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Review article: therapeutic aspects of bile acid signalling in the gut-liver axis

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Summary

Background: Bile acids are important endocrine modulators of intestinal and hepatic signalling cascades orchestrating critical pathophysiological processes in various liver diseases. Increasing knowledge on bile acid signalling has stimulated the development of synthetic ligands of nuclear bile acid receptors and other bile acid analogues.

Aim: This review summarises important aspects of bile acid-mediated crosstalk between the gut and the liver ("gut-liver axis") as well as recent findings from experimental and clinical studies.

Methods: We performed a literature review on bile acid signalling, and therapeutic applications in chronic liver disease.

Results: Intestinal and hepatic bile acid signalling pathways maintain bile acid homeostasis. Perturbations of bile acid-mediated gut-liver crosstalk dysregulate transcriptional networks involved in inflammation, fibrosis and endothelial dysfunction. Bile acids induce enterohepatic feedback signalling by the release of intestinal hormones, and regulate enterohepatic circulation. Importantly, bile acid signalling plays a central role in maintaining intestinal barrier integrity and antibacterial defense, which is particularly relevant in cirrhosis, where bacterial translocation has a profound impact on disease progression. The nuclear bile acid farnesoid X receptor (FXR) is a central intersection in bile acid signalling and has emerged as a relevant therapeutic target.

Conclusions: Experimental evidence suggests that bile acid signalling improves the intestinal barrier and protects against bacterial translocation in cirrhosis. FXR agonists have displayed efficacy for the treatment of cholestatic and metabolic liver disease in randomised controlled clinical trials. However, similar effects remain to be shown in advanced liver disease, particularly in patients with decompensated cirrhosis.

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1 | INTRODUCTION

Bile acids (BAs) modulate numerous signalling cascades in the intestine and the liver that are vital for the maintenance of BA homeostasis, enterohepatic circulation, metabolism and intestinal barrier integrity. Dysregulation of BA signalling becomes particularly relevant in chronic liver diseases, as perturbations of BA-mediated gut-liver crosstalk may affect transcriptional networks involved in inflammation, fibrosis, endothelial dysfunction and ultimately affect disease progression. The physiological interactions between the gut and liver include (a) the uptake and metabolism of nutrients and BAs, (b) endocrine signalling between gut and the liver, and (c) the hepatic immune response to gut-derived (inflammatory) signals and pathogens and are commonly subsumed by the term "gut-liver axis." In this review, we summarise how BA signalling in the gut-liver axis affects BA synthesis and enterohepatic circulation, intestinal barrier integrity and bacterial translocation, the relevance of BA signalling in (advanced) chronic liver disease and discuss emerging therapeutic strategies.

2 | REVIEW CRITERIA

Literature research was conducted on PubMed, considering relevant papers on BA signalling without publication date restrictions. For well-established concepts and general knowledge on BA physiology, review articles from peer-reviewed high-impact journals were cited. Regarding experimental studies, we focused on publications investigating the molecular mechanisms of BA signalling, as well as therapeutic interventions targeting the gut-liver axis, specifically considering animal liver disease models. Regarding clinical studies, we prioritised randomised clinical trials (RCTs) and interventional studies using bile acid analogues or synthetic ligands of nuclear BA receptors registered at "ClinicalTrials.gov." Peer-reviewed publications in English and recently published abstracts from RCTs were taken into consideration. This review is not designed as a systematic review.

3 | BILE ACIDS AND TARGET RECEPTORS

3.1 | Bile acid species, chemical features and synthesis

BAs are produced from cholesterol in the liver and mediate the resorption of dietary lipids and fat-soluble vitamins.[1] BAs are classified by certain biochemical characteristics that determine their physiological activity. First, BAs are categorised as primary BAs (BAs synthesised by the liver) or secondary BAs (primary BAs chemically modified by gut bacteria).[2] The primary BA pool in humans essentially consists of cholic acid (CA) and chenodeoxycholic acid (CDCA), accounting for approximately 70%–80% of the total BA pool, while the secondary BA pool comprises lithocholic acid (LCA), deoxycholic acid (DCA) and ursodeoxycholic acid (UDCA).[2] Second, BAs are differentiated as unconjugated and conjugated BA (bound to taurine or glycine).[1,3] Third, BA subtypes exhibit different degrees of hydrophobicity, which is determined by hydroxyl groups and the stereochemistry of BAs.[4] The BA pool displays considerable plasticity which may impact digestive function, nuclear receptor binding, bile fluid solubility, and BA-associated toxicity[4] and significantly shifts between healthy individuals and patients with liver diseases.[5,6]

De-novo BA synthesis by hepatocytes follows either the classical ("neutral") or the alternative ("acidic") biosynthetic pathway, summarised in Figure 1. In the classical pathway, cholesterol is modified by the cholesterol 7α-hydroxylase (encoded by the *CYP7A1* gene).[7] Further metabolisation by *CYP8B1* leads to the formation of CA or, alternatively, modification by *CYP27A1* produces CDCA.[7,8] The expression of *CYP7A1* is considered the rate-limiting enzymatic step for overall BA synthesis,[9] while the expression of *CYP8B1* defines the BA pool as the synthesis of CA is contingent on *CYP8B1*.[10] The paradigm that the alternative pathway exclusively results in the synthesis of CDCA[7] was recently challenged since the knockout of *CYP7A1* in mice resulted in a shift towards the alternative pathway while CA was still synthesised,[11] potentially explained by a subsequent study reporting that human *CYP8B1* (expressed by cultured yeast cells) is able to convert CDCA to CA.[12]

3.2 | Bile acid transporters and enterohepatic circulation

The majority of BAs undergoes efficient "recycling" by enterohepatic circulation, which is characterised by the intestinal re-uptake of BAs (predominantly in the ileum), delivery to the liver *via* the portal venous system, uptake in the liver and, again, secretion into the bile canaliculi (Figure 2). Hence, only about 5% of circulating BAs is lost in the faeces.[13] Efficacious transport mechanisms are important for enterohepatic circulation, since only a few (primarily unconjugated) BA are absorbed passively in the gut and the liver, whereas intestinal absorption and hepatic uptake of most BA relies on active transport across cell membranes.[14] More specifically, enterohepatic circulation of BA in the gut-liver axis is mainly contingent on four transporters with specific expression patterns and location at the cellular membranes of intestinal epithelial cells and/or hepatocytes (summarised in Figure 3): The apical sodium-dependent bile acid transporter (ASBT, *SLC10A2*), organic solute transporter-α and -β (OST-α, *SLC51A*; OST-β, *SLC51B*), Na^+-taurocholate cotransporting polypeptide (NTCP, *SLC10A1*) and the bile salt export pump (BSEP; *ABCB11*).[15]

3.3 | Farnesoid X receptor

Farnesoid X receptor (FXR) belongs to the family of nuclear hormone receptors (NHR; ie, receptors exerting transcription factor activity upon modulation by ligands) and is a nuclear receptor for BAs.[16,17]

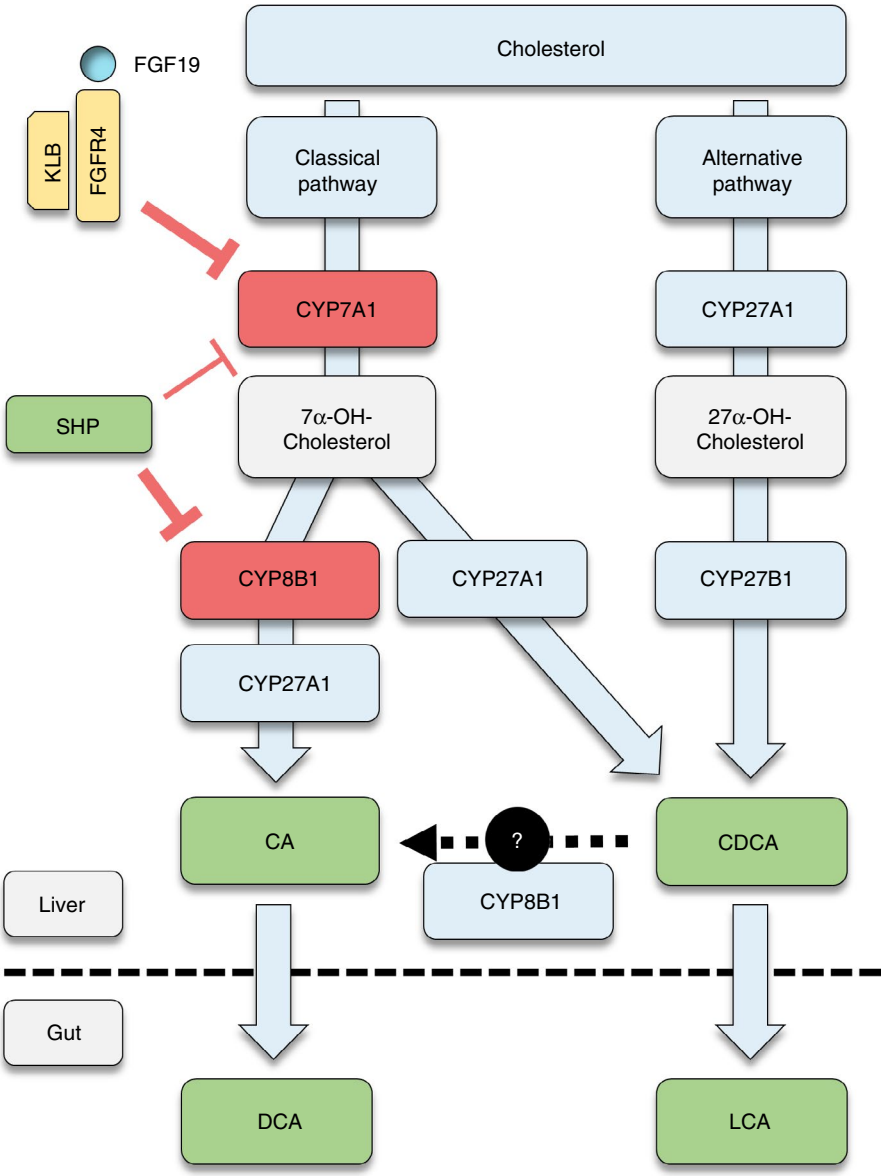

FIGURE 1 Regulatory pathways of bile acid synthesis. Primary bile acids (BA) are synthesised from cholesterol in hepatocytes, following either the "classical" or the "alternative" pathway. In the classical pathway, cholesterol is first modified by CYP7A1 and subsequently by CYP8B1 to produce cholic acid (CA) or, alternatively by CYP27A1 to produce chenodeoxycholic acid (CDCA). In the alternative pathway, CYP27A1 initiates cholesterol modification, followed by CYP7B1-dependent biotransformation, resulting in formation of CDCA. Expression of CYP7A1 is the rate-limiting enzymatic step for BA synthesis, while CYP8B1 defines the BA pool as it is critical for production of CA. Metabolisation of BAs by gut bacteria leads to the formation of the secondary BAs deoxycholic acid (DCA) and lithocholic acid (LCA). BA synthesis is mainly regulated by two mechanisms: First, intrahepatic farnesoid X receptor (FXR) activation induces the expression of small heterodimer partner (SHP), which suppresses the expression of CYP8B1 and (to a lesser extent) CYP7A1. Second, activation of FXR in the intestines induces the release of fibroblast growth factor-19 (FGF19) into the portal venous system. FGF19 binds to the FGF receptor 4 (FGFR4) and its co-receptor beta-Klotho (KLB) on hepatocytes, thereby strongly suppressing CYP7A1 expression. Abbreviations: BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; FGF19, fibroblast growth factor-19; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; KLB, beta-Klotho; LCA, lithocholic acid; SHP, small heterodimer partner

Upon activation by ligands, FXR binds to target promoter regions in heterodimerisation with retinoid X receptor-alpha;[18,19] however, FXR can also modulate gene transcription in monomeric conformation.[20] FXR signalling regulates numerous downstream signalling cascades, for example, transcriptional networks involving peroxisome proliferator-activated receptors (PPAR).[21] Expression mapping of nuclear receptors in mice revealed that FXR is predominantly expressed in the liver, intestines, and kidney.[22] Along the different sections of the gastrointestinal tract of mice, FXR displays the highest expression in the ileum.[22,23] In the mouse liver, FXR is most abundantly expressed by hepatocytes, and to considerably lower extent in liver sinusoidal endothelial cells (LSEC) and Kupffer cells,[24] whereas hepatic stellate cells (HSC) reportedly do not express FXR.[25] Several synthetic FXR agonists were developed in recent years. These

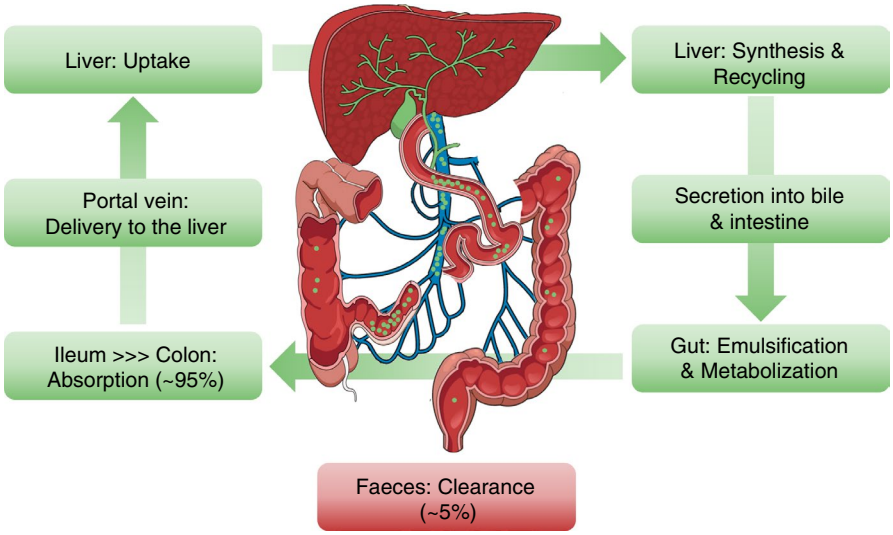

FIGURE 2 Enterohepatic circulation of bile acids: anatomical overview. Primary bile acids (BA; indicated as green dots) are released into bile canaliculi and secreted into the duodenum, where they mediate absorption of nutrients, for example emulsification of lipids and fat-soluble vitamins, and regulate signalling pathways in the gut-liver axis. Metabolisation of BA by gut bacteria leads to the formation of secondary BAs. Most BAs undergo enterohepatic circulation: the highest proportion of BAs is reabsorbed in the ileum, transported into the portal circulation, and delivered back to the liver *via* the portal vein. After reuptake in hepatocytes, BAs are recycled and secreted into the bile, and again reach the gut, thus completing the enterohepatic cycle. Abbreviation: BA, bile acid

compounds may be differentiated as steroidal *vs* non-steroidal FXR agonists, the latter being characterised by improved pharmacokinetics and side effect profile. Detailed biochemical and pharmacological features of FXR agonists were recently reviewed.[26,27]

3.4 | Takeda G protein-coupled receptor-5

Takeda G protein-coupled receptor-5 (TGR5; encoded by *GPBAR1*) is an epithelial receptor for BAs, which marks an important difference to nuclear BA receptors.[28,29] Similar to NHRs, TGR5 modulates downstream transcriptional activity, for example, *via* the intracellular protein kinase A,[29,30] protein kinase B,[31] extracellular signal-related kinase 1/2,[32] or Rho kinase[33] signalling pathways. Expression of TGR5 varies across different anatomical compartments and displays high expression in gallbladder epithelium[34,35] and the intestine (particularly ileum and colon), while exhibiting lower expression in the liver.[28,36] TGR5 is also expressed in other organs such as skeletal muscle and brown adipose tissue.[29,30,34,37] Again, these expression profiles are mostly deduced from animal tissues. In the liver, TGR5 is expressed by cholangiocytes,[32,35] Kupffer cells,[38] LSEC[39] and, against earlier assumptions, also in hepatocytes.[40,41]

3.5 | Other nuclear bile acid receptors

BAs also interact with the vitamin D receptor (VDR; *NR1I1*), pregnane X receptor (PXR; *NR1I2*) and constitutive androstane receptor (CAR; *NR1I3*).[42] While these receptors have been ascribed some modulatory effects on BA homeostasis and metabolism, experimental and clinical data on drug development or therapeutic effects directly mediated by these receptors is scarce.[43,44] Therefore, this review rather concentrates on BA signalling effects mediated by FXR and TGR5, since these receptors have been studied extensively in experimental and clinical settings.

4 | FEEDBACK REGULATION OF BILE ACID SYNTHESIS AND ENTEROHEPATIC CIRCULATION

4.1 | Gut-liver signalling modulates bile acid synthesis

Regulation of BA synthesis marks an important inhibitory feedback mechanism that is tightly controlled by intestinal and hepatic BA signalling pathways. These regulatory cascades ensure BA homeostasis and protection from cytotoxicity occurring in supraphysiological concentrations.[45,46]

First, intrahepatic FXR activation by BAs induces the expression of a small heterodimer partner (SHP; *NR0B2*) (Figures 1, 3).[47] SHP forms heterodimers with nuclear receptors, while not being able to bind DNA, resulting in transrepression of transcription factors.[48] Concordantly, SHP upregulation results in the downregulation of *CYP7A1* and *CYP8B1* gene expression.[47,49,50] Nevertheless, studies in mice suggest that the "intrahepatic" FXR-SHP feedback pathway mostly regulates *CYP8B1* (ie, BA pool composition) and has relatively small impact on the expression of *CYP7A1* (ie, BA pool size).[51,52]

Second, hepatic BA synthesis is regulated by an "enterohepatic" signalling pathway *via* fibroblast growth factor-19 (FGF19). The term "FGF19" will be used consistently in this review to denote both human FGF19 and its murine equivalent FGF15 (when referring to

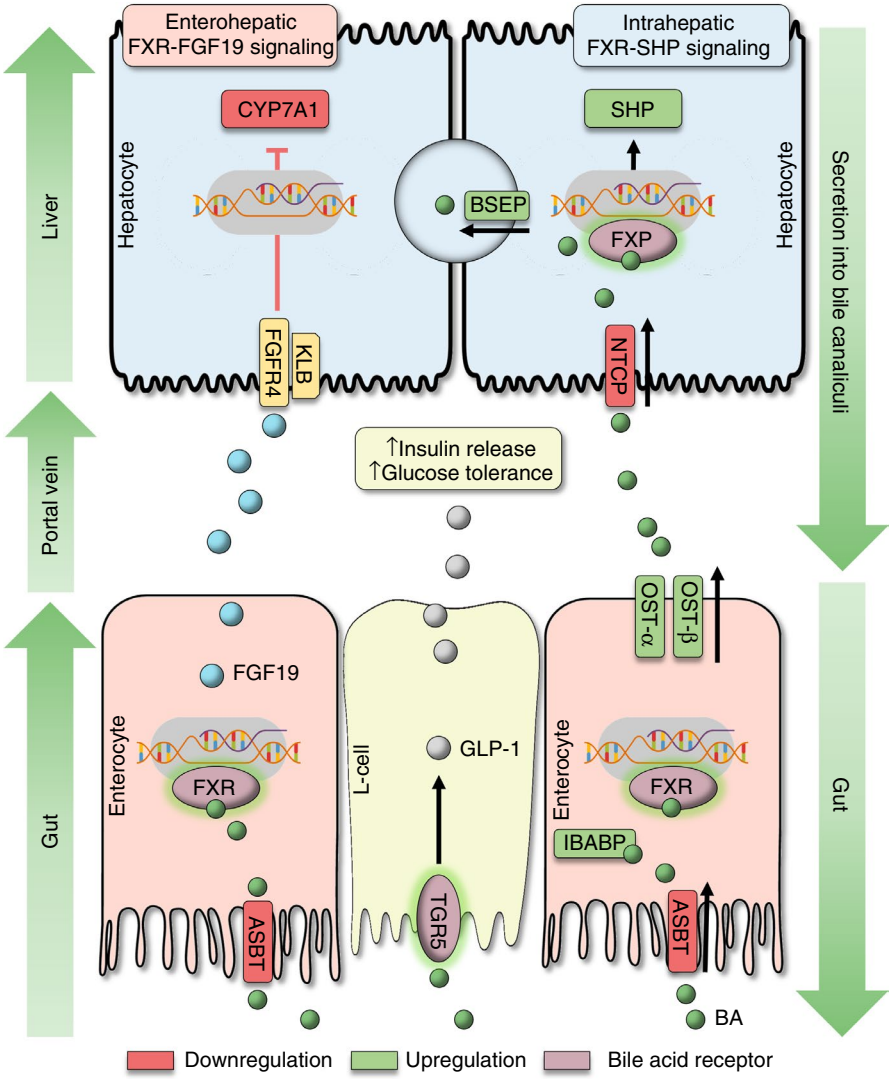

FIGURE 3 Bile acid gut-liver axis signalling modulates the enterohepatic circulation, bile acid synthesis and glucose homeostasis. (i) Enterohepatic circulation of bile acids (BA) is contingent on four important transporters in the gut-liver axis: ASBT, OST-α/-β, NTCP and BSEP. ASBT mediates BA uptake from the intestinal lumen (primarily ileum), whereas OST-α/-β releases BAs into the portal circulation. Ileal bile acid binding protein (IBABP) binds intracellular BAs and protects enterocytes from BA toxicity. NTCP facilitates BA uptake from sinusoidal blood into hepatocytes, and BSEP mediates BA secretion into bile canaliculi. Activation of FXR downregulates ASBT and NTCP and upregulates OST-α/-β, BSEP and IBABP (indicated in red and green color). (ii) Bile acid synthesis is regulated by the enterohepatic FXR-FGF19 pathway, and the intrahepatic FXR-SHP pathway. Activation of FXR in the intestines (primarily in the ileum) leads to release of FGF19 into the portal circulation, which represses BA synthesis (*CYP7A1* gene) by binding to FGFR4/KLB ('enterohepatic' feedback signalling). Activation of FXR in hepatocytes induces expression of SHP, which acts as a transrepressor of genes for BA synthesis ("intrahepatic" feedback signalling). (iii) Activation of TGR5 on intestinal L-cells induces release of GLP-1, which induces insulin secretion and enhances glucose tolerance. Abbreviations: (ASBT) apical sodium dependent bile acid transporter; (BA) bile acids; (BSEP) bile salt export pump; (FXR) farnesoid X receptor; (FGF19) fibroblast growth factor 19; (FGFR4) FGF receptor 4; (GLP-1) glucagon-like peptide-1; (IBABP) ileal bile acid binding protein; (KLB) beta-klotho; (NTCP) sodium/taurocholate cotransporting polypeptide; (OST-α/-β) organic solute transporter alpha and beta; (SHP) small heterodimer partner; (TGR5) transmembrane G protein-coupled receptor-5

animal studies). Activation of FXR in the intestines induces the expression of FGF19 (primarily in the ileum), which is subsequently released into the portal venous system.[53] FGF19 strongly suppresses *CYP7A1* expression in hepatocytes by interaction with the FGF receptor 4 (FGFR4; *FGFR4*)[53,54] and its co-receptor beta-Klotho (KLB; *KLB*)[55-57] (Figures 1, 3). Of note, FGF19-mediated downregulation of BA synthesis may act through a signalling cascade that is independent from SHP,[58] as Src-mediated signalling cascades activate both SHP-dependent and -independent mechanisms to suppress BA synthesis.[59,60]

Although these two feedback mechanisms are widely accepted, some important aspects should be considered: For example, while Inagaki et al reported no detectable induction of FGF19 in mouse liver tissue upon FXR activation,[53] other studies demonstrated FXR-dependent upregulation of FGF19 in primary human hepatocytes[58] and expression of FGF19 in liver tissue of patients with biliary

atresia[61] and primary biliary cholangitis (PBC),[62] suggesting that humans also display intrahepatic auto-/paracrine FGF19 feedback signalling. Furthermore, intestinal FGF19 release in mice is also stimulated by serum BAs (basolateral side), indicating that enterohepatic FXR-FGF19 feedback may not exclusively rely on BAs absorbed from the intestinal lumen (apical side).[63]

Interestingly, human liver cell lines displayed a continuous time-dependent downregulation of KLB upon persistent exposure to FGF19,[64] while activation of FXR led to upregulation of KLB in mice,[65] suggesting that the FGF19-FGFR4/KLB signalling cascade is subject to autoregulation by FXR and circulating FGF19. Studies in humans with liver disease put these experimental findings into clinical context: Byun et al reported downregulation of KLB, Src and FXR, as well as upregulation of FGFR4 in liver tissue of patients with PBC as compared to healthy liver tissue,[59] while Wunsch et al demonstrated that serum FGF19 levels and hepatic FGF19 expression positively correlated with disease severity in patients with PBC.[62] Moreover, patients with primary sclerosing cholangitis (PSC) exhibited increased hepatic FGF19 and FGFR4 gene and/or protein expression as compared to healthy liver tissue, while *CYP7A1* (paradoxically) was not repressed.[66] These observations indicate that the enterohepatic BA feedback mechanism may be impaired in certain pathological conditions, particularly in advanced disease stages.

Conclusively, modulation of the FXR-FGF19 axis emerged as therapeutic target, backed by experimental studies reporting that intestinal activation of FXR in mice with cholestasis ameliorates liver damage associated with BA toxicity,[67] and that overexpression of FGF19 mitigates alcohol-induced liver injury in mice,[68] and has already led to application in humans with different aetiologies of chronic liver disease. Clinical trials investigating the use of FXR agonists and FGF19 analogues are discussed below.

4.2 | FXR signalling determines the enterohepatic circulation of bile acids

The enterohepatic circulation of BAs and, more specifically, BA transporter expression is subject to feedback regulation. These transporters enable the circulation of BAs and determine the BA pool size by regulation of secretion and reuptake and are recognised as important cornerstones of BA homeostasis but also as potential therapeutic targets.[15]

First, experimental studies in cell culture demonstrated that ASBT is downregulated by BA-induced activation of the FXR-SHP pathway (Figure 3).[69,70] Interestingly, FGF19 also downregulated expression of ASBT in a colon cancer cell line and in the intestines of mice *via* FGFR4-mediated signalling.[71] Inhibition of ASBT ameliorated liver injury and downregulated the expression of proinflammatory and profibrogenic genes related to BA toxicity in a mouse model of chronic cholestasis (ie, *Mdr2*-knockout).[72,73]

Second, OST-α and OST-β expression is upregulated upon FXR activation, as demonstrated in human liver cell lines in vitro,[74,75] human ileum ex vivo,[74] as well as in the small intestine and kidney of mice in vivo.[76] OST-α/OST-β are present on the basolateral membrane of enterocytes and protect enterocytes from BA toxicity (Figure 3).[77] Induction of these transporters at the basolateral membrane of hepatocytes may provide an alternative efflux route under cholestatic conditions.[78] Both OST-α/OST-β exhibited low expression in healthy liver tissue of mice and humans, and were significantly upregulated (OST-β»OST-α) in bile-duct ligated (BDL; ie, animal model for cholestasis) rats and mice as well as patients with PBC and non-alcoholic steatohepatitis (NASH).[79,80] Hence, the upregulation of OST-α/OST-β in the liver might serve as a basolateral "pressure relieve valve" for supraphysiological intracellular BA concentrations. However, the induction of OST-α/OST-β alone will not eliminate BAs definitively, unless this adaptive response is accompanied by induction of metabolizing enzymes and transporters that will facilitate final elimination of BAs from the hepatocytes and the systemic circulation. The effects of PPAR-α signalling and fibrates on the synthesis, metabolisation and excretion of BAs (in addition to FXR agonists) may therefore hold interesting perspectives for the future, as discussed recently in the context of PBC.[81]

Third, FXR-induced upregulation of SHP represses the expression of NTCP in hepatocytes in vitro,[82] which was confirmed in vivo using BDL rats and mice, indicating that this regulatory mechanism protects hepatocytes from BA toxicity (Figure 3).[83-86] Interestingly, a recent in vitro study suggested that endoplasmic reticulum stress may also downregulate NTCP independently from FXR,[87] which may be relevant apart from "primary" cholestatic liver diseases such as PBC,[88] since NTCP was also downregulated in mice fed with ethanol,[89] a rat model of non-alcoholic fatty liver disease (NAFLD),[90] and patients with alcohol(ALD)- and hepatitis C virus-associated cirrhosis, as compared to healthy liver tissue.[91,92] NTCP has emerged as an important therapeutic target since it was identified as an entry point for the hepatitis B (HBV) and D (HDV) virus.[93] Myrcludex B (bulevirtide), a selective inhibitor of NTCP, has emerged as a novel therapy for HBV/HDV and is already in clinical use,[94] but also displayed hepatoprotective effects in cholestatic mouse models.[95]

Finally, studies in cell culture and FXR knockout mice showed that FXR activation induces BSEP expression (Figure 3).[96-98] BSEP is the rate-limiting transporter for BA secretion into bile canaliculi and holds an important role in the enterohepatic cycle, as evident from genetic BSEP deficiencies causing cholestasis in humans.[15,99] However, it seems less clear whether BSEP expression is different in liver diseases: Expression and function of BSEP were preserved in rats after BDL,[100] and no significant differences of BSEP gene expression were found in (non-cirrhotic) patients with PBC or hepatitis C,[101] as well as BSEP protein expression in advanced PBC,[88] as compared to healthy liver tissue. Conversely, patients with NAFLD exhibited downregulation of BSEP on liver histology paralleled by increasing disease activity.[102] Of note, BSEP knockout mice exhibited a milder phenotype compared to humans with BSEP deficiency, which is probably related to species-dependent compensatory mechanisms,[103,104] indicating the need for further studies in humans.

4.3 | Metabolic gut-liver axis signalling by glucagon-like peptide 1

BA signalling regulates multitudinous pathways involved in the homeostasis of cholesterol, lipid and glucose metabolism.[105] To this end, the discovery of TGR5-mediated glucagon-like peptide-1 (GLP-1) signalling marks an important example of BA signalling in the gut-liver axis. Katsuma et al were among the first researchers to describe that the activation of TGR5 in intestinal enteroendocrine cells (L-cells) induces the release of GLP-1 (Figure 3).[106] The delivery of GLP-1 to the liver and pancreas induced insulin secretion and ameliorated glucose tolerance in obese mice, which was also achieved by administration of the synthetic TGR5 agonist INT-777.[107] Interestingly, a similar effect was achieved by the ASBT inhibitor 264W94 in rats and the BA sequestrant colesevelam in mice, presumably related to the increased luminal availability of BAs and high expression of TGR5 in the colon.[108,109] Naturally, these findings were considered as therapeutic options in diabetes and NAFLD (as discussed below).

5 | INTESTINAL BARRIER AND BACTERIAL TRANSLOCATION

Next to the transport of nutrients, maintenance of BA homeostasis and metabolism, recent research efforts have shaped the understanding that the intestines and the liver strongly interact on an immunological level, which represents an important dimension of the gut-liver axis.[110] This crosstalk is determined by intestinal barrier integrity and the translocation of gut bacteria and pathogen-associated molecular patterns (PAMPs)—subsumed by the term "bacterial translocation"—that circulate to the liver *via* the portal venous system and trigger pro-inflammatory and profibrotic responses (Figure 4).[111]

5.1 | Pathophysiological impact and clinical relevance of bacterial translocation

Advanced chronic liver disease (ACLD), a disease spectrum characterised by advanced liver fibrosis/cirrhosis and portal hypertension, marks one of the most important clinical examples where the concept of the bacterial translocation-induced hepatic and systemic inflammatory response has been attributed a disease-modifying role (Figure 4).[112] In-depth reviews on the microbiome and gut-liver immunology have been published recently[113-115] and are not the focus of this review.

The paradigm of increased bacterial translocation in ACLD is supported by the observation that patients with ACLD are more prone to develop infections as compared to the general population,[116] and the associated increased mortality risk.[117] Importantly, while systemic inflammation is a common feature of distinct syndromes such as acute hepatic decompensation and acute-on-chronic liver failure,[118] systemic inflammation also progresses in clinically stable patients across higher ACLD disease stages without evidence of infection and predicts liver-related complications and/or mortality.[119] The concept of bacterial translocation has led to the rationale that antibiotic prophylaxis may reduce intestinal bacterial overgrowth and, thus, diminish the hepatic and systemic exposure to bacterial translocation and protect against its detrimental impact on ACLD.[112] RCTs reported that antibiotic prophylaxis may reduce mortality in patients with ACLD, however, indicated that only certain patient subgroups benefit from this treatment.[120,121] Nevertheless, the long-term prophylactic use of antibiotics is highly controversial (eg, antibiotic resistance), suggesting that other therapeutic strategies targeting the intestinal barrier and bacterial translocation are warranted.

From a pathophysiological point of view, the recognition of bacteria or PAMPs from the portal circulation by toll-like receptors (TLR; ie, receptors of the innate immune system that recognise bacterial antigens) in the liver induces an immune response. This process is accompanied by activation of KCs (and other immune cells) and HSCs, leading to an increase of inflammation and extracellular matrix deposition ("fibrogenesis") (Figure 4).[122] Concordantly, administration of lipopolysaccharide (LPS) activates TLR-4 and induces hepatic fibrogenesis *via* transforming growth factor-beta signalling in mice.[123] Furthermore, LPS dysregulates endothelial and inducible NO synthase (eNOS/iNOS) activity in LSECs in cell culture and rats,[124-126] implicating that bacterial translocation impairs the regulation of the intrahepatic vascular tone by LSECs. These effects likely aggravate portal hypertension, as supported by a study demonstrating that beta glucan-induced activation of KCs resulted in vasoconstrictor release and increased portal pressure in rats.[127]

From a clinical point of view, these mechanisms are highly relevant targets since fibrosis and portal hypertension are central drivers of disease progression in ACLD.[128] FXR agonists displayed promising effects to ameliorate fibrosis and portal hypertension in experimental studies: The FXR agonist obeticholic acid (OCA; formerly INT-747) reduced HSC activation and liver fibrosis in rats with thioacetamide(TAA)-induced cirrhosis.[129] This effect was linked to the inhibition of LSEC and Kupffer cell activation by LPS and tumor necrosis factor-alpha in cell culture.[129] Moreover, OCA improved portal hypertension in rats with BDL- and TAA-induced cirrhosis, which was related to elevated intrahepatic eNOS activity.[130] Concordantly, the non-steroidal FXR agonist PX20606 (a precursor substance to cilofexor) reduced portal hypertension in rats with CCl_4-induced cirrhosis by amelioration of liver fibrosis and sinusoidal dysfunction,[131] and similar beneficial effects on portal hypertension and fibrosis were demonstrated with the non-steroidal FXR agonist cilofexor in a rat model of NASH.[132] Of note, experimental studies suggested that PPAR-α and PPAR-γ, which are closely linked to FXR signalling, are essential intersections for the induction of hepatic and systemic inflammation, endothelial dysfunction, or HSC activation.[133-136] Intriguingly, the therapeutic effects of FXR agonists—particularly in cirrhosis and portal hypertension—may be connected to the amelioration of bacterial translocation, which underlines the significance of BA signalling in the gut-liver axis.

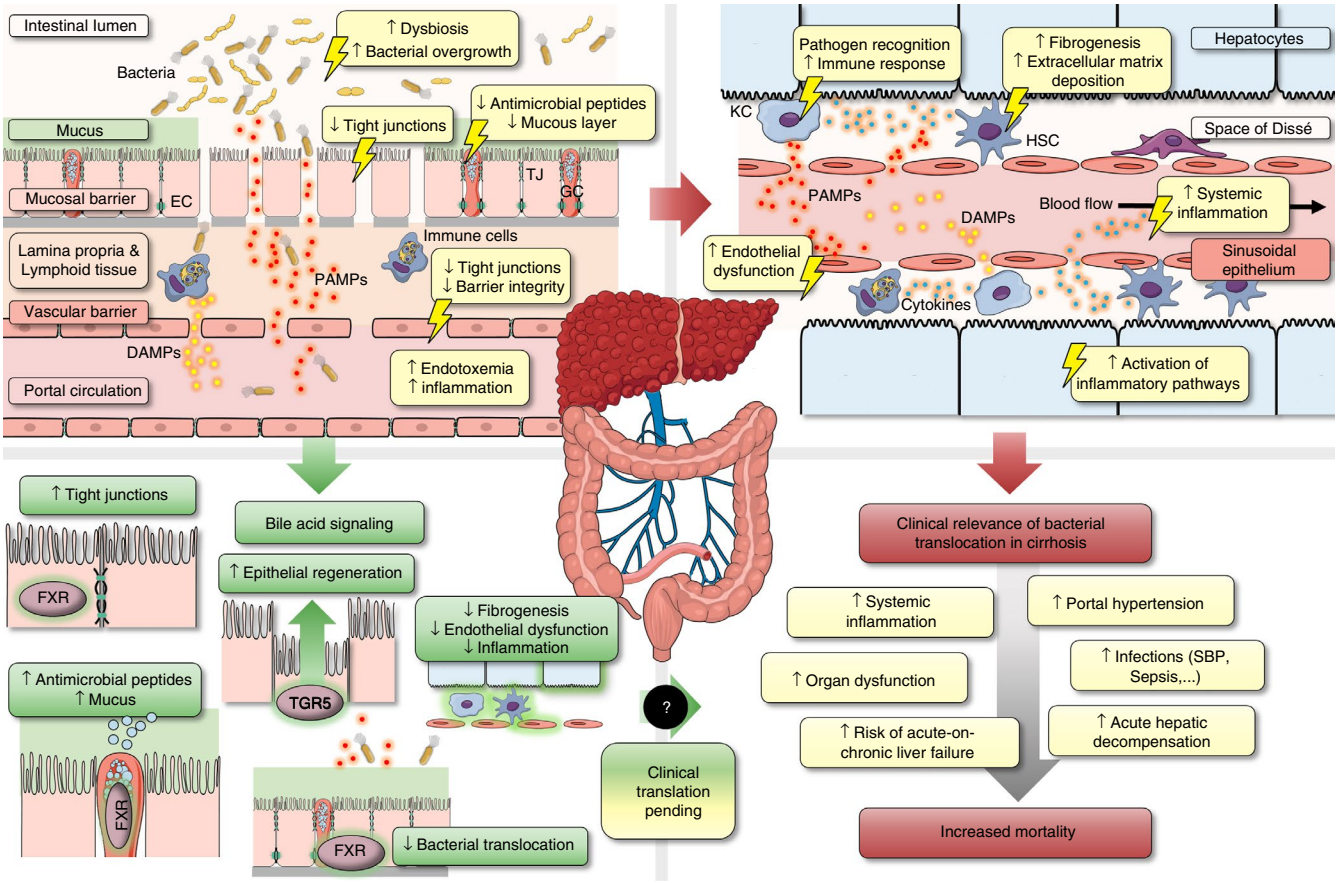

FIGURE 4 Bacterial translocation in cirrhosis: Pathophysiological aspects and therapeutic implications of bile acid signalling in the gut-liver axis. Left upper panel: Advanced chronic liver disease (or cirrhosis) is associated with increased bacterial translocation, which is characterised by (i) dysbiosis and small intestinal bacterial overgrowth, (ii) reduced excretion of antibacterial peptides and mucus thickness, (iii) disruption of epithelial integrity associated with reduced expression of tight junction (TJ) proteins, and (iv) an impaired gut-vascular barrier, which enables the translocation of gut bacteria and danger/pathogen associated molecular patterns (PAMPs/DAMPs) into the portal circulation. Right upper panel: Bacterial translocation induces—directly or indirectly—an intrahepatic inflammatory response, which comprises (i) activation of Kupffer cells (KC) and other immune cells associated with increased shedding of cytokines and systemic inflammation, (ii) activation of hepatic stellate cells (HSC) and induction of fibrogenesis and (iii) endothelial dysfunction of liver sinusoidal epithelial cells (LSEC) which aggravates portal hypertension. Left lower panel: Bile acid signaling may ameliorate intestinal barrier integrity and bacterial translocation via FXR- and TGR5-mediated upregulation of antibacterial defense, TJ proteins, epithelial regeneration, which ultimately leads to amelioration of fibrogenesis, endothelial dysfunction and systemic inflammation in cirrhosis (data based on experimental studies in animals). Right lower panel: The clinical relevance of bacterial translocation in cirrhosis is underlined by the association of portal hypertension and systemic inflammation with the incidence of clinical complications that are associated with increased mortality. Abbreviations: DAMPs/PAMPs, danger/pathogen associated molecular patterns; EC, enterocyte; FXR, farnesoid X receptor; GC, goblet cell; HSC, hepatic stellate cell; KC, Kupffer cell; LSEC, liver sinusoidal epithelial cell; TGR5, transmembrane G protein-coupled receptor-5; TJ, tight junction

5.2 | Bile acid signalling modulates antibacterial defense and intestinal barrier integrity

Regarding the development of bacterial translocation, it is vital to consider that the permeability of the intestinal barrier is tightly regulated in physiological conditions. Therefore, the presence of bacterial translocation indicates the disruption of multiple mechanisms protecting against the migration of bacteria and PAMPs across the intestinal epithelium and the gut-vascular barrier into the bloodstream, such as antimicrobial peptides, mucous layer and tight junctions (TJ) (Figure 4).[112] Concordantly, bacterial translocation was associated with the downregulation of (a) antimicrobial peptides, (b) reduced mucus thickness, (c) reduced expression of mucosal TJ proteins (primarily in ileum and colon), and (d) an impaired gut-vascular barrier in rats and mice with CCl_4-/BDL-induced cirrhosis.[137-139]

Early experimental data indicated that oral BA administration ameliorated intestinal bacterial overgrowth and bacterial translocation in rats with CCl_4-induced cirrhosis that had already developed ascites.[140] Verbeke et al linked these observations to FXR signalling by demonstrating that reduced expression of TJ proteins in BDL rats with cirrhosis was associated with reduced FXR activation as evident from downregulation of SHP in the ileum.[138] Importantly, since reduced FXR activation in the ileum would be expected in the cholestatic BDL model (ie, depriving the gut from BA), treatment

with OCA strongly upregulated both SHP and TJ expression in the ileum, which was paralleled by decreased bacterial translocation, immune cell recruitment and interferon-gamma expression in the ileum.[138] Interestingly, SHP was also downregulated in the ileum of rats with CCl_4-induced cirrhosis. Treatment with OCA upregulated the expression of TJ proteins and antimicrobial peptides, leading to reduced bacterial dysbiosis and mucosal inflammation in the ileum, as well as amelioration of liver fibrogenesis.[139] Finally, Sorribas et al found that the (basolateral) gut-vascular barrier is also impaired in mice with BDL-/CCl_4-associated cirrhosis and confirmed that OCA and the non-absorbable FXR agonist fexaramine reduce bacterial translocation by strengthening of the intestinal barrier.[141] A recent study in piglets subjected to BDL confirmed the beneficial effects of the FXR agonist tropifexor on intestinal inflammation and the gut barrier and indicated significant changes of the microbiome.[142]

Importantly, the significance of BA signalling for intestinal mucosal integrity is not only restricted to ACLD: Sorrentino et al recently demonstrated that TGR5 activation mediates enterocyte regeneration in intestinal organoids and ameliorates epithelial injury in a mouse model of colitis (Figure 4).[143] Treatment with OCA also improved intestinal barrier integrity in mice with experimentally induced colitis.[144] Taken together, BA signalling is increasingly recognised as a therapeutic target for diseases with a compromised intestinal barrier; however, it must be recognised that confirming human data is, to the best of our knowledge, not available to date.

6 | CLINICAL TRANSLATION OF BILE ACID SIGNALLING

6.1 | Bile acid receptor ligands

Despite the accumulation of (mostly experimental) data on the central role of BA signalling in the gut-liver axis, and successful therapeutic interventions with FXR and TGR5 agonists in various in vivo experiments, clinical translation towards their use in humans is still on the "test stand." While FXR agonists are already investigated in clinical trials, the transfer of TGR5 agonists into clinical application was not successful, due to concerns regarding side effects (further discussed below). Recent and ongoing clinical trials with FXR agonists are summarised in Table 1.

First of all, studies in humans have demonstrated that FXR agonists induce FGF19 serum levels and downregulate BA serum levels, which supports the concept of FXR-FGF19 signalling.[145-147] Al-Khaifi et al indicated that the FXR agonist PX-102 suppresses BA synthesis at a very low dosage even in the absence of FGF19 serum level upregulation in healthy individuals, hypothesising that this effect was explained by hepatic FXR activation.[146]

In patients with PBC, the central role of FXR in BA homeostasis served as a rationale for treatment with FXR agonists. In the phase 3 RCT "POISE," OCA exhibited efficacy in PBC patients unresponsive to UDCA towards the primary endpoint defined as the reduction of alkaline phosphatase (ALP) levels (below 1.67x ULN, and −15% from baseline) and normal bilirubin levels.[147] The open-label extension of the "POISE" study demonstrated a persistent decrease in ALP and long-term drug safety upon OCA treatment; however, it reported no significant effect on the composite endpoint death or liver transplantation.[148] A recent study reporting histological long-term outcomes in 17 patients from the "POISE" trial indicated that OCA improves or stabilises fibrosis and liver injury in PBC.[149] Results of the ongoing phase 4 RCT "COBALT" (NCT02308111) investigating the efficacy of OCA in PBC towards clinical endpoints are eagerly awaited. Regarding non-steroidal FXR agonists, the phase 2 RCT assessing the efficacy of tropifexor (LJN452; NCT02516605) in PBC patients has been completed, while full results have not yet been published. Preliminary results of the phase II RCT with the non-steroidal FXR agonist cilofexor (formerly GS-9674; NCT02943447) showing reduced levels of ALP, gamma-glutamyl transferase and transaminases in PBC patients after 12 weeks of treatment were presented at an international conference in 2019.[150] Interestingly, a recent observational study indicated that the combined use of UDCA, OCA and fibrates ("triple therapy") in patients with PBC and ineffectiveness of second-line treatment led to an improvement of liver injury markers,[151] potentially related to complementary effects of FXR and PPAR signalling.[81] Nevertheless, further studies are needed to confirm these results.

In PSC, the phase 2 RCT "AESOP" investigating the use of OCA showed a significant dose-dependent decline of ALP levels.[152] Importantly, another phase 2 RCT found that the non-steroidal FXR agonist cilofexor also exhibited dose-dependent reduction of serum markers associated with cholestasis and liver injury in PSC patients without cirrhosis. Of note, pruritus (one of the main side effects of OCA) was not associated with the use of cilofexor in this study.[153] The ongoing phase 3 RCT "PRIMIS" (NCT03890120) investigates the efficacy of cilofexor in patients with PSC, with fibrosis progression after 96 weeks as the primary endpoint.

In patients with ALD, the phase 2 RCT "TREAT" (NCT02039219) designed to investigate the safety and efficacy of OCA in patients with acute alcoholic hepatitis was terminated due to hepatoxicity concerns.

In patients with NASH, the interim analysis of the phase 3 RCT "REGENERATE" displayed improved histological fibrosis (and no aggravation of NASH) upon treatment with 25 mg OCA and will continue to assess clinical endpoints.[154] Cilofexor monotherapy significantly improved hepatic fat fraction in (non-cirrhotic) patients after 24 weeks in a phase 2 RCT.[155] The phase 2b RCT 'ATLAS' investigated the use of different combination regimens including cilofexor for 48 weeks in patients with compensated ACLD, however, did not report an effect on the primary endpoint (≥1-stage improvement in fibrosis without worsening of NASH).[156] The combination of cilofexor and firsocostat led to an improvement of histological NASH activity, improved serum biochemistry, and reduction of non-invasive fibrosis markers.[156] Furthermore, the phase 2 RCT 'FLIGHT-FXR' investigates the use of tropifexor in patients with fibrosis level F2/F3 on liver histology, and reported dose-dependent decline of hepatic fat

TABLE 1 Recent and ongoing clinical trials (phase 2 or higher) with steroidal and non-steroidal FXR agonists

Substance	Trial phase	Study population	Endpoints	Results	Status*	Reference
Cilofexor (GS9674)	II	PSC (< F4)	Primary: safety at W12 (randomised; vs placebo)	• No safety concerns • Cilofexor reduced ALP, GGT, ALT, AST • Cilofexor reduced C4 and BA levels • Pruritus: 14%–20% in cilofexor vs 40% in placebo group	Completed	NCT02943460[153]
Cilofexor (GS9674)	III	PSC (< F4)	Primary: fibrosis progression at W96 (randomised; vs placebo) Secondary: ALP, GGT, ALT, AST, BA, hepatic collagen, histological changes, fibrosis biomarkers	• No results published	Recruiting	PRIMIS NCT03890120
Cilofexor (GS9674)	II	NASH (< F4)	Primary: safety at W24 (randomised; vs placebo)	• No safety concerns • Hepatic fat fraction −22.7% in cilofexor vs +1.9% in placebo group • Cilofexor reduced GGT, C4, BA levels	Completed	NCT02854605[155]
Cilofexor (GS9674)	II	NASH (< F4)	Primary: safety at W24 (randomised; Semaglutide, Firsocostat, Cilofexor in different combinations; no placebo)	• No results published	Completed	NCT03987074
Cilofexor (GS9674)	II	NASH (No dACLD)	Primary: safety at W12 (different combinations of selonsertib, firsocostat, cilofexor, fenofibrate, icosapent ethyl; no placebo)	• No results published	Completed	NCT02781584
Cilofexor (GS9674)	II	NASH (F3/F4) (No dACLD)	Primary: safety, ≥1 stage fibrosis improvement without NASH worsening at W48 (randomised; Selonsertib, Firsocostat, Cilofexor vs placebo)	• No effect on primary endpoint across all treatment regimens • No effect by cilofexor on hepatic collagen proportion on liver biopsy • Cilofexor/firsocostat improved histological NASH activity • Cilofexor/firsocostat reduced ALT/AST, ELF score, liver stiffness	Completed	ATLAS NCT03449446[156]
OCA	II	PBC (No dACLD)	Primary: ALP change at W12 (randomised; combination with UDCA; vs placebo) Secondary: GGT, ALT, PK	• OCA reduced ALP, GGT and ALT • Pruritus: 50% in placebo group; similar in 10mg (47%) OCA group, higher in 25mg (87%) and 50mg (80%) groups	Completed	NCT00550862[184]
OCA	II	PBC (No dACLD)	Primary: ALP change at W12 (randomised; vs placebo) Secondary: GGT, AST, ALT, bilirubin	• OCA reduced ALP • Pruritus: 35% in placebo group, higher in in 10mg OCA (70%) and in 50mg OCA (94%) groups	Completed	NCT00570765[185]

(Continues)

TABLE 1 (Continued)

Substance	Trial phase	Study population	Endpoints	Results	Status*	Reference
OCA	II	PBC (No dACLD)	Primary: ALP change at W12 (randomised; in different combinations with bezafibrate) Secondary: AST, ALT, GGT, bilirubin, life quality, BA, C4	• No results published	Recruiting	NCT04594694
OCA	III	PBC (No dACLD)	Primary: ALP <1.67 ULN and −15%, normal bilirubin at 12 months (UDCA non-responders; randomised; vs placebo) Secondary: ALP, bilirubin, AST, ALT, GGT	• Composite endpoint met by 10% in placebo group, 46% in 5-10mg OCA, 47% in 10mg OCA groups • Pruritus: 38% in placebo group, 56% in 5-10mg OCA, 68% in 10mg OCA groups • More SAEs in OCA groups	Completed	POISE NCT01473524 [147,148]
OCA	IV	PBC (No dACLD)	Primary: composite endpoint of hepatic decompensation, MELD ≥15, LT, death (randomised; vs placebo) Secondary: decompensation, death, HCC, fibrosis markers, FGF19, liver dysfunction	• No results published	Recruiting	COBALT NCT02308111
OCA	II	PSC (No dACLD)	Primary: ALP change at W24 (randomised; vs placebo) Secondary: AST, ALT, bilirubin, GGT, FGF19, C4	• OCA reduced ALP, but not bilirubin levels • Pruritus: 46% in placebo group, 60%–67% in OCA group	Completed	AESOP NCT02177136 [152]
OCA	II	NASH (No dACLD)	Primary: LDL concentration and particle size at W16 (randomised; combination with statins; vs placebo)	• OCA increased LDL concentration and LDL particle size • Atorvastatin normalised LDL levels	Completed	CONTROL NCT02633956 [186]
OCA	II	NASH (< F4)	Primary: histological NAS score at W72 (randomised; vs placebo) Secondary: NASH resolution, fibrosis improvement, histological NAS components, serum markers of glucose tolerance, systemic haemodynamics, BMI, life quality	• OCA improved liver histology in 45%; vs 21% in placebo group (RR 1.9, 1.3-2.8) • OCA increased VLDL and LDL • Pruritus: 6% in placebo group, 23% in OCA group	Completed	FLINT NCT01265498 [187,188]
OCA	III	NASH (< F4)	Primary: fibrosis improvement without NASH worsening, or NASH resolution without fibrosis worsening; decompensation and mortality at 18 months (randomised, vs placebo) Secondary: histological dynamics, liver biochemistry	• Interim analysis: significant improvement of fibrosis, but no higher rate of NASH resolution • Pruritus: 19% in placebo group, 28% in 10mg OCA, 51% in 25mg OCA groups	Active, not recruiting	REGENERATE NCT02548351 [154]

(Continues)

TABLE 1 (Continued)

Substance	Trial phase	Study population	Endpoints	Results	Status*	Reference
OCA	II	DM type 2	Primary: insulin resistance at W6 (randomised; vs placebo) Secondary: liver dysfunction markers	• OCA increased insulin sensitivity (24.5% in combined OCA group vs 5.5% in placebo group) • OCA reduced GGT and ALT • OCA increased FGF19 and decreased BA levels	Completed	NCT00501592 [189]
OCA	II	Obese and gallstone patients	Primary: insulin resistance, triglycerides, expression of transport proteins and ER stress markers (randomised; vs placebo) Secondary: serum lipid levels	• OCA increased FGF19 levels • OCA decreased C4 and BA levels • OCA decreased BA concentration and increased hydrophobicity index in the gallbladder • OCA induced FGF19 expression in gallbladder epithelium	Completed	OCABSGS NCT01625026[190]
OCA	II	BA diarrhea	Primary: FGF19 changes (non-randomised, open label)	• OCA increased FGF19 levels • OCA decreased C4 and BA levels • OCA improved stool frequency, stool form, and diarrhea index	Completed	OBADIAH1 NCT01585025[145]
OCA	II	Familial Partial Lipodystrophy	Primary: change liver triglycerides at W8 (randomised; vs placebo)	• No results published	Recruiting	NCT02430077
OCA	II	ALD (Acute AH)	Primary: MELD score, safety (randomised; vs placebo) Secondary: bacterial translocation, intestinal inflammation, cytokines	• Terminated due to hepatotoxicity concerns	Terminated	TREAT NCT02039219
PX104	II	NAFLD (No dACLD)	Primary: Safety at W4; (non-randomised) Secondary: hepatic fat (%), oGTT, FGF19, plasma BA, PK	• Early termination due to 2 cases of cardiac arrhythmia • PX104 decreased ALP and GGT • PX104 improved insulin sensitivity	Terminated	NCT01999101 [191]
Tropifexor (LJN452)	II	PBC (No dACLD)	Primary: GGT, RR, HR, Temperature, ECG, Hb at W4/W12 (randomised; vs placebo) Secondary: PK, PBC-40 score, pruritus	• Interim analysis: Tropifexor induced dose-dependent decline of GGT and ALT • Final results pending	Completed	NCT02516605[192]
Tropifexor (LJN452)	II	NASH (< F4)	Primary: Safety, TA levels, hepatic fat (%) at W12 (randomised; vs placebo) Secondary: GGT, FGF19, fibrosis biomarkers, lipid profile, pruritus, BMI, serum C4	• Interim analysis: Tropifexor reduced hepatic fat fraction, ALT, and body weight • Final results pending	Completed	FLIGHT-FXR NCT02855164[157]

(Continues)

TABLE 1 (Continued)

Substance	Trial phase	Study population	Endpoints	Results	Status*	Reference
Tropifexor (LJN452)	II	NASH (F2/F3)	Primary: Safety at W48 (randomised; monotherapy vs combination with cenicriviroc) Secondary: fibrosis improvement (>1 point), NASH resolution	• No results published	Completed	TANDEM NCT03517540
Tropifexor (LJN452)	II	NASH (F2/F3)	Primary: fibrosis improvement without NASH worsening, NASH resolution without fibrosis worsening at W48 (randomised; monotherapy vs placebo vs combination with licogliflozin) Secondary: NASH resolution, fibrosis improvement, body weight, hepatic fat (%), AST, ALT, GGT, safety	• No results published	Recruiting	ELIVATE NCT04065841

Abbreviations: AH, alcoholic hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bile acids; BMI, body-mass index; c/dACLD, compensated/decompensated advanced chronic liver disease; C4, serum 7-alpha-hydroxy-4-cholesten-3-one; DM, diabetes mellitus; ECG, electrocardiography; FGF19, fibroblast growth factor 19; GGT, gamma-glutamyl transferase; Hb, haemoglobin; HCC, hepatocellular carcinoma; HDL, high density lipoprotein; HR, heart rate; LT, liver transplantation; MELD, Model of End Stage Liver Disease score; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; oGTT, oral glucose tolerance test; PBC, primary biliary cholangitis; PK, pharmacokinetics; PSC, primary sclerosing cholangitis; RR, blood pressure; SAE, serious adverse event; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; V/LDL, (very) low density lipoprotein.

*Trial status was obtained from "ClinicalTrials.gov".

fraction ≥30% (20% vs 64% in the placebo and tropifexor 200 μg groups respectively) and alanine aminotransferase after 12 weeks in an interim analysis,[157] however, final results are pending.

6.2 | Enterokines: FGF19 and GLP-1

Considering that FGF19 greatly determines the suppression of BA synthesis, it was hypothesised that FGF19 analogues may mitigate BA toxicity. However, concerns regarding a potential promotion of hepatocarcinogenesis with endogenous FGF19 have been raised.[158] The development of FGF19 analogues modified to lack certain hepatocarcinogenic structures, while suppressing *CYP7A1*, has enabled clinical trials. Recent and ongoing clinical trials with FGF19 analogues are summarised in Table 2.

In patients with PBC, a phase 2 RCT reported that NGM282 (a FGF19 analogue) reduced serum ALP and serum transaminases in patients unresponsive to UDCA after 12 weeks.[159] The phase 2b RCT has completed recruiting, however, final results are pending. In patients with PSC, NGM282 failed to ameliorate serum ALP levels after 12 weeks in a phase 2 RCT, however, it indicated that serum C4 levels (reflecting *CYP7A1* expression) were significantly reduced.[160]

In patients with NASH, NGM282 significantly reduced hepatic fat content (defined by a decline of ≥5%) in 74%/79% in the 3 mg/6 mg groups, as compared to 7% in the placebo group.[161] A recent follow-up analysis in 43 patients from the same study indicated that NGM282 ameliorated histological disease activity and reduced fibrosis.[162]

Finally, the therapeutic efficacy of GLP-1 agonists is well-established in patients with diabetes, and multiple phase 3 and 4 trials in patients with diabetes and/or metabolic syndrome are ongoing. A recent meta-analysis of RCTs considering patients with NAFLD and NASH indicated that the use of GLP-1 analogues is associated with significant reduction of hepatic fat content (mean reduction of 3.92%) and improved chances of NASH resolution without the aggravation of liver fibrosis (odds ratio 4.06, 95%CI 2.52–6.55).[163] Results of the phase 2 RCT on the use of the GLP-1 agonist semaglutide were published recently and reported an increased rate of NASH resolution (without worsening of fibrosis) as compared to the placebo group (36%–59% in treatment groups vs 17% in the placebo group).[164] However, it remains to be investigated if the efficacy of GLP-1 in NASH is mainly (indirectly) caused by improved diabetes control, weight loss or direct downstream signalling effects.

6.3 | Enterohepatic drugs: from UDCA to inhibition of bile acid transporters

UDCA is one of the first BA-derived drugs and has been used in patients with cholestatic liver disease for more than two decades, following the consideration that UDCA is more hydrophilic and less toxic than other BA and may exert hepatoprotective effects by the transformation of

TABLE 2 Recent and ongoing clinical trials (phase 2 or higher) with FGF19 analogues.

Substance	Trial phase	Study population	Endpoints	Results	Status*	Reference
NGM282	IIb	PBC (No dACLD)	Primary: change plasma ALP at W12 (randomised; three doses, no placebo) Secondary: change bilirubin, AST, ALT, GGT	• No results published	Completed	NCT02135536
NGM282	II	PBC (No dACLD)	Primary: change plasma ALP at W4 (randomised; vs placebo) Secondary: change plasma bilirubin	• No results published	Completed	NCT02026401
NGM282	II	PSC (No dACLD)	Primary: change plasma ALP at W12 (randomised; vs placebo) Secondary: AST, ALT	• No significant reduction of ALP levels • Reduction of C4 and fibrosis blood markers	Completed	NCT02704364[160]
NGM282	II	NASH (No ACLD)	Primary: absolute hepatic fat content at W12 (randomised; vs placebo) Secondary: relative hepatic fat content	• 5% reduction of hepatic fat fraction in 74%–70% with NGM282% vs 7% in placebo group • AEs more frequent than in placebo group (injection site reactions, diarrhoea, abdominal pain, nausea)	Completed	NCT02443116[161,162]
NGM282	II	NASH (cACLD, F4)	Primary: fibrosis improvement ≥1 stage without NASH worsening, safety at W48 (randomised; vs placebo)	• No results published	Recruiting	ALPINE 4 NCT04210245
NGM282	II	DM type 2	Primary: fasting plasma glucose at W4 (randomised; vs placebo) Secondary: HbA1c, lipids	• No impact on hyperglycemia • NGM282 reduced AST, ALT and C4 levels • FGF19 increased by bariatric RYGB surgery	Completed	NCT01943045[193]

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; c/dACLD, compensated/decompensated advanced chronic liver disease; DM, diabetes mellitus; FGF19, fibroblast growth factor 19; GGT, gamma-glutamyl transferase; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; RYGB, Roux-en-Y gastric bypass; W, week.

*Trial status was obtained from 'https://ClinicalTrials.gov'.

the BA pool and facilitating bile excretion. The pathophysiological mechanisms and detailed overview of studies with UDCA have been reviewed elsewhere.[165] UDCA particularly displayed efficacy in PBC, based on early reports that only 16% of patients developed oesophageal varices within 4 years of treatment as compared to 58% receiving placebo.[166] An international study comprising approximately 4000 patients with PBC showed that patients receiving UDCA exhibited decreased risk of death or liver transplantation (HR 0.46), even when considered biochemical "non-responders" to UDCA (HR 0.56).[167]

Furthermore, ASBT inhibitors have been investigated in clinical trials, considering that the increased clearance of BA *via* the faeces may ameliorate cholestasis. In patients with PBC and pruritus enrolled in a phase 2a RCT, the ASBT inhibitor GSK2330672 reduced pruritus severity; however, diarrhoea occurred in about one-third of patients in the treatment group as drug-associated side effect.[168] Conversely, also in patients with PBC, the phase 2 RCT "CLARITY" reported that the ASBT inhibitor maralixibat (LUM001), in combination with UDCA vs UDCA alone, had no significant effect on pruritus.[169] Other studies with ASBT inhibitors are ongoing, however, no results are available yet.

Finally, NTCP blockers have only been tested in the context of HBV/HDV treatment. Therefore, while Loglio et al. reported the increase of serum BA in patients with HBV/HDV treated with myrcludex B (which was well-tolerated),[170] clinical data indicating whether targeting this step in the gut-liver axis will have a therapeutic role besides antiviral efficacy, will hopefully become available in the future.

6.4 | Side effects and safety concerns

As outlined in Table 1 and recently demonstrated in a meta-analysis and an observational cohort study, pruritus is associated with the intake of OCA and a major cause of drug discontinuation.[171,172] Non-steroidal FXR agonists seem to exhibit a better side effect profile regarding pruritus.[153] However, both steroidal and non-steroidal

FXR agonists caused a deterioration of the lipid profile in previous studies, which is particularly relevant in metabolic liver disease as patients often exhibit an increased cardiovascular risk.[173] Furthermore, reports on cases of hepatotoxicity and liver failure related to the use of OCA remain a significant safety concern, particularly in patients with ACLD or acute liver dysfunction.[174] Patients with compensated ACLD due to PBC treated with OCA showed a higher risk of hepatic decompensation in a recent retrospective study, which underlines the concerns related to the use of OCA in patients with ACLD.[175] It remains to be investigated whether non-steroidal FXR agonists will exhibit a better safety profile and efficacy in ACLD. Furthermore, the FGF19 analogue NGM282 was associated with injection site reactions, diarrhoea, abdominal pain and nausea (Table 2).[161,162] The transfer of TGR5 agonists into clinical trials was not successful due to concerns towards aggravation of pruritus, blockade of gallbladder motility and increased gallstone formation,[176] as well as inhibition of apoptosis in cholangiocarcinoma cell lines.[177,178] Careful consideration of these aspects is important to optimise drug development, patient management and weighting the benefit-risk-ratio for emerging therapeutic strategies.

6.5 | Perspectives and future research agenda

Although previous experimental and clinical studies indicated that modulation of BA signalling in the gut-liver axis exerts promising therapeutic effects, future studies need to consider important issues related to methodological limitations and study designs to enable the clinical translation of novel therapies. First, experimental studies in cells and animals often display imperfect models of the human organism. For example, a landmark study on the FGF19 feedback mechanism in mice suggested that FGF19 is not expressed in the liver,[53] in contrast to studies using human hepatocytes and human liver tissue,[58,61,62] potentially explained by species-related differences. Similarly, currently established animal models of liver disease are only mimicking (instead of imitating) human liver disease.[179] For example, BDL in rodents completely and irreversibly abrogates the excretion of BAs by the liver, which marks a relevant difference to the natural course of cholestatic liver diseases in humans. Second, mechanistic evidence on the concept of bacterial translocation and an impaired intestinal barrier in cirrhosis (or the significance of BA signalling) has not been fully addressed in humans with ACLD. Previous studies have found changes of the stool microbiome in ACLD (indicating dysbiosis),[114] or reported increased epithelial permeability by the use of duodenum biopsies;[180] however, these findings may not account for relevant changes of the microbiome along the gastrointestinal tract and the actual significance of bacterial translocation in humans, as experimental studies in animals usually indicated that the ileum is the most relevant intestinal segment for bacterial translocation.[181-183] Third, previous clinical trials did not assess whether experimental evidence that FXR agonists improve the intestinal epithelial barrier and bacterial translocation in cirrhosis translates into improved clinical outcomes, as patients with (particularly decompensated) ACLD were usually excluded (Table 1). Non-steroidal or non-absorbable FXR agonists will hopefully become effective and safe therapeutic options to address this question in the future. Finally, as indicated by the efficacy of cilofexor in combination with firsocostat (an acetyl-CoA carboxylase inhibitor) in NASH,[156] and recent data on the combination of OCA and fibrates in PBC,[151] the use of combination treatment regimens may represent a promising approach to treat liver diseases. The use of human tissue or human organoids will be vital to close the gap between experimental data and human disease in future studies on BA signalling in the gut-liver axis.

7 | CONCLUSIONS

Modulation of BA gut-liver signalling may exert beneficial effects on BA homeostasis and intestinal barrier integrity. Pharmacological interventions targeting the gut-liver axis are currently focused on BA receptor ligands, FGF19, and enterohepatic drugs. Notably, the clinical use of FXR agonists in RCTs were mainly conducted in patients with non-cirrhotic liver disease, while patients with (decompensated) ACLD were usually excluded. However, it seems justified to further explore the therapeutic effects of FXR agonism on intestinal barrier integrity to ACLD patients, since bacterial translocation in the gut-liver axis is reportedly detrimental for the course of ACLD. Ultimately, several molecular targets of the presented BA signalling pathways remain to be explored for potential therapeutic modulations in patients with chronic liver disease.

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