Editorial

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Exploring new treatment paradigms for alcoholic hepatitis by extrapolating from NASH and cholestasis☆

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Alcoholic hepatitis (AH) is the most severe form of alcoholic liver disease with a 30-day mortality rate of up to 30%.[1] Corticosteroids are currently the only effective therapy, but provide only a short-term survival benefit at best.[2] Therefore, there is an urgent need to identify novel therapeutic targets for this lethal condition. Important pathways that have been the focus of treatment investigations include: i) bacterial and endotoxin translocation through disrupted gut barrier function (*e.g.* anti-lipopolysaccharides antibody, probiotics, and zinc); ii) hepatocellular apoptosis, necrosis, and injury (*e.g.* caspase inhibitor, and IL-22); iii) innate immune system activation in the liver (*e.g.* IL-1 receptor antagonist).[3,4]

Recently, the bile acid pathway has become a major target for the treatment of primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH).[5] Bile acids activate farnesoid X receptor (FXR) in the ileum and liver, leading to the production of fibroblast growth factor 19 (FGF19). FGF19 is an endocrine gastrointestinal hormone that suppresses the hepatocyte expression of CYP7A1, a rate-limiting enzyme in the synthesis of bile acids (Fig. 1), thereby creating a negative feedback loop. Obeticholic acid (OCA), a semi-synthetic derivative of the chenodeoxycholic acid, has shown the most promising results in the treatment of NASH and PBC. OCA is an FXR agonist that protects hepatocytes against bile acid toxicity by inhibiting the synthesis of bile acids and upregulating bile acid transporters. In preclinical studies, OCA also improved steatosis, fibrosis and portal hypertension.[6] In the POISE trial, OCA was effective in reducing alkaline phosphatase, gamma-glutamyl transferase and aminotransferase levels in patients with PBC.[7] In the FLINT trial, OCA improved non-alcoholic fatty liver disease activity score (NAS) and alanine aminotransferase in patients with NASH.[8] Another therapeutic agent in the pipeline is NGM282, an FGF19 analogue. NGM282 can reduce liver fat content in patients with NASH[9] and a clinical trial of NGM282 in PBC is ongoing (NCT02135536). Following the positive findings in NASH and PBC and because cholestasis is a sentinel finding in AH, it is interesting to speculate whether bile acid pathway targets such as FXR agonist and FGF19 analogue could have beneficial effects in AH.

In the article by Brandl *et al.*, the authors evaluated the relationship between bile acids, FGF19 and clinical outcomes in patients with AH compared to patients with alcohol use disorder and controls without known liver disease. The important findings were: i) total serum and conjugated bile acid levels were higher in AH compared to controls and correlated with FGF19 levels and AH severity (measured by model for end-stage liver disease [MELD] score); ii) FGF19 levels were increased and C4 levels (7-hydroxy-4-cholesten-3-one, a marker of *de novo* bile acid synthesis) were decreased in AH, suggesting that the negative feedback loop in the synthesis of bile acids was intact but not effective in lowering serum bile acid levels; iii) Liver tissue of patients with AH demonstrated an increase in *FGF19* mRNA expression and stained positive for FGF19, suggesting the liver was a site of FGF19 production. Despite these novel findings, the authors did not demonstrate a correlation between FGF19 levels and survival in AH (although in the subgroup with very severe AH (MELD >30), FGF19 levels correlated modestly with 30-day survival).

Although this study provides insights on the interaction of bile acids and FGF19 in patients with AH, many questions still remain. First, it is unclear whether FGF19 has a protective effect on AH or it simply represents a marker of severity. FGF19 levels were 100 times greater in patients with AH compared to those with NASH or PBC.[7,10] Furthermore, when compared to healthy controls, patients with NASH had decreased FGF19 and increased C4 levels while patients with AH had increased FGF19 and decreased C4.[11,12] Thus, it is not clear whether further increments in FGF19 levels with FXR agonists or FGF19 analogues will be beneficial in AH. Second, the main source of FGF19 in patients with AH is still unknown. While an increase in hepatic FGF19 expression was observed in this study, the expression of FGF19 in the ileum was not assessed.

It is worth noting that there is a safety concern regarding the use of OCA. There were 19 deaths reported in patients receiving OCA over a period of 13 months. This was thought to be caused by incorrect dosing in the setting of hepatic impairment. As a consequence, the FDA has issued a black box warning for PBC patients with Child B or C or patients with prior hepatic decompensation to take OCA once weekly rather than the standard once a day dosing recommended for PBC patients with normal liver function.[13] Moreover, the side effects of OCA include pruritus,[7] elevations of total cholesterol and low-density

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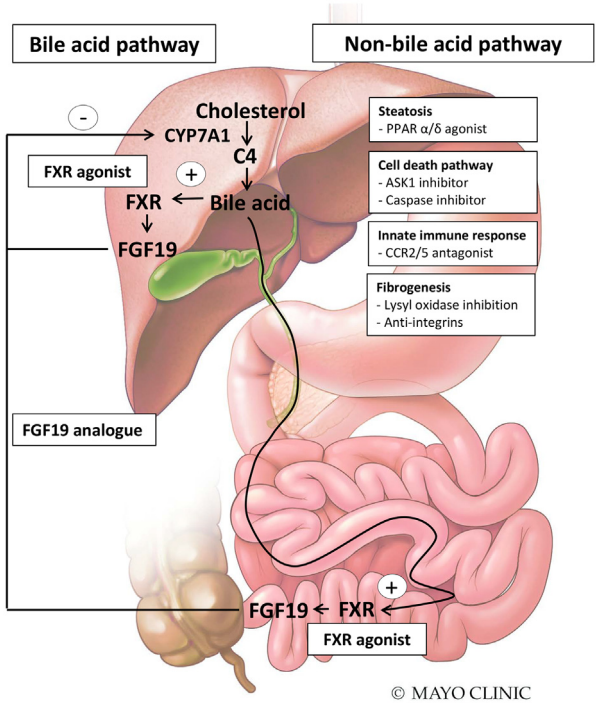

Fig. 1. Bile acid and non-bile acid treatment targets of non-alcoholic hepatitis and cholestasis that can be opportunities in alcoholic hepatitis. ASK1, apoptosis signal-regulating kinase 1, C4, 7α-Hydroxy-4-cholesten-3-one, CCR2/5, C-C chemokine receptor type 2/5, FGF, fibroblast growth factor, FXR, farnesoid X receptor, PPAR, peroxisome proliferator-activated receptor.

cholesterol, and lower levels of high-density cholesterol.[7–9] FGF19 may also advance the growth of hepatocellular carcinoma.[14] Newer agents, *e.g.* NGM282 (non-tumorigenic variant of FGF19 analogue) and tropifexor (non-bile acid compound FXR agonist) are being evaluated and it remains to be seen whether the newer compounds will have better safety profiles than OCA.

Current clinical trial activity in NASH dwarfs that of AH (149 clinical trials for NASH *vs.* 21 for AH/ASH-clinicaltrials.gov). Given the shared histological features of AH and NASH, bile acid independent targets investigated in NASH could be tested in AH.[15] For example, eleafibranor (GFT-505, peroxisome proliferator-activated receptor α/δ agonist) was found to reduce NAS score in patients with NAS score ≥4 in a *post hoc* analysis of phase II clinical trials.[16] Selonsertib (GS-4997, apoptosis signal-regulating kinase 1 inhibitor) and Cenicriviroc (c-c chemokine receptor type 2 and 5 antagonist) were shown to reduce liver fibrosis in patients with NASH in phase II clinical trials.[17,18] Emricasan (IDN-6556, caspase inhibitor) is being tested in NASH (NCT02686762) although the trial in AH was terminated early because of potentially toxic drug levels in patients with severe hepatic impairment. Clearly, more resources are needed in AH research given the higher all-cause mortality compared to NASH.[19] Because moderate AH (generally considered by expert opinion as MELD score 11–20) shares greater similarities with NASH than severe AH, it may be the best initial target for some of these non-bile acid pathway therapies currently being investigated in NASH (Fig. 1).

In conclusion, the bile acid pathway offers promising novel therapeutic targets for AH. Given the positive results in PBC and NASH, the results of the phase II clinical trial (NCT02039219) evaluating OCA in moderately severe AH are awaited with great expectation. Unfortunately, this study is currently on hold because of ongoing safety concerns as mentioned above. In addition to the bile acid pathway, there are many other potential targets (*e.g.* elafibranor, selonsertib and cenicriviroc *etc.*) being investigated in NASH that could also be tested in AH. Given the histopathological similarities between the two entities and the large clinical trial activity in the NASH space, hopefully effective treatments for AH will soon follow.

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Conflict of interest

VS reports personal fees from Novartis Pharmaceuticals, Durect Corporation, Merck Research Laboratories, Afimmune Ltd., outside the submitted work. The other authors have no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.05.012.

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Author names in bold designate shared co-first authorship

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