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Focus

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Attenuation of hepatic fibrosis: the search goes on

Fibrosis of the liver is a complex and progressive process initiated and maintained by a large number of stimuli. Significant progress has been made in the past two decades in elucidating the mechanism(s) of fibrogenesis and exploring old and new therapeutic modalities to slow down and possibly reverse ongoing scarring of the liver [1]. Various strategies to prevent, minimize, and even revert hepatic fibrosis have been and still are being evaluated in bile duct ligated (BDL) or CCL_4 treated rat model systems as well as in humans, including removal of the injurious stimuli, suppressing inflammation, down-regulating stellate cell activation and increasing apoptosis of Ito cells. Hepatic stellate cells (HSC) have emerged as an attractive target for controlling fibrosis. Proliferation of HSC which acquire a myofibroblast phenotype and synthesize increasing amounts of extracellular matrix is considered a cornerstone in generation of hepatic fibrosis. Already in 1994, Mallat and co-workers have shown *in vitro* that simvastatin inhibits hydroxyl-methylglutaryl-coenzyme A reductase activity and myofibroblast-like Ito cells, isolated from normal human liver, independent of its lipid lowering effects [2]. At that time it was still unknown if this effect also exists *in vivo*. Since then, several reports appeared describing the inhibitory effects of statins on hepatic inflammatory activity *in vitro* [3], portal hypertension [4], and indirectly on hepatic fibrosis [5]. Statins have also been reported to have an anti-fibrotic activity in non-hepatic disorders including pulmonary and renal fibrosis [6].

In this issue of the journal, Trebicka and co-workers have evaluated *in vivo* the anti-fibrotic effect of atorvastatin in a BDL rat model. The investigators employed a broad battery of assays to evaluate the effects of atorvastatin on HSC activation, proliferation, and apoptosis as well as degree of hepatic fibrosis. The BDL rat model is characterized by rapid development of hepatic fibrosis as assessed by an increased hydroxyproline content as well as deposition of extracellular matrix. Sham operated rats served as controls and rats were sacrificed at 1, 2, 3, 5, and 6 weeks post BDL. The main results of this study are the attenuation of HSC activation, hepatic fibrosis, and reduced accumulation of myofibroblasts observed in atorvastatin treated rats as compared to controls, when treatment was started immediately or early after BDL. In contrast, the anti-fibrotic effects of atorvastatin were diminished when treatment was started later, at 3–5 weeks post BDL. Still, even late intervention lead to reduced profibrotic cytokine expression with decreased apoptosis and proliferation. Interestingly, in contrast to previous reports, treatment had no effect on inflammatory activity and hepatocellular injury even increased. The investigators suggest that it is now time to test whether the anti-fibrotic effect of atorvastatin observed in the rat model system is also functional in humans i.e. with chronic liver disease. However, this is not expected to be an easy task. The BDL model in the rat is characterized by very rapid development of fibrosis which is usually present already at 1 week after bile duct ligation. In humans, evolution of fibrosis may take years or even decades and the option of performing serial liver biopsies to evaluate the effect of statins is limited, unless non-invasive markers for fibrosis will be accepted as surrogate end-points. Yet, there is already some indirect evidence that administration of statins in non-alcoholic liver disease is relatively safe and quite beneficial in reducing the hepatic fat content which is a well established risk factor for hepatic fibrosis [7]. In summary, analysis of the results obtained in this rat BDL model, confirm the original *in vitro* observation from 1994 regarding the anti-fibrotic properties of statins [2] which were later also shown to contribute to a reduction in portal hypertension in humans with cirrhosis [4].

Terra Incognita: paving the road for measurement of hepatic vein pressure gradient in children with chronic liver disease

Measurement of the hepatic vein pressure gradient (HVPG) in adults is considered a safe and straightforward procedure with a 95% success rate in experienced hands [8]. HVPG has been used for clinical evaluation of alcoholic liver disease, in patients awaiting liver resection, in patients with ascites and splenomegaly of undetermined etiology, in patients with esophageal varices, and for monitoring of therapy in portal hypertension. An HVPG measurement is also essential prior and after transjugular intrahepatic portosystemic shunting (TIPS) [9]. Cumulative experience suggests that in adults, bleeding from esophageal varices usually occurs at an HVPG of at least 12 mm Hg. In contrast to adults, there is very little information on the dynamics of portal pressure in healthy children as well as in children with chronic liver disease.

In this issue of the journal, Miraglia and co-workers report their experience in the measurement of HVPG in 20 children, eight months to ~16 years old with a wide spectrum of chronic liver diseases, of which nine had biliary atresia. HVPG between 10

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and 33 mm Hg – was found in 13/20 children, nine of whom also had esophageal varices. In addition, collateral circulation was also identified in 3/4 children with an HVPG of 8 mm Hg of whom two had esophageal varices. In contrast, none of the children with an HVPG between 2 and 3 mm Hg had collaterals or varices. Based on their preliminary results, the investigators suggest an HVPG $\geqslant$8 mm Hg should be considered as evidence for portal hypertension in children. This figure is lower by 2–4 mm Hg compared to the acceptable threshold of 10–12 mm Hg in adults. Information on HVPG levels in healthy children without liver disease is lacking for obvious reasons. Interestingly, 7/9 children with biliary atresia had intrahepatic veno-venous shunts which may lead to underestimation of the degree of portal hypertension, as observed in the 3/4 patients with an HVPG of 8 mm Hg. Finally, ten of the patients with an HVPG between 8 and 20 mm Hg received beta blocker treatment which was most probably under dosed.

The results of this pilot study suggest that measurement of HVPG in a pediatric population, which included also very small children, is safe and may be utilized for the same indications as in adults. This paper also provides a wealth of technical information which will be useful for radiologists and pediatric hepatologists alike. Finally, the results of this retrospective analysis may be useful for physicians who consider TIPS, which until recently was an uncommon procedure in children (reviewed in [10]).

Conflict of Interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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