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High dose ursodeoxycholic acid increases risk of adverse outcomes in patients with early stage primary sclerosing cholangitis

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Abstract

Background—Ursodeoxycholic acid (UDCA) in a dose of 28–30 mg/kg/day increases the likelihood of clinical deterioration of primary sclerosing cholangitis (PSC) patients.

Aim—Our aim was to compare the risk of adverse clinical endpoints in patients with varying disease status.

Methods—We reviewed records from patients previously enrolled in a study evaluating the effects of high-dose (28–30 mg/kg/day) UDCA in PSC. Patients were grouped according to treatment (UDCA vs. placebo) and baseline disease status (histologic stage of PSC, total serum bilirubin). Development of clinical endpoints including death, liver transplantation, cirrhosis, esophageal varices and cholangiocarcinoma was sought.

Results—One hundred fifty patients were included of which 49 patients developed endpoints. There was an increased development of endpoints amongst patients using UDCA vs. placebo (14 vs. 4, $p = 0.0151$) with early histologic disease (stage 1–2, $n = 88$) but not with late stage (stage 3–4, $n = 62$) disease (17 vs. 14, $p = 0.2031$). Occurrence of clinical endpoints was also higher in

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patients receiving UDCA vs. placebo (16 vs. 2, $p = 0.0008$) with normal bilirubin levels (total bilirubin 1.0 mg/dl) but not in patients with elevated bilirubin levels (15 vs. 16, $p = 0.6018$). Among patients not reaching endpoints 31.68% had normalization of their alkaline phosphatase levels as compared to 14.29% in patients who reached endpoints ($p = 0.073$).

Conclusion—The increased risk of adverse events with UDCA treatment as compared to placebo is only apparent in patients with early histologic stage disease or normal total bilirubin.

Keywords

primary liver disease; esophageal varices; adverse clinical endpoints; histological stage

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease affecting the biliary system through inflammatory and fibrotic changes that ultimately lead to biliary cirrhosis.¹ Patients with PSC are most commonly men in their forties with a concurrent history of inflammatory bowel disease (IBD). At the present time, there is no effective treatment for PSC.²

PSC is characterized by elevated but fluctuating serum alkaline phosphatase levels. Recently, a study evaluating the value of normalization of alkaline phosphatase levels concluded this was associated with better prognosis.³ Ursodeoxycholic acid (UDCA), a bile acid, is the most extensively studied drug for the management of PSC. When compared to placebo, UDCA significantly reduced the elevated levels of alkaline phosphatase in patients suffering from PSC.⁴ Unlike primary biliary cirrhosis (PBC), in which UDCA shows biochemical, histological and survival benefits, several studies aiming at determining the effectiveness of UDCA among PSC patients failed to show an improvement in outcomes.^{4–7}

An initial study showed that low dose UDCA (13–15 mg/kg/day) was ineffective in terms of reducing endpoints such as death, liver transplantation, histologic progression, development of varices, ascites and encephalopathy.⁶ Recently, high dose UDCA (28–30 mg/kg/day) was compared to placebo in a multicenter study and despite improving liver biochemistries, high dose UDCA was of no significant clinical benefit. Unexpectedly, patients receiving high dose UDCA had worse outcomes. Primary endpoints and adverse events were seen most commonly in patients with more advanced disease regardless of treatment group.⁴

In this study we aimed to compare the development of adverse clinical endpoints in patients with varying disease status and determine if disease status had an influence on the clinical response of those patients treated with UDCA.

Patients and Methods

Patients were included in the present study according to criteria followed for the double-blind study of high dose UDCA.⁴

Inclusion Criteria

Primary sclerosing cholangitis was defined as present when all the following criteria were met: (1) chronic cholestatic disease of at least 6 months' duration; (2) serum alkaline phosphatase at least 1.5 times the upper limits of normal; (3) retrograde, operative, percutaneous, or magnetic resonance cholangiography demonstrating intrahepatic and/or extrahepatic biliary duct obstruction, beading or narrowing consistent with PSC within 1 year of the study entry; (4) liver biopsy in the previous 1 year that was available for review and compatible with the diagnosis of PSC (7 patients did not have entry liver biopsy due to

low platelet count and/or presence of cirrhosis). Compatible biopsy features included fibrous cholangitis, ductopenia with periportal inflammation, and biliary fibrosis.

Exclusion criteria

Patients were excluded if they had any of the following: (1) coexistent conditions such as preexisting malignancies or severe cardiopulmonary disease that would limit their life expectancy to less than 2 years; (2) inability to provide consent; (3) treatment with UDCA, pentoxifylline, corticosteroids, cyclosporin, colchicine, azathioprine, methotrexate, D-penicillamine, budesonide, nicotine, pirfenidone, or tacrolimus in the 3 months prior to study entry; (4) inflammatory bowel disease patients requiring specific treatment in the preceding 3 months except for maintenance therapy with a 5-ASA compound; (5) anticipated need for liver transplantation within 2 years (expected survival of < 80% at 2 years based on Mayo risk score)⁸; (6) recurrent variceal bleeds, spontaneous uncontrolled encephalopathy, international normalized ratio 1.5 uncorrected by vitamin K or resistant ascites that suggested an anticipated survival of less than 1 year; (7) pregnancy or lactation (patients who became pregnant during the study were discontinued and referred to their physicians); (8) age less than 18 years or greater than 75 years; (9) findings highly suggestive of liver disease of other etiology such as chronic alcoholic liver disease, chronic hepatitis B or C infection, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease, congenital biliary disease, or cholangiocarcinoma; (10) previous intraductal stones or operations on the biliary tree, other than cholecystectomy, such as biliary drainage procedures preceding the diagnosis of PSC; or (11) recurrent ascending cholangitis requiring hospitalization occurring more than two times per year.

Patients were grouped according to treatment status (UDCA vs. Placebo), histological stage on liver biopsy and bilirubin level (normal bilirubin vs. elevated bilirubin). Patients with stage 1 or stage 2 PSC on liver biopsy were denoted as early stage and with stage 3 or stage 4 PSC on liver biopsy were denoted as late stage. Only those patients with pathology assessed by dedicated gastroenterology pathologists done at each site were included. Bilirubin level, alkaline phosphatase, albumin, prothrombin time and platelet counts were defined as the levels at enrollment or the next available result on the patient record.

Development of pre-established clinical endpoints that include death, liver transplantation, meeting minimal listing criteria, development of cirrhosis, varices and cholangiocarcinoma was assessed among different groups.

The study was approved by the Mayo Institutional Review Board on the basis of a minimal risk review of patient records.

Statistical analysis

Clinical, histological and total serum bilirubin level of the study patients at entry were classified by stage of PSC and treatment status then analyzed using unpaired two tailed t-tests. Based on stage of disease, bilirubin level and treatment status, chi square tests were performed to assess the difference in the development of endpoints between patient groups. Bar graphs were used to demonstrate the occurrence of endpoints among patients according to their stage of disease, bilirubin level and treatment status.

Results

One hundred and fifty patients were included in the analysis; no patients were excluded from the analysis. Baseline characteristics for early and late disease stages and treatment groups are shown in Table 1.

Forty nine patients (32.67 %) developed endpoints during the period of follow-up (7.5 years) from 8/6/2002 to 2/3/2010, 31 patients were male (N males = 86) and 18 patients were female (N females = 64) with an average age of 46.53 ± 12.61 years. In the patients developing endpoints, the average age at the diagnosis of PSC was 40.16 ± 12.48 years and the average age at the diagnosis of IBD was 31.75 ± 13.81 years. Thirty six patients had IBD of which 32 were ulcerative colitis, 3 were Crohns and 1 was unspecified at the time of enrollment.

A summary of the occurrence of endpoints that include death, cirrhosis, liver transplantation, development of varices and cholangiocarcinoma according to stage of disease is presented in Figure 1. The type of endpoints per disease stage, bilirubin level and treatment group are shown in Table 2. and Table 3. Fourteen patients (15.9%, 14/88) with early stage disease (stage 1 and stage 2) receiving UDCA developed endpoints whereas 4 patients (4.5%, 4/88) with early stage disease receiving placebo developed endpoints, this difference in development of endpoints was significant ($p = 0.0151$).

On the other hand, 17 patients (27.4%, 17/62) with late stage disease (stage 3 and stage 4) receiving UDCA developed endpoints whereas 14 patients (22.5%, 14/62) with late stage disease on placebo developed endpoints, this difference in development of endpoints was not significant ($p = 0.2031$).

Seven patients (4.7 %) did not have a liver biopsy due to limitations including presence of cirrhosis (5 patients) and low platelet levels (2 patients). Both patients with low platelet counts received UDCA whereas 2 patients with cirrhosis received UDCA and 3 patients received placebo. Only one patient with low platelets receiving UDCA and one cirrhotic patient receiving placebo had a serious adverse event (hospitalization) during the period of follow up.

Sixteen patients with a normal bilirubin level who received UDCA developed endpoints whereas 2 patients with a normal bilirubin level who received placebo developed endpoints, this difference in the development of endpoints was significant ($p = 0.0008$). Conversely, 15 patients with an elevated bilirubin level that received UDCA developed endpoints whereas 16 patients with an elevated bilirubin level that received placebo developed endpoints. Patients with an elevated bilirubin level that received UDCA were as likely to develop endpoints as patients with elevated bilirubin level that received placebo ($p = 0.6018$). Occurrence of endpoints in patients according to bilirubin level and treatment status is shown in Figure 2.

The point during therapy at which the endpoints occurred was at a mean of 2.77 ± 1.31 years in patients with early stage disease and a mean of 2.73 ± 1.41 years in patients with late stage disease. The timing to development of endpoints in patients receiving UDCA is shown in Figure 3. No difference in the timing to develop an endpoint is discernable between patients with early stage disease and patients with late stage disease.

In the 49 patients developing endpoints only 7 patients (14.29%) had normalization of alkaline phosphatase at 2.5 years of follow up, whereas 32 (31.68%) of the 101 patients without endpoints had a normalization of alkaline phosphatase at 2.5 years of follow up. A Chi square test showed that this difference approached statistical significance with a p value of 0.073.

Discussion

Our study interestingly demonstrates that patients with early stage PSC or with a normal total serum bilirubin level are more likely to suffer endpoints when on high dose UDCA

therapy when compared to patients on placebo. Although these findings are counter-intuitive, they reinforce the evidence of higher rates of serious side effects in patients with PSC receiving high dose UDCA therapy.⁴ Our analysis revealed that there was an increase in endpoints, especially the development of esophageal varices, in patients with early stage PSC on high dose UDCA as compared to placebo. Esophageal varices, unlike cirrhosis and death, may occur at an earlier stage of the disease. The mechanism by which UDCA increases the risk of varices in these patients deserves further study.

Earlier pilot studies involving usage of high doses of UDCA in PSC showed no evidence of adverse effects.^{7,9} A pilot study involving 30 patients with PSC receiving 25–30 mg/kg/day of UDCA at Mayo clinic showed a marked improvement in serum biochemistries after 1 year of therapy with no adverse effects.⁹ The absence of development of endpoints may be attributed to the short duration of therapy and the small subset of patients. A randomized controlled trial from Sweden with a total of 219 patients receiving 17–23 mg/kg/day of ursodeoxycholic acid or placebo showed a lowering of serum biochemistries in the first 6 months but no statistically significant beneficial effects on survival.⁷ Although, no adverse events occurred in this study however the dosage used was lower than that utilized in our patient population. This may indicate that the adverse events may have a dose dependant rather than idiosyncratic relation to UDCA, further studies with larger populations and multiple doses are needed to better define this relationship.

An earlier study evaluating the effect of a lower dose of UDCA (13–15 mg/kg/day) denoted no difference in the survival free of treatment failure in patients with early stage PSC (Stage 1 or 2).⁶ Although retrospective studies support the role of UDCA in reducing the risk of colorectal carcinoma.^{10–12} However, in our cohort of patients long term usage of high dose (28–30 mg/kg/day) UDCA was associated with an increased risk of colorectal neoplasia in patients with ulcerative colitis and PSC.¹³ A review article by Torres et al. describes this increased risk of colorectal neoplasia, which is maintained after liver transplant and proctocolectomy in patients with PSC and ulcerative colitis and suggests that surveillance programs may aid in early cancer detection and may be the only solution to decrease this risk.¹⁴ High dose UDCA is not recommended in PSC patients due to the abovementioned complications. However, long term administration of low dose UDCA has been suggested to reduce the annual incidence rate of cholangiocarcinoma, an unpredictable and serious complication in patients with primary sclerosing cholangitis.¹⁵ UDCA also inhibits cell growth in hepatocellular carcinoma through induction of tumor suppressor genes.¹⁶

A novel bile acid, 24-norursodeoxycholic acid has been shown to have positive outcomes in mouse models of cholangitis and biliary fibrosis, with a reversal of sclerosing cholangitis after 4 weeks of treatment.^{17, 18}

The management of PSC relies on dilatation and stenting of dominant biliary strictures and liver transplantation as the disease advances.¹⁹ Dominant strictures are associated with reduced transplant free survival²⁰ and UDCA therapy has not been shown to prevent the development of dominant stenosis in patients with PSC.²¹ However, a transplant-free survival advantage is suggested when combining UDCA and balloon dilatation or biliary stent placement.²¹ Patients with PSC and elevated immunoglobulin G subclass 4 (IgG4) should be managed with steroids which have been shown to produce a good biochemical response represented by an improvement in bilirubin, alkaline phosphatase and IgG4 levels.²² Corticosteroids have also been shown to reverse strictures on cholangiography and result in a resolution of jaundice in patients with IgG4-associated cholangitis.²³ Due to relapse occurring in almost 40% of patients following steroid therapy, azathioprine should be considered in patients who relapse following steroid therapy.¹⁹

UDCA has multiple proposed mechanisms of action including: 1) protection of injured cholangiocytes against toxic effects of hydrophobic bile acids, this results from modulation of the composition of mixed phospholipid mixed micelles, reduction of the cytotoxicity of bile acids in bile and decrease in the concentration of bile acids in cholangiocytes; 2) stimulation of impaired biliary secretion via calcium and protein kinase C- α -dependent mechanisms and/or activation of p38 and extracellular signal-regulated kinases; 3) stimulation of detoxification of hydrophobic bile acids; 4) inhibition of apoptosis of hepatocytes induced by bile acids involving inhibition of mitochondrial membrane permeability transition and stimulation of a survival pathway and 5) other mechanisms including membrane stabilizing and antioxidative effects.^{24–26}

UDCA expands the hydrophilic bile acid pool, causes hypercholeresis and leads to immunomodulation and cytoprotection.²⁷ It is currently unknown if any of these modes of action is accelerated under the high drug dose used in this study, eventually leading to harmful rather than beneficial effects. As we previously mentioned, UDCA is also known to modulate apoptosis.²⁸ It is possible that the high dose of UDCA prevented apoptosis of activated stellate cells leading to an increase rate of fibrogenesis, further studies will be needed to confirm this theory.

The point during therapy at which endpoints occurred was similar for patients with early and late stage PSC. This may indicate that the duration of exposure to UDCA may be related to the development of endpoints in all patients with PSC, regardless of histological stage.

Normalization of alkaline phosphatase is associated with better prognosis in patients with primary sclerosing cholangitis.³ Our study shows a similar relationship between the normalization of alkaline phosphatase and the development of endpoints; around the mean time to development of endpoints (2.5 years) fewer patients developing endpoints (14.29%) had normalization of their alkaline phosphatase as compared to patients not developing endpoints (31.68%). This relation approached significance with a p value of 0.073; we speculate that with a larger population this relationship may be more evident.

The initially proposed cause of increased endpoints due to high dose UDCA is modification of the drug into hepatotoxic bile acids.¹ A study evaluating the effect of high dose UDCA in PSC patients on bile acids determined that it causes a significant enrichment and expansion of the total bile acid pool including lithocholic acid (LCA). LCA may be produced due to overwhelmed small bowel absorption of UDCA from the high doses and conversion of unabsorbed UDCA by bacteria in the colon.²⁹

In rat livers perfused with LCA and isolated sections of the biliary epithelium marked alterations of the apical cell membrane were noted. Moreover, hepatocytes showed marked alterations of the canalicular membrane with LCA and tauro-LCA.²⁹ A trial in which swiss albino mice received either a control diet or 1% LCA diet showed that LCA feeding led to bile infarcts followed by destructive cholangitis with activation and proliferation of myofibroblasts. Lithocholic acid is shown to be hepatotoxic in animals and may cause periductal fibrosis, bile duct obstruction and destructive cholangitis.³⁰

Our study shows that outcomes are worse in patients with early stage disease when both groups are compared to placebo. Because only a small fraction of these patients had their bile acids analyzed, we could not determine the role of bile acids as a factor in the development of primary endpoints. Further study to identify the effects of bile acids on the development of primary endpoints as per disease stage and treatment status should be performed. Also, studies aimed at linking the mechanism of action of UDCA to the finding of increased endpoints in early stage PSC patients receiving high dose UDCA are needed.

Our study has some limitations including the fact that this is a sub-analysis of an earlier study and there are a small number of endpoints per group. However, no other studies evaluated the effect of high dose UDCA on the development of endpoints per disease stage.

In conclusion, this analysis showed that the increased occurrence of adverse events with high dose UDCA treatment as compared to placebo is only significant in patients with early histologic stage disease or normal total serum bilirubin levels.

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Abbreviations

IBD	Inflammatory bowel disease
LCA	Lithocholic acid
PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis
UDCA	Ursodeoxycholic acid

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Figure 1.

Number of endpoints* in primary sclerosing cholangitis patients according to stage of disease

* Endpoints include death, transplantation, meeting minimal listing criteria, development of varices, cholangiocarcinoma or progression to cirrhosis

Figure 2.

Number of endpoints* in primary sclerosing cholangitis patients according to total serum bilirubin level

* Endpoints include death, transplantation, meeting minimal listing criteria, development of varices, cholangiocarcinoma or progression to cirrhosis

Figure 3. Kaplan Meyer curve representing the time to development of endpoints in patients with early and late stage disease receiving UDCA.

Table 1

Clinical and laboratory characteristics of the study patients at entry classified by stage of PSC.

	Ursodeoxycholic acid	Placebo	p-value
Early Stage PSC (n = 88)			
Sex (F/M)	21/25	16/28	0.3707
Age	46.15 ± 11.78	44.50 ± 12.68	0.5240
Age at PSC	40.63 ± 11.96	41.68 ± 12.66	0.6867
Age at IBD	29.82 ± 14.25	32.42 ± 12.16	0.4273
Type of IBD:			1.000
Ulcerative colitis	26	29	
Crohns	7	4	
Unspecified	2	2	
Labs:			
Alkaline phosphatase	498 ± 305	599 ± 493	0.2558
Total Bilirubin	0.9 ± 0.6	1.2 ± 1.2	0.0781
Albumin	4.1 ± 0.3	4.1 ± 0.4	0.9620
Prothrombin	10.6 ± 1.8	11.0 ± 1.7	0.2615
Platelet counts	289 ± 101	269 ± 134	0.4207
Late stage PSC (n = 62)			
Sex (F/M)	17/13	10/20	0.0693
Age	48.97 ± 12.28	44.77 ± 15.26	0.5960
Age at PSC	44.23 ± 13.77	39.10 ± 13.75	0.4461
Age at IBD	34.84 ± 16.95	31.46 ± 14.79	0.4516
Type of IBD:			0.8044
Ulcerative colitis	15	21	
Crohns	4	3	
Unspecified	1	2	
Labs:			
Alkaline phosphatase	633 ± 383	655 ± 489	0.8496
Total Bilirubin	1.5 ± 0.8	1.4 ± 0.9	0.6719
Albumin	3.8 ± 0.4	3.9 ± 0.5	0.9310
Prothrombin time	11.3 ± 2.8	10.9 ± 2.2	0.6061
Platelet counts	242 ± 127	213 ± 98	0.3197

Table 2

Occurrence of endpoints according to disease stage and treatment status.

<i>Endpoints*</i>	Ursodeoxycholic acid	Placebo
<i>Early Stage PSC (n = 18)</i>		
Minimal listing criteria	3	3
Varices	11	1
Cirrhosis	3	0
Cholangiocarcinoma	1	0
OLT	5	1
Death	2	0
<i>Total endpoints</i>	<i>25</i>	<i>5</i>
<i>Late stage PSC (n = 31)</i>		
Minimal listing criteria	12	8
Varices	6	3
Cirrhosis	3	4
Cholangiocarcinoma	1	3
OLT	8	6
Death	3	6
<i>Total endpoints</i>	<i>33</i>	<i>30</i>

* Some patients developed multiple endpoints during the period of follow up.

Table 3

Occurrence of endpoints according to total serum bilirubin level and treatment status.

<i>Endpoints*</i>	Ursodeoxycholic acid	Placebo
<i>Normal Bilirubin (n = 18)</i>		
Minimal criteria	4	1
Varices	12	0
Cirrhosis	2	1
Cholangiocarcinoma	0	0
OLT	4	1
Death	2	0
<i>Total endpoints</i>	<i>24</i>	<i>3</i>
<i>Elevated Bilirubin (n = 31)</i>		
Minimal criteria	11	10
Varices	5	4
Cirrhosis	4	3
Cholangiocarcinoma	2	3
OLT	9	6
Death	3	6
<i>Total endpoints</i>	<i>34</i>	<i>32</i>

* Some patients developed multiple endpoints during the period of follow up.