The impact of direct-acting antivirals on hepatitis C associated hepatocellular carcinoma

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Abstract
The increased incidence of hepatocellular carcinoma (HCC) in the last several decades in the United States and worldwide has partly resulted from an increase in hepatitis C virus (HCV) infection. HCV carcinogenesis is speculated to be indirectly related to multiple steps from inflammation to fibrosis and advanced fibrosis/cirrhosis over 20 or more years. However, the direct carcinogenic potential from HCV may explain HCC occurring in non-cirrhotic HCV patients. Highly potent direct-acting antivirals (DAAs) in recent years have changed hepatitis C treatment significantly and have resulted in the sustained virologic response (SVR) rate exceeding 90%. Although initial reports concerned the increase in de novo and recurrent HCC associated with DAAs, more recent studies showed that DAA-induced SVR on the contrary reduced risk of HCV-associated HCC without increasing its recurrence. The International Consortium of Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) database and other resources of HCV patients treated with DAA collectively in the near future most likely will be able to show definitive evidence on the risk of HCC occurrence and recurrence after DAA with SVR. The long-term risk of HCC in chronic hepatitis C patients with advanced fibrosis or cirrhosis remains high after DAAs with SVR. Thus, HCC surveillance on this sub-group of patients is important for early detection and intervention of HCC.

Keywords: Direct-acting antivirals, hepatitis C virus infection, risk of hepatocellular carcinoma

INTRODUCTION
Liver cancer was predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018. Statistically, hepatocellular carcinoma (HCC) comprises 75%-85% cases of liver cancer[1].
The sharply increased incidence of HCC in the last several decades in the United States and worldwide has partly resulted from an increase in hepatitis C virus (HCV) infection[1]. In the United States, chronic hepatitis C accounts for approximately 20%-31% of HCC deaths[2,3].

**HCV AND HCC**

HCV carcinogenesis is speculated to be indirectly related to multiple steps from chronic inflammation to fibrosis, advanced fibrosis and cirrhosis with somatic genetic/epigenetic alterations, and malignant transformation of hepatocytes over 20 or more years[4,5]. Patients with HCV cirrhosis had a three-fold higher adjusted risk of HCC than those with cirrhosis from other etiologies, implying direct carcinogenic effects of the virus[6-9]. HCC may develop in non-cirrhotic HCV patients, suggesting a direct HCV oncogenic effect[10]. Additionally, HCV core protein was shown to have oncogenic potential by using transgenic mouse models, indicating its direct involvement in carcinogenesis[11].

HCV-infected patients with advanced fibrosis or cirrhosis and older age are well-established risk for HCC development[4,12-14]. The prevalence of HCC is especially high in cirrhotic HCV patients with an estimated annual risk of 2%-4%[14].

**HCV ERADICATION BY INTERFERON-BASED THERAPY AND HCC RISKS**

Long-term eradication of HCV reduced HCC risk, which was initially demonstrated in patients who achieved SVR by interferon (IFN)-based therapies[14-18]. An analysis from 12 observational studies demonstrated that IFN-induced SVR led to nearly four-fold HCC risk reduction irrespective of liver disease stage[19].

Van der Meer et al.[20] found that the 10-year cumulative HCC incidence with SVR was 5.1%, vs. 21.8% in those without SVR (P < 0.001).

Although IFN has potential anti-inflammatory and/or immunomodulatory effects for the prevention of HCC, HCV eradication does not eliminate the risk of HCC[21,22]. El-Serag et al.[22] reported an overall incidence rate of 0.33% in new HCC development, which could occur more than 10 years after HCV eradication by IFN-based therapy.

**HCV ERADICATION BY DAAS AND HCC RISKS**

DAAs for HCV infection directly targeting viral protease, polymerase, or non-structural proteins have replaced IFN-based therapy over the past few years. They have changed the management of hepatitis C virus infection significantly, as the treatment is easy to administer, well-tolerated, safe, and highly effective with an SVR rate exceeding 90%[23-25].

DAAs can be used in HCV infection with advanced and complicated liver disease[25-31]. Multiple large cohort studies have shown that DAA-induced SVR is associated with a reduced risk of HCC[14,32-35]. Kanwal et al.[35] reported a significantly reduced risk of HCC (0.9 vs. 3.45 HCC/100 person-years) in 22,500 hepatitis C patients treated by DAAs with SVR compared to those without.

Piñero et al.[35] showed an overall 73% relative risk reduction for de novo HCC in DAAs-treated HCV patients with SVR, but the risk remained high in patients with advanced fibrosis and cirrhosis. Furthermore, reduced HCC risk by DAAs with SVR was demonstrated in patients with or without cirrhosis by Ioannou et al.[34].

**HCC RISK IN CHRONIC HEPATITIS C TREATED BY DAA COMPARED TO THAT OF IFN THERAPY**

IFN, an immune modulator, inhibits proliferation and may prevent the development of HCC. IFN-based HCV antiviral therapy due to its potential side effects was used mostly on patients without cirrhosis.
On the contrary, DAAs have been used on HCV patients with advanced fibrosis and cirrhosis who are at high risk of HCC. It was speculated that there would be more HCV-associated HCCs after DAA with SVR than those post-IFN with SVR ones in the United States, given that the largest cohort of chronic hepatitis C patients in the United States are baby boomers with advanced age, cirrhosis\textsuperscript{[36]}, and rising prevalence of metabolic syndrome-associated co-morbidities\textsuperscript{[37]}.

Waziry \textit{et al.}\textsuperscript{[38]} reported a random-effects meta-analysis comparing HCC occurrence and recurrence in patients treated by DAA and IFN therapy and showed no evidence of difference in HCC risk between the two groups after meta-regression adjustment of age and study follow up duration. Ioannou \textit{et al.}\textsuperscript{[34]} published a large VA cohort study of 21,498 chronic hepatitis C (CHC) patients with DAA-induced SVR, showing that it is associated with reduced risk of \textit{de novo} HCC compared to treatment failure and that the risk for HCC after DAA therapy is similar to the risk after IFN therapy.

Singer \textit{et al.}\textsuperscript{[39]} using administrative claims data demonstrated that the risk of HCC was lower in DAA-treated patients (adjusted HR = 0.69; 95%CI: 0.59-0.81).

**DAAS AND \textit{DE NOVO} HCC**

Earlier studies of first-generation DAAs showed increased risk for \textit{de novo} and recurrent HCC, which brought concerns that DAAs might have carcinogenic effects\textsuperscript{[40-43]}. A retrospective multicenter study from Spain reported a short-term HCC incidence of 3.73 HCC/100 patient-years (95%CI: 2.96-4.70), within a median 10.3 months after starting DAA therapy on 1123 HCV patients with cirrhosis\textsuperscript{[44]}.

HCC risk with DAAs is related to the severity of liver histology\textsuperscript{[33,45,46]}. The annual incidence of HCC after SVR was higher in those with cirrhosis than those without cirrhosis (1.82 vs. 0.34/100 person-years)\textsuperscript{[14,33]}.

Ioannou \textit{et al.}\textsuperscript{[47]} reported that an increased risk for HCC in hepatitis C patients with baseline cirrhosis or high FIB-4 treated with either IFN-based therapy or DAAs could persist up to 10 years after SVR. Kanwal \textit{et al.}\textsuperscript{[48]} also showed that an increased risk for HCC after DAAs with SVR remained for up to 3.6 years of follow up, and it was particularly high in patients with cirrhosis.

**DAAS AND RECURRENT HCC**

Hepatitis C virus stimulates immune response. HCV-specific T cells produce cytokines including IFN with anti-HCC effects\textsuperscript{[49-52]}. The recurrence of HCC was speculated to be due to reduced immune surveillance, cytokine imbalance, and angiogenesis\textsuperscript{[50-53]}.

A meta-analysis by Singal \textit{et al.}\textsuperscript{[54]} demonstrated that IFN-based treatment for HCV patients after curative HCC therapy reduced HCC recurrence and improved the outcomes. Nishibatake Kinoshita \textit{et al.}\textsuperscript{[55]} reported no significant difference of HCV-related early HCC recurrence after HCC treatment between 156 patients in the IFN-based group and 147 patients in the DAA group.

Several earlier studies showed different results regarding DAAs and the risk of HCC recurrence\textsuperscript{[56-58]}. Some studies that reported an increased risk for HCC recurrence with use of DAAs correlated earlier HCC recurrence with a shorter interval between complete response to HCC treatment and the DAA agent\textsuperscript{[40,59]}.

A meta-analysis of HCC recurrence after DAAs by Saraiya pointed out that some studies lacked a comparison cohort or had different patient selection criteria, timing of DAA therapy, and follow up schedules. Nevertheless, they found no significant difference in HCC recurrence among the study groups\textsuperscript{[60]}.

The benefits of DAA therapy including regression of fibrosis, decrease in portal hypertension, and hepatic failure are weighed against potential risk for HCC recurrence. A large retrospective study of 793 patients in...
North America (304 received DAA therapy vs. 489 received no HCV therapy) published by Singal et al.\[61\] showed no association between DAA therapy and HCC recurrence (HR = 0.90; 95%CI: 0.70-1.16).

Dang et al.\[62\] reported a 60%-70% improvement in 5-year all-cause and liver-related mortality in HCV-related HCC patients after DAAs with SVR, compared to patients untreated for HCV. Singal et al.\[14\] hypothesized that, by decreasing HCV viral load and slowing or preventing liver decompensation, DAA therapy could reduce the risk for late HCC recurrence.

**ACTIVE HCC EFFECT ON SVR, AND TIMING OF DIRECT-ACTING ANTIVIRAL THERAPY**

Lower HCV SVR rates were reported in the presence of HCC\[63-69\]. It is speculated that the low HCV SVR rates were due to altered inflammatory state in the tumor microenvironment, DAA uptake into hepatocyte, resistant profiles in the context of HCC, immune escape mechanism, HCC reservoir, and penetration of DAAs to HCV-infected HCC tissue\[63,69\].

Although Ahmed et al.\[70\] showed that pre-liver transplant HCV treatment with DAAs provided great outcomes and the most cost-effective management for CHC patients with HCC or decompensated cirrhosis while waiting for liver transplant in the US, a study on US veterans with HCV observed an SVR rate of 74.4% in patients who received DAAs during active HCC compared to 91.1% in patients without HCC\[64\]. Deferring DAA therapy until six months after completion of either liver resection or ablation is recommended in HCC patients who are eligible for curative HCC treatment\[14\].

Radhakrishnan et al.\[71\] using HCV-TARGET database demonstrated a 50% reduced SVR in HCV patients with HCC, but SVR was not different among patients who received complete, partial, or no treatment at all.

Median wait time, availability of hepatitis C-positive organ, and severity of liver decompensation are the determinants of timing of DAA therapy in HCV-associated HCC patients who are on the liver transplantation (LT) list. DAA therapy for patients awaiting LT is usually deferred until after transplant so patients will be eligible to receive an HCV positive donor\[14\].

Reduced liver-related deaths on LT waiting list and decreased progression of liver disease from post-transplant HCV reinfection by DAA have been observed\[72,73\]. Some patients treated by DAAs with SVR while awaiting LT had sufficient improvement in liver function to receive other curative therapies or forego transplant\[72-73\]. Although Yang et al.\[76\] suggested DAAs might be associated with a higher rate of HCC recurrence post-LT in a small group of patients, Emamaullee and colleagues demonstrated that HCV eradication pre-LT did not impact rates of delisting for HCC progression or rates of HCC recurrence post-LT in a larger retrospective study\[77\].

**DAA THERAPY IN PATIENTS WITH UNTREATED ADVANCED HCC**

Limited data are available regarding the use of DAAs in hepatitis C patients with untreated advanced HCC. A theoretical benefit from DAAs in this setting is that it may improve liver decompensation and allow continued HCC therapy. Tumor burden, life expectancy, and patient preference need to be considered for DAA therapy since it is palliative\[14\].

**SUMMARY**

Highly potent DAAs in recent years have revolutionized hepatitis C treatment and have high SVR rate exceeding 90%. Numerous studies have shown that DAA-induced SVR reduces risk of hepatitis C-associated HCC. Although recent research demonstrated no increased risk of HCC in HCV patients after DAA with SVR, the HCV-TARGET database and other resources, such as DAA manufacturers’ database and
Surveillance, Epidemiology and End Results Program in the United States, collectively are most likely to show definitive evidence on the risk of HCC occurrence and recurrence after DAA with SVR.

Nevertheless, the risk of HCC in chronic hepatitis C patients with advanced fibrosis or cirrhosis remains after DAAs with SVR. The concerns of DAA-associated de novo HCC and its recurrence in HCV patients warrant further investigation. Clinical parameters and/or potential molecular biomarkers in the near future may enable better identification of HCC in high-risk HCV patients treated by DAAs with SVR. Thus, this subset of patients will benefit from proper surveillance, early detection, and intervention of HCC.

DECLARATIONS

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Study concept and design, literature search, drafting of the manuscript: Lee TP
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