Research Article

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Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts

The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts) *

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Background & Aims: Sustained virological response following interferon-based antiviral treatment of chronic hepatitis C is associated with decreased long-term risk of hepatocellular carcinoma (HCC) in advanced liver fibrosis. An unexpected high rate of HCC recurrence following antiviral treatment using direct-acting antiviral (DAA) has recently been reported.

Methods: We analyzed data individually from three French prospective multicentre ANRS cohorts including more than 6000 patients treated with DAA and we focused on HCC patients who underwent curative procedures before DAA treatment. The aim was to assess the rates of HCC recurrence in these patients according to antiviral treatment regimen.

Results: In the ANRS CO22 "Therapeutic options for hepatitis B and C: a French cohort" (HEPATHER) cohort, 267 patients with chronic hepatitis C who were previously treated for HCC were analyzed, among whom 189 received DAA and 78 did not. The rates of recurrence were 0.73/100 and 0.66/100 person-months, respectively. In the ANRS CO12 "Cirrhose Virale" (CirVir) cohort, 79 cirrhotic patients in whom HCC was diagnosed and treated, 13 received DAA and 66 did not. The rates of recurrence were 1.11/100 and 1.73/100 person-months, respectively. In the ANRS CO23 "Compassionate use of Protease Inhibitors in viral C Liver Transplantation" (CUPILT) Cohort, 314 liver transplant recipients for HCC who were subsequently treated with DAA were analyzed. Seven HCC recurrences were reported after a median time of 70.3 months after liver transplantation. The rate of recurrence was 2.2%.

Conclusions: In three distinct prospective cohorts, we did not observe an increased risk of HCC recurrence after DAA treatment, notably in patients who underwent curative HCC treatment including liver transplantation.

Lay summary: Since an unexpected high rate of hepatocellular carcinoma (HCC) recurrence after direct-acting antiviral (DAA) treatment has been suggested in a retrospective study, we analyzed data from three French prospective multicentre ANRS cohorts of >6000 DAA-treated patients who underwent curative HCC therapies. We did not observe an increased risk of HCC recurrence after DAA treatment: the rates of recurrence were similar in treated and untreated patients (0.73/100 and 0.66/100 person-months in in the ANRS CO22 HEPATHER cohort including 189 DAA+ and 78 DAA− and 1.11/100 in 13 DAA+ and 1.73/100 person-months in 66 DAA− in the ANRS CO12 CirVir cohort), respectively. Finally, in the ANRS CO23 CUPILT Cohort, HCC recurred in only 7 among 314 (2.2%) liver transplant recipients for HCC subsequently treated after 70 months after liver transplantation.

Keywords: Hepatitis C virus; Hepatocellular carcinoma; Direct-acting antivirals.
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Abbreviations: ANRS, (France REcherche Nord & sud Sida-vih Hépatites); HCV, hepatitis C virus; RNA, ribonucleic Acid; DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; SVR, sustained virological response; RR, relative risk; INF, interferon; US, ultra-sound; CT scan, computer tomodensitometry; MRI, magnetic resonance imaging; SD, standard deviation; *vs.*, versus; cumI, cumulative incidence; PLC, primary liver cancer; LT, liver transplantation.

Introduction

Currently, high rates of sustained virological response (SVR) are achieved in patients with chronic hepatitis C treated with direct-acting antivirals (DAAs) [1–3].

Viral eradication is associated with a reduced risk of liver complications, including the occurrence of hepatocellular carcinoma (HCC), as reported in a recent meta-analysis: relative risk (RR) = 0.24 in all stages of fibrosis; RR = 0.23 in advanced liver disease [4]. These results were only supported by studies with interferon (IFN)-based regimens.

Surprisingly, a high rate of tumor recurrence has been recently reported after antiviral treatment of chronic hepatitis C using DAAs in 16 of 58 patients (28%) with apparent complete remission after HCC treatment [5]. Most of these patients had previous surgical resection or radio-frequency ablation and had favorable prognostic factors with an expected low rate of HCC recurrence (<4–5%) [6]. Another study of 59 patients with HCC remission at start of DAA therapy reported a 29% rate of early HCC recurrence within 6 months of therapy [7]. Similar data has not been suggested by pivotal controlled trials performed in the population of patients with cirrhosis, however patients with a history of HCC had been systematically excluded.

This data prompted us to assess the risk of HCC recurrence in three distinct prospective cohorts of the French ANRS (France REcherche Nord&sud Sida-vih Hépatites) agency including HCV-infected patients with or without cirrhosis who received DAA therapy. The current analyses are focused on HCC patients who underwent curative management for their liver tumor based on hepatic resection, percutaneous ablation or liver transplantation (LT) before starting DAA therapy. The rates of HCC recurrence were assessed in this population according to antiviral therapy.

Patients and methods

The present work analyzed three distinct prospective cohorts, sponsored and funded by the ANRS (France REcherche Nord&Sud Sida-HIV Hépatites), namely, the ANRS CO22 "Therapeutic options for hepatitis B and C: a French cohort" (HEPATHER) cohort, the ANRS CO12 "Cirrhose Virale" (CirVir) cohort, and the ANRS CO23 Compassionate use of Protease Inhibitors in viral C Liver Transplantation (CUPILT) cohort.

ANRS CO22 HEPATHER cohort

The ANRS CO22 HEPATHER cohort is a multicentre observational cohort, which is looking to include 15,000 HCV- and 10,000 HBV-infected patients. The aims of the cohort are to quantify the clinical efficacy and safety of new hepatitis treatments in real-life, and to identify, at the patient level, which treatment will most likely improve overall health (ClinicalTrials.gov, NCT01953458). HCV-positive patients are defined as patients with positive HCV-RNA or positive anti-HCV antibodies. Each patient gave written informed consent before enrollment and the protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the "Comité de Protection des Personnes (CPP) Ile de France 3" Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM). By December 31st 2015, 14,379 participants with past or active chronic hepatitis C infection had been recruited; among whom 5458 had begun a DAA therapy from entry. We selected all participants with chronic active hepatitis C and a history of treated hepatocellular carcinoma (HCC) prior to inclusion (n = 307), and we excluded patients with progressive or active recurrence of HCC upon inclusion (n = 40).

ANRS CO12 CirVir cohort

The ANRS CO12 CirVir cohort is a multicentre observational cohort which aims to characterize the incidence of complications occurring in biopsy-proven compensated cirrhosis and to identify the associated risk factors using competing risks analysis [8]. Patients were recruited in 35 French clinical centres between 2006 and 2012. Inclusion criteria were: histologically proven cirrhosis due to HCV or HBV; Child-Pugh A; and no previous hepatic complications [8]. Patients were seen by physicians every 6 months, and the usual clinical and biological data were recorded. Examination by Doppler US was performed every 6 months. When HCC diagnosis was established, treatment was determined using a multidisciplinary approach according to American association for the study of liver diseases (AASLD) guidelines for HCC [6,9].

All events occurring during follow-up, liver-related or not, were recorded based on information obtained from patient medical files from each centre. Likely cause(s) of death were established.

A total of 1822 cirrhotic patients were included. Among them, 151 were subsequently excluded from analysis after reviewing individual data either due to non-compliance with inclusion criteria (n = 142) or consent withdrawal (n = 9). Consequently, 1671 patients among whom 1354 had HCV-related compensated cirrhosis, were selected for further analysis. On January 5, 2016, after a median follow-up of 58.6 [36.5–79.1] months, a first hepatic focal lesion was observed in 409 patients (30.2%) with a 5-year cumulated incidence (CumI) estimated at 32.3%. Following a diagnostic procedure, more than half of these focal liver lesions remained indeterminate or were considered benign (n = 214, 52.3%). A definite diagnosis of primary liver cancer (PLC) was established in the remaining 195 patients: HCC (n = 189) and intra-hepatic cholangiocarcinoma (n = 6). HCC 5 yr CumI was 13.9%.

ANRS CO23 CUPILT cohort

The ANRS C023 CUPILT study is a multicentre, cohort study implemented in 24 French and one Belgian LT centres (ClinicalTrials.gov number NCT01944527). To be enrolled in this cohort, patients must comply with the following associated criteria, which include: (1) having received a LT for an HCV infection, (2) having experienced an HCV recurrence in any stage of fibrosis, (3) having been treated with second-generation DAAs. All patients provided their informed consent before inclusion.

Among the 699 liver transplant recipients enrolled between October 2013 and December 2015, 330 (47%) received LT for HCC. We excluded patients

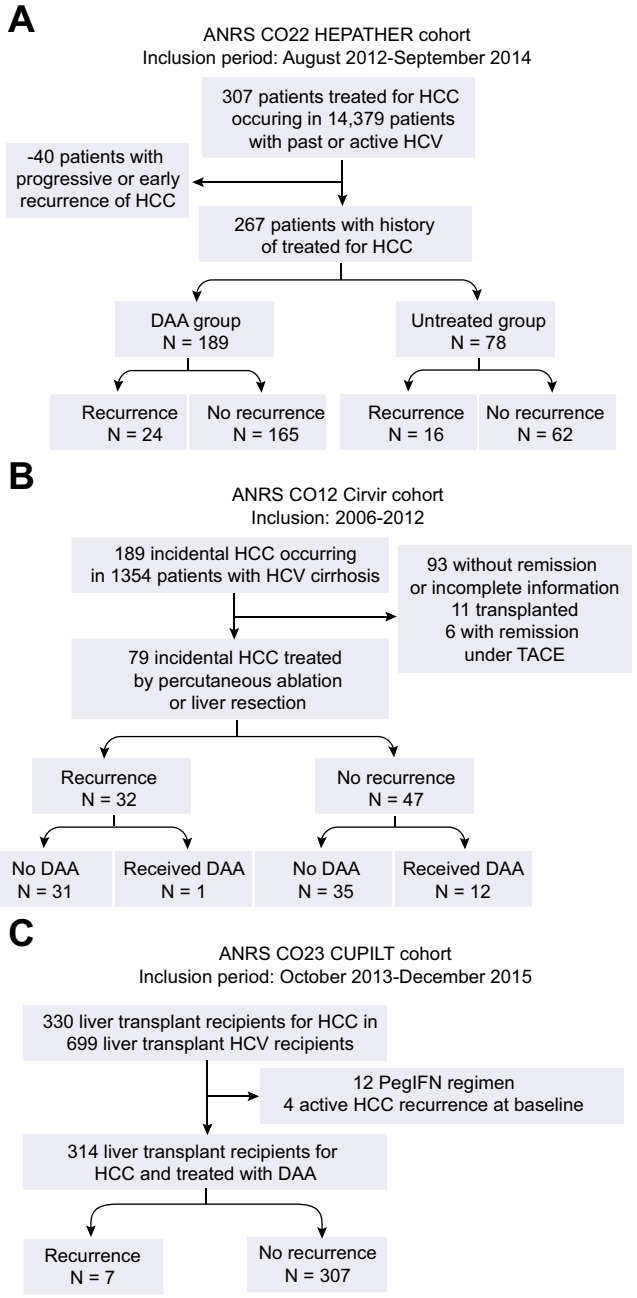

Fig. 1. Flow-chart of the 3 multicentre prospective ANRS cohorts. (A) ANRS CO22 HEPATHER. (B) ARNS CO12 CirVir. (C) ARNS CO23 CUPILT.