



Are direct-acting antivirals against hepatitis C virus infection not associated with the recurrence of hepatocellular carcinoma?

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Hepatitis C virus (HCV) infection is one of the major causes of end-stage liver disease and hepatocellular carcinoma (HCC). Before the use of direct acting antivirals (DAAs) against HCV, liver transplantation was one of the best ways to achieve long-term survival and a better prognosis in patients with HCV infection and advanced liver fibrosis (1). In the interferon era, it is difficult for HCV infected patients with advanced liver fibrosis to achieve sustained virological response (SVR) because interferon therapy causes severe adverse events and these completely hamper this treatment in these patients.

Interferon-free combination treatment with DAAs against HCV with or without ribavirin could lead to higher SVR rates (~95%) with a shorter treatment duration and fewer adverse events even in HCV-infected patients with advanced liver fibrosis or decompensated cirrhosis (2). In the interferon era, the achievement of SVR could prevent the progression of liver fibrosis, reduce hepatic decompensation and the occurrence of HCC, and improve extrahepatic manifestations such as chronic kidney disease associated with HCV infection, improving the prognosis of hepatic and extrahepatic diseases (3); however, interferon therapy leads to only ~20–50% SVR rates.

A meta-analysis performed by Singal *et al.*, revealed that interferon treatment after curative hepatic resection or ablation therapy for HCC prevented HCC recurrence and improved survival in HCV-infected patients with cirrhosis (4). HCV-infected patients who achieved SVR

before the hepatic resection of HCC had better liver function and a better long-term prognosis than those who had not achieved SVR (5). Thus, SVR achieved by interferon improved liver function as well as reduced the risk of HCC occurrence (6). Therefore, various adjuvant treatments including interferon, have been recommended for the recurrence of HCC (7).

Several studies have shown an unexpectedly high rate of the early recurrence of HCC in patients after DAA treatment in patients with prior HCC and that HCC is not reduced in successfully DAA-treated cirrhotic patients (8,9). In a recent article, Singal *et al.* (10) performed a retrospective cohort study of patients with HCV-associated HCC with a complete response to resection, local ablation, transarterial chemo- or radioembolization, or radiation therapy at 31 health systems in the United States and Canada. They found that 1,075 patients with HCV infection and HCC had a complete response; however, they excluded 282 patients (10). Among the 793 patients who were included in the final analysis, 304 and 489 were and were not treated with DAA therapy, respectively. There were 128 (42.1%) and 288 (58.9%) recurrences of HCC in the DAA-treated and DAA-untreated patients, respectively (10). Cox regression analyses with adjustment for study site, age, gender, Child-Pugh score, alpha-fetoprotein level, tumor burden and HCC treatment modality showed that DAA therapy was not associated with the recurrence of HCC (10).

In this study, treatment leading to a complete response

at base line was observed in fewer of the 384 DAA-treated patients than those in the 489 DAA-untreated patients ($P<0.01$) as follows: Among the DAA-treated and DAA-untreated patients, 64 (21.1%) and 47 (9.6%) underwent resection; 107 (35.2%) and 157 (32.1%) underwent local ablation; 107 (35.2%) and 253 (51.7%) underwent transarterial chemoembolization; 26 (8.5%) and 30 (6.1%) underwent transarterial radiation, stereotactic body radiation therapy and others; and the data for 0 (0%) and 2 (0.4%) were missing, respectively (10). Interestingly, surgical resection was performed more frequently among the DAA-treated patients. The number of HCC therapies required to achieve complete response was lower in the DAA-treated patients than in the DAA-untreated patients ($P=0.04$). The age of the DAA-treated patients was higher at the time of complete response than that of the DAA-untreated patients ($P=0.03$). Hepatic function was better in DAA-treated patients than in DAA-untreated patients (Child Pugh class at complete response, $P<0.001$; presence of ascites, $P=0.001$; presence of hepatic encephalopathy, $P=0.006$; and platelet count at complete response, $P<0.001$) (10).

Notably, this study excluded 45 patients who had initiated DAA treatment and 12 patients with HCC recurrence within 30 days of HCC complete response. DAA treatment induces the changes in cytokine/chemokine levels, complement cascades and neutralizing antibodies during and immediately after DAA treatment, which may be related to hepatocarcinogenesis (11). Careful attention should be paid to the very early recurrence of HCC. The other limitation of this study was that the duration of study of the DAA-treated patients was only 5 years.

We appreciate the demonstration by Singal *et al.* that DAA therapy was not associated with the recurrence of HCC in a large cohort study of North American patients with a complete response to HCC treatment (10). It is very important to perform surveillance with imaging modalities and tumor markers at regular intervals (every 3–4 months) in all patients after HCC complete response and to early detect the recurrence of HCC (10,12).

In conclusion, clinicians should pay a special attention to the very early, early and total recurrence of HCC. Longer-term follow-up is needed for patients with HCV-associated HCC with complete response and SVR.

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Footnote

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

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