ELSEVIER

Journal of Hepatology 48 (2008) 792–800

Journal of Hepatology

www.elsevier.com/locate/jhep

High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis is safe and effective☆

Susan N. Cullen[1,*], Christian Rust[2], Kenneth Fleming[3], Cathryn Edwards[4], Ulrich Beuers[2,5], Roger W. Chapman[3]

[1]*Gastroenterology Department, Wycombe General Hospital, High Wycombe HP11 2TT, UK*
[2]*Department of Medicine II, Klinikum Großhadern, University of München, Germany*
[3]*Gastroenterology Unit, John Radcliffe Hospital, Headley Way, Headington OX3 9DU, UK*
[4]*Gastroenterology Department, Torbay Hospital, Torquay TQ2 7AA, UK*
[5]*Department of Gastroenterology & Hepatology, AMC, University of Amsterdam, The Netherlands*

See Editorial, pages 692–694

***Background/Aims*: Ursodeoxycholic acid (UDCA) has been shown to improve serum liver tests in primary sclerosing cholangitis (PSC), but controlled trials have shown inconsistent effects on liver histology, and did not reveal a survival benefit. This pilot, randomised dose-ranging trial attempted to determine whether further enrichment of the bile acid pool with UDCA would lead to an improvement in outcome for PSC patients.**

***Methods*: Thirty-one patients with PSC were randomised to treatment with either 10 mg/kg (low dose), 20 mg/kg (standard dose) or 30 mg/kg (high dose) daily of UDCA for 2 years. Patients were assessed every 12 weeks and underwent liver biopsy at the beginning and end of the trial.**

***Results*: Serum liver tests improved in all groups taking UDCA. Survival probability at 1–4 years as evaluated by the Mayo risk score tended to improve for all patients and significantly improved for the high dose group ($p < 0.02$). Only 3 (10%) of all patients had a Ludwig score showing histological deterioration over the trial period.**

***Conclusions*: High dose UDCA is well-tolerated and is associated with an improvement in survival probability. A trend towards stability/improvement in histological stage was also observed. This treatment appears to be effective for PSC and deserves further evaluation.**

***Keywords*: Primary sclerosing cholangitis; Ursodeoxycholic acid; Mayo risk score; Survival probability**

Received 5 August 2007; received in revised form 19 November 2007; accepted 11 December 2007; available online 14 February 2008
Associate Editor: M. Trauner

☆ Authors (S.N.C., U.B. and R.W.C.) have received speaker's fees on different occasions from, e.g., the Falk Foundation, Roche and Schering-Plough during recent years. The authors are not aware of serious conflicts of interest.

* Corresponding author. Tel.: +44 1494 425959; fax: +44 1494 425597.
E-mail address: sue.cullen@buckshosp.nhs.uk (S.N. Cullen).

Abbreviations: 6-MP, 6-mercaptopurine; ALT, alanine transferase level; ALP, alkaline phosphatase; AST, aspartate aminotransferase; AZA, azathioprine; GGT, γ-glutamyl transferase; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; SD, standard-deviation; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease which is strongly associated with inflammatory bowel disease (IBD) [1]. It is characterized by concentric obliterative fibrosis and bile duct strictures and is a progressive condition, ultimately leading to biliary cirrhosis, portal hypertension and hepatic failure.

Ursodeoxycholic acid is a physiological component of normal human bile and has been used with therapeutic benefit in various cholestatic diseases of the liver including primary biliary cirrhosis and intrahepatic

0168-8278/$34.00
doi:10.1016/j.jhep.2007.12.023

cholestasis of pregnancy [2,3]. It has a wide range of potentially beneficial effects and the relative importance of each in alleviating cholestasis remains unclear [2]. UDCA appears to have a protective effect on the biliary epithelium, possibly by buffering toxic bile acids through modulation of micelle formation and by changing biliary bile acid composition. In addition, UDCA has an anti-cholestatic effect, stimulating biliary secretion of phospholipids and bile acids by up-regulating the synthesis, insertion and activation of transporter molecules in the hepatocyte canalicular membrane mainly via post-translational mechanisms as shown in experimental models of cholestasis [4]. UDCA also exerts anti-apoptotic effects; UDCA reduces mitochondrial membrane permeability to ions and mitochondrial cytochrome C release upon various apoptotic stimuli by yet only partly resolved mechanisms in which activation of the epidermal growth factor receptor, mitogen-activated protein kinases (MAPK), as well as glucocorticoid receptor-dependent signaling may be involved [5–7]. A number of other less well characterized potential modes of action of UDCA have been discussed. UDCA reverses aberrant expression of HLA class I molecules on hepatocytes in PBC and PSC, possibly secondary to its anti-cholestatic effect. UDCA has also been shown to activate the glucocorticoid receptor in a rat model and to suppress IFN-γ induced MHC Class II expression.

Various trials have investigated the effects of UDCA treatment in PSC since Hayashi's and Chazouillères' first open label studies in 1990 [8,9]. The first double-blind placebo controlled trial of UDCA by Beuers et al. in 1992 demonstrated a significant improvement in serum liver tests and a multiparametric histological score which included features such as portal and parenchymal inflammation [10]. Similar results were described by Stiehl in 1994. A larger randomised controlled trial by Lindor et al. with a longer follow-up confirmed the effects of UDCA on serum liver tests, but did not show a survival benefit with 13–15 mg/kg/day of UDCA [11,12]. Most subsequent studies have found an improvement in serum liver tests but no consistent improvement in liver histology in patients taking UDCA. Interpretation of the trials has been limited by the variation in dosage of UDCA used (most studies using a dose of 10–15 mg/kg, the standard dose for treatment of PBC), and a relatively short follow-up period.

Biliary enrichment of UDCA increases with increasing dose and reaches a plateau at a daily dose of 22–25 mg/kg in the bile of patients with PSC [13]. Higher doses than have been used in most trials to date might therefore be needed to provide sufficient enrichment of the bile acid pool, in the context of cholestasis, to demonstrate a therapeutic effect [13]. There has been interest in using higher than conventional doses of UDCA in Oxford for some years and a trial of 20–25 mg/kg was published in 2001. This small trial appeared to show significant improvements in both the cholangiographic features of PSC and in the degree of liver fibrosis [14]. An open study from the Mayo clinic showed a significant improvement in projected survival using the Mayo risk score in patients treated with high dose, but not conventional doses of UDCA [15]. Although the Mayo risk score is the best of all prognostic markers evaluated so far in PSC, it is only a surrogate marker of survival, indicating survival *probability* and no direct measure of liver fibrosis was undertaken in this trial. The most recent study in this area is a trial from Sweden of 219 patients treated for 5 years with between 17 and 23 mg/kg of UDCA or placebo [16]. Although a trend towards improved survival in the UDCA treated group was demonstrated, the trial was insufficiently powered to produce a result of statistical significance; in addition, patients treated with UDCA showed only a minor biochemical response in contrast to the results of other controlled trials [10–12,14].

This paper outlines a pilot study of UDCA in primary sclerosing cholangitis, using three daily doses; 10 mg/kg (referred to as "low dose"), 20 mg/kg ("standard dose") and 30 mg/kg ("high dose"). The "high dose" arm of the trial uses the largest dose of UDCA ever studied to establish if this is adequately tolerated by patients with PSC, many of whom have an underlying colitis. The dose was chosen to ensure that maximum biliary enrichment with UDCA was achieved and to determine if this further enrichment of the bile acid pool might lead to additional benefits in terms of progression of disease.

2. Methods

The study was carried out in two centres; the John Radcliffe Hospital in Oxford, UK, and Klinikum Großhadern, University of München, Germany. Ethical approval for this study was granted by the Central Oxford Research Ethics Committee (CM00.017) and the Ethics Committee at the University of München. Informed written consent was obtained from all patients.

The entry criteria for the study were as follows: older than 18 years of age; clinical, biochemical and radiological features of PSC all apparent; increased activity of alkaline phosphatase (ALP) or γ-glutamyl transferase (GGT) at the beginning of study; liver histology compatible with PSC. Exclusion criteria included previous biliary tract surgery (excluding simple cholecystectomy), major extra-hepatic or hilar duct stricture causing jaundice, cholangiocarcinoma, decompensated liver disease, anti-mitochondrial antibodies (AMA) positive, pregnancy or breast-feeding, and women of childbearing age not using safe contraception.

Thirty-three patients were recruited by the authors (SC, CR, UB and RWC) but 2 patients were excluded from the full analysis set as they attended the baseline visit but then did not continue with the study. These patients were however included in the safety analysis. The clinical characteristics of the patients are summarized in Table 1. The mean duration of PSC at entry to the study was 4.7 ± 4.9 years. Of these patients, 21 (68%) had underlying ulcerative colitis, 4 (13%) had Crohns' disease, 1 (3%) had indeterminate colitis and 5 (16%) had no diagnosis of inflammatory bowel disease. The patients were randomly assigned to the "low" (10 mg/kg), "standard" (20 mg/kg) or "high" (30 mg/kg) dose of ursodeoxycholic acid. This randomisation was carried out by an independent blinded trial pharmacist in each centre using a predetermined randomisation scheme. Patient numbers were issued sequentially within a centre. Patients received their