의학석사 학위논문

Additional fibrate treatment in UDCA-refractory PBC patients

우르소데옥시콜산 불응성 원발성 담즙성 담관염 환자들에서 추가적인 파이브레이트 치료의 효과에 대한 연구

2023년 2월

서울대학교 대학원

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정 성 원

Additional fibrate treatment in UDCA-refractory PBC patients

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초 록

서론: 아직까지 우르소데옥시콜린산에 불응하는 원발성 담즙성 담관염에 대한 치료는 명확히 확립되지 않은 상황이다. 여러 후보 약제들 중 파이브레이트들의 경우 간수치를 포함한 생화학적 지표들의 호전을 보인다는 보고들은 일부 있었으나, 장기간 효과들에 대해서는 아직 명확히 확인된 바가 없는 상황이다. 이에 본 연구에서는 우르소데옥시콜린산 불응성 원발성 담즙성 담관염 환자들에게 있어 파이브레이트 치료와 임상적 지표들 간의 관계를 확인하고자 하였다.

방법: 두 개의 3차 병원에서 원발성 담즙성 담관염으로 진단받고 치료 받는 환자들 중 충분한 용량(13mg/kg의 우르소데옥시콜린산)을 1년 넘게 사용하였음에도 혈중 알카리성 인산화분해효소가 정상화 되지 않은 환자들을 대상으로 연구가 진행되었다. 일차 평가 변수로는 알카리성 인산화분해효소의 정상화 여부였으며, 이차 평가 변수로는 간경화 및 간부전 발생 여부였다. 조기발견기간 오류의 문제를 해결하기 위해서 Mantel-Byar 방법을 활요하였다.

결과: 총 100명의 우르소데옥시콜린산 불응성 원발성 담즙성 담관염 환자들이 연구에 포함되었다: 71명의 환자들은 우르소데옥시콜린산만 처방 받았으며(UDCA 군), 29명의 환자들은 파이브레이트를 동시 처방 받았다(fibrate/UDCA 군). 관찰 기간 중, fibrate/UDCA 군에서 알카리성 인산화분해효소 수치의 정상화의 가능성이 UDCA군에 비해서 유의하게 높았다(위험도 [HR]=5.00, 95% 신뢰구간 = 2.87-8.27, P<0.001). 간경변이 없는 58명의 환자(UDCA 군 43명, fibrate/UDCA 군 15명)들에서 19명(44.1%)의 환자들에서 간경변이 발생하였는데, 이는 모두 UDCA 군에서만 발

생하였다(HR=0.12, P=0.04). 간부전(2점 이상의 차일드-퓨 점수 증가, 또는 비대상성 간경변의 발생) 또한 17명(23.9%) 에서 발생하였는데, 모두 UDCA 군에서만 발생하였다(HR=0.12, P=0.04).
결론: 우르소데옥시콜린산 불응성 원발성 담즙성 담관염 환자들에게 있어 추가적인 파이브레이트 치료를 하는 경우, 알카리성 인산화분해효소의 정상화의 확률이 높아지는 것과 간부전 또는 간경화 발생 감소와 연관성이 있어보인다.

주요어 : 베자파이브레이트, 간경화, 페노파이브레이트, 원발성 쓸개관 담관염
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Introduction

Primary biliary cholangitis (PBC), previously designated as primary biliary cirrhosis, is a disease with an unclear aetiological factor.[1,2] Initially, PBC may display mild biochemical abnormalities such as slight elevations in the levels of alkaline phosphatase (ALP) and/or gamma-glutamyltransferase (GGT). As the disease progresses, non-specific symptoms such as pruritus and fatigue develop, ultimately leading to cirrhosis or death due to liver failure.[1-3] PBC patients have higher risk of hepatocellular carcinoma (HCC) compared to the general population, and ursodeoxycholic acid (UDCA) non-responders have a higher risk of HCC compared to UDCA responders.[4,5]

UDCA has been the only drug that modifies the course of PBC disease.[1,2,6] Although UDCA improves serum ALP and GGT levels and delays liver disease progression in most patients, some patients fail to achieve ALP and GGT normalization with UDCA monotherapy. UDCA non-responders have worse prognosis than UDCA responders.[5-7] However, there is no proven treatment for UDCA-refractory PBC. A randomized controlled trial showed that obeticholic acid, a farnesoid X receptor agonist, significantly reduced serum ALP in patients with suboptimal response to UDCA.[8] However, the side effects (such as pruritus) were more frequent than in the control group, the cost of obeticholic acid is high, and the effect on long term patient outcome is uncertain.

Fibrate is a peroxisome proliferator activator receptor (PPAR)-α agonist and is used primarily for the treatment of dyslipidaemia.

PPAR-α agonists also act on cytochrome P450 7A1 to reduce bile acid production and enhance the expression of MDR 3 (ABCB4), which exports phospholipids (important for micelle formation of bile acids) to the bile ducts.[9-11] PPAR suppresses the expression of pro-inflammatory transcription factors such as nuclear factor kappa B and activator protein 1, which may reduce bile duct damage and adjacent hepatic inflammation in PBC patients.[9,11] A randomized placebo controlled trial using bezafibrate in UDCA-refractory patients recently showed that bezafibrate significantly improved liver function compared to the placebo group.[12] However, the long term effect of additional fibrate treatment on clinical outcomes was not thoroughly evaluated in that clinical trial, since it was designed and powered for evaluating biochemical improvement.

Here, we evaluated the effect of additional fibrate treatment on biochemical responses and long term clinical outcomes in UDCA-refractory PBC patients.

Method

Patients

This retrospective cohort study included consecutive patients with PBC who underwent UDCA treatment for more than 1 year at two tertiary referral centres (Seoul National University Hospital, Seoul, Korea and Severance Hospital, Seoul, Korea) from January 2005 to August 2018. PBC was diagnosed when the patient met two out of three following criteria: (a) positive antimitochondrial antibody (AMA) at titres of at least 1:40, (b) unexplained ALP elevation exceeding 1.5-times the normal upper normal limit for more than six months and (c) patients with liver biopsy compatible with PBC.[13] Among patients who met the diagnostic criteria of PBC, only patients who were treated with sufficient UDCA doses (at least 13 mg/kg/d) for ≥ 1 year and failed to achieve ALP normalization (defined as UDCA-refractory PBC patients) were included in the study.[2] Exclusion criteria were previous or current malignancies including HCC; chronic liver disease other than PBC, such as chronic hepatitis B/C or alcoholic hepatitis; prior history of liver transplantation; any clinical evidence of acute liver failure; severe comorbidities (e.g., heart failure, end stage renal disease and chronic obstructive lung disease); insufficient UDCA dose to treat PBC; and history of the use of obeticholic acid.

Baseline characteristics such as demographic features and laboratory findings were obtained at the index date. Fatty liver was diagnosed if liver echogenicity exceeded that of renal cortex and spleen along with attenuation of the ultrasound wave, loss of

definition of the diaphragm and poor delineation of the intrahepatic architecture.[14] If ultrasound results were not available, precontrast computed tomography images were used. Fatty liver was diagnosed if the attenuation of the liver was at least 10 Hounsfield units less than that of the spleen or 40 Hounsfield units.[15,16] Autoimmune hepatitis and PBC (AIH-PBC) overlap syndrome were defined as patients who meet the simplified diagnostic criteria for both autoimmune hepatitis [17] and PBC.[13]

The study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital. The requirement for informed consent from patients was waived.

Treatment

Patients were assigned into two groups according to their fibrate treatment: the UDCA group and the fibrate/UDCA group. Both groups took at least 13 mg of UDCA per kg body weight per day.[1,2,18] The fibrate/UDCA group concomitantly received either 160 mg of fenofibrate or 400 mg of bezafibrate when patients failed to achieve ALP normalization within one year of UDCA monotherapy. The addition of the specific fibrate depended on physicians' preference. All physicians treating PBC were experienced hepatologists with >10 years of experience.

Outcomes and evaluation

The primary outcome was ALP normalization with/without GGT normalization. Secondary outcomes were overall survival, transplantation free survival and new development of liver related events (i.e., hepatic deterioration, cirrhosis development in non

cirrhotic patients and HCC development). The index dates were set as one year after initiation of UDCA treatment for the UDCA group and the date of additional fibrate implementation in the fibrate/UDCA group respectively. Hepatic deterioration was defined as Child Pugh score increase of ≥2 points compared to baseline or signs of decompensated cirrhosis such as hepatic encephalopathy, variceal bleeding or refractory ascites event.[19]

Cirrhosis was diagnosed using the following three criteria: (a) stage F4 fibrosis in liver biopsy; (b) detection of portal hypertension, defined as a hepatic venous pressure gradient of more than 6 mmHg, gastroesophageal varices detected in esophagogastroduodenoscopy or ascites detected in physical examination; and (c) at least two signs of cirrhosis, including 12 mm or larger portal vein diameter or nodular liver surface in two consecutive imaging tests or platelet count less than 100,000 per mm^3 in two consecutive studies.[20-22] HCC was diagnosed by pathology or typical imaging findings according to the American Association for the Study of Liver Diseases guidelines.[23,24]

GLOBE scores were used to evaluate 5-year, 10-year and 15-year estimated transplantation free survival probabilities and UK-PBC scores for estimation of risk of transplant or liver related death rate.[25,26] GLOBE and UK-PBC scores at index date and at 1 year were used for comparison.

Statistical analysis

Categorical baseline characteristics were evaluated with chi square test or Fisher's exact test. Continuous variables were evaluated with Student's t-test or Mann-Whitney test. The rates of ALP with/without GGT normalization, transplantation free survival,

cirrhosis development, hepatic deterioration and new HCC development were estimated with Kaplan Meier survival methods; for comparisons, log rank tests were performed. The hazard ratio (HR) and 95% confidence interval (CI) were estimated with Cox proportional regression analyses or Firth method for rare events.[27] To compare the change in GLOBE and UK-PBC scores within 1 year of treatment, repeated-measures ANOVA testing was performed. To compare the change within the treatment group, Wilcoxon-signed rank testing was performed.

The baseline characteristics were balanced between the two groups using inverse probability of treatment weighting (IPTW). A generalized boosted regression model was used for propensity score calculation. When the number of outcomes was less than ten events, only univariable analysis was performed, as multivariable analysis of data from less than ten events per variable can lead to incorrect results.[28]

The initiation date of fibrate varied among the patients, which can lead to immortal time bias in clinical outcomes.[29,30] To overcome this potential source of bias, the Mantel-Byar method was applied.[29-31] If there was more than three month time lag between the date of UDCA use for one year and the starting date of additional fibrate, the time between the date of UDCA use for one year and the start date of fibrate use was regarded as the UDCA group and then considered as the fibrate/UDCA group. Counting process style of input was applied, which allowed multiple records per patient.[31]

R language version 3.50 (r Foundation for Statistical Computing, Vienna, Austria) and SPSS version 21.0 (SPSS Inc, Chicago, IL) were used for analysis. Data were considered as statistically significant

when $P < 0.05$.

Results

Baseline characteristics

A total of 87 patients were included in the analyses. Thirteen patients started fibrate treatment after the cohort entry (UDCA use for more than 15 months). After adjustment with the Mantel-Byar method, a new cohort was created in which 71 patients were classified as the UDCA group (patients treated with UDCA only) and 29 patients were classified as the fibrate/UDCA group (patients treated with both UDCA and fibrate) (Figure 1).[31]

Within the fibrate/UDCA group, 26 patients were treated with fenofibrate (160 mg once a day) and three patients were treated with bezafibrate (200 mg twice a day). Median patient age was 56 years, and there were no significant differences between the two groups (P = 0.77). Most patients were female (86.0%), and most were AMA positive (92.0%). The median UDCA dose per body weight was significantly lower in the UDCA group, although all included patients received sufficient UDCA dose for PBC treatment (at least 13 mg/kg/d) (P = 0.001). Baseline aspartate aminotransferase (AST) level was higher, and albumin level was lower in the UDCA group than in the fibrate/UDCA group (P = 0.02 and P = 0.002 respectively). There were no statistically significant differences in baseline ALP levels, Child-Pugh score, the incidence of fatty liver or the incidence of AIH-PBC overlap syndrome between the two groups (P = 0.31, P = 0.15, P = 0.36 and P = 0.43, respectively; Table 1). According to conventional criteria,[7,32-35] there was no significant difference in the ratio of UDCA failure criteria between two

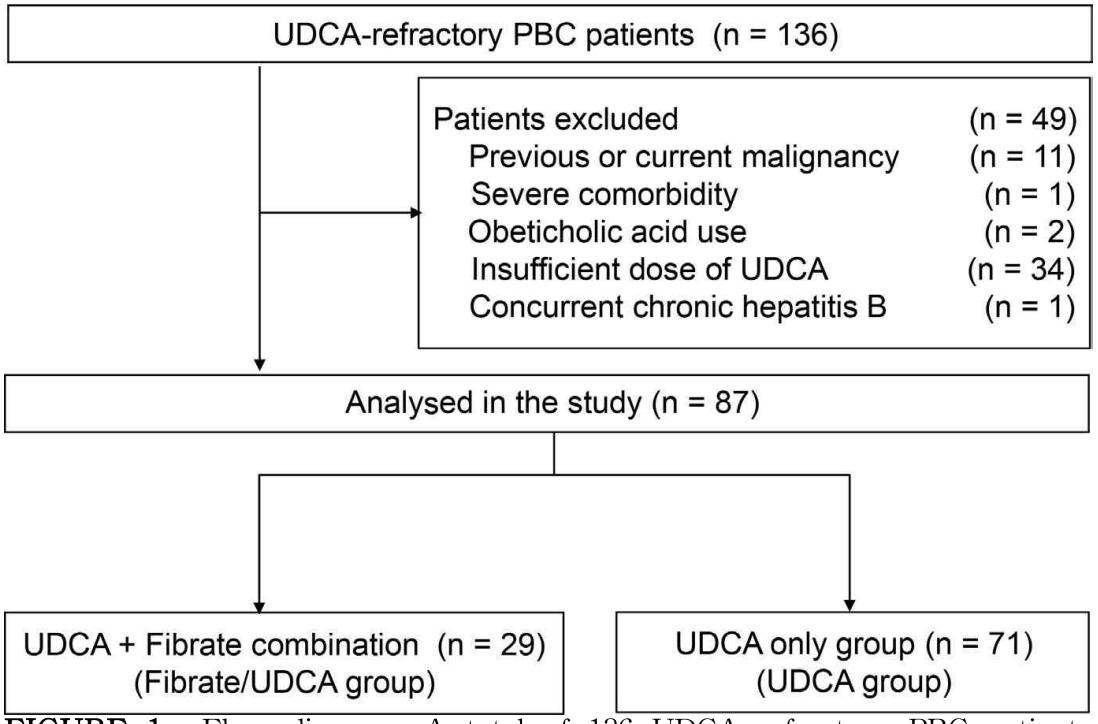


FIGURE 1. Flow diagram. A total of 136 UDCA-refractory PBC patients were identified and 49 patients were excluded. Thirteen patients in the fibrate/UDCA group started fibrate after 15 mo of UDCA treatment. A total of 100 patients were classified into two groups according to the fibrate treatment (fibrate/UDCA group vs UDCA group). PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

Characteristics	UDCA group (n = 71)	Fibrate/UDCA group (n = 29)	P value
Female, n (%)	63 (88.7)	23 (79.3)	0.22
Age, median (IQR), y	56.0 (50.0-63.0)	56.0 (53.0-62.0)	0.77
Body weight (IQR), kg	55.0 (50.0-61.2)	56.0 (50.0-63.0)	0.42
UDCA dose per body weight, median (IQR), mg/kg	16.9 (14.7-19.5)	20.1 (17.1-23.2)	0.002
AMA positivity, n (%)	66 (93.0)	26 (89.7)	0.69
AIH-PBC overlap syndrome, n (%)	20 (28.2)	11 (37.9)	0.35
Fatty liver, n (%)	27 (38.0)	8 (27.6)	0.36
Laboratory data, median (IQR)			
ALP, IU/L	167.0 (135.5-232.5)	151.0 (130.0-172.0)	0.31
GGT, IU/L	96.0 (67.0-247.0)	105.0 (66.0-181.0)	0.93
Total bilirubin, mg/dL	0.9 (0.7-1.2)	0.8 (0.6-0.9)	0.45
Albumin, g/dL	4.1 (3.8-4.3)	4.3 (4.1-4.4)	0.001
AST, IU/L	39.0 (31.0-63.0)	32 (26.0-44.0)	0.02
ALT, IU/L	37.0 (23.0-66.5)	32.0 (22.0-70.0)	0.92
Baseline Child-Pugh score, median (range)	5 (5-10)	5 (5-7)	0.15
Child-Pugh Class A, n (%)	64 (90.1)	28 (96.6)	0.43

Table 1. Demographic and baseline characteristics of the patients (Mantel-Byar method adjusted). Data represent n (%) or median (IQR). Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transferase; IQR, interquartile range; UDCA, ursodeoxycholic acid.

treatment groups (Table 2). Baseline characteristics of the unadjusted cohort are presented in Table 3.

Biochemical normalization

The median follow up duration was 47 months (interquartile range, 23.5-75.5 months). The rate of ALP normalization (Figure 2) was significantly higher in the fibrate/UDCA group (HR = 5.00, 95% CI = 2.87-8.73, P < 0.001; Table 4). At week 48, 86.2% (25 of 29) of the fibrate/UDCA group and 31.0% (22 of 71) of the UDCA group had normal ALP. In multivariable analysis, the fibrate/UDCA treatment group was an independent predictor of ALP normalization (adjusted HR [aHR] = 6.13, 95% CI = 3.07-12.25, P < 0.001; Table 4). Patients with elevated baseline ALP levels (1.5 × upper normal limit) and female sex were independent negative predictors of ALP normalization (Table 4).

When biochemical normalization was defined as normalization of both ALP and GGT, the fibrate/UDCA group still showed significantly higher biochemical response in both univariable (HR = 5.58, 95% CI = 2.73-11.40, P < 0.001; Figure 3) and multivariable (aHR = 12.63, 95% CI = 4.89-32.64, P < 0.001) analyses. Patients with high initial ALP level (1.5 × upper normal limit), female and old age were independent negative predictors of ALP and GGT normalization (Table 5).

After baseline characteristics were balanced utilizing IPTW, the baseline ALP, AST, albumin, Child-Pugh score and UDCA dose per body weight were well balanced between the two treatment groups (Table 6). The probability of both ALP normalization (HR = 3.44, 95% CI = 1.87-6.34, P < 0.001) and ALP + GGT normalization (HR = 2.85, 95% CI = 1.27-6.37, P = 0.01) was significantly higher in the

Characteristics	UDCA group (n=71)	Fibrate/UDCA group (n=29)	P value
UDCA-failure, n (%) According to each criteria*			
Barcelona criteria, (n=100)	48 (67.6)	15 (51.7)	0.17
Toronto criteria (n=72)	24 (41.4)	4 (28.6)	0.54
Paris II criteria (n=100)	37 (52.1)	10 (34.5)	0.13
Rotterdam criteria (n=100)	24 (33.8)	7 (24.1)	0.48
Ehime criteria (n=86)	30 (50.0)	13 (50.0)	1.00

Table 2. Baseline characteristics depending on each conventional UDCA-refractory criteria (Mantel-Byar method adjusted). Data represent n (%) or median (IQR).

*Most patients (89 patients in total, 64 patients in the UDCA group and 25 patients in the fibrate/UDCA group) did not meet at least one clinical criteria of UDCA responsiveness.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotrasferase; AMA, anti-mitochondrial antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IQR, interquartile range; UDCA, ursodeoxycholic acid.

Characteristics	UDCA group (n = 58)	Fibrate/UDCA group (n = 29)	P value
Female, n (%)	53 (91.4)	23 (79.3)	0.17
Age, median (IQR), y	57.0 (50.3-63.8)	56.0 (53.0-62.0)	0.95
UDCA dose per body weight, median (IQR), mg/kg	16.1 (14.7-19.5)	20.1 (17.1-23.2)	<0.001
AMA positivity, n (%)	54 (93.1)	26 (89.7)	0.68
AIH-PBC overlap syndrome, n (%)	16 (27.6)	11 (37.9)	0.34
Fatty liver, n (%)	22 (37.9)	8 (27.6)	0.47
UDCA-failure, n (%)			
According to each criteria*			
Barcelona criteria, (n=87)	42 (72.4)	15 (51.7)	0.09
Toronto criteria, (n=64)	21 (42.0)	4 (28.6)	0.54
Paris II criteria, (n=87)	31 (53.4)	10 (34.5)	0.11
Rotterdam criteria, (n=87)	21 (36.2)	7 (24.1)	0.33
Ehime criteria, (n=73)	23 (51.1)	13 (50.0)	1.00
Laboratory data, median (IQR)			
ALP, IU/L	172.0 (138.8-239.0)	151.0 (130.0-172.0)	0.18
GGT, IU/L	112.0 (66.5-255.8)	105.0 (66.0-181.0)	0.92
Total bilirubin, mg/dL	0.9 (0.7-1.3)	0.8 (0.6-0.9)	0.28
Albumin, g/dL	4.1 (3.8-4.3)	4.3 (4.1-4.4)	<0.001
AST, IU/L	40.5 (32.0-67.8)	32 (26.0-44.0)	0.01
ALT, IU/L	37.0 (22.0-67.8)	32.0 (22.0-70.0)	0.88
Baseline Child-Pugh score, median (range)	5 (5-10)	5 (5-7)	0.10
Child-Pugh Class A, n (%)	51 (87.9)	28 (96.6)	0.26

Table 3. Demographic and baseline characteristics of the patients (Mantel-Byar method unadjusted). Data represent n (%) or median (IQR).

* Most patients (77 patients in total, 52 patients in the UDCA group and 25 patients in the fibrate/UDCA group) did not met at least one clinical criteria of UDCA responsiveness.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyl-transferase; IQR, interquartile range; UDCA, ursodeoxycholic acid.

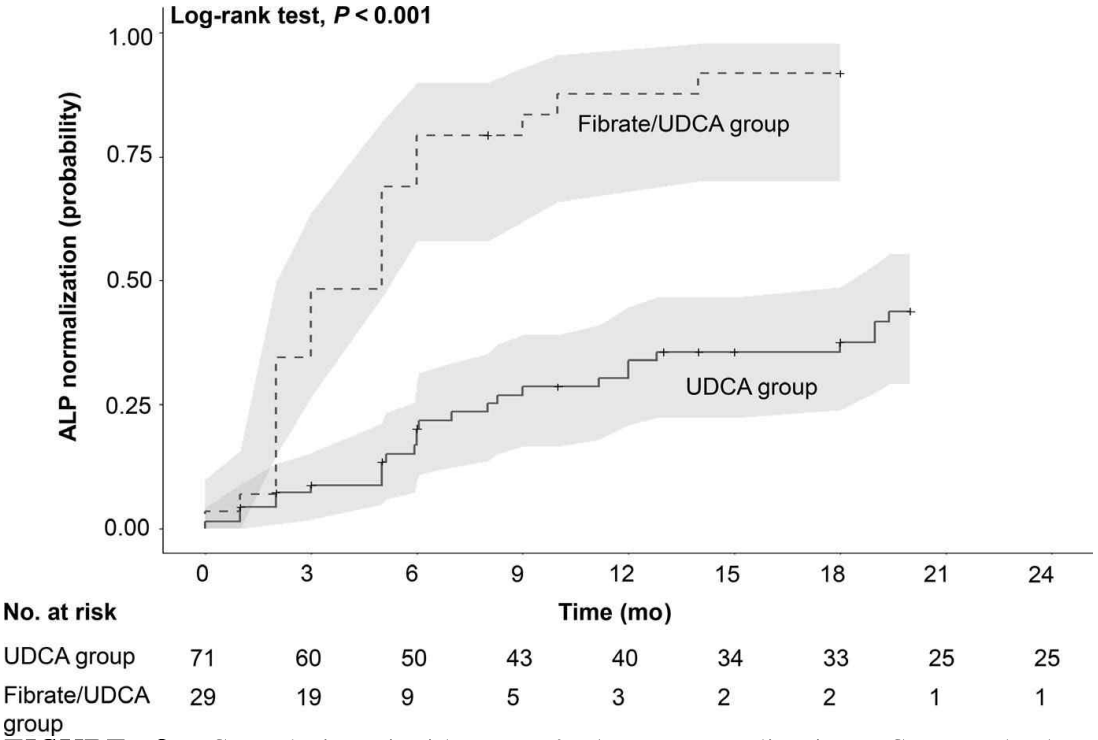


FIGURE 2. Cumulative incidence of ALP normalization. Censored data represent patients who failed to achieve ALP normalization. Grey area represents 95% confidence interval. Survival curves were compared with the log rank test. ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Treatment group				
UDCA group	1 [Reference]		1 [Reference]	
Fibrate/UDCA group	5.00 (2.87-8.73)	<0.001	6.13 (3.07-12.25)	<0.001
Age, y	1.03 (1.00-1.05)	0.02	1.02 (0.99-1.05)	0.13
Female	0.45 (0.23-0.87)	0.02	0.44 (0.21-0.89)	0.02
AMA				
Negative	1 [Reference]			
Positive	0.52 (0.22-1.21)	0.13		
AIH-PBC overlap syndrome				
No	1 [Reference]			
Yes	0.91 (0.51-1.61)	0.74		
Fatty liver				
No	1 [Reference]			
Yes	1.16 (0.69-1.94)			
Underlying cirrhosis				
Absent	1 [Reference]			
Present	1.01 (0.61-1.70)	0.96		
Initial ALP, IU/L				
≤172.5 (=1.5 x UNL)	1 [Reference]		1 [Reference]	
>172.5 (=1.5 x UNL)	0.24 (0.13-0.43)	<0.001	0.22 (0.12-0.42)	<0.001
Child-Pugh class				
Class A	1 [Reference]			
Class B or	0.60 (0.19-1.91)	0.39		
UDCA dose, mg per kg	1.06 (0.99-1.13)	0.06	1.03 (0.95-1.11)	0.47

Table 4. Univariable and multivariable Cox proportional hazards regression analysis for ALP normalization.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; UDCA, ursodeoxycholic acid; UNL, upper normal limit.

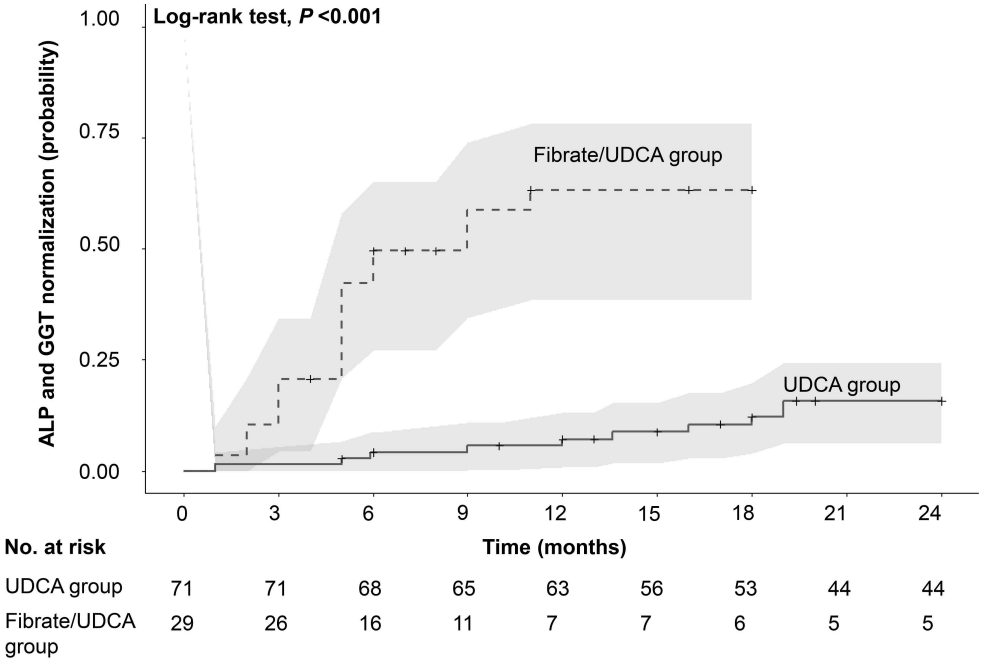


Figure 3. Cumulative incidence of ALP + GGT normalization. Censored data represent patients who failed to achieve ALP + GGT normalization. Grey area represents 95% confidence interval. Survival curves were compared with the log-rank test.

Abbreviations: ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; no, number; UDCA, ursodeoxycholic acid.

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Treatment group				
UDCA group	1 [Reference]		1 [Reference]	
Fibrate/UDCA group	5.58 (2.73-11.40)	<0.001	12.63 (4.89-32.64)	<0.001
Age, y	1.05 (1.01-1.08)	0.005	1.07 (1.03-1.12)	0.001
Female	6.43 (0.83-47.08)	0.07	18.69 (2.33-150.21)	0.06
AMA				
Negative	1 [Reference]			
Positive	0.75 (0.23-2.47)	0.64		
AIH-PBC overlap syndrome				
No	1 [Reference]			
Yes	0.88 (0.23-2.47)	0.64		
Fatty liver				
No	1 [Reference]			
Yes	0.56 (0.26-1.20)	0.75		
Underlying cirrhosis				
Absent	1 [Reference]			
Present	1.03 (0.52-2.04)	0.94		
Initial ALP, IU/L				
≤172.5 (=1.5 x UNL)	1 [Reference]		1 [Reference]	
>172.5 (=1.5 x UNL)	0.22 (0.09-0.54)	<0.001	0.18 (0.07-0.46)	<0.001
Child-Pugh class				
Class A	1 [Reference]			
Class B or C	0.45 (0.06-3.28)	0.43		
UDCA dose, mg per kg	1.09 (1.00-1.17)	0.06	1.03 (0.93-1.13)	0.55

Table 5. Univariable and multivariable Cox proportional hazards regression analysis for ALP+GGT normalization.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; GGT, gamma-glutamyltransferase; UDCA, ursodeoxycholic acid; UNL, upper normal limit.

	Fiberate/UDCA group		UDCA group		Standardized effect size (unweighted)	P-value (unweighted)	Standardized effect size (weighted)	P-value (weighted)
	Mean	SD	Mean	SD				
ALP, IU/L	178.7	72.7	196.8	98.1	-0.25	0.31	0.08	0.77
AST, IU/L	39.5	18.9	50.8	29.3	-0.60	0.02	-0.06	0.83
Albumin, g/dL	4.3	0.2	4.0	0.5	1.02	0.002	-0.02	0.95
UDCA dose, mg per kg	20.4	3.9	17.5	3.7	0.74	0.001	0.24	0.35
Baseline CPS, points	5.1	0.4	5.3	0.9	-0.47	0.15	0.09	0.66

Table 6. Checking balance.

Abbreviations: ALP, alkaline phosphatse; AST, aspartate, aminotransferase; CPS, Child-Pugh score; SD; standard deviation; UDCA, ursodeoxycholic acid.

fibrate/UDCA group (Tables 7 and 8).

Long-term liver-related events

During follow up, 17 cases (23.9%) of hepatic deterioration with Child Pugh score increase of ≥2 points or signs of decompensated cirrhosis occurred in the UDCA group, whereas there were no cases in the fibrate/UDCA group (Figure 4). There were significant differences between the two groups in both univariable (HR = 0.12, 95% CI = 0.001-0.88, log-rank P = 0.04) and multivariable (aHR = 0.08, 95% CI = 0.001-0.76, P = 0.02) analyses (Table 9). In cirrhotic patients at the index date (n = 42), ten events occurred in the UDCA group (n = 28) and no events occurred in the fibrate/UDCA group (n = 14) (Figure 5); this difference was statistically significant (HR = 0.09, 95% CI = 0.001-0.68, log-rank P = 0.01) (Table 10).

At baseline, 15 patients in the fibrate/UDCA group and 43 patients in the UDCA group had no evidence of cirrhosis (Figure 6). Among these patients, none in the fibrate/UDCA group and 19 patients (44.1%) in the UDCA group developed cirrhosis during the study period, which was statistically significant in both univariable (HR = 0.12, 95% CI = 0.001-0.87, log-rank P = 0.04) and multivariable (aHR = 0.10, 95% CI = 0.001-0.78, P = 0.02) analyses (Table 11).

Two new cases of HCC developed during the follow-up period (Figure 7). One case occurred in the fibrate/UDCA group, and one case occurred in the UDCA group. There was no significant difference in HCC occurrence between the two groups (log-rank P = 0.31; Table 7).

Four patients underwent liver transplantation and four patients died during the follow up period. All of these cases occurred in the UDCA group, although there was no significant difference between

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Treatment group				
UDCA group	1 [Reference]		1 [Reference]	
Fibrate/UDCA group	3.44 (1.84-6.34)	<0.001	15.97 (6.50-39.23)	<0.001
Age, y	1.03 (1.003-1.06)	0.03	1.01 (0.97-1.06)	0.56
Female	0.38 (0.18-0.81)	0.02	0.24 (0.10-0.57)	0.001
AMA				
Negative	1 [Reference]		1 [Reference]	
Positive	0.41 (0.16-1.01)	0.05	0.17 (0.06-0.46)	<0.001
AIH-PBC overlap syndrome				
No	1 [Reference]		1 [Reference]	
Yes	0.45 (0.22-0.92)	0.03	0.54 (0.25-1.18)	0.12
Fatty liver				
No	1 [Reference]			
Yes	1.39 (0.77-2.52)	0.27		
Underlying cirrhosis				
Absent	1 [Reference]			
Present	0.84 (0.42-1.68)	0.62		
Initial ALP, IU/L				
≤172.5 (=1.5 x UNL)	1 [Reference]		1 [Reference]	
>172.5 (=1.5 x UNL)	0.19 (0.10-0.37)	<0.001	0.09 (0.03-0.23)	<0.001
Child-Pugh class				
Class A	1 [Reference]		1 [Reference]	
Class B or C	0.50 (0.33-0.74)	<0.001	2.00 (0.41-9.90)	0.39
UDCA dose, mg per kg	0.98 (0.90-1.07)	0.62		

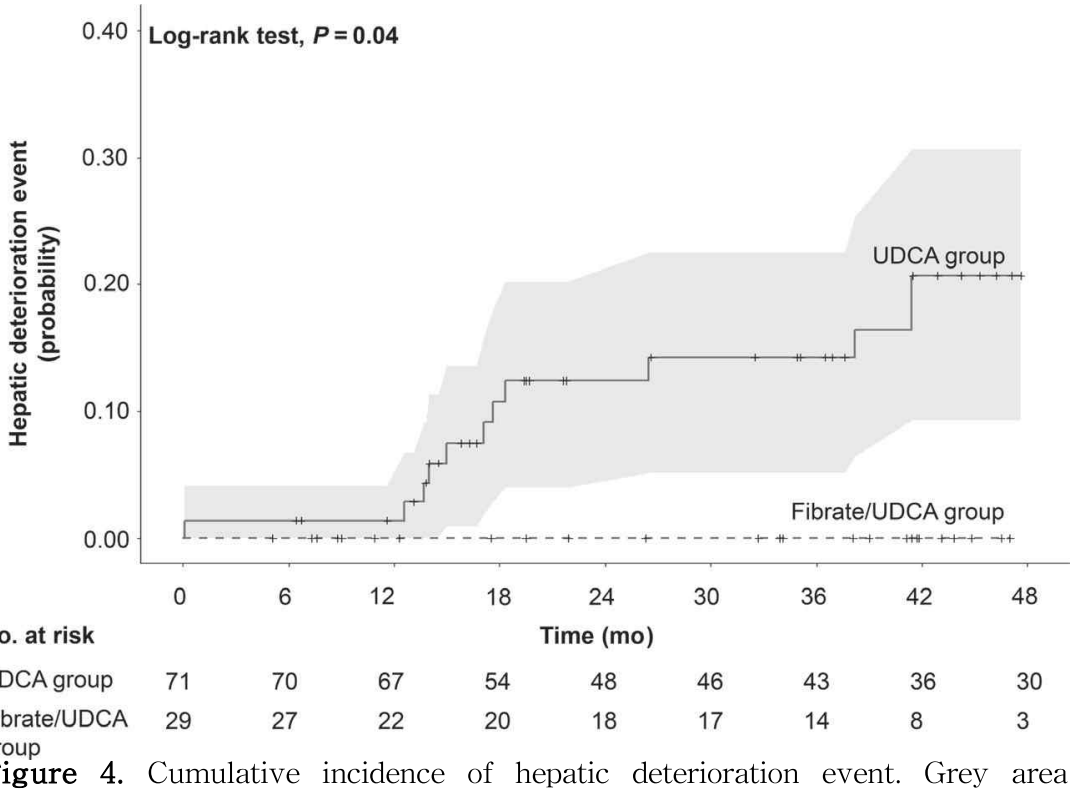
Table 7. Univariable and multivariable Cox proportional hazards regression analysis for ALP normalization after IPTW.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; IPTW, inverse probability of treatment weighting; UDCA, ursodeoxycholic acid; UNL, upper normal limit.

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Treatment group				
UDCA group	1 [Reference]		1 [Reference]	
Fibrate/UDCA group	2.85 (1.27-6.37)	0.01	3.87 (1.71-8.74)	0.001
Age, y	1.05 (1.01-1.09)	0.009	1.08 (1.02-1.15)	0.01
Female	5.03 (0.60-41.98)	0.14		
AMA				
Negative	1 [Reference]			
Positive	0.59 (0.12-3.04)	0.53		
AIH-PBC overlap syndrome				
No	1 [Reference]			
Yes	0.69 (0.26-1.86)	0.46		
Fatty liver				
No	1 [Reference]			
Yes	0.76 (0.32-1.76)	0.51		
Underlying cirrhosis				
Absent	1 [Reference]			
Present	0.62 (0.27-1.47)	0.28		
Initial ALP, IU/L				
≤172.5 (=1.5 x UNL)	1 [Reference]		1 [Reference]	
>172.5 (=1.5 x UNL)	0.34 (0.12-0.95)	0.04	0.24 (0.10-0.61)	0.003
Child-Pugh class				
Class A	1 [Reference]		1 [Reference]	
Class B or C	0.05 (0.003-0.68)	0.03	1.15 (0.04-36.13)	0.94
UDCA dose, mg per kg	1.08 (0.98-1.18)	0.12		

Table 8. Univariable and multivariable Cox proportional hazards regression analysis for ALP+GGT normalization after IPTW.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; GGT, gamma-glutamyltransferase; IPTW, inverse probability of treatment weighting; UDCA, ursodeoxycholic acid; UNL, upper normal limit.



No. at risk									
UDCA group	71	70	67	54	48	46	43	36	30
Fibrate/UDCA group	29	27	22	20	18	17	14	8	3

Figure 4. Cumulative incidence of hepatic deterioration event. Grey area represents 95% confidence interval. Survival curves were compared with the log-rank test. Hepatic deterioration was defined as Child-Pugh score increase of ≥2 points compared to baseline or signs of decompensated cirrhosis such as hepatic encephalopathy, variceal bleeding or refractory ascites event.

Abbreviations: no, number; UDCA, ursodeoxycholic acid

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Treatment group*				
UDCA group	1 [Reference]		1 [Reference]	
Fibrate/UDCA group	0.12 (0.001-0.88)	0.03	0.08 (0.001-0.76)	0.02
Age, y	1.00 (0.95-1.04)	0.90		
Female*	0.38 (0.18-0.81)	0.02		
AMA				
Negative	1 [Reference]			
Positive	0.34 (0.10-1.78)	0.18		
AIH-PBC overlap syndrome				
No	1 [Reference]		1 [Reference]	
Yes	1.24 (0.40-3.90)	0.71	1.70 (0.49-4.93)	0.37
Fatty liver				
No	1 [Reference]		1 [Reference]	
Yes	0.56 (0.18-1.72)	0.31	1.05 (0.30-3.20)	0.94
Underlying cirrhosis				
Absent	1 [Reference]			
Present	0.84 (0.42-1.68)	0.62		
Initial ALP, IU/L				
≤172.5 (=1.5 x UNL)	1 [Reference]			
>172.5 (=1.5 x UNL)	4.17 (1.36-12.81)	0.01	2.63 (0.92-9.00)	0.07
Child-Pugh class				
Class A	1 [Reference]		1 [Reference]	
Class B or C	16.57 (5.26-52.21)	<0.001	12.95 (3.89-43.58)	<0.001
UDCA dose, mg per kg	0.80 (0.67-0.98)	0.03		

Table 9. Univariable and multivariable Cox proportional hazards regression analysis for the rate of hepatic deterioration compared to baseline.

* Univariable and multivariable factors were analyzed with Firth method.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; UDCA, ursodeoxycholic acid; UNL, upper normal limit.

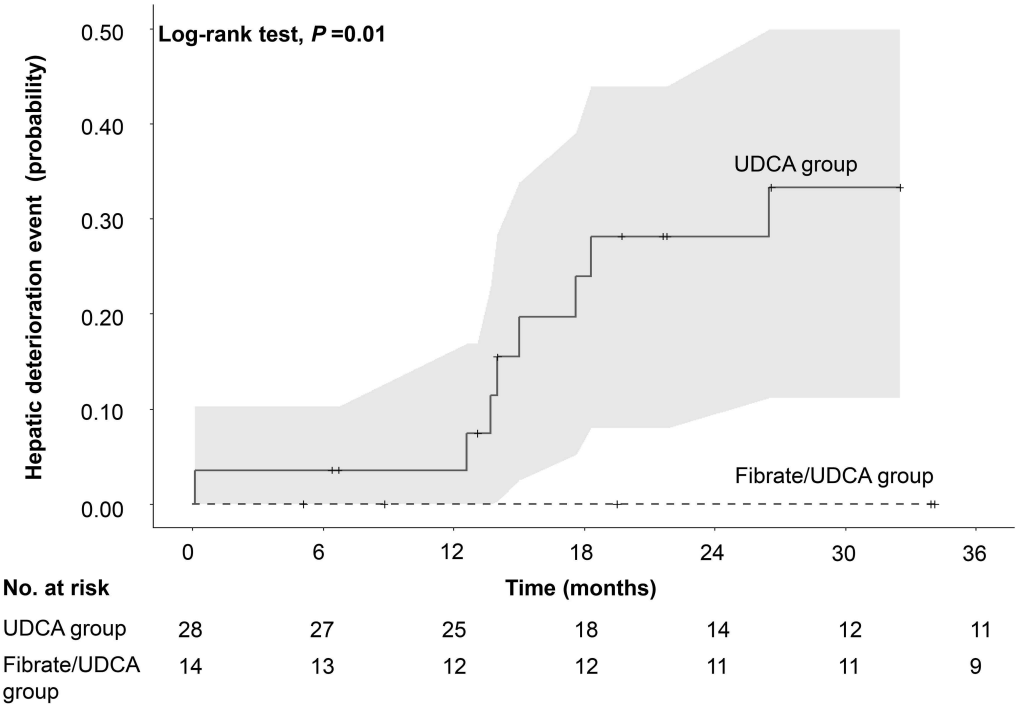


Figure 5. Cumulative incidence of hepatic deterioration compared to baseline in cirrhotic patients. Grey area represents 95% confidence interval. Survival curves were compared with the log-rank test. Hepatic deterioration was defined as Child-Pugh score increase of ≥2 points compared to baseline, or signs of decompensated cirrhosis such as hepatic encephalopathy, variceal bleeding or refractory ascites event.

Abbreviations: no, number; UDCA, ursodeoxycholic acid

	Univariable analysis	
	Hazard ratio (95% CI)	P value
Treatment group*		
UDCA group	1 [Reference]	
Fibrate/UDCA group	0.09 (0.001-0.68)	0.01
Age, y	1.04 (0.98-1.10)	0.21
Female	5.71 (0.72-736.61)	0.11
AMA		
Negative	1 [Reference]	
Positive	0.59 (0.07-76.95)	0.74
AIH-PBC overlap syndrome		
No	1 [Reference]	
Yes	1.14 (0.23-5.64)	0.87
Fatty liver		
No	1 [Reference]	
Yes	0.37 (0.08-1.76)	0.21
Initial ALP, IU/L		
≤172.5 (=1.5 x UNL)	1 [Reference]	
>172.5 (=1.5 x UNL)	2.80 (0.72-10.96)	0.14
Child-Pugh class		
Class A	1 [Reference]	
Class B or C	12.25 (3.26-46.10)	<0.001
UDCA dose, mg per kg	0.65 (0.45-0.95)	0.02

Table 10. Univariable and multivariable Cox proportional hazards regression analysis for the rate of hepatic deterioration compared to baseline in cirrhotic patients.

* Univariable factor was analyzed with Firth method.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; UDCA, ursodeoxycholic acid; UNL, upper normal limit.

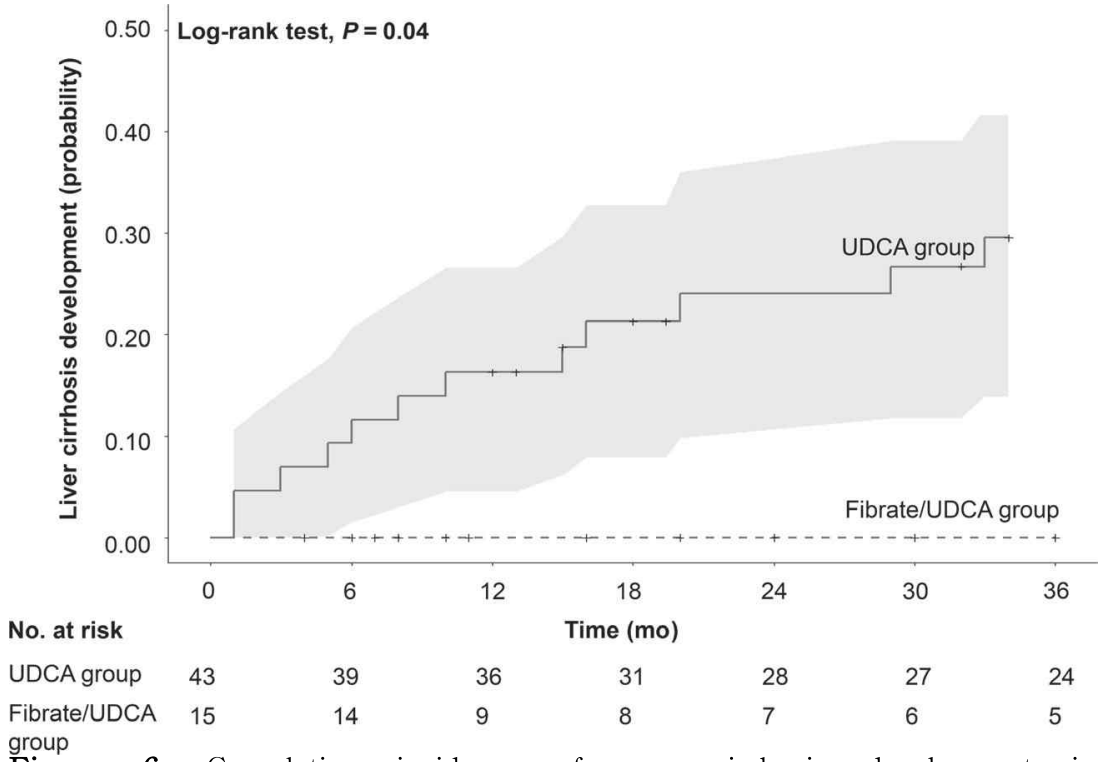


Figure 6. Cumulative incidence of new cirrhosis development in non-cirrhotic patients. Grey area represents 95% confidence interval. Survival curves were compared with the log-rank test.

Abbreviations: no, number; UDCA, ursodeoxycholic acid

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Treatment group*				
UDCA group	1 [Reference]		1 [Reference]	
Fibrate/UDCA group	0.12 (0.001-0.87)	0.03	0.10 (0.001-0.78)	0.02
Age, y	0.99 (0.95-1.03)	0.63		
Female	0.51 (0.15-1.79)	0.29		
AMA				
Negative	1 [Reference]			
Positive	1.36 (0.34-12.34)	0.71		
AIH-PBC overlap syndrome				
No	1 [Reference]		1 [Reference]	
Yes	1.60 (0.62-4.08)	0.33	2.17 (0.80-5.64)	0.12
Fatty liver				
No	1 [Reference]		1 [Reference]	
Yes	3.29 (1.32-8.22)	0.01	3.87 (1.53-10.45)	0.004
Initial ALP, IU/L				
≤172.5 (=1.5 x UNL)	1 [Reference]		1 [Reference]	
>172.5 (=1.5 x UNL)	4.27 (1.62-11.29)	0.003	4.15 (1.63-11.75)	0.003
UDCA dose, mg per kg	0.99 (0.87-1.12)	0.85		

Table 11. Univariable and multivariable Cox proportional hazards regression analysis for cirrhosis development.

* Univariable factor was analyzed with Firth method.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; UDCA, ursodeoxycholic acid; UNL, upper normal limit.

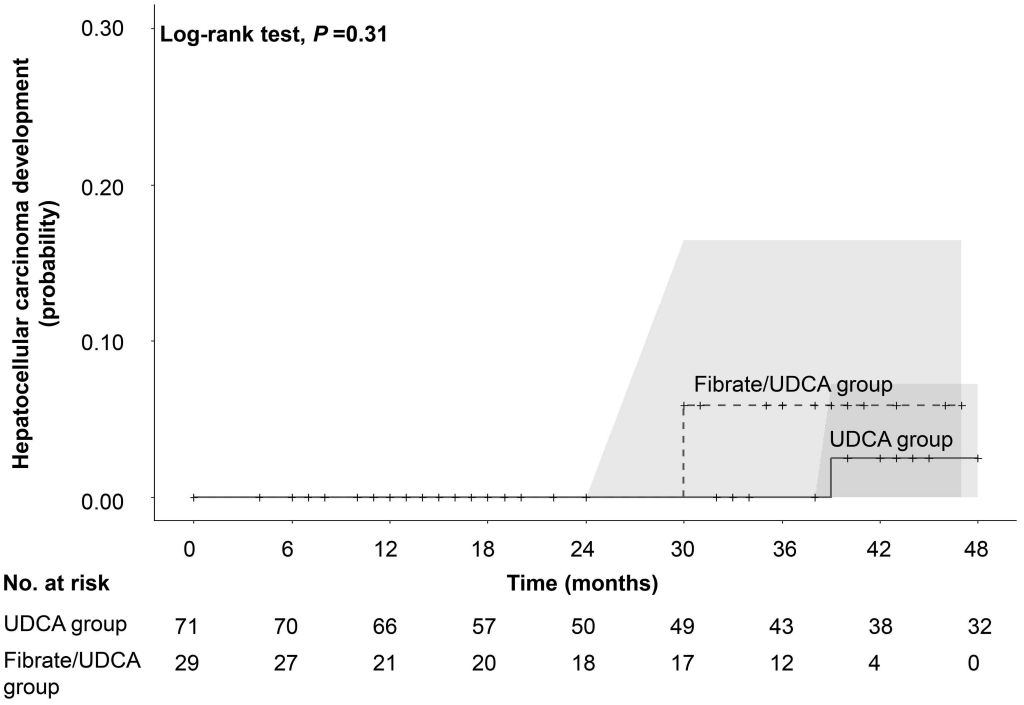


Figure 7. Cumulative incidence of hepatocellular carcinoma development. Grey area represents 95% confidence interval. Survival curves were compared with the log-rank test.

Abbreviations: no, number; UDCA, ursodeoxycholic acid

	Univariable analysis	
	Hazard ratio (95% CI)	P value
Treatment group*		
UDCA group	1 [Reference]	
Fibrate/UDCA group	3.80 (0.23-62.31)	0.35
Age, y	1.12 (0.97-1.29)	0.13
Female	0.19 (0.01-3.02)	0.24
AMA*		
Negative	1 [Reference]	
Positive	0.32 (0.02-44.07)	0.52
AIH-PBC overlap syndrome		
No	1 [Reference]	
Yes	0.76 (0.005-9.42)	0.85
Fatty liver*		
No	1 [Reference]	
Yes	8.49 (0.69-1173.24)	0.10
Underlying cirrhosis		
Absent	1 [Reference]	
Present	1.65 (0.10-26.43)	0.72
Initial ALP, IU/L		
≤172.5 (=1.5 x UNL)	1 [Reference]	
>172.5 (=1.5 x UNL)	1.38 (0.09-22.03)	0.82
Child-Pugh class		
Class A	1 [Reference]	
Class B or C	4.39 (0.03-54.01)	0.42
UDCA dose, mg per kg	1.03 (0.72-1.49)	0.86

Table 12. Univariable Cox proportional hazards regression analysis for HCC development.

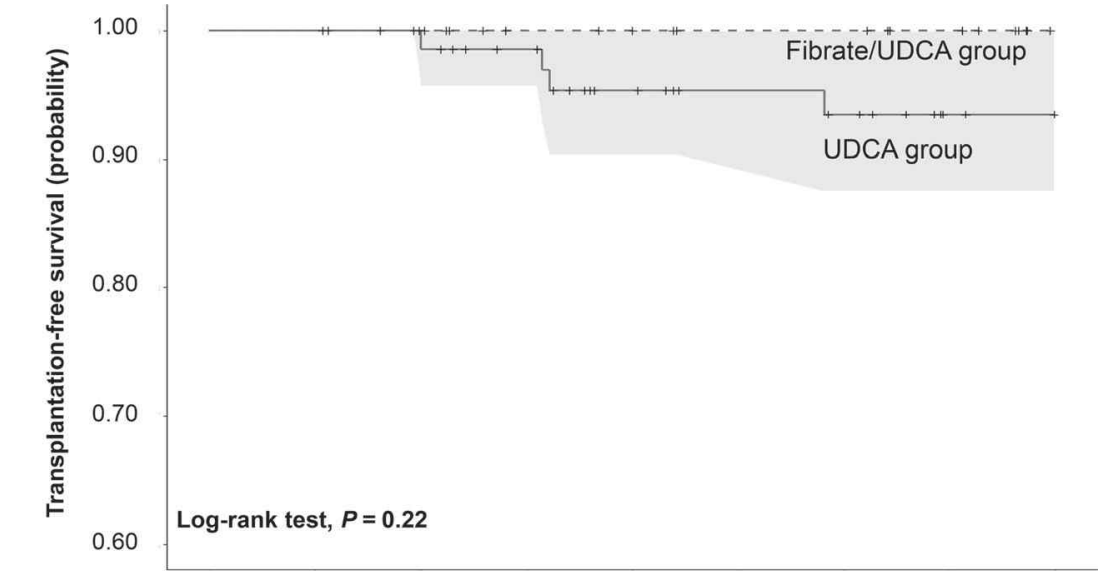
* Univariable factor was analyzed with Firth method.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; CI, confidence interval; HCC, hepatocellualar carcinoma; UDCA, ursodeoxycholic acid; UNL, upper normal limit.

the two groups (HR = 0.30, 95% CI = 0.002-2.72, log-rank P = 0.22; Figure 8). To estimate the transplantation free survival, two established risk estimators (i.e., GLOBE and UK-PBC) were calculated.[25,26] At the index date, there was no significant difference in GLOBE and UK-PBC scores between the two treatment groups (P = 0.46 and P = 0.30 respectively). After 1 year of fibrate treatment, the mean 5-year, 10-year and 15-year GLOBE score estimates of transplantation-free survival probabilities were significantly increased (all P < 0.001; Table 13). The mean GLOBE score estimates of transplantation free survival probabilities in the UDCA group, on the other hand, showed no significant change (Table S11). Similarly, the mean UK-PBC risk scores significantly improved in the fibrate/UDCA group (P = 0.001; Table 14), while the UDCA group did not show significant change (Figures 9 and 10). There were significant differences in the change of 10-year and 15-year UK-PBC/GLOBE risk scores between the two treatment groups (Figures 9 and 10).

Previously AIH-PBC overlap syndrome has shown poor prognosis than typical PBC.[36] Thirty one AIH-PBC overlap syndrome patients were subgrouped and outcomes were evaluated. There were no statistical difference in secondary outcomes (hepatic deterioration, cirrhosis development) between the fibrate/UDCA group (n = 11) and the UDCA group (n = 20) (HR = 0.18, 95% CI = 0.001-1.72, log-rank P = 0.12, HR = 0.20, 95% CI = 0.001-1.73, log-rank P = 0.12 respectively).

Different PBC refractoriness criteria (i.e., Barcelona criteria,[32] Toronto criteria,[33] Paris II criteria,[34] Rotterdam criteria,[35] Ehime crteria[7]), PBC patients without AIH-PBC overlap syndrome patients and PBC patients without fatty liver were subgrouped and secondary



No. at risk									
UDCA group	71	71	68	63	55	51	49	43	41
Fibrate/UDCA group	29	29	26	21	20	17	17	14	7

Figure 8. Cumulative incidence of transplantation-free survival. Grey area represents 95% confidence interval. Survival curves were compared with the log-rank test.

Abbreviations: no, number; UDCA, ursodeoxycholic acid

GLOBE score estimation (transplanation-free survival probability)

	Fibrate/UDCA group (n=27)			UDCA group (n=61)			
	Index date	Year 1	P value	Index date	Year 1	P value	Repeated measure ANOVA
5-year	91.8%	94.1%	<0.001	87.2%	85.3%	0.09	0.01
10-year	79.8%	85.5%	<0.001	72.6%	70.6%	0.18	0.002
15-year	67.6%	76.2%	<0.001	59.9%	58.2%	0.29	<0.001

Table 13. GLOBE score estimation of 5-year, 10-year, and 15-year transplantation-free survival probability.

Abbreviations: ANOVA, anlysis of variance; UDCA, ursodeoxycholic acid.

UK-PBC score estimation (risk of transplant or liver-related death)

	Fibrate/UDCA group (n=27)			UDCA group (n=61)			
	Index date	Year 1	P value	Index date	Year 1	P value	Repeated measure ANOVA
5-year	2.6%	1.7%	0.001	3.9%	5.4%	0.16	0.15
10-year	8.0%	5.5%	0.001	11.7%	14.4%	0.11	0.045
15-year	13.9%	9.6%	0.001	19.3%	21.2%	0.30	0.03

Table 14. UK-PBC score estimation of 5-year, 10-year, and 15-year risk of transplantation or liver-related death.

Abbreviations: ANOVA, analysis of variance; UDCA, ursodeoxycholic acid.

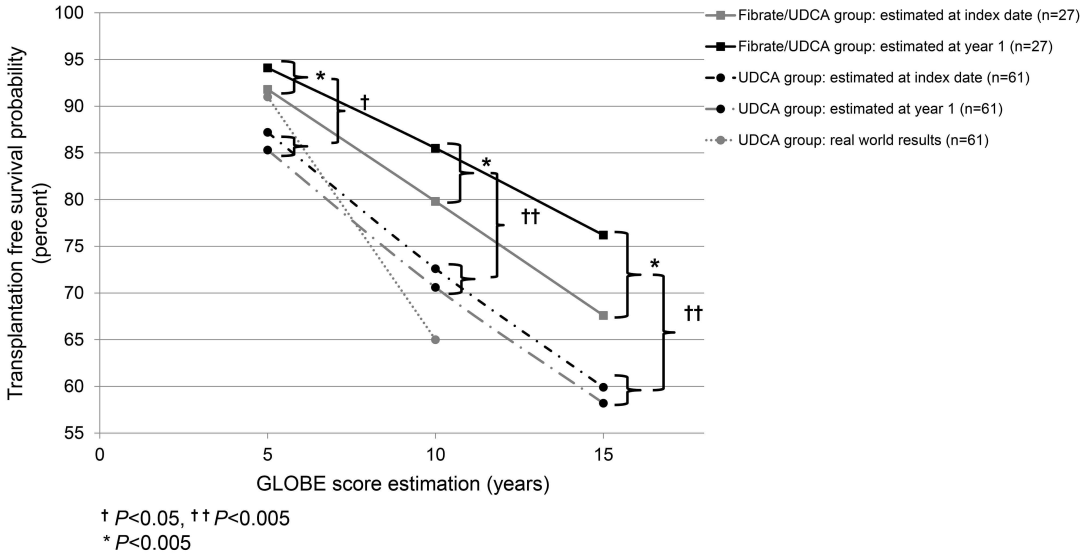


Figure 9. GLOBE score estimation of transplantation-free survival probability: estimated at index date and year 1.
Abbreviation: UDCA, ursodeoxycholic acid

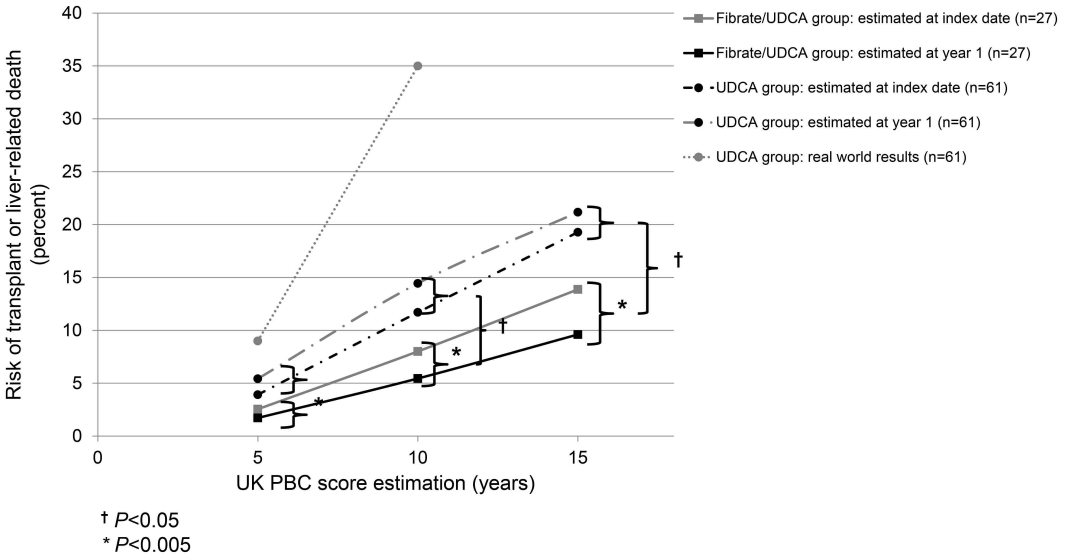


Figure 10. UK-PBC score estimation of risk of transplantation or liver-related death: estimated at index date and year 1.
Abbreviation: UDCA, ursodeoxycholic acid

outcomes were analyzed (Figure 11). Most of the considered factors have shown benefit on secondary outcomes (hepatic deterioration, cirrhosis development) for the fibrate/UDCA group over the UDCA group in most of the analyzed subgroups (Figure 11).

Safety

During the follow up period, no severe systemic adverse event occurred within the fibrate/UDCA group. Six cases (20.6%) of AST or alanine aminotransferase (ALT) elevation >80 IU/L were detected in the fibrate/UDCA group, whereas 21 cases (29.6%) occurred in the UDCA group (Fisher's exact test P = 0.36). No fulminant hepatitis event occurred in both group during follow up. Only one patient (3.4%) stopped fibrate for more than 6 months in the fibrate/UDCA group, whereas 8 patients (11.2%) did not take UDCA for more than 6 months in the UDCA group (Fisher's exact test P = 0.22).

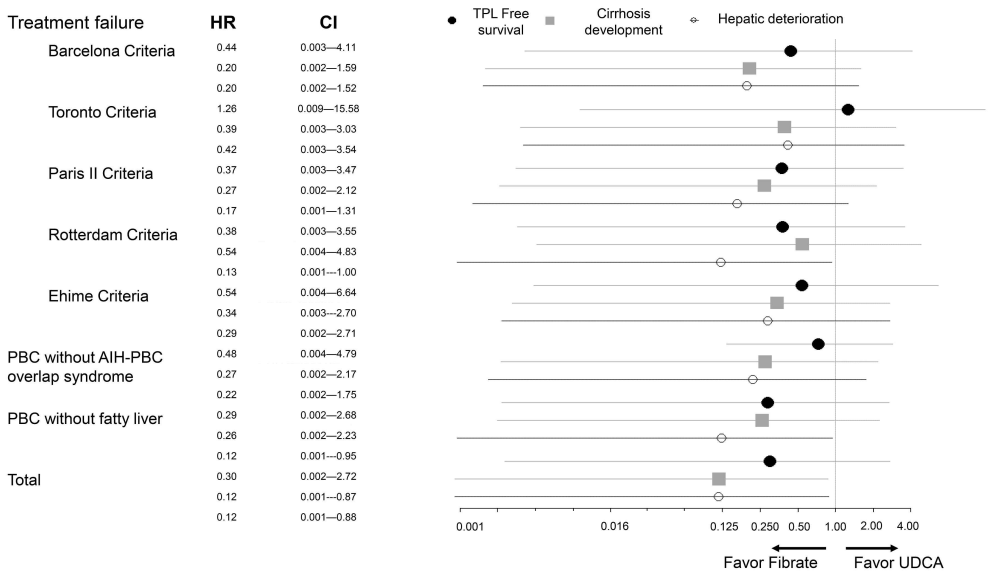


Figure 11. Forest plots of clinical outcomes. Horizontal lines represent 95% confidence interval. Confidence interval and hazard ratio were computed with Firth method. Barcelona criteria treatment response was defined as ALP normal levels or decrease greater than 40% of pretreatment after 1 year of UDCA treatment. Toronto criteria treatment response was defined as ALP level lower than 1.67x upper normal limit after 2 years of UDCA treatment. Paris II criteria treatment response was defined as AST and ALP below 1.5x upper limit after 1 years of UDCA treatment. Rotterdam criteria treatment response was defined as normalization of abnormal albumin and/or bilirubin level after 1 years of UDCA treatment. Ehime criteria treatment response was defined as decreased in GGT above 70% of pretreatment or normal levels from 6 months after start of UDCA treatment.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; GGT; gamma-glutamyltransferase; HR, hazard ratio; PBC, primary biliary cholangitis; TPL, transplantation; UDCA, ursodeoxycholic acid.

Discussion

In this study, fibrate was administered as a rescue therapy for PBC patients who did not respond to UDCA treatment. Fibrate plus UDCA resulted in ALP normalization in almost 90% of patients within 1 year, and significantly higher rates of both ALP and GGT normalization compared to the UDCA group. Fibrate treatment was associated with significantly lower risk of further deterioration in liver function (Child-Pugh score increase of ≥2 points or any signs of decompensated cirrhosis) and cirrhosis development. No death or liver transplantation event occurred in the fibrate/UDCA group, whereas four transplantations and four deaths occurred in the UDCA group, although this difference was not statistically significant. This study was the first to report the effect of additional fibrate treatment on long term outcomes including death, cirrhosis, HCC and hepatic deterioration in patients with PBC who did not respond to UDCA.

Patients with an incomplete biochemical response to UDCA therapy also have poor overall prognosis, and several studies have investigated post UDCA treatment.[6,7] Fibrate has been associated with ALP normalization in several small studies and recently proven in a randomized control trial.[12,37-39] The result of the current study supports the conclusions of the previous studies. These results suggest that fibrate inhibition of cytochrome P450 7A1 reduces the production of bile acids[40] and upregulates MDR3 expression, which excretes phospholipids (essential for micelle formation of bile acids) from hepatocytes.[10,41,42] By ultimately reducing bile acids formation, fibrate may rescue hepatocytes from excessive exposure to

cytotoxic bile acids.

Fibrates have anti inflammatory effect and prevent fibrosis.[9,43] This study showed that fibrates prevent the progression of cirrhosis and reduce the incidence of new cirrhosis. A recent randomized control trial showed that bezafibrate improved liver elasticity, but failed to show the prevention of portal hypertension development.[12] This might have occurred because the study period of the randomized control trial (24 months) was shorter than in our study (median 47 months) and since significant cirrhosis development or hepatic deterioration development is less likely to develop within 24 months. Most patients were treated with fenofibrate in our study instead of bezafibrate but this different pharmacological effect needs further validation with future studies.

In addition, patients with AIH-PBC overlap syndrome were excluded from the clinical trial. AIH-PBC overlap syndrome has shown dismal prognosis in previous study.[36,44,45] Our current study included a higher proportion of AIH-PBC overlap syndrome patients than in previous studies.[45] This might be due to selection bias, since this study was a retrospective one. However, patients with AIH-PBC overlap syndrome were evenly distributed between both treatment groups, and AIH-PBC overlap syndrome was not significantly associated with either biochemical improvement or clinical deterioration. Even though it was not statistically significant, probably due to small sample size, fibrate seems to prevent further cirrhosis development or further hepatic deterioration in AIH-PBC overlap syndrome patients without significant adverse events.

The risk of developing HCC for a patient with PBC is higher than the HCC risk for the general population, especially if the PBC patient does not respond to UDCA.[46] It is unclear whether fibrate may

affect the risk of HCC or other cancer. PPAR is involved in the cell cycle, programmed cell death and anti inflammation.[47] A retrospective study reported that fibrate reduced serum levels of fibroblast growth factor-18; this might prevent tumorigenesis because fibroblast growth factor-18 activates the signal trnsducer and activator of transcription 3 pathway, which is closely associated with tumour growth.[41,48] In our study, the risk of HCC did not significantly differ between the fibrate/UDCA and UDCA groups. Further investigations will be required to evaluate the association between fibrate use and the risk of malignant tumours including HCC.

This study included patients treated with either bezafibrate or fenofibrate into the fibrate/UDCA group. Both drugs act as PPAR-α agonists, but bezafibrate also may act as agonist against PPAR-γ/δ and the pregnane X receptor.[11] PPAR-γ has an anti inflammatory effect in an animal model,[49] and pregnane X receptor is reported to reduce nuclear factor kappa B expression.[50] In a recent randomized controlled trial, seladelpar, a PPAR-δ agonist, showed biochemical improvement as well as a decreased level of C4, which is a marker of bile acid synthesis in PBC patients.[51] Bezafibrate, a pan-PPAR agonist, is reported to have an additional PPAR-δ agonistic effect,[52] and it is expected that bezafibrate might be more effective than fenofibrate, that is a PPAR-α agonist. Further study is warranted to compare the effect of various PPAR agonists on the prognosis of UDCA-refractory PBC.

Fibrate has a relatively good safety profile, but abnormal hepatocellular pattern liver function has been reported.[53] Our study did not detect significant differences in adverse liver abnormality events between the fibrate/UDCA and UDCA groups. With proper

monitoring of liver function, long term fibrate use seems to be safe.

In our study, there was no significant association between additional fibrate treatment and transplantation free survival between the two treatment groups. This could be a result of the small sample size and short follow up duration. Instead, we have estimated the survival of the two treatment groups (i.e., the UDCA group and the fibrate/UDCA group) using two known risk estimators (i.e., GLOBE and UK-PBC) and we found there was a significantly different trend evident between the fibrate/UDCA group and the UDCA group. There was a significant improvement of both UK-PBC and GLOBE scores in the fibrate/UDCA group, but no improvement in the UDCA group. Recently, a Japanese retrospective study and the post hoc analysis of BEZURSO trial have shown improvement in both UK-PBC and GLOBE scores after fibrate treatment,[54,55] which is consistent with our study. Along with these studies, our current study implies that there may be a survival benefit from long term fibrate treatment in UDCA-refractory PBC patients.

There were several limitations in our study. Firstly, the median dose of UDCA was higher in the fibrate/UDCA group. The UDCA dose is important for PBC treatment. However, all cases used the recommended ≥13 mg/kg of UDCA, even in the UDCA group, and even after IPTW adjustment, fibrate was an independent prognostic factor of ALP normalization.

Secondly, this is a retrospective study from two tertiary centres. Unlike a randomized control study, there is a potential for selection bias, and there were some significant differences between the baseline characteristics of the two treatment groups; however, important factors such as baseline ALP level or Child-Pugh score did not differ significantly. IPTW and multivariable analysis were performed to

overcome these potential limitations and still indicated significant differences in ALP and GGT normalization between the two groups. This strongly supports the fact that fibrate increases the rate of ALP normalization in UDCA-refractory PBC patients. In addition, the limited available data on symptoms such as the presence and grade of pruritus did not allow us to compare the two treatment groups.

Thirdly, our study might include an immortal time bias. To minimize this potential bias, patients in the fibrate/UDCA group before fibrate treatment and after 15 months of UDCA treatment were considered as the UDCA group using the Mandel-Byar method.[29] This analysis was included to reduce the risk of overestimation of treatment effect. Ultimately, there was significantly higher probability of biochemical improvement and reduced risk of long term adverse liver events in the fibrate/UDCA group even after minimizing the immortal bias. In conclusion, this study showed that fibrate is associated with higher ALP normalization rates in UDCA-refractory PBC patients, and fibrate prevents the progression and development of cirrhosis. This study supports previous studies in indicating the efficacy of additional fibrate treatment for UDCA-refractory PBC patients. A future prospective randomized trial with long term follow up is warranted.

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Abstract

Additional fibrate treatment in UDCA-refractory PBC patients

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Background & Aims: There is no proven treatment for ursodeoxycholic acid (UDCA) refractory primary biliary cholangitis (PBC) other than obeticholic acid. Although fibrates have been reported to improve biochemical parameters, the long term effects remain unclear. This study evaluated the effect of fibrate on clinical outcomes of UDCA refractory PBC.

Methods: Patients whose alkaline phosphatase (ALP) was not normalized with at least 13 mg/kg of UDCA treatment for >1 year were included from two tertiary referral centres. The primary outcome was ALP normalization. Secondary outcomes included the development of cirrhosis and hepatic deterioration. Immortal time bias was adjusted using the Mantel Byar method.

Results: A total of 100 UDCA refractory PBC patients were included: 71 patients received UDCA alone (the UDCA group) and 29 patients received UDCA plus additional fibrate treatment of 160 mg/d

fenofibrate or 400 mg/d bezafibrate (the fibrate/UDCA group). During the follow up period, the probability of ALP normalization was significantly higher in the fibrate/UDCA group (hazard ratio [HR] = 5.00, 95% confidence interval = 2.87-8.27, P < 0.001). Among 58 non cirrhotic patients (43 in the UDCA group and 15 in the fibrate/UDCA group), 19 patients (44.1%) in the UDCA group and none in the fibrate/UDCA group developed cirrhosis (HR = 0.12, P = 0.04). Hepatic deterioration (Child Pugh score increase or signs of decompensated cirrhosis) occurred in 17 patients (23.9%) of the UDCA group and none in the fibrate/UDCA group in which the difference was significant (HR = 0.12, P = 0.04).

Conclusions: In patients with UDCA refractory PBC, additional fibrate treatment is associated with a higher probability of ALP normalization and a lower risk of cirrhosis development and hepatic deterioration.

keywords : bezafibrate, cirrhosis, fenofibrate, primary biliary cholangitis

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