Significant decrease of liver fibrosis in HIV-HCV co-infected patients treated for HCV infection

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Background: To evaluate prospectively the regression of liver stiffness and the kinetics of two biochemical tests of liver fibrosis (FIB-4 and APRI) in HIV/HCV co-infected patients treated for their hepatitis C.
Methodology: In the ANRS CO13 HEPAVIH Cohort, patients with HIV and chronic hepatitis C who (1) received anti-HCV treatment with pegylated interferon-α and ribavirin and (2) had a liver stiffness measurement by transient elastometry before and after anti-HCV treatment were included. The kinetics of liver stiffness, FIB-4 and APRI were characterized during therapy and thereafter in patients with sustained virological response (SVR) and in patients with treatment failure.
Results: Among the 160 patients included, 69 (43%) had a SVR while 91 were non responders (NR). After a median follow-up duration of 36 months (IQR: 23.4-46.3), a significant liver stiffness decrease was observed after treatment in patients who achieved a SVR. In this group, the median decrease of liver stiffness was 19% after 1 to 2 years (p=0.007), 31% after 2 to 3 years (p=0.002), and 25% after 3 to 4 years (p=0.009). Similar dynamics were observed with APRI and FIB-4 and the liver stiffness decrease was observed in cirrhotic as well as in non-cirrhotic patients. In the NR group, there was a transient but non sustained decrease in the first year following the end of treatment. In the multivariate analysis, only the SVR was associated with long-term improvement of liver stiffness (odds ratio: 2.79; 95% confidence interval: 1.19-6.51, p=0.017).
Conclusions: In HIV/HCV co-infected patients, liver stiffness is significantly reduced after treatment, and this improvement continues off treatment in patients who achieve a SVR.

BACKGROUND

The goal of HCV treatment is to obtain a sustained virological response (SVR) and therefore to reduce fibrosis and risks of HCV-related complications.
Elastometry measurement (FibroScan) is considered as a reliable method for fibrosis evaluation in HIV-HCV co-infected patients.

AIM

- To evaluate the effect of SVR to anti-HCV treatment on liver fibrosis in HIV-HCV co-infected patients, using repeated measurements of Fibroscan, APRI and FIB4 indexes.
- To determine factors associated with decrease of liver fibrosis in HIV-HCV co-infected patients, using liver stiffness (LS) results

PATIENTS

- 226 HIV-HCV co-infected patients enrolled in the ANRS CO13 HEPAVIH prospective French cohort since January 2006 were included in this study
- Inclusion criteria:
  - anti-HCV treatment for at least 3 months
  - available data on treatment response: SVR or treatment failure
  - One LS result before treatment beginning and at least one after the date of treatment response evaluation
- Non inclusion criteria:
  - patients with pre-treatment LS result <7.1kPa

METHODS

- Longitudinal study
- Liver fibrosis was measured by Fibroscan, APRI and FIB4
- Definition of SVR: an undetectable HCV-RNA at least 6 months after the end of anti-HCV treatment
- Definition of treatment failure (TF): treatment discontinuation with a detectable HCV-RNA
- Baseline for the study is the date of evaluation of the treatment response: date of SVR for responder patients, date of detectable HCV-RNA for non-responder patients
- Statistical analysis:
  - quantitative variables were expressed as median (IQR), qualitative variables as N (%)
  - a Cox regression model was performed to identify factors associated with liver fibrosis regression (the dependent variable).
  - Regression in LS was defined as at least 30% decrease between the baseline and the first post-treatment LS results.

RESULTS (1)

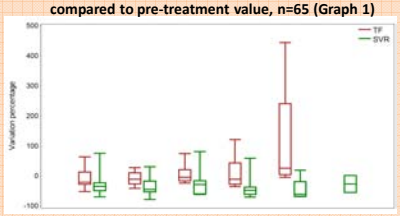
Baseline patients characteristics n=65 (Table 1)

	TF n=25	SVR n=40	p-value ¥
Men	20 (80)	31 (78)	0.8115
Age (years)	47 (44-52)	46 (45-51)	0.3844
CD4 (/mm³, n=52)	500 (369-613)	394 (337-645)	0.5518
Platelets (Giga/L, n=52)	197 (121-263)	205 (170-249)	0.5518
ASAT (X ULN)	0.98 (0.89-1.81)	0.82 (0.58-1.03)	0.6800
ALAT (X ULN)	1.26 (0.88-1.69)	0.59 (0.39-0.76)	<0.0001
Gamma GT (X ULN, n=58)	1.54 (1.08-2.19)	0.67 (0.42-1.31)	0.0012
HCV viral load (log_{10} IU/mL)	5.53 (5.04-6.63)	-	
Pre-treatment liver stiffness (kPa)	11.8 (9.2-15.7)	10.6 (9.0-14.1)	0.7261
Pre-treatment APRI index (n=64)	0.71 (0.44-1.43)	0.95 (0.51-1.92)	0.4457
Pre-treatment FIB4 index (n=64)	1.89 (1.37-3.36)	2.03 (1.35-2.94)	0.4457
HCV genotype 1-4	19 (76)	22 (55)	0.0879
HIV viral load < 50 copies/mL (n=52)	9 (56)	30 (83)	0.0791
High alcohol consumption (n=51)	1 (5)	0 (0)	0.4314

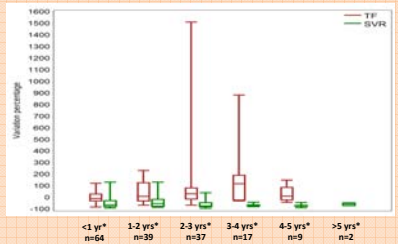
¥ Tests of X^2 or median FIB-4 = [age (years) x AST (IU/L)]/[platelet count (10(9)/L) x ALT (IU/L)1/2]. APRI (AST/Platelet ratio index) was calculated according to the formula: APRI = [(AST/ULN) x 100]/platelet count 10(9)/L where ULN = the upper limit of normal ; ULN: upper limit of normal

RESULTS (2)

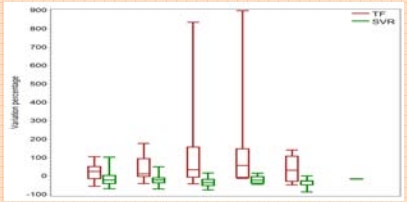
Variation of post-treatment liver stiffness measures compared to pre-treatment value, n=65 (Graph 1)



Variation of post-treatment APRI values compared to pre-treatment value, n=65 (Graph 2)

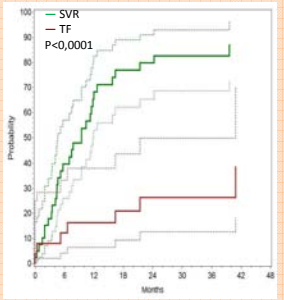


Variation of post-treatment FIB4 values compared to pre-treatment value, n=65 (Graph 3)



* time after treatment response evaluation

Probability for regression of the post-treatment liver stiffness result of more than 30%, compared to pre-treatment result (Graph 4).



Univariate analyses of factors associated with regression of liver fibrosis (Table 2)

	RR (CI95%)	p-value
Sex (women vs men)	0.863 (0.395-1.884)	0.7113
Age (years)	1.017 (0.955-1.083)	0.6076
BMI (kg/m²)	0.922 (0.904-1.089)	0.8666
ALAT (X ULN)	0.440 (0.218-0.889)	**0.0220**
ASAT (X ULN)	0.530 (0.272-1.034)	**0.0626**
Gamma GT (X ULN)	0.801 (0.590-1.089)	**0.1565**
Platelets (Giga/L)	0.999 (0.994-1.003)	0.5588
HCV genotype (1-4 vs 2-3)	0.625 (0.322-1.214)	**0.1655**
SVR vs TF	4.839 (2.109-11.105)	**0.0002**
CD4 (/mm³)	1.000 (0.999-1.002)	0.6054
HIV viral load (< 50 copies/mL vs > 50)	2.032 (0.867-4.761)	**0.1025**

In multivariate analysis, after adjustment on ALT, AST, GGT and HIV viral load, only treatment response (SVR vs TF) was associated to significant liver stiffness decrease (RR = 4.2; 95% CI: 1.6-11.3; p=0.004).

CONCLUSION

In HIV-HCV co-infected patients, liver stiffness was significantly reduced after HCV treatment in patients achieving SVR and this result was confirmed when using APRI and FIB4 for fibrosis evaluation.

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