

# Hepatocellular carcinoma and direct-acting antivirals: A never ending story?

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Handling Editor: Mario Mondelli

A large body of evidence accumulated over the two decades of the “interferon era” shows conclusively that HCV eradication (sustained virological response, SVR) in patients with cirrhosis reduces both liver and non-liver-related deaths.<sup>1,2</sup> When cirrhosis is subclassified according to the stage of portal hypertension, it is apparent that the benefit of SVR is higher in patients without clinically significant portal hypertension.<sup>3</sup> In all cohorts studied the risk of developing hepatocellular carcinoma (HCC) for patients with IFN-induced SVR, albeit reduced in comparison to those with persistent HCV infection, is not cancelled altogether.<sup>4,5</sup> Hence, continuing HCC surveillance is recommended in patients with HCV cirrhosis after SVR.<sup>5</sup>

The introduction of direct-acting antivirals (DAAs) made possible to eradicate HCV effectively at all stages of liver disease and has led to the rapid accumulation of large cohorts of patients with cirrhosis in whom treatment has been initiated regardless of the stage of the disease, including decompensated cirrhosis, in order to obtain an improvement of liver function and thus ameliorate the short and long-term outcome.

This “all-comers” approach has included patients with HCC whose tumour had been successfully treated. Also in this setting, DAAs obtain exceedingly high SVR rates thus likely prolonging the life span of these patients and creating a further period of time for HCC recurrence. After the first report by Reig et al.,<sup>6</sup> who raised a first warning about an unexpected high rate of recurrence of HCC in these patients, various groups have reported their experience on the recurrence and/or occurrence of HCC in cirrhotic patients treated with DAAs, mostly with negative results. The “Debates” section of this issue of Liver International hosts a thoughtful review by Alberti and Piovesan focusing on this highly controversial issue.<sup>7</sup>

When discussing recurrence, we should bear in mind that the estimated likelihood of HCC recurrence after its presumed cure in

patients with HCV cirrhosis untreated with antivirals approximates 10% at 6 months, 20% at 12 months and 50% after 24 months since HCC treatment.<sup>8</sup> Hence, against such a high background of reappearance of cancer in viraemic patients, a healthy dose of caution should be exercised before concluding that DAA-induced SVR is associated with an unexpected rate of HCC recurrence. An extensive body of data not confirming the Spanish hypothesis comes from the pooling of DAA-treated patients who underwent curative HCC therapies enrolled in three French prospective multicenter ANRS cohorts. These data, encompassing over 500 subjects with sufficient follow-up, do not show an increased risk of HCC recurrence after DAA-induced SVR and report instead a comparable rate of reappearance of cancer among DAA-treated and untreated patients.<sup>9</sup> In support of the French findings, data from the large cohort from the UK show a reduction in HCC rates in DAA-treated patients with advanced cirrhosis.<sup>10</sup> Last but not least, when the interval between complete tumour eradication and antiviral therapy is quite long as in the cohort reported by Zavaglia et al.,<sup>11</sup> the recurrence rate is actually low suggesting that the longer the interval, the lower the risk that residual cancer is still present at the start of DAA therapy.

We recently evaluated in the setting of a regional database (RESIST-HCV), 185 cirrhotic patients (84% Child A) with complete response after curative treatment of HCC treated with DAAs.<sup>12</sup> Over a mean follow-up of 24 weeks (range 8–60) since starting treatment, 24 patients had a recurrence of HCC with a crude rate of 13%. The 6 and 12 months. HCC recurrence rates were 7.9% and 16.3% respectively. One patient died during follow-up. The pattern of HCC recurrence was nodular in 83% patients (20/24) and infiltrative in 17% (4/24).

Many concerns about this side of the controversy can be linked to:

- High heterogeneity of the groups of patients with HCC in terms of clinical features (stage of cirrhosis; morphology of HCC)

- Different treatments, from palliative (transarterial chemoembolisation) to potentially curative (ablation and surgery)
- Time elapsed between presumed cure of HCC and treatment with DAAs.

In fact, some cases of cancer relapse within a few days or weeks after starting DAAs, which have been counted as HCC recurrence, are most likely instances of incompletely cured HCC already present at the time of initiation of DAA use, not detected by imaging.

Moving to occurrence, ie, de novo HCC in patients with cirrhosis treated with DAAs, it must be stressed that extrapolation of data from patients treated with interferon-based regimens to those who received the all-oral regimens is inappropriate. In fact, the strong selection effect due to the low tolerability of IFN has restricted antiviral therapy, until the availability of DAAs, to patients with lesser stages of cirrhosis, ie, to those who are intrinsically less likely to develop HCC.<sup>3,13</sup> By the way, Kozbial et al.<sup>14</sup> in a small series of patients with cirrhosis observed a 6.6% overall (13/195) and 5.2% (10/192 in patients with SVR) of rate of HCC after DAAs and compared them with the estimated 1% per year frequency of HCC in patients with SVR treated with IFN/RBV.<sup>3,15</sup> As expected patients treated with IFN were younger and all had compensated cirrhosis, while those on DAAs could also have decompensated cirrhosis or significant comorbidity. As a further confirmation, when the incidence of HCC during and after DAAs is assessed after stratifying for stage of cirrhosis, patients with Child A cirrhosis develop HCC at a rate comparable to historical cohorts of patients treated with IFN based therapies. Indeed, two recently reported large Italian prospective cohorts<sup>16,17</sup> demonstrate that the rate of occurrence of HCC in patients with Child A HCV cirrhosis and no or mild portal hypertension does not exceed 2% at 1 year of follow, while patients with Child B HCV cirrhosis have a significantly higher rate of occurrence of HCC (more than 3% despite SVR). For the latter, there is no historical benchmark of comparison, given the impossibility to treat the patients with IFN.

Further evidence supporting a positive effect of DAAs on the overall reduction in HCC comes from these cohorts<sup>16,17</sup> by the finding of a higher incidence of cancer, and of all liver-related disease events, in patients who fail to obtain SVR on DAAs as compared to those with SVR.

Whether the morphological pattern of expression and the clinical behaviour of HCC in eradicated patients will be more aggressive than its usual course, as suggested by the NAVIGATORE experience,<sup>16</sup> will need careful confirmation by prospective studies with careful characterisation of the growth pattern and molecular characteristics of the tumour.

In summary, while cirrhotic patients treated with DAAs seem, in our opinion, to have a reduction in the overall risk of HCC, there might be a subset of subjects in whom the imbalance induced by SVR in the inflammatory response and in the tumour microenvironment could originate and/or favour the growth of HCCs with an "aggressive" clinical phenotype. Hence, the challenge for the future is to identify features which allow the profiling of patients to evaluate the risk of HCC in the individual patient.

### Key Points

- The benefit of SVR is higher in patients without clinically significant portal hypertension
- HCC occurrence in patients with compensated cirrhosis is comparable to historical controls of patients who achieved SVR after interferon-based therapy.
- Patients who achieve SVR with DAAs had a lower risk of developing liver cancer than those patients whose HCV infection was not cured.
- Data available on patients with previous HCC do not show an increased risk of HCC recurrence and report a comparable rate of reappearance of cancer among DAA-treated and untreated patients.

### CONFLICT OF INTEREST

Vincenza Calvaruso: Travel Grant, Speaking, and Participation to Advisory Boards for: AbbVie, BMS, Gilead Sciences and Intercept. Grant and research support: MSD. Antonio Craxi: Research grants, lecturing fees, advisory boards, scientific consultancy for Novartis, Abbvie, Gilead Sciences, BMS, Achillion, Janssen Cilag, Abbott Diagnostics, Intercept.

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**How to cite this article:** Calvaruso V, Craxì A. Hepatocellular carcinoma and direct-acting antivirals: A never ending story? *Liver Int.* 2017;37:812-814. <https://doi.org/10.1111/liv.13421>