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Review

Role of assessing liver fibrosis in management of chronic hepatitis C virus infection

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ABSTRACT

Fibrosis progression is common in hepatitis C. Both host and viral factors influence its natural history. Liver fibrosis is a key predictive factor for advanced disease including endpoints such as liver failure, cirrhosis and hepatocellular carcinoma (HCC). METAVIR fibrosis stages F3–F4 have been considered as the threshold for antiviral therapy. However, this aspect is controversial after the advent of new direct-acting antivirals (DAAs) because they show an excellent efficacy and safety profile. Moreover, in the DAA era, fibrosis stage seems not to be a predictive factor of a sustained virological response (SVR). Viral eradication decreases liver damage by improving the inflammation, as well as by regressing fibrosis irrespective of the treatment regimen. Non-invasive methods are useful in the assessment of liver fibrosis, replacing liver biopsy in clinical practice; but their usefulness for monitoring fibrosis after SVR needs to be demonstrated. Fibrosis regression has been demonstrated after the eradication of hepatitis C virus infection and is associated with a lower risk of hepatic cirrhosis and liver cancer. However, patients showing advanced fibrosis and cirrhosis must be followed-up after SVR, as risks of portal hypertension and HCC remain. **I. Carmona, CMI 2016;22:839**

Introduction

The advent of the new direct-acting antivirals (DAAs) for hepatitis C virus (HCV) has increased enormously the sustained virological response (SVR) rates. However, the main goal is to increase survival and quality of life by modifying the natural history of the infection (interrupting the sequence of fibrosis > cirrhosis > hepatocellular carcinoma (HCC)) beyond eradication of the virus [1]. In addition, HCV infection can lead to extra-hepatic manifestations that could be improved with SVR [2]. Nevertheless, universal access to the treatment has not been possible due to its higher cost comared with previous therapy. Liver fibrosis is the essential factor in the management of HCV disease. Its assessment is crucial to make therapeutic decisions and determine the adequate follow up of the patients. Hence, the fibrosis stage is one of the main predictive factors to become complicated once the virus is eradicated. Consequently, fibrosis regression has become a new surrogate goal of HCV therapy [1,3].

Prioritize antiviral treatment according to fibrosis stage

Antiviral therapy including DAAs has increased SVR rates >95% in almost all scenarios, simplifying the course of treatment (oral administration for 8, 12 or 24 weeks) and protecting from serious adverse effects [1,3]. During previous interferon (IFN) -based regimens, fibrosis was strongly related to success in HCV eradication and also to the risk of developing serious adverse events. Antiviral treatment was indicated in patients with significant fibrosis to improve the balance between risk of development of complications and risk of adverse events. Currently, using safe DAAs, all HCV patients should receive the treatment [1,3]. The only reservoir for HCV is the human and treatment of all infected people could achieve eradication of the outbreak. Hence, fibrosis could direct therapy during the first years but, at the end of the day, we should treat all patients to combat the infection.

Monitoring fibrosis progression

Hepatitis C virus with active replication is the most important factor for fibrosis progression [4–6]. Therefore, those patients who

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do not receive antiviral treatment due to mild fibrosis should be monitored to determine the risk of progression and anticipate starting therapy [1,3]. Fibrosis progression is also influenced by exogenous factors, which must be identified and actively corrected, such as human immunodeficiency virus or hepatitis B virus co-infection, alcohol consumption and metabolic derangement like non-alcoholic fatty liver disease (Fig. 1) [6]. Liver biopsy is the reference standard used to determine liver fibrosis. Studies comparing paired biopsies have demonstrated the progression of liver fibrosis in non-treated patients or those showing non-SVR [7–9]. However, liver biopsy is an invasive method with potential complications that has limitations, such as sampling error or inter- and intra-observer variability [10]. Non-invasive methods have been developed to assess and monitor liver fibrosis (Table 1). The diagnostic accuracy of non-invasive methods increases when determining the presence of advanced fibrosis or when excluding fibrosis; it is suboptimal when defining intermediate stages [11]. The accuracy of these methods can vary depending on the prevalence of each fibrosis stage in the study population that limits the comparison of results across different study cohorts [11]. Serum and imaging biomarkers have also been developed. Serum-based non-invasive methods can be direct tests (measuring compounds of extracellular matrix produced by stellate cells) or indirect tests (laboratory parameters) [11]. No significant differences have been found in the accuracy of diagnosis between direct or indirect methods [12]. The main limitation of these serum biomarkers is that they are not liver-specific and may be influenced by age, extra-hepatic inflammatory processes, haemolysis or alanine amino-transferase (ALT) flares. Imaging biomarkers usually assess liver stiffness, with Transient Elastography (TE) being the most widely

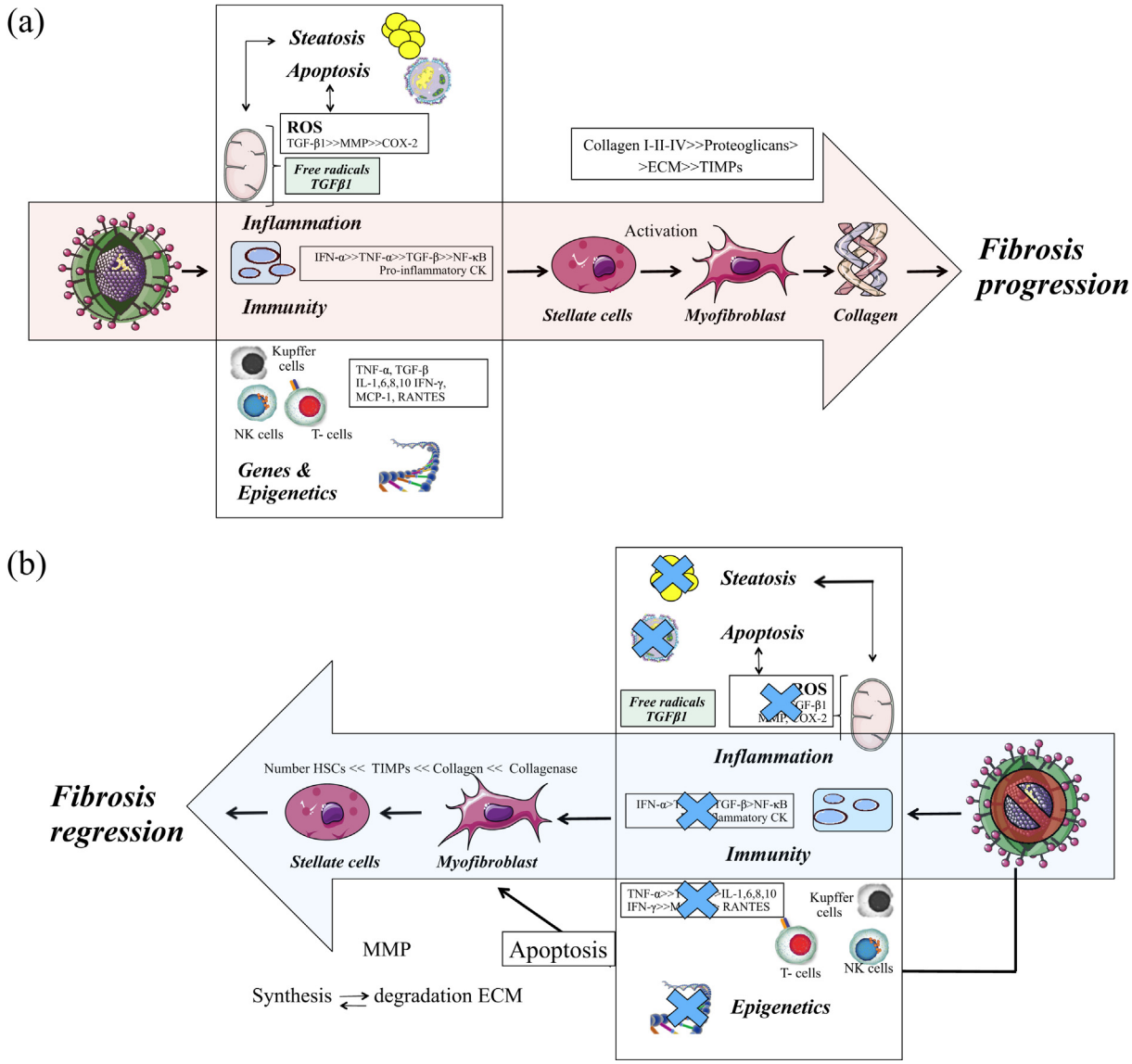

Fig. 1. Mechanism of hepatitis C virus (HCV) -associated liver fibrosis. (a) HCV fibrosis progression. The hepatic injury promotes the activation of immune and inflammatory systems and the progression of fibrosis is mediated by signalling molecules. HCV encourages steatosis; promotes fibrosis and several genetic factors have been described as risk factors for progressive fibrosis. Cytokine production together with the formation of reactive oxygen species (ROS) and all the risk factors previously cited, activate stellate cells, inducing their transformation into myofibroblasts. Myofibroblasts produce large amounts of collagen and slow matrix degradation, leading to tissue fibrosis. (b) HCV fibrosis regression. Virus clearance results in fibrosis improvement. Virus elimination by DAAs does not activate inflammation, steatosis and fibrogenesis pathways. Myofibroblasts are inactivated or even eliminated by apoptosis. Manipulating matrix degradation or enhancing haematopoietic stem cell apoptosis might be expected to reduce fibrosis and promote a return to normal liver architecture and function.