

HEPATIC STEATOSIS IN HIV AND HEPATITIS C VIRUS COINFECTED PATIENTS RECEIVING ANTIRETROVIRAL THERAPY

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INTRODUCTION

- Previous results of retrospective studies suggest a role of antiretroviral therapy and/or metabolic syndrome in the development of fatty liver disease

- Advances in factors influencing the development of steatosis could permit to adapt the management of antiretroviral drugs in patients with risk factors.

- Our objective was to assess prevalence, severity of hepatic steatosis and risk factors influencing hepatic steatosis in HIV and HCV coinfecting patients.

PATIENTS AND METHODS

◆ Retrospective analysis of 127 HIV and HCV coinfecting patients, who underwent liver biopsies from 01.1995 to 07.2005 and followed antiretroviral therapy (ART)

◆ Patients were eligible for the study if :

- HIV-1 infection
- HCV infection with detectable HCV-RNA in the serum or treated by ART.

◆ Patients were excluded if : positivity of HBs Ag testing, negative HCV-RNA, no previous exposure to ART

◆ Following data were recorded at the time of biopsy:

- Demographic characteristics: age, gender, ethnicity, past history of IV drugs or alcohol abuse,

- HIV parameters: CD4 cell count, plasma HIV RNA level, exposure duration of each drug

- HCV parameters: HCV genotype, plasma HCV-RNA level expressed in KUI/ml as recommended.

- Laboratory parameters : glycemia, ALT, AST, alkaline phosphatases, GGT, serum total cholesterol, triglycerides

◆ Histologic evaluation

- Liver biopsies were performed to establish the state of infection and to decide therapy for chronic hepatitis C
- Biopsies read by the same pathologist
- Liver steatosis was graded according to the percentage of hepatocytes affected: 0, none; 1, steatosis involving <33% of hepatocytes; 2, 33-66% and 3, >66%

◆ Statistical analysis

Median and interquartile ranges (IQRs) described continuous variables. Comparisons were performed using Wilcoxon rank-sum or Fisher' exact tests. Univariate and multivariate logistic regression analyses were used to identify determinants of liver steatosis. To take into account the modification of antiretroviral therapy, exposure to ART was studied after adjustment on period of biopsy (before 1998, 1999-2001, 2002+).

RESULTS

CHARACTERISTICS OF STUDY POPULATION

Demographic characteristics (n=127) expressed as median (IQR) or number (%)	
Age at biopsy [years]	39 (35-43)
Male	104 (82)
Ethnicity	
Caucasian	113 (89)
Black	15 (11)
Intravenous drug use	99 (78)
Alcohol abuse	45 (35)
HCV genotype	
1	62 (58)
2	5 (5)
3	29 (27)
4	11 (10)
HCV RNA [KUI/ml]	3.160 (2.920-3.540)
CD4 cell counts [mm ³]	320 (196-448)
HIV RNA (copies/ml)	8,589 (1,860-62,389)
ALT [U/l]	91 (62-134)
AST [U/l]	71 (49 - 101)
Alkaline phosphatases (AP) [U/l]	89.5 (67-113)
GGT [U/l]	72.5 (33-174)
Glycemia [mmol/l]	4.8 (4.3-5.2)
Cholesterol [mmol/l]	4.33 (3.57 - 5.26)
Triglycerides [mmol/l]	1.46 (0.98 - 2.14)
Cumulative exposure to ARV (months)	
NRTI	53
NNRTI	13
PI	22

Table 1 : Demographic characteristics of the 127 patients at the time of liver biopsy

HEPATIC STEATOSIS, FIBROSIS AND ACTIVITY

◆ Representation of different genotypes (1 to 4), grade of fibrosis (0 to 4) and steatosis (0 to 3) according to steatosis or no steatosis in Figure 1.

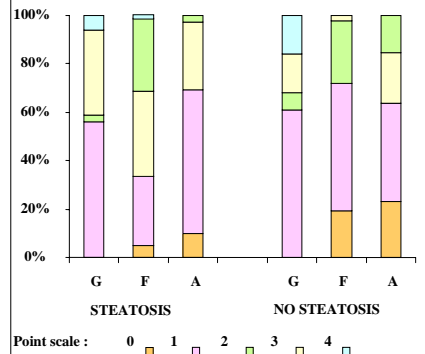


Figure 1: Genotype, fibrosis and activity in percentage, according to the presence or absence of steatosis.

◆ We observed in univariate analysis a positive correlation between steatosis and liver fibrosis (p=0.003), but not correlation with necroinflammatory activity (p=0.54)

HEPATIC STEATOSIS AND HIV, HCV, BIOLOGICAL AND DEMOGRAPHIC DATA

◆ Results of univariate analysis was summarized in the Table 2.

	Patients n=127	NO STEATOSIS n=48	STEATOSIS n=79	p
age	39 (35-43)	27 (34-41)	39 (36-44)	0.04
Male sex	104 (82%)	35 (73%)	69 (87%)	0.06
IVDU	99 (78%)	36 (77%)	63 (80%)	0.82
Alcohol abuse	45 (35%)	18 (37%)	27 (34%)	0.71
CD4	320 (196-448)	342 (193-483)	298 (196-400)	0.28
HIV viral load (log10)	2.30 (2.30 - 3.40)	2.36 (2.30 - 3.93)	2.30 (2.30 - 3.40)	0.62
HCV RNA (log10)	3.16 (2.92-3.54)	3.0 (2.75-3.42)	3.25 (3.03-3.67)	0.013
cholesterol	4.33 (3.57-5.26)	4.66 (3.81-5.38)	4.0 (3.3-5.1)	0.01
triglycerides	1.46 (0.98-2.14)	1.46 (0.97-2.04)	1.41 (0.98-2.25)	0.94
ALT level	91 (62-134)	83.5 (41-150)	103 (70-133)	0.21
AST level	71 (49-101)	65.5 (38-90)	78 (53 - 112)	0.02
AP	89.5 (67-113)	89.5 (65-112.5)	89.5 (68 - 113)	0.80
GGT	72.5 (33-174)	54 (29-119)	84 (33 - 200)	0.10
Glycemia	4.8 (4.3-5.2)	4.65 (4.2-5.1)	4.85 (4.4 - 5.3)	0.24
Genotype				
1	62 (58%)	27 (61%)	35 (56%)	0.07
2	5 (5%)	3 (7%)	2 (3%)	
3	29 (27%)	7 (16%)	22 (35%)	
4	11 (10%)	7 (16%)	4 (6%)	
Fibrosis				0.003
0	15 (12%)	11 (23%)	4 (5%)	
1	41 (32%)	19 (40%)	22 (28%)	
2	38 (30%)	10 (21%)	28 (35%)	
3	31 (25%)	7 (15%)	24 (30%)	
4	1 (1%)	0	1 (1%)	
Activity				0.54
0	17 (13%)	9 (19%)	8 (10%)	
1	72 (67%)	25 (53%)	47 (59%)	
2	34 (27%)	12 (26%)	22 (28%)	
3	3 (2%)	1 (2%)	2 (3%)	

Table 2: Univariate analysis between hepatic steatosis and demographic and biological parameters

HEPATIC STEATOSIS AND ANTIRETROVIRAL DRUGS

Patients	NO STEATOSIS n= 48	STEATOSIS n=79	AOR (IC95%)	p
AZT	38 (79%)	67 (85%)	1.47 (0.58-3.72)	0.47
3TC	43 (90%)	69 (87%)	0.80 (0.26-2.51)	0.78
D4T	37 (77%)	54 (68%)	0.64 (0.28-1.46)	0.32
DDI	28 (58%)	52 (66%)	1.38 (0.66-2.88)	0.45
DDC	4 (8%)	13 (16%)	2.17 (0.66-7.08)	0.28
TFV	0	2 (2%)		0.53
ABA	10 (21%)	4 (5%)	0.20 (0.06-0.69)	0.008
NRTI	48 (100%)	79 (100%)		
RTV	12 (25%)	16 (20%)	0.76 (0.32-1.79)	0.66
IDV	22 (46%)	28 (35%)	0.65 (0.31-1.35)	0.26
NFV	12 (25%)	16 (20%)	0.76 (0.32 -1.79)	0.66
SQV	9 (19%)	12 (15%)	0.78 (0.30-2.0)	0.63
LPV	2 (4%)	1 (1%)	0.29 (0.03-3.34)	0.56
IP	30 (62%)	49 (62%)	0.98 (0.47-2.05)	1.0
EFV	12 (25%)	18 (23%)	0.88 (0.38-2.05)	0.83
NVP	16 (33%)	15 (19%)	0.47 (0.21-1.07)	0.09
NNRTI	22 (46%)	30 (38%)	0.72 (0.35-1.50)	0.46

Table 3: Univariate analysis between hepatic steatosis and antiretroviral drugs

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UNIVARIATE ANALYSIS

- ◆ All patients have been exposed to NRTI with 53 months median duration exposure, 79/127 to PI with 22 months median duration exposure and 52/127 to NNRTI during 13 months.
- ◆ Results for all drugs used were described in the Table 3.

In univariate analysis,

- ◆ no association was found between steatosis and exposure to PI (p=1) and to NNRTI (p=0.46)
- ◆ Abacavir and nevirapine were associated with a decrease risk of hepatic steatosis. After adjustment on the period of biopsy, only abacavir remain associated with lower risk of steatosis development.
- ◆ Moreover, only the duration exposure to abacavir was considered as protective (p=0.04).

MULTIVARIATE ANALYSIS

In multivariate analysis, independent determinants of hepatic steatosis were

- age>45 years (AOR, 2.65; 95% CI, 0.75-9.32)
- genotype 3 (AOR, 2.72; 95% CI, 0.99-7.47).
- abacavir use remained associated with decreased risk of hepatic steatosis (AOR 0.19; 95% CI; 0.04-0.84).

CONCLUSION

◆ In our cohort, liver steatosis appears in 62% of HIV and HCV coinfecting patients receiving ART.

◆ In multivariate analysis, liver steatosis was associated with age>45 years, genotype 3 and abacavir use remained associated with decreased risk of hepatic steatosis.

◆ Results about the protective effect of abacavir, a non thymidinic drug group with less mitochondrial damage, showed the possible key role of DNA mitochondrial toxicity sparing in the genesis of steatosis.

◆ Moreover, these results suggest a new opportunity to prevent hepatic steatosis in HIV and HCV coinfecting patients.

◆ Nevertheless, the role of drug classes and drugs within classes should be investigated in future prospective studies.