Increased risk of hepatocellular carcinoma after hepatitis C direct-acting antiviral drugs: the threat that never was

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Direct-acting antiviral agents (DAAs) are associated with more than a 95% cure rate in hepatitis C virus (HCV) infection in the non-cirrhotic population and 85–90% cure rate in the cirrhotic population (1). Previously, interferon-based therapy (INF) was the treatment of choice but was limited by intolerability, side effects, and a poor likelihood of treatment success: a 25–44% sustained virological response (SVR) (1,2). Fortunately, DAAs have replaced interferon to become the main stay HCV treatment in the general population and in the liver transplant (LT) setting.

In terms of the natural untreated history of HCV, multiple studies have unequivocally confirmed that chronic HCV infection is an important independent risk factor in the development of hepatocellular carcinoma (HCC). Both HCV and inflammatory processes are theorized to drive HCC tumor-genesis. Long-term follow up studies have suggested that SVR was associated with improvement in histological and inflammation scores in those with greater than stage 2 fibrosis (3) that are considered important in hepatic oncogenesis. In the LT population, HCV reinfection of the allograft is expectedly universal in the absence of SVR pre-LT, this can lead to an increased risk of HCC in comparison to those achieved SVR. Thus in both the non-transplant and post-LT population, one would expect the HCC risk to be significantly lowered by SVR.

Indeed in 2013, a meta-analysis of IFN-based studies reported that achieving SVR, resulted in an overall reduction in the development of HCC (1). Another meta-analysis highlighted the benefit of SVR in cirrhotic populations, via IFN-based therapy, that significantly reduced the HCC risk (RR =0.43) while no such effect was found in treatment non-responders (4). Nevertheless, it is important to keep in mind that aside from HCV, advanced fibrosis including cirrhosis is also an independent risk factor of HCC and unfortunately advanced cirrhosis is not completely reversed by HCV eradication. Therefore, the risk of HCC remains in those with advanced fibrosis and cirrhosis despite SVR (5).

Recently, there have been reports that created serious concerns of an increased risk of HCC developing post DAA-induced SVR. A Spanish study examined HCC recurrence in patients with prior HCC and HCV treated by DAAs, and reported an unexpectedly high HCC recurrence rate of 27.6% (6). Similarly, Conti *et al.* followed 284 patients with established cirrhosis for a total of 24 weeks post DAAs, and reported that HCC similarly recurred in 28.8% with a *de novo* HCC rate of 3.16% (7), despite an impressive SVR in over 90%. Finally, there was a post-LT study, of whom all were transplanted for HCV-associated HCC, and the DAA treatment group pre-LT was found to have a higher trend towards HCC recurrence compared to the untreated (8).

Although the appearance of these reports did lead to a concern that DAAs themselves were risk factors for HCC in predisposed patients, caution was also advised against drawing definitive conclusions from these studies. First, one could not decisively conclude DAAs promote HCC as there was no direct evidence. Second, the studies tended to be

small in sample sizes with even smaller numbers of HCC, which limited the clinical significance and generalizability of their findings. Furthermore, all of them focused on HCC recurrence rather than occurrence.

More recently, there are a number of large retrospective and prospective studies lending support to the contrary view, specifically that the risk of HCC is reduced, not increased by DAA-induced SVR. In a study of 22,500 patients treated by DAAs, the overall risk was 0.94 HCC/100-persons years in SVR group versus 3.49 HCC/100-persons years in those without SVR (9). The study found no evidence to support the hypothesis that HCC was promoted by DAA exposure. However, the HCC risk remained significantly high in the cirrhotic population (1.82 HCC/100-persons year) to warrant ongoing HCC surveillance (9). The situation is not unique to DAA treated populations. A study that examined HCV patients post IFN-induced SVR, reported an overall incidence rate of HCC at 0.33% per year after treatment (2). HCC risk was particularly high in those with cirrhosis (1.39%) and those cured after age 64 (0.95%) (2). Thus one should entertain the idea of indefinite surveillance process for HCC in those with cirrhosis, irrespective of SVR status. This is especially important considering a number of other independent HCC risk factors have been reported including male gender, increasing age, African descent, diabetes, obesity, decompensated liver disease, and smoking (10,11). Looking at the French (ANRS) viral cirrhosis (CirVir) cohort that ended in 2012, most SVR were achieved by IFN and not surprisingly led to a reduction in all liver-related complications including HCC, however the study was unable to comment specifically on those treated by DAAs (12). In 2016, the same French ANRS collaborative study group examined three separate cohorts. First there was a retrospectively studied cohort of 267 patients who had HCV related HCC, amongst them, 189 received DAAs. The group found HCC recurrence rate was the same in DAA and non-DAA groups (0.73 *vs.* 0.66/100-person months) (13). In the separate cirrhotic cohort, HCC recurrence rate was 1.11 (DAA treated) and 1.72 (non-DAA) respectively, which were similar. In the LT cohort, all 314 patients transplanted for HCV related HCC were treated with DAA post-LT, the rate of HCC recurrence was 2.2% in 7 patients at median time of 70 months (13). Overall the study found no increased HCC recurrence rate post DAAs. To strengthen the argument, in 2017 a pooled meta-analysis found no evidence of increased occurrence or recurrence of HCC post-SVR by DAAs in comparison to IFN-based therapy (14).

The publication by Ioannou *et al.* in 2017 pertinently shed more light on this debate. In this retrospective study, HCC incidence rate rather than recurrence rate was evaluated, and 62,354 patients with 3,271 HCC incidence cases were assessed, making it one of the largest single studies to date on the subject (15). The study found no evidence of higher HCC incidence in those achieved SVR by DAAs, or DAA+ INF, compared to IFN group, despite the fact that the DAA group was older on average, with more patients of African descent and had more advanced fibrosis/cirrhosis. It found cirrhosis and the lack of SVR to be two independent risk factors of HCC over the 6-year study period, with cirrhosis being the greater risk factor (1.97 per 100 patient year) more important than lack of SVR (0.87) with the combination increasing the risk more than either alone (3.25 per 100 patient year). Overall, DAA-induced SVR was associated with 71% reduction in HCC risk.

In summary, we can definitely state that DAAs do not increase the risk of HCC development. Previous reports of an unexpectedly high rate of HCC post DAAs were likely an artifact of patient selection bias, lack of control for age, small sample size and disproportionately higher advanced fibrosis and cirrhosis in those receiving DAAs as these patients would not have been treated with IFN based treatment in the earlier era. Regardless, HCV patients who do achieve a SVR and have cirrhosis/advanced fibrosis should continue to be screened for HCC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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