Letter to the Editor

Is direct acting antiviral therapy for hepatitis c viral infection associated with increased risk of hepatocellular carcinoma before or after liver transplantation?

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Response to: Singal AG, Rich NE, Mehta N, *et al.* Direct-Acting Antiviral Therapy Not Associated With Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study. Gastroenterology 2019;156:1683-92.e1.

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Direct acting antiviral (DAA) therapy revolutionized the curative therapy for >90% of hepatitis C virus (HCV) infected patients. Initially, in late 2016, concerns were raised by several European centers that DAA therapy may be increasing the incidence of hepatocellular carcinoma (HCC) recurrence or *de novo* HCC (*Table 1*). Singal *et al.* (1) compared the frequency of HCC recurrence in patients who received DAA therapy for HCV versus patients who did not receive DAA, among patients with HCV positive patients associated HCC, cured with complete response by various modalities [resection, trans arterial chemo embolization (TACE), local ablation, stereotactic body radiation therapy (SBRT) or other methods]. This was a large multicenter study which included 31 centers from North America and Canada. There were 304 HCV-positive patients treated with DAA therapy after HCC cure and 489 HCV-positive subjects without DAA therapy after curing the HCC. Singal *et al.* found the total recurrence rate was 42.1% (128 patients) in the treatment group and 58.9% (288 patients) without treatment group (P=0.33), that was statistically not significant (1).

While this data is essential to demonstrate the recurrence of HCC with DAA therapy, anxiety remains for the group of patients who develop *de novo* or recurrent HCC following DAA therapy even after liver transplantation (2). However, in the above Singal *et al.* study, the untreated group included some of the patients claimed to have received DAA therapy after 365 days of complete response to HCC or after various landmark time frames. This makes the control group somewhat unsatisfactory.

In the non-liver transplant patients, a controversy has emerged over if the rate and recurrence of HCC is higher post DAA therapy to treat HCV-induced cirrhosis. Some European centers suggest with DAA therapy higher risk of *de novo* HCC and recurrence of HCC. Reig *et al.* reported, from four participating centers from Spain, consisting of 103 patients with HCC who received DAA, 27.6% either had an increased in size of HCC or developed *de novo* HCC at a median follow up of 5.7 months (3). Another study from Japan by Toyoda *et al.* included 413 patients after sustained virologic response (SVR) with DAA therapy. They observed a significant increase in the incidence of HCC in patients more than 65 years of age with cirrhosis, and double rate of HCC after the SVR from DAA therapy, on a yearly basis (4). Conti *et al.* from Italy in 2016 accounted for 344 patients post-DAA therapy (5). Within the six months follow-up period, they observed nine cases of *de novo* HCC out of 285 cases. Furthermore, 17 patients out of 59 stable HCC treated patients had a rapid recurrence of HCC. Kozbial *et al.* from the AURIC (Austrian Ribavirin/Interferon-Free Cohort) clinical trial, consisting of HCV positive patients treated with DAA therapy, observed an unexpected increased rate of HCC (6).

However, Cheng *et al.* from the UK group, in 406 HCV positive patients treated with DAA therapy, did not observe an increased rate of HCC post-DAA therapy (7). Similarly, a French multicenter ANRS group also did not observe increased risk of HCC in over 6,000 patients post DAA

Table 1 Increased risk of HCC with DAA therapy for HCV infection

Reference	Includes patients who received LTx	Center/population	Study of cases	DAA with SVR	Recurrence of HCC	De novo HCC
Cheung *et al.*	No	HCV Research UK registry	Prospective study of 406 patients with decompensated cirrhosis who received 12 weeks of all-oral DAA, with comparison to retrospectively collected data of 261 untreated patients	SVR12 in 329 patients (81%)	2 patients (6.9%)	27 patients (7.2%)
Conti *et al.*	No	Several centers in the area of Bologna, Italy	Prospective analysis of 344 cirrhotic patients without HCC, and 59 patients with previous HCC, who were treated with DAA, and followed for 24 weeks	SVR12 in 314 patients (91%)	17 patients (28.8%)	9 patients (3.2%)
Jain *et al.*	Yes	Penn State Hershey Medical Center, Hershey, PA	Retrospective analysis of 63 patients who received LTx for HCC (27 received DAA for HCV, 36 untreated for HCV)	SVR12 in 20 patients (74%)	3 patients (11.1%)	NA
Kozbial *et al.*	No	Australian ribavirin/ interferon-free cohort (AURIC)	Patients who developed *de novo* or recurrence of HCC who had completed DAA therapy	SVR48 in 14 patients (73.7%)	3 patients	16 patients
Reig *et al.*	No	4 Spanish referral hospitals	Study of 58 patients with HCV and prior history of treated HCC with complete response who were then treated with all-oral DAAs	SVR12 in 39 patients (67.2%)	16 patients (27.6%)	NA
ANRS collaborative study group	Yes	3 French multicenter ANRS cohorts	Prospective analysis of cohort of 516 patients treated with DAA who also underwent curative procedures for HCC	SVR in 404 patients (78.3%)	32 patients (6.2%)	NA
Toyoda *et al.*	No	Ogaki Municipal Hospital, Japan	Compared age and presence of cirrhosis as factors influencing the annual incidence of HCC after SVR in 578 IFN-treated patients and 413 DAA-treated patients	413 patients	NA	2.58 estimated annual cases in DAA group *vs.* 1.61 in IFN group
Ioannou *et al.*	No	Veterans Affairs	Retrospective analysis of 45,810 patients who received antiviral therapy (64% DAA-only, 22.5% interferon-only) with a mean follow-up of 2.5 years	34,096 patients (74%)	NA	1,412 cases after 180 days starting DAA (0.3% to 25.9%) with highest rates for age >65 years, cirrhosis and without SVR

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; DAA, direct acting antiviral; SVR, sustained virologic response.

therapy (8). Recently, Ioannou *et al.* have suggested a model for estimating the risk of HCC after antiviral treatment for HCV infection. They studied 45,810 patients from Veterans affairs and developed a model to assess the risk of HCC post DAA therapy. Authors describe a group of patients >65 years of age, with cirrhosis, who did not achieve SVR, with an unusually elevated three-year risk of HCC of up to 26% (9). This is somewhat similar to what we have observed in post-liver transplant recipients at our institution who did not maintain SVR (2).

A hypothetical possibility is that viral relapse may stimulate an immune or oncogenic environment in the host which could promote HCC recurrence, including after liver replacement with immunosuppression. To answer this question, we would need data from a larger population, involving multiple centers. If this is a real phenomenon, then a major change in the practice of LTx for HCC within Milan criteria may be required. If there is a significant effect on DE Novo or recurrence HCC post-DAA therapy than this potential risk should be discussed with the patients. However, efficacy of DAA therapy to eradicate the virus is so vital for over 90% of HCV positive subjects that a separate approach can be considered. We have suggested a trial where Sorafenib, in a prophylactic dose can be utilized with DAA therapy (10). Furthermore, we have discussed transcriptome signature gene analysis to find early recurrence of HCC after DAA therapy as another approach for this group of patients with cellular biological and immunologic-based experiments (2), A large multicenter prospective trial, specifically designed to identify the risk of De Novo or recurrent HCC with the use of DAA therapy, in transplant or non-transplant subjects, with SVR or without SVR, is required to answer this vital question.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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