PANCREAS, BILIARY TRACT, AND LIVER

Association Between Reduced Levels of Alkaline Phosphatase and Survival Times of Patients With Primary Sclerosing Cholangitis

LINA LINDSTRÖM,* ROLF HULTCRANTZ,* KIRSTEN MURI BOBERG,‡ INGALILL FRIIS–LIBY,§ and ANNIKA BERGQUIST*

*Department of Gastroenterology and Hepatology, Karolinska University Hospital, Stockholm, Sweden; ‡Section for Gastroenterology, Department of Transplantation Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway; and §Department of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Göteborg, Sweden

BACKGROUND & AIMS: Ursodeoxycholic acid (UDCA) has not been shown to stop progression of primary sclerosing cholangitis (PSC). However, patients with primary biliary cirrhosis treated with UDCA whose levels of alkaline phosphatase (ALP) decrease have longer survival times than patients whose levels do not decrease. We compared survival times between patients with PSC treated with UDCA or placebo, with and without decreased levels of ALP.

METHODS: We collected data from patients enrolled in the Scandinavian PSC UDCA trial. Patients were randomly assigned to groups given UDCA (17–23 mg/kg/day, n = 97) or placebo (n = 101) from 1996–2001 and were followed until 2010. End points were death, liver transplantation, or cholangiocarcinoma. They were considered to be biochemical responders if they had serum levels of ALP that were normal or reduced by ≥40% after 1 year in the trial (regardless of whether they received UDCA or placebo). Numbers of patients surviving until the study end point were compared by using the Kaplan–Meier method.

RESULTS: There were no differences in survival at the end of the study between patients given UDCA or placebo (P = .774, log-rank); 26 patients in the UDCA group and 29 in the placebo group reached an end point. On the basis of ALP levels, there were 79 responders and 116 nonresponders overall. Of patients given UDCA, significantly more biochemical responders survived for 10 years than nonresponders (P = .03, log-rank). However, differences remained significant regardless of group assignment; overall, patients with reductions in ALP level survived longer than patients without reductions in ALP (P = .0001, log-rank).

CONCLUSIONS: There is no significant difference in long-term survival between patients with PSC given UDCA (17–23 mg/kg/day) or placebo for 5 years. However, patients who have reduced or normal levels of ALP have longer survival times, regardless of whether they receive UDCA or placebo.

Keywords: Liver Failure; Bile Acid; Randomized Placebo-Controlled Clinical Trial; Follow-up Study.

Although several medical treatments for primary sclerosing cholangitis (PSC) have been tested, no treatment has yet been shown to halt the progression of the disease.[1] When the liver eventually fails, transplantation is the only life-saving treatment option. Median survival time from PSC diagnosis to death or liver transplantation is reported to be between 12 and 18 years.[2] The main cause of death is liver failure, followed by death from cholangiocarcinoma.[3]

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that is believed to exert a number of effects in chronic cholestatic conditions, including direct and indirect cytoprotection, stim-

ulation of hepatobiliary secretion, immunomodulation, and protection of hepatocytes from bile-induced apoptosis.[4] UDCA may also have chemoprotective effects that are indicated by its ability to inhibit proliferation of tumor cell lines in vitro.[5] The drug is commonly used for the treatment of primary biliary cirrhosis (PBC),[6] where UDCA has been shown to improve the results of serum liver function tests and levels of antimitochondrial antigens and also delay histologic progression of the

Table 1. Clinical Characteristics of the Study Population

Variable	UDCA (n = 97)	Placebo (n = 101)	Overall (n = 198)
Male sex, n (%)	71 (73)	69 (68)	140 (70)
IBD, n (%)	80 (82)	85 (84)	165 (83)
Age at enrollment, y, mean (SD)	44 (13)	43 (11)	43 (12)
Duration of PSC at enrollment, y (SD)	6 (6)	6 (5)	6 (6)
Asymptomatic at enrollment, n (%)	45 (46)	51 (50)	96 (48)
Mean ALP at enrollment, microkat/L (SD)	11.8 (9.5)	12.5 (11.4)	12.2 (10.5)
Follow-up years after enrollment, median (range)	10 (0.41–13)	11 (0.15–13)	10.7 (0.15–13)

NOTE. Normal range for ALP is 0.8–4.6 microkat/L.
IBD, inflammatory bowel disease; SD, standard deviation.

disease. Although beneficial effects on survival and reduced need for liver transplantation remain to be shown,[7] the rates of liver transplantation for PBC have decreased in Europe and the United States since UDCA treatment was introduced, suggesting a positive effect.[8,9] Thus, UDCA is currently recommended as standard treatment for patients with PBC.[10] In addition, PBC patients with a biochemical response to UDCA seem to have higher survival rates than nonresponders.[6,11] A number of studies that used different definitions of response to UDCA have been described in PBC, most including alkaline phosphatase (ALP).[6,11–13] UDCA was initially tested in PSC at a dose of 13–15 mg/kg/day. The first large randomized study included 105 patients, and the outcome was time to treatment failure, defined as death, liver transplantation, or histologic and/or clinical progression. The study showed no clinical benefit of UDCA; however, UDCA was associated to biochemical improvement as measured by liver function tests.[14] The drug was considered safe, and a small study with higher drug dose indicated even more favorable outcomes on liver tests.[15] In 2005, a Scandinavian randomized controlled trial on UDCA (17–23 mg/kg/day) vs placebo was published.[16] This study indicated increased survival of patients treated with UDCA, but the study was unfortunately underpowered.[17]

More recently, treatment with a very high dose of UDCA (28–30 mg/kg/day) has been shown to be associated with poorer clinical outcomes compared with placebo.[18] The study that used a very high dose of UDCA included 150 patients randomized to UDCA or placebo, but it had to be terminated early because of the unexpected finding of more adverse effects among UDCA-treated patients. Despite the lack of evidence for a beneficial clinical effect, UDCA is commonly used at lower doses for patients with PSC in many countries today.

This study aimed to investigate the long-term effects of UDCA at 17–23 mg/kg/day by using an extended follow-up of the Scandinavian trial and to determine whether a biochemical response to UDCA is associated with a better prognosis.

Methods

Between 1996 and 2001, a 5-year randomized, double-blind, placebo-controlled trial was conducted that investigated the effect of UDCA on survival without liver transplantation in patients with PSC.[16] A total of 219 patients were randomized to UDCA or placebo. Twenty-one patients were excluded because they did not come to any follow-up appointments or never started taking the capsules. Thus, 97 treated and 101 placebo patients remained and were included in the trial.

In 2009/2010 we performed an additional follow-up of the 198 patients. Each study center provided data collected from medical records. Defined end points for the extended follow-up period were death, liver transplantation, or diagnosis of cholangiocarcinoma.

We aimed to identify responders and nonresponders to UDCA. For this purpose we used levels of ALP from the trial database; ALP was measured before the patient entered the trial and thereafter every 6 months throughout the study period. We used the same definition of a response to UDCA for the patients with PSC as for those with PBC. Thus, all patients whose ALP levels had decreased at least 40% after 1 year in the trial and all whose ALP levels were consistently normal after 1 year were defined as biochemical responders.[6]

The ethics committee of Stockholm County approved the study (number 2010/62-31/2).

Statistical Analyses

End point–free survival was assessed by using the Kaplan–Meier model with the Wilcoxon log-rank test. Data on patients who did not reach an end point were censored at time of last date of clinical observation. Follow-up was missing in 28 patients, and these were censored at last date of follow-up in the trial. Binomial values were compared by using Pearson χ^2 test or Fisher exact test when appropriate.

All testing was done by using the conventional two-tailed level of 0.05 and was performed with the software Statistica 10.1 (StatSoft, Tulsa, OK).

Results

Patient Characteristics

Baseline characteristics are described in Table 1. Treated and untreated patients were similar in terms of sex, concomitant inflammatory bowel disease, age, duration of PSC, treatment with UDCA after the original trial, follow-up years, PSC symptoms, and mean ALP at enrollment.

Outcome at Follow-up in 2009/2010

Fifty-five patients had reached an end point at follow-up in 2009/2010. Twenty-nine patients underwent liver transplantation, 14 patients had died, and 12 patients had been diagnosed with cholangiocarcinoma. Frequencies and causes of death are described in Table 2.

Comparison of patients who reached an end point vs those who did not revealed no differences in sex (73% vs 70% males),