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EDITORIAL

Targeting the renin–angiotensin system in liver fibrosis

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Liver fibrosis is the progressive accumulation of extracellular matrix (ECM) in the liver as a result of a persistent liver injury. If fibrogenesis persists, the accumulation of ECM disrupts the liver architecture leading to cirrhosis, the most advanced stage of liver disease, and portal hypertension, with the subsequent development of complications of cirrhosis. Two important components determine the increased portal pressure, first a structural component, which is mainly the accumulation of ECM that disturbs normal blood flow in the liver, and second, a dynamic component, which is the result of a high intrahepatic contractility and swelling, resulting from the activation of hepatic stellate and liver myofibroblasts and an increased liver inflammation [1].

Portal hypertension associated with cirrhosis leads to a vasodilation of splanchnic circulation, which causes a decrease in effective blood volume and the induction of vasoconstrictors such as the sympathetic nervous system or renin–angiotensin system (RAS) [2, 3]. Activation of systemic RAS further enhances circulatory dysfunction with sodium retention causing the formation of ascites. Besides the activation of systemic RAS as a result of hyperdynamic circulation in cirrhosis, human and experimental evidences have shown the existence of a local intrahepatic RAS system, which is believed to play an important role in the development of fibrosis [4–6]. However, it is not clear what the relationship is between the systemic and local activation of RAS and which is the impact of increased systemic levels of angiotensin I or II in intrahepatic resistance and enhanced ECM production. Experimental evidence suggests that hepatic local RAS is activated at earlier stages of disease progression, and local rather than systemic RAS activation may be the major player in HSC activation, tissue remodeling and fibrosis progression [5, 7, 8].

Local RAS has a highly pleiotropic role, and is involved in hepatic stellate cell activation, contractility of liver myofibroblasts, increased intrahepatic resistance, but also it mediates an enhanced inflammation and promotes the expression of extracellular matrix components and mediators of inflammation and fibrosis [9–12]. Several mechanisms of action can account for a potential positive effect of RAS inhibition on liver fibrogenesis, but most of them have been described in experimental models of fibrosis. First, angiotensin II (AngII), the main effector of RAS is known to enhance oxidative stress thus promoting hepatocyte injury, endothelial dysfunction and macrophage and stellate cell activation [12–14]; second, AngII is a well-known vasoconstrictor known to enhance stellate cell contraction and increase intrahepatic resistance [9, 11]; third, AngII acts as a local and systemic cytokine enhancing expression of inflammatory mediators and promoting liver inflammatory cell infiltrate [12, 14, 15]. The pleiotropic role of RAS in the liver has for a long time now suggested that RAS could be an appealing target to prevent liver disease progression and fibrogenesis. A number of experimental, clinical and epidemiological data support this hypothesis; however, to what extent drugs targeting the RAS system are effective to reduce hepatic fibrogenesis and reduce liver disease progression is not definitively proven in well controlled clinical trials [7, 16, 17].

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Kim et al. published a systematic review and meta-analysis of clinical trials and reports assessing the impact of RAS inhibitors on liver fibrosis by histological assessment in this issue of Hepatology International [18]. Although a number of reports have been published describing the treatment of patients with liver disease with RAS inhibitors, few of them are correctly designed to assess its effect on fibrogenesis at histological level. The follow-up time in most studies is too short to observe regression of fibrosis, and other parameters associated with fibrogenesis such as inflammation or HSC activation are not appropriately recorded.

Although most studies included in Kim et al. [18] report a non-significant reduction in liver fibrosis scores, the inclusion of seven studies and the meta-analysis performed suggest a beneficial effect of RAS inhibitors in reducing fibrosis scores and therefore suggesting RAS inhibitors as a potential therapeutic strategy for liver fibrosis. Importantly, this study suggests that, most probably, the failure to show beneficial effects of RAS inhibitors in previous reported studies may be due to low number of patients included or an inappropriate study design. While Kim et al. highlights the importance of performing meta-analysis studies to help interpret pieces of information otherwise with unclear outcome, the overall conclusion of this report needs to be taken cautiously. Only those studies considering histological assessment were included, and this is a small proportion of studies performed, only seven out of 354 studies published; also, the meta-analysis did not consider studies addressing indirect determination of fibrosis, such as biomarkers or expression of active mediators of fibrogenesis. Nevertheless, this systematic review clearly emphasizes that bigger and longer randomized clinical trials are still needed to evaluate the potential of RAS as a target to treat liver fibrosis progression and disease pathogenesis.

In the current scientific literature, there is a lack of good clinical trials to prevent liver fibrogenesis or to revert fibrosis, and this is not only regarding RAS inhibitors. Liver fibrogenesis is a slow progressing disease and fibrosis usually takes years to develop. Moreover, regression of advanced fibrosis is also a slow process, which, if possible, may require years even after removal of the causal factor [10, 19]. For these reasons, clinical trials aiming to reduce fibrosis content at a histological level require of long-term treatment and follow up. Moreover, it has to be taken into consideration that biopsy, although currently the gold standard to address liver fibrosis, has an important sample variability introducing variability in fibrosis assessment. In the future, liver fibrosis should be assessed by a combination of approaches, such as liver histology, but also liver elastography, measurement of portal hypertension, non-invasive biomarkers of fibrosis, as well as indirect assessment of active fibrogenesis.

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