J Gastroenterol 2003; 38:573–578

Journal of Gastroenterology

Bezafibrate treatment: a new medical approach for PBC patients?

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Background. A new medical approach to primary biliary cirrhosis (PBC) has been desired. We investigated the feasibility of using combination ursodeoxycholic acid (UDCA)-bezafibrate therapy in patients with PBC nonresponsive to UDCA monotherapy. ***Methods.*** During a 6-month period, 22 PBC patients with elevated serum alkaline phosphatase (ALP) despite UDCA monotherapy received either UDCA at 600 mg/day (control group) or UDCA at 600 mg/day plus bezafibrate at 400 mg/day (bezafibrate group). Each patient underwent detailed clinical and biochemical evaluation. ***Results.*** During treatment, changes in ALP level were greater in the bezafibrate group than in the control group ($P < 0.01$). During and at the end of treatment, serum ALP levels were significantly lower than those before treatment in patients receiving UDCA plus bezafibrate ($P < 0.05$). At the end of the 6 months, normalization of serum ALP was observed in 5 of 11 (45.4%) patients given bezafibrate and in 2 of 11 (18.1%) patients not given bezafibrate ($P < 0.16$). Bile acid proportions during the combination therapy did not change. Pruritus disappeared in 1 of 7 bezafibrate-group patients with this symptom. ***Conclusions.*** UDCA at 600 mg/day plus bezafibrate at 400 mg/day may be considered as a new therapeutic option for patients with PBC.

Key words: bezafibrate, bile acid, PBC

Introduction

Ursodeoxycholic acid (UDCA) is the only drug currently recognized worldwide for the treatment of primary biliary cirrhosis (PBC).[1–5] However, the effect of UDCA is limited. Progression of PBC to the terminal phase in patients receiving UDCA is common, indicating resistance to UDCA therapy.[6] The biochemical response and the degree of severity of lymphocytic piecemeal necrosis assessed in patients receiving UDCA therapy are independent predictors of disease progression. Liver transplantation is the treatment of choice for patients with endstage disease.[7] In Japan, because of the legal difficulties associated with brain death and cadaveric donation, cadaveric donor-liver transplantation has been performed in only a few cases.[8] So, a new medical approach to PBC has been eagerly awaited for some time.

Bezafibrate, a fibric acid derivative, is commonly used in the management of several lipid disorders.[9] A reduction in serum alkaline phosphatase (ALP) activity occurs during bezafibrate treatment, and this has often been used as an indicator of its effectiveness.[10] Recent reports[11–15] suggest that bezafibrate provides a beneficial effect in the treatment of PBC. Furthermore, Kurihara et al.[16] reported that bezafibrate resulted in histological improvement in PBC patients. Still, concrete evidence of the safety and effects of bezafibrate therapy for patients with PBC is lacking.

Combined medical treatment may provide further benefit to PBC patients administered with UDCA.[17] Controlled trials were performed to establish the benefit/risk ratio of such combination therapies.[18–20] However, a controlled study comparing UDCA plus bezafibrate and UDCA monotherapy has not been reported, except for one reported as a letter.[14] In addition, bile acid proportions during combination therapy have not been well described.

Hence, the purpose of this study was to investigate the shortterm outcome (6 months) of combined UDCA (600 mg/day) and bezafibrate (400 mg/day) therapy in PBC patients nonresponsive to UDCA monotherapy. We report here our experience using combined

Received: August 22, 2002 / Accepted: November 22, 2002
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bezafibrate therapy in PBC, in which we compared the biochemical changes in the UDCA monotherapy and combination-therapy groups. Furthermore, we also report on the bile acid proportions during the combination therapy.

Patients and methods

Patients

From March 1995 through December 2000, 22 consecutive patients who had already been diagnosed histologically as having PBC,[21] and who had been treated with 600 mg/day of UDCA for at least 6 months, and had elevated serum alkaline phosphatase (ALP), were enrolled in this study (19 women and 3 men; age, 56 ± 10 years [mean ± SD]; range, 38–78 years). The enrollment criteria were as follows: (1) serum ALP level above the upper limit of normal (359 IU/l) despite receiving 600 mg/day of UDCA; (2) liver-biopsy proven PBC; (3) serum hepatitis B surface antigen (radioimmunoassay), anti-hepatitis C virus (HCV) (enzyme-linked immunosorbent assay [ELISA]; third generation), and human immunodeficiency virus negativity, and no other cause of liver disease, such as alcohol use of more than 30 g/day, metabolic disorders (genetic hemochromatosis, Wilson's disease), or drug-induced liver injury; (4) no ascites, hepatic encephalopathy, esophageal varices, or hyperbilirubinemia (total bilirubin ≥ 2.0 mg/dl); (5) no previous colchicine, corticosteroid, or immunosuppressive treatment; (6) no thyroid or renal dysfunction (serum creatine level ≥ 2.0 mg/dl); and (7) prior compliance with UDCA therapy (as determined by levels of individual serum bile acids). Informed consent was obtained from all patients.

Study design

Patients were randomly assigned to one of two groups. The first group was the bezafibrate group (UDCA plus bezafibrate): for 6 months, 11 patients were given 400 mg per day of bezafibrate (Kissei Pharmaceutical, Matsumoto, Japan) divided into two orally administered doses, post-breakfast and post-dinner, along with 600 mg per day of UDCA (Mitsubishi-Tokyo Pharmaceuticals, Tokyo, Japan) divided into three orally administered post-meal doses. These patients received the same dose of UDCA alone as they had before this study and they received the same dose of UDCA alone after the 6-month period. The second group was the control group (UDCA without bezafibrate): 11 patients who received no bezafibrate during the study. All patients were given 600 mg per day of UDCA in the same manner before, during, and after the 6-month period.

All patients participated in the study for at least 7 months. Patients' data are shown in Table 1.

Each patient underwent detailed clinical and biochemical evaluation before entry into the trial, and once

Table 1. Demographic, laboratory, and histologic characteristics of the 22 patients at entry

	Bezafibrate group (UDCA with bezafibrate)	Control group (UDCA alone)	*P*
Number of patients	11	11	
Age (years)[a]	56 ± 9	56 ± 12	NS[b]
Male/female	3/8	0/11	NS[c]
AST (IU/l)[a]	59 ± 53	75 ± 47	NS[b]
ALT (IU/l)[a]	54 ± 37	37 ± 13	NS[b]
γ-GT (IU/l)[a]	46 ± 30	34 ± 14	NS[b]
ALP (IU/l)[a]	700 ± 270	550 ± 220	NS[b]
TBA (nmol/ml)[a]	34 ± 41	41 ± 43	NS[b]
T-Cho (mg/dl)[a]	210 ± 35	210 ± 33	NS[b]
Platelets (×1000/μl)[a]	250 ± 62	220 ± 69	NS[b]
UDCA therapy before entry (months)[a]	59 ± 53	37 ± 13	NS[b]
Histological stage (I/II/III/IV)[d]	3/3/4/1	2/5/3/1	NS[c]
Pruritus yes/no	7/4	5/6	NS[c]

UDCA, ursodeoxycholic acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TBA, total bile acid; T-Cho, total cholesterol; NS, statistically not significant

[a] Mean ± SD values

[b] Statistically not significant (NS) by Student's *t*-test

[c] Statistically not significant (NS) by Fisher's exact test

[d] Histological stage of PBC was determined according to Ludwig[21]

a month during and after the study. Serum samples were submitted to routine liver biochemical tests by automated techniques. Mitochondrial antibodies were assayed by immunofluorescence microscopy. Total and individual serum bile acids in some patients were determined by high-performance liquid chromatography, according to the method of Takano et al.[22] and Okuyama et al.[23]

Statistical analysis

Data values were expressed as means ± standard deviation. Statistical analysis was performed using Student's *t*-test and Fisher's exact test when appropriate. The difference in mean values was regarded as significant when the two-tailed *P* value was less than 0.05.

Results

The baseline characteristics of patients in the bezafibrate and control groups were similar (Table 1). Twelve patients had pruritus, and 10 patients had no symptoms apart from fatigue.

Changes in clinical variables

One month after starting the trial, pruritus had decreased significantly in one patient taking UDCA plus bezafibrate. No significant changes in the size of liver and spleen, or in the development of new ascites, upper gastrointestinal bleeding, or hepatic encephalopathy were observed in patients taking UDCA plus bezafibrate.

Changes in biochemical variables

The changes in biological variables after treatment are shown in Figs. 1 and 2. The mean ALP value in the bezafibrate group fell progressively during the trial period, from 700 to 390 IU/l, whereas that of the control group fluctuated a little between 550 and 540 IU/l and was consistently higher than that of the bezafibrate group. In the bezafibrate group, the mean ALP value was significantly lower at 1, 2, 3, 4, 5, and 6 months than at entry. One month after stopping bezafibrate (7 months after starting the therapy), the mean ALP levels in both groups were approximately the same, and had increased to the baseline level of the control group (Fig. 1a). ALP was within the normal range at 6 months in five members of the bezafibrate group and in only two of the control group (Fig. 2). However, none of the other tests showed any statistically significant changes compared with baseline levels, although IgM (257 ± 265 mg/dl) at 6 months tended to be lower than at entry (392 ± 304 mg/dl).

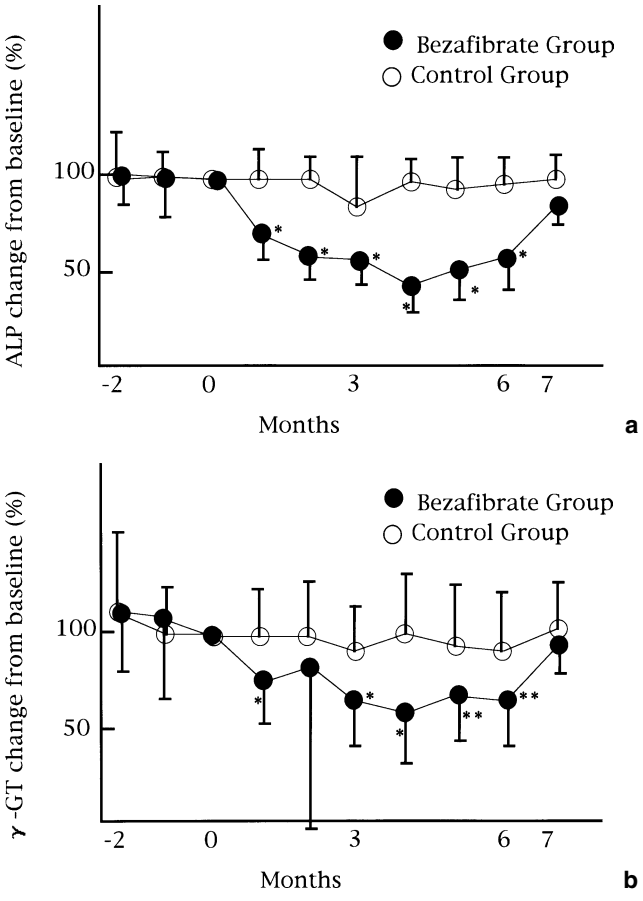

Fig. 1a,b. Rates of change of **a** alkaline phosphatase (*ALP*) and **b** γ-glutamyl transpeptidase (γ-*GT*) levels *Significantly lower than control group ($P < 0.01$); **Significantly lower than control group ($P < 0.05$). *Error bars* indicate SD

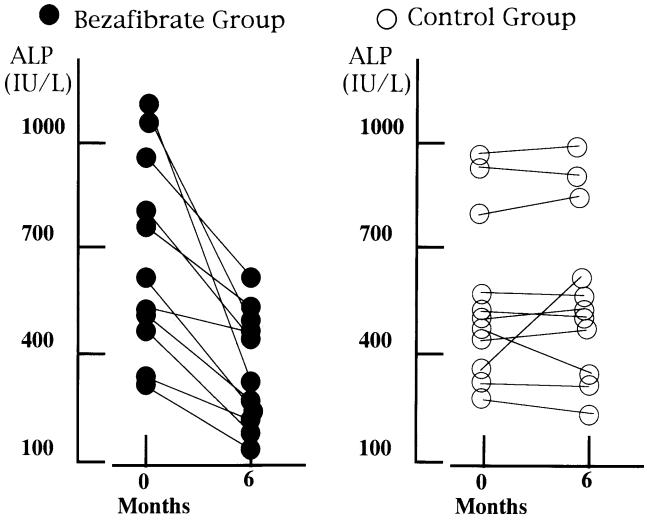

Fig. 2. Changes in ALP levels from entry to 6 months in the bezafibrate group (ursodeoxycholic acid [UDCA] plus bezafibrate) and control group (UDCA alone). Upper limit of normal ALP is 359 IU/l

Table 2. Changes in bile acid composition in bezafibrate group and control group

	Total bile acids (nmol/ml)	UDCA (%)	CA (%)	CDCA (%)	DCA (%)	LCA (%)
	Entry/6 months	Entry/6 months	Entry/6 months	Entry/6 months	Entry/6 months	Entry/6 months
Bezafibrate group (UDCA plus bezafibrate; $n = 7$)	34 ± 41/41 ± 43	55 ± 18/59 ± 18	12 ± 11/10 ± 9	16 ± 13/20 ± 8	16 ± 14/8 ± 4	0.4 ± 0.4/1.1 ± 1.0
Control group (UDCA alone; $n = 11$)	29 ± 26/31 ± 35	65 ± 12/65 ± 6	5 ± 6/5 ± 6	20 ± 6/17 ± 4	7 ± 5/9 ± 4	0.7 ± 0.8/1.0 ± 0.7

UDCA, ursodeoxycholic acid; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid

During treatment, the changes in ALP level were greater in the bezafibrate group than in the control group ($P < 0.01$; Fig. 1a). In the bezafibrate group, the ALP rates as a percentage of baseline were 65% at 1 month, 58% at 2 months, 53% at 3 months, 43% at 4 months, 52% at 5 months, and 55% at 6 months. Changes in γ-glutamyl transpeptidase (γ-GT) level were also significantly greater in the bezafibrate group than in the control group at 1, 3, and 4 months ($P < 0.01$), and at 5 and 6 months ($P < 0.05$; Fig. 1b). In the bezafibrate group, the γ-GT rates as a percentage of baseline were 69% at 1 month, 83% at 2 months, 65% at 3 months, 54% at 4 months, 69% at 5 months, and 68% at 6 months.

Changes in bile acid levels

The patients' prior compliance with UDCA monotherapy was evident from the finding that UDCA was the predominant bile acid in the serum of all subjects at entry (Table 2). During treatment, concentrations of the principal serum bile acids did not change significantly. The levels of total unconjugated bile acids were negligible in the pretreatment and posttreatment serum samples (data not shown).

Adverse events

Severe side effects were not seen in any of the patients, and only one minor side effect, polydipsia, was observed, at 4 months, in one patient receiving UDCA plus bezafibrate. However, this symptom subsided within a few days without the treatment being interrupted. No other side effect was seen in either group.

Discussion

Our present results indicate that the shortterm administration of bezafibrate (400 mg/day) can safely result in clinical, and, especially, biochemical improvement in patients with PBC. In PBC, the chronic cholestasis that arises after the disappearance of bile ductules is thought to initiate or aggravate liver cell injury because of the accumulation of endogenous, relatively hydrophobic, and potentially toxic bile acids.[2,24] PBC is usually a progressive disease.[25,26] The mode of action of UDCA against PBC is still unclear, but it is hypothesized that its efficacy in chronic liver disease resides in its ability to maintain the hydrophilic/hydrophobic balance of the bile composition.[18,20,27] Thus, some data support the proposal that UDCA prevents or reverses the hepatocellular damage induced by hydrophobic bile acids.[25] Moreover, apoptosis may be involved in the pathogenesis of PBC, and a possible effect of UDCA may be to

reduce nuclear DNA fragmentation in biliary epithelial cells.[28,29]

UDCA is safe and may be useful for preventing the progression of PBC. Some studies have indicated, however, that UDCA treatment did not significantly influence the time to death or to liver transplantation, nor did it prevent clinical complications.[5,6,30] UDCA may have either minor or no beneficial effect on the histological findings of the liver,[31–33] but in one study a subset of patients with PBC showed improved histology after UDCA therapy.[34] In fact, it is known that PBC can be resistant to UDCA therapy.[2,6] Colchicine seemed to decrease the mortality rate related to liver failure and to improve the results of biochemical tests of liver function, but it exerted no beneficial effects on symptoms or histologic findings.[35,36] Corticosteroids improve liver function,[37] but their longterm use increases bone loss in some patients, and they are generally considered unsafe for PBC treatment. Cyclosporine,[38] methotrexate,[39,40] penicillamine,[41] and azathioprine[42] were not efficacious or were unsafe. No therapeutic agent other than UDCA has shown convincingly favorable results in the treatment of PBC.

Combination therapy has been advocated in PBC to achieve additional benefits, especially in terms of clinically relevant events.[17] Kurihara et al.[12,16] reported that bezafibrate alone and the combination of bezafibrate plus UDCA were effective in the treatment of PBC. Unfortunately, many of the studies of combination therapy of bezafibrate plus UDCA for PBC have not been controlled trials.[11,13,15] Thus, we performed a controlled trial in patients with PBC nonresponsive to UDCA monotherapy, even though, admittedly, our patient population was rather small.

Most of our patients were not in an advanced stage of PBC. The biochemical response and the degree of severity of lymphocytic piecemeal necrosis assessed in patients receiving UDCA therapy are reported as two independent predictors of the development of cirrhosis.[6] Our present results showed that the use of bezafibrate for PBC was safe and produced improved ALP levels, consistent with previous studies.[11–15] We found no evidence of any additional effect of UDCA plus bezafibrate therapy on transaminase levels, which are already known to be reduced by UDCA monotherapy.[1,2] Any significance of a reduction in liver ALP activity during treatment with bezafibrate and a related role in lipid metabolism is uncertain.[10] The rationale for the use of UDCA is to induce qualitative changes in the bile-acid pool.[18,20] We found no evidence of any effect of UDCA plus bezafibrate therapy on the UDCA proportion of bile acid. Bezafibrate is a ligand of peroxisome proliferative-activated receptor alpha, which is involved in immune function.[43] Recently, Ishimaru and Iino[44] reported that bezafibrate lowered the proportion of Fas antigen-positive T cells in the peripheral blood of PBC patients. In the present study, IgM tended to be lower during the combination therapy. This may indicate that bezafibrate interferes with the host's immune function and suppresses the inflammatory response in PBC patients. Bezafibrate induces the expression of a multiple drug-resistant gene, *mdr2*, whose knockout mice are a model of familial intrahepatic cholestasis.[45,46] It is suggested that bezafibrate may lower the ALP level via a pathway other than that used by UDCA. Thus, combination therapy seemed to be more effective in terms of the biochemical and clinical features of PBC patients because of the pharmacological differences between bezafibrate and UDCA.

Our study did not investigate the longterm effects of the combined use of UDCA and bezafibrate, and such a trial is needed before this treatment can be introduced into clinical practice. Additionally, the shortterm nature of this study prevented the evaluation of histologic changes, and such a trial is also needed. Our study suggests that shortterm treatment with UDCA plus bezafibrate might constitute a safe, effective therapy for PBC that is nonresponsive to UDCA monotherapy. The results must be confirmed by a longterm study.

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