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Editorial
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HCC and DAA: Open Issue or Closed Wrangling?

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Editorial

Since the introduction of Direct-Acting Antiviral Agents (DAAs), the treatment of HCV is radically improved with Sustained Virological Response (SVR) rates exceeding 95%. Although several robust scientific evidences sustain the benefic role of SVR after interferon therapy in the natural history of cirrhosis with a decreased incidence of Hepatocellular Carcinoma (HCC), currently a hot debate about the impact of DAAs on HCC development animates the scientific community. In spring 2016 this topic became particularly hot for the publication of two papers [1,2] suggesting a potential increase of HCC occurrence and recurrence rates in patients undergoing DAA schedules. Since those publications, more than 100 papers, letters or communications have been published until now.

Among studies evaluating the risk of HCC occurrence after DAA treatment, de novo incidence rate ranged from 0% to 7.3% [3]. In particular, in a recent Italian prospective study, Calvaruso et al. [4] showed that only 78/2,249 cirrhotic patients (3.4%) developed HCC during a mean observation time of 14 months from the start of DAA treatment. Of interest, the occurrence of HCC is significantly reduced in patients with compensated cirrhosis without signs of portal hypertension, while in patients with advanced liver disease eradication of HCV infection reduced the risk of developing HCC. Moreover, none of these patients had a multinodular or aggressive HCC pattern, discouraging the hypothesis that HCC occurred after DAA is more aggressive and more difficult to treat [4]. Likewise, Romano et al. [5] showed that the risk of "de novo" HCC during the first year after DAAs is not higher, and later might be even lower than that observed in HCV-untreated patients (median follow-up: 523 days), and the only risk factor associated to HCC occurrence is the antiviral treatment failure [5]. Similarly, analyzing the American cohort of Veterans treated with DAAs, Mun et al. [6] found no association between DAA regimen and HCC risk, suggesting the absence of a direct carcinogenic effect related to DAAs. Compared to IFN-regimens, less consistent data are available about the impact of DAAs therapy on HCC occurrence. Moreover, the HCC risk after DAAs in comparison to IFN is biases by recruitment of two different kind of populations being heterogeneous and incomparable for age, presence of comorbidities, stages of cirrhosis and for the short follow up for DAA. In conclusion, the studies comparing the HCC risk after DAA to the one after IFN treatment showed similar behavior with SVR representing the milestone to obtain the clinical advantage. In the same trail, Ioannou et al. [7] demonstrated that the incidence of HCC is highest in patients with cirrhosis experiencing treatment failure and that SVR is associated with a significant decreased risk of HCC (71% risk reduction) in DAA-treated cohort, and in the same way in the IFN cohort HCC developed in 2.5% of SVR-patients and in 9.8% in patients without SVR [7]. Similarly, these data have been recently confirmed in a German study enrolling 819 patients treated with DAA and 351 patients treated with IFN: de novo HCC rates did not differ between the two groups: only twenty-five cirrhotic DAA-treated patients developed HCC (3.1%) (median follow-up: 263 days) while 19 patients (5.4%) were diagnosed with de novo HCC in the IFN group (median follow-up: 52 months) [8]. Finally, in a recent meta-analyses Waziry et al. [9] confirmed there is no evidence that DAA therapy is associated with a higher risk of HCC development after HCV eradication, and for this reason there is no need to defer or withhold the DAA-therapy considering the advantages of this excellent therapeutic strategy [9]. Among studies evaluating the risk of HCC recurrence after DAA treatment, the HCC recurrence rate ranged from 0% to 47.8% [3]. The available data are conflicting, and the published studies show different and relevant methodological limitations: HETEROGENEOUS cohorts, potential misclassification of HCC, the absence of an adequate control group, short follow-up time and different length of follow-up [10]. Cabibbo et al. [11] found that 6-month and 1-year probability of HCC recurrence after DAAs was 12% and 26.6%, respectively. The authors identified previous history of HCC recurrence, as also reported by Toyoda et al. [12], and tumor size as the only two independent risk factors for HCC early recurrence [11]. More recently, Lleo et al. [13] confirmed a significant reduction in HCC recurrence in cirrhotic patients treated with DAA who achieved SVR, identifying baseline alpha-fetoprotein levels and

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signs of portal hypertension as independent predictors that can help to stratify patients according to HCC risk and therefore to guide their management [13].

In the previous studies it was hypothesized that the rapid control of inflammation after DAA could impact anti-tumoral immune control, allowing the emergence of tumor clones with development of early HCC, while IFN does not result in this emergence because of its anti-tumoral immune effect [1,2]. In this context, Nishibatake Kinoshita et al. [14] demonstrated that the achievement of SVR is not significantly associated with the risk of early HCC recurrence, suggesting that early HCC is not associated with viral state or antiviral regimen in patients undergoing IFN- or DAA-based therapy after successfully HCC treatment [14].

In conclusions, the use of DAAs does not seem to increase the occurrence and recurrence of HCC, even if a long period of follow-up will be necessary to establish if there is a long-term increased HCC risk after DAAs. Relevantly, achievement of SVR is of utmost importance for HCC development reduction. Nonetheless, patients with cirrhosis even after SVR obtainment still remain at risk for HCC and should continue the HCC surveillance program.

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