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Commentary

Hepatocellular carcinoma after direct-acting antiviral agents: Can liver stiffness kinetics help identify patients at lower risk?

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Hepatitis C virus (HCV) is one of the main causes of chronic hepatitis resulting in cirrhosis and hepatocellular carcinoma (HCC) [1–3]. Despite the rare occurrence of HCC in patients with mild liver fibrosis [4,5], its annual prevalence is 3–7% in the presence of cirrhosis [6,7]. The HCV eradication is associated to a substantial decrease in all-cause mortality and liver disease progression [8]. Several studies have demonstrated that the risk of developing HCC decreases following interferon (IFN)-induced sustained virological response (SVR) [9–12]. However, the risk of HCC after SVR attainment primarily persists in patients with advanced fibrosis or cirrhosis [13]. SVR rates with direct-acting antivirals (DAAs) are >90%, while these were about 50% during the era of IFN-based therapy [14,15]. This high SVR rate has led to the assumption that the incidence of HCC would considerably decline.

In an extensive retrospective cohort study, Kanwal et al. have recently reported that the risk of HCC after SVR achieved by DAAs has considerably decreased as compared to that in patients without SVR [16]. In addition, they have confirmed that the absolute risk of HCC remained high in patients with established cirrhosis. In a meta-analysis study, Waziry et al. showed that, in patients with HCV-related cirrhosis, there is no evidence for a difference in the risk of developing HCC when SVR is achieved by DAA as compared to IFN-based therapy [17].

Whether the effect of a DAA-based SVR correlates with the recurrence of HCC following the curative treatment of early-stage HCC is another topic to debate. In 2016 Reig et al. were the first to report that an unpredictably high rate of tumor recurrence was observed in patients who attained SVR by DAAs [18]. However, several studies could not determine any evidence to support an elevated risk of HCC recurrence [17,19–21]. Although well-designed trials are warranted to ascertain the effect of DAAs on the recurrence of HCC, patients with HCV-related cirrhosis who have undergone curative therapies should not be dissuaded from receiving DAAs to prevent the progression of liver disease.

As discussed earlier, those patients attaining SVR by DAAs are not free from screening for HCC. However, the risk of occurrence or recurrence of HCC after HCV eradication would be markedly different. In this scenario, clinicians would very much like to be able to stratify cirrhotic patients according to their risk of developing HCC and identify those at higher risk, who then require strict surveillance. Since the residual risk of developing HCC after HCV eradication has been demonstrated to correlate with liver disease severity [16], a surrogate marker of liver disease severity would indeed be helpful. Liver stiffness measurement (LSM) by transient elastography (FibroScan®) allows the non-invasive assessment of liver disease severity [22]. In HCV patients LSM has shown to hold a prognostic value in terms of mortality prediction: the higher LSM the lower the 5-year survival probability [23]. In addition, LSM has proved to allow HCC risk stratification in HCV patients: in the study by Masuzaki et al. [24], the incidence rates of HCC increased in accordance with LSM, with a progressive increase of risk for HCC with an hazard ratio of 45.5 in patients with LSM >25 kPa as compared to patients with LSM ≤10 kPa. As expected, higher LSM was found to be a significant risk factor for HCC in both IFN-treated and IFN-untreated patients.

Several studies have shown that LSM decreases after antiviral treatment in patients with chronic hepatitis C. In the pre-DAA era, LSM dynamics were described in patients treated with Peg-IFN plus ribavirin [25,26]: a decrease of LSM at the end of treatment and at 24-week follow-up, and an increase of it in patients with treatment failure after therapy withdrawal have been shown [25]. However, in spite of the global trends, the main matter is the liver stiffness kinetics in individual patients: 42% of patients expe-

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rienced a LSM decrease ≥30% from baseline at 24 weeks after the end of therapy [25]. More recently, some papers have shown that approximately half of the cirrhotics who had achieved SVR after DAAs had a significant LSM decrease (>30% from baseline) at 24 week follow-up. [27–29]. However, the significance of LSM decrease in terms of improvement of inflammatory reaction *vs.* fibrosis regression or improvement of portal hypertension has not been fully elucidated yet. In the study by Mandorfer et al.[30], the relative change in LSM was a predictor of a hepatic venous pressure gradient (HVPG) decrease ≥10% among patients with a baseline clinically significant portal hypertension. Furthermore, in a small group of HIV/HCV patients who underwent LSM, HVPG measurement and transjugular liver biopsy before and after antiviral treatment, IFN-free therapy induced HVPG reduction in 86% of patients and stopped histological necroinflammatory activity in 61% of patients [31]. Interestingly, both those patients achieving a decrease in HVPG ≥10% from baseline and the patients with post-treatment absence of residual histological inflammation showed more pronounced decreases in LSM [31]. As portal pressure drives the development of liver-related complications and mortality in cirrhotic patients, a decrease in HVPG is expected to translate into immediate clinical benefit.

Along these lines, a retrospective study conducted on 30 liver-transplanted HCV patients, who had undergone both LSM and liver biopsy before and post-DAA treatment, showed that SVR induced significant improvement in sinusoidal fibrosis for more than 50% of treated recipients. Improvement was detected from the significant LSM decrease following DAAs [32]. Even if it is not fully clear yet how structural, inflammatory and haemodynamic processes affect liver stiffness and which one is mostly and earliest modified by HCV eradication, the impression is that LSM decrease after antiviral treatment is advantageous, as it carries a general meaning of liver damage improvement, whatever it is, that may in turn translate into better prognosis.

In this issue of *Digestive and Liver Disease*, Ravaioli et al. have suggested that a change in LSM after DAA therapy is a convenient parameter to predict the development of HCC [33]. In this single-centre retrospective analysis of 139 HCV cirrhotic patients treated with DAAs, 44% of patients exhibited significant LSM reduction (>30% from baseline) following antiviral therapy. During follow-up, 14% of treated patients experienced recurrent or *de-novo* HCC in a relatively short period of time from the end of treatment (median 7 months). The patients who developed HCC following DAAs had both significantly more advanced liver disease at baseline (a significantly higher proportion of patients in the Child-Pugh-Turcotte class B) and significantly lower LSM reduction after treatment than the patients who had not developed HCC. History of previous HCC, Child-Pugh-Turcotte class B and failure to achieve significant LSM reduction after treatment (*i.e.* any decrease lower than 30% from baseline values) were found to be independent predictors of HCC after DAAs. In patients without HCC history the latter two variables were confirmed as predictors of *de-novo* HCC.

The main matter is how to transfer these findings in clinical practice. In other words, how can clinicians be confident that, if for an individual patient LSM does not change after DAAs (*i.e.* LSM does not decrease >30% than baseline), that patient is at higher risk of HCC after antiviral treatment? And on establishing that the same patient is at increased risk of HCC occurrence, the second crucial question is whether he or she therefore requires more intense surveillance than cirrhotic individuals who have achieved SVR and obtained significant LSM decrease.

Actually, the data of the study by Ravaioli and colleagues has showed the other side of the coin: that is, the achievement of LSM decrease after DAAs identifies a "protective state" against the risk of HCC, having a 95% negative predictive value and being fairly useful (negative likelihood ratio 0.30) to exclude HCC development during follow-up. On the contrary, the failure to achieve any significant reduction of LSM following DAAs does not necessarily mean increased HCC risk and is not a useful indicator for confirming HCC development during follow-up (positive predictive value 22%, positive likelihood ratio 1.68). Accordingly, clinicians can potentially reassure treated patients who have obtained a significant LSM decrease after DAAs, being confident that the reduced LSM may likely translate into clinical benefit (including the reduced, albeit not abolished, risk of developing HCC). However, clinicians are not warranted to frighten those cirrhotic patients who have not achieved LSM reduction following therapy, by starting more intensive surveillance because of concerns for a worse outcome (including increased HCC risk). Surely, particular attention — by means of larger studies — should be paid to those patients with persistently elevated post-treatment LSM, in order to assess whether such patients may benefit of enhanced follow-up towards the early detection of liver-related complications.

In conclusion, the intensity of surveillance of HCC after DAA therapy is still controversial. This study by Ravaioli et al. has pointed to a validation of LSM as a convenient non-invasive and objective indicator for predicting HCC development after DAA treatment. It will be an advantageous tool for differentiating the intensity of follow-up in the clinical practice, each patient's clinical history remaining also crucial.

Conflict of interest

None declared.

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