73 HISTOLOGICAL COURSE OF PRIMARY BILIARY CIRRHOSIS (PBC) TREATED WITH URSODEOXYCHOLIC ACID (UDCA).

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The combined analysis of French, American et Canadian randomized controlled trials of UDCA therapy in PBC has demonstrated a beneficial effect of UDCA on survival free of transplant at 4 years (1). However, effects of long term UDCA therapy on histological progression have not been described. In the absence of efficient therapy, development of cirrhosis at 4 years has been reported in more than 50 % of cases (2). We therefore studied the histological course of initialy non cirrhotic PBC patients under long term UDCA treatment.

Patients and methods : 50 patients with PBC (44 females, 6 males, age : 49±2 years) seen and followed in a unique institution, underwent liver biopsy before and after at least 2 years of UDCA therapy (13-15 mg/kg/d). 123 biopsies were available (2 to 4 per patient). Criteria of Ludwig et al for histological staging were applied : stade 1 : portal, stage 2 : periportal, stage 3 : extensive fibrosis, stage 4 : cirrhosis.

Results :Progression according to the initial stage is shown below, after 52±5 months of UDCA (median : 43 ; range : 24-151 months).

	Histological stages		
Initial	**1** (n = 7)	**2** (n = 33)	**3** (n = 10)
Final	0 : n = 2 1 : n = 2 2 : n = 3	1 : n = 1 2 : n = 23 3 : n = 8 4 : n = 1	2 : n = 2 3 : n = 5 4 : n = 3
Follow-up (mo)	52 ± 17	53 ± 6	50 ± 7

Histological stage was stable in 30 patients (60 %) (follow-up (f-up): 47±6 months) and improved (- 1 stage) in 5 (10 %) (f-up : 86±21 months). Worsening was observed in 15 (30 %) (f-up : 52±7 months) : +1 stage in 14, +2 stages in 1. Progression to cirrhosis was seen in only 4 cases (8 %).

Conclusions : Compared with published data on the natural course of PBC, these results suggest that long term UDCA therapy markedly delays the histological progression of PBC.

(1) Heathcote et al, Gastroenterology, 1995. (2) Christensen et al, Gastroenterology, 1980.

74 PREDICTORS OF UNFAVORABLE OUTCOME OF URSODEOXYCHOLIC ACID TREATMENT FOR PRIMARY BILIARY CIRRHOSIS.

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Ursodeoxycholic acid (UDCA) is established as an effective treatment for primary biliary cirrhosis (PBC); although, a small number of UDCA-treated patients require liver transplantation or die. **AIM:** The purpose of this study was to identify factors that may predict unfavorable outcomes from UDCA treatment among PBC patients. **METHODS:** We retrospectively evaluated 89 patients who constituted the treatment arm in a previously reported randomized trial where ten patients died or received liver transplantation during the follow up. These patients were analyzed in comparison with the remaining 79 patients who survived without liver transplantation with respect to 1) their baseline characteristics including the Mayo risk score, liver biochemical parameters, histology, and status of portal hypertensive complications, and 2) interim improvement in the liver function during the first year of follow up. **RESULTS:** Death or transplantation during the UDCA treatment was associated with the following factors at the time of entry: higher Mayo risk score, higher serum bilirubin level, lower albumin level, presence of esophageal varices, history of variceal bleeding, and ascites. These variables showed the same association in the placebo group. When followed serially at 3, 6, and 12 months, those who died or required transplantation showed a comparable degree of improvement in their liver biochemical parameters to those with better outcome. **SUMMARY:** PBC patients with clinically advanced liver disease are more likely to be subject to early death or liver transplantation in spite of treatment with UDCA. Nonetheless, they do respond to UDCA with biochemical improvement as they did in terms of treatment failure in our previous report. **CONCLUSION:** We propose that patients with advanced PBC should not be excluded from receiving treatment with UDCA; although, they need close follow up for possible decompensation and, if indicated, referral for transplantation.

75 URSODEOXYCHOLIC ACID DELAYS THE ONSET OF ESOPHAGEAL VARICES IN PRIMARY BILIARY CIRRHOSIS.

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Ursodeoxycholic acid (UDCA) has been demonstrated in randomized controlled trials to be an effective therapy for the treatment of primary biliary cirrhosis. Long-term observational studies have suggested that the use of this medication is associated with stabilization or reduction in portal pressure in patients with primary biliary cirrhosis. The effect of UDCA therapy on development of esophageal varices is unknown. **AIM:** To address this issue, we compared, as part of a prospective treatment trial, the risk of developing varices in primary biliary cirrhosis patients receiving UDCA versus those receiving placebo. Patients received either UDCA, 13-15 mg/kg/d, or an identically matched placebo for a period of up to four years. Upper endoscopy was performed every two years or as indicated clinically. At the end of the four-year period, all patients in the placebo group were switched to UDCA. After four years of follow up, the risk of developing endoscopically confirmed varices was assessed for each group according to their originally assigned treatment.. **RESULTS:** At entry, 41 patients demonstrated varices on initial examination, and 139 patients had no varices. During follow up of these patients without varices, 7 of 58 (12%) of the UDCA treated patients and 12 of 48 (25%) of the placebo treated patients had developed varices by two years ($p<0.08$) and 8 of 24 (33%) of the UDCA patients and 18 of 24 (75%) of the placebo patients developed endoscopically confirmed varices ($p=0.004$) at four years. Among the patients receiving UDCA, age, gender, or biochemical changes induced by the drug did not differ between those who did and did not develop varices. **SUMMARY:** The use of UDCA was associated with a significantly lower risk of developing varices. **CONCLUSION:** In addition to biochemical improvement, delay in death and orthotopic liver transplantation, UDCA is now demonstrated to decrease the risk of developing varices in patients with primary biliary cirrhosis.

76 CYCLICAL ETIDRONATE VERSUS SODIUM FLUORIDE FOR TREATMENT OF OSTEOPENIA IN PRIMARY BILIARY CIRRHOSIS. EFFECTS AFTER TWO-YEARS.

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Sodium fluoride (F) prevents bone loss in primary biliary cirrhosis (PBC) but has some adverse effects. Cyclical etidronate (E) has proven to be useful for the treatment of osteopenia in postmenopausal osteoporosis, and therefore, we have compared the effects of this drug versus F in 32 women with PBC (age: 57 ±1.3 years) who were randomly assigned to receive E (400 m/d during 14 days every 3 months) or F (50 mg/d, enteric- coated tablets). All patients received calcium supplements and low doses of vitamin D. Bone mineral density of the lumbar spine (L), femoral neck (Fn), femoral Ward's triangle (Fw) and femoral trochanter (Ft) were measured by dual X-ray absorptiometry initially and every 6 months. Vertebral and bone peripheral fractures were evaluated initially and every year. Serum bone Gla-protein (Gla) as an index of bone formation, and urinary hydroxyproline excretion as an index of bone resorption were also measured initially and every 6 months.

Sixteen patients were allocated into each group, which were comparable with respect to the severity of PBC and osteopenia. Thirteen patients with E and 10 patients with F completed two years of follow-up. Three patients with F left the trial because of gastric symptoms and one because of voluntary withdrawal. One patient with E died before one year. Two other patients in each group did not complete two years. In the E group, BMD did not change after two years (L:0.899 ± 0.038 vs 0.904 ± 0.040; Fn:0.713 ± 0.030 vs 0.708 ± 0.032; Fw:0.586 ± 0.038 vs 0.585 ± 0.040; Ft:0.585 ± 0.029 vs 0.606 ± 0.029 g/cm^2). In the F group, lumbar BMD did not change significantly after two years (L:0.888 ± 0.022 vs 0.869 ± 0.025 g/cm^2), but femoral BMD decreased (Fn:0.773 ± 0.018 vs 0.762 ± 0.023; Ft: 0.660 ± 0.023 vs 0.643 ± 0.032 g/cm^2), particularly in the Ward's triangle (Fw:0.658 ± 0.020 vs 0.608 ± 0.023 g/cm^2, p=0.007). Two patients with F (20%) and none with E developed new vertebral fractures. The rate of new bone peripheral fractures was similar in both groups (E:23%; F:20%). Gla and Hprol decreased significantly in patients receiving E (Gla:17.6 ± 2.4 vs 13.8 ± 1.6 ng/ml $p<0.01$; Hprol: 88.4 ± 10.2 vs 59.6 ± 5.9 nmol/mg Cr, p=0.03). Neither treatment impaired liver function or cholestasis in PBC.

We conclude that, after two years, cyclical etidronate is more effective and better tolerated than sodium fluoride for preventing bone loss in primary biliary cirrhosis.