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## The Effectiveness of Fenofibrate in Comparison to Bezafibrate for Patients with Asymptomatic Primary Biliary Cirrhosis

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### Abstract

**Background/Aims :** Ursodeoxycholic acid (UDCA) is currently the only available pharmacological treatment for asymptomatic primary biliary cirrhosis (aPBC). Fibrates may be useful for treating aPBC patients who exhibit incomplete responses to UDCA. The mechanism of action of such fibrates involves the regulation of the expression of various kinds of lipids and proteins through the activation of peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ), which increases the phospholipid output into the bile and reduces the cytotoxicity of hydrophobic bile acids. Among these fibrates, the binding activity of fenofibrate to PPAR- $\alpha$  is stronger than that of bezafibrate. Because the majority of PBC patients exhibit a slow progression of their disease, and since the administration of UDCA plus fibrate may further delay the liver deterioration, cardiovascular risk factors, such as dyslipidemia may thus have a bigger impact on the long-term survival of PBC patients. The aim of this study was to evaluate the effects of fenofibrate in patients with aPBC who are refractory to UDCA and to simultaneously compare the effectiveness of fenofibrate with that of bezafibrate.

**Methods :** This study included 14 patients with aPBC treated with fenofibrate (80 mg/day) plus UDCA (fenofibrate group) for 48 weeks and seven patients with aPBC treated with bezafibrate (400 mg/day) plus UDCA (bezafibrate group) for 48 weeks. The data for the aPBC patients in both groups were analyzed to compare the effects of fenofibrate and bezafibrate.

**Results :** In the patients in the fenofibrate group, the serum alkaline phosphatase (ALP),  $\gamma$ -glutamyl transpeptidase ( $\gamma$  GTP) and serum IgM levels decreased from  $522.5 \pm 181.4$  to  $236.8 \pm 47.8$  IU/l,  $197.1 \pm 98.4$  to  $47.2 \pm 37.5$  IU/l and  $337.6 \pm 160.6$  to  $174.5 \pm 101.1$  mg/dl ( $p < 0.0001$ ), respectively. In the patients in the bezafibrate group, the serum levels of ALP,  $\gamma$  GTP and IgM decreased from  $595.9 \pm 247.8$  to  $238.0 \pm 80.4$  IU/l,  $188.3 \pm 85.6$  to  $46.3 \pm 31.9$  IU/l and  $304.7 \pm 165.2$  to  $155.1 \pm 45.4$  mg/dl ( $p < 0.0001$ ), respectively. The serum levels of triglycerides (TG) and low-density lipoprotein cholesterol (LDL) significantly decreased in both groups and the LDL levels significantly decreased in the patients in the fenofibrate group compared to those in the bezafibrate group ( $p = 0.0357$ ). In addition, the serum uric acid levels of the patients in the fenofibrate group decreased significantly (from  $4.7 \pm 1.4$  to  $3.6 \pm 0.9$  mg/dl,  $p < 0.0001$ ), while those in the patients in the bezafibrate group did not change from  $4.1 \pm 0.6$  to  $4.1 \pm 0.4$  mg/dl. **Conclusion :** Combination therapies with fenofibrate plus UDCA and bezafibrate plus UDCA induce significant biochemical improvements in patients with aPBC. However, the ability of fenofibrate to reduce the LDL and uric acid levels in aPBC patients is superior to that of bezafibrate. As a result, the use of fenofibrate might translate into a decreased risk of developing cardiovascular events and renal failure in patients with aPBC.

**Limitation :** Short follow-up, small number of samples, retrospective and single center study and no evidence of the effect of fibrates on the liver histology.

**Key words :** Fenofibrate · Bezafibrate · Primary Biliary Cirrhosis · Fibrate · Efficacy

## Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by a chronic non-suppurative destructive cholangitis that eventually leads to cholestasis, fibrosis, cirrhosis and subsequent hepatic failure and death if left untreated<sup>1)</sup>. Although there is no established etiology for this disease, PBC has been attributed to autoimmunity, primarily due to its association with autoantibodies, especially anti-mitochondrial antibodies (AMA) and elevated levels of immunoglobulin M (IgM).

The only available therapeutic agent for PBC is ursodeoxycholic acid (UDCA), which has been demonstrated to delay the development of fibrosis as well as to improve the patient survival without the need for liver transplantation<sup>2)~4)</sup>. However, not all patients achieve a complete biochemical response to UDCA, and 10~20% will progress to cirrhosis or require liver transplantation, indicating a clear need for additional therapies<sup>5)6)</sup>. Of the immunosuppressive drugs tested to date for the treatment of PBC, azathioprine, cyclosporine and methotrexate were not found to improve the patient survival<sup>7)~9)</sup>.

Fenofibrate is a fibric acid derivative used in the treatment of hypercholesterolemia and hyperglyceridemia that has been incidentally noted to cause decreases in serum liver biochemical markers. However, there are scarce data on the effects of fenofibrate in patients with PBC<sup>10)~15)</sup>. The proposed mechanism of action of fibric acid derivatives involves regulation of the expressions of various kinds of lipids and proteins, as well as cell proliferation, through the activation of peroxisome proliferator-activated receptor (PPAR)- $\alpha$ <sup>16)~18)</sup>. Therefore, fibric acid has been referred to as a "PPAR- $\alpha$  agonist". However, bezafibrate activates all three isoforms of human PPAR; PPAR- $\alpha$ , PPAR- $\delta$ , and PPAR- $\gamma$ , at similar concentrations (i.e., 50, 20 and 60 $\mu$ M, respectively)<sup>15)19)</sup>. Therefore, the term "pan-PPAR" agonist is a more accurate descrip-

tion for bezafibrate. On the other hand, fenofibrate has been confirmed to exhibit stronger binding activity for PPAR- $\alpha$  than bezafibrate<sup>19)</sup>. Hence, fenofibrate is referred to as "PPAR- $\alpha$ -selective" agonist<sup>15)</sup>. In addition, fibric acid derivatives also upregulate the expression of multidrug resistant gene 3 (MDR3) and increase the biliary phospholipid secretion into the bile<sup>20)</sup>, both of which decrease the cytotoxic effects of hydrophobic bile acids on biliary epithelial cells.

Several studies from Japan have suggested that bezafibrate is effective in the treatment of PBC<sup>21)~24)</sup>. However, no clinical studies comparing the effectiveness of fenofibrate with that of bezafibrate in treating asymptomatic PBC (aPBC) have been published.

Generally, dyslipidemia and hyperuricemia cause cardiovascular disease and renal disease<sup>25)26)</sup>. Dyslipidemia is a common feature in the majority of PBC patients, 75~90% of all cases exhibiting dyslipidemia<sup>27)28)</sup>. Due to the fact that the majority of PBC patients exhibit slow progression of their disease, and that treatment with UDCA plus fibrate may further delay the liver deterioration, the cardiovascular risk factors such as dyslipidemia and hyperuricemia may have a bigger impact on the long-term survival of PBC patients that has been observed so far<sup>29)30)</sup>. In addition, the PPAR- $\alpha$  activation brought about by fibrates has been shown to decrease the expression of cyclooxygenase 1 and the release of thromboxane A<sub>2</sub>, leading to the prevention of atherosclerotic changes<sup>31)</sup>. Based on all of these favorable and potentially favorable effects of fibrates, we therefore, evaluated the effects of fenofibrate in patients with aPBC who were refractory to UDCA, and simultaneously compared the effectiveness of fenofibrate with bezafibrate, including the biochemical characteristics, such as the levels of lipids and uric acid in aPBC patients.

## Patients and Methods

### Patients

From 2008 to 2011, we consecutively recruited 14 patients with aPBC treated with fenofibrate plus UDCA for more than 48 weeks (fenofibrate group); and this fenofibrate group was compared with a retrospective cohort of seven patients with aPBC treated with bezafibrate plus UDCA for more than 48 weeks (bezafibrate group).

The patients included in this study were diagnosed based on the eligibility criteria, which included: (i) an established diagnosis of PBC according to published criteria<sup>32</sup>, which were: cholestatic liver biochemical findings of PBC (elevated alkaline phosphatase and/or  $\gamma$ -glutamyl transpeptidase), compatible serological tests (antimitochondrial antibody) at a titer of  $> 1:40$  and/or compatible or diagnostic liver histology, (ii) treatment with 13–15 mg/kg/day of UDCA for at least six months and (iii) persistent elevation of the serum ALP level greater than two-fold the upper limit of normal in two separate measurements. Twenty-one patients (20 females and one male) with aPBC who showed incomplete responses to UDCA for at least six months were evaluated. Fourteen patients (13 females and one male,  $52.7 \pm 10.6$  years old) were given 80 mg/day of fenofibrate and seven patients (seven females,  $56.6 \pm 18.5$  years old) were given 400 mg/day of bezafibrate in addition to their usual dosage of UDCA. The dose of 80 mg/day of fenofibrate was chosen based on our previous paper, in which the amount of fenofibrate showed an effectiveness for decreasing the ALP and IgM levels at that dose<sup>11</sup>. On the other hand, the dose of 400 mg/day of bezafibrate was chosen based on the previous reports showing the effectiveness of the agent for decreasing the levels of liver enzymes<sup>24,33</sup>. Whether fenofibrate or bezafibrate was administered depended on the free choice of three physicians (Dohmen K, Tanaka H and Haruno M). All patients in both groups were negative for serum hepatitis B surface antigens and hepatitis C

virus antibodies. Patients with known CVD, diabetes mellitus, cancer, renal disease or thyroid disease were excluded. No patients had received a treatment with D-penicillamine, corticosteroids, colchicine or immunosuppressive agents within four weeks. Liver biopsies were not required by the inclusion criteria.

### Methods

The patients underwent history and physical examinations at the time of administration of fenofibrate or bezafibrate. Laboratory tests for liver biochemical findings, the lipids, uric acid and serum creatinine levels and complete blood cell counts were performed at the initiation of fenofibrate or bezafibrate therapy and at weeks 6, 12, 24, 36 and 48. The serum IgM levels were evaluated at entry and at weeks 24 and 48. The various characteristics of the 21 overall patients treated with fenofibrate or bezafibrate were analyzed and compared with those of the 14 patients treated with fenofibrate and the seven patients treated with bezafibrate. The study of the addition of fibrate to UDCA was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Chihaya Hospital Ethics Committee.

### Statistical analysis

All values are expressed as the means  $\pm$  standard deviation (SD). The analyses were conducted using the Wilcoxon rank test, Student's t-test, the  $\chi^2$ -test, the Mann-Whitney U-test and Fisher's exact test as appropriate. A value of  $p < 0.05$  was considered to be statistically significant.

## Results

### Baseline characteristics

Fourteen patients treated with fenofibrate plus UDCA (fenofibrate group) and seven patients treated with bezafibrate plus UDCA (bezafibrate group) were analyzed. Table 1 displays the baseline characteristics of both groups. The age,

the levels of total bilirubin, alanine aminotransferase (ALT), serum alkaline phosphatase (ALP),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GTP), albumin, total cholesterol (T. Chol), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TGs), uric acid, IgM and serum creatinine (Creat) did not differ substantially between the groups.

***The changes in the biochemical characteristics after fenofibrate treatment or bezafibrate treatment in addition to UDCA***

The biochemical characteristics obtained at the initiation of fibrate treatment and after 48 weeks of treatment are summarized in Table 2. In the fenofibrate group, the serum ALP,  $\gamma$  GTP and IgM levels at baseline decreased at 48 weeks from  $522.5 \pm 181.4$  to  $236.8 \pm 74.8$  IU/l,  $197.1 \pm 98.4$  to  $47.2 \pm 37.5$  IU/l and  $337.6 \pm 160.6$  to  $174.5 \pm 101.1$  mg/l ( $p < 0.0001$ ), respectively. The serum levels of ALP ( $595.9 \pm 247.8$  to  $238.0 \pm 80.4$  IU/l),  $\gamma$  GTP ( $188.3 \pm 85.6$  to  $46.3 \pm 31.9$  IU/l) and IgM ( $304.7 \pm 165.2$  to  $155.1 \pm 45.4$  mg/l) decreased in

**Table 1** Baseline characteristics in the fenofibrate group and bezafibrate groups

Characteristics	Fenofibrate	Bezafibrate	P value
N (M/F)	14 (1/13)	7 (0/7)	0.4687
Sheuer's stage (1/ND)	9/5	3/4	0.3496
Age (years)	$52.7 \pm 10.6$	$56.6 \pm 18.5$	0.8823
TB (mg/dl)	$0.6 \pm 0.2$	$0.9 \pm 0.3$	0.1239
ALT (IU/l)	$66.3 \pm 58.5$	$48.3 \pm 31.1$	0.5819
ALP (IU/l)	$522.5 \pm 181.4$	$595.9 \pm 247.8$	0.5332
$\gamma$ -GTP (IU/l)	$197.1 \pm 98.4$	$188.3 \pm 85.6$	0.8539
ALB (g/dl)	$4.0 \pm 0.3$	$4.1 \pm 0.3$	0.4613
TC (mg/dl)	$193.9 \pm 42.5$	$211.3 \pm 44.1$	0.3432
HDL (mg/dl)	$62.8 \pm 13.3$	$72.6 \pm 17.6$	0.2326
LDL (mg/dl)	$112.3 \pm 36.2$	$153.7 \pm 46.0$	0.1243
TG (mg/dl)	$135.4 \pm 96.2$	$117.9 \pm 18.4$	0.8251
UA (mg/dl)	$4.7 \pm 1.4$	$4.1 \pm 0.6$	0.3611
IgM (mg/dl)	$337.6 \pm 160.6$	$304.7 \pm 165.2$	0.7406
CK (IU/l)	$70.1 \pm 59.5$	$68.9 \pm 20.3$	0.2457

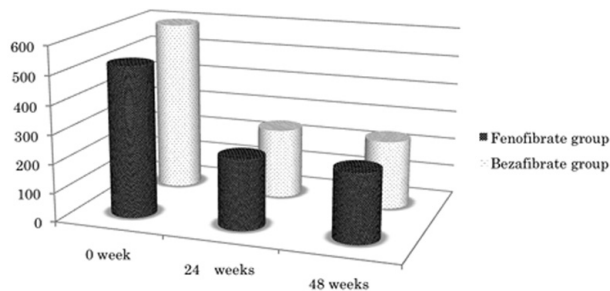
**Table 2** The changes in the characteristics in the fenofibrate group and bezafibrate groups

	Fenofibrate			Bezafibrate			Fenofibrate vs Bezafibrate
	Baseline	48 weeks	p	before	48 weeks	p	p
Total Bil (mg/dl)	$0.6 \pm 0.2$	$0.5 \pm 0.1$	0.0461	$0.9 \pm 0.3$	$0.6 \pm 0.2$	0.1052	0.1114
ALT (IU/l)	$66.3 \pm 58.5$	$24.5 \pm 11.9$	0.0012	$48.3 \pm 31.1$	$14.1 \pm 3.1$	0.0007	0.0165
ALP (IU/l)	$522.5 \pm 181.4$	$236.8 \pm 74.8$	$< 0.0001$	$595.9 \pm 247.8$	$238.0 \pm 80.4$	$< 0.0001$	0.8757
$\gamma$ GTP (IU/l)	$197.1 \pm 98.4$	$47.2 \pm 37.5$	$< 0.0001$	$188.3 \pm 85.6$	$46.3 \pm 31.9$	$< 0.0001$	0.9376
Alb (g/dl)	$4.0 \pm 0.3$	$4.1 \pm 0.3$	0.6534	$4.1 \pm 0.3$	$4.2 \pm 0.3$	0.2696	0.2777
Total Chol (mg/dl)	$193.9 \pm 42.5$	$177.7 \pm 22.0$	0.4018	$211.3 \pm 44.1$	$187.6 \pm 44.5$	0.1032	0.4841
HDL (mg/dl)	$62.8 \pm 13.3$	$73.6 \pm 14.5$	0.011	$72.6 \pm 17.6$	$81.1 \pm 15.7$	0.0446	0.3086
LDL (mg/dl)	$112.3 \pm 36.2$	$87.9 \pm 22.8$	$< 0.0001$	$153.7 \pm 46.0$	$127.4 \pm 39.6$	0.0003	0.0357
TG (mg/dl)	$135.4 \pm 96.2$	$89.0 \pm 68.6$	0.0036	$117.9 \pm 18.4$	$97.7 \pm 23.1$	0.0335	0.0619
Uric acid (mg/dl)	$4.7 \pm 1.4$	$3.6 \pm 0.9$	$< 0.0001$	$4.1 \pm 0.6$	$4.1 \pm 0.4$	0.9776	0.1411
IgM (mg/dl)	$337.6 \pm 160.6$	$174.5 \pm 101.1$	$< 0.0001$	$304.7 \pm 165.2$	$155.1 \pm 45.4$	0.0007	0.4844
CK (IU/l)	$70.1 \pm 59.5$	$71.4 \pm 35.4$	0.9999	$68.9 \pm 20.3$	$69.4 \pm 23.1$	1.0000	0.7677

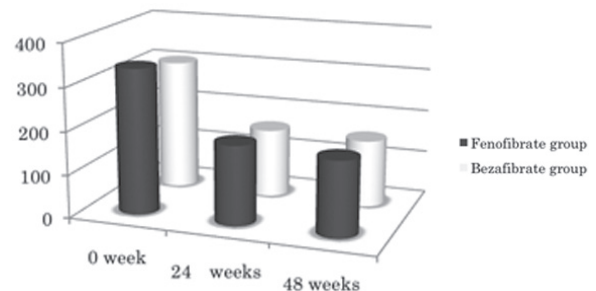
the bezafibrate group as well ( $p < 0.0001$ ) (Figs. 1, 2). No significant differences in the changes in the levels of ALP,  $\gamma$ GTP or IgM were observed between the two groups. The serum levels of ALT decreased significantly from  $66.3 \pm 58.5$  to  $24.5 \pm 11.9$  IU/l in the fenofibrate group ( $p = 0.0012$ ) and from  $48.3 \pm 31.1$  to  $14.1 \pm 3.1$  IU/l in the bezafibrate group ( $p = 0.0007$ ). However, the reduction rate of ALT in the bezafibrate group was superior to that observed in the fenofibrate group ( $p = 0.0165$ ).

The levels of serum LDL and TGs in the fenofibrate group decreased significantly from  $112.3 \pm 36.2$  to  $87.9 \pm 22.8$  mg/l ( $p < 0.0001$ ) and from  $135.4 \pm 96.2$  to  $89.0 \pm 68.6$  mg/dl ( $P = 0.0036$ ), respectively. In the bezafibrate group, the levels of serum LDL and TGs decreased significantly from  $153.7 \pm 46.0$  to  $127.4 \pm 39.6$  mg/l ( $p < 0.0003$ ) and from  $117.9 \pm 18.4$  to  $97.7 \pm 23.1$  mg/dl

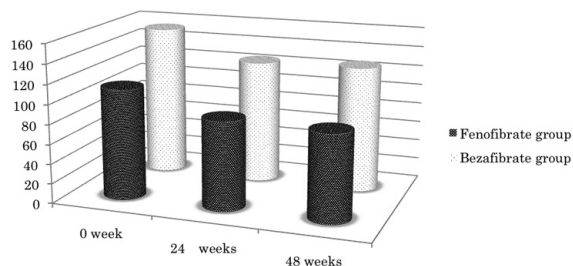
( $p = 0.0335$ ), respectively. The LDL reduction rate in the two groups was significantly different (Fig. 3). The serum levels of HDL in both the fenofibrate and bezafibrate groups increased significantly from  $62.8 \pm 13.3$  to  $73.6 \pm 14.5$  mg/l ( $p = 0.0110$ ) and from  $72.6 \pm 17.6$  to  $81.1 \pm 15.7$  mg/dl ( $p = 0.0446$ ), respectively. However, the difference in the increase between the two groups was not statistically significant. The serum uric acid levels in the fenofibrate group decreased significantly from  $4.7 \pm 1.4$  to  $3.6 \pm 0.9$  mg/dl ( $p < 0.0001$ ), although those in the bezafibrate group did not change from  $4.1 \pm 0.6$  to  $4.1 \pm 0.4$  mg/dl (Fig. 4). The reduction rate between the levels measured at baseline and those measured after 48 weeks of treatment in both groups were not significantly different. No adverse events such as transient elevations of the transaminase levels<sup>34,35</sup>, renal dysfunction, the development of



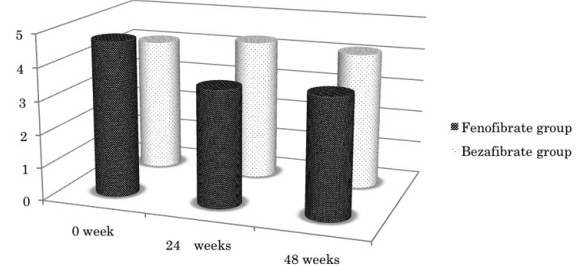
**Fig. 1** The changes in the levels of ALP following fenofibrate or bezafibrate treatment in addition to UDCA (fenofibrate group ;  $p < 0.0001$ , bezafibrate group ;  $p < 0.0001$ , fenofibrate group vs bezafibrate group ;  $p = 0.8757$ )



**Fig. 2** The changes in the levels of IgM following fenofibrate or bezafibrate treatment in addition to UDCA (fenofibrate group ;  $p < 0.0001$ , bezafibrate group ;  $p = 0.0007$ , fenofibrate group vs bezafibrate group ;  $p = 0.4844$ )



**Fig. 3** The changes in the levels of LDL following fenofibrate or bezafibrate treatment in addition to UDCA (fenofibrate group ;  $p < 0.0001$ , bezafibrate group ;  $p = 0.0003$ , fenofibrate group vs bezafibrate group ;  $p = 0.0357$ )



**Fig. 4** The changes in the levels of uric acid following fenofibrate or bezafibrate treatment in addition to UDCA (fenofibrate group ;  $p < 0.0001$ , bezafibrate group ;  $p = 0.9776$ , fenofibrate group vs bezafibrate group ;  $p = 0.1411$ )



rhabdomyolysis or the development of esophagitis, which are known adverse effects, were observed in either group.

### Discussion

Our present study demonstrates that combination therapy with UDCA and fenofibrate for 48 weeks in patients with aPBC who have previously demonstrated incomplete responses to UDCA monotherapy is effective for eliciting biochemical responses. In addition, combination therapy with UDCA and bezafibrate resulted in significant reductions in the parameters measured in seven patients with aPBC.

Since aPBC patients with an incomplete biochemical response to UDCA in the first three months generally have a poor outcome, a new therapeutic approach is needed for these patients<sup>36</sup>. According to several studies from Japan, bezafibrate successfully lowers the levels of biliary liver enzymes for patients with PBC<sup>21–24</sup>. In the earliest study, Nakai et al. randomized 23 patients to receive either UDCA at a dose of 600 mg/day or UDCA at a dose of 600 mg/day plus bezafibrate at a dose of 400 mg/day for one year<sup>21</sup>. Combination therapy with UDCA and bezafibrate resulted in greater reductions in the levels of serum liver biochemical markers and IgM without inducing significant side effects. Similar results were obtained in a number of subsequent studies conducted in Japan<sup>22–24</sup>. Hazzan et al. demonstrated that the addition of bezafibrate to UDCA significantly and safely improved the biochemical profiles of Caucasian patients with PBC<sup>33</sup>.

In contrast, there have been only a few studies that have investigated the effects of fenofibrate in PBC patients<sup>10–15</sup>. In one study, treatment with fenofibrate in addition to UDCA for six months resulted in reductions in the levels of liver biochemical parameters such as ALT,  $\gamma$  GTP and IgM in seven patients with PBC<sup>10</sup>. In another study, the serum levels of ALP and IgM were significantly reduced following fenofibrate treat-

ment, and the titers of AMA decreased in four of nine patients with aPBC<sup>11</sup>. Walker et al. reported the first European experience with a fibric acid derivative in PBC patients<sup>37</sup>. The investigators reviewed the effects of 134–200 mg/day of fenofibrate in 16 patients who had previously failed to respond to 13–15 mg/day of UDCA. These patients received combination therapy for a mean 22.4 months. Both the serum ALP and IgM levels dropped significantly, with 89% of the patients exhibiting normalized serum ALP levels. Another pilot study of six patients with PBC treated with fenofibrate plus UDCA showed significant reductions in the levels of ALP,  $\gamma$  GTP and ALT compared to the levels observed in four patients with PBC treated with UDCA alone<sup>13</sup>. Similarly, Levy et al. reported significant decreases in the levels of ALP and IgM following combination therapy with fenofibrate and UDCA in 20 patients with PBC who had not responded to UDCA alone<sup>12</sup>. Furthermore, Han et al. investigated the effectiveness of combination therapy with fenofibrate and UDCA in 22 Chinese patients with PBC who had a partial response to UDCA, and confirmed that the levels of ALP,  $\gamma$  GTP, TG, AST and ALT were decreased and no obvious adverse effects were observed during the combination therapy<sup>13</sup>.

The proposed mechanism of action of fibric acid derivatives in PBC involves the regulation of the expressions of various kinds of lipids and proteins, as well as cell proliferation, via activation of PPAR- $\alpha$ <sup>16,18</sup>. Through PPAR- $\alpha$  activation, fibrates can inhibit NF- $\kappa$  B activation, leading to decreased expression levels of IL-1 and IL-6, thereby potentially decreasing the inflammatory and immune responses<sup>17,18</sup>. In addition to regulating proteins and lipids, the benefits of fibrates in PBC may result from cross-talk between PPAR- $\alpha$  and the bile acid-activated nuclear receptor farnesoid-X-receptor (FXR)<sup>38</sup>. Pineda-Torra et al. demonstrated that bile acid-activated FXR enhances PPAR- $\alpha$  transcription in human hepatic stellate cells<sup>38</sup>. Furthermore, fibrates may

facilitate the expression of multidrug resistance gene 3 (MDR), one of the transport elements of the ATP-dependent bile secretion system found in biliary membranes<sup>18)20)39)40)</sup>. An increased expression of MDR-3-encoded proteins would lead to increased secretion of biliary phospholipids and improved inactivation of hydrophobic bile acids via micellization, thereby protecting hepatocytes and the biliary epithelium. In our study, combination therapy with a fibrate and UDCA for aPBC confirmed the findings of previous studies that there were significant reduction in the serum levels of ALP,  $\gamma$  GTP and IgM.

The activity of fenofibrate on PPAR- $\alpha$  is stronger and more specific than that of bezafibrate<sup>15)19)</sup>. However, it has not been clarified whether fenofibrate exerts more favorable effects in patients with aPBC compared with bezafibrate. Therefore, we compared the differences in the reductions in the levels of ALP,  $\gamma$  GTP and IgM in 14 patients with aPBC who received therapy with fenofibrate plus UDCA and seven patients with aPBC who received bezafibrate plus UDCA. The results revealed that therapy with fenofibrate and UDCA is equally as effective as therapy with bezafibrate and UDCA for reducing the serum levels of ALP,  $\gamma$  GTP and IgM. Although we observed that the reduction rate of ALT in the fenofibrate group was inferior to that observed in the bezafibrate group ( $p = 0.0165$ ), the difference in the serum level of ALT at the base line ( $66.3 \pm 58.5$  in the fenofibrate group vs  $48.3 \pm 31.1$  in the bezafibrate group) might have resulted in this difference, while the values of ALT in both groups decreased to within the normal range by 48 weeks after treatment. A large study would be needed to draw definitive conclusion about whether there are differences between the agents in this regard. In our study, there were no apparent tendencies for fenofibrate or bezafibrate to cause elevations in the levels of total bilirubin, transaminase or creatinine. In addition, no patients developed adverse effects such as rhabdomyolysis or miosis, showing no elevation in the level of serum

creatinine phosphokinase (CK).

Confirming the results previously demonstrated by Feusnner<sup>41)</sup> in the patients with hyperlipoproteinemia in our study, the serum levels of LDL were reduced more significantly in the fenofibrate group compared with that observed in the bezafibrate group ( $p = 0.0357$ ), while the TG reductions showed no significant differences in the two groups. It has now well accepted that hypercholesterolemia should be treated in order to prevent cerebrovascular and cardiovascular diseases. The serum lipid levels are often markedly elevated in patients with PBC, however, it is not clear whether the hyperlipidemia in patients with PBC is associated with accelerated cardiovascular disease<sup>42)</sup>. One Dutch study retrospectively analyzed the causes of death in 596 PBC patients over a 14-year period from 1979 to 1992<sup>29)</sup>. Hepatic failure accounted for death in 417 cases (70%), whereas circulatory system diseases were responsible in 61 cases (12%)<sup>29)</sup>. Among 770 PBC patients registered between 1987 and 1994 analyzed by Prince et al.<sup>30)</sup>, the proportion of deaths related to liver disease was lower in initially asymptomatic than in symptomatic patients (31% of deaths vs 57% of deaths, respectively,  $p = 0.004$ ). One hundred and twelve (45%) of 248 initially asymptomatic PBC patients who died during follow-up died of causes unrelated to their liver disease. Among these patients, death occurred due to ischemic heart disease in 37 cases (14.9% of deaths), cerebrovascular disease in 17 cases (6.9%), peripheral vascular disease in three cases (1.2%) and other cardiac disorders in six cases (2.4%)<sup>30)</sup>.

Therefore, the use of lipid-lowering treatment is reasonable in aPBC patients with good prognoses. Although statins, the mainstay of lipid lowering therapy, have been found to be safe and effective for improving the lipid profiles in PBC patients<sup>43)~45)</sup>, these drugs do not ameliorate cholestasis or the progression of the disease<sup>44)</sup>. On the other hand, a few reports have shown that fenofibrate exhibits more favorable effects on the



lipid profiles than bezafibrate<sup>41)46)</sup>. Furthermore, fenofibrate is associated with beneficial effects on the vascular events in patients with diabetes<sup>47)</sup>, as well as improvements in non-alcoholic fatty liver disease<sup>48)</sup> further supporting its use in PBC patients.

A meta-analysis recently demonstrated that, in participants with no history of vascular disease (low-risk group), reducing the levels of LDL cholesterol reduced the risk of vascular mortality compared to that observed in participants with a definite history of vascular disease (high-risk group)<sup>49)</sup>. Most patients with aPBC are categorized into a low-risk group for vascular disease. Therefore, lowering the LDL cholesterol with fenofibrate therapy in low-risk groups patients, such as the 21 patients with aPBC evaluated in this study, might lead to a prolongation of their survival.

Additionally, in this study, significant uric acid reductions were noted in the fenofibrate group compared with that observed in the bezafibrate group. It is known that fenofibrate decreases the serum uric acid levels by increasing its urinary excretion through the inhibition of urate transporter 1<sup>50)</sup>. Using multivariate longitudinal approaches, hyperuricemia has been found to be positively associated with metabolic syndrome incidence rate ratios (IRR = 1.73)<sup>25)</sup>. The serum uric acid levels are also independent markers of increased cerebrovascular disease<sup>51)</sup>, and chronic kidney disease<sup>26)</sup>. As aPBC patients are now expected to live normal length lives due to the development of agents such as UDCA and fibrates, the complications associated with aPBC should be avoided. Therefore, among agents such as statins and fibrates, fenofibrate should be considered first for the treatment of aPBC patients, because the treatment of hypercholesterolemia and hyperuricemia in patients with PBC is more beneficial than has previously been indicated<sup>52)</sup>.

In conclusion, our study provides evidence that the administration of fenofibrate in addition to

UDCA is safe for aPBC patients, and that it effectively reduces the levels of LDL, uric acid and hepatobiliary enzymes. These effects might help to prevent cardiovascular events in aPBC patients during their expected long-term survival.

The main limitations of this study are the small sample size, the short period of observation and the lack of histological assessment. Further clinical studies will be needed to confirm the safety and efficacy of long-term treatment with fenofibrate in addition to UDCA for treating the dyslipidemia and cardiovascular risk factors in patients with PBC.

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(和文抄録)

## 無症候性原発性胆汁性肝硬変における fenofibrate と bezafibrate の有効性の差異

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【背景と目的】 ウルソ酸 (UDCA) に不応性の無症候性原発性胆汁性肝硬変 (aPBC) に対し, ウルソ酸とフィブラート剤の併用療法による有効性はよく知られている. フィブラート剤は核内受容体のひとつである  $\alpha$  型ペルオキシゾーム増殖剤活性化受容体 (PPAR  $\alpha$ ) のリガンドであり, PPAR  $\alpha$  を活性化させることで胆汁酸代謝や炎症の調節を行なっている. フィブラート剤の中で fenofibrate (リピディル<sup>®</sup>) は bezafibrate (ベザトール<sup>®</sup>) よりも PPAR  $\alpha$  に対する特異性が高く, かつ活性が強い. そのため fenofibrate は PPAR  $\alpha$  選択的アゴニスト (PPAR  $\alpha$ -selective agonist) と, PPAR  $\alpha$ , PPAR  $\delta$ , PPAR  $\gamma$  に対して選択性のない bezafibrate は汎 PPAR アゴニスト (pan-PPAR agonist) と, それぞれ呼称される. aPBC に対する fenofibrate と bezafibrate との効果を生化学的諸検査にて比較した.

【方法】 14 例の aPBC 患者に対し, fenofibrate (80 mg/日) + UDCA (600 mg/日) (fenofibrate 群) を, 7 例の aPBC 患者に対し, bezafibrate (400 mg/日) + UDCA (600 mg/日) (bezafibrate 群) をそれぞれ投与し, 48 週後に種々の因子を比較した.

【結果】 治療開始時の両群間の背景因子に有意差はみられなかった. 治療前と治療 48 週後の比較において, fenofibrate 群では ALP,  $\gamma$  GTP ならびに IgM は  $522.5 \pm 181.4$  から  $236.8 \pm 74.8$  IU/l,  $197.1 \pm 98.4$  から  $47.2 \pm 37.5$  IU/l,  $337.6 \pm 160.6$  から  $174.5 \pm 101.1$  mg/dl にそれぞれ低下した ( $p < 0.0001$ ). bezafibrate 群においても同様に ALP,  $\gamma$  GTP, IgM は  $595.9 \pm 247.8$  から  $238.0 \pm 80.4$  IU/l,  $188.3 \pm 85.6$  から  $46.3 \pm 31.9$  IU/l,  $304.7 \pm 165.2$  から  $155.1 \pm 45.4$  mg/dl にそれぞれ低下した ( $p < 0.0001$ ). TG と LDL は両群において有意に低下したが, LDL の低下度を両群で比較すると fenofibrate 群の低下度が有意であった ( $p=0.0357$ ). 尿酸値は fenofibrate 群では有意に低下したが ( $4.7 \pm 1.4$  から  $3.6 \pm 0.9$  mg/dl,  $p < 0.0001$ ), bezafibrate 群では変化はみられなかった ( $4.1 \pm 0.6$  から  $4.1 \pm 0.4$  mg/dl).

【考察】 UDCA と fenofibrate あるいは bezafibrate の併用療法はいずれも aPBC 症例に対し, 生化学的諸検査の値を有意に改善させた. 薬剤に反応性のよい aPBC 患者は長期生存が得られることが知られており, UDCA とフィブラート剤の併用療法は aPBC 患者の予後を改善すると期待される. aPBC 患者の死因として肝不全死に次ぎ, 動脈硬化性疾患の頻度が高いとする報告から, LDL, 尿酸値を有意に低下させる fenofibrate は bezafibrate と比較し, 動脈硬化性疾患を予防し, 長期生存に有益である可能性がある.