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The effects of statins on cholestasis: good, bad or indifferent?

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HMG CoA reductase inhibitors, or statins, are widely prescribed for the treatment of dyslipidemias. Physicians who prescribe these drugs are well aware of the small risk of increased transaminase levels that is seen in 1–3% of patients. This side effect is usually asymptomatic and reversible after dosage reduction or drug withdrawal [1]. The clinical insignificance of this side effect is underscored by retrospective analyses that support the use of statins in patients with chronic viral hepatitides and non-alcoholic fatty liver disease [2]. In the vast majority of patients using statins, therefore, clinically significant liver injury does not arise.

The relationship between statins and cholestastic liver disease, however, is not as straightforward. Cause and effect are difficult to discern and disentangle. Statins have been rarely associated with cholestatic liver injury manifesting with jaundice and histologic abnormalities [3]. Such cholestatic liver disease has been described in association with the use of pravastatin [4, 5] and atorvastatin [6–9]. In each case, symptoms resolved after drug withdrawal.

Is statin therapy safe to use in patients with cholestatic liver disease? Retrospective analyses of patients with primary biliary cirrhosis (PBC) prescribed statins show that these drugs are well tolerated, effective in improving serum lipid profiles, and without adverse effects in terms of biochemical parameters of cholestasis. For example, in a retrospective analysis of 58 PBC patients on statin therapy for variable periods of time, with the mean duration of treatment of 41 months (range 3–125 months), statins were well tolerated and induced reductions in serum cholesterol levels as anticipated [10]. Thus, safety does not appear to be a significant issue for the majority of patients with PBC with cardiovascular risk factors in addition to dyslipidemia for whom statins are prescribed [11].

Statins have also been associated with beneficial effects on markers of cholestasis in patients with cholestaticliver disease. A report described lower cholesterol and serum total bile acid levels in PBC patients after the initiation of pravastatin [12]. Another case report described marked improvements in cholestasis and hypercholesterolemia with simvastatin in a patient with PBC [13]. In six patients with PBC treated with simvastatin, alkaline phosphatase, γ-glutamyltransferase (GGT), and IgM levels were reduced significantly [14]. More recent reports, however, have not corroborated these observations [15]. Liver biochemistries were not significantly changed in 15 PBC patients [16]. In PBC patients with an incomplete biochemical response to ursodeoxycholic acid, treatment with atorvastatin did not show improvements in parameters of cholestasis [17]. Thus, whether statins improve cholestasis remains unclear, with the preponderance of the evidence suggesting that they do not.

What can animal models of cholestasis tell us about the effects of statins on cholestasis? The most commonly used animal model of cholestasis is that of bile duct ligation (BDL) in rodents, which causes obstructive jaundice and cholestasis which over time leads to histological changes in the liver including the development of cirrhosis. This model has been

widely used to study the effects of cholestasis on hepatobiliary transport mechanisms, bile formation, inflammation, and fibrogenesis [18].

Cholestasis induced by BDL induces a myriad of physiologic effects on hepatobiliary physiology, especially with respect to bile acid and cholesterol homeostasis. Under cholestatic conditions, when intrahepatic and systemic bile acid levels rise, an orchestrated adaptive response occurs which is coordinated by a complex interplay of nuclear receptors that attempt to counteract the liver injury induced by cholestasis. These adaptive responses are centered in the liver, but also involve physiological alterations in transport pathways in the small intestine, biliary epithelia and kidneys [19].

The rodent BDL model has been used to investigate whetherstatins can have beneficial effects on the cholestatic liver. Rosuvastatin ameliorated hepatic injury, inflammation, and lipid peroxidation; and increased antioxidant enzyme activity in rats subjected to BDL [20]. Simvastatin decreased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in mice after BDL. Simvastatin also reduced hepatic formation of CXC chemokines and restored sinusoidal perfusion in the liver, and decreased cholestatic liver injury and inflammation [21]. Fluvastatin decreased high levels of AST, ALT, and GGT induced by BDL in rats and ameliorated hepatic inflammation, lipid peroxidation and tissue injury [22]. Thus, studies in animal models of obstructive cholestasis induced by BDL have shown beneficial effects of statins on various markers of liver injury, including markers of inflammation. While the mechanisms whereby statins induce these beneficial effects on the liver remain to be defined, the myriad effects observed suggest that these might not depend solely on the inhibition of HMG CoA reductase.

One key to deciphering the mechanisms whereby statins induce beneficial effects on cholestasis in the rodent BDL model involves a detailed understanding of the role of nuclear receptors. These mechanistic insights havebeen recently reviewed [19, 23]. Nuclear receptors serve as key transcriptional regulators controlling an intricate web of transport pathways that serve to mitigate the effects of cholestasis on the hepatobiliary and intestinal systems. The key nuclear receptors involved in the adaptive response to cholestasis induced by BDL are farnesoid × receptor (FXR), liver × receptor alpha (LXRα), short heterodimer partner (SHP), pregnane × receptor (PXR), constitutive androstane receptor (CAR) and peroxisomal proliferator-activated receptor alpha (PPAR-α). Of these, FXR is central to the response as it is the intracellular bile acid sensor regulating the majority of processes involved in bile acid formation, transport, and detoxification. FXR limits hepatocellular bile acid overload through several mechanisms. Bile acids bind to FXR and inhibit their own synthesis by repression of transcription of CYP7A1 by induction of SHP. In the intestine, FXR induces fibroblast growth factor 15 (FGF-15), which binds to and activates hepatic fibroblast growth factor receptor 4 (FGFR-4) signaling to inhibit bile acid synthesis in the liver. FXR inhibits hepatocellular import of bile acids in a feedback loop by repressing hepatocellular basolateral bile acid uptake via the sodium taurocholate co-transporting polypeptide (NTCP) in a SHP-dependent manner. FXR also induces the excretion of bile acids into the biliary canaliculus in a feed-forward fashion by stimulating the bile salt export pump (BSEP). In addition, FXR stimulatesretrograde bile acid export back into portal blood via the organic solute transporter alpha and beta (OSTα/β). The canalicular bilirubin pump MRP2 is also induced by activation of FXR, thereby providing a means to transport tetrahydroxylated bile acids that accumulate during cholestasis [24, 25]. The nuclear receptors PXR and CAR contribute to bile acid excretion during cholestasis by activating phase I and phase II detoxification pathways that render bile acids more hydrophilic and less toxic, and therefore more amenable to urinary excretion. These pathways are also regulated by FXR. Other key nuclear receptors that serve in an adaptive role during cholestasis are LXRα, the key intracellular cholesterol sensor; and PPAR-α, which induces bile acid

conjugation via UGT2B4 and UGT1A3, represses CYP7A1, and increases biliary phospholipid secretion [24, 25].

The paper by Kolouchova et al in this issue reports on the effects of pravastatin on transporters, enzymes, and nuclear receptors involved in cholesterol and bile acid homeostasis in the setting of BDL-induced cholestasis in rats [26]. This data offers a glimpse into the complex regulatory networks controlled by nuclear receptors and the potential roles that statins may play in altering the functions of these master transcriptional regulators.

Changes in the mRNA expression of a host of transporters and enzymes integral to bile acid and cholesterol homeostasis were found. Likewise, the mRNA expression levels of key nuclear receptors involved in bile acid and cholesterol homeostasis were altered with pravastatin treatment in the BDL compared to sham operated rats. Interestingly, FXR expression was markedly downregulated in the BDL rats treated with either dose of pravastatin. This decrease in FXR expression was in contrast to the increase in FXR expression noted in the BDL animals treated with vehicle or the sham-operated animals treated with pravastatin. Thus, statin therapy appears to have a depressive effect on FXR expression in the setting of BDL but not in the sham operated setting. This finding raises several questions: If FXR upregulation is an adaptive response to cholestasis induced by BDL, then might not downregulation of FXR by statin therapy in this setting be construed as counteracting this beneficial homeostatic response? What then does one make of the decrease in serum bile acid levels in the low dose pravastatin-treated BDL animals but not the high dose pravastatin-treated BDL animals?

Our current state of knowledge regarding the effects of statin therapy on nuclear receptor regulatory networks in cholestasis has not developed to the point where definitive answers can be given to these and other questions raised by the data presented in the paper by Kolouchova et al. Caveats to keep in mind in interpreting the data include the fact that these are gene expression data that may not correspond to protein expression levels or activity of nuclear receptors and transporters; the use of particular doses and type of statin; and the duration oftreatment. Nevertheless, one can appreciate the bigger picture that statin therapy appears to have wide-ranging effects on bile acid and cholesterol transport and nuclear receptor regulatory networks in the rat BDL model. Whether these changes are relevant to patients with PBC or to patients given statins who develop cholestatic liver disease remains to be seen.

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