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Novel aspects in the management of cholestatic liver diseases

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Short title: Cholestatic liver diseases

Abstract

Background: There is a great need for risk stratification in patients with chronic cholestatic diseases in order to allow for more personalized care and adapted management as well as for well-designed therapeutic trials. Novel tools for monitoring primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) patients have been recently proposed. In addition, major insight has been gained into bile acid physiology during the last decade including the role of bile acids as metabolic modulators and the gut-liver axis. As a consequence, alongside drugs targeting immune response or fibrotic processes, a number of novel anti-cholestatic agents have undergone pre-clinical and clinical evaluation and have shown promising results although none has been approved yet. **Key Messages:** Biochemical non-response to UDCA (mainly defined by bilirubin and ALP levels at one year) is a strong prognostic factor in PBC whereas present biochemical surrogates are far from robust in PSC. By contrast, liver stiffness measurement by vibration-controlled transient elastography (VCTE) is a very promising tool in both PBC and PSC. Novel therapeutic approaches include (i) agonists of nuclear receptors, especially farnesoid X receptor (FXR), pregnane X receptor (PXR), glucocorticoid receptor (GR) and peroxisome proliferator-activated receptor α (PPAR α) that are transcriptional modifiers of bile formation; (ii) agonists of TGR5, a bile acid membrane receptor expressed in various tissues; (iii) inhibitors of the ileal apical sodium bile acid transporter (ASBT); (iv) derivatives of the FXR-induced fibroblast growth factor 19 from the ileum that suppresses hepatic bile acid synthesis; and (v) *nor*UDCA, a side chain shortened UDCA derivative with specific physicochemical and therapeutic properties. The most advanced clinical evaluation (PBC patients) relates to agonists for PPAR α , FXR and GR/PXR most often in combination with UDCA, namely fibrates, obeticholic acid (OCA) and budesonide respectively. Existing results look promising even though some side effects are worrisome such as pruritus in OCA treated patients. Results of large well designed studies are eagerly awaited. **Conclusions:** Major advances in the management of cholestatic liver diseases are in progress and promising times for these patients seem likely in the near future.

Key words: elastography, fibrates, obeticholic acid, primary biliary cirrhosis, primary sclerosing cholangitis.

Introduction

Ursodeoxycholic acid (UDCA) is the current backbone of the treatment of chronic cholestasis. Its use is universal in primary biliary cholangitis (PBC) but depends on local policy in primary sclerosing cholangitis (PSC) because of the lack of proven benefit on survival of PSC patients despite improvement in liver tests (1). Nevertheless, even in PBC, not all patients respond to UDCA and there is a clear need for second-line therapy. Efforts have been made to provide risk stratification in chronic cholestatic diseases (2). Recent tools such as vibration-controlled transient elastography are likely to play a major role in the management of both PBC and PSC whereas the prognostic value of the biochemical course (including response to UDCA) is well established in PBC only.

Major insight has been gained into bile acid physiology during the last decade including the role of bile acids as metabolic modulators and the gut-liver axis. As a consequence, alongside drugs targeting immune response or fibrotic processes, a number of novel anti-cholestatic agents have undergone pre-clinical and clinical evaluation and have shown promising results although none has been approved yet.

Risk stratification and follow-up monitoring

Patients with chronic cholestatic diseases remain a heterogeneous cohort (especially those with PSC) with variable clinical progression. There is a great need for risk stratification in these patients in order to allow for more personalized care and adapted management as well as for well-designed therapeutic trials (2). In this regard, biochemical course and vibration-controlled transient elastography have been the most studied markers of prognosis.

Biochemical course

PBC

UDCA is currently the only drug approved specifically for the treatment of PBC. Its use is universal and recommended regardless of histological stage (3). As a consequence, a major issue is to identify non-invasive surrogate markers of progression in UDCA-treated PBC. A number of studies have shown that the “biochemical response” 1-2 years after UDCA treatment has a strong prognostic value and thus has a role in clinical practice. Different definitions have been proposed (Table 1) (4-8). Beside serum bilirubin, serum alkaline phosphatase (ALP) has emerged as an excellent surrogate, although there is still some debate about the optimal cut-off for ALP, probably 1.5 -2.0 ULN (9). Assessing biochemical response at 6 versus 12 months has been proposed but further validation is

needed (10). All these response criteria have been independently and externally validated with Paris criteria discriminating best in a very large UK study (11). Complex scoring systems derived from large multicenter cohorts, UK-PBC (12) and Global PBC Study Group (13), have been recently published and were aimed to provide a range of possible scores, instead of crude dichotomization (responder versus non-responder).

PSC

Regarding biochemical surrogates as well as effective treatment, PSC stands far behind PBC. Despite two decades of randomized trials, there is still no firm evidence that UDCA is truly beneficial in improving transplant free survival in PSC (1, 14). Bilirubin has been shown to be a marker of prognosis but levels only rise in late-stage PSC, fluctuate with flares of cholangitis and are potentially modified by biliary interventions. As a result, bilirubin is considered unsuitable as endpoint for clinical trials according to the International PSC Study Group (15). The prognostic value of ALP is still debated although a number of studies have fuelled the notion that ALP (irrespective of UDCA receipt) could be a surrogate marker for transplant-free survival (16-19). However ALP thresholds differed from one study to another as well as time points and cross-validation is lacking (2). In addition, it should be kept in mind that, in the very high UDCA trial, clinical worsening occurred in the treated group despite significantly more improvement in ALP levels compared to placebo (20). Consequently, ALP is currently viewed more as a useful parameter for stratification in clinical trials than as a validated surrogate endpoint for clinical outcome (15).

Vibration-controlled transient elastography (VTCE)

Liver stiffness measurement by VTCE has proven to be an excellent non-invasive marker of fibrosis as well as a powerful predictor of prognosis in chronic hepatitis C despite some limitations including an incomplete applicability with an approximate 15% rate of failure or unreliable results. A number of studies have evaluated the performance of VTCE in chronic cholestatic diseases.

In PBC, accuracy of VTCE in fibrosis staging has been demonstrated in several hundreds of patients (21, 22). Even more interesting was the finding that baseline measurements and rate of liver stiffness progression were strongly and independently linked with outcomes (21). In PSC, similar findings have been reported in terms of both fibrosis staging and prognostic value (but in a smaller number of patients) (23) and VTCE was recently identified by the International PSC Study Group as the most promising non-invasive surrogate endpoint for clinical trials (15). However, a special attention should be paid to major biliary obstruction by dominant strictures that has been shown to increase liver stiffness, irrespective of fibrosis (24).

Generally speaking, VTCE performs best at extremes of histological stages (mild fibrosis and

extensive fibrosis) and has poorer discriminative capacity for intermediate fibrosis stages, as usually reported with other non-invasive markers of fibrosis. In PBC and PSC, diagnostic thresholds of liver stiffness (Tables 2 and 3) remain to be refined in larger studies especially for PSC. In this regard, an international prospective study of the prognostic value of VTCE is underway in PSC patients (FICUS Study). However, available data strongly support now VTCE-derived liver stiffness (absolute values and variations over time) as major prognostic markers. Nowadays, VTCE every one or two years is part of the routine follow-up of patients with chronic cholestatic diseases in some reference centers.

Novel potential therapeutic approaches in cholestatic disorders

Generally speaking, therapeutic opportunities in PBC or PSC are offered by targeting the so-called “upstream” immune response, “midstream” biliary injury leading to cholestasis and “downstream” fibrotic processes (25). Novel therapeutic approaches targeting primarily cholestasis include i) agonists of nuclear receptors: farnesoid X receptor (FXR), retinoid X receptor (RXR), pregnane X receptor (PXR), glucocorticoid receptor (GR), peroxisome proliferator-activated receptor α (PPAR α) and vitamin D receptor (VDR) that are transcriptional modifiers of bile formation, ii) agonists of TGR5, a bile acid membrane receptor expressed in various tissues, iii) inhibitors of the ileal apical sodium bile acid transporter (ASBT), iiiii) derivatives of the FXR-induced fibroblast growth factor 19 (FGF19) from the ileum that suppresses hepatic bile acid synthesis and iiiiii) *norUDCA*, a 23-C homologue of UDCA with specific physicochemical and therapeutic properties (26). In addition, a number of these agents have also anti-inflammatory, anti-fibrotic and metabolic effects. The transcriptional regulation of hepatocellular bile formation and the potential therapeutic targets in the enterohepatic bile acid circulation are illustrated in Fig 1 and 2, respectively (26, 27).

The most advanced clinical evaluation (PBC patients) relates to agonists for PPAR α , FXR and GR/PXR most often in combination with UDCA, namely fibrates, obeticholic acid and budesonide respectively, even though most of the data are issued from uncontrolled and/or short term studies.

Fibrates (fenofibrate or bezafibrate) are PPAR α agonists with beneficial effects in chronic cholestasis through anti-inflammatory actions, decreased bile acid synthesis and enhanced phospholipids biliary secretion (Fig 1) (28). Numerous open studies (especially in Japan) have found that either fibrate monotherapy or in combination with UDCA have clear favourable effects (biochemical normalization or marked improvement) in patients with PBC (29, 30). Notably, a significant improvement of pruritus was reported (31). Adverse effects include myalgias and heartburn. Monitoring serum creatinine is recommended. Although these results look impressive and very promising, rigorous evaluation of fibrate effectiveness and safety is still lacking (32). In this regard, results of the large

ongoing phase III trial (BEZURSO study) assessing bezafibrate (400 mg/d) as an adjuvant therapy to UDCA will be available in 2017.

Obeticholic acid (OCA) is a potent FXR agonist. Among numerous functions including regulation of key aspects of carbohydrate and lipid metabolism, FXR has a major role in the enterohepatic circulation of bile acids and reduces bile acid synthesis (Fig 1 and 2). A large 3-month, placebo-controlled, dose response trial of OCA added to UDCA in PBC patients with an inadequate UDCA response showed at least a 20% reduction in alkaline phosphatase levels in the OCA groups, together with a significant decrease in transaminase, γ -glutamyl transferase, IgM and endogenous bile acid serum levels (33). A 12-month extension trial showed a maintained biochemical response. Pruritus was the principal adverse event with marked worsening in patients receiving 25 or 50 mg/d OCA. The mechanisms of OCA-related pruritus remain unclear. This dose-dependent pruritus seems to limit treatment at doses higher than 10 mg/d but could be overcome through dose-titration. OCA treatment was also associated with decreases in total and HDL cholesterol raising the issue of potential cardiovascular risks in the long term. Interestingly, in the FLINT study testing OCA (25 mg/d) in patients with non-alcoholic steatohepatitis, 23% of patients developed pruritus (vs 6% in the placebo group) and a decrease in HDL cholesterol was also observed (34). Longer term studies are needed with focus on safety and long-term clinical efficacy; full results of the large POISE study are expected to be published soon.

Budesonide is a steroid with an extensive first pass hepatic extraction and, in non-cirrhotic patients, has limited systemic availability and side effects. In hepatocytes, budesonide is a combined GR/PXR agonist involved in bile acid synthesis, metabolism and transport (Fig 1) (35). In PBC patients, budesonide (6-9 mg/d) combined with UDCA was more effective (biochemistries and histology) than UDCA alone in two randomized trials (36, 37) but this was not observed in another study including late stage PBC patients who also developed serious side effects (38). Results of the large ongoing phase III study are eagerly awaited.

norUDCA is a UDCA derivative with one fewer methylene group in its side chain. In experimental models, this side chain structure determines unique physiologic and pharmacologic properties including the ability to undergo cholehepatic shunting and to directly stimulate cholangiocyte secretion, both resulting in a HCO₃-rich hypercholeresis reinforcing the “biliary bicarbonate umbrella” (39). When 24-norUDCA is used in the Mdr2 knockout mice, sclerosing cholangitis improves dramatically (40). The final results of a double-blind, randomized, placebo-controlled, phase II dose-finding trial in patients with PSC are pending.

Evaluation of other potential anticholestatic agents is less advanced (ASBT inhibitors that interrupt the enterohepatic circulation bile acid circulation, non-tumorigenic FGF derivatives, TGR5 or PXR agonists) but experimental or preliminary clinical findings look promising (26). Vitamin D receptor (VDR) agonists are also of interest since VDR is involved in innate and immune activation, bile acid metabolism and detoxification, bile duct integrity and fibrogenesis (26, 41) but only experimental data are available at this time. Lastly, novel potential targets for treating pruritus have been also identified since recent studies have shown that lysophosphatidic acid (LPA), a potent activator of itch neurons, and autotaxin (ATX), the enzyme which forms LPA, are key elements of the pruritogenic signalling cascade (42). In this regard, the beneficial actions of rifampicin on pruritus appear to be mediated through PXR-mediated down regulation of ATX transcription.

Conclusions

Novel tools for monitoring PBC and PSC patients have recently emerged. Their use represents a step forward in risk stratification in order to allow for more personalized care and adapted management as well as for well-designed therapeutic trials. Biochemical non-response to UDCA (mainly defined by bilirubin and ALP levels at one year) is a strong prognostic factor in PBC whereas present biochemical surrogates are far from robust in PSC. By contrast, liver stiffness measurement by VTCE is a very promising tool in both PBC and PSC although large-scale replication studies are needed. These advances have already begun to be applied in clinical practice. For example, liver biopsy in PBC patients is presently mainly indicated in non-responders to UDCA and no longer at the time of diagnosis. Regarding therapy, a number of novel anti-cholestatic agents are under evaluation in terms of efficacy and safety profile. Interestingly, while anti-cholestatic effects of UDCA involve mainly post-transcriptional mechanisms, these novel agents act differently since they are mostly transcriptional modulators and thus, constitute candidates for future combined treatment with UDCA. Promising times for patients with cholestatic diseases seem likely in the near future, provided that “off-target effects” of these drugs are mild!

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FIGURE LEGENDS

Fig 1. Simplified transcriptional regulation of hepatocellular bile formation (adapted from ref 27).

Expression of hepatobiliary transporters is tightly regulated by nuclear receptors (NRs). NRs provide a network for the control of intracellular concentration of biliary constituents. Bile acid (BA)-activated FXR is a central player that represses BA uptake and synthesis (by inhibiting CYP7A1 that is the rate limiting enzyme in BA synthesis), promotes bile secretion via induction of canalicular transporters and induces BA elimination via alternative export systems at the basolateral membrane. Stimulation of AE2 expression increases biliary bicarbonate secretion, thus reducing bile toxicity (“bicarbonate umbrella”). UDCA has no relevant affinities for dedicated BA receptors and post-transcriptional processes (including vesicular targeting of transporters to the membrane) as well as modification of the bile through cholangiocytes (bicarbonate secretion) also play an important role in bile formation (not shown). BA, bile acids; Bili-glu, bilirubin glucuronide; BSEP, bile salt export pump; CAR, constitutive androstane receptor; Chol, cholesterol; CYP7A1, cholesterol-7 α -hydroxylase; FXR, farnesoid X receptor; GR, glucocorticoid receptor; HNF4, hepatocyte nuclear factor; MDR3, multidrug resistance protein 3; MRP2, multidrug resistance-associated protein 2; MRP4, multidrug resistance-associated protein 4; NTCP, sodium taurocholate co-transporting polypeptide; PC, phosphatidylcholine; PXR, pregnane X receptor; PPAR α , peroxisome proliferator-activated receptor alpha; RAR, retinoic acid receptor; SHP, small heterodimer partner; UDCA, ursodeoxycholic acid.

Fig 2. Potential therapeutic targets in the enterohepatic bile acid circulation (adapted from ref 26).

Primary bile acids are absorbed in the ileum via the apical sodium-dependent bile acid transporter (ASBT) where they activate FXR before entering the portal circulation and are taken up in the liver where they activate hepatocellular FXR. In the ileum, activation of FXR leads to FGF19 expression. FGF19, that acts as hormone in inter-organ signalling (gut to liver), enters the portal circulation, binds to the FGFR4/ β Klotho receptor on hepatocytes and, via activation of MAP-kinases, decreases CYP7A1 expression. TGR5 is a G protein-coupled BA membrane receptor expressed in various tissues with the highest expression in gallbladder and colon. In liver, hepatocytes do not express TGR 5 in contrast to Kupffer cells, sinusoidal endothelial cells and intrahepatic bile ducts. Activation of TGR5 inhibits inflammatory processes.

ASBT, apical sodium-dependent bile acid transporter; BA, bile acids; CYP7A1, cholesterol-7 α -hydroxylase; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor;

Table 1. Biochemical response criteria in UDCA-treated PBC (major studies).

	Definition	Time frame	Clinical endpoint	Non response %
Barcelona (4)	>40% decrease of ALP or normalization	12 months	Transplant-free survival	39
Paris 1 (5)	ALP \leq 3 ULN and AST \leq 2 ULN and Normal bilirubin	12 months	Transplant-free survival	39
Paris 2* (6)	ALP and AST \leq 1.5 ULN and Normal bilirubin	12 months	Transplant and hepatic complication-free survival and progression to cirrhosis	52
Rotterdam (7)	Normal Bilirubin and/or albumin	12 months	Transplant-free survival	24
Toronto (8)	ALP \leq 1.67 ULN	24 months	Histological progression	43

*designed for early stage PBC

ALP, alkaline phosphatase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Table 2. Fibrosis staging by VTCE in PBC patients (according to ref 21).

Histological stage of fibrosis*	Number of patients	Cut-offs (kPa)	AUROC
≥ F1	92	7.1	0.80
≥ F2	52	8.8	0.91
≥ F3	30	10.7	0.95
F4	15	16.9	0.99

*METAVIR fibrosis score.

AUROC, area under receiver operating characteristic curve.

Table 3. Fibrosis staging by VTCE in PSC patients (according to ref 23).

Histological stage of fibrosis*	Number of patients	Cut-offs (kPa)	AUROC
≥ F1	60	7.4	0.71
≥ F2	32	8.6	0.84
≥ F3	15	9.6	0.93
F4	9	14.4	0.95

*METAVIR fibrosis score.

AUROC, area under receiver operating characteristic curve.

Fig 1.

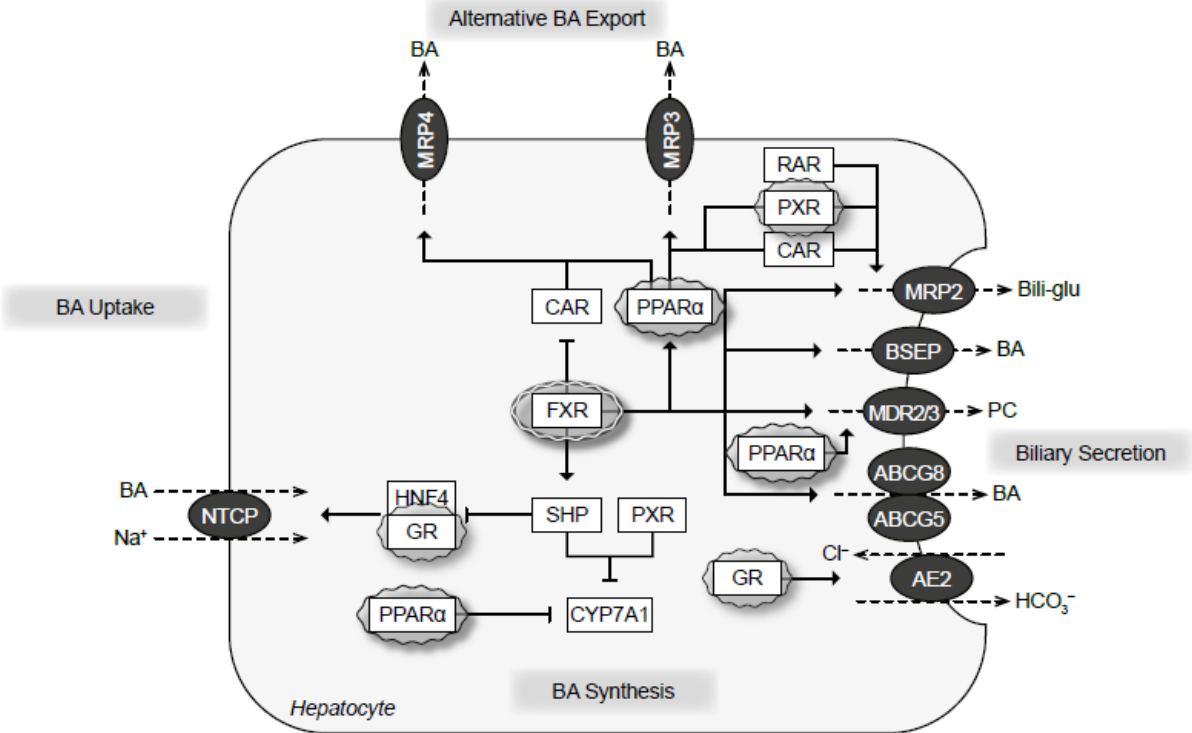


Fig 2.

