

Fenofibrate in Primary Biliary Cirrhosis: A Pilot Study

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Abstract: *Background:* Most patients with primary biliary cirrhosis (PBC) are treated with ursodeoxycholic acid (UDCA); however, some do not respond fully. PBC is also associated with dyslipidemia, but a link with vascular risk has not been confirmed.

Methods and Results: In this study we compared UDCA monotherapy with fenofibrate plus UDCA in PBC patients with incomplete biochemical response to UDCA monotherapy for ≥ 8 months. Ten patients (57.2 ± 13.3 years old) with PBC and persistent elevations of liver enzymes after treatment with UDCA (600 mg/day) were randomized to continue UDCA (4 patients) or to receive micronized fenofibrate (200 mg/day) plus UDCA (6 patients) for 8 weeks. Significant reductions in total cholesterol, triglycerides and non-high density lipoprotein cholesterol were observed in the combination treatment group. The serum activities of alkaline phosphatase, gamma-glutamyl transpeptidase and alanine aminotransferase also decreased in this group compared with baseline (-32.6%; $p=0.012$, -44%; $p=0.031$ and -16.9%; $p=0.029$, respectively). In contrast, no significant alterations in liver enzymes or lipid profile were observed in patients who continued UDCA monotherapy. The changes in the lipid and enzyme variables differed significantly ($p < 0.03$) between the 2 groups. Fenofibrate was well tolerated.

Conclusions: The administration of fenofibrate plus UDCA seems to be safe and may improve lipid and liver indices in patients with PBC who do not respond fully to UDCA monotherapy. Whether the improved lipid profile translates into a decreased risk of vascular events remains to be established.

Keywords: Fibrates, ursodeoxycholic acid, primary biliary cirrhosis, liver enzymes, dyslipidemia.

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by inflammation and destruction of interlobular bile ducts, which may eventually lead to liver fibrosis, biliary cirrhosis and subsequently hepatic failure and death [1]. Although there is no established aetiology for the disease, PBC has been attributed to autoimmunity primarily due to its association with autoantibodies [especially antimitochondrial antibodies (AMA)] and elevated levels of immunoglobulin M (IgM) [1].

Ursodeoxycholic acid (UDCA), the most commonly used drug for PBC, [2] may ameliorate cholestasis [2]. However, some patients do not achieve complete biochemical response with UDCA treatment [3]. Fibrates (mainly bezafibrate), which are potent ligands of peroxisome proliferator-activated receptor α (PPAR α), have been tested in patients with PBC with promising results [4-11]. However, there are scarce data on the effects fenofibrate (a commonly used fibrate) in PBC. Therefore, we conducted this pilot study to compare the effects of UDCA monotherapy with the combination of UDCA and fenofibrate in patients with PBC who

had incomplete biochemical response following UDCA monotherapy for ≥ 8 months.

PBC is associated with dyslipidemia. However, it has not been established if this represents an increased risk of cardiovascular disease (CVD) [12]. Therefore, using a fibrate in patients with PBC may potentially improve both PBC-related liver damage and vascular risk.

MATERIALS AND METHODOLOGY

Participants

Ten patients (2 men and 8 women, 57.2 ± 13.3 years old) with histologically confirmed PBC (stages I and II) were included in the present study. These patients had persistent elevations of liver enzyme activities [specifically: alkaline phosphatase (ALP) > 3 -fold upper limit of normal] after treatment with UDCA (600 mg/day) for at least 8 months. Patients with known CVD, diabetes mellitus, cancer, renal disease (serum creatinine levels > 1.6 mg/dL) and hypothyroidism [thyroid stimulating hormone (TSH) > 5 IU/mL] were excluded from the study. Patients taking lipid lowering drugs or having stopped them less than 6 weeks before study entry, as well as those currently taking other drugs that affect lipid metabolism (e.g. beta-blockers, thiazide diuretics, contraceptive pills or steroids) were also excluded. The patients were randomized to continue open-label UDCA (4 patients)

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or receive combined treatment with micronized fenofibrate (200 mg/day) and UDCA (600 mg/day) for 8 weeks (6 patients). Patients were instructed to follow their usual diet. Compliance with medication was assessed by pill count. All participants gave their written informed consent prior to enrolment and the Ethics Committee of the University Hospital of Ioannina approved the study protocol.

Laboratory Determinations

The activities of ALP, aspartate aminotransferase (AST) alanine aminotransferase (ALT) gamma glutamyl transpeptidase (γ GT) and amylase as well as the levels of glucose, total and conjugated bilirubin, uric acid, creatinine and the lipid profile [i.e. total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), non-HDL-C and triglycerides] were assessed at baseline before randomization and after 8 weeks of treatment. The samples were collected after an overnight fast and assayed in the laboratory of the University Hospital of Ioannina using an Olympus AU 600 analyzer (Olympus Diagnostica GmbH, Hamburg, Germany). Glucose was measured by the hexokinase method. LDL-C levels were calculated using the Friedewald equation ($\text{LDL-C} = \text{total cholesterol} - \text{HDL-C} - \text{triglycerides}/5$ in mg/dL) and non-HDL-C was defined as total cholesterol – HDL-C.

Statistical Analysis

All parameters were checked for normality using the Kolmogorov-Smirnov test. All values are expressed as mean \pm standard deviation (SD) except for non-Gaussian distributed variables which are expressed as median (range). The paired-samples *t*-test (or Wilcoxon's rank test for non-Gaussian parameters) was used for assessing the effect of treatment in each group. Analysis of covariance (ANOVA), adjusted for baseline values, was used for comparisons between treatment groups. Significance was defined as $p < 0.049$ due to multiple comparisons ($\times 2$) [13]. All analyses were carried out using the SPSS 15.0 statistical package for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics of the participants did not differ between the 2 groups (Table 1). Body mass index (BMI) did not change during the study in either group.

The addition of fenofibrate to UDCA resulted in significant decreases in the levels of total cholesterol, triglycerides and non-HDL-C (Table 2). Furthermore, significant reductions in the serum activities of ALP (-32.6%, $p=0.012$), γ GT (-44%, $p=0.04$) and ALT (-16.9%, $p=0.029$) compared with baseline were observed in the combination treatment group (Table 2). On the other hand, no significant alterations in liver enzyme activities and lipid profile were demonstrated in patients who continued on UDCA monotherapy (Table 2). The change in the lipid and liver enzyme variables differed significantly ($p < 0.03$) between the 2 groups (Table 2). No significant changes in glucose, total and conjugated bilirubin, uric acid, amylase, creatinine and AST compared with baseline were observed in the 2 treatment groups.

Fenofibrate was well tolerated by all patients.

DISCUSSION

Significant improvements in lipid profile and liver enzyme activities were demonstrated in PBC patients who had an incomplete biochemical response to UDCA monotherapy and now received combined fenofibrate+UDCA treatment. In contrast, no change in these parameters was noted in the patients who continued on UDCA monotherapy.

Several small studies have investigated the effects of fibrates, either alone or in combination with UDCA in patients with PBC [5-7, 10, 14, 15]. In a prospective pilot study 23 patients with PBC who had been treated with UDCA for 1-5 years were randomly assigned to continue UDCA treatment (600 mg/day, $n=13$) or receive UDCA (600 mg) and bezafibrate (400 mg) ($n=10$) for 12 months [7]. Significant reductions in ALP, γ GT and IgM at 3 ($p < 0.05$), 6, 9 and 12 months ($p < 0.01$) were observed in the bezafibrate+UDCA treatment group. The decrease in ALP and IgM was more pronounced as compared with that in the UDCA monotherapy group [7]. Comparable results have been demonstrated in other studies with similar design [4, 11].

Two studies compared the effects of bezafibrate with that of UDCA in patients with PBC. In 1 study 24 patients were randomly assigned to receive bezafibrate 400 mg/day ($n=12$) or UDCA 600 mg/day ($n=12$) for 12 months [6]. Significant reductions in ALT, ALP, γ GT and IgM were demonstrated in both treatment groups ($p < 0.0001$); these changes were more pronounced in patients who received bezafibrate [6]. In contrast, in the other study bezafibrate was equally effective with UDCA [15]. However, it is not known whether these effects were translated into histological improvement as no biopsies were performed in the aforementioned studies.

There is few data in literature regarding the long-term efficacy of bezafibrate in patients with PBC [5, 10, 16]. Nakamuta *et al.* followed 3 patients with PBC who were treated with bezafibrate (400 mg/day) and UDCA (600 mg/day) for an average of 37.5 months after treatment with UDCA for more than 4 years [16]. The mean levels of ALT, γ GT, IgM and the titer of AMA were decreased after treatment ($p=0.079$ for ALT and γ GT and $p=0.043$ for IgM vs baseline) [16].

Similar results in biochemical parameters along with histological changes were observed in 3 women with PBC after bezafibrate administration for 3, 4 and 5 years, respectively [5]. Substantial reductions in the levels of ALT, ALP, γ GT, IgM and AMA, as well as a significant increase in apolipoprotein A-II levels were demonstrated in all patients. Furthermore, 2 of the 3 patients exhibited histological improvement while in the other patient there were no signs of deterioration [5]. This report indicated an association between biochemical and histological changes after bezafibrate treatment in PBC patients. In contrast, long-term bezafibrate treatment (6.5 and 6 years) did not lead to histological improvement in 2 patients with asymptomatic PBC and elevated liver enzymes [10].

There are some promising results in terms of fibrosis progression [9]. Seventeen patients with PBC who received bezafibrate (400 mg/day) and UDCA (600 mg/day) were followed for a mean of 59 months. The administration of

Table 1. Baseline Characteristics of Study Participants

	Fenofibrate Plus UDCA (n=6)	UDCA (n=4)	p	Reference Range
Mean duration of UDCA monotherapy (months)	8.6±0.8	8.8±0.7	NS	
Age (years)	55.3±4.5	54.8±7.3	NS	
Sex (male/female)	1/5	1/3	NS	
Smoking (yes/no)	2/4	1/3	NS	
Body mass index (kg/m ²)	27.2±2.8	27.9±3.1	NS	
ALP (IU/L)	195±73	232±74	NS	30-125
AST (IU/L)	42±15	38±10	NS	10-35
ALT (IU/L)	49±25	41±13	NS	10-35
γGT (IU/L)	96 (38-479)	112 (56-419)	NS	10-52
Total bilirubin (mg/dL)	0.70±0.14	0.73±0.18	NS	0.1-1.0
Conjugated bilirubin (mg/dL)	0.16±0.04	0.17±0.07	NS	0.0-0.3
Uric acid (mg/dL)	4.3±1.3	4.1±1.2	NS	3.4-8.0 (men) 2.4-6.1 (women)
Creatinine (mg/dL)	0.74±0.15	0.76±0.12	NS	0.6-1.2
Amylase (IU/L)	63±15	68±16	NS	30-90
Total cholesterol (mg/dL)	283±40	302±45	NS	110-200
Triglycerides (mg/dL)	145±67	136±68	NS	40-175
HDL-C (mg/dL)	68±17	71±18	NS	35-70
LDL-C (mg/dL)	189±29	198±24	NS	Target values depend on individual cardiovascular risk
non HDL-C (mg/dL)	215±27	221±29	NS	
Glucose (mg/dL)	96±19	92±16	NS	70-125

UDCA: ursodeoxycholic acid, ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGT: gamma glutamyl transpeptidase, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, NS: not significant
Values are expressed as mean ± SD, except for γGT which is expressed as median (range)

To convert bilirubin values to μmol/L multiply by 17.1. To convert uric acid values to μmol/L multiply by 59.48. To convert creatinine values to μmol/L multiply by 88.4. To convert cholesterol values to mmol/L multiply by 0.026. To convert triglyceride values to mmol/L multiply by 0.0113. To convert glucose values to mmol/L multiply by 0.05551.

bezafibrate and UDCA was associated with significant reductions in hepatic fibrosis markers [9].

The activity of fenofibrate on PPARα is stronger than that of bezafibrate,[17] while fenofibrate exhibits more favourable effects on lipid profile compared with bezafibrate [18, 19]. Furthermore, fenofibrate is a commonly used fibrate. However, there are only 3 studies on the effects of fenofibrate in PBC patients. In 1 study 7 patients with abnormal biochemical profile (elevated ALP, γGT and IgM) despite treatment with UDCA (600-900 mg/day) for 1-8 years were administered fenofibrate (150-200 mg/day) in addition to UDCA [20]. Treatment for 6 months resulted in reductions in the levels of these parameters in all 7 patients (p<0.05 vs baseline) [20]. In another study fenofibrate was added to UDCA for 12 weeks in 9 patients with asymptomatic PBC who failed to respond to UDCA monotherapy

[21]. The serum levels of ALP and IgM were significantly reduced after fenofibrate treatment (p<0.05), while the titer of AMA decreased in 4 of 9 patients. Lipid levels (total cholesterol, LDL-C, HDL-C and triglycerides) did not change significantly [21]. Consistently, in a recent study the addition of fenofibrate (134-200 mg/day) to UDCA for 23 months resulted in significant reductions in IgM (p=0.0015) and ALP (p=0.0016) in 16 patients with lack of biochemical response (no significant decrease in ALP, ALT or IgM) to UDCA monotherapy (for a mean of 22.8 months) [22]. The findings of the aforementioned studies are consistent with the results of our study, suggesting that fenofibrate may be useful for the treatment of PBC, especially in patients resistant to UDCA.

Data regarding the long-term effects of fenofibrate in PBC is not available. To the best of our knowledge only

Table 2. Biochemical Biomarkers and Lipid Profile at Baseline (Before Randomization) and After 8 Weeks of Treatment

	Baseline	8 Weeks	Change (%)
ALP (IU/L)			
Fenofibrate plus UDCA	195±73	132±70	-32.6 ^{†,‡}
UDCA	232±74	245±81	+5.6
AST (IU/L)			
Fenofibrate plus UDCA	42±15	41±19	-3.0
UDCA	38±10	37±11	-2.0
ALT (IU/L)			
Fenofibrate plus UDCA	49±25	41±27	-16.9 ^{†,‡}
UDCA	41±13	39±14	-5.0
γGT (IU/L)			
Fenofibrate plus UDCA	96 (38-479)	54 (19-348)	-44.0 ^{†,‡}
UDCA	112 (56-419)	120 (62-430)	+1.0
Total bilirubin (mg/dL)			
Fenofibrate plus UDCA	0.70±0.14	0.64±0.29	-8.5
UDCA	0.73±0.18	0.65±0.24	-11.0
Conjugated bilirubin (mg/dL)			
Fenofibrate plus UDCA	0.16±0.04	0.14±0.09	-12.5
UDCA	0.17±0.07	0.15±0.08	-12.0
Uric acid (mg/dL)			
Fenofibrate plus UDCA	4.3±1.3	4.0±1.5	-7.0
UDCA	4.1±1.2	4.0±1.3	-2.0
Creatinine (mg/dL)			
Fenofibrate plus UDCA	0.74±0.15	0.82±0.13	+6.0
UDCA	0.76±0.12	0.79±0.12	+4.0
Amylase (IU/L)			
Fenofibrate plus UDCA	63±15	62±10	-1.0
UDCA	68±16	62±13	-9.0
Total cholesterol (mg/dL)			
Fenofibrate plus UDCA	283±40	257±39	-9.5 ^{†,‡}
UDCA	302±45	297±39	-2.0
Triglycerides (mg/dL)			
Fenofibrate plus UDCA	145±67	108±35	-25.6 ^{†,‡}
UDCA	136±68	122±28	-10.0
HDL-C (mg/dL)			
Fenofibrate plus UDCA	68 ±17	68±14	0.0
UDCA	71±18	70±16	-1.5
LDL-C (mg/dL)			
Fenofibrate plus UDCA	189±29	167±22	-10.0
UDCA	198±24	201±26	+1.0
non HDL-C (mg/dL)			
Fenofibrate plus UDCA	215±27	188±29	-12.5 ^{†,‡}
UDCA	221±29	209±32	-5.0
Glucose (mg/dL)			
Fenofibrate plus UDCA	96±19	85±11	-1.0
UDCA	92±16	94±15	+2.0

For abbreviations and conversions to SI units see Table 1

[†]p<0.049 vs baseline[‡]p<0.03 vs UDCA monotherapy

Values are expressed as mean ± SD, except for γGT which is expressed as median (range).

Nakamuta *et al.* reported the effects of treatment with fenofibrate (150 mg/day) and UDCA (600 mg/day) in 2 patients with PBC [16]. After an average of 37.5 months the mean levels of ALT, γ GT, IgM and the titer of AMA were decreased ($p=0.079$ for ALT and γ GT and $p=0.043$ for IgM vs baseline) in both patients [16]. It is surprising that most of the studies discussed above did not report lipid levels.

The mechanisms by which fibrates may improve the histology in PBC have not been fully elucidated. These actions may be mediated *via* PPAR α , the main target of fibrates, which are involved in the inflammatory and immunologic response. Fibrates inactivate leukotriene B₄, a leukocyte activator, by activating β and ω oxidation of fatty acids [23]. Furthermore, by suppressing the activation of the nuclear factor-kappaB (NF-kappaB), fibrates decrease the levels of interleukins 1 and 6 and cyclooxygenase 2 and subsequently the production of prostaglandin E₂ and immunoglobulin [24]. The fibrate-associated increase in apolipoprotein A-II levels leads to suppressed expression of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 [25]. Of note, these adhesion molecules are involved in the inflammatory process in the biliary system [26]. It is, therefore, likely that these PPAR α -mediated anti-inflammatory and immunomodulatory effects of fenofibrate contribute to the improvement of PBC.

Biliary fibrosis in PBC results from cholestasis and intrahepatic accumulation of cytotoxic bile acids [1]. Fibrates facilitate the expression of the multiple drug resistance gene 3 which encodes the canalicular phospholipid translocator [27, 28]. This receptor increases biliary phospholipid secretion and induces the formation of micelles with hydrophobic bile acids, thus inactivating the latter and protecting biliary epithelial cells [27, 28].

Furthermore, bile acids increase the expression of regulated on activation normal T-cell expressed and secreted (RANTES), which migrates memory type CD4⁺ T-lymphocytes to inflamed tissues, in the hepatocytes of patients with PBC [29]. Bezafibrate and fenofibrate decrease the chenodeoxycholic acid- and tumor necrosis factor- α -induced mRNA expression and production of RANTES protein in human hepatoma cells [30, 31]. These findings indicate that fibrates may inhibit inflammatory cell migration by RANTES to the liver in patients with PBC.

The 'hepatic' safety of fibrates has been confirmed by large clinical studies, while most of the adverse effects associated with fibrate treatment have been scarce [32].

It has not been clarified whether the lipid abnormalities in PBC are associated with increased risk for CVD [12]. Overall, data do not support a strong association between excess CVD risk and PBC. In this context, it has been suggested that hypercholesterolemia should be treated when other risk factors exist [33-35]. Statins, the mainstay of lipid lowering therapy, have been found to be safe and effective in improving the lipid profile in PBC patients,[36-40] overcoming the concerns about inducing elevations of liver enzymes [41]. However, statins do not seem to ameliorate cholestasis

or progression of the disease;[38] none of these studies included histological findings.

Of note, fenofibrate has been associated with some beneficial effects on vascular events in patients with diabetes, [42] as well as with improvement (liver function tests and ultrasound) in non-alcoholic fatty liver disease [43]. However, as for statins, large, controlled, long-term studies are warranted to evaluate the efficacy of fibrates on histological improvement, symptom control and survival in patients with PBC.

Interestingly, the reduction in γ GT may be clinically relevant in terms of CVD risk. Indeed, evidence suggests that the serum γ GT concentration is an independent prognostic factor for CVD, including coronary heart disease, diabetes, stroke and CVD mortality [44-48]. Furthermore, γ GT levels have been positively correlated with several other cardiovascular risk factors (e.g. LDL-C, triglycerides, uric acid, BMI, serum glucose, metabolic syndrome, smoking, hypertension and prehypertension),[46, 47, 49] some of which are commonly found in patients with PBC.

The main limitations of this study are the small sample size and the lack of histological assessment after treatment. However, most of the studies that investigated the effects of fibrates in PBC were small and mainly only assessed biochemical markers. Therefore, there is no definite evidence to support the histological improvement or the delay of disease progression after treatment with fibrates. On the other hand, the design of this study is relevant to clinical practice, i.e. what options are available when patients fail to achieve a biochemical response while on UDCA monotherapy. In addition, most studies did not record the lipid levels. The issue of CVD risk in patients with PBC warrants further investigation.

Our data, along with others, suggest that the addition of fenofibrate is safe and probably a useful option in this setting.

CONCLUSION

UDCA is currently the most commonly used drug for the treatment of PBC. However, several patients do not achieve full biochemical response with UDCA and need supplementary treatment. Fibrates may improve the biochemical and probably the histological abnormalities in PBC. Fenofibrate, a widely available and potent fibrate, seems to be a safe alternative or adjunct therapeutic option and simultaneously improve the lipid profile (and possibly vascular risk) in patients with incomplete response to UDCA.

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