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ABSTRACT

Background & Aims: Beneficial effect of bezafibrate (BZF) on symptoms and biochemical features of primary biliary cholangitis (PBC) with incomplete response to ursodeoxycholic acid (UDCA) has been reported but long-term efficacy on survival remains unknown. In Japan, BZF has been used as a *de facto* second-line therapy for PBC since 2000. Herein, we compared the survival rates between patients treated with and those without BZF in a large nationwide Japanese PBC cohort.

Methods: All consecutively-registered patients of this cohort who started UDCA therapy from 2000 onwards and had a follow-up ≥ 1 year were included. Association between BZF exposure and mortality or need for liver transplantation (LT) was assessed using time-dependent, multivariable- and propensity score-adjusted Cox proportional hazards models. Clinical benefit was quantified using the number needed to treat (NNT).

Results: Of 3908 eligible patients, 3162 (81%) received UDCA only and 746 (19%) UDCA and BZF over 17360 and 3932 patient-years, respectively. During follow-up, 183 deaths (89 liver-related) and 21 LT were registered. Exposure to combination therapy was associated with a significant decrease in all-cause and liver-related mortality or need for LT (adjusted hazard ratios: 0.3253, 95% CI 0.1936 – 0.5466 and 0.2748, 95% CI 0.1336 – 0.5655, respectively; p<0.001 for both). This association was consistent across various risk groups at baseline. The NNTs with combination therapy to prevent one additional death or LT in 5, 10, and 15 years were 29 (95% CI 22 – 46), 14 (10 – 22), and 8 (6 – 15), respectively.

Conclusions: In a large retrospective cohort study of treatment effects in patients with PBC, the addition of BZF to UDCA was associated with improved prognosis.

Abbreviations

AC, all-cause

ALP, alkaline phosphatase

AMA, anti-mitochondrial autoantibody

BZF, bezafibrate

CI, confidence interval

HR, hazard ratio

IPTW, inverse probability of treatment weighting

LR, liver-related

LT, liver transplantation

NNT, number needed to treat

OCA, obeticholic acid

PBC, primary biliary cholangitis

PPAR, peroxisome proliferator-activated receptor

PXR, pregnane X receptor

UDCA, ursodeoxycholic acid

ULN, upper limit of normal range

Lay summary

The long-term efficacy of bezafibrate (BZF) on liver transplantation (LT) – free survival of patients with PBC with an incomplete response to ursodeoxycholic acid (UDCA) remains to be determined. In this Japanese nationwide retrospective cohort study, the use of UDCA-BZF combination therapy, compared to UDCA alone, was associated with lower risk in all-cause and liver-related mortality or need for LT. These results indicate that BZF is so far the only drug in PBC to have demonstrated efficacy in improving symptoms, biochemical markers, and long-term outcomes.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease, potentially progressing to cirrhosis and liver failure without appropriate treatment.[1] The burden of PBC is growing worldwide and an increasing trend of the prevalence is universally observed.[2, 3] PBC is considered a model autoimmune disease because of disease-specific autoantibodies, i.e. anti-mitochondrial autoantibodies (AMA), marked infiltration of mononuclear cells in the vicinity of intrahepatic small-sized bile ducts, and a high prevalence of autoimmune diseases as comorbidities. Nevertheless, immunosuppressing agents such as corticosteroids have no or little effect for altering the natural course, and clinical trials of biologics targeting cytokines or chemokines playing a crucial role in pathogenesis have failed to meet endpoints to date.[4-6] This is probably because autoimmune attack against biliary epithelial cells initiating the disease course of PBC may not be a dominant factor contributing to disease progression in clinical settings, and rather chronic cholestasis following bile duct injury should be targeted.[7, 8]

Indeed, a globally-approved first-line treatment for PBC is ursodeoxycholic acid (UDCA), a hydrophilic, tertiary bile acid with choleretic and anticholestatic properties. UDCA was demonstrated to be effective both in decreasing liver biochemical abnormalities[9, 10] and improving the liver transplantation (LT)-free survival of patients with PBC.[11-13] On the other hand, based on historical criteria, 30-40% of UDCA-treated patients exhibit an incomplete biochemical response resulting in a significantly worse outcome, while treatment failure defined by non-normalization of liver tests is much higher.[14-19] To improve the long-term outcome of these patients, a number of drugs and compounds have been tested.[8, 20] Currently, the only drug approved for this population is obeticholic acid (OCA), a steroidal farnesoid X receptor agonist. [21] However, OCA is still unsatisfactory for several reasons, including frequent development of pruritus as an adverse effect,

uncertainty in terms of improvement of long-term outcome, and potential liver toxicity in patients with advanced disease.[22, 23]

Another promising candidate as a second-line treatment for patients with incomplete response to UDCA is bezafibrate (BZF). BZF is a dual pan-peroxisome proliferator-activated receptors (PPARs) / pregnane X receptor (PXR) agonist with efficacy against cholestasis, and officially labeled for hyperlipidemia.[24] The beneficial effects of BZF in pre-cirrhotic PBC patients was first reported in 1999.[25] Thereafter, several pilot studies and prospective, randomized controlled studies in Japan showed the biochemical efficacy of short-term combination therapy with BZF and UDCA,[26-28] and BZF has been used in this country as a *de facto* second-line treatment for PBC patients with incomplete response to UDCA.[29] Besides, a double-blinded, randomized, placebo-controlled study in France (BEZURSO trial) demonstrated that a 2-year combination treatment with UDCA and BZF resulted in a significantly higher rate of complete biochemical response (defined by normal levels ALP, total bilirubin, and aminotransferases) and improvement of non-invasive measures of liver fibrosis compared to placebo.[30] Indeed, ALP normalization in this trial occurred in two thirds of patients in the BZF group compared to only 2% in the control group. Nevertheless, even if reduction in mortality or need for LT has been predicted by prognostic models,[31, 32] it remains uncertain whether BZF combination therapy truly improves survival of PBC patients, and it is unlikely that large, adequately-powered trials will address this issue because PBC is a slowly progressive disease.

In Japan, nationwide surveys for PBC have been conducted almost every 3 years since 1980, and nearly 10,000 patients with PBC have been registered to date. Clinical information at diagnosis including age, gender, liver biochemistries, histologic stage, and treatment as well as outcome were recorded. In the present study, we took advantage of this large-scale nationwide cohort to

determine whether BZF in combination with UDCA may improve transplant-free survival of patients with PBC.

METHODS

Study population

The nationwide surveys in Japan are a cohort study of patients with PBC that was initiated in 1980 and has been conducted almost every 3 years by the Intractable Hepato-Biliary Diseases Study Group for Research on Measures for Intractable Disease, which is supported by Health Labor Science Research Grants in Japan. The survey protocol was previously described by Nakano and colleagues.[33] It was approved by the Ethics Committee at Teikyo University (approval no. 14-200), as well as the local institutional review board at each participating institution. In the most recent survey (the 16th in 2017), questionnaires were sent to 556 institutions (including 229 tertiary referral centers and 327 primary/secondary care centers) throughout Japan that were affiliated with active members of the Japan Society of Hepatology and the Japanese Society of Gastroenterology. All patients with PBC, both newly diagnosed and those already followed-up in their institutions, were registered.

To date, 9,919 patients with PBC have been included in the cohort. The diagnosis of PBC was made according to the criteria established by the Intractable Hepato-Biliary Diseases Study Group of Japan.[29] Patients who met at least two of the following criteria were diagnosed as having PBC: biochemical evidence of chronic cholestasis; positive AMA in sera; histologic features compatible with PBC. In this registry, center type, date of birth and gender, date of diagnosis, presence of pruritus and biochemical test findings (ALP, total bilirubin, and albumin) at the time of diagnosis, histologic stage (Scheuer's classification), treatment protocol (UDCA and/or BZF), and the final follow-up date and outcomes at that time (LT, liver-related and all-cause death) were recorded.

Longitudinal data, including biochemical liver tests, response to treatment, and histologic stage, were not available.

The patient selection criteria for the primary analysis of the study were as follows: 1) complete data set available in terms of date of birth, gender, diagnosis date, treatment protocol, final follow-up date and outcome; 2) UDCA therapy initiated in 2000 or after; and 3) follow-up ≥ 1 year. All the patients who met the criteria 1) and 3) were included in a sensitivity analysis covering the whole cohort. In addition to the patients selected for primary analysis, the whole cohort included patients who started UDCA therapy before 2000, and those who received no treatment during their follow-up.

Data analysis

Total bilirubin and albumin values were categorized into normal and abnormal values, ALP level into low (≤1.67xULN) and high (>1.67xULN) levels, and histologic stage into early (1-2) and late (3-4) stages. Missing values were imputed using a predictive mean matching method. Starting and discontinuation dates for UDCA and BZF were collected for each patient. Inconsistent starting dates, as those prior to diagnosis or those subsequent to the final follow-up date, were considered as missing. Over 2000-2017, UDCA starting dates were missing in 1573 (40%) out of 3908 UDCA-treated patients. They were imputed according to the following rules: when diagnosis was prior to June 1st, 1987 and the final follow-up was after this date, UDCA was assumed to have been started on June 1st, 1987, i.e. the year when the efficacy of UDCA was first reported both in English [9] and Japanese literature [34]; when diagnosis was after June 1st, 1987, the UDCA starting date was imputed at the date of diagnosis. The median difference between imputed and original dates was 0.01 year (interquartile range -0.03 – 0.07). Starting dates for BZF were missing in 108 (14%) out of 746 BZF-

treated patients. They were imputed according to a predictive mean matching method based on the covariates at baseline (center type, date of diagnosis, age, gender, total bilirubin, albumin, ALP, pruritus, and histologic stage), assuming that the probability of response to UDCA depends on pre-treatment disease features, as recently shown in several large Western and Asian PBC cohorts.[35, 36] When UDCA or BZF treatment was notified as discontinued but with no stopping date available, which occurred in 3% of patients for UDCA and 0.4% for BZF, stopping dates were imputed at the mid-period of time between starting date and last follow-up.

Exposures to UDCA and BZF were handled as time-varying covariates. Two main outcomes were defined: survival without LT, and survival without liver-related death or LT. These outcomes were assessed using 5 different survival models: Model 1, time-dependent Cox model unadjusted for baseline covariates; Model 2, time-dependent Cox model adjusted for baseline covariates (center type, age, gender, year of diagnosis, pruritus, total bilirubin, ALP, albumin, and histologic stage); Model 3, inverse probability of treatment weighted (IPTW) Cox model unadjusted for baseline covariates; Model 4, IPTW Cox model adjusted for baseline covariates; and Model 5, imputation-free, time-dependent Cox model adjusted for baseline covariates. Model 2 was considered the primary model and models 4 and 5 were used as sensitivity analyses. All analyses have been done with 50 imputation datasets combined following the Rubin's rules. Unadjusted and adjusted survival curves were generated based on models' predictions. The absolute efficacy of BZF was assessed using the number needed to treat (NNT) to prevent one death or LT, or one liver-related death or LT. It was computed as the reciprocal of the difference of predicted event rates between treatment groups at various time points using the primary model estimates.[37]

RESULTS

Baseline population

A total of 3908 (39%) out of 9,919 patients was eligible for primary analysis (**Figure 1**). The characteristics of these patients at diagnosis are shown in **Table 1**. As compared to patients exposed to UDCA only (UDCA-only group, n=3162), patients who were additionally exposed to BZF at any time of the study (UDCA-BZF group, n=746) were more frequently followed-up in tertiary centers, were younger, had higher ALP and albumin levels, and more advanced histologic stage at diagnosis. These 2 groups did not differ according to gender, pruritus frequency, and total bilirubin level.

Treatment exposures

Over 2000-2017, the study included 17360 patient-years of exposure to UDCA in 3908 patients and 3932 patient-years of exposure to BZF in 746 patients. The mean (SD) time of exposure to UDCA was 5.0 (3.5) years in the UDCA-only group and 6.9 (4.0) years in the UDCA-BZF group. In the UDCA-BZF group, BZF was started an average of 1.4 (2.6) years after UDCA began, and the mean time of exposure to BZF was 5.3 (3.8) years. The permanent treatment discontinuation rate was 0.7% (28 out of 3908 patients) for UDCA and 5.9% (44 out of 746) for BZF.

Main outcomes

The overall average (SD) follow-up from UDCA initiation was 5.5 (3.8) years, ranging from 1.0 to 15.9 years. It was 5.2 (3.6) years for the UDCA-only group and 7.3 (4.1) years for the UDCA-BZF group. All-cause death, liver-related death, and LT occurred in 161, 76, and 20 patients, respectively in the UDCA-only group and 22, 13, and 1 patients, respectively in the UDCA-BZF group. The crude incidence rates of these events according to groups are shown in Appendix (Table S1). In all survival models studied, including the imputation-free model, exposure to BZF was associated with a

significant decrease in all-cause and liver-related mortality or need for LT as compared to UDCA alone (**Table 2**). Detailed results are shown in Appendix (Tables S2 – S7). According to the primary model, addition of BZF to UDCA was associated with a 67% decrease in all-cause mortality or need for LT as compared to UDCA alone: adjusted hazard ratio (aHR) 0.3253 (95% CI: 0.1936 – 0.5466; p<0.0001). The corresponding aHR for liver-related mortality or LT was 0.2748 (95% CI: 0.1336 – 0.5655; p<0.0001). Both unadjusted and multivariable-adjusted survival curves are shown in **Figure 2**. The survival curves derived from actual data are shown in Appendix (Figure S1). A significant association between exposure to BZF and decreased mortality or need for LT was observed in almost all risk groups at baseline except male gender (**Figure 3**).

Absolute clinical benefit and sample size calculation

The absolute clinical benefit of UDCA-BZF therapy as compared to UDCA alone was assessed using the NNT to prevent one additional death or LT (**Table 3**). On average, 29 (95% CI: 22 -46), 14 (10 – 22), and 8 (6 – 15) patients with UDCA would have to be added on BZF to prevent one death or LT in 5, 10, and 15 years, respectively. The estimated number of subjects that would need to be enrolled in a 5-year clinical trial with a 2-year recruitment period in order to have 80% power at a 5% significance level to detect a treatment effect on LT-free survival is 1000 individuals equally distributed between groups (500 in the control group and 500 in the treatment group).

Complementary analysis

A sensitivity analysis was conducted on all patients with available data registered between 1980 and 2017 (n=8180), consisting of 7030 (86%) patients with UDCA, of whom 6087 (74%) with UDCA monotherapy and 943 (12%) with BZF-UDCA therapy, and 1133 (14%) patients with no

treatment. In this full population, aHR of UDCA-BZF therapy *vs* UDCA alone for all-cause mortality or LT was 0.2305 (95%CI: 0.1498 – 0.3546; p<0.0001) while aHR of UDCA alone *vs* no treatment was 0.5278 (95%CI: 0.4495 – 0.6198; p<0.0001). Detailed results and corresponding survival curves are shown in Appendix (Tables S8 – S9, Figure S2).

DISCUSSION

In this nationwide retrospective cohort study of patients with PBC in Japan, combination of UDCA with BZF, as compared to UDCA alone, was significantly associated with a lower risk in all-cause and liver-related mortality or need for LT. These findings were consistent in almost all patient subgroups at baseline, including those with abnormal bilirubin or albumin levels, or advanced histologic stage. Since the main indication for BZF adjunctive therapy was biochemical resistance to UDCA, these results support the clinical efficacy of UDCA-BZF combination in patients with PBC and incomplete response to UDCA.

A 2-year placebo-controlled trial of BZF in PBC has recently shown biochemical efficacy in patients with an incomplete response to UDCA.[30] Improvement of pruritus reported in this trial has further been confirmed in a short-term, randomized study.[38] However, it has yet to be proven that these beneficial effects on biochemical features and symptoms of the disease can translate into lower mortality or need for LT. In this regard, it can be estimated from the present data that 1,000 patients equally recruited in the first 2 years of a 5-year placebo-controlled trial would be required to observe a difference in survival. It seems unlikely that such a large trial in PBC can be designed in the future.

Large-scale observational studies seem to be the only way to provide evidence for BZF clinical efficacy in PBC. The present cohort, where BZF was used as a *de facto* second-line therapy,[29] provided us with a unique opportunity to address this issue. While UDCA therapy, compared to no treatment, was confirmed to reduce mortality or need for LT by nearly 50%, in line with a recent report from the Global PBC Study Group,[13] BZF therapy was associated with a further 70% decrease in risk when added to UDCA. These findings, based on a large-scale retrospective data analysis, are the best currently available evidence of BZF efficacy in UDCA-resistant PBC. Whether BZF and UDCA combination therapy could benefit to all PBC patients, however, remains an outstanding question.[39]

Previous studies of BZF (or fenofibrate) long-term use in PBC have been reported.[32, 40-42] They were all limited to small or medium-sized PBC cohorts, including no more than 118 patients with fibrates combination therapy as compared with 943 in the present study. All but one has provided findings in line with our data. The only long-term prospective study available, an unblinded randomized trial of UDCA-BZF combination therapy, did not find an improvement in survival despite a significant reduction in the Mayo risk score.[40] However, this study, that included only 27 patients followed-up for 8 years, was not powered enough to assess hard endpoints such as death or LT.

Although BZF has an excellent safety profile during long-term use, a progressive increase in serum creatinine level has been reported as a potential concern. In the BEZURSO trial, creatinine levels in the BZF group increased 5% within the first 3 months and remained stable afterwards until 24 months.[30] Dose reduction or discontinuation of BZF could occur because of increased creatinine level.[30, 40] In the present cohort, data on renal function was lacking. Over 2000-2017, the estimated rate of permanent discontinuation of BZF was approximately 6%. Unfortunately, we were unable to determine whether drug cessation was related to creatinine elevation or other adverse effects like myalgias.

Our study has some limitations mainly related to its retrospective nature and inherent biases. In addition, many starting dates for UDCA or BZF, as well data on biochemical response to treatment were missing. If imputation of missing starting dates for UDCA was quite easy to assume, considering that treatment was likely initiated at diagnosis in all patients diagnosed after 1987,[9 34] imputing missing starting dates for BZF based on disease characteristics at diagnosis might appear questionable. However, this approach made sense since pre-treatment features have been shown to predict biochemical response to UDCA.[35, 36] In addition, the median time between original and imputed dates was marginal and we took care to valid our findings based on actual data. Nevertheless, whether non-captured, time-dependent confounders may have had an influence on results cannot be completely excluded.

In conclusion, in a large retrospective study of treatment effects in patients with PBC, the addition of BZF to UDCA was associated with improved prognosis. At this time, BZF is the only PBC drug to have shown efficacy evidence on the symptoms, biochemical markers, and prognosis of the disease.

Table 1. Characteristics of patients at diagnosis

Characteristic	Patients exposed to UDCA-only (n=3162)	Patients exposed to UDCA-BZF (n=746)	p-value
Age (year)	60.0 ± 11.7	55.7 ± 10.8	<0.0001
Missing data	0 (0%)	0 (0%)	
Gender			
Female	2679 (85%)	627 (84%)	0.4789
Male	483 (15%)	119 (16%)	
Missing data	0 (0%)	0 (0%)	
Pruritus			
Absent	2365 (75%)	542 (73%)	0.4796
Present	788 (25%)	202 (27%)	
Missing data	9 (0%)	2 (0%)	
Total bilirubin (mg/dL)	0.92 ± 1.22	0.99 ± 1.11	0.1277
Missing data	0 (0%)	0 (0%)	
ALP (xULN)	1.77 ± 1.36	2.31 ± 1.90	<0.0001
Missing data	0 (0%)	0 (0%)	
Albumin (g/L)	40.1 ± 5.0	40.8 ± 4.6	0.0012
Missing data	0 (0%)	0 (0%)	
Histologic stage			
Early stage (I-II)	1732 (55%)	453 (61%)	<0.0001
Late stage (III-IV)	264 (8%)	92 (12%)	(*)
Missing data	1166 (37%)	201 (27%)	
Center			
Tertiary	2690 (85%)	711 (95%)	<0.0001
Primary/secondary	472 (15%)	35 (5%)	
Missing data	0 (0%)	0 (0%)	
UDCA start period†			
2000 – 2004	853 (27%)	169 (23%)	0.0296
2005 – 2009	1056 (33%)	275 (37%)	
2010 – 2015	1253 (40%)	302 (40%)	

Data are expressed as mean ± standard deviation for continuous variables and number (%) for categorical variables. UDCA, ursodeoxycholic acid. BZF, bezafibrate. ALP, alkaline phosphatase. ULN, upper limit of normal range. P-values are those for the Student's t-test or the Fisher's exact test. (*) p=0.0288 when missing data are not considered. † The date of diagnosis was used when UDCA starting date was missing.

Table 2. Hazard ratio for death or liver transplantation in patients exposed to combination therapy versus UDCA only

Cox model	All-cause mortality or LT		Liver-related mortality or LT	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1	0.3196 (0.1927 – 0.5299)	<0.0001	0.3372 (0.1715 – 0.6631)	0.0016
Model 2†	0.3253 (0.1936 – 0.5466)	<0.0001	0.2748 (0.1336 – 0.5655)	0.0005
Model 3	0.2571 (0.1502 – 0.4401)	<0.0001	0.2513 (0.1221 – 0.5171)	0.0002
Model 4	0.2832 (0.1643 – 0.4880)	<0.0001	0.2649 (0.1252 – 0.5607)	0.0005
Model 5	0.2547 (0.1337 – 0.4850)	<0.0001	0.1882 (0.0745 – 0.4754)	0.0004

UDCA, ursodeoxycholic acid. LT, liver transplantation. HR, hazard ratio.

Model 1: time-dependent Cox regression model unadjusted for baseline covariates; Model 2: time-dependent Cox regression model adjusted for baseline covariates; Model 3: inverse probability of BZF treatment weighted Cox regression model unadjusted for baseline covariates; Model 4: inverse probability of BZF treatment weighted Cox regression model adjusted for baseline covariates; Model 5: time-dependent Cox regression model adjusted for baseline covariates without imputation of missing covariates at baseline and BZF starting dates.

† Primary model.

Table 3. Number needed to treat with combination therapy to prevent one additional death or liver transplantation compared to UDCA only

Treatment duration	All-cause mortality or LT		Liver-related mortality or LT	
	NNT	95% CI	NNT	95% CI
5 years	29	22 – 46	48	34 – 81
10 years	14	10 – 22	22	15 – 39
15 years	8	6 – 15	13	9 – 30

UDCA, ursodeoxycholic acid. LT, liver transplantation. NNT, number needed to treat. CI, confidence interval.

FIGURE LEGENDS

Fig. 1. Flow chart of the study.

UDCA, ursodeoxycholic acid; BZF, bezafibrate; LT, liver transplantation.

Fig. 2. Survival without liver transplantation and survival free of liver-related death or liver transplantation according to treatment exposure.

Upper panel shows all-cause mortality or liver transplantation. Lower panel shows liver-related mortality or liver transplantation. Left panel shows unadjusted survival curves. Right panel shows multivariable-adjusted survival curves. Survival rates were estimated using time-dependent Cox model unadjusted for baseline covariates (model 1) and adjusted for baseline covariates (center type, age, gender, year of diagnosis, pruritus, total bilirubin, ALP, albumin, and histologic stage), defined as the primary model (model 2). Levels of significance: $p<0.0001$ for both upper panels (unadjusted or multivariable-adjusted survival for all-cause mortality or liver transplantation), $p=0.0016$ for lower and left panel (unadjusted survival for liver-related mortality or liver transplantation), $p=0.0005$ for lower and right panel (multivariable-adjusted survival for liver-related mortality or liver transplantation).

Fig. 3. Adjusted hazard ratio of combination therapy versus UDCA only for all-cause death or liver transplantation across different risk groups at baseline

HR, hazard ratio; UDCA, ursodeoxycholic acid; BZF, bezafibrate; ALP, alkaline phosphatase.

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Association of bezafibrate with transplant-free survival in patients with primary biliary cholangitis

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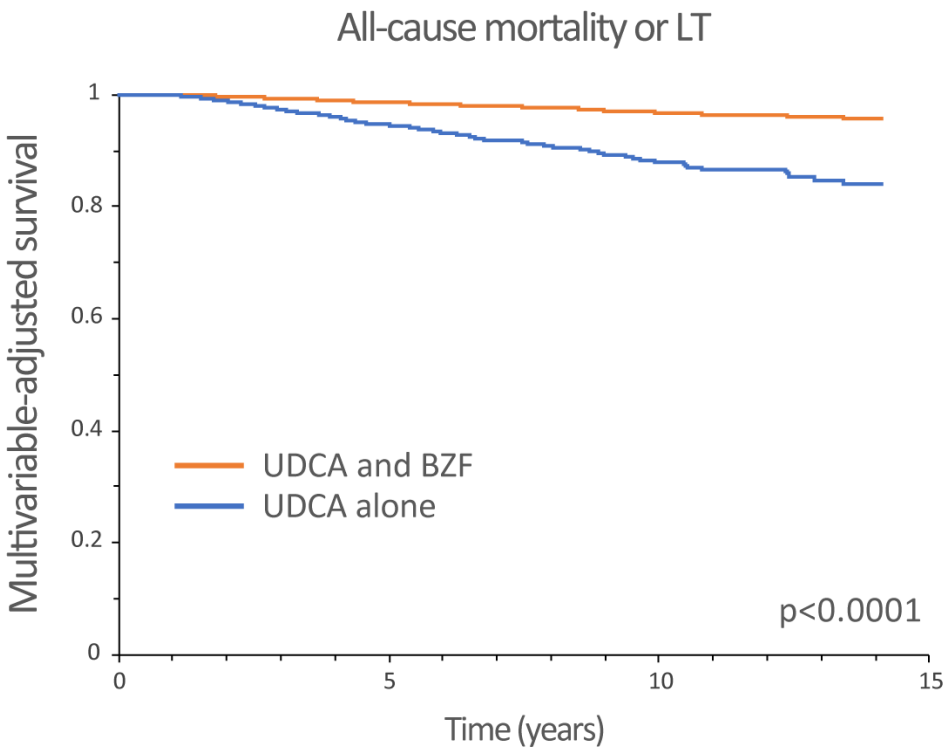
Fig. S1. Multivariable-adjusted survival curves after exclusion of missing BZF starting dates and baseline missing data (p-values for BZF time-dependent, multivariable-adjusted Cox model)



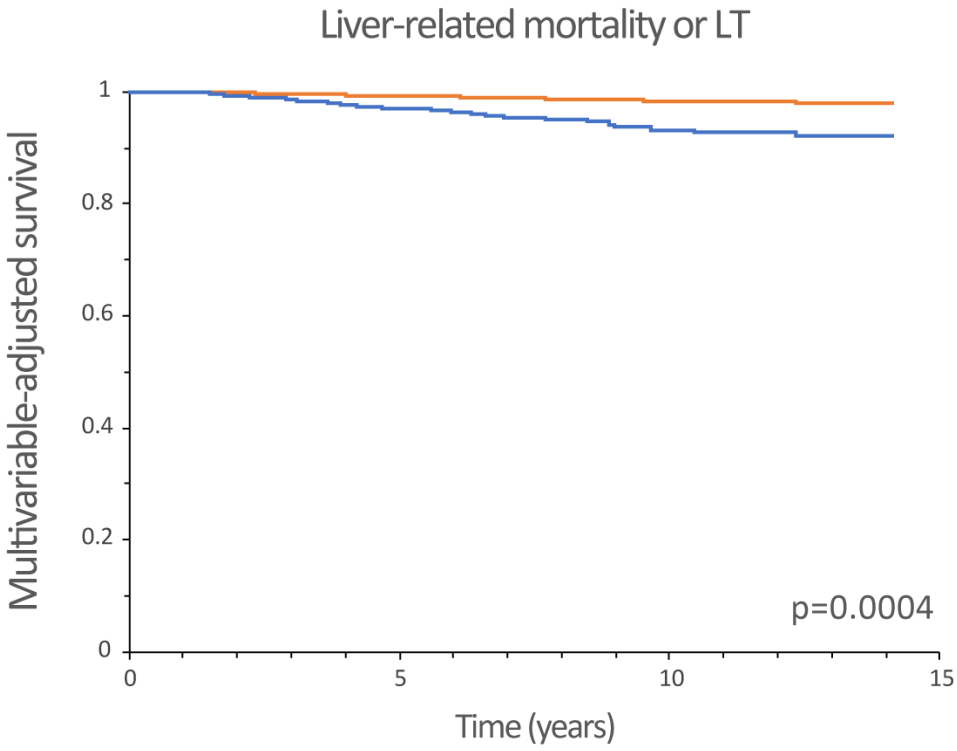
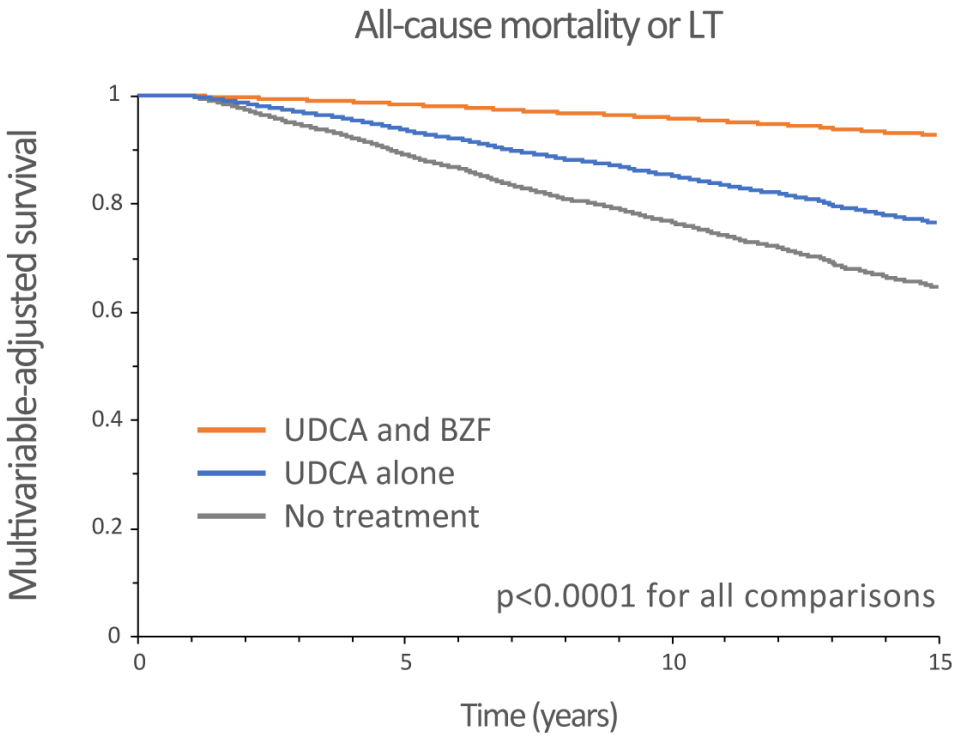


Fig. S2. Multivariable-adjusted survival curves as predicted by model 2 after inclusion of all analyzable patients since 1980 (p-values for BZF and UDCA time-dependent, multivariable-adjusted Cox model)



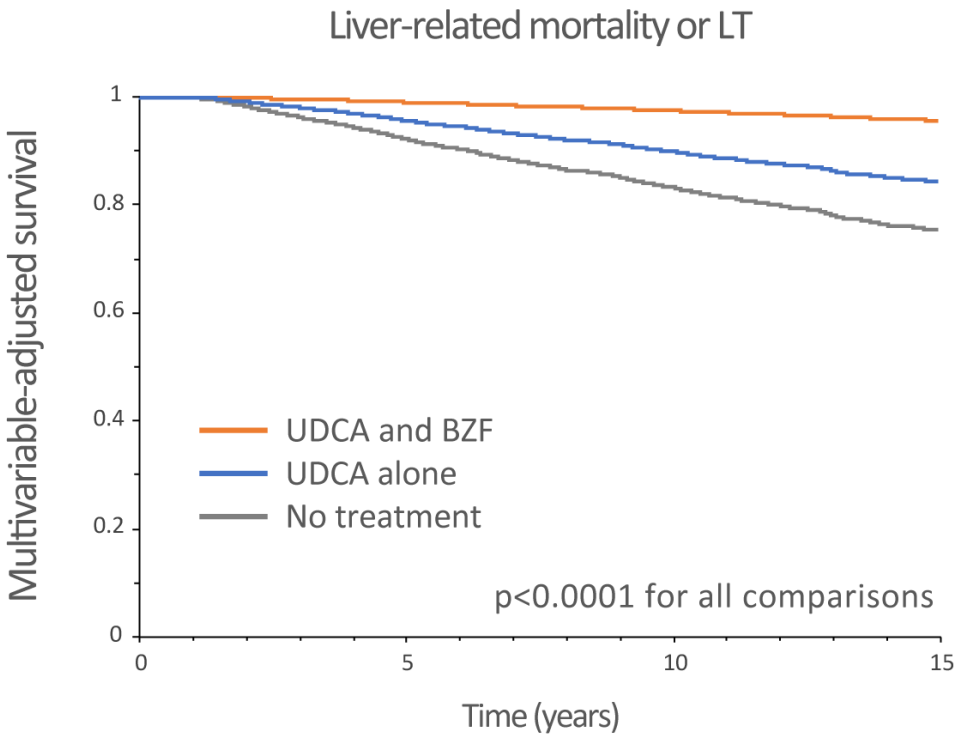


Table S1. Crude incidence rates (95% confidence interval) per 1000 person-years of the main clinical outcomes by treatment group

Outcomes	UDCA-only	UDCA-BZF	P-value
All-cause death	9.62 (8.24 – 11.16)	4.32 (2.60 – 6.78)	0.0005
Non-liver-related death	5.01 (4.04 – 6.15)	1.78 (0.78 – 3.52)	0.0029
Liver-related death	4.55 (3.63 – 5.64)	2.54 (1.29 – 4.53)	0.0697
Liver transplantation	1.15 (0.70 – 1.78)	0.25 (0.00 – 1.42)	0.0928

P-values are the mid-p values for the Fisher's exact test.

Table S2. Parameters of Model 2 (BZF time-dependent, multivariable-adjusted, 100-dataset imputation of missing BZF starting dates and baseline data): all-cause mortality or liver transplantation

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P-value
UDCA-BZF (*vs* UDCA-only)	-1.1231	0.2648	-1.6422	-0.6040	-4.24	<0.0001
Gender (male)	0.5724	0.1801	0.2195	0.9254	3.18	0.0015
Age (per decade)	0.3906	0.0756	0.2424	0.5389	5.16	<0.0001
Pruritus (yes)	0.7999	0.1659	0.4747	1.1251	4.82	<0.0001
ALP (> 1.67 xULN)	0.4822	0.1518	0.1846	0.7797	3.18	0.0015
T. bilirubin (> 1.5 mg/dL)	0.9958	0.1962	0.6113	1.3804	5.08	<0.0001
Albumin (< 35 g/L)	0.9763	0.1948	0.5944	1.3583	5.01	<0.0001
Histological stage (III-IV)	0.7542	0.1980	0.3653	1.1431	3.81	0.0002
Diagnosis era (per decade)	-0.1039	0.1704	-0.4379	0.2300	-0.61	0.5419
Tertiary referral center (no)	-0.1493	0.2533	-0.6457	0.3471	-0.59	0.5556

SD, standard error. LL, lower limit. UL, upper limit.

Table S3. Parameters of Model 2 (BZF time-dependent, multivariable-adjusted, 100-dataset imputation of missing BZF starting dates and baseline data): liver-related mortality or liver transplantation

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P-value
UDCA-BZF (*vs* UDCA-only)	-1.2917	0.3682	-2.0133	-0.5701	-3.51	0.0005
Gender (male)	0.2403	0.2831	-0.3145	0.7950	0.85	0.396
Age (per decade)	0.1369	0.0905	-0.0405	0.3142	1.51	0.1304
Pruritus (yes)	1.4309	0.2504	0.9402	1.9217	5.71	<0.0001
ALP (> 1.67 xULN)	0.7191	0.2217	0.2846	1.1536	3.24	0.0012
T. bilirubin (> 1.5 mg/dL)	0.9368	0.2470	0.4526	1.4210	3.79	0.0002
Albumin (< 35 g/L)	1.1003	0.2560	0.5984	1.6023	4.30	<0.0001
Histological stage (III-IV)	0.9290	0.2689	0.4009	1.4572	3.46	0.0006
Diagnosis era (per decade)	-0.2879	0.2479	-0.7738	0.1980	-1.16	0.2455
Tertiary referral center (no)	-0.4728	0.4057	-1.2679	0.3223	-1.17	0.2438

SD, standard error. LL, lower limit. UL, upper limit.

Table S4. Parameters of Model 4 (BZF IPTW, BZF time-dependent, multivariable-adjusted, 100-dataset imputation of missing BZF starting dates and baseline data): all-cause mortality or liver transplantation

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P-value
UDCA-BZF (*vs* UDCA-only)	-1.2617	0.2777	-1.8059	-0.7175	-4.54	<0.0001
Gender (male)	0.4932	0.1859	0.1289	0.8576	2.65	0.0080
Age (per decade)	0.3403	0.0772	0.1890	0.4916	4.41	<0.0001
Pruritus (yes)	0.8446	0.1688	0.5137	1.1755	5.00	<0.0001
ALP (> 1.67 xULN)	0.5190	0.1532	0.2186	0.8193	3.39	0.0007
T. bilirubin (> 1.5 mg/dL)	1.0101	0.2002	0.6176	1.4025	5.04	<0.0001
Albumin (< 35 g/L)	0.9219	0.2004	0.5290	1.3149	4.60	<0.0001
Histological stage (III-IV)	0.8141	0.1948	0.4318	1.1963	4.18	<0.0001
Diagnosis era (per decade)	-0.0922	0.1688	-0.4230	0.2386	-0.55	0.5850
Tertiary referral center (no)	-0.1847	0.2530	-0.6806	0.3112	-0.73	0.4654

SD, standard error. LL, lower limit. UL, upper limit.

Table S5. Parameters of Model 4 (BZF IPTW, BZF time-dependent, multivariable-adjusted, 100-dataset imputation of missing BZF starting dates and baseline data): liver-related mortality or liver transplantation

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P-value
UDCA-BZF (*vs* UDCA-only)	-1.3282	0.3825	-2.0779	-0.5785	-3.47	0.0005
Gender (male)	0.1703	0.2915	-0.4011	0.7417	0.58	0.5591
Age (per decade)	0.0954	0.0923	-0.0855	0.2762	1.03	0.3014
Pruritus (yes)	1.4337	0.2559	0.9321	1.9353	5.60	<0.0001
ALP (> 1.67 xULN)	0.7442	0.2214	0.3101	1.1782	3.36	0.0008
T. bilirubin (> 1.5 mg/dL)	0.9960	0.2580	0.4902	1.5018	3.86	0.0001
Albumin (< 35 g/L)	1.0241	0.2617	0.5111	1.5372	3.91	<0.0001
Histological stage (III-IV)	0.9894	0.2644	0.4704	1.5084	3.74	0.0002
Diagnosis era (per decade)	-0.2593	0.2414	-0.7325	0.2138	-1.07	0.2827
Tertiary referral center (no)	-0.4912	0.4046	-1.2842	0.3018	-1.21	0.2248

SD, standard error. LL, lower limit. UL, upper limit.

Table S6. Parameters of Model 5 (BZF time-dependent, multivariable-adjusted, exclusion of missing BZF starting dates and baseline data): all-cause mortality or liver transplantation

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P-value
UDCA-BZF (*vs* UDCA-only)	-1.3678	0.3287	-2.0121	-0.7236	-4.16	<0.0001
Gender (male)	0.5359	0.1840	0.1753	0.8965	2.91	0.0036
Age (per decade)	0.4019	0.0773	0.2505	0.5533	5.20	<0.0001
Pruritus (yes)	0.8624	0.1685	0.5321	1.1927	5.12	<0.0001
ALP (> 1.67 xULN)	0.5146	0.1526	0.2155	0.8136	3.37	0.0007
T. bilirubin (> 1.5 mg/dL)	0.9076	0.1968	0.5219	1.2934	4.61	<0.0001
Albumin (< 35 g/L)	0.9653	0.1975	0.5781	1.3524	4.89	<0.0001
Histological stage (III-IV)	0.7285	0.2066	0.3225	1.1345	3.53	0.0005
Diagnosis era (per decade)	-0.1290	0.1751	-0.4722	0.2141	-0.74	0.4612
Tertiary referral center (no)	-0.1531	0.2545	-0.6519	0.3457	-0.60	0.5475

SD, standard error. LL, 95%CI lower limit. UL, 95%CI upper limit.

Table S7. Parameters of Model 5 (BZF time-dependent, multivariable-adjusted, exclusion of missing BZF starting dates and baseline data): liver-related mortality or liver transplantation

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P-value
UDCA-BZF (*vs* UDCA-only)	-1.6703	0.4728	-2.5969	-0.7437	-3.53	0.0004
Gender (male)	0.2315	0.2901	-0.3372	0.8002	0.80	0.4249
Age (per decade)	0.1524	0.0937	-0.0312	0.3360	1.63	0.1037
Pruritus (yes)	1.5648	0.2611	1.0531	2.0766	5.99	<0.0001
ALP (> 1.67 xULN)	0.7815	0.2224	0.3455	1.2175	3.51	0.0004
T. bilirubin (> 1.5 mg/dL)	0.8410	0.2448	0.3611	1.3209	3.44	0.0006
Albumin (< 35 g/L)	1.0641	0.2602	0.5539	1.5742	4.09	<0.0001
Histological stage (III-IV)	0.9195	0.2813	0.3665	1.4725	3.27	0.0012
Diagnosis era (per decade)	-0.2979	0.2605	-0.8085	0.2127	-1.14	0.2529
Tertiary referral center (yes)	-0.4672	0.4082	-1.2673	0.3330	-1.14	0.2525

SD, standard error. LL, lower limit. UL, upper limit.

Table S8. Parameters of Model 2 (BZF time-dependent, multivariable-adjusted, 10-dataset imputation of missing BZF starting dates and baseline data) after inclusion of all analyzable patients since 1980: all-cause mortality or liver transplantation.

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P
UDCA-BZF (*vs* UDCA-only)	-2.141651	0.236964	-2.60616	-1.67714	-9.04	<0.0001
UDCA-only (*vs* Untreated)	-0.638162	0.083841	-0.47369	-0.80264	-7.61	<0.0001
Gender (male)	0.484904	0.090192	0.30811	0.66170	5.38	<0.0001
Age (per decade)	0.228448	0.032438	0.16484	0.29206	7.04	<0.0001
Pruritus (yes)	1.006241	0.067659	0.87347	1.13901	14.87	<0.0001
ALP (> 1.67 xULN)	0.262714	0.079933	0.10287	0.42256	3.29	0.0022
T. bilirubin (> 1.5 mg/dL)	1.028014	0.077719	0.87561	1.18042	13.23	<0.0001
Albumin (< 35 g/L)	0.712757	0.095776	0.52355	0.90197	7.44	<0.0001
Histological stage (III-IV)	0.555517	0.084296	0.38769	0.72334	6.59	<0.0001
Diagnosis era (per decade)	-0.235064	0.045188	-0.32367	-0.14646	-5.20	<0.0001
Tertiary referral center (no)	-0.357961	0.089745	-0.53400	-0.18193	-3.99	<0.0001

SD, standard error. LL, lower limit. UL, upper limit.

Table S9. Parameters of model 2 (BZF time-dependent, multivariable adjusted, 10-dataset imputation of missing BZF starting dates and baseline data) after inclusion of all analyzable patients since 1980: liver-related mortality or liver transplantation

Parameter	Estimate	SD	95%CI LL	95%CI UL	t-test	P
UDCA-BZF (*vs* UDCA-only)	-1.604819	0.286463	-2.16629	-1.04335	-5.60	<0.0001
UDCA-only (*vs* Never-treated)	-0.686600	0.100929	-0.48864	-0.88456	-6.80	<0.0001
Gender (male)	0.331910	0.117433	0.10171	0.56211	2.83	0.0047
Age (per decade)	0.014742	0.037957	-0.05969	0.08918	0.39	0.6978
Pruritus (yes)	1.241546	0.088035	1.06854	1.41455	14.10	<0.0001
ALP (> 1.67 xULN)	0.321271	0.105823	0.10795	0.53459	3.04	0.0040
T. bilirubin (> 1.5 mg/dL)	1.231081	0.089981	1.05455	1.40761	13.68	<0.0001
Albumin (< 35 g/L)	0.727706	0.113454	0.50280	0.95261	6.41	<0.0001
Histological stage (III-IV)	0.603724	0.096301	0.41305	0.79439	6.27	<0.0001
Diagnosis era (per decade)	-0.231400	0.053992	-0.33727	-0.12553	-4.29	<0.0001
Tertiary referral center (no)	-0.471934	0.111893	-0.69145	-0.25242	-4.22	<0.0001

SD, standard error. LL, 95%CI lower limit. UL, 95%CI upper limit.