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Mechanism of bempedoic acid induced cholelithiasis: a role for statins to limit this adverse effect?

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Bempedoic acid is first-in-class adenosine triphosphate-citrate lyase (ACL) inhibitor with hypocholesterolemic activity. Bempedoic acid has been generally well-tolerated in clinical trials, although elevations in creatinine and uric acid levels with a higher incidence of gout (especially in individuals with a prior history of gout) has been observed. The recent results of the CLEAR Outcomes trial confirmed similar adverse events but also highlighted a higher incidence of cholelithiasis (2.2% vs. 1.2%) in the bempedoic acid group compared to placebo (1).

While the low-grade and reversible increase in plasma uric acid and creatinine, associated with bempedoic acid therapy, are clearly a consequent to the competition for OAT2 in the renal tubules.

The reason of the increased incidence of cholelithiasis is instead still debated but may involve the inhibition of other drug transporters, such as the organic anion transport protein 1B1 and 1B3 (OATP1B1/3) expressed mainly in hepatocytes. Statins are mainly substrates of OATP1B1/3, whereas bempedoic acid and its glucuronide are weak inhibitors of both transporters. For this reason bempedoic acid raises plasma levels (as Area Under the Curve, AUC) of simvastatin 40 mg, atorvastatin 80 mg, pravastatin 80 mg, and rosuvastatin 40 mg by 2, 1.4, 1.5, and 1.5 fold, respectively. OATP1B1 is also a major transporter for bile salt uptake in the enterohepatic circulation (Figure). Negative modulation of OATP1B1 can be responsible for a lower relative concentration of bile salts in the gallbladder and may lead to the formation of cholesterol stones (2). Liver uptake of bile salts is, in fact, a rate limiting step in the enterohepatic circulation (Figure).

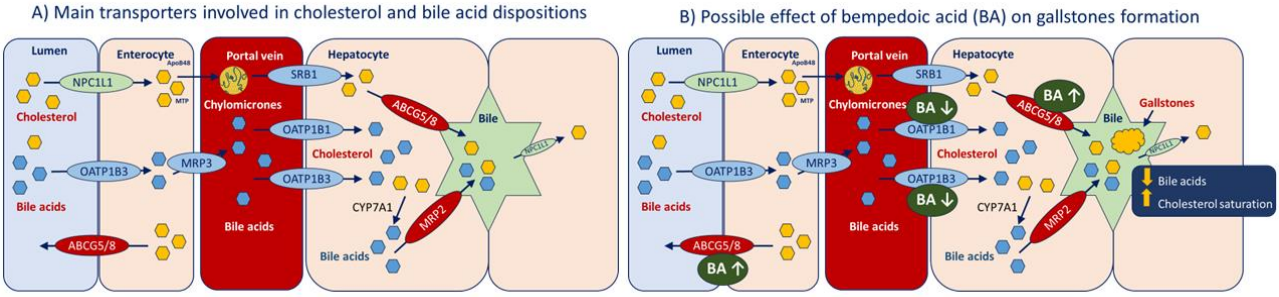

Figure. Schematic representation of the effect of bempedoic acid (BA) on cholelithiasis.

Single nucleotide polymorphisms (SNPs) associated with a loss of function of SLCO1B1 have been associated with gallstone susceptibility (3). A pharmacological inhibition of SLCO1B1 by bempedoic acid and its metabolite, may be the cause of the higher incidence of cholelithiasis observed in the CLEAR Outcomes study (1).

The use of peroxisome proliferator-activated receptor (PPAR) alpha agonist fenofibrate, is also associated with a higher incidence of cholelithiasis. Fenofibrate may increase the concentration of biliary cholesterol and phospholipids and reduce that of bile acids by antagonizing the transcription of CYP7A1, responsible for the rate-limiting step in the conversion of cholesterol to bile acids (Figure). Through this mechanism, fenofibrate predisposes patients to the formation of gallstones (4). Similarly, bempedoic acid has been hypothesized to enhance fecal neutral sterol excretion via bile or trans-intestinal cholesterol efflux, potentially by increasing the expression of adenosine triphosphate-binding cassette transporter 5 (ABCG5) and ABCG8 (5). This effect may explain the lower hepatic cholesterol content and the hypocholesterolemic activity of bempedoic acid in mice lacking the low-density lipoprotein (LDL) receptor (LDL receptor null mice) (5). Thus, the relative reduction of bile salt concentrations may contribute to the higher incidence of cholelithiasis after bempedoic acid.

The target of ezetimibe, Niemann-Pick C1-Like protein 1 (NPC1L1), is not exclusively expressed by the enterocytes, but also in the hepatocytes, where it mediates the uptake of cholesterol from bile to the liver, while ABCG5/8 have the opposite effect (Figure). Thus, also treatment with ezetimibe has been hypothesized to raise the biliary cholesterol content, and hence the risk of cholelithiasis. Indeed, ezetimibe given to dogs increased the concentration of gallbladder cholesterol by two- to four-fold, likely due to reduced NPC1L1 expression in the liver. In humans, however, ezetimibe demonstrated a protective effect on gallstone formation by lowering biliary cholesterol saturation and retarding crystallization in bile (6). The effect has been justified by the very low expression of NPC1L1 in the liver compared to intestine, avoiding the increased cholesterol saturation in response to its pharmacological inhibition by ezetimibe (Figure).

Finally, statins, by inhibiting cholesterol biosynthesis, elicit a protective effect on cholelithiasis by reducing the biliary cholesterol concentration (7). It is thus, tempting to hypothesize a lower incidence of cholelithiasis by bempedoic acid when given in combination with statins.

In conclusion, bempedoic acid represents the newest opportunity to manage dyslipidemia with a good safety profile. The fixed-dose combination with ezetimibe, together with the possibility to modulate statin doses, represents a new combination therapy for treating the majority of hypercholesterolemic patients. While the side-effects reported in clinical trials may be easily managed, cholelithiasis represents a potential issue for the therapy with bempedoic acid. Although this side effect has been observed exclusively in the CLEAR

Outcomes study and must be confirmed in wider real life observational studies, a molecular explanation can be provided also envisioning a possible protective effect by statins.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.