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EFFECT OF DAA REGIMENS ON MORTALITY IN HIV/HCV-COINFECTED PATIENTS WITH CIRRHOSIS

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ABSTRACT

OBJECTIVE: To assess the impact of all-oral direct antiviral agents (DAA) regimens on mortality in HIV/HCV-coinfected patients with cirrhosis.

METHODS: 637 HIV/HCV-coinfected patients with cirrhosis prospectively recruited in the HEPAVIR-cirrhosis cohort from 2006 were followed-up until death or December 2018. The primary end-point was death of any cause and secondary end-point was liver-related death. The incidence rate (IR) (95% CI) of death of any cause in different groups were computed. Time-to-event analyses were performed to identify predictors of death.

RESULTS: After a median (Q1-Q3) follow-up of 72 (39-104) months, 131 (21%; 95% CI: 17-23) patients died, 59 (45%) of them due to liver-related complications. IR (95% CI) of death was 3.4 (2.8-4.1) per 100 person-years (PY). 480 (75%) patients achieved sustained virological response (SVR) during follow-up, 90 after interferon (IFN)-based regimens and 390 after all-oral DAA regimens. The median follow-up after all-oral DAA was 34 (23-41) months. 28 out of the 131 deaths and 8 out of the 59 liver-related deaths occurred after SVR. IR (95% CI) of death after SVR was 1.8 (1.2-2.7) per 100 PY versus 17.7 (14.6-21.5) per 100 PY in those not achieving SVR during follow-up (p<0.0001). When only patients with SVR were considered, the IR (95% CI) of death after SVR with all-oral DAA regimens was 2.1 (1.4-3.3) per 100 PY whereas it was 1.3 (0.5-2.8) per 100 PY in those achieving SVR with IFN-based regimens (p=0.27). The respective figures for liver-related death were 0.7 (0.3-1.5) and 0.2 (0.03-12.8) per 100 PY respectively (p=0.26). Figure 1 summarizes the trends in overall and liver-related mortality according to the changes of treatment strategies for hepatitis C in the cohort. Achieving SVR with an all-oral DAA regimen during follow-up was independently associated with a lower risk of death (adjusted hazard ratio 0.04; 95% CI: 0.02-0.07; p<0.0001). The type of regimen leading to SVR (all-oral DAA vs IFN-based) had no impact on the risk of liver-related death in a competing risk model adjusted by propensity score (adjusted sub-hazard ratio 1.91; 95% CI: 0.21-17.09; p=0.56).

CONCLUSION: SVR with all-oral DAA regimens reduces the risk of death in HIV/HCV-coinfected patients with cirrhosis. The sum of this effect to the high uptake and SVR rates of this therapy has led to a decline in the incidence of liver-related mortality in our cohort.

BACKGROUND

- Sustained virological response (SVR) with interferon-based regimens has been associated with a reduction in mortality in HIV/HCV-coinfected patients.
- Besides, cohort studies in HCV-monoinfected patients have also shown that the consecution of SVR with all-oral direct-acting antiviral (DAA) regimens increases survival.
- To date, the effect of all-oral DAA regimens on mortality in HIV/HCV-coinfected patients has not been assessed.

OBJECTIVE

- To assess the impact of all-oral direct antiviral agents (DAA) regimens on mortality in HIV/HCV-coinfected patients with cirrhosis.

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PATIENTS AND METHODS

Study design

- Multicenter prospective cohort study (2006-2018).

Patients

- HEPAVIR-cirrhosis cohort. Inclusion criteria:
  - HIV infection.
  - Chronic HCV infection with detectable serum HCV RNA at inclusion.
  - Diagnosis of cirrhosis based on a liver stiffness (LS) ≥ 14 kiloPascals (kPa).
  - No previous liver decompensation (LD).

Clinical data and follow-up

- Clinical visits and US every 6 months (every 3 months if decompensated).
- HCV therapy during follow-up according to treating physician criteria.

Variables of the study

- Primary end-point: death of any cause.
- Secondary end-point: liver related death (LRD).
- Treatment strategies for hepatitis C were classified in 3 groups: pegylated IFN plus ribavirin; DAA in combination with IFN and DAA IFN-free regimens.

Statistical analyses

- The incidence rate (IR) of death and LRD after SVR and its evolution over time were analyzed.
- The time from SVR to death, as well as its predictors, were evaluated.
- Survival analyses: Cox and competing-risk Fine-Gray regression models with propensity score (PS) adjustment.

RESULTS

Table 1. Characteristics of the study population (n=637).

Parameter	Overall population (n=637)	SVR after IFN +/- DAA (n = 86)	SVR after all-oral DAA (n = 390)	p[1]
Age (years)[2]	46 (42-50)	45 (42-48)	47 (43-51)	0.008
Male sex, n (%)	556 (87)	77 (89)	339 (87)	0.5
Alcohol intake > 50 grs/day, n (%)	128 (20)	12 (14)	77 (20)	0.2
Active IDU, no. (%)	11 (2)	0 (0)	5 (1.3)	0.6
HBsAg positive, no. (%)	21 (3)	3 (3.5)	10 (2.6)	0.7
CDC stage C, no. (%)	236 (37)	29 (34)	139 (36)	0.7
CD4 cell count < 200/mL, no. (%)	127 (20)	11 (13)	71 (18)	0.2
Antiretroviral therapy, n (%)	579 (91)	80 (94)	364 (93)	0.8
Child-Pugh stage B, no. (%)	48 (8)	2 (2.3)	17 (4.4)	0.5
Liver stiffness > 21 kPa, no. (%)	343 (54)	39 (45)	200 (51)	0.3
Platelets < 100.000/mm³, no. (%)	202 (32)	19 (22)	119 (30)	0.1

[1]For the comparison between IFN +/- DAA group vs All-oral DAA group; [2]Median (Q1-Q3). SVR: Sustained virological response; IFN: Interferon; DAA: Direct-acting antiviral; IDU: Intravenous drug use; CDC: Centers for Disease Control.

RESULTS

Figure 1. Mortality during follow-up and causes of death.

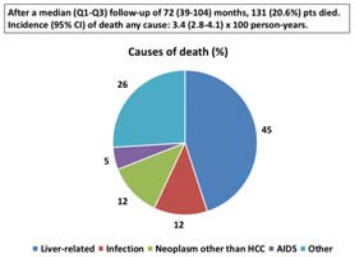


Table 2. Causes of death by period.

Number and causes of deaths	Period (no. of patients on follow-up) 2006-2011 (n=382)	2012-2014 (n=483)	2015-2018 (n=557)	Any time (n=637)
Any cause (%)	23 (6)	42 (8.7)	66 (11.8)	131 (20.5)
Liver-related (%)	14 (3.6)	22 (4.5)	22 (3.9)	59 (9.2)
AIDS (%)	0 (0)	1 (0.2)	6 (1.1)	7 (1.1)
Infection (%)	2 (0.5)	3 (0.6)	9 (1.6)	14 (2.2)
Neoplasm other than HCC (%)	2 (0.5)	8 (1.6)	8 (1.4)	18 (2.8)
Cerebrovascular accident	3 (0.8)	1 (0.2)	5 (0.9)	9 (1.4)
Sudden death	1 (0.2)	2 (0.4)	5 (0.9)	8 (1.2)
Drug overdose	0 (0)	0 (0)	4 (0.7)	4 (0.6)
Other	1 (0.2)	5 (1.1)	6 (1.1)	12 (1.8)

% of deaths refers to the total of patients on follow-up in each period

Table 4. Incidence rates of death according to HCV therapy and response.

Category	No. of events	Follow-up (person-years)	Incidence rate (95% CI)	p
Death of any cause				
Global	131	3831.16	3.4 (2.8-4.1)	
SVR				
No SVR	103	580.25	17.7 (14.6-21.5)	<0.0001
SVR	28	1437.5	1.8 (1.2-2.7)	
Therapy leading to SVR				
IFN-based	7	461	1.3 (0.5-2.8)	0.27
All-oral DAA	21	974.91	2.1 (1.4-3.3)	
Liver-related death				
Global	59	3831.16	1.5 (1.1-1.9)	
SVR				
No SVR	51	580.25	8.4 (6.3-11.1)	<0.0001
SVR	8	1437.5	0.5 (0.2-1.1)	
Therapy leading to SVR				
IFN-based	1	461	0.2 (0.03-12.8)	0.26
All-oral DAA	7	974.91	0.7 (0.3-1.5)	

Figure 2. Mortality of any cause during follow-up according to type of HCV therapy and response.

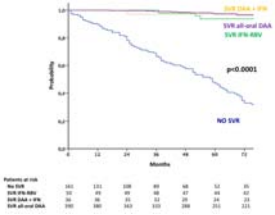


Table 3. Independent predictors of death of any cause during follow-up (n=637).

Parameter	Adjusted hazard ratio (95% CI)	p
Age	1.031 (1.002-1.061)	0.039
Male sex	0.643 (0.335-1.235)	0.185
HBs Ag positive	2.285 (0.966-5.408)	0.060
CD4 cell count < 200/mL	1.250 (0.833-1.876)	0.281
Liver stiffness > 21 kPa	1.503 (0.984-2.297)	0.060
Alcohol intake > 50 grs/day	1.536 (1.007-2.342)	0.046
Child-Pugh stage B (vs A)	1.044 (0.643-1.695)	0.863
HCV therapy during follow-up		
No therapy or not SVR	Reference category	
SVR after IFN-RBV	0.057 (0.023-0.146)	<0.0001
SVR after IFN-DAA	0.039 (0.009-0.160)	<0.0001
SVR after all-oral DAA	0.046 (0.028-0.074)	<0.0001

Table 5. Independent predictors of liver-related death after SVR (n=463).

Parameter	Adjusted sub-hazard ratio (95% CI)	p
Age	1.035 (0.879-1.219)	0.674
Male sex	1.50 x 10⁷ (5293384-4.23 x 10⁷)	<0.0001
Liver stiffness > 21 kPa	2.018 (0.413-9.858)	0.385
Child-Pugh stage B (vs A)	7.432 (1.446-38.207)	0.016
Propensity score DAA	0.358 (1.61 x 10⁻⁷ - 799309)	0.891
HCV therapy leading to SVR		
IFN based (+/- DAA)	Reference category	0.565
All-oral DAA	1.904 (0.212-17.095)	

Competing risk model adjusted by propensity score for receiving all-oral DAA (vs IFN-based). There were 8 liver-related deaths after SVR (1 in IFN-based, 7 in all-oral DAA). HBV-infected patients were excluded from this analysis.

Figure 3. Probability of liver-related death during follow-up according to HCV therapy and reponse (n=637)

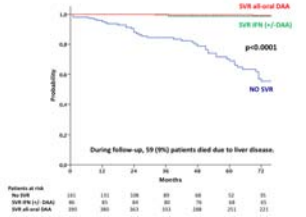
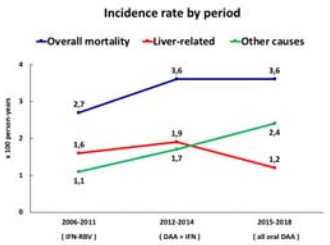


Figure 4. Trends in overall and liver-related mortality according to the evolution of treatment for hepatitis C in HIV/HCV-coinfected patients with cirrhosis



CONCLUSIONS

- SVR with all-oral DAA regimens reduces the risk of death in HIV/HCV-coinfected patients with cirrhosis.
- The sum of this effect to the high uptake and SVR rates of this therapy has led to a decline in the incidence of liver-related mortality in our cohort.
- The effect of SVR on mortality exerted by all-oral DAA regimens does not seem to differ to that observed with IFN-based regimens.