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Editorial

DAAs prevent HCC – the plot thickens

Successfully treating hepatitis C virus (HCV) infection for many years has been shown to improve patient outcomes including overall survival, liver-related mortality, and development of hepatocellular carcinoma (HCC) [1]. The rationale for the latter is easy to understand, as inflammation has been linked to tumor development including HCC [2]. Direct-acting antivirals (DAA) have revolutionized the treatment of HCV with excellent safety and cure rates, and this translates into rapid clearance of inflammation in the liver [3]. It was a surprise when a study reported increased HCC recurrence with DAA treatment for HCV after successful treatment of HCC [4]. Since then, the argument has been going back and forth, with pooled data on meta-analysis of retrospective and prospective studies showing that DAA treatment was not associated with increased recurrence or occurrence of HCC [5]. Clearly, development of SVR after HCV treatment is the single most important factor associated with improved survival in a non-cirrhotic population as well as in patients with cirrhosis [5–7].

In a recent issue of the Journal, Lleo and coworkers present data on a prospectively collected cohort of almost 2000 HCV cirrhotics from 10 academic centers in Italy, including 161 patients with prior and successfully treated HCC and at least 1 year of follow-up [8]. The authors analyzed the HCC development separately in a cohort of patients with treated HCC in past (HCC recurrence) and in another cohort of patients without history of previous HCC (HCC occurrence or *de novo* HCC). In this study, incidence of HCC recurrence was quite considerable at 24.8 per 100 person-years. However, it must be noted that many patients received non-curative treatment for HCC such as TACE. Apart from lack of SVR, AFP level was a predictor for HCC recurrence, a variable reflecting tumor behavior. Another study confirmed tumor behavior as risk factor for HCC recurrence and number of treatments for HCC in the past emerged as predictors for HCC recurrence after DAA treatment [9].

On the other hand, the risk of *de novo* HCC in this study was 2.4 per 100 person-years among patients with HCV cirrhosis, which is similar to ≈3% annual HCC-rate among historical cohorts of patients with HCV cirrhosis [10]. Apart from lack of SVR, age and portal hypertension emerged as predictors of HCC occurrence. Specifically, patients with platelets >110,000/μL and a liver stiffness reading of <25 kPa, a group recommended to not require endoscopic screening for varices [11], had the lowest HCC-incidence of 0.5% at one year. These data are like a recently reported prospective study, wherein stage of liver disease including portal hypertension and serum albumin were predictors of HCC occurrence after exposure to DAA [7].

Taken together, these findings are relevant for clinical practice when physicians need to make decisions on HCC surveillance after treatment of HCV with DAA in patients with previous cirrhosis and/or HCC. Clearly, patients who fail DAA therapy should be considered at high risk for HCC and undergo surveillance for HCC. However, patients who develop SVR with high risk factors for HCC including older age, other comorbidities including alcohol consumption or concomitant other liver disease etiologies, and portal hypertension with decompensated cirrhosis should be closely followed for HCC surveillance. Large prospective multicenter data are needed before clear recommendations can be drawn for HCC surveillance after exposure to DAA for HCV therapy. In the meantime, we may continue to treat HCV using DAA and prioritize patients for this treatment considering risk stratification and need for therapy.

Conflict of interest

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Investigator: Abbott, Arqle-Daiichi, Bayer, BMS, Boehringer-Ingelheim, Gilead, Imclone, Novartis, Roche.

Speaker, Advisor: Abbott, Bayer, BMS, Boehringer-Ingelheim, Eisai, Gilead, Ipsen, MSD, Roche.

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