

Natural history of compensated hepatitis C virus-related cirrhosis in human immunodeficiency virus-infected patients

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ABSTRACT

Background: Compensated HCV-related cirrhosis is a common finding in the HIV-infected population in areas where HCV/HIV coinfection is prevalent. There are scarce data on the clinical outcome of this condition. The aim of this study was to provide information about the incidence of hepatic decompensations, the mortality and the predictors thereof in HIV-infected patients with compensated HCV-related cirrhosis.

Methods: In this retrospective study, all 154 HIV and HCV-coinfected patients in whom a new diagnosis of compensated, Child-Pugh-Turcotte (CPT) class A, cirrhosis was made in the Infectious Diseases Units of seven hospitals, from January 1996 to September 2006, were included. Time from diagnosis to the first hepatic decompensation and survival were evaluated.

Results: The median (Q1-Q3) follow-up of the population studied was 29.1 (14.9-51.3) months. Thirty-six (23.4%) patients developed a liver decompensation. The density of incidence of hepatic decompensations was 8.88 per one hundred person-years. The probability of decompensation at 3 and 5 years was 27 and 33%, respectively. Ascites was the most common first decompensation of cirrhosis, followed by hepatic encephalopathy (HE) and portal hypertensive gastrointestinal bleeding (50%, 17% and 17%, respectively). The factors independently associated [HR (95%CI)] with the emergence of liver decompensation were lack of HCV therapy during the follow-up [3.71 (1.25-10.99)], a baseline CD4 cell counts lower than 300/mm³ [2.12 (1.06-4.25)], a CPT score of 6 versus 5 [4.38 (2.03-9.43)], and a diagnosis of cirrhosis based on clinical findings [3.81 (1.8-8.05)]. Fifteen (9.7%) patients died during the follow-up. Eleven (73%) of them died due to liver disease. HE was the cause of death in nine (81%) patients. The mortality rate due to liver failure was 2.44 deaths per one hundred person-years. The 3 and 5-year survival estimates were 91 and 82%, respectively. HE as the first liver decompensation [29.75 (6.25-141.51)] and a higher baseline CPT [5.59 (1.28-24.42)] score were independently associated with liver-related mortality.

Conclusions: Clinical liver events are more frequent in HIV/HCV-coinfected patients with compensated CPT class A cirrhosis than previously reported in HCV-monoinfected patients. Liver disease is the main cause of death in this population. Lower baseline CD4 cell counts, lack of therapy against HCV, and higher CPT score are the factors related to the occurrence of clinical liver events.

BACKGROUND

HIV infection accelerates the course of HCV-related liver damage to cirrhosis, end stage liver disease (ESLD) and death.

The incidence of clinical liver events in large cohorts of HCV-monoinfected subjects are extremely low. The annual incidence of clinical decompensation were from 3.1% to 3.9%. In relation to liver-related death, previous data showed annual rate of 1.9%.

Little information is available regarding the natural history of compensated cirrhosis in HIV/HCV-coinfected subjects.

OBJECTIVES

To obtain information about the clinical outcome of HCV-related compensated cirrhosis in HIV-infected patients, as well as to analyze the predictors of liver decompensation and death in this population.

PATIENTS AND METHODS

From January, 1996 to September, 2006, all the HIV/HCV-coinfected individuals that fulfilled the following inclusion criteria were analyzed: (i) Detectable plasma HCV-RNA at baseline; (ii) A diagnosis of Child-Pugh-Turcotte (CPT) class A cirrhosis at or after the inclusion in the cohort, and (iii) No decompensation of liver disease had emerged before entering the cohort. Individuals who presented a liver decompensation at the time of cirrhosis diagnosis were excluded from the study.

Patients were followed until death, lost to follow-up, liver transplantation or the censoring date (30th September 2006). Visits, including a clinical, virologic, immunologic and biochemical evaluation, were carried out at least every six months.

The diagnosis of liver cirrhosis was based on one of the following diagnostic methods:

- Histology: A fibrosis grade F4, according to the Knodell scoring system modified by Scheuer, in a liver biopsy.
- A hepatic stiffness ≥ 14.6 kPa measured by transient elastometry (FibroscanTM; Echosens, Paris, France).
- Clinical, laboratory and ultrasound data consistent with cirrhosis.

Disorders included as a decompensated cirrhosis: ascites, upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatocellular carcinoma, non-obstructive jaundice and hepatic encephalopathy.

The development of the first episode of hepatic decompensation, the occurrence of death due to liver failure and that of death due to any cause were the endpoints analyzed in this study. Estimated survival functions were calculated using the Kaplan-Meier method, and survival curves were compared via log-rank test. Covariates with *P* value equal to or less than 0.1 on bivariate analysis were introduced in a Cox regression model.

RESULTS

One hundred and fifty-four HIV/HCV-coinfected individuals with compensated CPT class A cirrhosis were included in this study.

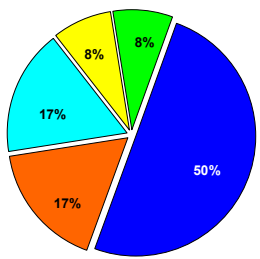
The median (Q1-Q3) follow-up time was 29.1 (14.9-51.3) months. Thirty-six (23.4%) patients developed a first hepatic decompensation and 15 (9.7%) died. The density of incidence of first hepatic decompensations was 8.8 per one hundred person-years. The probability of developing a first decompensation at five years was 33%. Eleven (73%) patients died due to liver disease. The rates of deaths was 2.44 per one hundred person-years. The probability of staying alive at five years was 82%.

Characteristics of the population

Parameter	Value
Age (years)*	39.9 (37.1-44.1)
Former or active intravenous drug users (%)	133 (86)
HCV genotype 1 (%)†	87 (63)
Age at HCV infection*‡	21 (19-27)
Duration of HCV infection (years)*‡	18 (14.2-20.9)
MELD*§	8 (7-10)
Child A5 score (%)	108 (70)
HCV therapy during the follow-up (%)	66 (43)
Sustained virologic response to HCV therapy during the follow-up (%)	19 (29)
CDC stage C (%)	53 (34)
Highly active antiretroviral therapy during the follow-up (%)	145 (94)
Baseline CD4 cell counts*	403 (255-572)
Patients with baseline undetectable plasma HIV viral load	107 (68)
% of follow-up with undetectable plasma HIV-RNA load*	64.7 (20.6-87.6)
Diagnosis of cirrhosis (%)	
Liver biopsy	98 (64)
Transient elastometry	10 (6)
Other	46 (30)

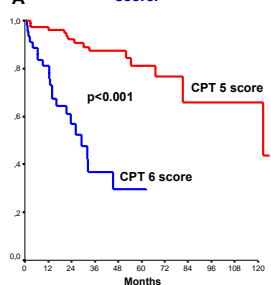
*Median (interquartile range) †It could be assessed in 137 patients. ‡Available in 135 patients.

Frequency of specific events as first liver decompensation

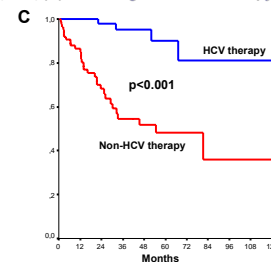
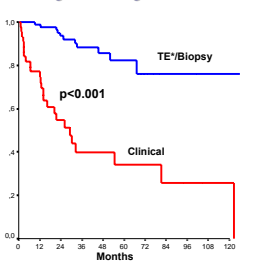


Event	Percentage
Ascites	50%
Hepatic encephalopathy	17%
Portal hypertensive gastrointestinal bleeding	17%
Hepatocellular carcinoma	8%
Jaundice	8%

(A) Probability of remaining free of developing a hepatic decompensation according to the diagnosis of CPT score.



(B) Probability of remaining free of developing a hepatic decompensation according to the diagnosis of cirrhosis, and, (C) according to the HCV therapy.



Patients at risk	Months	Patients at risk	Months
TE/Biopsy 108 87 65 48 32 22 11 6 5 3 3	0 12 24 36 48 60 72 84 96 108 120	HCV therapy 69 62 46 32 18 13 5 3 3 1 1	0 12 24 36 48 60 72 84 96 108 120
Clinical 46 31 17 10 7 6 5 3 2 1 1		Non-HCV therapy 85 56 33 23 17 10 6 3 2 2 2	

*TE: Transient elastometry.

CONCLUSIONS

- In HIV/HCV-coinfected patients with CPT class A cirrhosis, clinical liver events are more common than previously reported in HCV-monoinfected subjects.
- Liver disease is the main cause of death in this population.
- Lower baseline CD4 cell counts, lack of therapy against HCV, and higher CPT score are the factors related to the occurrence of clinical liver events.
- Even among patients with CPT category A, CPT score is a strong predictor of hepatic decompensation and liver-related death.

RESULTS

Predictors of the emergence of the first hepatic decompensation

Variable	No. (%)	p univariate	Hazard ratio (95% CI)	p multivariate
Age (years)				
≤ 39	16 (19.8)			
> 39	20 (28.2)	0.217	-	-
Gender				
Male	29 (22.1)			
Female	7 (33.3)	0.257	-	-
HCV therapy				
Yes	4 (5.6)			
Not	32 (38.3)	<0.001	3.71 (1.25-10.99)	0.006
HBV coinfection				
Not	30 (20.8)			
Yes	6 (60)	0.05	-	0.629
HDV coinfection				
Not	34 (22.5)			
Yes	2 (66.7)	0.5	-	-
CDC stage				
A or B	22 (21.7)			
C	14 (26.4)	0.252	-	-
Daily alcohol intake > 50 g/day				
Not	19 (15.7)			
Yes	17 (50.0)	<0.001	-	0.153
Risk category				
No intravenous drug users	8 (38.1)			
Intravenous drug users	28 (21)	0.012	-	0.252
Child score				
5	15 (13.8)			
6	21 (45.6)	<0.001	4.38 (2.03-9.43)	<0.001
MELD score				
≤ 8	12 (15.6)			
> 8	24 (31.2)	<0.001	-	0.081
HAART during the follow-up				
Not	2 (22.2)			
Yes	34 (23.4)	0.448	-	-
Diagnosis of cirrhosis				
Clinical	25 (54.3)			
TE/Biopsy	11 (10.2)	<0.001	3.81 (1.8-8.05)	<0.001
CD4 gain after HAART				
≤ 300	20 (38.5)			
> 300	16 (15.7)	<0.001	2.12 (1.06-4.25)	0.032
% of follow-up with plasma HIV-RNA load below the detection level				
> 60	25 (31.5)			
≤ 60	11 (13.9)	0.006	-	0.442

Predictors of death due to liver failure

Variable	No. (%)	p univariate	Hazard ratio (95% CI)	p multivariate
Age (years)				
≤ 39	5 (7.3)			
> 39	6 (8.5)	0.302	-	-
Diagnosis of cirrhosis				
Clinical	7 (15.2)			
TE/Biopsy	4 (3.7)	0.023	-	0.657
HCV therapy				
Not	2 (2.8)			
Yes	9 (10.2)	0.039	-	0.347
HBV coinfection				
Not	9 (6.2)			
Yes	2 (20)	0.306	-	-
HDV coinfection				
Not	9 (5.9)			
Yes	2 (66.7)	0.023	-	0.138
Daily alcohol intake > 50 g/day				
Not	5 (4.1)			
Yes	6 (17.6)	0.007	-	0.374
Child score				
5	4 (3.7)			
6	7 (15.2)	<0.001	5.59 (1.28-24.42)	0.022
MELD score				
≤ 8	5 (5.6)			
> 8	6 (7.8)	0.491	-	-
HAART during the follow-up				
Not	1 (11.1)			
Yes	10 (6.9)	0.034	-	0.383
HE† as the first decompensation				
Not	7 (4.7)			
Yes	4 (50)	<0.001	29.75 (6.25-141.51)	<0.001
Baseline CD4 cells count				
≤ 300	5 (9.6)			
> 300	6 (5.9)	0.042	-	0.072
% of follow-up with plasma HIV-RNA load below the detection level				
> 60	7 (9.6)			
≤ 60	4 (5.1)	0.295	-	-

*TE: Transient elastometry; †HE: Hepatic encephalopathy