Budesonide Combined With UDCA to Improve Liver Histology in Primary Biliary Cirrhosis: A Three-Year Randomized Trial

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Ursodeoxycholic acid (UDCA) is a safe medical therapy for primary biliary cirrhosis (PBC), but its effect on liver histology remains uncertain. Budesonide is a glucocorticoid with high receptor activity and high first-pass metabolism in liver. We evaluated the combination of budesonide and UDCA on liver histology and compared this with UDCA alone in a 3-year prospective, randomized, open multicenter study. Patients with PBC (n = 77), at stages I to III, were randomized into 2 treatment arms, A (n = 41): budesonide 6 mg/d and UDCA 15 mg/kg/d and B (n = 36): UDCA 15mg/kg/d. Liver histology was assessed at the beginning and at the end of the study. Liver function tests and glucose and cortisol values were determined every 4 months. Paired liver biopsy specimens were available from 69 patients (A = 37 and B = 32). Stage improved 22% in group A but deteriorated 20% in group B (*P* = .009). Fibrosis decreased 25% in group A but increased 70% in group B (*P* = .0009). S-PIIINP decreased significantly in group A. Inflammation decreased in both groups, 34% in group A (*P* = .02), but only 10% in group B (*P* = NS). Serum liver enzymes decreased significantly in both treatment arms. Bilirubin values rose in group B but stayed stable in group A (A/B *P* = .002). A mild systemic glucocorticoid effect from budesonide was evident after 2 years. In conclusion, budesonide combined with UDCA improved liver histology, whereas the effect of UDCA alone was mainly on laboratory values. Studies with longer follow-up using a combination of budesonide and UDCA are warranted to confirm safety and effects. (HEPATOLOGY 2005;41:747–752.)

Primary biliary cirrhosis (PBC) is a chronic cholestatic autoimmune liver disease of unknown etiology characterized by small bile-duct destruction, which may eventually progress to hepatic fibrosis, biliary cirrhosis, and liver failure.[1]

Ursodeoxycholic acid (UDCA) is a safe medical therapy widely used in the treatment of PBC. Although it has been shown to improve biochemical markers in PBC,[2,3] two recent metaanalyses[4,5] and a Cochrane review[6] showed controversial results concerning its effect on liver histology and patient survival. The latest combined analysis of 4 placebo-controlled UDCA studies showed histological benefit in stages I to II, but the rate of progression was not significantly lower in the UDCA group in stages I to III.[7] A recent 12-year prospective randomized study of UDCA was unable to show any demonstrable effect on long-term outcome of PBC.[8] Combination of prednisolone with UDCA has improved liver histology but at the cost of serious glucocorticoid-dependent side effects.[9] For the moment, UDCA has remained the only approved medical therapy for PBC.

Budesonide is a nonhalogenated glucocorticoid absorbed in the small intestine. Of an oral dose, 90% is metabolized during the first liver pass in healthy individuals. After hepatic uptake, budesonide is metabolized to two major metabolites: 16α-hydroxy-prednisolone and 6β-hydroxy-budesonide. Glucocorticoid activity of these

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ALP, alkaline phosphatase; HBsAg, hepatitis B surface antigen; HCV-ab, hepatitis C antibody; ALT, alanine aminotransferase; PIIINP, amino-terminal propeptide of type III procollagen.

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metabolites is only 1% to 10%.[10] Compared with prednisolone, glucocorticoid receptor binding activity of budesonide is 15 to 20 times higher, so its effect on liver inflammation may be greater. In patients with inflammatory bowel disease, oral budesonide has been shown to exert fewer systemic side effects than do conventional corticosteroids.[11] The pharmacodynamic action of budesonide in healthy volunteers and patients with early-stage PBC seems equal,[12-14] but its effects on patients with cirrhosis with PBC are unfavorable.[14]

The combination of budesonide with UDCA has been evaluated in patients with PBC in two studies, with encouraging results for liver histology and biochemistry. Budesonide 9 mg + UDCA 10-15 mg/kg/d has improved liver histology and biochemistry compared with the effects of UDCA alone in a 2-year trial with very few glucocorticoid-related side effects.[15]

Budesonide 9 mg combined with UDCA in patients with suboptimal response to UDCA has had a significant positive effect on bilirubin and alkaline phosphatase (ALP) levels.[16] The fact that patients with cirrhosis were also included may explain the increase in Mayo Risk Score, worsening of osteoporosis, and hyperglycemia.

In this 3-year prospective randomized controlled study, we compared the effect of a lower dose of budesonide combined with UDCA with that of UDCA alone on liver histology and liver function tests in patients at the noncirrhotic stage of PBC.

Patients and Methods

PBC stage I to III patients (n = 77) were randomized into two treatment arms: (A) UDCA 15 mg/kg/day (divided into two doses) and budesonide 6 mg/day (single morning dose), n = 41 or (B) UDCA 15 mg/kg/day, n = 36. Study design was randomized but open because placebo for budesonide was not available for us. The study endpoint was the change in liver histology. There was no washout period for patients receiving UDCA before the study.

A study information letter was sent to internists and gastroenterologists at local hospitals to recruit PBC patients to the trial at university hospitals in three cities in Finland. Consecutive patients were enrolled into the study, if inclusion and exclusion criteria were met. Before study entry and randomization, the diagnosis and severity of PBC was confirmed serologically (antimitochondrial antibodies, over 100 units [normal, <50]) and elevated serum ALP >300 U/L (normal, <275 U/L) and determined by a recent (within 12 months) liver biopsy. Randomization was done centrally at Helsinki University Hospital with sealed envelopes in a block of 10, and patients were stratified according to previous use of UDCA, and stages I to II and III according to the criteria of Ludwig et al.[17] An upper endoscopy was performed to exclude esophageal varices, and Doppler ultrasound of the liver confirmed that the portal and hepatic veins and arteries were open with no signs of cirrhosis or reversed portal flow or collaterals.

Exclusion criteria were age younger than 18 or older than 70 years, pregnancy or inadequate contraceptive use, systemic use of corticosteroids or immunosuppressive medication, clinically significant concomitant liver disease or positive hepatitis B surface antigen (S-HBsAg), hepatitis C antibody (S-HCV-ab), smooth muscle antibodies (S-SMA), and liver–kidney–microsomal antibodies and stage IV PBC.

At study entry, a complete medical history was taken and physical examination performed. At 4-month intervals, each patient had a physical examination and laboratory tests: ALP, γ-glutamyltranspeptidase, alanine aminotransferase (ALT), bilirubin, albumin, prealbumin, prothrombin time, hemoglobin, leukocytes, platelets, erythrocyte sedimentation rate, plasma cortisol level, and fasting blood glucose were measured at every visit. The following laboratory tests were made at 12-month intervals: amino-terminal propeptide of type III procollagen (S-PIIINP), immunoglobulin M, and immunoglobulin G.

At the beginning and end of the study, tests were done to detect urinary N-telopeptide-collagen, serum HBsAg, serum HCV-ab, antimitochondrial antibodies, serum SMA, liver–kidney–microsomal antibodies, and antinuclear antibodies. After 3 years of therapy, a liver biopsy, upper endoscopy, and Doppler ultrasound of the liver were performed. Liver biopsies were evaluated by one single pathologist (P.K.), who was blinded to clinical data and biopsy sequence. Ludwig criteria[17] were used to analyze stage (I = portal hepatitis, II = periportal hepatitis, III = bridging necrosis or fibrosis or both, IV = cirrhosis) and METAVIR point score[18] to evaluate inflammatory activity from 0 to 3, which is based on lobular and interface inflammation. Lobular inflammation is graded: 0 = less than 1 focus, 1 = 1 focus per lobule, and 2 = multiple foci per lobule or bridging necrosis and interface inflammation: 1 = focal in some portal areas, 2 = focal in most portal areas or diffuse in some, 3 =diffuse in all portal areas. The METAVIR point score[18] was also used to assess fibrosis: 0 = normal, 1 = portal expansion, 2 =portoportal septa formation, 3 = porto-central septa formation, and 4 = cirrhosis. Stainings were at least hematoxylin-eosin for inflammation and van Gieson or Herovici for fibrosis.

Histological analysis was based on results from 69 patients. Of the 4 dropouts in group A, one had to stop

Table 1. Baseline Characteristics of PBC Patients, N = 69

	Group A Budesonide + UDCA	Group B UDCA	Statistical Difference *P**
Number (male)	37 (5)	32 (4)	
Age mean (range)	52.4 (33–67)	53.6 (25–70)	NS
Body mass index kg/m^2 (range)	24.7 (18.2–37.9)	25.7 (20.1–30.1)	NS
Duration of PBC years (range)	3.38 (0–16)	4.41 (0–16)	
Previous treatment with UDCA	29	26	NS
Stage I	12	11	NS
Stage II	10	15	.05
Stage III	15	6	.05
Grade 0	11	4	NS
Grade I	11	14	NS
Grade II	9	9	NS
Grade III	6	5	NS

* $P \leq .05$ considered significant, NS = nonsignificant.

budesonide at 20 months because of glucocorticoid- dependent side effects, two refused the follow-up biopsy, and one liver specimen was inadequate in size. In group B, one patient died during the study for non–liver-related reasons, and 3 patients refused the follow-up biopsy for personal reasons.

Statistics. The primary end point was improvement in liver histology. Sample size calculation was based on an assumption that 30% improvement will be seen at liver histology in the combination group compared with UDCA alone. Using α of 0.05 and 80% power, a sample size of 80 patients allows sufficient power to detect a 30% improvement in liver histology. All data are expressed as mean ± SD. For comparison, the Student *t* test and Mann-Whitney *U* test were used. When variances were unequal, or their distribution was not normal, the Kruskal-Wallis multiple comparison test was used. A comparison of incidences was performed with chi-square statistics or Fisher exact test, all of which were performed with NCSS-2000 software for Windows (NCSS Statistical Software, Kaysville, UT). The study was approved by the Ethics Committee of Helsinki University Hospital, and all patients gave informed consent for their participation.

Results

The baseline characteristics of patients appear in Table 1. All patients were negative for serum HBsAg, serum-HCV-ab at the beginning and at the end of the study. Homogenous antinuclear antibodies were found in 8.1% and in 6.3% in groups A and B, respectively.

Biochemical Variables. Values for serum ALP, serum ALT, and serum γ-glutamyltranspeptidase in both groups improved (Table 2). A significant statistical difference between groups appeared for bilirubin. Although mean bilirubin levels were within normal limits in both groups, the levels stayed stable in group A *(P* = NS) and rose in group B *(P* = .01). Mean albumin and prealbumin levels remained unchanged in group A, whereas in group B mean albumin rose *(P* = NS) and prealbumin decreased *(P* = .01), still remaining within normal range, however. Values are within normal limits, so contradictory changes have no clinical significance. Galactose elimination test, prothrombin time, and platelets remained stable in both groups (Table 2). Serum immunoglobulin G, erythrocyte sedimentation rate, and also a marker for fibrosis, serum PIIINP, decreased significantly in group A. Urinary-N-telopeptide-collagen showed no difference between groups, suggesting that bone resorption was not increased in group A (Table 2). Mean levels of plasma cortisol decreased after 2 years in group A, demonstrating a slight systemic effect for budesonide (Fig. 1). Glucose values did not rise compared with group B levels (Fig. 1). No changes were detected in Doppler ultrasound or at gastroscopy in any patients compared with baseline, except the one who developed hypocortisolism. She was dropped from the study at 20 months. Doppler ultrasound demonstrated some minimal changes in her liver with no collaterals, but gastroscopy revealed grade 1 varices.

Liver Histology. Ninety-six percent of liver biopsy specimens either contained more than 6 portal tracts or the length was 10 mm or longer. Mean length of biopsy specimens/number of portal areas at beginning and at the end of the study were for group A 14.0 mm/8.9 and 16.4 mm/8.6 and for group B 16.2 mm/8.7 and 17.3 mm/9.8. At baseline, more patients who were randomized into combination therapy already had stage III disease, 15 versus 6,*(P* = .05) (Table 1). Analysis of liver histology after 36 months of therapy between groups indicated significant differences in the change of stage *(P* = .009) and in fibrosis *(P* = .0009) in favor for the combination group (A). This marked difference in stage was due to 22% improvement *(P* = .06) in group A and 20% deteriora-

Table 2. Laboratory Values at Baseline and After 36 Months

Variables Mean (±SD)	Group A Budesonide + UDCA			Group B UDCA			Change Between Groups	Normal Values
	0 Months	36 Months	*P*	0 Months	36 Months	*P*	*P*	
S-ALP, U/L	490 (313)	345 (210)	.0002	516 (434)	377 (220)	.02	NS	60–275
S-Alt, U/L	64 (50)	40 (25)	.0003	61 (40)	45 (25)	.02	NS	10–35
S-GT, U/L	203 (203)	107 (133)	.0005	242 (297)	144 (296)	.02	NS	5–50
S-Bil, μmol/L	12.2 (4.7)	11.2 (4.0)	NS	10.8 (4.4)	12.4 (4.8)	.01	.002	<20
S-Albumin, g/L	41.3 (2.9)	40.9 (2.3)	NS	41.7 (2.7)	42.5 (2.8)	NS	.04	36–45
S-Prealbumin, mg/L	235 (49)	229 (57.5)	NS	237 (41)	227 (42.3)	.01	NS	230–370
P-Prothrombin time, %	122.5 (26)	109.5 (45.5)	NS	127.2 (28)	111.7 (36.4)	NS	NS	70–130
B-Platelets, E9/L	264 (56)	262 (66)	NS	267 (108)	253 (94)	NS	NS	150–400
Galactose elimination test, mm	13 (6.4)	14 (5.0)	NS	16 (4.7)	16 (6.5)	NS	NS	
S-IgM, g/L	3.4 (2.0)	2.3 (1.3)	<.0001	4.2 (2.6)	3.4 (2.5)	.02	NS	0.47–2.84
S-IgG, g/L	14.0 (3.3)	11.1 (2.1)	<.0001	13.4 (3.3)	12.5 (2.4)	.01	.0007	6.8–15
B-ESR, mm/h	35 (21)	22 (14)	<.0001	32 (20)	29 (16)	NS	.02	1–10
S-PIIINP, μg/L	4.6 (1.7)	3.1 (1.5)	<.0001	4.2 (1.3)	3.6 (1.6)	.02	.01	1.7–4.2
U-NTX, nmol/mmol creatinine	50.8 (38.4)	43.6 (21.3)	NS	40.1 (20.6)	29.6 (15.2)	.007	NS	15–80

NOTE. Values are presented as means (±SD); $P \leq .05$ considered significant, NS = nonsignificant.

Abbreviations: UCDA: Ursodeoxycholic acid, S-ALP: alkaline phosphatase; S-ALT: alanine aminotransferase; S-GT: γ-glutamyltranspeptidase; S-BIL: bilirubin; ERS: erythrocyte sedimentation rate; S-IgM: immunoglobulin M; S-IgG: immunoglobulin G; S-PIIINP: amino-terminal propeptide of type III procollagen; U-NTX: urinary-N-telopeptide-collagen.

tion ($P = .07$) in group B. Fibrosis decreased 25% in group A ($P = .08$), whereas the increase was 70% in group B ($P = .005$). The inflammation decreased in both groups, 34 % in Group A ($P = .02$) and 10% in group B, (P = NS) (Fig. 2). The mean change in stage (Δstage) according to baseline stage stratification, presented in Table 3, demonstrates statistically significant difference between the treatment arms only at stage II. When the effect of the degree of grade on change of stage was analyzed, a significant difference between groups was found. If the grade was 2 or higher, the stage improved significantly in group A compared with UDCA alone, −0.67 versus 0.27, $P < .01$. If the grade was 1 or less, the difference of the delta stage did not reach statistically significant difference (−0.27 vs. 0.4 in groups A and B, respectively).

Adverse Events. In addition to the patient who stopped her budesonide therapy because of steroid-related side effects, another patient also had low cortisol values, which were normalized by reduction of the budesonide dose to 3 mg/day. Seven patients reported mild glucocorticoid-related side effects: bruises, thinning of skin, acne, nausea, mild hirsutism, and some weight gain (three patients). None of these were severe, and neither required any change in treatment or in budesonide dose. Most of the side effects appeared in patients with stage III PBC (five compared with two at earlier stages). In group B, two patients had itching related to elevation of UDCA dosage.

Discussion

This multicenter randomized open study showed budesonide combined with UDCA to be more effective in improving and stabilizing the stage of liver histology than UDCA alone in PBC patients in stages I to III. Fibrosis, assessed by both liver histology and serum PIIINP, decreased significantly in the combination group.

Safety of the medication was monitored every fourth month by serum glucose and cortisol values. If cortisol values decreased under normal limit, adrenocorticotropic hormone level was measured. This turned out to be sufficient to reveal any systemic effect of budesonide. Mean levels of plasma cortisol decreased after 2 years in group A, demonstrating a slight systemic effect from budesonide.

Leuschner et al[15] have shown the same positive effect of combination therapy on liver histology (stage, fibrosis, and inflammation) and laboratory values but with a higher dose of budesonide (9 mg/day) during 2 years of therapy. In our study, a lower dose (6 mg) during 3 years of therapy was effective in improving both stage and fibrosis. The improvement of stage for 22% in the combination group compared with deterioration of 20% in UDCA group is a clinically important finding because 40% of patients were already at stage III at baseline in that group (A). When the treatment response was analyzed according to baseline stage stratification, addition of budesonide to UDCA seems to improve liver histology in early stages (I-II) but no more in stage III. The improve-

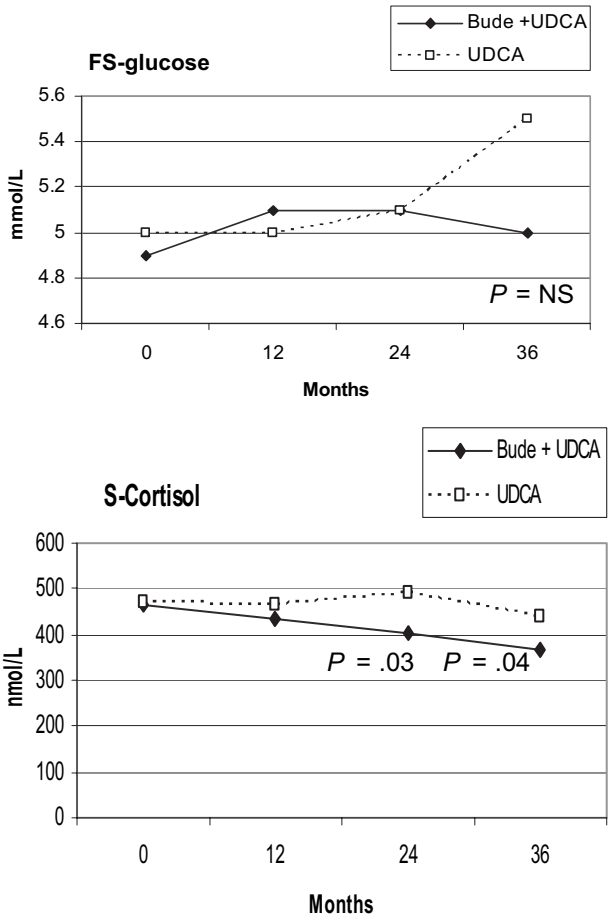

Fig. 1. Annual fasting serum glucose and serum cortisol values. Budesonide (Bude) + UDCA vs UDCA alone. $P \leq .05$ considered significant.

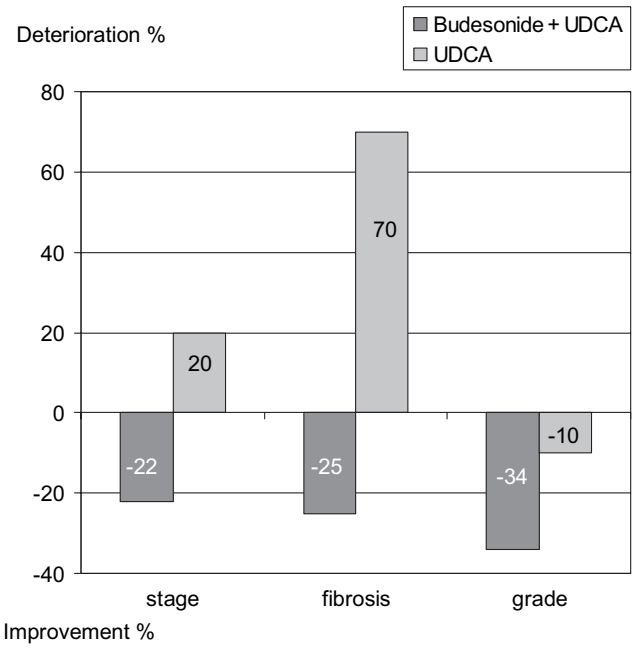

Fig. 2. Change in histology delta values for stage, fibrosis, and grade. Comparison with Bedesonide + UDCA vs. UDCA at stage ($P = .009$), fibrosis ($P = .0009$), and grade (P is not significant).

ment of stage also depended on the grade of inflammation: if grade was equal to or higher than 2, the addition of budesonide significantly improved the stage compared with UDCA monotherapy.

Although inflammatory activity was significantly reduced in the combination group ($P = .02$), no statistical difference appeared between treatment arms. This may be caused by the lower dose (6 mg) of budesonide or because the UDCA group also showed a beneficial but nonsignificant effect on inflammation. The dose of UDCA was higher during the study than during the pre-study treatment in most patients, and this may explain why the UDCA group also had some improvement in inflammation activity. So far, UDCA has been the only accepted therapy for PBC, and most patients were already on UDCA with no washout period before study entry. The lower dose of budesonide seems reasonable for long-term use, based on the signs of a systemic glucocorticoid effect after 2 years.

Compared with pretherapy data, laboratory values (ALP, ALT, γ-glutamyltranspeptidase, immunoglobulin M) improved in both treatment groups, but with no statistical differences between groups. A higher dose of budesonide might have reached significance, as it did in the Leushner groups study.[15] Bilirubin value is considered the only laboratory factor for predicting PBC outcome, hence the important finding that bilirubin values stayed stable (P = NS) in the combination group, but rose ($P = .01$) in the UDCA group.

As expected, liver function tests (albumin, prealbumin, prothrombin time, platelets, galactose elimination test) did not change markedly in this precirrhosis patient population. Serum PIIINP decreased in both groups, but the drop in the combination group was still more pronounced, in accordance with the result of liver histology. Angulo et al[16] found improvement in laboratory values with budesonide 9 mg/day and UDCA but at the cost of many side effects. Our study resulted in few side effects, and only two patients had to stop budesonide or to reduce

Table 3. Delta Stage According to the Initial Stage

	Delta Stage, Mean (±SD)		
Initial Stage	Budesonide and UDCA	UDCA	P
I and II	−0.14 (1.13)	0.5 (0.99)	.04
I	0.4 (0.67)	1 (0.89)	NS
II	−0.8 (1.12)	0.13 (0.92)	.04
III	−0.87 (1.106)	−0.33 (0.52)	NS

NOTE. Delta stage = stage at 36 months − stage at 0 months. NS = nonsignificant.

the dose. The explanation for this difference between studies is probably patient selection: their patients had more advanced liver disease, and patients with portosystemic shunts were not excluded, whereas we included only patients at the precirrhosis stage without signs of portal hypertension or portosystemic shunts.

The fact that the natural course of PBC is expected to be progression from the early stage to cirrhosis in 4 to 6 years[19-21] makes it important to start the therapy early enough, well before inflammation has destroyed the interlobular bile ducts. UDCA is shown to have a beneficial effect on liver histology in patients in PBC stages I to II, but histological outcome in stages I to III was suboptimal.[7] Some 20% to 30% of patients have shown a complete response to UDCA treatment,[22] whereas the rest do need more effective medical therapy. A combination of UDCA and budesonide 6 mg/day is effective and well tolerated by stage I to III PBC patients but requires continuous careful monitoring, especially in stage III patients. Combination therapy might be beneficial for all PBC patients with precirrhosis liver disease, but for asymptomatic patients with stable early PBC on UDCA therapy, the potential systemic glucocorticoid effect would carry an unnecessary risk for diabetes and osteoporosis during long use. Patients with stage IV PBC are no longer objects for combination therapy.[14] Studies with a longer follow up using the combination of budesonide and UDCA are warranted to confirm its safety and its effect on postponing or preventing the need for liver transplantation.

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