EDITORIAL

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Direct-acting antivirals trigger a favorable, sustained virological response in patients with chronic hepatitis C infections and hepatocellular carcinoma

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Hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. Chronic infection usually progresses to liver fibrosis and then cirrhosis and (sometimes) hepatocellular carcinoma (HCC) [1]. Thus, HCV infection is associated with increased risk for liver-related mortality from end-stage liver disease and HCC.

The HCV treatment paradigm has dramatically changed in recent times. Interferon therapy is no longer used; direct-acting antivirals (DAAs) have become the standard therapy [2], associated with outstanding efficacy and low rates of adverse events. All DAAs are given orally; the recent DAAs are pangenotypic in action and the treatment durations short (8 to 12 weeks in the absence of previous treatment) [3]. Treatment of HCV infection is now very simple, and there only a few contra-indications, principally a limited life expectancy because of non-hepatic comorbidities. Prior to prescribing a DAA regimen, it is necessary to consider whether decompensated cirrhosis (Child-Pugh class B or C) is present, whether renal function is decreased, possible drug–drug interactions, and possible co-infection with hepatitis B virus or human immunodeficiency virus [2].

Some aspects of DAA treatment of HCV infection in patients with HCC remain of concern. First, it is unclear whether DAAs reduce HCC recurrence, or liver-related or all-cause mortality, in patients with HCV-related HCC. It is necessary to separately consider the utility of DAA treatment for patients with "cured or inactive HCC" and "active HCC" [4]. The former patients lack any viable tumor after HCC treatment, including curative therapy. As eradication of HCV by DAAs could improve liver function and hinder hepatic decompensation, DAAs for patients with "cured HCC" could reduce liver-related mortality. Also, recent data indicate that DAAs may not increase the risk of HCC recurrence. "Active HCC" refers to untreated or untreatable HCC. Such cases usually exhibit poor liver function or intermediate-/advanced-stage tumors. HCC treatment (e.g., repeated transarterial chemoembolization) may compromise liver function [4]. Therefore, it is unclear whether DAAs improve the life expectancies of such patients and whether they reduce tumor

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progression.

The second issue is whether the DAAs used to treat HCV infections are similarly efficacious in patients with or without HCC. In a previous meta-analysis, the efficacy of DAA treatment of HCV infection was lower in patients with than without HCC (sustained virological response [SVR], 89.6% vs. 93.3%, $p = 0.0012$) [5]. However, subgroup analyses showed that the SVR differed between patients with "cured or inactive HCC" and "active HCC." The SVRs were 92.6% and 73.1%, respectively ($p = 0.002$) [5]. In another meta-analysis, the SVR in patients with HCV-related HCC was lower than in those without HCC (88.2% vs. 92.4%, $p < 0.001$) [6]. The efficacy of DAAs in cirrhotic patients is lower than in non-cirrhotic patients. But that meta-analysis reported no significant difference in the SVR between HCC patients and non-HCC patients with liver cirrhosis (89.1% vs. 89.4%, $p = 0.087$) [6]. Kwan et al. [7] studied the efficacy and safety of DAAs in patients with chronic hepatitis C infections with or without HCC. A total of 192 patients were given DAAs to treat HCV infections (168 patients without HCC and 24 patients with "cured or inactive HCC"). The SVRs after DAA treatment did not differ between the non-HCC and HCC groups (all patients, and propensity score-matched patients; SVRs in the matched patients 89.6% vs. 91.7%, $p = 1.000$). Also, the adverse event rate after DAA treatment did not differ between non-HCC and HCC patients. Considering the previous meta-analyses [5,6] and the current study [7], the efficacy of DAAs in terms of elimination of HCV infection seems to not differ between non-HCC and HCC patients after adjusting for several confounders. However, the study of Kwan et al. [7] had several limitations. First, the statistical power may be low because the number of HCC patients was small (n = 24). Second, it is unclear whether DAAs affected the recurrence rate of HCV-related HCC because there was no control group (patients with "cured or inactive HCC" who did not receive DAAs). Finally, it would have been better had the study investigated the long-term outcomes (hepatic decompensation, liver-related mortality, and all-cause mortality) of HCC patients given DAAs to treat HCV infections. Despite these limitations, the study significantly improves our understanding of the utility of DAAs in patients with HCV-related HCC. Further prospective studies are needed to clarify the abovementioned issues.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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