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Direct-acting antiviral therapy decreases hepatocellular carcinoma recurrence rate in cirrhotic patients with chronic hepatitis C

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HCV: hepatitis C virus

HCC: hepatocellular carcinoma

SVR: sustained virologic response

DAA: direct-acting antivirals

BCLC: Barcelona-Clinic Liver Cancer

AASLD: American Association for the Study of Liver Diseases

EASL: European Association for the Study of the Liver

HIV: human immunodeficiency virus

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ABSTRACT

Background and Aims: Arrival of direct-acting antiviral (DAA) agents against hepatitis C virus (HCV) with high-sustained virological response (SVR) rates and very few side effects has drastically changed the management of HCV infection. The impact of DAA exposure on hepatocellular carcinoma (HCC) recurrence after a first remission in patients with advanced fibrosis remains to be clarified.

Methods: 68 consecutive HCV patients with a first HCC diagnosis and under remission, subsequently treated or not with a DAA combination, were included. Clinical, biological, and virological data were collected at first HCC diagnosis, at remission and during the surveillance period.

Results: All patients were cirrhotic. Median age was 62 years and 76% of patients were male. Twenty-three patients (34%) were treated with DAAs and 96% of them achieved SVR. Median time between HCC remission and DAA initiation was 7.2 months (IQR: 3.6 – 13.5; range: 0.3 – 71.4) and median time between DAA start and HCC recurrence was 13.0 months (IQR: 9.2 – 19.6; range: 3.0 – 24.7). Recurrence rate was 1.7/100 person-months among treated patients vs 4.2/100 person-months among untreated patients (p=0.008). In multivariate survival analysis, the hazard ratio for HCC recurrence after DAA exposure was 0.24 (95% confidence interval: 0.10–0.55; p<0.001).

Conclusions: HCC recurrence rate was significantly lower among patients treated with DAA compared with untreated patients. Given the potential impact of our observation, large-scale prospective cohort studies are needed to confirm these results.

Keywords: HCV, DAA, hepatocellular carcinoma, recurrence

KEYPOINTS

- Recent studies found an unexpected increased rate of HCC recurrence after HCC remission among HCV patients treated with DAA combination.

- HCC recurrence rate was compared in patients with a first HCC remission receiving or not a DAA-treatment. Untreated patients had a higher HCC recurrence rate compared with DAA-treated patients.

- A similar association with an increased risk of HCC recurrence among untreated patients was observed in a multivariate survival analysis.

- Our study suggests that DAA combination treatment could potentially induce a beneficial effect on HCC recurrence.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection leads to cirrhosis in 10-15% of patients within the first 20 years and once cirrhosis is established, patients have an estimated 3-5% annual risk of developing hepatocellular carcinoma (HCC) as well as a 3-6% annual risk of hepatic decompensation, which are the major causes of death following HCV infection. [1,2] Primary objective of HCV treatment is to reach sustained virological response (SVR), which is associated with regression of fibrosis, reduction in portal hypertension and attenuated risk of developing hepatic decompensation and HCC. [2,3]

HCV treatment has recently undergone a revolution with the development of direct-acting antivirals (DAA). [2] SVR rate now reaches 95% and above, even for patients infected with HCV genotype 3 and very few side effects have been reported compared with previous therapy. [2]

The expected outcome of DAA-induced SVR is to decrease the complications of chronic hepatitis C, including HCC development. [4] However, the positive impact of DAA therapy in patients with HCC remission has recently been challenged. A recent study conducted by the *Barcelona-Clinic Liver Cancer* (BCLC) group showed indeed an increased rate of HCC recurrence after HCC remission among HCV patients treated with DAA combination compared with the real-life recurrence rate. [5] Analysis of the impact of DAA therapy on HCC recurrence in a large French cohort of patients with a variety of comorbidities did not show similar results. [6] Notably, two other studies have reported an unexpected high incidence of HCC in patients following DAA therapy. [7,8]

Therefore, we evaluated in a well-defined population of HCV patients, with a first HCC diagnosis followed by remission after treatment, the impact of DAA on HCC recurrence among patients who received antiviral therapy compared with untreated patients.

MATERIAL AND METHODS

Patients

All HCV infected patients from the Department of Hepatology, Croix-Rousse Hospital, Lyon, France developing a first HCC and receiving or not a DAA combination therapy after HCC remission between January 2009 and March 2016 were considered. Inclusion criteria were defined as: 1) first HCC diagnosed by invasive or non-invasive criteria following the American Association for the Study of Liver Diseases (AASLD) guidelines during the study time horizon [9], 2) complete remission after HCC treatment defined by the European Association for the Study of the Liver (EASL) criteria as absence of residual tumor/complete necrosis at imaging one month after the end of HCC treatment. [10]

Exclusion criteria were: 1) prior history of HCC before January 2009, 2) liver transplantation before HCC diagnosis, 3) presence of “non-characterized nodules” after HCC treatment at

imaging, 4) history of DAA treatment before the first HCC diagnosis, 5) hepatic decompensation, 6) human immunodeficiency virus (HIV) coinfection.

In this retrospective analysis of prospectively followed patients, demographic, clinical, biochemical, virological, radiologic tumor response and surveillance imaging data were collected at first HCC diagnosis, at the remission time (liver imaging at least 1 month after the end of HCC treatment), at different time points during follow-up (every 3 months within the first year following HCC remission and every 3 to 6 months thereafter, according to AASLD routine clinical practice guidelines) and at the time of HCC recurrence, if any. [9]

DAA-based therapy

Antiviral therapy and treatment duration were decided for each patient during the weekly multidisciplinary meeting in the Department of Hepatology according to the national and international guidelines at the time of treatment initiation. [11,12] SVR was defined as undetectable HCV RNA by sensitive assay (Abbot real-time PCR, Abbott Molecular, Des Plaines, IL, USA) 12 weeks after the end of treatment (SVR_{12}). The lower limit of quantification of HCV RNA was 12 IU/mL.

Ethical considerations

All patients included in this study gave their written inform consent to allow the use of their personal clinical data in accordance with the ethics regulation defined in France by the CNIL (Commission Nationale de l'Informatique et des Libertés). This study is a retrospective observational study and as defined by the French ethics regulation, no approval by a local ethics committee was needed.

Statistical analysis

Nominal and categorical parameters were expressed as absolute numbers and percentages. For quantitative variables, median and interquartile ranges (IQR) were calculated, as well as minimum and maximum (range).

To assess the impact of DAA exposure on HCC recurrence, we conducted an univariate survival analysis using Kaplan-Meier estimator and secondly a multivariate analysis using a Cox proportional hazards model. To face the lack of proper randomization, we calculated a propensity score and we integrated it as a covariate in the Cox model to reduce bias and increase precision through regression adjustment by taking into account a lot of covariates that were not integrated directly in the multivariate analysis due to the restricted sample size and the risk of over parameterizing the model (see Appendix for the list of covariates and detailed statistical analysis, Supplementary Table 1 and Supplementary Figure 1). [13,14] For all analyses, a two-tailed significance testing and a significance level of 0.05 were used. Analyses were conducted using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients' characteristics

Between January 2009 and March 2016, 227 chronic hepatitis C patients followed at the Department of Hepatology, Croix-Rousse Hospital, Lyon, France, developed an HCC. One hundred and fifty-nine of them were excluded from the analysis (Figure 1). Among 68 patients included, 34% (N=23) were treated with DAA after HCC remission whereas 66% (N=45) did not receive any DAA combination after HCC remission (Appendix).

Patient's characteristics are reported in Supplementary Table 2. No clear-cut difference appeared between both groups of patients. Male gender was predominant (76%, N=52) and

untreated patients were older than treated patients (p=0.002). About 67% (N=41) were infected by genotype 1, 70% (N=46) were non-responders to a previous non-DAA HCV therapy and all patients were cirrhotic.

DAA-treated and untreated patients had similar characteristics at the time of HCC diagnosis. The time between HCC diagnosis and HCC treatment was similar in both groups with a median delay of 51 days (range: 17 – 440). Regarding HCC treatment, 63% (N=43) were treated with radiofrequency ablation, 7% (N=5) with chemoembolization+conformal radiotherapy, 3% (N=2) with chemoembolization, 15% (N=10) by surgical resection and 12% (N=8) with different treatment combinations.

DAA treatment characteristics

Median time between HCC remission and DAA initiation was 7.2 months (IQR: 3.6 – 13.5; range: 0.3 – 71.4) and median time between DAA start and HCC recurrence was 13.0 months (IQR: 9.2 – 19.6; range: 3.0 – 24.7), with 64% (N=7) of patients with HCC recurrence having a follow-up >12 months after DAA treatment start. Among treated patients 96% (22/23) achieved a SVR_{12} and 1 had virological relapse and HCC recurrence 6.4 months after DAA treatment start. The mostly-used DAA combination was sofosbuvir+daclatasvir. Ten patients (43%) received ribavirin in addition to the DAA combination. Antiviral treatment duration was 12 weeks in 57% of cases (Supplementary Table 2).

Hepatocellular carcinoma surveillance after remission

The median time between HCC remission and recurrence was 17.4 months (IQR: 12.3 – 34.9; range: 5.3 – 44.4) among DAA-treated patients and 10.1 months (IQR: 5.6 – 27.2; range: 2.3 – 59.4) among untreated patients. Among patients without HCC recurrence, the median follow-up

time was 35.7 months (IQR: 27.5 – 39.0; range: 9.5 – 94.7) for treated patients and 15.4 months (IQR: 6.9 – 35.2; range: 3.9 – 79.5) for untreated patients (Appendix). We found a significant difference in HCC recurrence rate when comparing both groups with 11 recurrences of HCC among treated patients (at a rate of 1.7/100 person-months) and 33 recurrences of HCC among untreated patients (at a rate of 4.2/100 person-months; p=0.008). We also observed a similar difference between both groups in the survival analysis, with an overall lower recurrence probability over time for treated patients (log rank p-value=0.006, Figure 2).

To take into account the lack of randomization, we conducted a Cox proportional hazard regression including as a covariable a propensity score estimated on patients characteristics at first HCC diagnosis (Supplementary Table 3). We observed a similar association with a hazard ratio for HCC recurrence after DAA exposure of 0.24 (95% confidence interval: 0.10 – 0.55, p<0.001).

Among patients receiving DAA, we then compared characteristics at first HCC diagnosis between those presenting HCC recurrence and those without HCC recurrence. No significant difference was observed between both groups (Supplementary Table 4). As a sensitivity analysis, we conducted similar survival analyses in subgroups of patients to take into account potential biases of selection: (1) by excluding all patients with HCC recurrence within six months after HCC remission and (2) by excluding all patients treated with a non-curative option for their first HCC. In both analyses, we observed similar associations (Supplementary Table 5 and 6 and Supplementary Figure 2 and 3, respectively). We also assessed the potential impact of previous IFN-based therapy exposure on HCC recurrence using univariate survival analysis and we observed no significant association (Supplementary Figure 4).

DISCUSSION

The present study reports a potential decrease of HCC recurrence rate among patients with a first HCV-related HCC diagnosis followed by remission and consecutively treated with DAA compared with similar patients not receiving DAA.

These findings are contradictory with the recently published study by Reig et al. reporting an opposite association between DAA exposure and HCC recurrence with an increased recurrence rate among DAA-treated patients. [5] However, the authors had no control group but instead compared their crude estimates with historical untreated groups using the STORM trial. [15] Control group is crucial in this type of study, as a recently published meta-analysis reported that recurrence risk is extremely variable in HCV-untreated patients with successfully treated HCC. [16] Other potential concerns that have been raised regarding Reig's study were the use of crude recurrence rate (with a wide confidence interval) instead of Kaplan-Meier curve, bias in selection of patients (single vs multi-nodular HCC), wide range elapsed between HCC remission and DAA start and high clinical, biological and epidemiological heterogeneities of early HCC. [17] Moreover, patients included in their study had a complete radiologic remission of their HCC but multiple recurrences of HCC were not considered as an exclusion criterion. This difference in the selection of patients could explain why our findings are opposite, as multiple recurrences of HCC could reflect a certain degree of severity of the disease. Among these patients with multiple HCC recurrences, presence of residual tumor undetectable by imaging after first HCC treatment is more likely. Similar differences regarding patients' selection exist with the study conducted by Pol et al. in which the authors did not consider multiple recurrences of HCC as an exclusion criterion. Moreover, the different populations considered in their study were more heterogeneous compared with ours. [6]

A recent large-scale cohort study showed that HCC incidence was decreased after HCV eradication with IFN-based therapy in a cirrhotic population sharing similar characteristics as ours. [18] Regarding HCC recurrence, a recent meta-analysis showed a positive impact of SVR

with a decreased HCC recurrence rate. [19] In our study, 96% of patients (22/23) achieved SVR_{12} after DAA therapy which could potentially explain the lower HCC recurrence rate observed.

Our study has some limitations. First, the number of patients treated with DAA was relatively small due to the recent introduction of DAA in routine clinical practice and to the inclusion/exclusion criteria needed to analyze a homogeneous and well-defined population. Second, patients were not randomized as this was a retrospective cohort study. Third, we did not have histological information regarding HCC grade for all patients (44% (N=32) of patients had available information) and the severity of HCC was only assessed using the size and number of nodules. Fourth, our cohort was only composed of patients with cirrhosis, frequently associated with comorbidities. Unfortunately, information on alcohol consumption or smoking after HCC diagnosis was not available, as in many other studies on this topic. [5,6] Given the clinical impact of these findings, our results need to be reproduced in a larger and more heterogeneous HCV-HCC population, more particularly regarding the severity of the disease.

Our study does have some strengths. Lack of randomization and comparability of both groups were partially controlled by using a propensity score as a covariate in the multivariate analysis, which allowed to decrease the risk of confounding effects in the analysis as well as selection bias. [13] We also conducted two sensitivity analyses in subgroups of patients without HCC recurrence within the first 6 months following remission or with a curative treatment option for their HCC and we observed similar associations. Furthermore, exclusion of patients with multiple history of HCC strengthened the relevance of comparing both groups and the potential validity of a potential effect of DAA exposure on HCC recurrence rate. Our study was also a single center study that ensured homogeneity regarding patients' population.

In conclusion, the increased HCC recurrence rate reported in the literature is not observed in our study, which on the contrary suggests that DAA combination treatment could possibly

induce a beneficial effect among HCV patients with compensated cirrhosis after first HCC curative treatment. Given the potential impact of our observation, large-scale prospective cohort studies are needed to confirm these results.

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FIGURE LEGEND

Figure 1. Flow chart showing patient selection. HCC: hepatocellular carcinoma, DAA: direct-acting antiviral drug.

Figure 2. Hepatocellular carcinoma recurrence over time among HCV patients according to direct acting antiviral therapy exposure. Time zero is the date of HCC remission for all patients. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The number of patients at risk in each group (i.e. without HCC recurrence and/or not lost to follow-up) is indicated at the bottom of the figure.