Commentary

Direct acting antivirals for hepatitis c and hepatocellular carcinoma recurrence: an unsolved mystery

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With the development of direct acting antivirals (DAA), we have seen a significant improvement in outcomes in treatment of hepatitis C. DAAs have provided an effective, well tolerated treatment for hepatitis C in patents with cirrhosis (1). With the high success rates of DAAs, the medical community was hopeful that this would translate to decreased hepatocellular carcinoma (HCC) recurrence rates. Achieving sustained viral response (SVR) with interferon (IFN) based treatment regimens has been shown to decrease the risk of recurrence of HCC, and thus there was hope for similar effects with DAAs (2). However, several studies have shown unexpectedly high rates of recurrence of HCC in the early post DAA treatment time period.

Italian researchers Conti *et al*. published a retrospective cohort study of 344 cirrhotic patients treated with DAAs and rates of HCC occurrence and recurrence. Investigators analyzed data from 448 patients with advanced liver disease treated with DAAs. Patients with HIV, active alcohol consumption, or evidence of HCC were excluded. Additionally, the study was limited to patients with Child-Pugh Class A or B liver cirrhosis with no history of previous HCC or with previous HCC treated with curative therapy (complete response to surgical resection or loco-regional ablation). Prior to starting antiviral therapy, all patients underwent abdominal imaging to assess for the presence of HCC. Imaging was repeated at the end of viral therapy, at 12 weeks follow up, and at 24 weeks follow up.

There were 344 patients included in the study; the majority of the patients were Child Pugh class A, with only 11.3% classified as Child Pugh class B. Of the 344 patients analyzed, 59 patients had previously been diagnosed and treated for HCC. Of these patients, 19 had been treated with surgical resection, 2 with resection and radiofrequency ablation, 2 with resection and TACE, 18 with radiofrequency ablation alone, 4 with radiofrequency ablation and TACE, 6 with percutaneous ethanol injection, and 5 with TACE alone. The time between completion of HCC therapy and initiation of antiviral drugs ranged from 45 to 2,706 days (median 376). The patients with a history of HCC were older and more likely to have diabetes. They were not significantly different from patients without a history of HCC in regards to liver stiffness or Child Pugh class.

Sustained virological response (SVR) was achieved in 91% of patients. HCC was identified in 26/344 (7.6%) patients, 17 (28.8%) of these patients had a history of HCC and 9 (3.4%) did not. The patients who developed HCC were more likely to have more severe fibrosis by transient elastography and Child Pugh score. Only Child Pugh score and previous history of HCC predicted risk of developing HCC post DAA treatment.

Looking specifically at patients who had a history of HCC, those with more severe fibrosis were at increased risk of recurrence. Interestingly, a younger age was also associated with HCC risk. The authors found that HCV genotype and specific DAA regimen did not correlate with risk of HCC recurrence. Additionally, there was no association between how the patients' HCC was initially treated or by the disease free interval between cancer treatment and initiation of DAAs. All of the patients who experienced HCC recurrence had tumors that were within the Milan criteria, except for one patient.

The authors highlight the fact that HCC recurrence is not uncommon, and HCC may be considered cured despite the presence of an incomplete resection or ablation of the tumor. It is estimated that following surgical resection or RFA, 20% of HCC patients will have recurrence within 1 year. Given that several of the patients in this study were treated by other means, the recurrence rate of 28% observed in the study is not necessarily surprising (3). However, the 17 patients with a median HCC free survival of 446 days who developed HCC 'recurrence' within months of starting DAAs was noteworthy.

HCC is thought to develop over time as the liver is exposed to inflammation and develops fibrosis. Thus, if DAAs can eliminate inflammation mediated by HCV, the risk of HCC should decrease. However, several centers have observed that this actually may not be the case (3,4). Tumorigenesis occurs through a multistep, multifactorial process. Eliminating HCV-induced inflammation may not be enough to decrease risk of HCC.

The authors of this study hypothesize that direct acting antivirals may actually increase the risk of HCC by inhibiting immunosurveillance. The body's natural immune system is programmed to detect and destroy cells with non-self antigens, such as tumor cells, through NK and T cells. DAA therapy has been shown to decrease the activity of NK cells. Thus, by treating the hepatitis C, the drugs may also eliminate the body's protective mechanisms against tumor growth. Patients with more severe liver fibrosis already have impaired immunosurveillance, which would put them at an even higher risk of recurrence (3).

Similar results to those described by Conti *et al*. have been seen by other treatment centers. Reig *et al*. published on surprisingly high rates of HCC recurrence in their cohort of patients with previous HCC treated with curative therapy. Their study included 58 patients treated with DAAs following treatment of HCC. The study found a recurrence rate of 27.6% within 3.5 months. Patients had a median time between HCC treatment and DAA initiation of 11.5 months. Of the 16 patients who had recurrence, 8 of them were found to have recurrence during the treatment course with DAAs. The authors point out that the short interval of recurrence observed in both studies is surprising (3,4).

The relatively fast recurrence of HCC following DAAs could be due to the effects of DAA treatment on the body's immunosurveillance mechanisms for preventing tumor growth (3). The rapid reduction in viral load generally resulting in HCV RNA negativity within days to week may have a negative effect on cancer control through mechanisms that remain hypothetical at this point.

In contrast to the above studies, the ANRS study group published data from three cohorts, which showed no increased risk of HCC recurrence after treatment with DAAs. The first cohort included 267 patients with a history of HCC, 189 of which were treated with DAA agents and 78 of which were not treated. There was no significant increase in risk of HCC recurrence for those who received DAA agents (Hazard ratio =1.21; 95% CI, 0.62–2.34). Although, it should be noted that patients who received DAAs and those who did not were different in that the treated group were younger, more likely to have had previous treatment, and more likely to have severe fibrosis. The cohort included 17 patients who received interferon with the DAA regimen, and these patients were also not significantly less or more likely to have recurrence. The second cohort studied included 79 patients treated for HCC and found to be in complete remission and found that there were no more recurrences in those who did receive DAAs than those who did not (5).

The above cohorts included both patients who did and did not receive treatment with DAAs allowing for a direct comparison between the groups. The study is limited in that there were baseline differences between the patients who received treatment and who did not as well as by the small size, observational nature, and lack of de novo design to study this issue. However, the study does allow for a more direct comparison between those receiving and not receiving treatment.

The final cohort studied by the ANRS group specifically looked at patients who had received liver transplant (LT) for treatment of HCC and then had received DAA therapy. Only 7 of 314 patients (2.2%) had recurrence, and 2 of them had recurrence prior to initiating DAA therapy. This cohort is unique in looking at transplant patients; however, it was small and did not have a control group. The rates of post LT recurrence were significantly lower than expected (5). This data provides reassurance that treatment prior to liver transplantation provides benefits in preventing HCC recurrence. However, a recently conducted study looking at 18 patients with HCC treated with pre-transplant DAAs showed a trend towards higher HCC recurrence rates in the treated patients relative to the untreated patients, 5/18 or 27.8% relative to 6/63 or 9.5% untreated patients (P=0.06). This data raises significant concerns regarding whether pre-transplant DAA treatment is the best option for patients with HCV related HCC (6).

As we gain more experience with using DAA agents for hepatitis C, we will undoubtedly learn more about their effect on HCC. While the observations described by Conti *et al*. and Reig *et al*. are concerning because of the significant clinical implications, we need more information before we can draw firm conclusions. All of the aforementioned studies suffer from at least one or more limitations including relatively small numbers, heterogeneity of population (curative *vs*. non curative therapy), and lack of a de novo, prospective strategy to evaluate the relationship between HCV treatment with DAAs, and HCC. The effects of DAAs on HCC need additional attention and research with prospectively designed trials.

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Footnote

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