INCIDENCE OF EXTRAHEPATIC COMPLICATIONS IN HIV/HCV PATIENTS WHO ACHIEVED SVR

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SUMMARY

Background: There is increasing evidence that the achievement of sustained virologic response (SVR) after interferon plus ribavirin treatment reduces the incidence of liver-related events. Data on the effects of SVR on the outcome of extrahepatic complications are scarce. Therefore, we conducted this study to assess the impact of SVR on the incidence of chronic kidney disease (CKD), diabetes mellitus (DM), and cardiovascular disease (CVD) in a cohort of HIV/HCV patients.

Methods: We analyzed coinfected HIV/HCV patients in the MASTER cohort in order to estimate the incidence of CKD, DM and CVD. Only event-free patients with a serum HCV-RNA determination at the baseline were eligible for the study. Patients were divided into 4 groups: INF-exposed with SVR; INF-exposed without SVR; INF-free with SVR; INF-free without SVR. CKD and DM were defined as eGFR and fasting glucose plasma levels <60 mL/min/1.73 m^2 and >126 mg/dL in 2 consecutive time points, respectively. All major CVD, including coronary heart disease, cerebrovascular disease, chronic heart failure and peripheral vascular disease were evaluated. Cirrhosis was defined by a FIB-4 score >3.25. Kaplan-Meier curves and Cox regression analyses were used.

Results: Data of 2227 patients were analysed (73.01% male, 46.12% IVDU, GT1 23.84%, cirrhosis 14.14%). Overall, the incidence of CKD, DM, CVD and death were 5.14 (95%CI 3.96-6.57), 9.37 (95%CI 7.72-11.28), 6.40 (95%CI 5.06-7.99), 12.34 (95%CI 10.46-14.46) per 1000 PYFU, respectively. In the Cox regression analysis for treated patients, SVR was not associated with a lower risk of CKD (RH 1.05;95%CI 0.29-3.9), DM (RH 0.95;95%CI 0.27-3.37), CVD (RH 0.76;95%CI 0.38-1.52), and death (RH 1.17; 95%CI 0.21-6.35) compared to non-SVR. Cirrhosis was significantly associated with the risk of CKD (RH 2.13;95%CI 1.06-4.31), DM (RH 3.48;95%CI 2.18-5.57), death (RH 6.18;95%CI 4.1-9.31) but not of CVD (RH 1.14;95%CI 0.57-2.3).

Conclusions: Our results suggest that the achievement of an SVR after anti-HCV treatment in patients coinfected with HIV/HCV does not reduce liver-related extrahepatic complications and mortality. However, people with cirrhosis have an increased risk of CKD, DM, and death. Thus, coinfected patients should early be treated to prevent the progression of liver fibrosis.

INTRODUCTION

•The widespread use of combined antiretroviral therapy (cART) has substantially improved the prognosis of HIV-1-infected patients. As a consequence of the increase in survival, non-AIDS-related diseases now account for more than 50% of all deaths.

•Liver disease is becoming a leading cause of death among persons with HIV infection, especially in the south part of Europe, where the prevalence of co-infected patients is high.

•The risk for HCC, liver decompensation, and death in patients with liver cirrhosis related to HCV is reduced after SVR (sustained virologic response). However, data on the effects of SVR on the outcome of extrahepatic complications are scarce.

•Therefore, we conducted this study to assess the impact of SVR on the incidence of chronic kidney disease (CKD), diabetes mellitus (DM), and cardiovascular disease (CVD) in a cohort of HIV/HCV patients.

PATIENTS

Patients were selected from the Italian MASTER (*Management of Standardized Evaluation of Retroviral HIV Infection*) cohort, which is a prospective longitudinal multicentre cohort composed of the general HIV patient population in referral centres throughout Italy. The distinguishing characteristic of this cohort is that data are collected by a common electronic database (NetCare™ or Health&Notes™) in use in 10 Italian centres for clinical purposes since 1999. The electronic database is implemented to manage everyday activity of the outpatient HIV clinics in each centre. The resulting cohort is, therefore, an open cohort in which non-preselected patients are continuously enrolled. Demographics, medication and disease history are recorded at enrolment and updated on a 3 monthly basis. All event-free (without CKD, DM, and CVD at baseline) coinfected HIV/HCV patients were evaluated. Of these, only the patients with a serum HCV-RNA determination at the baseline were eligible for the study. Patients were divided into 4 groups: a) INF-exposed with SVR (patients who achieved a SVR); b) INF-exposed without SVR (patients who did not achieved a SVR); c) INF-free with SVR (untreated [after the enrollment] patients with HCV Ab-positive and negative serum HCV-RNA); d) INF-free without SVR (untreated [after the enrollment] patients with HCV Ab-positive but positive HCV-RNA.

DEFINITIONS

SVR was defined as an undetectable serum HCV-RNA level 24 weeks after discontinuation of therapy. Patients not fulfilling SVR criteria, including those who relapsed after achieving end-of-treatment response, were classified as non-SVR. CKD and DM were defined as eGFR and fasting glucose plasma levels <60 mL/min/1.73 m^2 and >126 mg/dL in 2 consecutive time points, respectively. All major CVD, including coronary heart disease, cerebrovascular disease, chronic heart failure and peripheral vascular disease were evaluated. Cirrhosis was defined by a FIB-4 score >3.25.

STATISTICAL ANALYSIS

Descriptive results are presented as medians with interquartile range (IQR) and percentages with 95% confidence intervals (CI). The person-years of follow-up (PYFU) were calculated for each participant as the time from the enrollment date either to the date at death or to 31 December 2012 for those who were still alive then. Incidence of extrahepatic events and death was expressed per 1000 PYFU. The cumulative risk of events was estimated by the Kaplan–Meier method and the statistical significance of the difference was examined by log-rank test. Cox proportional hazard models were used to explore baseline factors predictive of extrahepatic events and deaths. Statistical significance levels were determined by a 2-sided *P* value of .05.

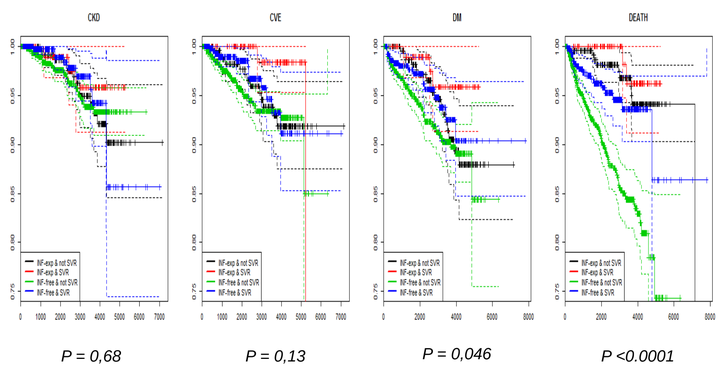
RESULTS

There were 2227 anti-HCV seropositives in this study. Their baseline characteristics are shown in Table 1. In brief, 73.01% were male, the median age was 40.6 years (IQR 36.0-45.6), 14.1% had a cirrhosis, 2.83% had prior AIDS-defining conditions, 15.49% had a CD4+ cell count <200/mmc. Overall, the incidence of CKD, DM, CVD and death were 5.14 (95%CI 3.96-6.57), 9.37 (95%CI 7.72-11.28), 6.40 (95%CI 5.06-7.99), 12.34 (95%CI 10.46-14.46) per 1000 PYFU, respectively. Kaplan-Meier curves showing the occurrence of extrahepatic events and deaths according to the study-groups is reported in Figure 1. The probability of events according to anti-HCV-therapy- and HCV-RNA-status are shown in Figures 2-5. In the Cox regression analysis for treated patients, SVR was not associated with a lower risk of CKD (RH 1.05;95%CI 0.29-3.9), DM (RH 0.95;95%CI 0.27-3.37), CVD (RH 0.76;95%CI 0.38-1.52), and death (RH 1.17; 95%CI 0.21-6.35) compared to non-SVR. Cirrhosis was significantly associated with the risk of CKD (RH 2.13;95%CI 1.06-4.31), DM (RH 3.48;95%CI 2.18-5.57), death (RH 6.18;95%CI 4.1-9.31) but not of CVD (RH 1.14;95%CI 0.57-2.3) (Table 2).

Table 1: Main patients' characteristics

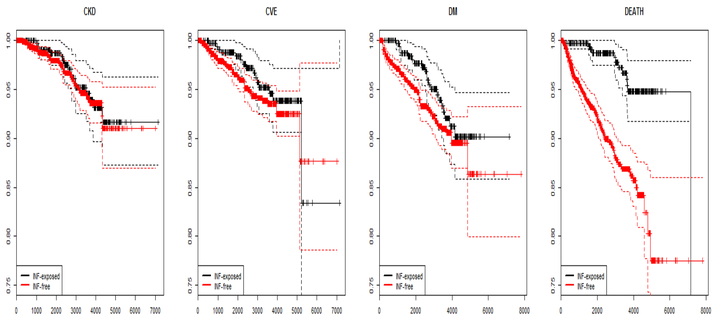
Characteristics	N.	%
Male	1626	73,01%
Mode of HIV Transmission		
Heterosexual	549	24,65%
Homosexual	268	12,03%
IDU	1027	46,12%
Other/Unknown	383	17,20%
Genotype		
1	531	23,84%
2	37	1,66%
3	318	14,28%
4	112	5,03%
Other/Unknown	1229	55,19%
HBsAg	162	7,27%
HCV-RNA		
Detectable	1676	75,26%
Undetectable	551	24,74%
Cirrhosis	315	14,14%
CD4+ cell count		
<200/mmc	345	15,49%
200-499/mmc	1003	45,04%
>500/mmc	798	35,83%
unknown	81	3,64%
HIV-RNA		
>5000 cp/ml	582	26,13%
500-4999 cp/ml	328	14,73%
<500 cp/ml	1231	55,28%
unknown	86	3,86%
AIDS events		
No	2164	97,17%
Yes	63	2,83%
N. who started INF		
No	1877	84,28%
Yes	350	15,72%
INF-SVR status at last FU		
No	244	69,72%
Yes	106	30,28%

Figure 1: Kaplan-Meier curves showing the occurrence of events according to the study-groups



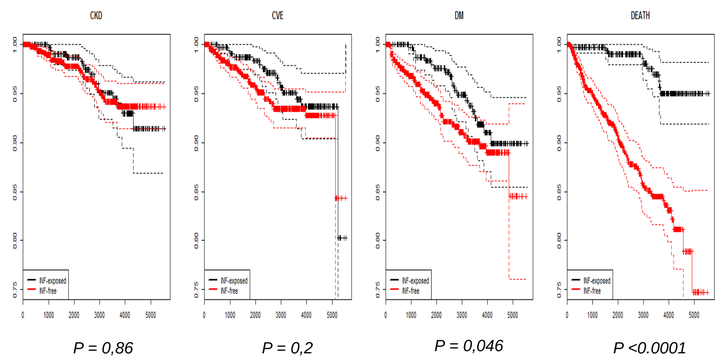
P = 0,68 P = 0,13 P = 0,046 P <0.0001

Figure 2: Kaplan-Meier curves showing the occurrence of events according to the anti-HCV-therapy-status (all patients)



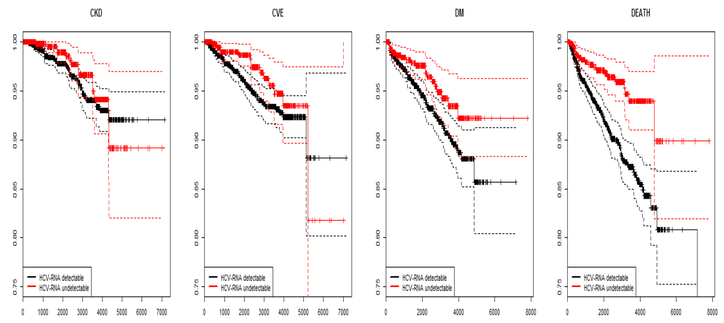
P = 0,74 P = 0,23 P = 0,097 P <0.0001

Figure 3: Kaplan-Meier curves showing the occurrence of events according to the anti-HCV-therapy-status (only patients with HCV-RNA positive at the baseline)



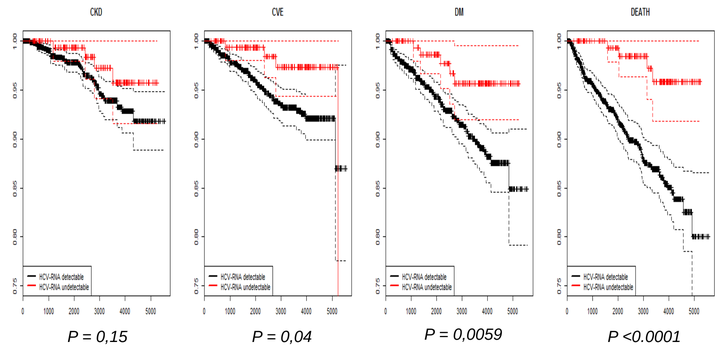
P = 0,86 P = 0,2 P = 0,046 P <0.0001

Figure 4: Kaplan-Meier curves showing the occurrence of events according to the HCV-RNA status (all patients)



P = 0,37 P = 0,083 P = 0,022 P <0.0001

Figure 5: Kaplan-Meier curves showing the occurrence of events according to the HCV-RNA status (only patients with HCV-RNA positive at the baseline)



P = 0,15 P = 0,04 P = 0,0059 P <0.0001

Table 2: Cox regression analysis in patients with HCV-RNA positive at the baseline

	HR (95%CI)			
	CKD	DM	CVE	Death
Cirrhosis	2.13 (1.06-4.31)	3.48 (2.18-5.57)	1.14 (0.57-2.3)	6.18 (4.1-9.31)
INF-SVR vs. INF-not-SVR	1.05 (0.29-3.9)	0.95 (0.27-3.37)	0.76 (0.38-1.52)	1.17 (0.21-6.35)
INF-free/not-SVR vs.INF-not-SVR	0.65 (0.31-1.34)	0.83 (0.46-1.5)	0.66 (0.08-5.26)	2.84 (1.33-6.07)
DM	0.98 (0.32-2.99)	NA	3.15 (1.04-9.53)	2.03 (1.11-3.73)
CVE	2.4 (0.79-7.27)	1.94 (0.68-5.56)	NA	2.35 (1.07-5.16)
CKD	NA	1.06 (0.24-4.65)	3.15 (1.04-9.53)	2.42 (1.03-5.64)

DISCUSSION

Our study shows that the achievement of an SVR after anti-HCV treatment in patients coinfected with HIV/HCV does not reduce liver-related extrahepatic complications and mortality. However, the results are likely influenced by sample size. Overall, the exposure to a anti-HCV treatment is associated with significantly lower death rate. Moreover, people with cirrhosis have an increased risk of CKD, DM, and death. Thus, coinfected patients should early be treated to prevent the progression of liver fibrosis.

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