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Primary biliary cholangitis: Old and novel therapy

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ABSTRACT

Primary biliary cholangitis (PBC), formerly called primary biliary cirrhosis, is a chronic cholestatic liver disease that progresses slowly to end-stage liver disease. The first Food and Drug Administration (FDA)-approved treatment for PBC was ursodeoxycholic acid (UDCA). This treatment slows the progress of the disease, but approximatively 30–40% of patients fail to respond to UDCA. A number of options are under investigation as second line treatment. Obeticholic acid (OCA), a Farnesoid X Receptor agonist, has been approved in May 2017 by FDA for patients non responders or intolerant to UDCA. The results of a randomized, double blind, phase 3 study of OCA (mg or 10 mg) compared to placebo, showed that approximatively 50% of patients reached a significant reduction in serum alkaline phosphatase, a marker predictive of disease progression, liver transplantation or death. Other emerging therapies include: agents targeting fibrosis, inflammation, or immunological response. Indeed, after 30 years of UDCA therapy as unique choice for PBC patients, a number of targets, derived from a deeper knowledge of the pathophysiology of the disease, has been discovered and they offer different and new therapeutic approaches that are now under evaluation.

1. Introduction

Primary biliary cholangitis (PBC), formerly called primary biliary cirrhosis is a chronic cholestatic autoimmune disease, predominantly affecting middle-aged women, that may progress to end-stage liver disease (1).

Ursodeoxycholic acid (UDCA) is nowadays the first choice and most established therapy for patients with PBC with abnormal biochemical values, administered at the recommended adult dosage of 13–15 mg/kg/day in 2 divided doses [2,3]. UDCA is the 7-β epimer of the primary human bile acid (BA) chenodeoxycholic acid (CDCA), is a hydrophilic bile acid that is mainly absorbed in the small intestine, transported into the liver through the portal circulation (with a 50% first pass extraction rate), conjugated with glycine and taurine, and actively secreted into bile. Conjugated UDCA competes with endogenous bile acids for active transport into portal bloodstream and undergoes enterohepatic recirculation, whereas non-absorbed UDCA molecules are de-conjugated, then converted into lithocholic acid by intestinal bacteria and finally eliminated into stools.

Different mechanisms of action are involved in UDCA's beneficial effect a): choleretic and anti-cholestatic effects, due to intracellular molecular signalling pathways that stimulate cellular secretions by promoting vesicular exocytosis and trans-membrane carriers' insertion [4]; b): cytoprotection against toxic effects of BAs and cytokine-induced injury, by stabilization of cell membranes, enhancement of the defences against oxidative stress and inhibition of apoptosis [5]; in addition to this, UDCA contributes to the biliary bicarbonate ($HCO3^-$) umbrella enhancing biliary $HCO3^-$ secretion against the acidification of the apical surface of cholangiocytes and hepatocytes due to acid BAs [6], and up-regulates liver glutathione synthesis [7]; c) immunomodulation and anti-inflammatory effects, by inhibiting prostaglandin E2 (PGE2) thus blocking the propagation of autoimmune liver injury; moreover, UDCA strongly decreases the hepatocellular expression of MHC class I and the biliary expression of MHC class II, thus interfering with the autoimmune basic mechanisms [8]; it also decreases eosinophil levels in blood stream, and suppresses the immune reaction against PAMPs such LPS's Lipid A [7]; d) increase of the hydrophilicity of the circulating endogenous BA pool [7].

The introduction of UDCA as the first-line therapy for PBC [9] drastically changed the natural history of the disease, lowering the mortality of PBC patients, especially when administered at early stages, as demonstrated in many studies; the survival rate of patients with stage 1 or 2 treated with UDCA long-term was similar to that of general population [10–12]. It was widely demonstrated that UDCA improves blood markers of cholestasis and consistently reduces IgM levels in blood and AMA titres [9,13–19]; moreover, UDCA improves the histological features of PBC patients [20] and decreases the risk of development of oesophageal varices [21]. Patients with PBC do not all respond to UDCA therapy the same way: in fact, UDCA is effective in up to 60% of patients. Biochemical response to treatment has an important impact on prognosis in PBC, and

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can be evaluated using many criteria that focus on prognostic biomarkers and cross-validation of predicting values of response (Table 1, refs. [11, 22–26]). Regardless the differences between each criterion, it is evident that normalization of liver enzymes is a strong predictor of transplant-free survival [27].

It has been demonstrated that the biochemical response to UDCA predicts long-term outcomes [28,29]: therefore, the Global PBC Study Group recently developed a validated scoring systems to predict transplant-free survival of UDCA-treated patients with PBC [30], whereas the UK-PBC Study Group developed a scoring system to predict long-term end-stage liver disease in PBC [31]; moreover, an alteration in the microRNA profile of a cohort of PBC patients non-responders to UDCA therapy was demonstrated [32]. UDCA-responsive patients will generally show biochemical improvement within 6–9 months; however, non-responder patients, up to 40%, are at risk for progressive decline of their condition [33]. Factors that influence response to treatment and therefore PBC outcome are: sex and age at diagnosis, with male sex and young age at diagnosis being independent predictors of UDCA non-response [34], in addition to PBC-specific Anti-Nuclear Antibodies (ANA) positivity (anti-multiple nuclear dot, anti-nuclear envelope protein, and anti-rim-like/membranous anti-nuclear autoantibodies) [1,2], biochemical markers of fibrosis, liver stiffness, presence of cirrhosis and/or portal hypertension, and ductopenia [35,36].

A number of options are under investigation as second line treatment for patients non responders to UDCA.

2. Budesonide

Budesonide is a synthetic steroid with high first-pass metabolism in the liver limiting its systemic side effects compared to standard treatment of glucocorticoids. Budesonide was firstly used for treatment of inflammatory bowel diseases, and the first controlled trial in PBC was started in 1999 [37]. Twenty patients, mainly with early-stage disease were treated with standard dose UDCA plus 3 mg Budesonide 3 times daily, and 19 patients were treated with UDCA plus placebo. After two years liver enzymes, IgM and IgG levels decreased significantly in both groups, but the improvement was more pronounced in the combination groups UDCA + budesonide. Notably, no significant effects on bone density loss or adrenal suppression were identified. In contrast, an open label observational study on 22 PBC patients with a suboptimal response to UDCA, showed only an amelioration in alkaline phosphatase (ALP) after 1 year of treatment with budesonide, but a significant increase in Mayo score prognostic index and a significant loss of bone mass [38]. Moreover, a 3-year open-label trial was performed utilizing a suboptimal dose of budesonide (6 mg daily) plus standard dose UDCA vs UDCA as monotherapy [39]. In the combination arm treated with budesonide plus UDCA liver fibrosis decreased by 25% but increased 70% in the group taking UDCA alone. Finally, a triple therapy with UDCA, budesonide and mycophenolate mofetil was administered in a three-year open study in 15 patients with PBC with suboptimal response to UDCA and with significant interface hepatitis without cirrhosis at liver histology [40]. Patients also received calcium and vitamin D supplementation, and rifampicin for pruritus if necessary. Six out of the 15 patients (41%) experienced a complete normalization of liver function tests, and liver biopsy showed a marked improvement in both activity and fibrosis. Despite its promising results, budesonide cannot be extensively recommended for therapy in PBC patients, due to the risk of serious adverse effects, particularly portal vein thrombosis [41]. Thus, the main contraindication of budesonide is the presence of cirrhosis.

3. PBC investigational targets

Actually, the main investigational targets for treatment of PBC are: i) the farnesoid X receptor (FXR); ii) the peroxisome proliferator activated receptor (PPAR); iii) the fibroblast growth factor 19 signalling (FGF19); iv) biologics.

i) **FXR**

6a-ethyl-chenodeoxycholic (6-ECDCA) or obeticholic acid (OCA) is a potent and selective agonist of FXR. FXR has several mechanisms of action including: 1. Inhibition of bile salt synthesis from cholesterol by down-regulation of several enzymes; 2. Enhancement of bile acid conjugation by increasing several enzymes including the bile acid CoA synthase (BACS); 3. Anti-inflammatory effects through the reduction of several cytokines; 4. Anti-fibrotic effects in multiple animal models [42–44].

The tolerability and efficacy of OCA was evaluated in a double-blind study including 165 patients with PBC and levels of ALP 1.5 to 10-fold the upper limit of normal [45]. Patients were randomly assigned to 3 groups given 10 mg, 25 mg, or 50 mg doses of OCA or placebo once a day for 3 months. Patients maintained their existing dose of UDCA throughout the study. The primary endpoint was change in ALP from baseline to the end of the study. The results of this trial showed a highly statistical and clinically significant reduction in ALP with all three doses (10, 25, and 50 mg) of OCA vs placebo, mean ALP reduction were approximately 20–25% compared to 3% with placebo. Statistically significant improvements were also seen in GGT, ALT, AST and in conjugated bilirubin levels. In the open extension study over 12 months 78 patients experienced a further decrease in ALP. Pruritus was the only clear clinically meaningful adverse event that differed between OCA treatment and placebo, and was dose-related.

Recently, a phase 3, double-blind, placebo-controlled trial and long term extension OCA in patients with PBC has been published [46]. Two hundred and seventeen patients with inadequate response to UDCA or intolerant to UDCA were randomly assigned to receive OCA at a dose of 10 mg, or to a OCA titration group (starting with 5 mg with adjustment to 10 mg) or placebo (indeed this group continued to receive UDCA). The primary end-point was an ALP level of <1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, and a normal total bilirubin level. At the time of the design of the phase 3 clinical study, ALP <1.67 × upper normal value after 1 year of follow-up was shown to be predictive of histological progression of PBC, both alone and in combination with bilirubin [29]. The minimum 15% reduction in Alp was included in the composite to ensure that patients who initiated the study with an ALP close to the 1.67 cut-off had a clinically meaningful ALP response in order to be considered to have met the primary end-point. This outcome occurred in more patients in the 5–10 mg group (46%) and in the 10 mg group

Table 1
Established criteria for response to UDCA.

Criteria	Biochemical endpoints	Evaluation time
Barcelona (11)	ALP 40% decrease or normalization	1 year
Paris I (22)	ALP <3 × ULN and ALT <2 × ULN and bilirubin <1 mg/dl	1 year
Paris II (23)	ALP <1.5 × ULN and ALT <1.5 × ULN and bilirubin <1 mg/dl	1 year
Rotterdam (24)	Normalization of bilirubin and albumin	1 year
Toronto (25)	ALP <1.67 × ULN	2 years
Beijing (26)	Barcelone, Paris I, or Toronto criteria	6 months

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; ULN: upper limit of normal.

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