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Commentary

Need to Face Liver Cirrhosis after HCV Cure with Antivirals

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Current pangenotypic direct-acting antivirals (DAA) eradicate hepatitis C virus (HCV) infection from more than 95% of patients with chronic hepatitis C, including those with liver cirrhosis (Soriano et al., 2017). Although improvements in hepatic function are recognized soon after HCV cure even in patients with decompensated cirrhosis, a complete normalization of liver parameters may take time and occasionally might never occur (Fernández-Montero and Soriano, 2016). Moreover, despite evidence of regression of hepatic fibrosis following virus elimination with antiviral treatment (Soriano et al., 2006; Mallet et al., 2008; Labarga et al., 2014; Elsharkawy et al., n.d.), the risk of developing hepatocellular carcinoma remains increased in HCV cured cirrhotics (Nahon et al., 2017; Waziry et al., n.d.). Thus, the unprecedented success seen in HCV therapeutics during the last couple of years would not be completed if threats derived from liver cirrhosis itself are not properly addressed after HCV clearance with antivirals. In this regard, the advent of hepatic anti-fibrotic agents should be viewed as an unmet medical need for HCV-associated cirrhotics even in the DAA era.

In this issue of *EBioMedicine*, a Japanese team lead by Kiminori Kimura reported the first proof-of-concept of significant improvement of hepatic fibrosis in a small subset of patients with compensated cirrhosis due to chronic hepatitis C that received escalating doses of PRI-724, an experimental CBP-β-catenin small molecule inhibitor (Kimura et al., n.d.). The study drug was given as continuous intravenous infusion for 12 weeks as 6 cycles of 1 week on, 1 week off. Changes in liver fibrosis were examined in a group of cirrhotic patients with active HCV infection.

There are at least three caveats when interpreting the results of the study. Firstly, prior HCV clearance with oral antivirals before PRI-724 testing would have provided a more adequate scenario and closer realistic approach for assessing anti-fibrotic effects of PRI-724, eliminating the interference caused by persistent viral replication. Secondly, the interval of 3 months after completing 12 weeks of PRI-724 therapy could be too short for unveiling significant changes in hepatic fibrosis, a process that generally occurs over years. Thirdly, and most important, the population examined was too small to drawn any conclusion. Only one patient on the highest dose experienced grade 3 bilirubin elevation that returned to baseline levels after stopping the drug, supporting moving forward further testing of tolerability with lower doses. However, significant changes in hepatic fibrosis were inconclusive, with improvement in 3 and worsening in 2 out of 12 patients that completed PRI-724 therapy.

Enthusiasm unabated, the race for finding hepatic anti-fibrotics should continue. Given that replacement of dead hepatocytes by fibrotic tissue seems to be the final step of a wide range of hepatic diseases –and not just hepatitis C-, the development of specific anti-fibrotic agents would be a huge therapeutic breakthrough. Of note, advanced liver fibrosis associated with conditions other than hepatitis C could benefit from drugs specifically targeting hepatic fibrosis, including alcoholic and non-alcoholic fatty liver disease, illnesses that are currently replacing viral hepatitis as cause of cirrhosis globally (Bellentani, 2017).

The benefits of anti-fibrotics for treating cirrhosis of any origin should be recognized in at least three clinical fronts. Firstly, providing the opportunity for hepatocyte regeneration, improving the synthetic function of the damaged liver, which can be easily measured by albumin and coagulation. Secondly, ameliorating portal hypertension and its clinical complications, including ascites, encephalopathy, and variceal bleeding. Lastly, reducing the risk of hepatocellular carcinoma on residual scarring hepatic regions (Nahon et al., 2017; Waziry et al., n.d.), by far the most feared complication in the mid-long term.

Disclosure

The authors declared no conflicts of interest.

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