Hepatocellular carcinoma and direct acting antiviral treatments: Controversy after the revolution

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Interferon (IFN)-free regimen using new direct acting antiviral (DAA) is a revolution for the treatment of patients with chronic hepatitis C. More than 95% of patients have a sustained viral response (SVR) using DAA except for genotype 3 virus in cirrhotic patients where SVR is still insufficient [1]. If the high rate of SVR seems constant among several clinical trials testing DAA, the impact on complications of cirrhosis is still unknown. We can only speculate from the results of observational studies among compensated cirrhotic patients treated by IFN regimens. In these patients, SVR were obtained mostly by the combination IFN and ribavirin treatments and decreased the occurrence of liver decompensation, of hepatocellular carcinoma and of death [2,3]. The rate of hepatocellular carcinoma (HCC) occurrence is strongly decreased after SVR but not abolished with an incidence of HCC ranging from 0.4 to 2% per year after viral eradication [3]. In contrast, the evidence of decreased liver related complications after viral clearance using DAA is still scarce. Some studies report an improvement of liver function after DAA treatments in patients with decompensated cirrhosis without decreased of mortality and rates of liver transplantation maybe due to the short follow-up after viral clearance [4]. However, until recently, no studies have reported the impact of DAA treatments on the rate of HCC occurrence in patients without HCC at baseline or on the rate of tumor recurrence after curative treatment of HCC.

Two studies published in this issue of the Journal reporting increased aggressiveness and rates of HCC recurrence in patients who cleared hepatitis C virus (HCV) with DAAs after achieving a complete response to resection or local ablation, fuel the debate around such a highly unmet clinical need as adjuvant therapy of HCC [5,6]. Owing to the absence of robust evidence of effectiveness, adjuvant therapy is not recommended by the international societies. Indeed, despite many efforts at bench level to disentangle recurrence caused by pretreatment tumor cells dissemination (metastasis) from a second primary tumor nodule originating from an inflamed liver environment, classification of recurrence still relies on rather disputed chronological criteria [7,8]. Conventionally, tumors recurring within two years from a curative treatment are classified as a tumor metastasis, a risk that is fueled by high tumor burden and cell dedifferentiation, microscopic vascular invasion, high alpha-fetoprotein level and non-anatomical resection [9]. Conversely, later occurring recurrences fall in the domain of second primary tumors, an event that is driven by degree of liver cell inflammation and proliferation, i.e., severity of the underlying liver disease, and therefore is potentially amenable to prevention by antiviral therapy [9]. With all the caveats of such a fragile classification, evidence has not been gathered to support pharmacological prevention of early tumor recurrence, including the use of molecularly targeted antitumor regimens [10]. By the same token, prevention of second primary tumors in patients who achieve a pharmacological control of viral hepatitis, has been reported, yet it remains highly disputed in consideration of many methodological weaknesses of studies [11]. In the HCV scenario, in fact, a cumulative 74% reduction of tumor recurrence was calculated in a pooled analysis of 10 cohorts of patients treated with IFN-based regimens, however in the face of numerous methodological weaknesses [12]. In the present issue of the Journal three studies that retrospectively evaluated HCC recurrence in patients who had a small HCC eradicated by resection or ablation while HCV was cleared with DAAs, provided conflicting results with respect to prevention of HCC recurrence. In a multicenter study in Spain of 58 patients and a single center study in Italy of 59 patients, recurrences after curative therapies in DAA treated patients appeared unusually high (28% and 29%, respectively) [5,6]. In the multicenter study in
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Spain, recurrence rates were calculated to be higher than those annotated in the placebo arm of the multinational STORM study, which evaluated sorafenib as adjuvant therapy in patients subject to curative ablation or resection for a HCC of various etiologies [10]. Confronted with a recent meta-analysis of 11 studies of adjuvant therapy with IFN (Cabibbo et al. Submitted), the two reports in this issue of the Journal suggest accelerated HCC recurrence after DAA therapy. In fact, the 6-month recurrence rate in 701 untreated patients scrutinized by the meta-analysis ranged between 0 and 12.5% compared to more than 28% of the DAA studies. In contrast, the retrospective scrutiny of the France REcherche Nord&Sud Sida-hiv Hepatites (ANRS) study in France presented in this same issue of the Journal, did not confirm any aggressive and accelerated pattern of recurrence seen in the multicenter study in Spain and in the single center study in Italy. In the ANRS study, in fact, the 6-month recurrence rate was 10.6% in a cohort of 189 patients receiving adjuvant DAA therapy compared to 18.7% in 267 untreated patients [13]. Before attempting any interpretation of the discrepancies between the above mentioned reports, we should acknowledge that an increased aggressiveness and rate of recurrence in the 6-month period following a curative resection or ablation of a HCC is likely to reflect a biological process of cancer cell dissemination rather than metachronous tumorigenesis, the former being unlikely to be prevented by antiviral therapy. One possible explanation for the accelerated rates of HCC recurrence observed in some DAA treated patients could reflect a bias of selection owing to the fact that DAA allowed to treat patients with far impaired liver function with invisible HCCs at imaging, i.e., patients who in the past would never qualify for IFN therapy.

The mechanism that could explain the high rate of tumor relapse after DAA treatment is one of the main issues rising from these studies. Microenvironment and viral induced inflammation play a key role in chronic liver injury and tumor initiation [14]. In contrast, the immune system has also an anti-tumor function [15]. Overall, there is a complex and fragile equilibrium between a pro tumor and anti-tumor function of the immune system. Some studies have proposed that DAA treatment could modify natural killer function and expression of IFN response gene [16,17]. One of the hypothesis is a dysregulation of the anti-tumor response after the brutal decrease of HCV viral load induced by DAA that promotes tumor recurrence. Recurrence could be accelerated by DAA boosting the growth of invisible HCC as a consequence of a perturbation of immune surveillance caused by a swift clearance of HCV, a phenomenon that was unlikely in patients exposed to IFN owing the slowly developing antiviral effects of this cytokine coupled with its discrete immune modulatory and anti-proliferative properties. However, this mechanism is purely speculative and no robust preclinical studies support this hypothesis as well as an elusive direct pro oncogenic role of DAA. Overall, the high rate of HCC recurrence after DAA treatments in patients with prior HCC suggests that a close follow-up of these patients remains mandatory as well as a reassessment of these observations in prospective dedicated studies.

On the other side, in patients with untreated HCV related cirrhosis and without any previous history of HCC, the rate of HCC occurrence varies from 2 to 5% per year [18]. The risk of HCC development is modulated by host features such as gender (male), age, metabolic syndrome and by the severity of the underlying liver disease with a higher rate of HCC occurrence in Child Pugh B and C patients and in patients with portal hypertension [19]. In contrast to observational studies that reported a reduced incidence of HCC after SVR using IFN regimens [2,3], the study of Conti et al. recently published in the Journal, reports a high incidence (3.17% after 24 weeks of follow-up) of HCC after viral clearance [6]. However, IFN treatments were mostly successfully performed in patients with compensated cirrhosis often without clinically significant portal hypertension that have a lower incidence of HCC [2,3] whereas DAA treatments are currently used in unselected Child Pugh B patients or with significant portal hypertension, a population at high risk of HCC development. Interestingly, Cheung et al. report a decreased HCC incidence in decompensated cirrhotic patients with SVR obtained by DAA compared to patients without SVR despite DAA treatments and compared to a cohort of untreated patients [20].

These different studies bring no strong evidence for an increased risk of HCC occurrence in “HCC naïve” patients treated by DAA. However, the persistent risk of HCC development strongly justifies HCC screening after viral clearance in patients with HCV related cirrhosis.

Conflict of interest

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