The Dynamic Effect of Direct-acting Antiviral Treatments on the Risk of Hepatocellular Carcinoma in Patients with Cirrhosis and Chronic Hepatitis C

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The dynamic effect of direct-acting antiviral treatments on the risk of hepatocellular carcinoma in patients with cirrhosis and chronic hepatitis C.

Running title: Effect of DAAs on hepatocellular carcinoma.

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Conflict of interests.

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Author contribution.

CLN, HF, CD, MS, SP and FC have made substantial contributions to study conception and design. **HF, CD and SP** have made substantial contributions to acquisition of data. **CLN and FC** have been involved in drafting the manuscript and made substantial contributions to

statistical analysis of data. **HF, CD, MS and SP** have been involved in revising the manuscript critically for important intellectual content. All authors read and gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Abstract

There is still some controversy over a potentially increased short-term risk of developing hepatocellular carcinoma (HCC) after the initiation of direct-acting antiviral (DAA) therapy, even though a decreased long-term risk of HCC has been reported following a sustained virological response in patients with chronic hepatitis C virus (HCV) infection. We characterized the time-varying effect of DAAs on the risk of the occurrence of HCC in patients with cirrhosis and HCV infection. We analyzed patients with cirrhosis and chronic HCV infection from the ANRS CO22 HEPATHER cohort study. We excluded patients with active HBV coinfection, liver transplantation or a past history of HCC. We used a flexible weighted effect cumulative exposure Cox model to characterize the time-varying effect of DAAs on the risk of HCC. A total of 3595 patients, mean age 59.3 years old, 65% men, were eligible for the study. Median follow-up was 36.8 months (IQR 24.6-47.1). DAAs were started during follow-up in 3292 patients. Three hundred and fifty-six HCCs were reported (275 treated, 81 untreated). Overall, a constant decrease in the risk of occurrence of HCC (vs untreated) was found from the start of treatment. Results were similar in patients without a history of decompensated cirrhosis (DC). Analysis of patients with a past history of DC showed a non-significant increase in the occurrence of HCC over the first 6 months, while the HR was significantly decreased at 14 months. These findings support the urgent initiation of DAAs in all patients.

Keywords: Hepatocellular carcinoma, Hepatitis C virus, Direct-acting antiviral agents, Weighted cumulative exposure model, time-varying effect.

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1. Introduction

Since 2014, the use of direct-acting antiviral (DAA) treatment has completely revolutionized the treatment of patients with chronic HCV infection. A combination of 2-3 DAAs results in a sustained virological response (SVR) in more than 95% of treated patients. This high SVR rate has raised hopes for a significant reduction in the incidence of HCC, like that reported with interferon-based regimens [1]. However, the dynamic impact of DAAs on the risk of HCC in patients with chronic HCV and how the risk of HCC varies over time in patients who receive DAAs compared to those who do not, remain unclear. Despite the overall decrease in the risk of *de novo* HCC reported in the 3 years following treatment, there has been some controversy concerning the increased short term risk of HCC following the initiation of DAAs, in particular in patients with cirrhosis [2, 3]. However, the use of a single measure, the average fixed hazard ratio (HR), during follow-up may not reflect the potentially complex time-dependent relationship between exposure to DAAs and the risk of HCC. Our objective was to characterize the effect of DAAs on the risk of the occurrence of HCC over time in patients with cirrhosis and HCV infection.

2. Methods

Patients were selected from the ANRS CO22 HEPATHER cohort study [4] and enrolled from August 6, 2012 to December 31, 2015. All patients with cirrhosis at entry in the cohort were selected and patients with active HBV coinfection defined by detectable HBsAg (n=35), liver transplantation (n=107) or a past history of HCC (n=442) were excluded.

Cirrhosis was based on a platelet count < 150,000/μL or a prothrombin time < 70% at entry in 1772 patients. These criteria were validated in 757 patients who had also been evaluated for liver fibrosis, including 755 who had been classified with cirrhosis by other procedures (liver biopsy=45, fibroscan=682, fibrotest=332, fibrometer=46, hepascore=85, a patient could have several procedures). In other patients, cirrhosis was based on liver biopsy (n=110) or another non-invasive test (liver stiffness measurement (Fibroscan®>12·5 kPa) (n=594), Fibrotest®>0·75 (n=421), Fibrometer®>0·98 (n=184), or the Hepascore>0·84 (n=26) that was performed closest to the date of inclusion, but less than 1 year before and up to 3 months after inclusion. If a recent measurement of fibrosis was not available or in case of discrepancies between non-invasive fibrosis markers, we used the physician's assessment of cirrhosis at enrolment based on past assessments of liver fibrosis and the patient's history of liver-related comorbidities (n=488).

Patients were further categorized according to a history of decompensated cirrhosis (DC), defined as past episodes or the presence of ascites, variceal hemorrhage, encephalopathy, and/or jaundice at entry [5], and their sustained virological response (SVR) status. Follow-up included systematic visits (every 6 months for patients with cirrhosis) and spontaneous reports of particular events including the diagnosis of *de novo* HCC on specific data forms. Survival time was calculated as the time between inclusion in the study or the initiation of DAAs and the diagnosis of HCC or February 1, 2019, whichever occurred first. To take into account competing events, HCC-free survival was censored in case of death or liver transplantation

during follow-up**.** Participants who initiated DAAs were considered to be exposed until the end of follow-up. To characterize the time-varying effect of DAAs on the risk of HCC, we used a flexible weighted cumulative exposure (WCE) Cox model with DAAs exposure modeled as a weighted sum of the months following the initiation of treatment [6]. The weighted function was estimated using regression with cubic B-splines, allowing the HR to increase or decrease smoothly over time from the beginning of treatment. For comparison purposes, we also computed the fixed HR using a conventional multivariable Cox proportional hazards model. We estimated the time-varying and fixed hazard ratio according to SVR status (yes or no compared to not exposed to DAAs), with SVR status evaluated from 3 months after the last day of DAAs [4]). Exposure to DAAs was also entered as a time-dependent covariate and adjusted for age, gender, geographic origin, HCV genotype, a history of decompensated cirrhosis (DC), albuminemia, platelet count and alfa fetoprotein as fixed covariates. All calculations were performed using SAS v9.4 software (SAS Institute Inc, Cary, NC, USA).

3. Results

A total of 3,595 patients (3043 and 552 without and with a history of DC, respectively), mean age 59.3 years old, 65% men, were eligible for the study. DAA treatment was started in 3292 (92%) patients during follow-up while 303 (8%) patients remained untreated at the end of the follow-up, representing 8755 Person-Years (PY) exposed and 1718 PY unexposed to DAAs. The median follow-up was 36.8 months (IQR 24.6 – 47.1). SVR status was available in 3045 (92%) treated patients, 2613 (92%) and 432 (93%) in patients without and with a history of DC, respectively. A SVR was achieved in 2779 (91%), 2406 (92%) and 373 (86%) patients, respectively. Three hundred and fifty-six HCCs (3.4/100 PY) were reported including 275 (3.1/100 PY) in patients exposed to DAAs and 81 (4.7/100 PY) in unexposed patients, 263 (2.9/100 PY) and 93 (6.6/100 PY) in patients without and with a history of DC, 192 (2.3/100 PY) and 67 (9.3/100 PY) in patients exposed to DAAs with or without a SVR, 167 (2.2/100

PY) and 52 (8.6/100 PY) in patients without a history of DC with or without a SVR and 54 (5.0/100 PY) and 20 (16/100 PY) in patients with a history of DC with or without a SVR, respectively. Two hundred and eighty-four deaths and 71 liver transplantations were reported. Time-varying and fixed HR are shown in Figure 1. Overall, a constant decrease in the risk of occurrence of HCC (vs untreated) was found from the start of treatment. The HR was significant at 9 months (0.65 (95% CI 0.43; 0.97)) and reached a minimum of 0.47 (95% CI 0.27; 0.81) at 30 months (Fig 1a.). Results were similar when the analysis was limited to 3043 patients without a history of DC (fig 1b.). An analysis of 552 patients with a past history of DC showed a slight non-significant increase in the occurrence of HCC in treated versus untreated patients over the first 6 months, while the HR was significantly decreased at 14 months (0.39 (95% CI 0.18; 0.85)) to reach a minimum at 22 months (0.18 (95% CI 0.07; 0.47)) (Fig 1c.). Similar results were found when analyses were performed in patients who achieved a SVR (Fig 1: d-f). A progressive increase in the risk of occurrence of HCC (vs untreated) was found in all subgroups of patients who did not achieve a SVR (Fig 1: d-f). Fixed-HR estimates indicated a significant association between exposure to DAAs and a decreased risk of HCC, except in patients with a past history of DC. This confirmed the increased risk of HCC in patients who did not achieve a SVR.

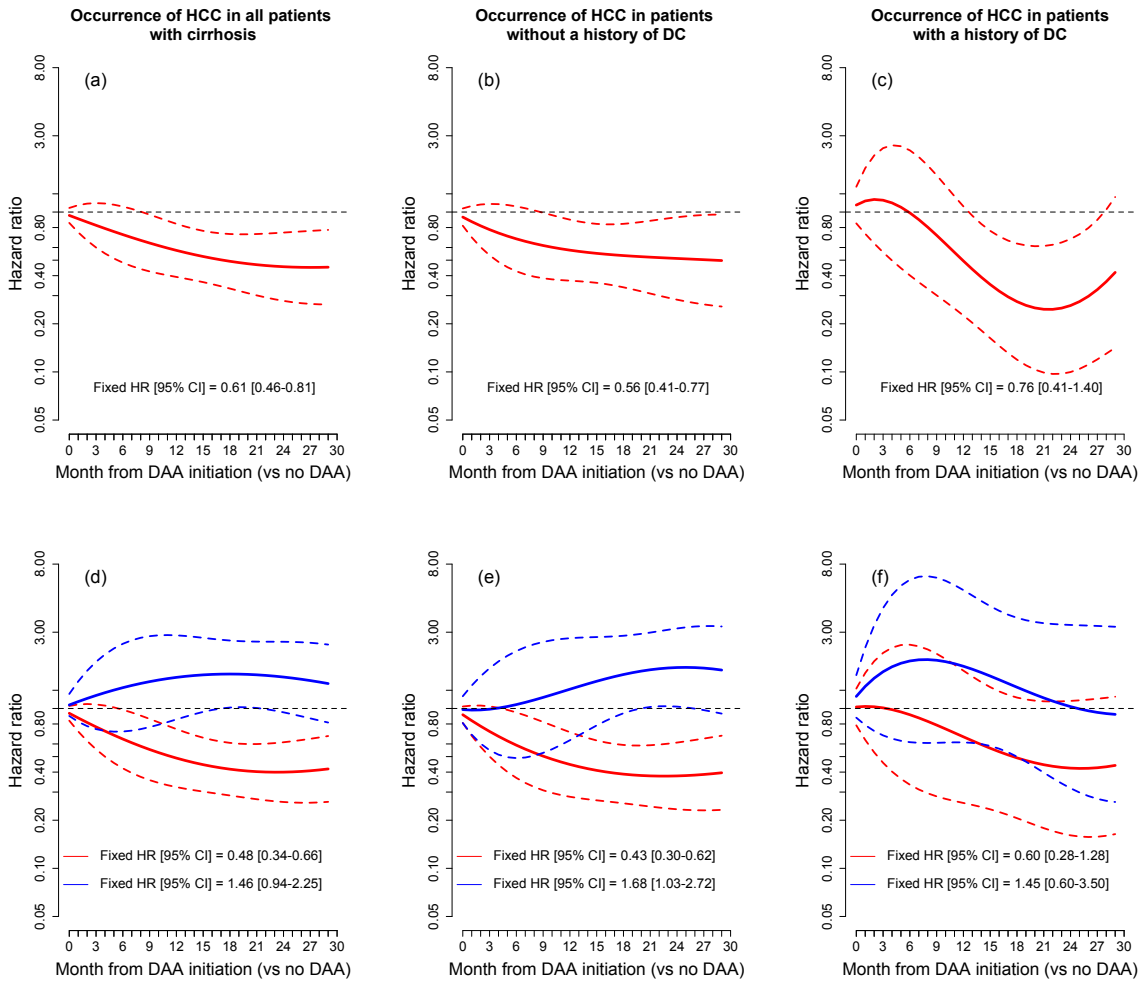

Figure 1. Time-varying effects (solid curves) and 95% point-wise confidence bounds (dotted curves) of DAAs on HCC. Upper panel shows time-varying effects in all patients who received DAAs (a-c) compared to those who did not receive DAAs. Lower panel (d-f) shows time-varying effects in patients who achieved (red curve) and those who did not achieve a SVR (blue curve) compared to patients who did not receive DAAs.

4. Discussion

This study shows that the risk of the occurrence of HCC in patients with cirrhosis and chronic HCV infection progressively decreases after the initiation of DAAs compared to untreated patients. The present report updates a previous study [4] while highlighting that this association varies over time.

The main strengths of our study are the prospective design, the large number of patients with cirrhosis including patients with a history of DC, the 3-year median duration of follow-up, and especially, the comparison of treated and untreated patients with multivariate adjustment for the risk factors of HCC. The main limitation of this study was reverse causality. In particular, if patients with more advanced liver disease and a higher risk of HCC had a lower probability of starting treatment this could potentially explain the early negative association between the development of HCC and treatment exposure in the first year. However, the HR between treated and untreated patients continually decreased, except in the subset of patients with DC. This suggests that DAAs have a potentially rapid impact on the risk of HCC that accumulates over time in patients without DC. In patients with DC, the non-significant short-term increase risk of HCC over the first 6 months warrants further study, but appears to be associated with the lack of SVR in this subgroup of patients. Potentially missed HCC diagnoses are another limitation if some patients have been screened less regularly than recommended. However, the average number of follow-up visits and ultrasound examinations were higher in patients after than before treatment or in patients who remained untreated (11.0 and 2.6 vs 2.2 and 0.8, $P<0.0001$ and $P<0.0001$, respectively). Therefore, any screening bias would reinforce our conclusion.

Also, the rates of HCC in DAA treated patients in our study are consistent with those reported in therapeutic cohort studies in patients with cirrhosis [1-3] as well as other comparative studies suggesting that DAAs significantly reduce the short term risk of HCC [7].

Altogether, our findings support the urgent initiation of DAAs in all patients with chronic HCV and cirrhosis. The short-term influence of DAAs on HCC in patients with a history of decompensated cirrhosis must still be clarified.

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