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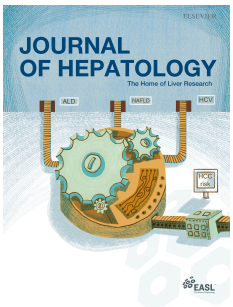

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Primary biliary cholangitis as a roadmap for the development of novel treatments of cholestatic liver diseases *

*This review is dedicated to Peter L. M. Jansen

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Short summary:

The discovery of nuclear receptors and transporters has contribute to the development of new drugs for the treatment of cholestatic liver diseases. Especially progress has been made in the second line therapy of PBC. These new drugs can be separated into compounds primarily targeting cholestasis, molecules targeting fibrogenesis and molecules with immune-mediated action. Finally, also drugs aimed at symptom relief (pruritus and fatigue) are further under investigation. Obeticholic acid is currently the only approved second line therapy for PBC. Drugs in the late phase of clinical development are the PPAR agonists, NorUDCA and the NOX 1&4 inhibitors.

Key points:

- Patients with PBC with an incomplete biochemical response to ursodesoxycholic acid are at risk for major complications within 10 years of follow up.

- One of the reasons for the remarkable progress in the successful development of new drugs for PBC is the availability of well validated risk scores and endpoints for clinical trials which unfortunately are not yet well validated for PSC.
- The target of most drugs in development focus on the anti-cholestatic effect. Preliminary data suggest that also drugs with an antifibrotic profile might be effective. The effect of drugs targeting the underlying immune-mediated pathogenesis are disappointing and most likely only effective in the early stages of the disease.
- The most promising drugs in the late stage of development to treat PBC are PPAR agonists which also have a beneficial effect on pruritus.
- Combination of bezafibrates and obeticholic acid in addition to ursodesoxycholic acid allow complete normalization of the markers of cholestasis in a substantial number of patients.

Introduction

Among the wide spectrum of chronic cholestatic liver diseases primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are the most frequent. Although these immune-mediated cholestatic liver diseases are rare and the number of liver transplants for PBC has fallen in recent years, cholestatic liver disease still represents a major indication for liver transplantation , which points out the need for more effective medical therapies (1,2,3). Despite our current shortcomings in fully understanding the pathogenesis of these diseases, several genetic and environmental factors have recently been identified both for PBC and PSC (4-8). As due to significant advances in our understanding the molecular mechanism of cholestasis and the regulation of bile acid (BA) homeostasis, several novel therapeutic targets have been successfully explored for cholestatic liver diseases (9). However, most of the therapeutic progress has been made in the treatment of PBC (9-11). Therefore we will use in this review

PBC as a roadmap to describe the progress in therapeutic breakthroughs for cholestatic liver diseases. PBC is a paradigm chronic cholestatic liver disease characterized by an inflammatory process targeting the interlobular bile ducts resulting in bile duct destruction and portal fibrosis that can progress to biliary cirrhosis (12). Recently 'the biliary HCO3- umbrella concept' has been proposed: HCO3- protects against toxic bile acids and diminished secretion of HCO3- by the cholangiocytes may aggravate immune-mediated bile duct injury in patients with a genetic predisposition (13).

One of the reasons for the remarkable progress in the successful development of new drugs for PBC is the availability of well validated risk scores and endpoints that are utilized in clinical trials. For instance, serum alkaline phosphatase (ALP) and bilirubin have been extensively validated for this purpose in large international cohorts of patients. A continuous relationship between ALP and bilirubin and long term outcome exists (14). In addition, this biochemical parameters offer the possibility to select in an easy way patients in need of second line therapies. Indeed, incomplete biochemical response to first line therapy with ursodesoxycholic acid (UDCA), results in major complications in about 30% of the patients after 10 years (15).

Since most of the studies have used the same inclusion and exclusion criteria as well as endpoints (POISE criteria), it is also easier to compare the effect of different drugs . The primary end point in de POISE trial was an ALP level of < 1.67 times the upper limit of normal range, with a reduction of at least 15% from baseline, and a normal total bilirubin level (16). However, as discussed later on in this review, we probably need to move to more stringent composite biochemical endpoints in trials. The most recent tools to select patients in need of second line therapy are the Globe and the UK-PBC scores which are continuous scoring systems (17,18). All these scores (GLOBE, UK-PBC and also the Mayo risk score) demonstrated comparable discriminating performance with regards to liver transplantation or death as well with high prediction accuracy (19). For decades liver biopsy was the gold standard for diagnosis, to assess

stage of the disease and the effect of treatment. However, a biopsy is no longer required for these purposes (20). Indeed PBC is the first cholestatic liver disease in which the value of elastography has been extensively investigated. Liver stiffness measurement by vibration-controlled transient elastography appeared to be a major predictor of PBC outcome that should be combined with biochemical response as surrogate composite endpoints for future clinical trials (21-24). Unfortunately, the situation is different in PSC. There is still no approved medical therapy and the endpoints for clinical trials are still under debate. However, irrespective of the drug used in PSC, patients with a ALP value < 1.5 ULN have a better survival (25). An expert panel recently concluded that no sufficiently validated endpoints have been defined yet to be used in clinical trials for PSC. Histology, ALP and elastography are the most promising surrogate endpoints but need further validation and combining multiple endpoints seems advisable (26,27).

I. New therapeutic targets for cholestatic liver diseases (preclinical data)

Further progress in the treatment of PBC occurred since the discovery of nuclear (hormone) receptors (NRs). The NR superfamily is the largest group of transcriptional regulators and consists of 48 members in humans. NRs act as ligand-activated transcription factors which control a broad spectrum of genes involved in BA homeostasis, lipid and glucose metabolism, inflammation, cell proliferation, tissue repair and fibrosis and are widely expressed in hepatocytes, cholangiocytes, HSCs, macrophages and other immune cells, which makes them attractive targets for the treatment of cholestatic disorders (28-30).

Natural ligands include both endogenous and exogenous molecules such as hormones, fatty acids , BAs , other intermediary products of metabolism, drugs and toxins. NRs offer a feedback mechanism to maintain cellular homoeostasis (31,32). Since BAs are potentially cytotoxic and

proinflammatory at higher concentrations, it is important to maintain their homoeostasis by controlling BA transport and metabolism . This is achieved through NRs such as the farnesoid X receptor (FXR), where BAs act as hormone-like signalling molecules binding (33-35). Other NRs of importance for cholestatic liver diseases are the peroxisome proliferator-activated receptors (PPARs) and pregnae X receptor and glucocorticoid receptor (GR) (36).

NR not only influence hepatobiliary homoeostasis but also gut inflammation and microbiota which make them of interest for the treatment of PSC. The interaction between BAs and intestinal microbiota and changes in gut microbiota (dysbiosis) may play a role in the pathogenesis of cholestasis in PSC (37,38). Specific gut pathobionts may disrupt the intestinal epithelial barrier and initiate a hepatic T helper 17 cell immune response (39). Vancomycin is one of the most promising agents but the mode of action may be complex also including direct immunoregulatory effects (40). In addition, faecal microbiota transplantation from lean donors has shown first promising results in PSC (41). Importantly, gut microbiota may not only serve as a trigger of liver injury but may also have protective actions. As such total elimination of intestinal microbiome in germ-free mice has been shown to aggravate liver injury in mouse models of liver fibrosis and PSC (42).

Overall, drug therapy in cholestatic disorders is based on disease pathogenesis. Drug targets can be separated into molecules primarily targeting (1) *cholestasis* (the hepatocellular retention of endogenous BAs), (2) molecules targeting *fibrogenesis* and (3) molecules *with immune-mediated action*. On the other hand there are also (4) drugs aimed at *symptom relief*. Indeed pruritus, fatigue and cognitive dysfunction are the most common complaints in patients with cholestatic liver disease. Pruritus appears to be particularly frequent in patients with PBC but may also become a significant problem in patients with PSC and other cholestatic conditions (43). Current guidelines provide a treatment algorithm in the management of pruritus but response rates less than 50% are common for most of the recommended drugs (20,44-

47).Concerning central fatigue with cognitive dysfunction, this problem is currently untreatable (48).

The stage of the disease influences the efficacy of some of the drugs used for the treatment of cholestatic liver disease. In this regards, Peter L.M. Jansen et al. developed the concept that cholestatic liver diseases, particularly PBC and PSC, have *an ascending pathophysiology* (49). Knowledge of this concept might allow one to use these drug in a more appropriate way. Indeed, the early lesions caused by immunological injury are in the "downstream" biliary tree which can lead to cholestasis. This causes BA –mediated toxic injury of the "upstream" liver parenchyma. High concentration of BAs are present in the canalicular network, bile ducts, and gallbladder. Leakage of bile from this network and ducts could be an important driver of toxicity. The liver has a great capacity to adapt to cholestasis by reducing uptake systems and BA synthesis while inducing (alternative) efflux systems (adaptation phase). According to this concept Ileal BA transporter (IBAT) inhibitors that reduce intestinal bile salts absorption lower the BA load may be most efficient in this stage. The effectiveness of BA synthesis–suppressing drugs, such as FXR agonists , is greatest when adaptation is not yet established. Anti-inflammatory agents are probably most effective in early disease. Finally, drugs that antagonize BA toxicity, such as ursodeoxycholic acid and nor-ursodeoxycholic acid, might be effective at all disease stages.

An overview of the mechanism of action of anticholestatic drugs cholestatic drugs is given in figure 1.

1. Improvement of cholestasis

a. Targeting the Nuclear bile acid receptor / Farnesoid–X receptor

The intracellular BA receptor and key regulator of BA homoeostasis, the nuclear bile acid receptor farnesoid-X (FXR) has become a central therapeutic target for cholestatic liver diseases (28-30). Moreover, FXR also modulates liver regeneration and inflammation (50). FXR is highly expressed in bile acid-handling tissues predominantly in the liver, intestine, and kidney (51). Because of its role as a ligand-activated transcription factor, FXR activation has pleiotropic effects in numerous biological processes in tissues where it is expressed. In this regards, FXR activation affects different pathways in the pathogenesis of PBC (52). Pharmacological activation of FXR reduces hepatocellular BA levels by stimulation of BA export while repressing BA uptake and synthesis (53). In addition, FXR has anti-inflammatory effects, mainly due to the antagonizing effects of nuclear factor kappa B (NFκB) (54). Expression of FXR is reduced by inflammation and in various cholestatic diseases such as in PBC which may at least in part be overcome by highly potent pharmacological FXR agonists which have higher affinity than endogenous BAs (55).

The steroidal FXR agonists **: Obeticholic acid** (OCA) was the first-in-class steroidal FXR agonist (still maintaining its BA structure) and is a synthetic BA derivative from the natural bile acid chenodeoxycholic acid (56). OCA improves in humans hepatic BA excretion and reduces exposure of hepatocytes to cytotoxic BAs (57). In addition to restoration of BA homeostasis, activation of FXR also promotes HCO3- secretion in mice which in humans may reinforce the HCO3- umbrella (58). FXR stimulation also reduces the inflammation in the liver and it has antifibrotic effects through inhibition of fibrosis progression, promotion of fibrosis resolution and inhibition of hepatic stellate cell activity (59). In addition, OCA which acts as a local NO donor in the liver lowers portal hypertension in animals (60,61). Finally, it reduces gut permeability in these animals (62-64).

The Non-steroidal FXR agonists : an increasing number of non-steroidal FXR ligands with higher affinity for FXR have been developed (65). In contrast to steroidal FXR agonists, non-

steroidal FXR ligands no longer have a BA structure and therefore, have different pharmacokinetic profiles, efficacy and safety profiles. Some of these agonists may operate as gut-preferential FXR ligands and have limited systemic exposure. However, side effects such as dyslipidaemia and pruritus are still encountered and appear to be dose-dependent class effects of FXR-targeted strategies (66,67). Two compounds are in further clinical development explored in Phase 2: **Cilofexor** and **Tropifexor.**

The FXR downstream target : Fibroblast growth factor 19

FXR stimulates the production of intestinal fibroblast growth factor 19 (FGF 19) in the terminal ileum, which after reaching the liver via the portal circulation and binding to FGFR4/ßKlotho receptor complex, inhibits hepatic BA synthesis through repression of the rate limiting enzyme CYP7A1 (68). In addition to its role in regulating BA homeostasis, FGF19 also stimulates cell proliferation in the liver which raises concerns regarding potential hepatic carcinogenesis. FGF-19 overstimulation by FXR ligands and aberrant FGF19-FGFR4 signalling has been identified in HCC (69). In contrast to the non-tumorigenic FGF19 mimetic M70/NGM282 improved liver injury in the *Mdr2/Abcb4–/–* mouse model of sclerosing cholangitis and protected *Mdr2/Abcb4–/–* and *Fxr–/–* mice from spontaneous hepatic fibrosis, cellular proliferation and HCC formation (70,71).

Aldafermin (NGM 282) is an engineered analogue of human FGF19 and is 95.4% identical to FGF19. Aldafermin differs from wild-type FGF19 in the amino terminus, a key region of the protein involved in receptor interactions and signalling modulation . In aldafermin, a 5-amino acid deletion (P24-S28) coupled with the substitution of three amino acids at critical positions (A30S, G31S, H33L) enable biased FGFR4 signalling so that aldafermin retains the ability to potently repress CYP7A1 expression but no longer triggers activation of signal transducer and activator of transcription 3, a signalling pathway essential for FGF19-mediated hepatocarcinogenesis (72-74).By engaging both FGFR4 and FGFR1c pathways to reduce bile

acid toxicity aldafermin has demonstrated anti-inflammatory, and anti-fibrotic activities in multiple animal models.

b. Targeting the peroxisome proliferator-activated receptors

The peroxisome proliferator-activated receptors belong also to the same nuclear receptor family as FXR. PPAR's act as transcriptional modifiers of bile formation and regulation of inflammation and fibrosis (29). There are three isoforms: PPAR alpha, gamma and delta. PPAR alpha is the predominant isoform in the liver. PPAR belong to the same nuclear receptor family as FXR. FXR and PPAR have a cross talk with other nuclear receptors. The three isoforms are expressed in different parenchymal and non-parenchymal liver cell compartments, making them highly attractive targets for therapy of cholestatic liver diseases.

Fibrates such as bezafibrate and fenofibrate are agents that act as PPARs agonists and are registered for the treatment of for dyslipidaemia for decades. Fibrates suppress BA synthesis (CYP/A1) in the liver and increase phospholipid excretion (MDR3) into the bile and have anti-inflammatory effects (via suppression of NFκB signalling) (75).

Bezafibrate is a potent pan-PPAR agonist (76) while **fenofibrate** is a more selective PPAR alpha agonist (77).

Seladelpar is an oral, once-daily selective PPAR delta agonist. PPAR-delta is expressed not only in hepatocytes but also in cholangiocytes, Kupffer cells an hepatic stellate cells. PPAR-delta profoundly influences BA levels and has effects on inflammation and fibrosis. PPAR-delta-triggered mechanisms could promote cancer cell survival and cancer progression, which has raised concerns regarding their clinical development (78). Seladelpar decreases BA synthesis and prevents their toxic accumulation in hepatocytes. Seladelpar also decrease the synthesis of cholesterol and inhibits its dietary absorption which results in a decrease of cholesterol available for the BA synthesis. In addition seladelpar has anti-inflammatory

effects. In contrast to the other PPAR's a direct role for PPARγ in the regulation of BA metabolism has not yet been reported.

Elafibranor, a PPAR agonists with affinity for alpha/delta, and **Saroglitazar,** a PPAR agonists with affinity for alpha / gamma, are under investigation. It has to be kept in mind that for some compounds of this class of drugs cardiovascular and renal side effects have been reported (79).

c. Targeting the glucocorticoid receptor

The anti-inflammatory and immunosuppressive effects of **budesonide** are well known and the drug is mainly used in the context of overlap syndromes and non-cirrhotic autoimmune hepatitis . However, it is a glucocorticoid receptor -ligand and recent data indicate that it also may controls BA detoxification (via PXR) and HCO3- secretion (80).

d. Other anti–cholestatic agents beyond NRs

Nor-ursodeoxycholic acid (**norUDCA**), recently assigned the new international non-proprietary name norucholic acid, is a side-chain- shortened derivate of UDCA and is resistant to side-chain conjugation with glycine and taurine (81). In contrast to UDCA, norUDCA undergoes cholehepatic shunting between cholangiocytes and hepatocytes, which results in the generation of a HCO3- – rich hypercholeresis and high intrahepatic enrichment (82). NorUDCA has shown anti-cholestatic, anti-inflammatory, immunomodulatory and anti-fibrotic actions in animal models and improves cholestatic liver and bile duct injury in the *Mdr2/Abcb4*–/– mouse model of sclerosing cholangitis (83-85). Since norUDCA reinforces the HCO3- umbrella, it may be a therapeutic approach for several cholangiopathies with defective HCO3-–secretion

such as PBC. Notably, norUDCA does not act via FXR or other NRs, making it an attractive combination partner for drugs targeting NRs.

2. Fibrogenesis

Lysyl oxidase-like 2 (LOXL2) contributes to fibrogenesis by cross-linkage of collagen and regulates bile duct permeability. **Simtuzumab** is a humanised monoclonal antibody against LOXL2. In patients with PSC increased serum levels of LOXL2 correlate with more advanced fibrosis and severity of portal hypertension (86,87).

Setanaxib is an oral small molecule and a first-in-class selective inhibitor of the NADPH oxidase 1 & 4 isoforms (NOX inhibitor). Activation of NOX enzymes is a key in many multifactorial disease and the drug has been studied in phase 2 trials in kidney fibrosis and idiopathic fibrosis. The compound has demonstrated potential to downregulate markers of oxidative stress (anti- inflammatory effect) and prevent progression to liver fibrosis in *in vitro* and animal studies (88,89).

3. Targeting the underlying (immune -mediated) pathogenesis

Examples to these latter compounds are : **Rituximab** a B-cell depleting monoclonal antibody targeting the CD20 antigen, **RhuDex** a novel, orally bioavailable, low molecular weight modulator of T-lymphocyte co-stimulation , **Cenicriviroc** a dual CCR2/CCR5 chemokine receptor antagonist and the **CCL24 monoclonal antibody CM-101**. Until today no convincing clinical data have been reported .These agents are most likely effective in the early stage of the disease.

4. Symptom relief

Pruritus: the mechanisms underlying cholestatic pruritus are stil not clear. Retention of toxic hydrophobic BAs is postulated to play a key pathogenetic role. In this regards cholestyramine is the current first-line treatment option for cholestatic pruritus. However, in the past Colesevelam an anion-exchange resin with a 7-fold higher bile acid-binding capacity and fewer side effects than cholestyramine decreased serum BA levels but was unable to demonstrate that it was more effective than a placebo in alleviating the severity of pruritus of cholestasis (90). Ileal bile acid transporter is an integral brush border membrane glycoprotein mainly expressed in the distal ileum. In cholestatic liver disease, ileal BA absorption is increased and inhibiting IBAT may prevent inappropriate conservation of BAs and may improve pruritus (91). Mas-related G protein-coupled receptor X4 (MRGPRX4) is a newly identified receptor for BAs and bilirubin and demonstrated its likely role in cholestatic itch. Its discovery provides a promising target for developing novel anti-itch treatments (92-94).

Fatigue: over-activation of GABA-A receptors by neurosteroids play a role in cognitive dysfunction and fatigue (95). **Golexanolone** is a novel small molecule GABA-A receptor-modulating steroid antagonist under development for the treatment of cognitive and vigilance disorders. It restores spatial learning and motor coordination in animal models of hepatic encephalopathy and has been investigated for hepatic encephalopathy (96).

II. Medical treatment : established drugs and drugs in the late phase of clinical development in PBC and PSC

PBC experience

The first- line drug for PBC is **ursodeoxycholic acid** (UDCA) and is effective in the majority of the patients with PBC (60-80% are biochemical responders). UDCA has a low cost and is

well tolerated at a standard dose of 13-15 mg/kg /d (97). Discontinuation due to digestive adverse events occurs in less than 5% of the patients (98).The earlier patients are treated, the higher the chances to achieve a response (99). UDCA improves cholestasis and underlying liver histology and it delays the development of oesophageal varices. The drug reduces the risk of hepatocellular carcinoma and based on open label extension studies it is accepted that it improves survival and prevents the need of liver transplantation (100-103).

Since the wide implementation of UDCA the need for liver transplantation for PBC in Europe has declined despite the fact that the prevalence of PBC did not decrease (104). UDCA also has a place after liver transplantation. Recurrence of PBC following liver transplantation is reported in up to 46% of the patients and can be prevented by UDCA when treatment is started early (105). Around 30-40 % of PBC patients have an incomplete response to UDCA which may result in disease progression during long term follow up (15). The strongest risk factor for an incomplete response to UDCA therapy are early age at diagnosis (<45y) and advanced stage at presentation (106,107). This observation has formed the rational for second line therapies in combination with UDCA. EASL clinical practice guidelines recommend a ALP level > 1.5 x ULN or abnormal levels of bilirubin as biochemical thresholds to initiate second line therapy (20). Before considering to introduce second line therapy drugs, it remains important to exclude other reasons for a suboptimal response to UDCA such as: adherence, inappropriate UDCA dosage and co- administration of bile acid sequestrants inhibiting uptake of UDCA.

An overview of the established drugs approved for PBC therapy and those in advanced stages of clinical development is given in table 1. It is important to note that none of these drugs have been investigated in patients with advanced disease.

Nuclear receptor ligands which were the first second line drugs for PBC, have also been widely investigated in the treatment of NASH. This valuable experience offers crucial information about dose and safety that can be extrapolated to the PBC population (30).

Algorithm for the treatment of PBC is given in figure 2.

FXR agonists:

Obeticholic acid is currently the only approved second line therapy for PBC. The starting dose is 5 mg with adjustment to 10 mg after 3-6 months if tolerable. Long-term clinical data have confirmed preclinical observations. Two prospective studies demonstrated that OCA in patients with an incomplete response to UDCA or intolerance to UDCA improves cholestasis in a dose dependent manner (108). In the POISE trial comparing OCA to placebo a significant reduction of ALP and bilirubin after 1 year was observed in 35 % and 8 %, respectively (16). OCA treatment also significantly reduced serum levels of gamma GT. The rate of serious adverse events was 16% in the 5-10 mg group vs 4 % in the placebo group. Pruritus is the most common adverse event, it is dose related and occurs especially in patients with pre-existing pruritus. There was no effect after 1 year on non-invasive measures of liver fibrosis (liver stiffness and Enhanced Liver Fibrosis score) . In paired biopsies in a small group of 17 patients included in the POISE trial improvements or stabilization of histological disease features, including ductular injury, fibrosis, and collagen morphometry were observed (109). The effect of the drug on the biochemical markers is sustained for at least 3 years (110). Real world data demonstrated a discontinuation rate between 12 and 17 % especially due to pruritus and confirmed the efficacy of the drug on the biochemical surrogate markers of outcome (111-113). 'Hard' clinical endpoints still need to be demonstrated. On the other hand the use of OCA has been associated with an increase in hepatic decompensation in patients with advanced liver disease. This led to a label change where it's use is a contraindication in patients with

decompensated cirrhosis, a history of prior decompensation and in patients with compensated cirrhosis and evidence of portal hypertension (114,115).

There are 2 non-OCA FXR agonists investigated. **Cilofexor:** a phase 2 study, only published as abstract (Kowdley KV et al 2019) , demonstrated that the drug given for 12 weeks improved biochemical parameters of cholestasis with pruritus as side effect . **Tropifexor:** a phase 2 study, also only published in abstract form thus far (Schramm C et al 2018) , has shown a dose-dependent decrease in gamma GT but no effect on ALP after 4 weeks of therapy again with pruritus as side effect.

***PPAR agonists*:**

Ten randomized clinical trials including the BEZURSO trial reported a positive effect of fibrates on cholestasis (116)). In the BEZURSO trial **bezafibrate** at dose of 400 mg /d improved ALP and bilirubin during a follow up of 2 years and a normalization of ALP and bilirubin was achieved in 31 % of patients vs 0% in the placebo group (117). There was also an improvement of non-invasive markers of liver fibrosis (liver stiffness values and the Enhanced Liver Fibrosis score). The drug was well tolerated and myalgia was the most common side effect, that occurred in 20% of the active group vs 10% in the placebo group. Serum creatinine increased in 5 % of patients at 2 years , a well-known class effect of fibrates with no long-term influence on renal function (118,119). Overall, a recent systematic review concluded that fibrates are safe and well tolerated in patients with PBC (120). In favour of the use of bezafibrates is the improvement of pruritus in some of the patients (121). In a large Japanese retrospective cohort study the combination of bezafibrate and UDCA improved transplant-free survival in a cohort in Japan (122). There are no data on safety in patients with advanced liver disease. Evaluation

of paired liver biopsies in 31 patients after 5 years showed a significant decrease in liver damage as reflected by Ludwig and Ishak scores. Overall, regression of fibrosis was attained in 48% of patients (123).

Bezafibrate is currently not approved for the treatment of cholestatic liver diseases and thus used off-label when prescribed to patients with PBC (124). Moreover, bezafibrate is not available in the USA, where fenofibrate with a narrower PPARα-spectrum is available and has also demonstrated beneficial effects in smaller studies (125). An update from the AASLD in 2021 mentioned that fibrates can be considered as off-label alternatives for patients with PBC and incomplete response to UDCA but are discouraged in patients with decompensated liver disease (115).

Seladelpar has been explored in 4 clinical studies. The first phase 2 study which used dosages of 50 mg and 200 mg/day was terminated early after 41 subjects were enrolled since 3 patients developed grade 3 elevations in ALT levels that were reversible after cessation of the drug (126).The next phase 2 study which has only been published in abstract (Levy C et al 2020) , used lower doses where 5 mg and the 10 mg consistently lowered ALP levels that was maintained over 52 weeks . Interestingly, 31% of patients in the 10 mg dose group achieved normalization of ALP by week 12. In this study an decrease in ALT levels was seen over 12 weeks The study also confirmed that ALT elevations are a dose-related phenomenon. In a subsequent phase 3 study using doses of 5 mg and 10 mg/day Seladelpar was well tolerated. However, this study was prematurely terminated shortly after completing enrolment (n=265) due to histological observations suggestive of drug induced liver injury in a separate study for a different indication , namely NASH patients. Finally, this observation was not confirmed. The data from this phase 3 study were consistent with those in phase 2 After 3 months of therapy reductions in ALP were highly significant and Seladelpar 10 mg achieved normalization of ALP in 27.3% of the patients. Seladelpar improved pruritus and fatigue in a dose dependent

manner; no cases of severe myalgia were observed (127). A phase 3 confirmation trial using 10mg/day is ongoing.

In a placebo controlled phase 2 study **Elafibranor** improved cholestasis after 12 weeks and also improves pruritus (128). A phase 3 study with 80 mg/day is ongoing . In an open label study **Saroglitazar** improved biochemical markers of cholestasis after 16 weeks of therapy (129).

Other drugs:

FGF 19 mimetic: **Aldafermin (NGM282)** improved ALP after 28 days. Gastrointestinal side effects such as diarrhoea, abdominal pain and nausea were seen but not pruritus (130). Interestingly, Aldafermin improved cholestatic liver enzymes in PBC but not in PSC (131). However, an improvement of non-invasive fibrosis markers was observed.

Budesonide : Several small studies in the past showed promising results with Budenoside (132-134). In the most recent study in patients at high risk of disease progression, Budenoside at a dose of 9 mg with a reduction to 3 mg in case of normalization of ALP values, in combination with UDCA, was associated with improved biochemical markers of cholestasis and improvement of the POISE score . However this combination did not improve liver histology and was associated with a high dropout rate. The adverse events leading to premature discontinuation of the study occurred in 23 % vs 9 % for the placebo group (135).

Setanaxib: A large, 24-week phase 2 trial was carried out exploring the possible effect of the drug on cholestasis , fibrogenesis and quality of life. Based on the positive results obtained in the study a phase 2/3 study is in progress focusing on patients with PBC and fibrosis.

Several trials investigating orally-administered, small-molecule IBAT inhibitors have been conducted in paediatric cholestasis with a few studies in adult patients with PBC (136,137). **Linerixibat** is an oral agent that is minimally absorbed and a selective inhibitor of human

IBAT (138). In a 14 day trial with 21 patients with PBC Linerixibat (GSK2330672) reduced pruritus and total serum BA concentrations compared with placebo and was generally well tolerated (139). **Maralixabat** (also known as lopixibat/ LUM001/SHP625) and **odevixibat** (A4250) have been successfully developed for the treatment of paediatric cholestatic liver diseases such as progressive familial intrahepatic cholestasis, Alagille syndrome and biliary atresia and have already received approval for some of these indications (140,141).In children with cholestatic diseases orally administered **odevixibat** was well tolerated, reduced serum bile acids, and improved pruritus and sleep disturbance (142).

In a phase 2 randomized controlled trial, **Rituximab** over the 12-month study period showed no evidence of effectiveness for the treatment of fatigue in PBC (143). Based on the findings that **Golexanolone** was well tolerated and improved cognitive performance in patients with hepatic encephalopathy, a phase 2 clinical trial was initiated to explore the effect of the drug in PBC patients suffering from central fatigue and cognitive dysfunction (96).

Experience in PSC

An overview of drugs in advanced development for PSC is give in Table 1.

UDCA: the value of UDCA has been extensively investigated. Based on published evidence, the role for UDCA at moderate/medium dose in slowing the progression of PSC-related liver disease is still unclear while high doses of UDCA is harmful and should be avoided (144-147).

Obeticholic acid was investigated in a phase 2, randomized, double-blind, placebo-controlled, dose-finding study. In this AESOP study treatment with OCA 5-10 mg reduced ALP during an initial 24-week treatment period. The result was sustained during a further 2-year, long term

extension of the study. The most common side effect of obeticholic acid in the study was again pruritus (148).

Cilofexor: in a 12-week, randomized, placebo-controlled study, cilofexor was well tolerated and led to significant improvements in liver biochemistries, markers of cholestasis and non-invasive markers of liver fibrosis without aggravation of pruritus (149). The risk of progression of fibrosis in patients without cirrhosis is currently investigated in a phase 3 study.

Aldafermin (NGM282) : in a 12 week double-blind, placebo-controlled phase 2 trial NGM282 potently inhibited bile acid synthesis and decreased fibrosis markers, without significantly affecting ALP levels with gastrointestinal symptoms more frequent in the NGM282 treatment groups possibly reflecting the direct anti-inflammatory and antifibrotic action of the compound (150).

Bezafibrate: In a small retrospective study the combined UDCA with bezafibrate resulted in a significant biochemical improvement and pruritus decrease in PSC patients with incomplete response to UDCA and the drug is currently further investigated in ongoing investigator initiated trials (151).

Seladelpar is investigated in an ongoing phase 2 trial.

NorUDCA : a randomized controlled trial, including 38 centres from 12 European countries, evaluated the safety and efficacy of 3 doses of oral norUDCA (500 mg/d, 1,000 mg/d or 1,500 mg/d) compared with placebo during 12 weeks. NorUDCA significantly reduced ALP values dose-dependently in all treatment arms. The safety profile was excellent and comparable to placebo (152). A phase 3 trial is ongoing.

Cenicriviroc a dual antagonist of CCR2 and CCR5 was investigated in a single-arm, open-label, exploratory study. After 24 weeks adults achieved a only modest reduction (median 18%) in the surrogate endpoint of ALP. The most frequent events were rash, fatigue, and dizziness (153).

Simtuzumab (a monoclonal antibody directed against LOXL2) was investigated in a large placebo controlled trial in 234 patients. The primary efficacy endpoint was mean change in hepatic collagen content assessed by morphometry between baseline and week 96. Additional endpoints included change in Ishak fibrosis stage. Treatment with the LOXL2 inhibitor simtuzumab did not provide clinical benefit in patients with PSC (154).

Conclusions and future perspectives

UDCA at a dose of 13-15 mg /kg is still the cornerstone for the treatment of PBC (Fig 2). In case of an incomplete response or intolerance, which is rare, second line therapy should be initiated. Incomplete response occurs especially in patients with an early age at diagnosis (<45y) and when diagnosed in advanced stages. An incomplete response is currently defined as ALP level > 1.5 x ULN or abnormal levels of bilirubin when a correct dose of UDCA (13 – 15 mg/kg) is given for at least 6 months. It is expected that in the near future, when several second line drugs become available and combination therapy is possible, that complete normalization of markers of cholestasis including ALP will be achieved (155,156). In this regard, any decrease in bilirubin (even within the normal range) is associated with an improvement of outcome (157). These parameters are therapeutic goals in a phase 2 combination study of OCA with bezafibrate which is ongoing.

The introduction of nuclear receptors has accelerated the development of second line therapies for PBC. The only approved second line therapy today is the steroidal nuclear receptor FXR agonist obeticholic acid where the dosage is limited by the occurrence of pruritus. It was hoped that treatment with non- steroidal FXR agonists such as cilofexor and tripifexor induces less pruritus. However, this evidence is lacking. In Europe another nuclear receptor bezafibrate, a pan-PPAR agonist , is frequently used as off label as second line therapy for PBC. Bezafibrate has the advantage that it also improves pruritus; however, in some patients myalgia may occur. Pruritus and fatigue are frequent and important symptoms of patients with PBC. In this regard, Seladelpar and Elafibronar which both are PPAR agonists, improved pruritus with no cases of severe myalgia, observed yet.

In the near future the availability of several second line drugs will allow a more individualized approach using a personalized combination of drugs based on whether the patient is in an early disease stage , whether there is fibrosis or if the patient suffers from pruritus or severe fatigue.

PBC is a rare disease and with the introduction of second line therapies in clinical practice the recruitment of PBC patients for future clinical trials will be a challenge. Placebo controlled trials will no longer be possible for this indication.

In the case of PSC there is no approved treatment yet. The design of clinical trials is hampered by the absences of well-defined and validated endpoints. Several new drugs are explored including nuclear receptor agonists and norUDCA.

Finally, medical treatment for patients with advanced stages of both PBC and PSC is not available. This remains an unmet need.

Abbreviations

PBC: primary biliary cholangitis ; PSC: primary sclerosing cholangitis ; BA: bile acid ; ALP : alkaline phosphatase ; UDCA: ursodesoxycholic acid ; NR: nuclear (hormone) receptors; FXR: farnesoid X receptor; PPAR: peroxisome proliferator-activated receptor; GR: glucocorticoid receptor ; IBAT: Ileal BA transporter ; OCA: obeticholic acid ; FGF : fibroblast growth factor; norUDCA: Nor-ursodeoxycholic acid ; LOXL2 : Lysyl oxidase-like 2 ; NOX : NADPH oxidase

References

In attachment

Tables

Table 1. An overview of the established drugs approved for PBC and those in advanced stages of clinical development for PBC and PSC

In attachment

Figures

Figure 1: Mechanism of action of anticholestatic drugs.

In attachment

In hepatocytes (left panel), activation of FXR downregulates BA uptake via the Na+/taurocholate co-transporting polypeptide (NTCP) and BA synthesis (via CYP7A1), while inducing bile salt export pump (BSEP), thus limiting hepatocellular BA load. CYP7A1 is also inhibited by FGF-19 (produced in the intestine, see below) as well as PPARα and δ. Both FXR and PPARα stimulate phospholipid secretion (via MDR3), thus counteracting intrinsic bile toxicity (right hepatocyte panel, centre). At the basolateral membrane organic solute transporter (OSTα/OSTβ), multidrug resistance-related protein (MRP) 3 and MRP4 facilitate alternative hepatic BA pump which is also in part induced by FXR (right hepatocyte panel). Drugs such as norUDCA undergo a cholehepatic shunting resulting in ductular HCO3-- secretion ('HCO3-- umbrella') and protecting cholangiocyte against BA toxicity (centre). In the intestine (lower left panel), BAs are normally taken up by the ileal BA transporter (IBAT) followed by efflux via OSTα/OSTβ. Intestinal FXR induces fibroblast growth factor (FGF) 19, which circulates via portal blood back to the liver and binds to its receptor FGFR4, subsequently inhibiting BA synthesis. IBAT inhibitors interfere with BA uptake in the terminal ileum, while FGF-19 mimetics have metabolic effects but lack the pro-proliferative, potentially pro-carcinogenic effects of intrinsic FGF-19. Moreover, therapies targeting FXR and PPARs and novel BA derivatives such as norUDCA also have direct and indirect anti-inflammatory, immunomodulatory and anti-fibrotic effects in immune cells and hepatic stellate cells (lower right panel, see text for further details). Other therapeutic approaches directly target underlying immune pathogenesis and fibrogenesis (not shown, see text for details)

Figure 2: Algorithm for the treatment of PBC

In attachment

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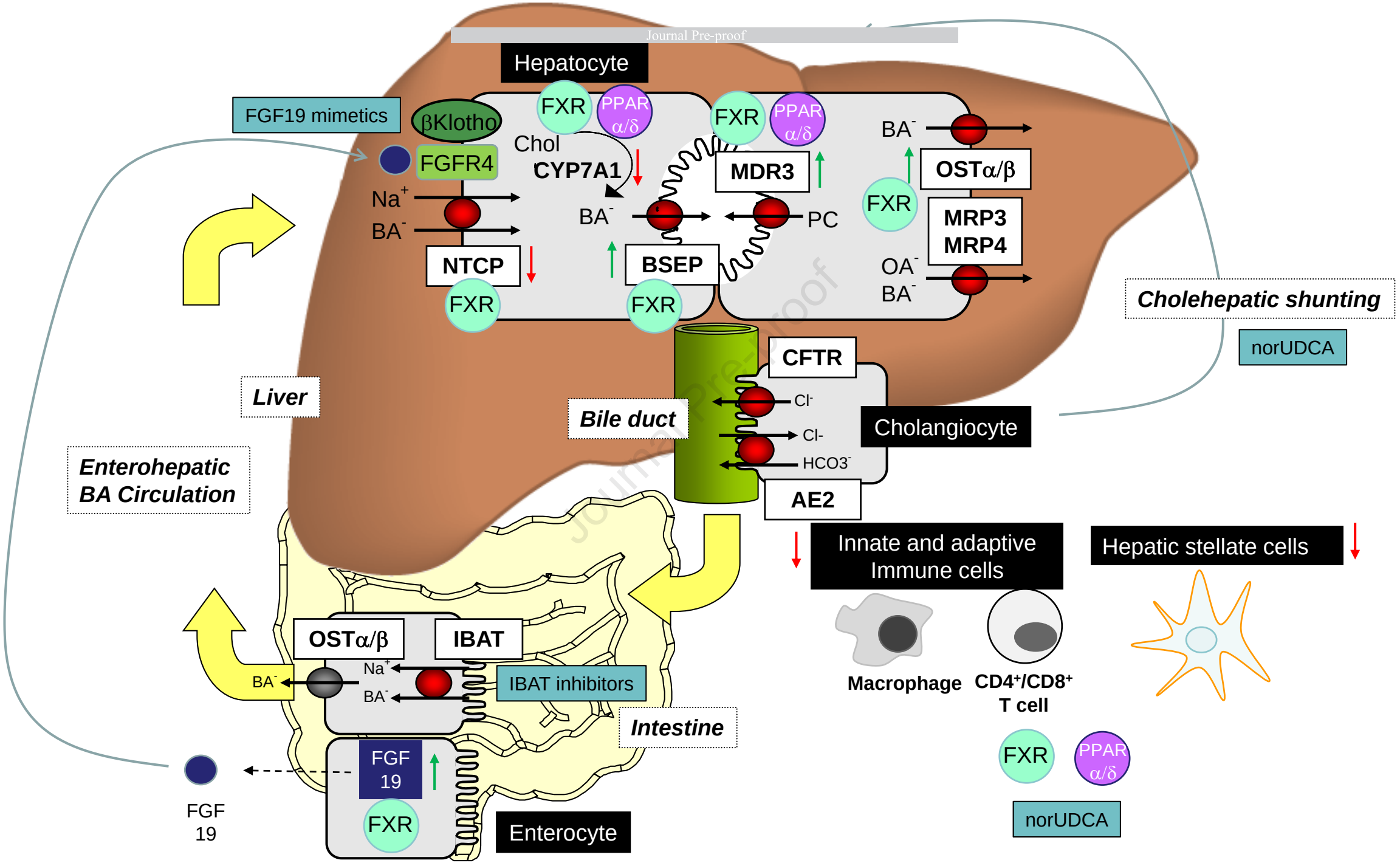
Table 1. Approved and drugs in advanced development for PBC and PSC with main results and side effects

Compound	PBC	PSC
Steroidal FXR agonists: - **Obeticholic acid**	POISE trial (ref 16): On the market (conditional approval)	Phase 2 (ref 148) : Reduction of ALP after 24 wks , maintained for 2 yrs / pruritus
Non-steroidal FXR agonists: - **Cilofexor** - **Tripifexor**	Phase 2 (abstract): Improved cholestasis after 12 wks / pruritus Phase 2 (abstract): Improvement of GGT after 4 wks / pruritus	Phase 2 (ref 149): Improvement of cholestasis and non-invasive markers of fibrosis Phase 3 in progress _
PPAR agonists: - **Bezafibrate** - **Seladelpar** - **Elafibranor** - **Saroglitazar**	BEZURSO trial (ref 117): Off label in Europe/ myalgia Phase 2 (ref 126, abstract): Improvement of cholestasis maintained for 52 wks Phase 3 ongoing Phase 2 (ref 128) : Improvement of cholestasis after 12 wks Phase 3 ongoing Open label (ref 129): Improvement of cholestasis after 16 wks	Small retrospective study (ref 151): Improvement of cholestasis and decrease in pruritus Phase 3 in progress Phase 2 ongoing _-_ _ -
FGF 19 mimetic: - **Aldafermin**	Phase 2 (ref 130) : Improvement of cholestasis after 28d/ gastrointestinal side effects	Phase 2 (ref 150): Reduction of markers of fibrosis after 12 wks / gastrointestinal side effects
NorUDCA	Phase 2 initiated	Phase 2 (ref 152): Dose dependent improvement of ALP after 12 wks Phase 3 ongoing
CCR2/CCR agonist: - **Cenicrivivoc**	_	Single arm open label study (ref 153): Modest reduction of ALP after 24 wks / rash, fatigue and dizziness
LOX L2 inhibitor: - **Simtuzumab**	_	Phase 2 (ref 154): No clinical benefit
NOX 1 & 4 inhibitor: - **Senataxib**	Phase 2 : Improvement of cholestasis Phase 3 initiated	_

Budenoside	Investigator driven (ref 135) Improvement of cholestasis/ no improvement of histology/ high dropout rate	–



First line therapy

- UDCA 13-15 mg/kg/d

↓

- *Incomplete response* after 6-12 months*
- *Intolerance (rare)*

Established second line therapy**

- Obeticholic acid 5-10 mg/d
  in function of tolerance and response rate
- Bezafibrate 400 mg/d (*off label)*

↓

- *Intolerance*
- *Inadequate response*

Drugs under investigation: phase 3**

- Combination of Obeticholic acid and Bezafibrate
- PPAR agonists
  - Seladelpar
  - Elafibranor

** Currently based on ALP ≥ 1,67 x ULN and total bilirubin ≤ 2 x ULN*

*** Patients with cirrhosis are excluded*