Patients with HIV and cirrhosis: the risk for hepatocellular carcinoma after direct-acting antivirals for hepatitis C virus

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Objectives: Hepatocellular carcinoma (HCC) has become a major issue in coinfected HIV/HCV patients with liver cirrhosis. We aimed to determine the rate of HCC occurrence after a direct-acting antiviral (DAA) treatment and to evaluate the factors associated with the risk of HCC in this population.

Design: We conducted a retrospective multicenter observational study including cirrhotic HIV/HCV-coinfected patients treated with DAAs, between October 2014 and January 2017.

Methods: We collected demographics characteristics, data regarding HIV and HCV infections and treatment with DAAs. We investigated the rate and the time of occurrence of HCC. Statistical analysis explored the factors associated to development of liver cancer.

Results: During a median follow-up of 55 months, 24 out of 232 patients developed HCC, after a median of 22.5 months from starting DAAs. Factors associated with HCC were a higher Child–Pugh Turcotte (CPT) score ($P = 0.002$), HCV genotype 3 ($P = 0.04$), previous HCC ($P < 0.001$) and $CD4^+$ cell count nadir greater than 350 cells/μl ($P = 0.001$), whereas antiretroviral therapy (ART) was associated to a lower rate of cancer ($P = 0.02$). At multivariable analysis CPT score and a history of HCC remained independently associated with HCC after DAAs ($P = 0.003$ and $P < 0.001$, respectively), and ART administration maintained its protective role ($P = 0.047$), regardless of HIV RNA at baseline.

Conclusion: Our study highlights the importance of a long-lasting follow-up for HCC after HCV eradication, mostly in those patients with advanced cirrhosis and history of

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HCC. Furthermore, our data showed a potential role of ART itself (and not of undetectable HIV RNA) in reducing the risk for HCC development.

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Introduction

The longer life expectancy because of the widespread of antiretroviral therapy (ART) has determined an increase in the burden of non-AIDS-defining cancers (NADCs) among people with HIV (PWH), whereas the burden of AIDS-defining cancers has remained relatively stable [1]. Liver cancer represents one of the most prevalent NADC in this population, because of the high prevalence of coinfection with viral hepatitis [1,2]. In addition, alcohol consumption is another known risk factor for hepatocellular carcinoma (HCC) among PWH [3]. HIV infection is known to a be a factor accelerating the course of HCV-related liver disease; therefore, the risk for HCC is higher in PWH when compared with the general population [2,4]. The introduction of direct-acting antivirals (DAAs) has led to a profound change in the treatment of HCV, with a rate of sustained virological response (SVR) of more than 95%, including in patients with concomitant HIV infection [5]. SVR obtained by Peg-Interferon (Peg-IFN) was associated with a decrease of HCC occurrence [6], whereas conflicting data have emerged on SVR after DAAs and its impact on the HCC risk in HCV-monoinfected patients with liver cirrhosis, who develop HCC at an annual rate of 1–7%, according to observational studies [6]. Two important studies showed a remarkably high rate of recurrence (about 28%) after DAAs [7,8] and Conti *et al.* [8] did not observe a reduction in HCC occurrence after HCV curative therapy in a short follow-up time (24 weeks) when compared with untreated cirrhotic patients. Yet, Roche *et al.* [9] reviewed the published data on the occurrence and recurrence of HCC after DAAs and did not find a negative effect of DAA treatments on de-novo HCC incidence, although they showed controversial results on the recurrence HCC risk following DAAs. However, little is known about HCC risk among PWH who undergo DAAs treatment, and whether HIV-related parameters (such as HIV RNA or $CD4^+$cell count) might play a role in HCC development after DAAs is still unclear.

The aim of this study was to determine the incidence of HCC occurrence in HIV/HCV-coinfected patients with liver cirrhosis treated with DAAs and to evaluate the factors associated to a greater risk of HCC in this population.

Methods

We carried out a retrospective multicenter study including all the HIV/HCV-coinfected adult patients with cirrhosis who have consecutively started and completed a IFN-free DAAs regimen from October 2014 (when the use of DAAs was firstly approved in Italy) to January 2017 at the Departments of Infectious Diseases of seven hospitals in Northern Italy. The individuals were diagnosed with liver cirrhosis when a METAVIR 4 stage was measured by histological assessment with liver biopsy or by transient elastography, before treatment start. Considering our outcome (HCC development), we focused our analysis only on individuals with HCV infection who had developed cirrhosis. We only included those who had been treated within January 2017 (in order to have a 3 years minimum follow-up time) and we excluded those who underwent a therapy including Peg-IFN even when combined with DAAs. We excluded patients with HCC or noncharacterized hepatic nodules at DAAs baseline, assessed by an ultrasound. We collected demographics and we reported the following data related to HCV infection and liver disease (at DAAs initiation): years since HCV diagnosis, HCV genotype, IFN-naïve/experienced, HBsAg status, liver stiffness (kPa), Child–Pugh Turcotte (CPT) score, alpha-fetoprotein levels, and history of HCC. Regarding HIV infection, we collected at baseline: years since HIV diagnosis and $CD4^+$ cell count nadir, current ART, $CD4^+$ cell count, and HIV RNA levels. We analyzed the rate of HCC (both *de novo* and recurrence) occurring over the follow-up (which started at DAAs beginning and ended at HCC diagnosis or in May 2020). During this time, all the patients have undergone abdominal ultrasound every 6 months, according European HCC surveillance program. Diagnosis of HCC was established by histological findings or radiologically according to the LI-RADS classification system. We reported the date of diagnosis, number and size of the nodules, local invasion, and Barcelona Clinic Liver Cancer (BCLC) stage.

Statistical analysis

To describe our study sample, we presented continuous variables as median (and interquartile range, IQR) and categorical variables as number and percentage. To compare the characteristics of the group of patients who presented HCC and those who did not, we performed the Mann–Whitney *U* test or median test and the chi-squared

test or Fisher test, as appropriate. A *P* value less than 0.05 was considered statistically significant. To evaluate the variables associated with HCC occurrence (and the hazard ratios), we performed COX regressions, including in the multivariable model demographics characteristics, as age and sex at birth, and variables, which presented a *P* value 0.1 or less at univariate analysis. All the analysis were performed using R, version 3.6.0 (R Foundation for Statistical Computing, Austria).

Results

We included 232 HIV/HCV-coinfected cirrhotic patients who completed a 24 weeks IFN-free regimen with DAAs. Baseline characteristics of our sample are shown in Table 1. At baseline, median years since HCV diagnosis were 19.5 (IQR 14–24), and 125 out of 232 (54%) had not experienced a previous antiviral treatment to eradicate HCV infection. Most of the patients had a compensated liver function, expressed by a CPT Score A (81.8%). Genotypes 1a and 3 were the most common (41.8 and 31%, respectively). Median time since HIV diagnosis was 25 years (IQR 18–29) and median $CD4^+$ cell count nadir at diagnosis was 152 cells/μl (IQR 75–280). At baseline, our study population showed a good immunovirological HIV status, with HIV RNA being undetectable (i.e. below 50 copies/ml) for 207 patients (89.2%) and median $CD4^+$ cell count of 522 cells/μl (313–7485). Five patients were not receiving ART at the

Table 1. Baseline characteristics of overall HIV/hepatitis C virus population and sorted by hepatocellular carcinoma occurrence.

Characteristics	Overall population (*N* = 232)	No HCC (*N* = 208) (89.7%)	HCC (*N* = 24) (10.3%)	*P* value *
Age (years)	52 (49–55)	51 (49–55)	52 (50.5–55)	0.198
Male	175 (75.4)	154 (74)	21 (87.5)	0.230
Alcohol intake	34 (14.7)	33 (15.9)	1 (4.2)	0.212
Missing	14 (6)	12 (5.8)	2 (8.3)	
Steatosis	89 (38.4)	81 (39)	8 (33.3)	0.641
Missing	26 (11.2)	22 (10.6)	4 (16.7)	
Diabetes	38 (16.4)	35 (16.8.)	3 (12.5)	0.774
HCV genotypes				0.402
1a	97 (41.8)	90 (43.3)	7 (29.2)	
1b	22 (9.5)	19 (9.1)	3 (12.5)	
2	5 (2.2)	5 (2.4)	0 (0)	
3	72 (31)	60 (28.8)	12 (50)	
4	34 (14.7)	32 (15.4)	2 (8.3)	
other	1 (0.4)	1 (0.5)	0	
Missing	1 (0.4)	1 (0.5)	0	
HBsAg positive	6 (2.6)	5 (2.4)	1 (4.2)	**0.049**
Missing	26 (11.2)	20 (9.6)	6 (25)	
Naïve to HCV therapies	125 (53.9)	115 (55.3)	10 (41.7)	0.293
Years since HCV diagnosis	20 (14–24)	19 (14–24)	23 (16–26)	0.140
Missing	14 (6)	11 (5.3)	3 (12.5)	
Alpha-fetoprotein (mg/dl)	5.8 (3.1–14.8)	5.4 (3.0–13.9)	9.0 (6.55–17)	0.087
Missing	118 (50.4)	105 (50.5)	13 (54.2)	
Child Pugh class				**0.009**
CP-A	171 (81.8)	158 (84.5)	13 (59.1)	
CP-B	36 (17.2)	28 (15)	8 (36.4)	
CP-C	2 (0.96)	1 (0.5)	1 (4.5)	
Missing	23 (9.9)	21 (10.1)	2 (8.3)	
Liver stiffness (kPa)	21 (14.6–33.8)	21 (15–32.6)	35 (14.4–44.7)	0.765
Missing	83 (35.8)	70 (33.7)	13 (54.2)	
HCC history	6 (2.6)	3 (1.4)	3 (12.5)	**0.016**
Years since HIV diagnosis	25 (18–29)	25 (17.5–29)	26 (20–28.5)	0.860
Missing	2 (0.86)	1 (0.5)	1 (4.2)	
Nadir $CD4^+$ count (cells/μl)				**0.012**
≤100	58 (32.8)	56 (34,8)	2 (12.5)	
101–350	95 (53.7)	87 (54)	8 (50)	
>350	24 (13.6)	18 (11.2)	6 (37.5)	
Missing	55 (23.7)	47 (22.6)	8 (33.3)	
$CD4^+$ count (cells/μl)				0.585
≤100	4 (1.7)	4 (2.0)	0	
101–350	66 (28.8)	57 (27.8)	9 (37.5)	
>350	159 (69.4)	144 (70.2)	15 (62.5)	
Missing	3 (1.3)	3 (1.4)	0	
ART administration	226 (97.4)	204 (98.1)	22 (91.7)	0.180
Missing	1 (0.43)	1 (0.48)	0	
HIV RNA less than 50 copies/ml	207 (89.2)	185 (88.9)	22 (91.7)	1
Missing	5 (2.16)	5 (2.4)	0	

Variables are expressed as median (and IQR, interquartile range) or as number (and percentage).
*Significant *P* values ($P < 0.05$) are indicated in bold. HCC, hepatocellular carcinoma.

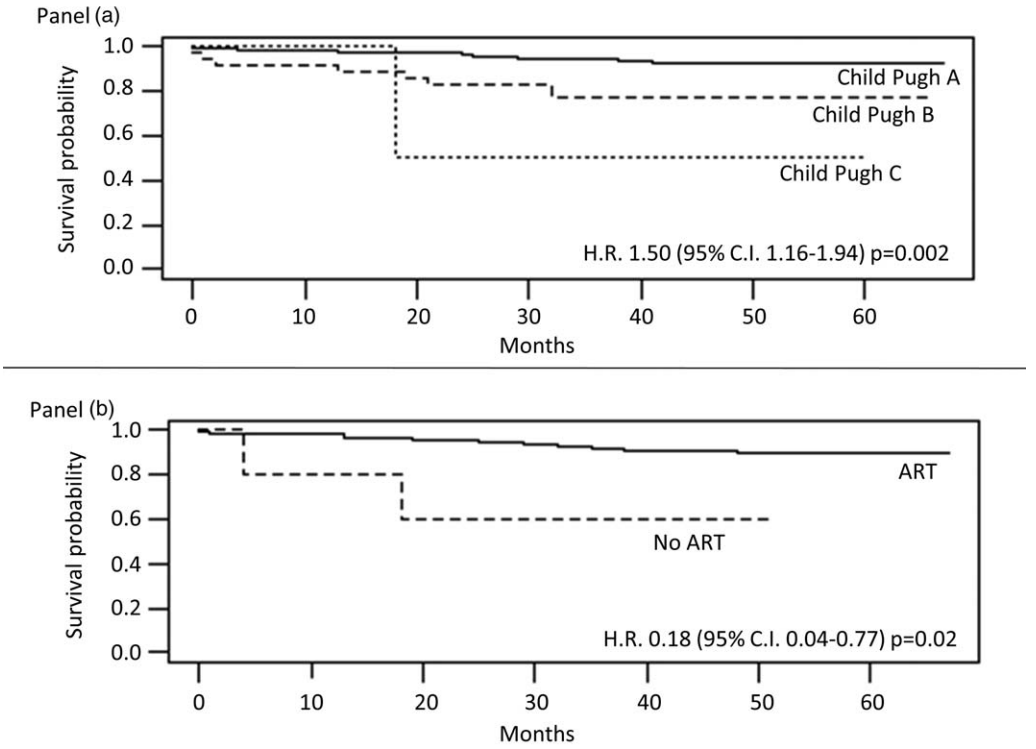

Fig. 1. Kaplan–Meier curves for hepatocellular carcinoma occurrence following direct-acting antivirals therapy according to Child–Pugh class (a) and according to antiretroviral therapy for HIV (b) at baseline. In our cohort, those with more advanced liver diseases (Child–Pugh B/C) presented a higher risk for liver cancer development over the follow-up (hazard ratio 1.50, 95% CI 1.16–1.93) and antiretroviral therapy administration at the beginning of DAAs showed a protective role in cancer development over the follow-up (hazard ratio 0.18, 95% CI 0.04–0.77). DAAs, hepatocellular carcinoma.

baseline. Two of those had been defined as long-term long progressors (LTNP) and three as elite controllers since HIV diagnosis (Supplementary Table 1, http://links.lww.com/QAD/C170). Although ART had been recommended, these patients refused it. In line with the guidelines of that period, the majority of our individuals were treated with Sofosbuvir with Daclatasvir or Sofosbuvir/Ledipasvir, with Ribavirin in combination in 82% of the cases. Ninety-four percentage of patients achieved SVR, assessed 12 weeks after the end of treatment.

During a follow-up of 55 months (50–59), we observed 24 patients developing HCC (10.3%), after a median of 22.5 months (IQR 13–32) from DAA regimen initiation, with a calculated HCC incidence of 2.39 event per 100 person-year. As shown in Supplementary Table 2, http://links.lww.com/QAD/C171, 6 out of 24 were diagnosed with multiple HCC, two had extrahepatic lesions and four presented vascular invasions. According to the BCLC classification, 68.8% were in category 0 and A, meaning very early or early stage at diagnosis. Three out of 24 (12.5%) had a history of previous HCC: two had been treated with hepatic resection and one with ablation. We measured a free from disease survival time of 14 months (IQR 13.5–35.5). Therefore, we found a rate of 9% of de-novo HCC among the overall study sample (21 of 232) and a rate of 50% of recurrence among patients with a history of HCC, after DAAs (3 of 6).

Performing COX regression analysis, we found that a higher CPT score [hazard ratio 1.50, 95% confidence interval (CI) 1.16–1.93, Fig. 1a], genotype 3 (hazard ratio 2.34, 95% CI 1.05–5.20), previous HCC history (hazard ratio 7.75, 95% CI 2.31–26.04) and $CD4^+$ cell count nadir greater than 350 cells/μl (hazard ratio 8.02, 95% CI 1.62–39.76) were associated with HCC occurrence. In addition, ART administration showed a protective role in cancer development (hazard ratio 0.18, 95% CI 0.04–0.77, Fig. 1b), whereas undetectable HIV RNA at baseline did not appear to reduce HCC risk. At multivariable analysis, higher CPT score, previous history of HCC, and ART administration remained independently associated with HCC after DAAs, as shown in Supplementary Table 3, http://links.lww.com/QAD/C172. We performed a sensitivity analysis reducing the number of covariates in the model, and the same results were obtained (data not shown). Although $CD4^+$ cell count nadir resulted statistically significant at univariate analysis, we decided not to insert it into the multivariable

analysis, because of the relevant amount of missing data in the HCC group. However, when we included this variable in multivariable analysis, it remained independently associated with HCC (hazard ratio 4.46, 95% CI 1.40–14.14, *P* value 0.011, data not shown), with lower $CD4^+$ cell count nadir reducing HCC development risk. The results did not change excluding the six patients with HCC history, with ART administration and CPT score remaining independently associated to HCC occurrence after DAAs.

Discussion

The advent of IFN-free regimens based on DAAs has completely changed the scenario of HCV treatment, with an extremely high rate of HCV eradication and an expected impact in the natural history of HCV infection as well [10]. However, conflicting data on HCC occurrence after HCV therapy have been emerged since the use of DAAs in monoinfected HCV patients, with some studies even suggesting an increased risk for HCC in these individuals [7,8]. Consistent data regarding HCC risk among people coinfected with HIV and HCV after DAAs treatment are scarce. However, thus far, DAAs do not seem to affect HCC occurrence, with HCC rates similar to those in pre-DAA era both for de-novo occurrence [10] and for recurrence [11]. In detail, Hasson *et al.* [11] described a de-novo HCC rate of 2.5% among 118 patients with advanced liver disease treated for HCV and an overall frequency of HCC of 0.88% was reported by Merchante *et al.* [12] after SVR with DAA-IFN-free regimens in a cohort of PWH with cirrhosis. Furthermore, Merchante *et al.* [12] showed a 74% reduction in HCC risk in those with compensated cirrhosis treated with DAAs when compared with no therapy in patients with similar clinical characteristics, with five events among 260 individuals who received IFN-free therapy. In our study sample, we found a not negligible rate of de-novo HCC following DAAs (9%) and an unexpectedly high rate of recurrence after DAAs (50%, although the number of patients treated for HCV after a first episode of HCC was very small), probably because of the more advanced liver disease and to the longer follow-up duration in comparison to other cohorts [7,8,12]. We observed an HCC incidence of 2.39 event per 100 person-year, which is in line with the amount previously reported in our country for patients with advanced fibrosis but who were not treated for HCV that was estimated of 3.2% at 1 year [8]. To our knowledge, our study presents one the longest follow-up duration among the studies, which have evaluated HCC after DAAs therapies, with 5 years of observation since DAA initiation. Only Ioannou *et al.* [13] observed their cohort for a comparable follow-up, with a median of 6.1 years. However, no similar studies on HIV–HCV-coinfected population present such a long observation period. In our study, only 54% of HCC cases were diagnosed in the first 2 years since DAAs start. This confirms that a long-lasting follow-up after DAAs has to be recommended. As expected, a more advanced liver disease (higher CPT score) and a previous HCC were found to be associated with a higher risk to develop hepatocellular carcinoma in our study sample, with an adjusted hazard ratio of 1.51 and 9.87, respectively. Our findings confirmed genotype 3 as a potential risk factor for HCC development, as already demonstrated by other studies that analyzed similar cohorts of HIV/HCV–coinfected people [12,14]. Interestingly, our study showed a protective role of ART (but not of undetectable HIV RNA) at DAA initiation in HCC development, also independently from the other analyzed factors. Consistently with that, 8% of patients who developed HCC were not taking ART at the time of our evaluation, because of their elite controller status, defined as ability to spontaneously keep their plasma HIV RNA below quantifiable levels for several years [15].

The lack of a control group of HCV monoinfected patients treated with DAAs or untreated represents the main limitations of our study, although we used similar experiences in our country to make comparisons. In addition, we have to acknowledge the retrospective nature and the amount of missing data.

In conclusion, we did find a not negligible rate of HCC occurrence after DAAs in our cohort of HIV/HCV patients with liver cirrhosis, albeit this was not increased when compared with similar population not treated with DAAs. However, our study did confirm the importance of keeping a long-lasting follow-up after HCV eradication in individuals with advanced liver disease.

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Conflicts of interest

There are no conflicts of interest.

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