# *De novo* hepatocellular carcinoma in the context of new direct acting antivirals: time seems to start talking

**Ezequiel Mauro[1], Gonzalo Crespo[2]**

[1]Liver Unit, Hospital Italiano, Buenos Aires, Argentina; [2]Liver Unit, Hospital Clínic, IDIBAPS, CIBERehd, University of Barcelona, Spain

*Correspondence to:* Gonzalo Crespo. Liver Unit, Hospital Clínic, IDIBAPS, CIBERehd, University of Barcelona, Spain. Email: gcrespo@clinic.cat.

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For years, hepatitis C virus (HCV) infection has been considered the main cause of liver cirrhosis and hepatocellular carcinoma (HCC) (1). The development of new treatments with direct acting antivirals (DAAs), that achieve very high rates of sustained virologic response (SVR) and thus viral eradication, is probably the most significant advance in the field of Hepatology in the last 50 years (2). The excellent safety profile and high efficacy of DAA regimens have allowed a high amount of patients with advanced liver disease and high risk of HCC to be treated and cured (3). The achievement of SVR, either with the old IFN-based treatments or with DAA, results in a significant impact by decreasing the risk of liver decompensation and need of liver transplant (LT), inducing regression of liver fibrosis and even causing a reduction of liver-related and overall mortality (4-8). Despite studies performed in the IFN era also showed a decrease in the incidence of HCC with SVR, the evidences on this fact in the context of DAA are at least controversial (9).

In patients with cirrhosis, the annual incidence of HCC is usually estimated at 3–7% (10). Multiple studies performed during the INF era were able to show that those patients who achieve SVR present a significant decrease in the risk of HCC when compared to those who did not achieve viral eradication (4). Therefore, the annual incidence of HCC after SVR with IFN-based regimens is around 1% (11,12). It is worth mentioning that patients with very advanced liver disease (Child Pugh C) could not undergo antiviral treatments based on INF, which is a key difference to take into account when comparing results with those of studies performed in the DAA era, as we will discuss below.

In the trials that evaluated the efficacy of the different DAA, the incidence of HCC was not a pre-specified outcome; therefore, the evidence regarding this aim has been obtained in post-commercialization clinical studies. Conti *et al.* (13) evaluated the incidence of HCC in 256 patients with cirrhosis treated with DAA. Twenty-four weeks after finishing antiviral treatment, 9 patients (3.16%, 95% CI: 1.45–5.90%) had presented *de novo* HCC. This study suggested for the first time that achieving SVR under DAA regimes may not impact the risk of HCC, at least in the short term. Similarly, in another retrospective study, 6/66 (9.1%) patients with cirrhosis who obtained viral eradication under DAA-based regimens developed HCC within 6 months after the end of treatment (14). It is important to underline that the presence of heterogeneous groups of patients, in addition to the small sample sizes and the lack of a control group for such studies, makes it difficult to compare them with the expected annual incidence of 3–7% of untreated patients or around 1% of those treated and cured with IFN regimens.

Recently, some larger studies have been conducted with the aim of trying to give a further insight into this question. Ioannou *et al.* (15) performed a retrospective study with 62,354 patients who received antiviral treatment in the Veterans Affair National Health Systems between 1999 and 2015. From this cohort, 58% received treatment with INF, 7.2% regimens with DAA combined with INF and 35% INF-free treatments (only DAA). The authors found that obtaining SVR enables a significant reduction in the incidence of HCC, whatever the type of treatment that induced viral eradication. In another study that included

22,500 patients (39% with cirrhosis) treated with DAA, Kanwal *et al.* (16) showed a significant reduction of the risk of HCC in those patients who obtained SVR versus those who did not achieve viral eradication (0.90 *vs.* 3.45 per 100 persons-years; HR =4.73, 95% CI: 3.34–6.68). Finally, a recent prospective study in patients with compensated and decompensated cirrhosis treated with DAA has shown that achieving viral eradication is associated with a decrease in the incidence of *de novo* HCC (17).

Globally, the results of these studies seem to suggest that DAA would not increase the risk of *de novo* HCC after achieving viral eradication (18). In part, patients treated with DAA seem to be patients with a much more advanced liver disease (decompensated cirrhosis), so it could be hypothesized that they are facing a greater absolute risk of HCC with respect to the one expected according to the historical cohorts treated with INF (compensated cirrhosis) (19), and this may be responsible in part for the controversial results obtained in this setting.

In view of this well-founded hypothesis, Kwong *et al.* (20) designed a retrospective study using information obtained from the Scientific Registry of Transplant Recipients (SRTR), with the aim of describing the incidence of HCC in HCV patients with decompensated cirrhosis included in the waiting list for a LT; and to compare the incidence of *de novo* HCC according to the availability of treatments over time.

The period of time of the study was from January 2003 to December 2015, and it was divided into three different eras according to the availability of antivirals: era 1: INF [2003–2010]; era 2: protease inhibitors (PIs) [2011–2013]; and era 3: DAA [2014–2015]. In order to avoid preexisting cases of HCC, patients with HCC at the time of enrollment, as well as those who received exception points within 180 days after being included in the waiting list were excluded from the study. Importantly, competing risk analysis was used in order to take into account liver transplantation and death as competing events potentially occurring while in the waiting list.

Authors included 48,158 patients, 41.6% of whom had HCV as primary diagnosis of liver disease. After a median follow-up of 493 days (IQR 189–1,083), 3,112 patients (6.5%) developed *de novo* HCC. In the whole cohort, there were no significant changes in the incidence rate (IR) of HCC per 100 person-years within the different eras, but there was a marked variability according to the diagnosis of liver disease. In HCV patients, the IR was 4.5 (95% CI: 4.2–4.7) in era 1; 5.3 (95% CI: 4.8–5.8) in era 2; and 6.6 (95% CI: 5.6–7.9) in era 3. The incidence of *de novo* HCC during the DAA era was 49% superior to the INF era (IRR 1.49, 95% CI: 1.24–1.79, P<0.001). Apart from the incidence of HCC, and also focusing in the events that can take place while in the WL, in the DAA era there was a statistically significant increase in de-listing due to improvement in HCV patients. In addition, HCV was associated with the smallest increase in transplant rate over time among the different etiologies, and there was a non-significant trend towards decreased wait-list mortality in the DAA era. Finally, it is interesting to underline that although in the multivariate analysis (adjusted by era, sex, age, diabetes, Child Pugh score and race) the DAA era had a HR of 1.22 (95% CI: 1.01–1.48) for the development of HCC with respect to the INF era, a competing risks analysis considering transplant and death as competitive events in the development of *de novo* HCC did not show a greater incidence of *de novo* HCC in the DAA era (sHR =0.83, 95% CI: 0.69–1). Gender, age, race and Child score were independently associated with the risk of HCC in the competing risk multivariate analysis.

Certainly, the findings of Kwong *et al.* provide more clarity about which is the real impact of DAA with regard to a hypothetical increase in the incidence of *de novo* HCC. According to their results, in the particular population of patients with advanced liver disease in the waiting list for a liver transplantation, when transplant-related competing risks are taken into account, a potential impact of DAA in the development of *de novo* HCC seems less significant. Altogether, the results from Kwong *et al.*, supporting data from other studies, suggest that several variables (age, grade of liver dysfunction) may explain in part the apparent rise in HCC in the DAA era. In addition, this study, in this particular population, shows: (I) that the transplant rate in HCV patients experienced the lowest increase of all etiologies; and (II) that HCV patients have lower probabilities of dying or getting too sick as to be withdrawn from the list. Besides, they are increasingly withdrawn from the list due to improvement, although the rate of waitlist removal for improvement is still very low (6%). All these results depict a scenario in which HCV patients achieve increasingly higher rates of SVR, deteriorate less and remain longer in the waiting list and thus are exposed to longer periods of at-risk time for HCC. Unfortunately, the lack of information about the number of patients that actually received DAA in this cohort precludes a complete interpretation of the results, as it is impossible to know the real impact of DAA, particularly the differences in the IR of HCC with respect to similar and contemporary patients

 

who did not receive treatment. In turn, the large sample size and the thorough statistical analysis, together with the consistency of the data of this and other large studies strengthen the conclusions of the study.

It is worth mentioning that, despite DAA did not seem to increase the IR of HCC, this was still surprisingly high in the DAA era in HCV patients. As developed earlier, this possibly reflects the changes in the characteristics of patients, also considering that this population (transplant candidates) comprises in general older patients with more advanced liver disease. This highlights the potential biases when directly comparing these results with those obtained in studies in which patients achieved SVR with IFN-based therapies. In addition, changes in the access to LT and in the events taking place in the waiting list (death or deterioration) in the context of a widespread access to DAA probably impact significantly the rate of HCC in the particular population of wait-listed cirrhotics.

The main hypothesis supporting a possible causality between DAA and *de novo* HCC is related to the deregulation of the anti-tumour response stipulated by the immune system, which would be secondarily affected by the rapid decline of the viral load that takes place when starting DAA (9). The postulated mechanism seems to be related to the fact that HCV induces genes that would activate INF vias, and modify the immune response mediated by natural killer cells (21). Such findings were backed up by recent studies that showed a decrease in the levels of CXCL10 and CXCL11, as well as the normalization of the phenotype and function of the natural killer cells in patients who achieved SVR with DAA (22,23). In spite of this, other studies have identified other profiles of immune mediators that were present before starting DAA therapy in patients who developed *de novo* HCC, compared to those who did not develop HCC, which may suggest that the immune deregulation precedes the starting of the antiviral therapy, with no temporary association (24).

To conclude, time seems to show that achieving viral eradication is associated with a significant reduction of liver decompensation, an improvement in portal pressure and even a regression of cirrhosis, as well as a significant decrease in overall and liver related mortality. In the DAA era, these effects induce a significant change in the demographic and clinical profile of patients with decompensated liver disease. Rather than a direct effect of DAA, the observed increase in the incidence of HCC in these patients may at least in part be explained by these changes, together with changes in waitlist trends in the particular population focus of the present study. It is clear that mechanistic studies will help clear the potential association between DAAs and HCC. In the meanwhile, close surveillance of HCC remains mandatory for patients with advanced fibrosis that achieve SVR with DAA.

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