Fibrosis Regression is Possible after Successful Treatment of Hepatitis C, Even with Cirrhosis

TUPEB241

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"I have no conflict of interest"

BACKGROUND

Liver cirrhosis has been typically considered a long-term irreversible damage. However, we now know that cirrhosis is not only the end-stage of fibrosis, but a more complex pathological condition with reversible and irreversible components (1,2).

HCV, now a curable disease, is one of the major causes of liver damage and is responsible for 70% of chronic hepatitis and 40% of decompensated cirrhosis. Suppressing the underlying disease that contributes the fibrosis process can lead to the reversal of fibrosis and even cirrhosis. Despite the scaling up of HCV treatment and evidence of an HCV cure, there have been few encouraging results showing fibrosis regression.

OBJECTIVE

The aim of this study was to document and assess the fibrosis dynamic in HCV-infected patients, specifically after HCV treatment but also in non-treated patients, and to determine the factors associated with fibrosis regression.

METHODS

Prospective and observational single site cohort study.

Inclusion criteria:

- Hepatitis C infected patients followed at Clinique médicale l'Actuel and enrolled in the HepVirAc *(Hépatite Virale à l'Actuel)* cohort;
- At least 2 interpretable measures (≥ 6 months apart) of liver fibrosis scores (METAVIR score) for non-treated patients and available pre- and post-treatment measures of liver fibrosis for treated patients.

Exclusion criteria:

- Patients who spontaneously cleared their HCV infection
- Patients who finished their treatment after January 2015
- Patients with a non reliable FS measure

The determinants of fibrosis regression were analysed by multiple logistic regression using SPSS17.0.1©. The fibrosis regression analyses were restricted to patients with METAVIR scores ≥F2 at baseline. All variables with p<0.20 in the simple model were included in the adjusted model.

RESULTS

A total of 396 patients (142 naïve and 254 treated) were included in this study. The majority of treated patients were naïve at baseline (n=189, 74%) while 26% had been treated before and either relapsed or failed their previous treatments. Patients were mostly men (77%), 49 years of age and infected by genotype 1 (71%). 25% were HIV-HCV co-infected and 11% had diabetes.

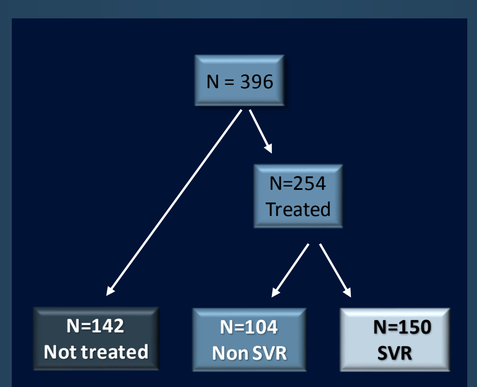
Patient characteristics are depicted in the following table:

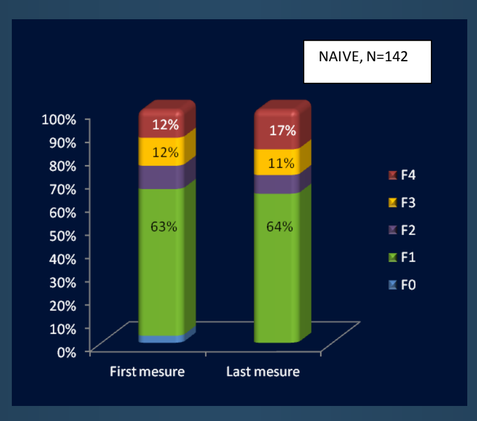
Patient characteristics	Naive (N=142) N(%)	Treated (N=254) N(%)	Total (N=396) N(%)	P-value
Gender				
Men	102(72)	203(80)	305(77)	0.044
Women	40(28)	51(20)	91(23)	
IDU	106(78)	187(74)	295(75)	0.396
Black	9(6)	11(4)	20(5)	0.475
Diabetics	11(8)	31(12)	42(11)	0.177
Alcohol abuse	46(36)	82(36)	129(36)	0.537
HCV Genotype				
GT-1,4	103(75)	190(75)	294(75)	
GT-2,3	33(24)	61(24)	94(24)	0.911
GT-other	1(1)	3(1)	4(1)	
HIV-HCV co infection	43(30)	58(23)	101(25)	0.083
HBV-HCV co infection	11(8)	7(3)	18(5)	0.023
No. of HCV treatment received				
0 treatment	142(100)	--- ---	142(36)	
1 treatment	--- ---	189(74)	189(47)	---
>1 treatment	--- ---	65(26)	65(16)	
Type of treatment				
PegINF + Riba	---	156(61)	156(61)	---
DAA + PegINF +/- Riba	---	73(29)	73(29)	
DAA (interferon free)	---	25(10)	25(10)	
Baseline MATAVIR score				
F0-F1	94(66)	69(27)	163(41)	<0.001
F2	14(10)	39(15)	53(13)	
F3	17(12)	45(18)	62(16)	
F4	17(12)	101(40)	118(30)	
Age at baseline†	48 (± 9)	49 (± 9)	49 (± 9)	0.452

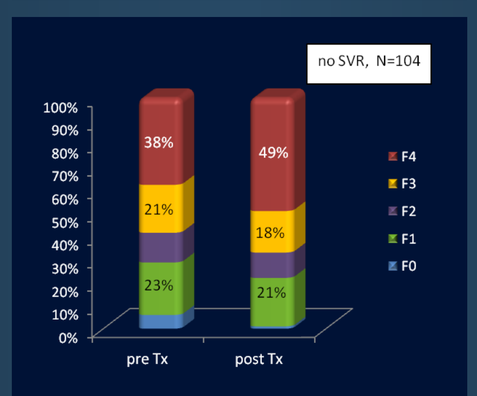
† Mean± SD

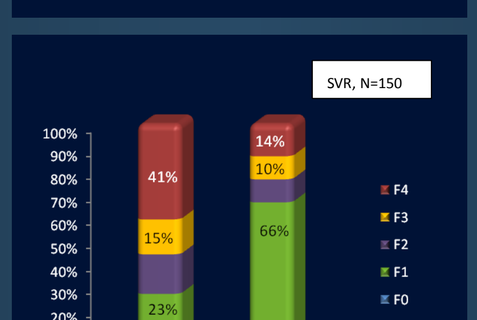
The non-treated group consisted of more women (28% vs. 20% in treated group, p=0.044), more HBV-HCV co-infected patients (8% vs. 3% in treated group, p=0.023) and more patients with no or slight fibrosis (66% vs. 27% in treated group, p<0.001). It is important to note that 40% of treated patients were cirrhotic prior to starting treatment.

The median follow-up was 2.7 years (IQR 1.5 – 4.2) for any pairs of fibrosis estimates.









Once cured of HCV, fibrosis regression occurred even in patients with baseline F4 scores (44/62 patients, 71%)

Sustained Virological Response

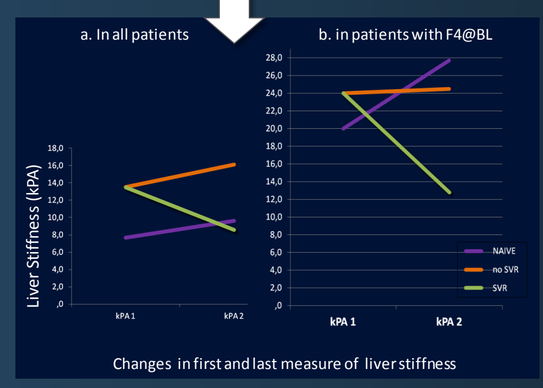
Overall, 150 (59%) treated patients had a sustained virological response (SVR) to treatment, while 104 (41%) were either non-responders or relapsers.

156 (61%) patients were treated by PEGINF + Riba, 73 (29%) with DAA+ PEGINF and only 25 (10%) received an interferon-free DAA treatment.

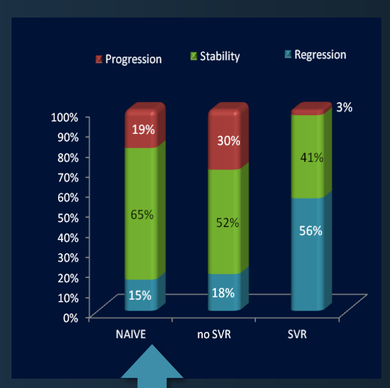
Fibrosis Progression/Regression

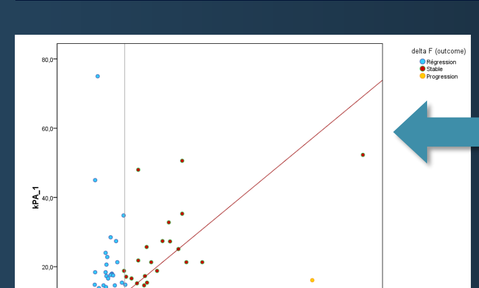
Patients with fibrosis scores of F3 or less were evaluated for fibrosis progression. Of the initial 396 patients included, 278 had a liver fibrosis stage of less than or equal to F3 at baseline. During the observation period, fibrosis progression occurred in 62 (22%) patients, which was greater in non-responders (48%) followed by naïve patients (22%).
Progression was observed in four patients after SVR: Three were alcoholic and one was co-infected with HBV-HDV.

Patients with fibrosis scores ≥ F2 were evaluated for fibrosis regression. Of the initial 396 patients included, 233 had a liver fibrosis stage of F2 or more at baseline. Fibrosis regression was observed in 125 (54%) patients. The regression was greater when SVR was achieved (76% vs. 26% in non-SVR and 46% in non-treated patients; p<0.001).



Changes in first and last measure of liver stiffness





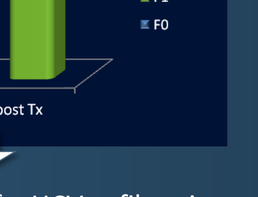
The Fibrosis Regression categorized as it is here is quite underestimated because patients with a very high BL kPA score who cleared their HCV and had a significant diminution of the fibrosis but not enough to switch from a category to an other, are considered as «stable».

Determinants of Fibrosis Regression

	N	Simple Model OR	(CI95%)	Adjusted Model aOR	(CI95%)
Age @ BL	234	1.0	(0.9 1.1	1.0	0.9 1.1
Men	234	0.9	(0.5 1.9	---	--- ---
Alcohol abuse	207	0.9	(0.5 1.5	---	--- ---
IDU	231	0.9	(0.5 1.6	---	--- ---
Genotype 2,3	231	1.2	(0.6 2.2	---	--- ---
HIV-HCV co-infection	233	1.5	(0.8 2.8	1.8	0.8 4.0
HBV-HCV co-infection	233	5.3	(0.6 43.8	---	--- ---
Diabetes	233	0.3	0.1 0.6	0.3	0.1 0.7
Baseline METAVIR score					
F3 vs. F2	233	1.2	0.6 2.5	1.1	0.4 2.8
F4 vs. F2		0.5	0.2 0.9	0.3	0.1 0.7
SVR					
No SVR vs. Not Treated	130	0.6	0.2 2.4	0.7	0.3 1.6
SVR vs. Not Treated		4.9	1.9 12.5	8.7	3.6 20.7

Even if among patients with SVR, we observe a significant proportion of fibrosis regression (based on the crude stiffness measure) in patients staged F4 @BL, it is harder to regress from F4 to a lower METAVIR stage once the liver is structurally heavily impaired [OR=0.3 in patients staged F4 @BL comparing to patients staged F2 @BL (p=0.004)] .

71% of patients with BL fibrosis staged at F4 shows regression of liver fibrosis after being treated and cured from HCV infection compared to 87% of F3 and 96% of F2@BL.



The treatment effect

Compared to naïve patients, fibrosis regression was greater after a SVR, and similar in non-responders or relapsers.

CONCLUSION

- Fibrosis regression occurs even in patients with advanced fibrosis and cirrhosis at BL. In cirrhotic patients particularly, the reduction in the stiffness is noteworthy after cure and even if based on the METAVIR stage the fibrosis evolution seems «stable» but in reality we observe an important regression of the liver stiffness in cirrhotic patients and the burden of their disease is significantly diminished.
- Fibrosis regression is significantly associated with achieving a SRV after HCV treatment.
- Fibrosis regression was observed equally in HCV-mono and HIV-HCV co-infected patients.
- Diabetes is associated with a reduced fibrosis regression. This finding warrant further analyses.

References

(1) Fallowfield J, Hayes P, Pathogenesis and treatment of hepatic fibrosis: is cirrhosis reversible? Clin Med, 2011, 11(2): 179-83.

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