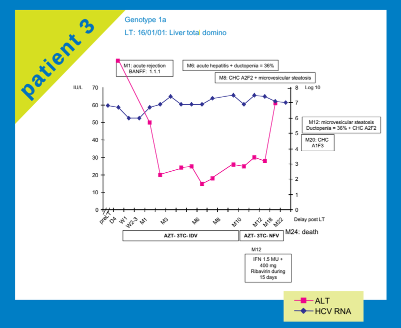
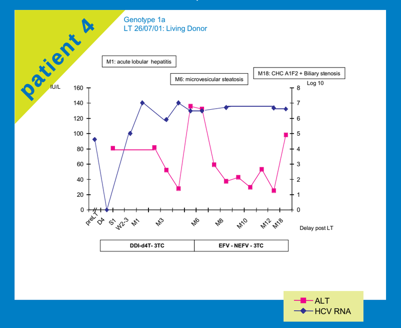
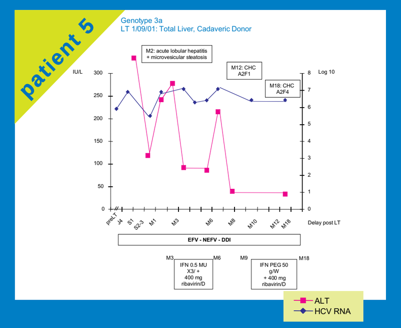
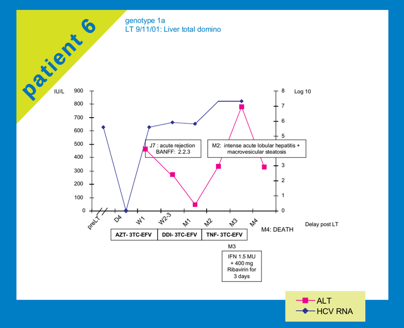
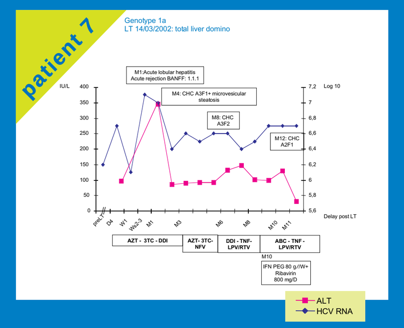
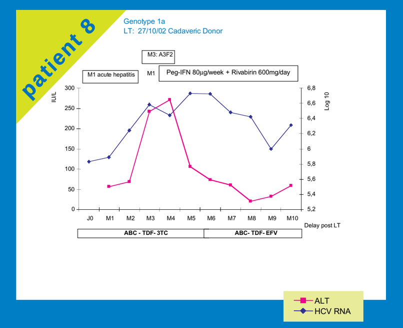
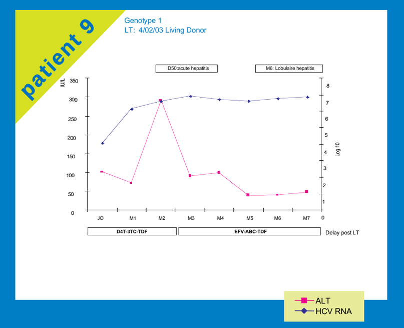
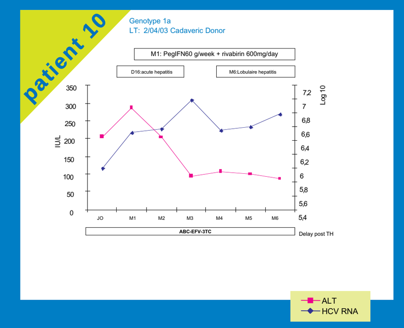
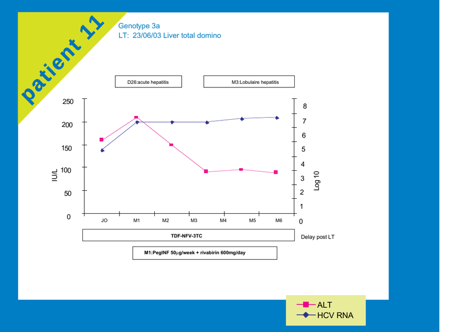
Mortality is higher in this selected population than in HIV (-) grafted patients.

Mitochondrial toxicity on the graft and high frequency of early microvesicular steatosis. are other issues. The precise features of this toxicity is unclear.

Our experience does not suggest short term deleterious effect on immune system. Drug interaction is not a limiting problem. LT requires a multidisciplinary partnership.



6 months post-LT 3 years post-LT



microvesicular steatosis at M2 post LT