Ursodeoxycholic Acid Treatment in Primary Sclerosing Cholangitis

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Overview and Clinical Epidemiology

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic disorder of the liver characterized by three major features: biliary inflammation and periductal fibrosis on liver histology, multifocal biliary strictures alternating with segmental ductal dilatation on cholangiography, and a cholestatic serum biochemical profile [1, 2]. Unlike most other cholangiopathies, i.e., disorders primarily of or affecting the biliary tract [3, 4], PSC can affect individuals of essentially all ages and racial backgrounds, remains etiopathogenically perplexing, and lacks established medical therapy despite decades of laboratory-based investigation, translational studies, and clinical trials [1, 5]. It is because of these factors that PSC has, unfortunately, been regarded as the "black box" of liver disease [6].

Although the fundamental underpinnings and optimal management approaches for PSC remain uncertain, it is clear that, as a result of these uncertainties and the generally progressive nature of PSC, there is substantial public health and patient-level burden due to this disorder. Indeed, PSC represents a major risk factor for cholangiocarcinoma (CCA) [7], carries a median liver transplantation (LT)-free survival of 15 years [8], and (despite its rarity) is a leading indication for LT in countries around the world [9]. Although LT can be curative for PSC and PSC-associated CCA, it is only performed in highly selected patients and centers, and even suitable candidates may experience recurrent disease (≈3–4 % per year) [10]. Lastly, quality of life (QOL) is also significantly impaired in patients with PSC, both pre- and post-LT, and is related to debilitating symptoms such as pruritus and fatigue as well as the unpredictable disease course and complications related to coexisting inflammatory bowel disease (IBD) [11–13].

Proposed Etiopathogenesis of and the Basis of Bile Acid Therapy in PSC

Although PSC remains an idiopathic disorder, prevailing hypotheses regarding its etiopathogenesis suggest that a disruption of gut-liver axis signaling at various levels may play a fundamental role [6]. These hypotheses are largely based on

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the premise that enterohepatic generation and/or circulation of microbial metabolites, derivatives, or other molecules can initiate and perpetuate aberrant or exaggerated cellular responses and subsequent biliary injury. This has been the subject of ongoing investigation over the last several decades, with the goal being to identify potentially causal molecules and pathways and develop targeted therapies accordingly.

Representing perhaps the most widely investigated molecule and certainly the most extensively studied pharmacotherapy in PSC is ursodeoxycholic acid (UDCA) [14]. First isolated over a century ago from *Thalarctos maritimus* (now known as *Ursus maritimus*), i.e., the polar bear, UDCA is a hydrophilic, 3,7-dihydroxy bile acid (BA). In most vertebrates, including *Homo sapiens*, UDCA is a secondary BA and only a minor component (<5%) of the BA pool; the major known exception among vertebrates is the Ursidae family, particularly *Ursus americanus* (the American black bear), wherein UDCA is typically a relatively major component (>5–30%) of the BA pool [6, 15]. BA physiology and the potential therapeutic applications of BA therapies are shown in Fig. 11.1 and discussed in greater detail in recent review articles [16, 17].

Based on studies in patients as well as various lines of experimental (e.g., model system) data, the mechanisms through which UDCA is believed to exert therapeutic effects in cholestatic disorders include dilution of hydrophobic (or otherwise "toxic") BAs, promotion of their excretion, upregulation of the biliary bicarbonate umbrella [18, 19], immunomodulation, and anti-inflammatory actions [2, 12, 15, 20–22. In addition, recent data suggest that UDCA may have anti-senescent properties [23]; while the liver has traditionally been regarded as an organ resistant to aging [24], recent studies have shown cellular senescence (in particular cholangiocyte senescence) to be increased in PSC [5], and this finding has been regarded as a marker and driver of biliary injury [23, 25].

Perhaps somewhat surprisingly, evidence supporting a therapeutic role for UDCA in PSC (or animal models thereof) has been inconsistent, with some studies even suggesting detrimental effects at high doses (discussed further below) [19, 26, 27]. As a result, because of the lack of consistently perceived benefits, in their respective practice guidelines, the American Association for the Study of Liver Diseases (AASLD) [21] and European Association for the Study of the Liver (EASL) [20] advise against and provide no specific recommendation, respectively, regarding the use of UDCA in patients with PSC.

Clinical Trials of UDCA in PSC

The earliest clinical studies of UDCA were published in the late 1980s [21, 28, 29] and, albeit uncontrolled, demonstrated promising symptomatic and objective improvements among patients with PSC [30]. These studies soon led to the first randomized controlled trial (RCT) of UDCA, which demonstrated significant improvements in multiple biochemical end points as well as in liver histology [31]. Since then, seven other RCTs have been conducted, initially with low (10–15 mg per kg body weight per day [mg/kg/d])-, then intermediate (17–23 mg/kg/day)-, and most recently high-dose (28–30 mg/kg/day) UDCA (Table 11.1) [14]. While low-dose UDCA was repeatedly shown to yield biochemical improvements, it has not been convincingly shown to improve outcomes, and thus its routine use in PSC is not recommended [21].

High-dose UDCA has been studied in PSC and shown to be associated with an increase in serious adverse outcomes. Specifically, treatment with 28–30 mg/kg/day was found to be associated with a significantly increased risk of major adverse events in a recent RCT of 150 patients with PSC, which was stopped early [19]. At the time of study termination (6 years' post-study initiation), 30 patients in the UDCA group (39%) versus 19 patients in the placebo group (26%) had reached one of the preestablished clinical end points, namely, development of cirrhosis, varices, CCA, LT, or death. After adjustment for baseline characteristics, the risk of a primary end point was 2.3 times greater for patients receiving UDCA compared to the placebo group ($p<0.01$) and 2.1 times greater for death, LT, or LT listing criteria ($p=0.038$). In addition, serious adverse events were more common in the UDCA group

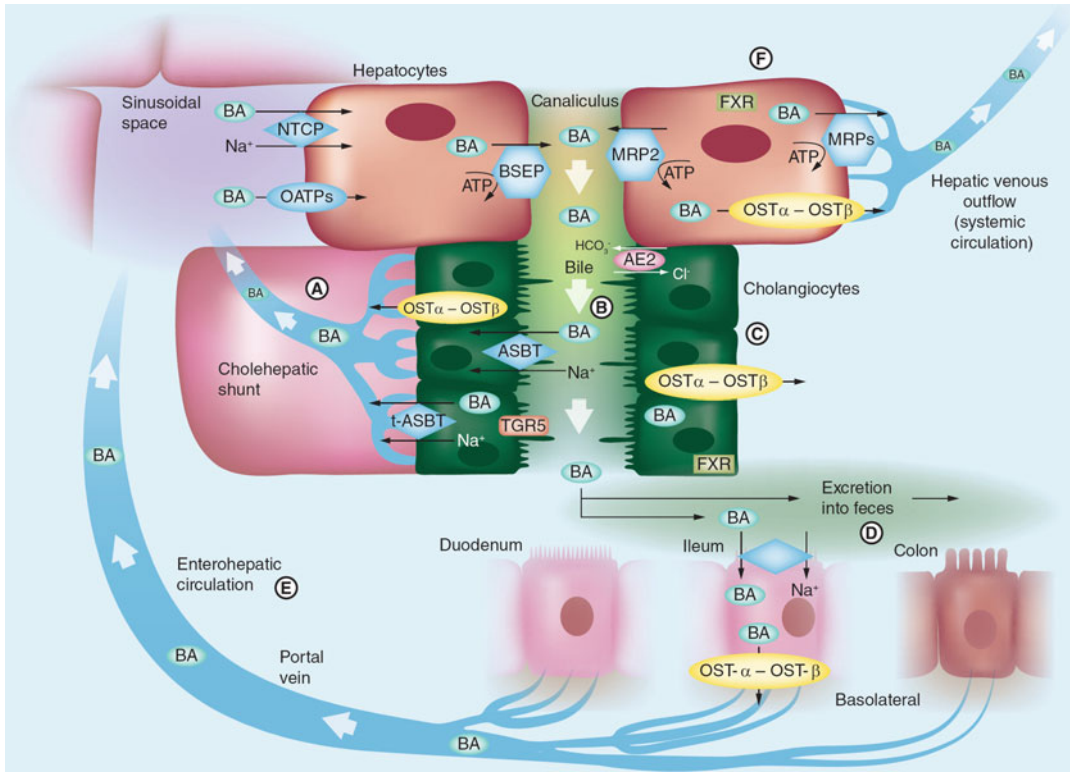

Fig. 11.1 Bile acid physiology and circulation: an avenue for therapeutic applications. Bile acids (*BAs*) are synthesized by hepatocytes and subsequently secreted into canalicular bile by means of specialized hepatocyte canalicular membrane transporters. Canalicular bile drains into the biliary tree and is modified by the epithelial cells lining it, that is, cholangiocytes. Bile then drains into the proximal small bowel, that is, duodenum, and is metabolized by enteric bacteria. Approximately 95% of BAs are reabsorbed in the terminal ileum and enter the portal vein to be recycled back to the liver via the enterohepatic circulation. Once in the sinusoids of the liver, BAs can be taken up by hepatocytes and secreted back into bile. A fraction of (unconjugated) BAs in the biliary tree is taken up by cholangiocytes at the apical membrane (i.e., prior to reaching the small intestine) and returned to the liver sinusoids via the cholehepatic shunt. Some endogenous and synthetic BAs as well as BA analogs have considerably distinct pharmacologic properties, including but not limited to the degree to which they are cholehepatically shunted (e.g., nor-UDCA being a potent stimulator of cholehepatic shunting) or their potency for agonizing receptors such as the farnesoid X receptor (e.g., obeticholic acid being a potent FXR agonist). The unique properties of some BAs and BA analogs can be harnessed for therapeutic purposes in hepatobiliary diseases including PSC; indeed, this represents an area of ongoing biomedical research. Key: *AE2* anion exchange protein 2, *ASBT* apical sodium-dependent bile acid transporter, *BSEP* bile salt export pump, *MRP* multidrug resistance protein, *NTCP* Na+ (sodium)-taurocholate cotransporting polypeptide, *OATP* organic anion-transporting polypeptide, *OST* organic solute transporter, *t-ASBT* truncated apical sodium-dependent bile acid transporter, *TGR5* G protein-coupled bile acid receptor 1 (Adapted with permission from the Mayo Foundation for Medical Education and Research. All rights reserved)

compared to the placebo group (63% versus 37%, $p<0.01$). While the mechanisms of these inferior outcomes with high-dose UDCA remain uncertain, they may ostensibly be due to toxic metabolites of supratherapeutic UDCA administration and seem to be particularly affect patients with early-stage disease [27]. Based on these results, high-dose UDCA is not recommended in PSC and should not be prescribed.

To date, the most intriguing and favorable RCT-derived data supporting the role of UDCA in PSC have been with use of intermediate-dose UDCA. For example, Mitchell et al. [32] found significant improvements in serum biochemistries, hepatic fibrosis stage, and cholangiographic appearance among patients treated with intermediate-dose UDCA (Table 11.1). Subsequently, and in the largest RCT of UDCA to date, Olsson et al. [33] reported

Table 11.1 Characteristics and results of randomized trials comparing UDCA vs. placebo (or no treatment) in patients with PSC

Lead author	Year	*n*	% male	% IBD	Daily dosage (mg)	Dose	Study duration (years)	Outcomes					
								Death/LT, *n* (%)		Cholangio CA		Histologic progression	
								UDCA	Ctrl	UDCA	Ctrl	UDCA	Ctrl
Beuers [31]	1992	14	79 %	79 %	600–800	Low	1	0 %	0 %	NA	NA	0 %	16.7 %
Lo [41]	1992	18	61 %	61 %	200	Low	2	0 %	0 %	NA	NA	NA	NA
Stiehl [42]	1994	20	NA	NA	500–1000	Low	.25	0 %	0 %	NA	NA	NA	NA
De Maria [43]	1996	40	70 %	70 %	750–1,500	Low	2	0 %	0 %	NA	NA	NA	NA
Lindor [44]	1997	102	60 %	60 %	600–800	Low	2	7.8 %	5.9 %	0 %	5.9 %	15.7 %	5.9 %
Mitchell [32]	2001	26	73 %	73 %	20/Kg	Interm.	2	0 %	7.7 %	0 %	0 %	18.2 %	50.0 %
Olsson [33]	2005	198	70 %	70 %	500–1000	Interm.	5	2.1 %	3.0 %	3.1 %	4.0 %	NA	NA
Lindor [19]	2009	149	58 %	557	750–1,500	High	6	6.6 %	4.1 %	2.6 %	2.7 %	NA	NA

Key: *Ctrl* control (placebo or no treatment), *Interm.* intermediate, *PSC* primary sclerosing cholangitis, *UDCA* ursodeoxycholic acid

a 34% relative reduction in need for LT, 31% relative reduction in mortality, and 22% relative reduction in diagnosis of CCA. These results did not reach statistical significance, perhaps due to the low incidence of these "hard end points" as well as inability to enroll the planned number of study participants; however, they have been regarded as showing a trend toward such by various expert investigators, many of whom continue to offer intermediate-dose UDCA to select patients with PSC (discussed in the subsequent section) [1, 6, 34]. This practice is supported by several long-term-outcome studies by our group and others from within the last several years which have shown that patients with persistently elevated ALP who achieve clinically significant improvement or normalization of ALP with UDCA therapy have decreased risk of major adverse events (e.g., CCA, need for LT, or liver-related death) [30, 35–37].

Of interest is a recent prospective European study evaluating the effects of 3 months of UDCA withdrawal on serum biochemical tests as well as QOL and symptoms among 26 patients with PSC who were receiving UDCA at a dose of 10–15 mg/kg/day [34]. At the end of UDCA withdrawal, there was a significant (76%) increase in ALP as well as ALT, AST, bilirubin, and Mayo PSC risk score. Changes in QOL were variable across specific parameters as well as within individual patients, and the majority did not change significantly; there was, however, near doubling in pruritus rating, and this coincided with worsened fatigue in 42% and deterioration in overall general health (a domain of the short form-36 quality of life instrument) in 60% of patients. This study represents the largest prospective evaluation of UDCA withdrawal in PSC, and despite several limitations [6], it suggests therapeutic benefit in at least a subset of patients with PSC.

Potential Chemopreventive Properties of UDCA Against Colorectal Cancer

A small body of data suggests that UDCA may play a chemopreventive role against colorectal cancer (CRC) in individuals with PSC-IBD. For example, in a cross-sectional study of 59 patients with PSC-UC undergoing colonoscopic surveillance, UDCA use was associated with decreased prevalence of colonic dysplasia [38]. In another randomized, placebo-controlled trial of 52 patients with PSC-UC, UDCA use was associated with a relative risk of 0.26 for developing colorectal dysplasia or CRC [39]. While specific recommendations have been made regarding CRC prevention in PSC-IBD [40], routine use of UDCA for this indication has not been recommended as additional studies remain needed to confirm its putative chemopreventive properties [21].

UDCA in Clinical Practice

Use of UDCA in routine clinical practice is highly varied among gastroenterologists and even among subspecialized hepatologists within individual referral centers. This is likely a result of mixed views as to the potential benefits of UDCA therapy and the paucity of consistent, high-quality data to suggest a definite therapeutic impact. It is interesting to note that although it is well described that >20% of patients with another cholestatic liver disease, primary biliary cirrhosis, are nonresponders to UDCA, this drug is still widely recommended as primary therapy; even in patients who are unlikely to respond (e.g., established cirrhosis) or seem to have no or minimal response to UDCA, societal guidelines do not recommend withholding it, perhaps with the hope being that some degree of benefit might still be achieved. Nevertheless, and for reasons that have not been well studied, there appears to be more reticence toward UDCA in PSC as compared to primary biliary cirrhosis, although many clinicians continue to use UDCA in patients with PSC.

Until safer and more effective pharmacotherapies become available, our current practice is to offer a trial of intermediate-dose UDCA (17–23 mg/kg/day) to patients with compensated PSC whose serum ALP remains >1.5× the upper limit of normal after 1 year since the time of diagnosis [45] or who have troublesome symptoms of cholestasis (e.g., pruritus), as shown in Fig. 11.2. If UDCA is not symptomatically well

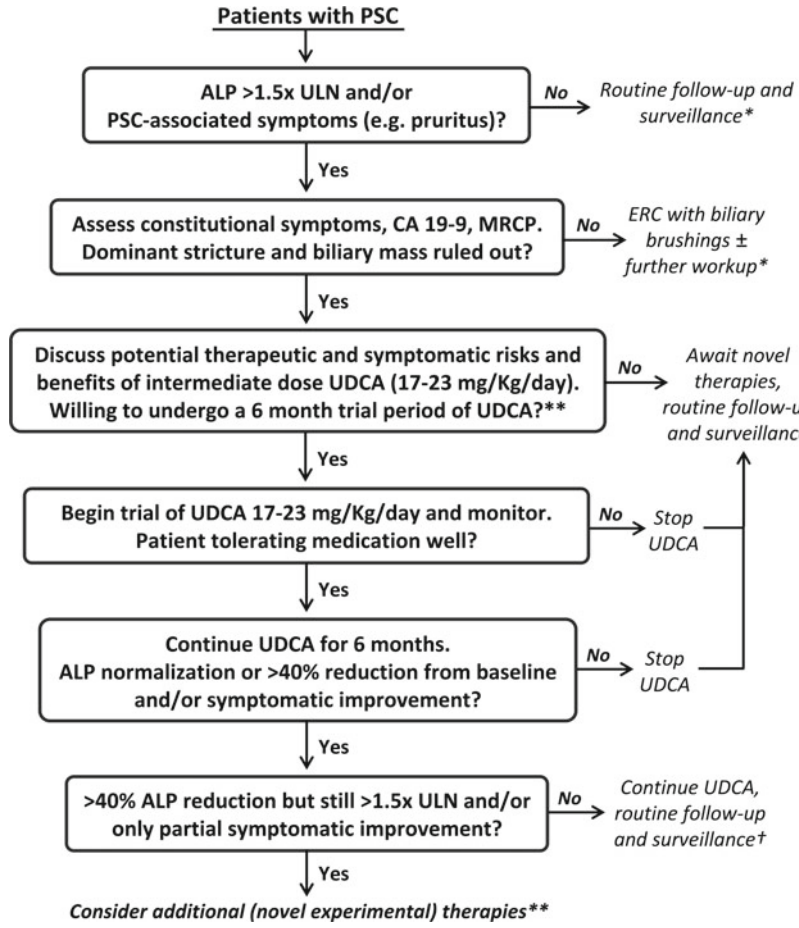

Fig. 11.2 Proposed algorithm for UDCA use in clinical practice and trials in PSC. *Surveillance and management options reviewed elsewhere [4]. **Consider referral to subspecialist in cholestatic liver disease and/or to tertiary care center. †Also consider decreasing UDCA dose to the lowest dose which maintains biochemical and/or symptomatic response on an individualized basis. Key: *ALP* serum alkaline phosphatase; *CA 19-9* carbohydrate antigen 19-9, *MRCP* magnetic resonance cholangiopancreatography, *PSC* primary sclerosing cholangitis, *UDCA* ursodeoxycholic acid, *ULN*, upper limit of normal

tolerated or if clinically significant improvement in ALP is not achieved, we discontinue UDCA treatment. These decisions are made with patients' direct involvement and input and based on careful interpretation of the available biomedical literature [6, 30–36, Ref Annals of Hep [DOI pending]]. Implementation of UDCA in this manner (1) offers patients with PSC the opportunity to potentially benefit from UDCA, (2) lends itself to prospective study in order to help expedite evidence-based treatment recommendations, and (3) can be implemented alongside novel experimental pharmacotherapies (e.g., nor-UDCA, the preclinical data for which indicate that it may well be more effective when used in combination with UDCA).

UDCA in PSC: Conclusions

Although many questions remain unanswered, given the morbidity and mortality of PSC, we believe that the existing evidence supports a role for judicious use of UDCA in patients with PSC, particularly in the absence of safer and more effective therapeutic options. Treatment with

UDCA can be implemented in unison with ongoing efforts to develop and rigorously test-emerging therapies through basic, translational, and clinical research endeavors.

The study of PSC pharmacotherapeutics appears to now be better positioned than ever, and with continued innovation, collaboration, and investigation, an even more broadly therapeutic treatment seems likely in the near future.

Conflicts of Interest, Disclosures James H. Tabibian – none

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