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Residual risk of disease progression after hepatitis C cure in HIV-HCV co-infected patients

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for the ANRS CO13 HEPAVIH

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Abstract

Background: Incidence rates of hepatic events and mortality after cure of HCV in HIV-HCV co-infected patients are not yet documented in real-life settings.

Methods: We included HIV-HCV co-infected patients with a sustained virological response (SVR24 – negative HCV-RNA ≥6 months after anti-HCV treatment completion) within the French nationwide ANRS CO13 HEPAVIH cohort. Hepatic events were defined as ascites, digestive hemorrhage, bilirubin level >2.05 mg/mL, hepatic encephalopathy and hepatocellular carcinoma (HCC). All events were validated by a medical committee. We estimated incidence rates (95% confidence intervals [CI]) and mortality rates overall, and separately in patients with severe (F3/F4) and mild/no fibrosis (F0/F1/F2). Crude incidence risk ratios (IRR) were assessed using Poisson regression.

Results: We included 235 patients with SVR treatment with peg Interferon + Ribavirin (n=157), triple therapy with Boceprevir/Telaprevir (n=59) or new direct active agents (DAA) (n=19). At SVR, median age was 49 years, median CD4 cell count was 330 (IQR 238-489)/mm^3, median BMI was 22 kg/m^2 (IQR 19-24), 4% had an excessive alcohol consumption (>3 glasses of alcohol/day for men and >2 for women), 41% had a severe fibrosis and 53% had a HCV genotype 1. Incidence rate of a first hepatic event was 3.9 per 1,000 person years (PY) (CI: 0.5-9.3) occurring 0.57 years in median after SVR. Patients with severe fibrosis had a similar risk of hepatic event compared to patients with mild/no fibrosis (IRR: 1.4 CI: 0.09; 23.1, *P*=0.80). Hepatic events were decompensation (n=2). Death occurred 1.7 years in median after SVR. Overall mortality rate was 7.7 per 1,000 PY (CI: 0.2-15.3), 9.4 (CI: 0.6-22.4) and 6.8 (CI: 0.6-16.2) per 1,000 PY in patients with severe and mild fibrosis, respectively (*P*=0.71). Causes of death were: cardio-vascular disease (n=1) and unknown (n=3).

Conclusion: Both hepatic events and death after cure were rare after short/mid-term follow-up. A residual risk of hepatic events after hepatitis C cure in HIV-HCV co-infected patients persisted after cure and patients with severe fibrosis tended to have a higher risk for a hepatic event. Our early findings underline the need for long-term follow-up and are in favor of an early access to anti-HCV treatment.

Background

- Data of incidence rates for hepatic events and mortality after sustained virological response (SVR) of HCV in HIV-HCV co-infected patients are sparse in real-life settings.
- In HCV mono-infected patients, a residual risk of disease progression persists and is higher for HCC than for decompensated cirrhosis.

Aims

- To describe hepatic events and causes of death in patients with SVR for HCV.
- To evaluate incidence of hepatic events or deaths after SVR for HCV in HIV-HCV co-infected patients.

Methods

➢ Study population:

HIV-HCV co-infected patients enrolled in the French nationwide ANRS CO13 HEPAVIH cohort were included in this analysis if:

- an anti-HCV treatment was initiated (all types of treatment) during cohort follow-up,
- sustained virological response (SVR) to this treatment was achieved,
- an evaluation of cirrhosis (either with an algorithm based on liver biopsy, Fibrotest, Fibroscan®, or with Fibroscan® only) was available before SVR.

Patients were not included in this analysis if they cleared spontaneously HCV (without any treatment) or were transplanted from liver before SVR.

➢ Statistical analysis and definitions:

- Baseline was defined as the date of SVR, calculated by the date of end of the treatment + 12 weeks.
- All hepatic events (hepatocellular carcinoma, cirrhosis decompensation) and deaths were validated by a validation committee.
- Patients with an elastometry value higher or equal to 12.5 kPa (measured by Fibroscan®) were considered cirrhotic. If that value was below 12.5 kPa, patients were considered non cirrhotic.
- Clinical covariables were described at SVR, or at the closest cohort visit before SVR (within a period of one year) .
- Descriptive results are presented as numbers (%) for qualitative variables and median (interquartile range, IQR) for quantitative variables.
- Crude incidence risk ratios were evaluated with Poisson regression.

Results

Study population

- Among the 1,011 patients of the cohort treated at least once, 465 patients were evaluable for SVR status during the cohort follow-up, and 246 achieved SVR (53%). Among them, 2 were liver transplanted and 9 didn't have a cirrhosis evaluation before SVR. Finally, 235 patients fulfilled the inclusion criteria.
- Sixty patients (26%) were cirrhotic, other characteristics are presented below, according to cirrhosis status.

Characteristics	Overall (n=235)	Cirrhotic (n=60)	Non cirrhotic (n=175)
Age (years)	49 (45-52)	49 (45-53)	48 (45-52)
Male sex	175 (75)	47 (78)	128 (73)
High alcohol consumption (>3 glasses/day ♂, >2 glasses/d ♀) (n=186)	8 (4)	2 (4)	6 (4)
CD4 (/mm^3) (n=229)	330 (238-489)	295 (224-408)	346 (240-506)
HIV-RNA < 50 copies/mL (n=230)	208 (90)	58 (97)	150 (88)
Total time under cART (years) (n=229)	12.7 (7.3-16.7)	14.3 (10.0-18.0)	12.1 (6.7-16.4)
HCV genotype (Gt)			
1	125 (53)	36 (60)	89 (51)
2	11 (5)	3 (5)	8 (5)
3	65 (28)	11 (18)	54 (31)
4	34 (14)	10 (17)	24 (13)
Elastometry (measured by Fibroscan®, kPa) (n=94)	8.0 (6.1-11.7)	14.3 (10.1-26.3)	6.9 (5.4-8.6)
Fibrosis score F3/F4* (n=232)	95 (41)	60 (100)	35 (20)
Previous hepatic event	0 (0)	0 (0)	0 (0)
HCV viral load at treatment initiation (log_{10} UI/mL) (n=229)	5.9 (5.3-6.5)	5.9 (5.1-6.4)	5.9 (5.3-6.5)
HCV infection duration (years) (n=180)	12.3 (7.8-17.9)	13.0 (8.9-19.4)	11.5 (7.4-17.5)
HBV coinfection (n=230)	6 (3)	3 (5)	3 (2)
HCV treatment received			
Peg-interferon (Peg-IFN) + Ribavirin	157 (67)	34 (57)	123 (70)
Triple therapy with Boceprevir or Telaprevir (PI)	59 (25)	18 (30)	41 (23)
Direct active agent (DAA)±Peg-IFN	19 (8)	8 (13)	11 (6)
Follow-up duration after SVR (years)	2.0 (0.6-3.3)	1.3 (0.4-2.9)	2.2 (0.7-3.4)

Notes: Results are presented in n (%) or median (IQR). IQR: inter-quartile range. cART: combination antiretroviral therapy.
* Defined with inclusion criteria: cirrhosis algorithm or elastometry value with Fibroscan® > 9.5 kPa.

Hepatic events

- Two patients developed an hepatic event (decompensated cirrhosis) after a median duration of 0.6 year after SVR (range: 0.2-1.0).
- There was no statistical difference between patients with severe fibrosis (evaluated as a fibrosis score F3/F4) and those with mild/no fibrosis (F0/F1/F2) (IRR: 1.44 CI: [0.09; 23.1], *P*=0.80) regarding the development of hepatic events.

	Incidence rates /1,000 PY (95% CI)
Overall	3.9 (0.5-9.3)
Cirrhotic patients	9.0 (0.6-26.6)
Non cirrhotic patients	2.5 (0.4-7.4)

Notes: CI: confidence interval. IRR: incidence risk ratio. PY: person years.

- For the two patients with an hepatic event, the last available Fibroscan value before the event was 10,3 and 27 kPa, 30 months and 6 months before the date of cirrhosis decompensation respectively.
- Both patients had HIV-RNA < 50 copies/mL at the time of event, and CD4 values were respectively 250 and 213 cells /mm^3.

Deaths

- Four deaths occurred, causes were bronchopneumonia in 1 (not linked to HCV neither HIV), and not yet validated by the independent committee for the three others. Median duration after SVR was 1.7 years (IQR: 0.6-3.8).

	Incidence rates /1,000 PY (95% CI)
Overall	7.7 (0.2-15.3)
Cirrhotic patients	8.6 (0.2-25.4)
Non cirrhotic patients	7.5 (1.0-16.0)

Notes: CI: confidence interval. PY: person years.

- The respective last available elastometry in patients who died were 7.1, 16.5, 6.8 and 21.3 kPa, and were measured 30, 26, 26 and 23 months before death.
- Last available CD4 cell count was 366, 401, 272 and 1,240 /mm^3, respectively.
- Three of the patients had undetectable HIV-RNA during the whole cohort follow-up, the fourth one had HIV-RNA < 50 copies/mL since the time of SVR but achieved 255 copies/mL 3 months before dying.

Conclusion

- Both hepatic events and death after SVR were rare after short/mid-term follow-up in patients cured from hepatitis C in the first 6 months post-SVR.
- A residual risk of hepatic events after hepatitis C cure in HIV-HCV co-infected patients persisted after SVR. However, our analysis is underpowered to detect a potential higher risk in patients with severe fibrosis.
- The study population achieved SVR mostly after a treatment with peg-interferon and ribavirin, thus probably represents a very selected population with particular characteristics which may differ to those patients with SVR after DAA or PI treatment.
- Our early findings underline the need for long-term follow-up and collaborative studies in order to have enough power to detect factors associated with disease progression after SVR.

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