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UK-Wide Multicenter Evaluation of Second-line Therapies in Primary Biliary Cholangitis

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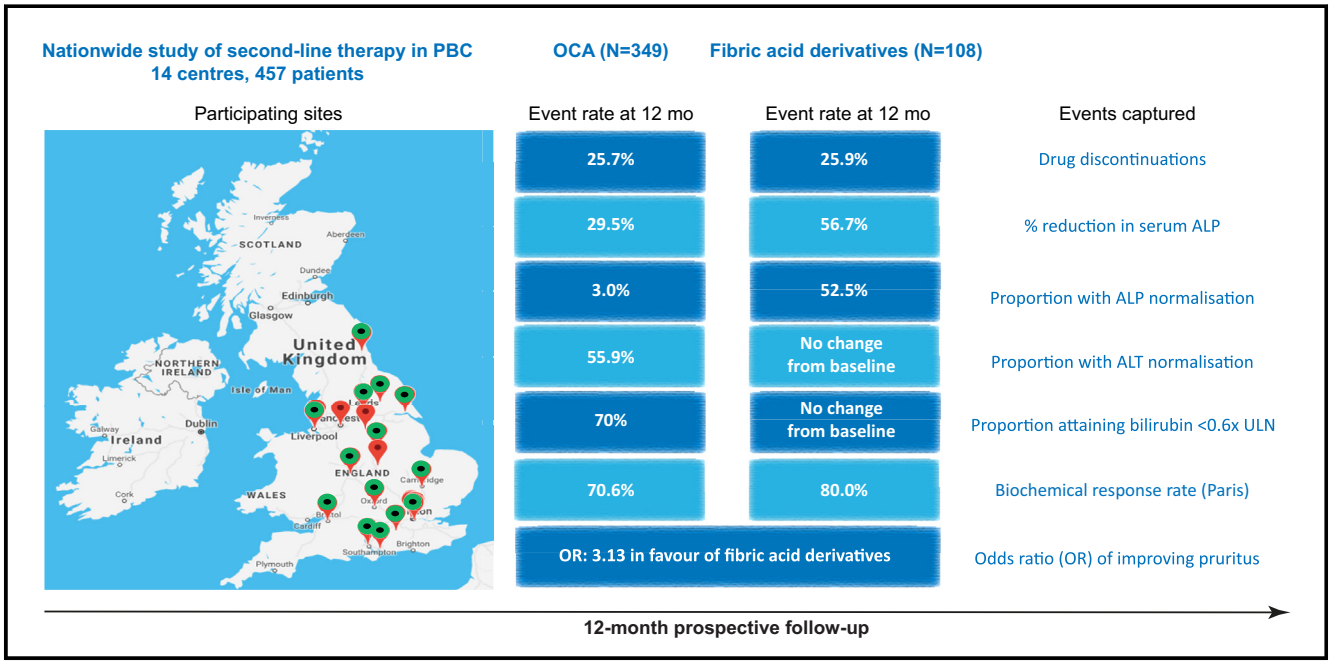

Abbreviations used in this paper: ALP, alkaline phosphatase; ALT, alanine transaminase; CI, confidence interval; FXR, farnesoid X receptor; OCA, obeticholic acid; ODN, Operational Delivery Network; OR, odds ratio; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; UK, United Kingdom; ULN, upper limit of normal.

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Most current article

BACKGROUND & AIMS: **Thirty-to-forty percent of patients with primary biliary cholangitis inadequately respond to ursodeoxycholic acid. Our aim was to assemble national, real-world data on the effectiveness of obeticholic acid (OCA) as a second-line treatment, alongside non-licensed therapy with fibric acid derivatives (bezafibrate or fenofibrate).**

METHODS: **This was a nationwide observational cohort study conducted from August 2017 until June 2021.**

RESULTS: **We accrued data from 457 patients; 349 treated with OCA and 108 with fibric acid derivatives. At baseline/pre-treatment, individuals in the OCA group manifest higher risk features compared with those taking fibric acid derivatives, evidenced by more elevated alkaline phosphatase values, and a larger proportion of individuals with cirrhosis, abnormal bilirubin, prior non-response to ursodeoxycholic acid, and elastography readings >9.6kPa ($P < .05$ for all). Overall, 259 patients (OCA) and 80 patients (fibric acid derivatives) completed 12 months of second-line therapy, yielding a dropout rate of 25.7% and 25.9%, respectively. At 12 months, the magnitude of alkaline phosphatase reduction was 29.5% and 56.7% in OCA and fibric acid groups ($P < .001$). Conversely, 55.9% and 36.4% of patients normalized serum alanine transaminase and bilirubin in the OCA group ($P < .001$). The proportion with normal alanine transaminase or bilirubin values in the fibric acid group was no different at 12 months compared with baseline. Twelve-month biochemical response rates were 70.6% with OCA and 80% under fibric acid treatment ($P = .121$). Response rates between treatment groups were no different on propensity-score matching or on sub-analysis of high-risk groups defined at baseline.**

CONCLUSION: **Across the population of patients with primary biliary cholangitis in the United Kingdom, rates of biochemical response and drug discontinuation appear similar under fibric acid and OCA treatment.**

Keywords: Bezafibrate; Cirrhosis; Fenofibrate; Fibric Acid; Obeticholic Acid; Cholestasis; Farnesoid-X-receptor (FXR); Fibrates; Peroxisome Proliferator Activated Receptor (PPAR).

Primary biliary cholangitis (PBC) is a chronic progressive liver disease, in which clinical outcomes are dictated by the development of cirrhosis and need for transplantation.[1] Timely treatment with ursodeoxycholic acid (UDCA) is associated with improved transplant-free survival[2–5]; however, 30%–40% of patients have an incomplete response to therapy, and a small minority suffer intolerable side effects. In the United States, the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) was approved as a second-line therapy in 2016.[6,7] The long-term extension studies that followed index clinical trials show sustained improvements in serum alkaline phosphatase (ALP) and alanine transaminase (ALT),[8] with emerging data using historic controls suggesting improved transplant-free survival following 5 years of treatment.[9]

Non-licensed interventions with fibric acid derivatives have also been shown to attenuate cholestasis.[10,11] Controlled-trial data demonstrate that >30% of UDCA non-responders attain complete normalization in liver biochemistry with the addition of bezafibrate,[12] and a subset of patients report improvements in pruritus.[13] Moreover, observational data from Japan show a significant reduction in all-cause and liver-related mortality under UDCA and bezafibrate combination therapy compared with UDCA alone.[14]

In the United Kingdom (UK), prescription of new and high-cost drugs (such as OCA) is wholly publicly funded as part of the National Health Service, with prescriptions restricted to a finite number of specialist centers serving a geographically defined Operational Delivery Network (ODN). We sought to use this national program to compare the efficacy of second-line therapy in PBC, in parallel to safety and self-reported drug tolerability. A further exploratory aim was to seek experience of second-line therapy in cirrhosis, alongside those failing to meet conventional biochemical response criteria with UDCA alone.

Methods

We analyzed data from a nationwide cohort of patients with an established diagnosis of PBC who were referred for second-line therapy in accordance with National Guidance.[15,16] All ODNs across England were invited to submit data prospectively, of which 14 participated including 5 liver transplant centers (Figure 1, *A*). The study was conducted from August 2017 (the UK market entry point for OCA), with study entry permitted until June 2020 and follow-up continuing to June 2021. Individuals with prior exposure to FXR agonists or peroxisome proliferator-activated receptor agonists (including clinical trials), those treated with OCA/fibric acid derivatives in combination, or previously treated with either agent only to

switch to the other, were excluded. Full inclusion/exclusion criteria, the nature of patient and public involvement, safety and tolerability assessment, and statistical methodology are presented in the Supplementary Appendix.

Treatment efficacy was quantified by the proportion of patients attaining biochemical response. Primarily, this is presented according to Paris I criteria, given extensive validation in the UK population, the fact it encompasses transaminases, bilirubin, and ALP values, and its applicability to all patients with PBC rather than only those with early stage disease. Validation of primary outcome data was also performed following propensity score matching according to baseline covariates, on the intent-to-treat population, and on predefined 'high-risk' subgroups defined pre-treatment. Biochemical response according to Barcelona, Toronto, Paris II, and POISE definitions are presented in the Supplementary Appendix. Exploratory analyses were conducted to determine the rates of putative drug-induced liver injury, predictors of response to OCA and fibric acid derivatives, and to interrogate relevant statistical interaction terms between individual covariates (Supplementary Appendix).

What you need to know

Background

- Thirty to forty percent of patients with primary biliary cholangitis (PBC) inadequately respond to first-line treatment with ursodeoxycholic acid (UDCA).
- Second-line therapy consists of either obeticholic acid (OCA) or fibric acid derivatives (bezafibrate or fenofibrate).
- However, data comparing the effectiveness of the two treatments is limited.

Findings

- Across a nationwide cohort of patients with PBC, the rates of biochemical response at 12 months were similar between treatment groups.
- The magnitude of reduction in serum alkaline phosphatase was greater in patients treated with fibric acid derivatives.
- Rates of normalization in alanine aminotransferase and bilirubin were greater in the group treated with OCA.
- OCA led to an improvement in all liver biochemical parameters in cirrhotic patients.
- Rates of treatment discontinuation exceeded 20% and were not different between the OCA and fibric acid groups.

Implications for patient care

- This study provides validation of treatment efficacy with regard to second-line therapies.
- The choice of second-line treatment may be guided by the desired biochemical end point of therapy.
- Drug discontinuation rates remain high, irrespective of treatment group, reinforcing the need for new treatment paradigms in PBC.

Results

Characteristics of the Patient Population

We report data from 457 individuals who received second-line therapy for PBC (n = 349 OCA, n = 48 bezafibrate, n = 60 fenofibrate). Given the comparatively low numbers, patients in the bezafibrate and fenofibrate treatment arms were pooled for downstream analysis (Supplementary Table 1). Overall, patients were mostly women (90.4%) with a median age at PBC diagnosis of 47 years (interquartile range, 41–54 years), and the majority were UDCA treated (88.3%). Prior to initiation of second-line therapy, the OCA group manifest higher-risk clinical features with greater baseline ALP values (2.89 × upper limit of normal [ULN] vs 2.27 × ULN; $P <$ .001), liver stiffness values (9.5 vs 7.1 kPa; $P = .002$), and a larger representation by patients with cirrhosis (16.5% vs 8.3%; $P = .035$), prior biochemical non-response (63.5% vs 45.4%; $P = .001$), and/or an abnormal bilirubin (22.1% vs 12%; $P = .02$). At the time of analysis, the proportion of patients completing 12 months of second-line therapy was no different between OCA- and fibric acid-treated groups (74.2% vs. 74.1%, $P = .87$) (Figure 1, *B*).

On-treatment Changes in Liver Biochemistry

Serum ALT and ALP values declined significantly in both treatment groups (Figure 2), with the magnitude of ALP reduction at month 12 being greater under fibric acid therapy than with OCA treatment (56.7% and 29.5%, $P <$ .001) (Supplementary Figure 1). Of patients who completed 12 months of second-line therapy, 8 of 259 (3%) and 42 of 80 (52.5%) attained normalization in serum ALP values ($P <$ .001 between groups).

By contrast, the proportion of patients attaining complete normalization in serum ALT (from an abnormal baseline value) increased significantly over time under OCA therapy, but not following treatment with fibric acid derivatives (Figure 3). At 12 months, the proportion of patients having normal ALT values was 55.9% and 32.5% in the OCA and fibric acid derivative groups, respectively ($P <$ .001 between treatment groups).

Serum bilirubin did not fall significantly in either group (Supplementary Figure 2). However, of patients having elevated baseline values in the OCA group, 36.4% normalized bilirubin at 12 months ($P <$ .001). Moreover, in a restricted analysis of patients having elevated bilirubin values >0.6 × ULN (a threshold used for stratifying risk in PBC),[17] we observed significant reductions in serum bilirubin under OCA treatment (Supplementary

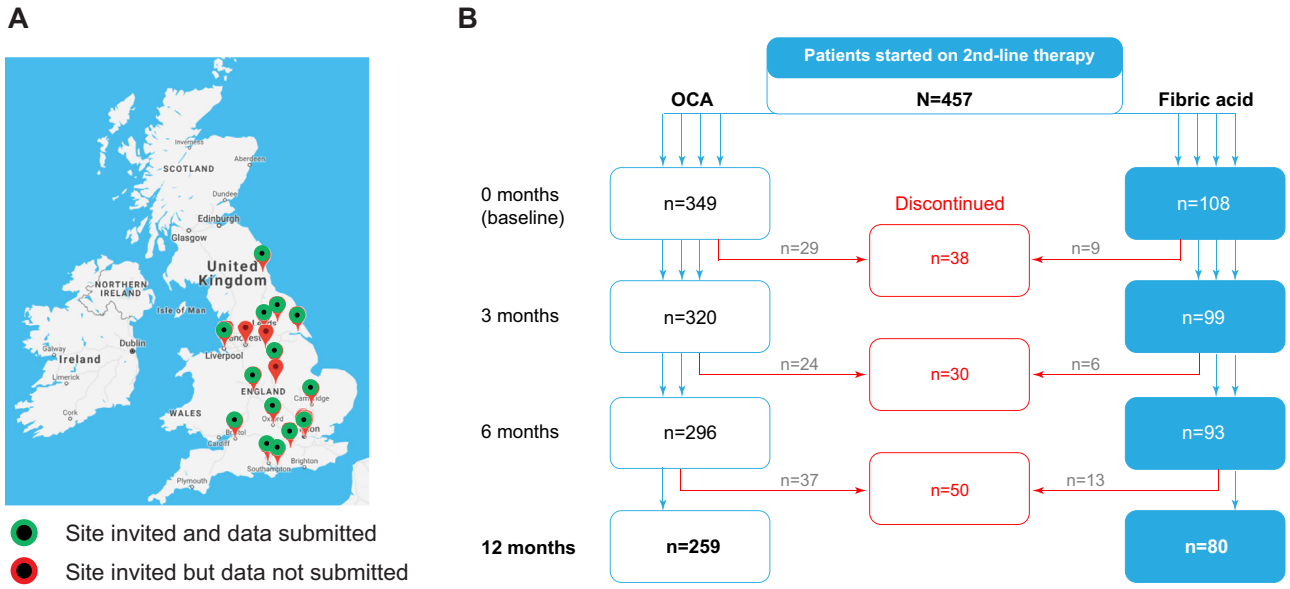

Figure 1. Participating sites and study population. Between August 2017 and June 2021, data was accrued from a total of 457 individuals across 14 of 24 UK centers (*green*) (*A*). Indicative numbers of patients completing 3, 6, and 12 months of treatment are shown in (*B*).

Figure 3). The proportion of patients with bilirubin values <0.6 × ULN rose from 58% at baseline (n = 203/349) to 70% following 12 months of OCA (n = 180/257; $P = .003$). Reductions in serum bilirubin were not significant under fibric acid therapy, even when restricting analysis to those with an abnormal bilirubin, or among those with baseline values >0.6 × ULN (Supplementary Figures 2 and 3).

Biochemical Response Rates

Of patients completing 12 months of treatment, the proportion of patients attaining biochemical response (Figure 4) was not significantly different between the OCA- and fibric acid-treated groups (71% and 80%; $P = .141$). No significant differences in biochemical response rate were observed in the putative intent-to-treat population (52.4% and 59.3%; $P = .21$), following propensity score matching for baseline characteristics (79.7% and 77.1%; $P = .713$) (Supplementary Tables 2, 3, and 4), or in subgroup analyses stratified by baseline covariates that differed between treatment groups (Supplementary Table 5). Biochemical response rates according to Barcelona, Paris II, Toronto, and POISE criteria are presented in Supplementary Figure 4 and Supplementary Table 4).

Treatment Experience in Cirrhosis

As patients with cirrhosis were under-represented in the fibric acid cohort (n = 9), subanalysis of treatment efficacy was restricted to those under OCA therapy (n = 57). Of the latter, 20 discontinued treatment before meeting the 12-month end of follow-up period; 7 patients developed gastrointestinal intolerance, whereas the remainder discontinued because of deterioration in biochemistry, disease progression, decompensation, and worsening pruritus.

In the 37 patients completing 12 months of OCA treatment, significant reductions in serum ALP and ALT values were observed from as early as 3 months on OCA and continued until month 12 (Supplementary Figure 5, *A–B*), and the proportion of patients having elevated bilirubin values >0.6 × ULN decreased from 84% to 25% ($P < .001$). The proportion of patients meeting biochemical response increased from 44.8% (n = 26/57) at baseline to 56.8% (n = 21/37) following 12 months of OCA therapy ($P = .03$).

Factors Associated With Biochemical Response

On univariate regression analysis, older age and concomitant UDCA therapy were positively associated with attaining biochemical response on OCA therapy, whereas a history of pruritus and elevated baseline ALT, ALP, or bilirubin values, were all associated with non-response (Table 1). In a multivariable model, older age, absence of pruritus at baseline, concomitant UDCA use, and baseline ALP and bilirubin retained predictive value. In the fibric acid derivative group, older age at starting second-line treatment, elevated baseline ALT, ALP, or bilirubin, or features of advanced liver disease (cirrhosis, splenomegaly) were negatively associated with the likelihood of attaining biochemical response. In a multivariable model (Table 1), elevated baseline ALT retained negative predictive value.

Observing the PBC cohort in its entirety, the choice of second-line treatment was not a predictor of biochemical

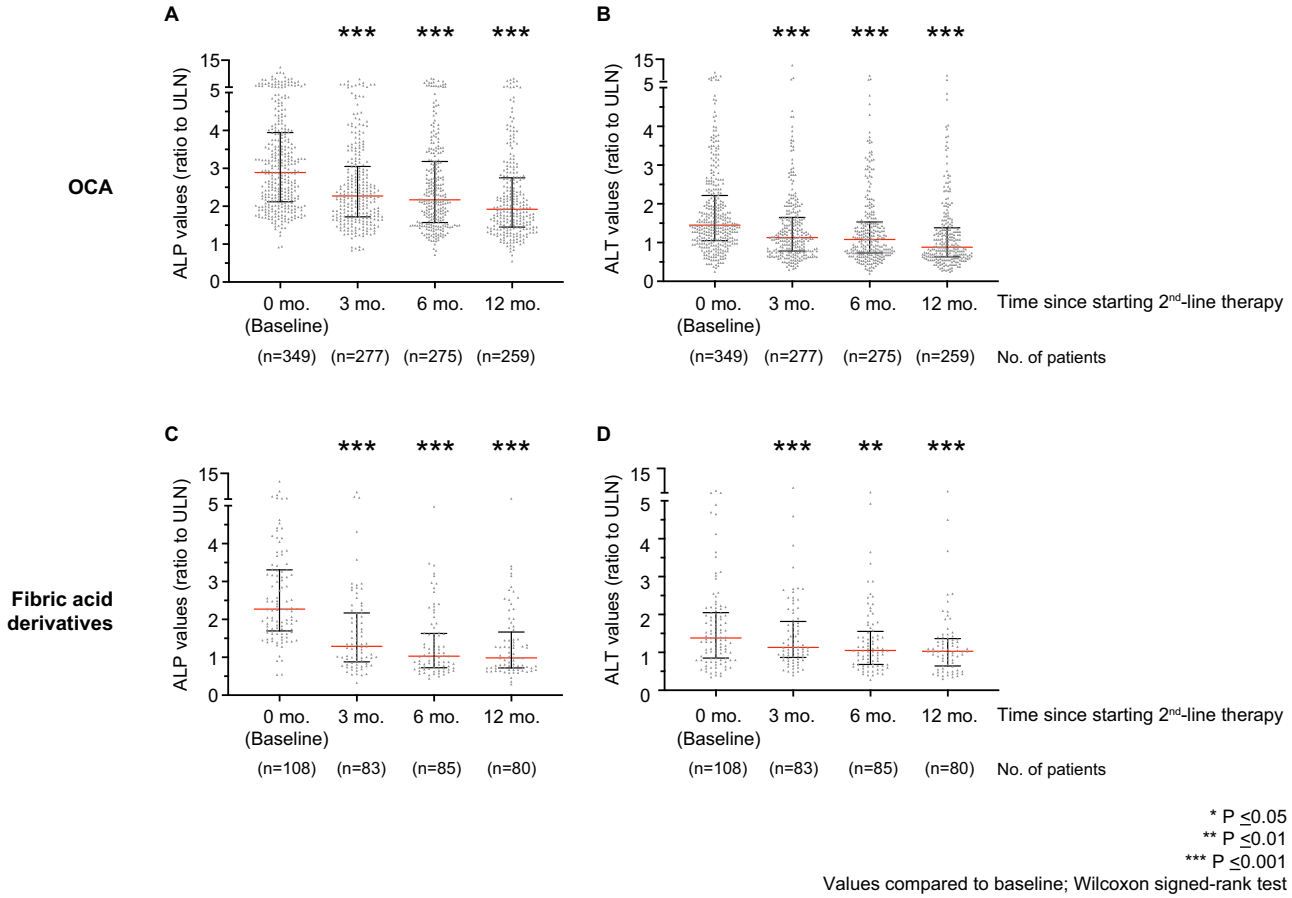

Figure 2. On-treatment biochemical changes. Serum ALP and ALT values are presented for the OCA (*A–B*) and fibric acid (*C–D*) treatment groups, respectively. Values expressed as a ratio to the ULN, with *red lines* indicating the median, and *black whiskers* indicating the interquartile range. *Asterisks* indicate significant *P* values when comparing matched patient data at specific timepoints with readings taken at baseline (Wilcoxon signed-rank test). n = 43 and n = 21 patients in the OCA group and n = 16 and n = 8 in the fibric acid group did not have blood tests performed at 3 and 6 months, respectively, but continued therapy until month 12.

response at 12 months, whereas age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.00–1.08), concomitant UDCA therapy (OR, 3.14; 95% CI, 1.18–8.36), pruritus status (OR, 0.40; 95% CI, 0.21–0.77), and baseline ALT (OR, 0.69; 95% CI, 0.48–0.98), ALP (OR, 0.67; 95% CI, 0.54–0.84), and bilirubin values (OR, 0.89; 95% CI, 0.86–0.93) retained statistical significance (Supplementary Table 6). The percentage accuracy classification of the model was 83.3% and was no different when the second-line treatment group was forced into multivariable regression analysis (Supplementary Table 6). However, analysis of statistical interaction terms identified an association between specific baseline covariates. Herein, the effects of pruritus status, serum ALT, and serum ALP values were moderated by treatment group with regards the probability of biochemical response (Supplementary Table 7; Figure 5). The percentage accuracy classifications for stepwise multivariable analyses incorporating different interaction terms were similar to the original model (data not shown).

In subanalysis of our propensity score-matched cohort, moderator effects of baseline ALT and ALP values were retained with regards probability of biochemical response to treatment (Supplementary Figure 6). However, the probability of biochemical response to OCA or fibric acid derivatives no longer differed according to baseline pruritus status.

Clinical Events

Across our intent-to-treat population, 9.2% of individuals (32/349) sustained at least one clinical event within 12 months of starting OCA. These encompassed hepatocellular carcinomas (n = 2), decompensation (n = 14; 7 ascites, 2 encephalopathy, and 7 individuals experiencing variceal bleeding), referral for transplantation (n = 14), or death from any cause (n = 10). In the fibric acid group, 14 of 108 patients (13.0%) developed a clinical event; namely hepatocellular carcinoma (n = 1), decompensation (n = 6; including 3 patients who developed ascites, 3 an episode of encephalopathy, and 1 variceal bleed), referral for transplantation (n = 4), and death from any cause (n = 7). The proportion of individuals experiencing at least one clinical event during

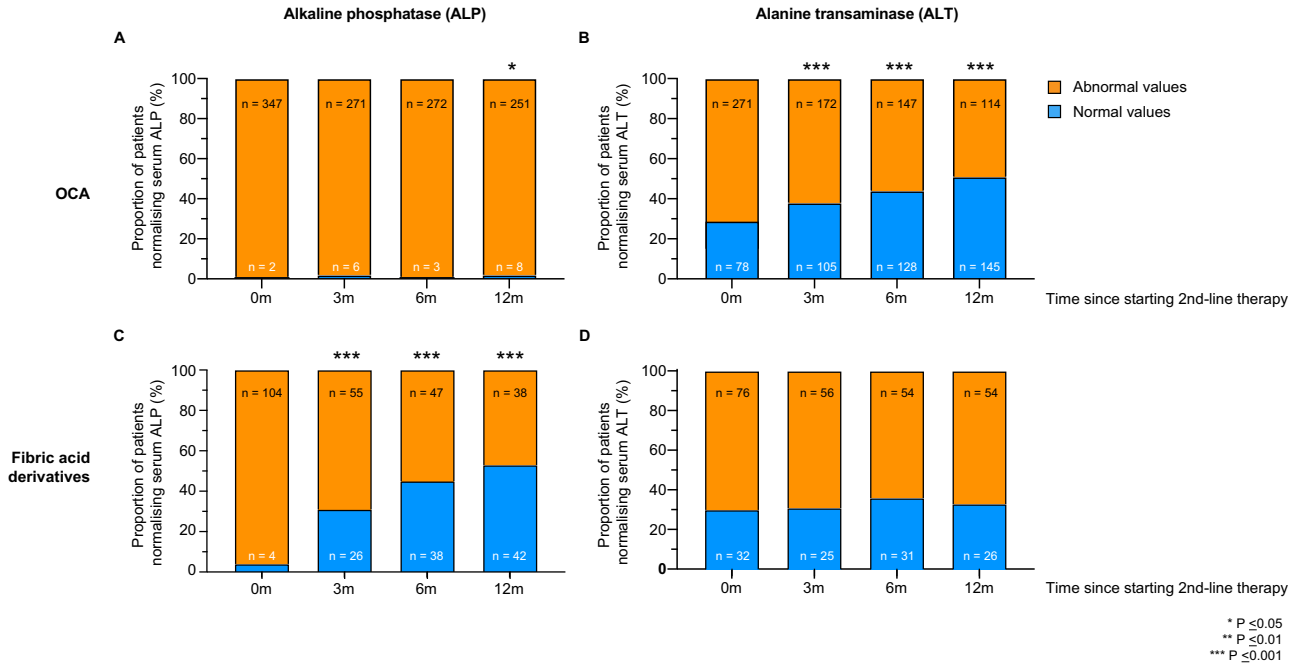

Figure 3. Rates of biochemical normalization. The proportion of patients normalizing serum ALP (*A and C*) and ALT (*B and D*) are presented, at 3, 6, and 12 months, respectively. Data shown for patients treated with OCA (*A–B*) and fibric acid derivatives (*C–D*). Asterisks indicate significant *P* values when comparing matched patient data at specific timepoints with readings taken at baseline (Fisher exact test). n = 43 and n = 21 patients in the OCA group and n = 16 and n = 8 in the fibric acid group did not have blood tests performed at 3 and 6 months, respectively, but continued therapy until month 12.

our study period was not significantly different between treatment groups ($P = .273$).

Safety and Tolerability

Twenty-one of 257 (8.2%) and 8 of 74 (10.8%) patients on OCA and fibric acid derivatives, respectively, developed elevated serum ALT and/or AST readings >3 × ULN, despite having transaminase values below this threshold prior to treatment initiation. Overall, 7.7% (n = 27/349) and 10.2% (n = 11/108) of patients taking OCA and fibric acid derivatives, respectively, developed mild-moderate elevations in biochemistry (as per Drug-Induced Liver Injury Network [DILIN] classification)[18] over the course of the study. Renal dysfunction secondary to fibric acid derivatives resulted in stoppage in one individual. Overall, 99 patients stopped second-line therapy (Supplementary Table 8), representing 22.1% (n = 77/349) of the OCA group and 21.3% (n = 22/108) of those exposed to fibric acid derivatives ($P = .86$).

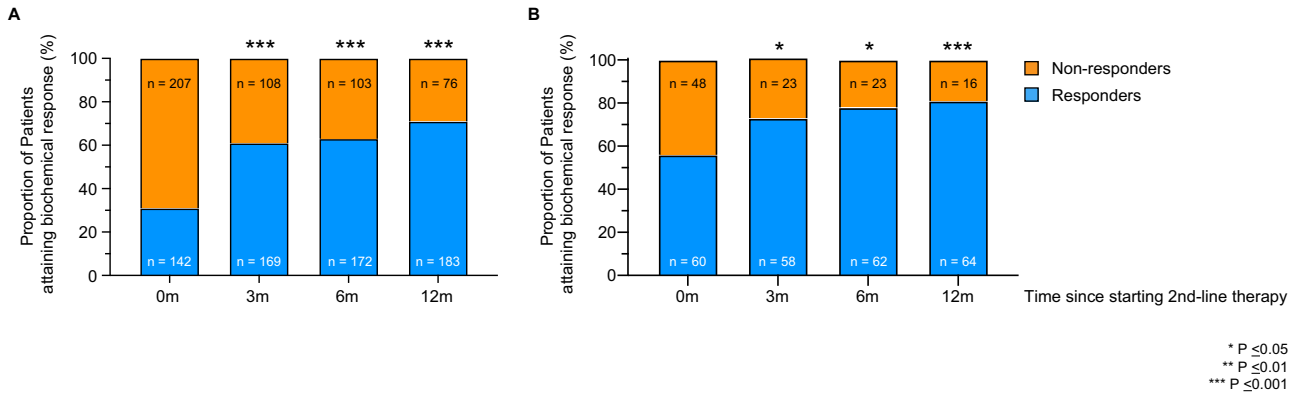

Figure 4. Biochemical response rates under second-line therapy. Biochemical response rates (Paris-I) are shown for patients under therapy with OCA (*A*) and fibric acid derivatives (*B*), indicating the number of patients meeting response/non-response criteria at baseline, 3, 6, and 12 months, respectively. *Asterisks* indicate comparisons between matched patient data at specific timepoints to readings taken at baseline (Fisher's exact test). n = 43 and n = 21 patients in the OCA and n = 16 and n = 8 in the fibric acid group did not have blood tests performed at 3 and 6 months, respectively, but continued therapy until month 12.

In the OCA group, 54% (n = 189/349) reported pruritus prior to initiation of second-line therapy. Exacerbation in pruritus (compared with baseline) was reported by 34%, 11%, and 20% patients at 3, 6, and 12 months, with 29 individuals discontinuing medication as a result of itch symptoms. For the majority (62%, 81%, and 76% at 3, 6, and 12 months), pruritus severity was reported as unchanged from baseline (Supplementary Figure 7, *A*). Conversely, 45% (49/108) reported pruritus prior to starting fibric acid derivatives, with 18%, 19%, and 15% of patients experienced improvement in itch symptoms, and 20%, 5%, and 10% reported an exacerbation (Supplementary Figure 7, *B*). No patient discontinued fibric acid derivatives due to pruritus.

Among the total cohort of patients who completed 12 months of second-line therapy, 55% (n = 142/259; OCA) and 64% (n = 51/80; fibric acid derivatives) reported total absence of pruritus, or well-controlled itch symptoms under treatment with a single anti-pruritic agent ($P = .20$). On logistic regression analysis, use of fibric acid derivatives compared with OCA was positively associated with an improvement in pruritus from baseline to month 12 (OR, 3.13; 95% CI, 1.29–7.60; $P = .011$).

Discussion

Herein, we report a large nationwide experience of second-line therapy in PBC. Our findings not only validate those of prior clinical trials and other real-world cohorts,[19–22] but also show that the magnitude of biochemical response is similar between licensed and non-licensed second-line therapies. These findings were further substantiated on propensity score matching and on sub-analysis of at-risk subgroups according to baseline covariates. Moreover, we show that a significant proportion of patients under OCA therapy normalize serum transaminases and bilirubin at 12 months, alongside significant reductions in serum ALP. However, ALP normalization was uncommon, which may be

Table 1. Factors Associated With Attaining Biochemical Response to Second-line Therapy at 12 Months

	OCA		Fibric acid derivatives	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Univariate analysis				
Female sex	1.81 (0.74–4.44)	.19	0.54 (0.06-4.76)	.58
Age at diagnosis (per year inc)	1.03 (1.00–1.07)	.03	1.04 (0.98-1.11)	.18
Age at starting second-line therapy	1.05 (1.02–1.08)	.002	1.06 (1.00-1.12)	.047
AMA-positive[a]	0.59 (0.16–2.16)	.59	-	
IgG	0.93 (0.85–1.03)	.16	0.97 (0.81-1.16)	.71
IgM	0.98 (0.88–1.11)	.86	0.95 (0.69-1.29)	.74
UDCA treated vs non-treated	2.60 (1.15–5.85)	.02	3.46 (0.69-17.3) 6)	.13
History of pruritus	0.35 (0.21–0.58)	< .001	1.00 (0.33-3.02)	1.00
Baseline laboratory values				
ALT	0.98 (0.97–0.99)	< .001	0.96 (0.93-0.98)	< .001
ALP	0.99 (0.99–0.99)	< .001	0.99 (0.99-1.00)	.03
Bilirubin	0.88 (0.85–0.92)	< .001	0.86 (0.78-0.94)	.001
Albumin	1.04 (0.99–1.10)	.11	0.96 (0.86-1.07)	.46
Platelet count	1.00 (1.00–1.00)	.06	0.99 (0.99-1.00)	.77
Creatinine	1.00 (0.99–1.01)	.79	1.00 (0.97-1.03)	.92
Liver cirrhosis	0.44 (0.22–0.92)	.13	0.29 (0.06-1.45)	.03
Spleen length, *cm*	0.89 (0.73–1.08)	.26	0.67 (0.39-1.18)	.17
Splenomegaly	0.62 (0.29–1.37)	.24	0.18 (0.03-1.09)	.06
Liver stiffness	0.98 (0.95–1.03)	.57	0.98 (0.88-1.09)	.74
OCA treated (vs fibric acid derivatives)				
Treatment initiated at a transplant unit	0.63 (0.28–1.39)	.25	1.56 (0.52-4.69)	.43
Multivariable analysis[b]				
Age at starting second-line therapy	1.04 (1.00–1.08)	.027	1.03 (0.93–1.13)	.56
UDCA treated vs non-treated	4.18 (1.23–14.17)	.022	(not included)	–
History of pruritus	0.23 (0.10–0.52)	< .001	(not included)	–
Baseline laboratory values[b]				
ALT	1.00 (0.99–1.01)	.64	0.95 (0.92–0.99)	.006
ALP	0.99 (0.99–0.99)	< .001	0.99 (0.99–0.99)	.07
Bilirubin	0.87 (0.82–0.91)	< .001	0.93 (0.85–1.03)	.15
Liver cirrhosis	(not included)	–	0.09 (0.01–1.19)	.07

ALP, Alkaline phosphatase; ALT, alanine transaminase; AMA, anti-mitochondrial antibody; CI, confidence interval; OCA, obeticholic acid; OR, odds ratio; UDCA, ursodeoxycholic acid.

[a]All patients under fibric acid treatment meeting 12 months' follow-up under treatment were AMA-positive.

[b]Factors with a *P* value < .1 on univariate analysis fed into respective multivariable models; splenomegaly not included in given an interaction term with cirrhosis.

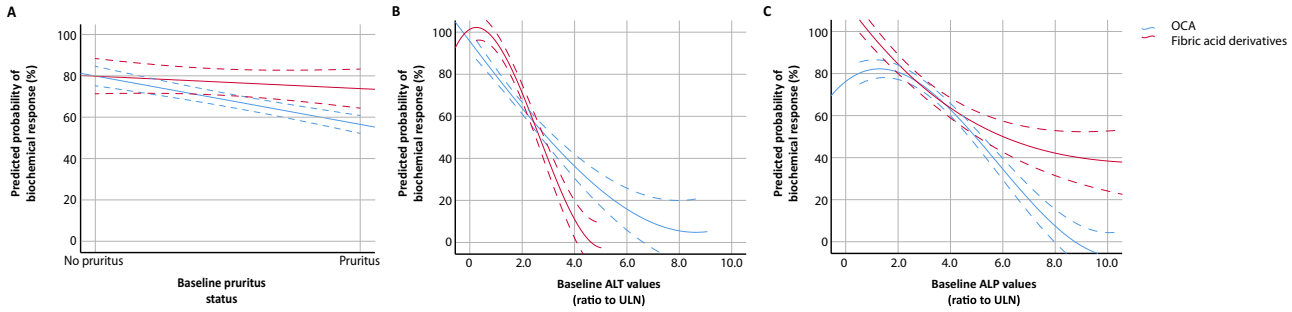

Figure 5. Interaction terms between treatment group and baseline covariates with regards adjusted probability of treatment response. The predicted probability of attaining biochemical response at 12 months is shown according to treatment with OCA (*blue*) and fibric acid derivatives (*red*), indicating statistical interactions with baseline pruritus status (*A*), baseline ALT values (*B*), and baseline ALP values (*C*). Estimated probabilities have been adjusted for age at starting second-line therapy, use of concomitant UDCA, presence of cirrhosis, and baseline bilirubin. Predicted probabilities in (*B*) and (*C*) have been estimated with cubic spline function. *Solid lines* indicate the estimated probability, and *broken lines* the 95% CIs.

because baseline starting values were significantly greater in the OCA group than for those taking fibric acid derivatives. Reciprocally, although many patients under fibric acid treatment normalize serum ALP values, the proportion attaining normal ALT and bilirubin was unchanged compared with baseline. In sub-analysis of patients with cirrhosis, OCA resulted in significant reductions across all liver biochemical parameters. We also identified how baseline covariates associate with response to treatment. In so doing, one second-line treatment does not appear to be superior to another; rather, we find that treatment regimen moderates the risk of non-response conferred by certain baseline variables. This has clear, practical implications for patient care, wherein the probability of biochemical response appears lower for OCA-treated patients than that for fibric acid derivatives when ALP values exceed 4 $\times$ ULN. This contrasts to elevated baseline ALT, which confers a lower probability of biochemical response to fibric acid derivates when values exceed 2.3 $\times$ ULN.

Across the overall cohort, likelihood of responding to OCA was also lower in individuals with a history of pruritus. Additionally, 34% of the OCA group experienced deterioration in itch symptoms as early as 3 months. These rates are akin to those recently presented by the Toronto group, and exacerbation of pruritus is an ongoing challenge reported by OCA-treated cohorts worldwide.[19] By contrast, the odds of itch improvement were approximately 3-fold greater with fibric acid derivatives compared with OCA. Although not a randomized controlled study, when taken together with data from the FITCH trial, our data supports the use of fibric acid derivatives in UDCA non-responders who experience pruritus.[13] Collectively, this signifies the need for long-term, confirmatory trials validating the anti-pruritic effects of fibric acid derivatives in patients with chronic cholestatic disease.

Case series from the United States have raised concerns about OCA and potential risks of drug-induced liver injury,[23,24] particularly when using high doses that are not approved in advanced liver disease. The risks of fibric acid induced hepatotoxicity are also well-documented, and apparent with prolonged rather than short-term use.[12,13,25] To this effect, clinician-reported deterioration in biochemistry was observed in a subset of fibrate-treated patients in our study, accepting the limitation that dedicated medical chart review was not performed to determine causality. Thus, rigorous exclusion of potential confounder medications cannot be guaranteed.

As the UK ODN model was devised to ensure equitable access of new (rather than repurposed) medicines for patients, variation in clinical practice is also inevitable. This includes access to transplantation for those with advanced disease and/or difficult to treat pruritus, which may partly explain the lack of cirrhotic patients exposed to fibric acid therapy. Accordingly, a national audit with regard to therapeutic decision-making is ongoing. A further limitation is the fact that quantitative symptom data is lacking, with the assessment of pruritus being patient- and clinician-reported as part of routine standard of care rather than through quantitative measures applied in clinical trials. More contemporary and abbreviated outcome measures (such as the PBC-10) may help facilitate real-world outcome and natural history studies moving forward, once they have been externally validated.[26] As the overall cohort size continues to grow, so too will the evidence-base regarding treatment efficacy and safety, and our understanding as to which second-line therapy performs best in larger sized, specific patient populations. This includes outcome assessment of those on combination triple therapy.

We also acknowledge that propensity score matching is not a panacea for removing bias, nor does it attempt to replace a dedicated randomized controlled trial. A practical limitation of this method is highlighted by sub-analysis of interaction terms within the propensity score matching cohort, wherein baseline pruritus status no longer moderated the effects of treatment group with regards probability of biochemical response. We suspect this relates to shrinkage of the OCA cohort who experienced pruritus at baseline (from n = 189 to n = 49),

whereas the number of patients experiencing pruritus in the fibric acid group remained relatively constant following propensity score matching (n = 49 and n = 45, respectively). Additionally, our propensity score matching did not allow for adjustment according to pruritus severity or intensity, as validated PBC quality of life tools are not employed in routine clinical practice. Nevertheless, our aim of including a propensity score matching step was to achieve a more balanced distribution of covariates, address confounding in a real-world observational cohort study, and to have a less biased estimation of effects between treatment groups.

The choice of second-line therapy herein was largely driven by center-specific practice and local expertise rather than governed centrally – all decisions being approved by a specialist autoimmune liver disease multidisciplinary team meeting prior to treatment initiation. As a result, comparative health economic analyses were outside the scope of our study. Given that the market cost of OCA is greater than that of fibric acid derivatives, this may favor bezafibrate or fenofibrate as 'default' second-line therapies of choice in PBC. However, as our data shows, rates of biochemical normalization differ between treatment groups, and evidence supporting the efficacy and safety of fibrates in cirrhosis is presently lacking.

In any event, the fact that >25% of patients discontinue second-line treatment underscores the need for new treatment paradigms in PBC, be they established or investigational. With involvement throughout the process, we strongly advocate a patient-centered approach to future studies, offering credible insight into the experience of second-line therapies, including on the broader domains of patient quality of life.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.07.038.

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Supplementary Appendix: Patients And Methods

Study setting and design

We analyzed data from a national cohort of well-characterized patients with an established diagnosis of primary biliary cholangitis (PBC) who were referred for consideration of second-line therapy; either due to biochemical nonresponse to ursodeoxycholic acid (UDCA) alone (following at least 12 months of treatment at a dose of 13 to 15 mg/kg/day) or because of UDCA intolerance. For the purposes of this study, all Operational Delivery Networks across England were invited to submit audit data via a dedicated case record form, of which 14 participated, including 5 liver transplant centers. Audit data was collected prospectively, including patient demographics, treatment exposure, experience of pruritus, laboratory parameters, evidence of cirrhosis, and the occurrence of clinical events.

Study definitions and timelines

This was a nationwide study conducted from August 2017 (the point of market entry for obeticholic acid [OCA]) until June 2021. In the United Kingdom (UK), indications for second-line therapy are in accordance with National Institute for Health and Care Excellence and British Society of Gastroenterology guidance; namely in patients with a persistently elevated alkaline phosphatase value $\geq$1.67 $\times$ upper limit of normal (ULN) and/or an elevated bilirubin (despite 12 months of UDCA therapy), or as monotherapy in the event of UDCA intolerance.[1,2]

For the purposes of this study, baseline was set as the point of starting second-line therapy (either OCA, bezafibrate, or fenofibrate). Given that liver biopsy is not routine standard of care in PBC, in the absence of histological confirmation, patients were categorized as cirrhotic according to available clinical, biochemical/hematological features (including enhanced liver fibrosis score), and/or when transient elastography readings exceeded 16.9 kPa,[3] as previously described.[4-6] Patients with baseline elastography readings of >9.6 kPa are also reported in both groups, as a threshold indicative of advanced fibrosis.[7]

Individuals were excluded from study if follow-up data were insufficient (<2 clinic visits recorded) and in the event of confirmed past/concomitant hepatitis B virus or hepatitis C virus infection, Wilson disease, alpha-1 antitrypsin deficiency, hereditary hemochromatosis, alcohol-related liver disease, primary sclerosing cholangitis, or patients taking immunosuppressive therapy (for instance, due to concern of an overlap phenotype with autoimmune hepatitis). Individuals with prior exposure to farnesoid X receptors or peroxisome proliferator-activated receptor agonists (including through clinical trials), treated with OCA and fibric acid derivatives in combination, or previously treated with either agent only to switch to the other, were also excluded.

Outcome assessment and analysis

Treatment efficacy was determined by the proportion of patients attaining biochemical response. Primarily, this is presented according to the Paris I criteria, given its extensive validation in the UK patient population, the fact it encompasses alanine transaminase in addition to bilirubin and alkaline phosphatase values, and its applicability to all patients with PBC rather than only those with early-stage disease.[5,8,9] Biochemical response rates according to Barcelona, Toronto, and Paris II definitions are presented as supplementary analyses. Additionally, we determined the proportion of patients who attained biochemical response according to criteria set out in the POISE study given relevance to contemporary PBC clinical trials.[10] On-treatment biochemical changes, drug stoppages, and the proportion of patients completing follow-up are presented at pre-specified intervals; namely at 3, 6, and 12 months. Exploratory analysis was conducted to determine predictors of response to second-line treatment at 12 months (logistic regression), with univariate and multivariable regression models fit to assess the impact of individual covariates on the rate of clinical events.

As our study is not an interventional trial (rather a real-world evaluation of clinical practice), use of disease-specific patient-reported outcome measures could not be performed routinely. However, all centers were asked to document the presence of pruritus (current or past) in a dichotomous manner, use of anti-pruritic therapy (past or present, and names of medication), patient-reported pruritus severity (most often this was provided on an ordinal scale from 0 to 10, and in other centers, was documented as none, mild, moderate, or severe), and on-treatment pruritus behavior (none or present; if present then to quantify whether pruritus was unchanged, worsened, or improved during the course of second-line therapy), and if an escalation in anti-pruritic therapy was required to combat symptoms. Escalation in anti-pruritic therapy was documented in the event any of the following criteria were met: (1) the dosage of existing anti-pruritic therapy was increased; (2) a reduction in obeticholic acid dosage was needed/performed; or (3) additional anti-pruritus therapy was started de novo. Clinician-reported drug-induced liver injury was categorized according to the Drug-Induced Liver Injury Network (DILIN) classification.[11]

Quality control

Completeness, plausibility, and validity of data were carefully verified at source by the referring centers, and

again at the study coordinating center (by investigators N.A. and P.T.). Where needed, individual site-center visits were conducted prior to June 2021, with personalized, objective review of historical medical charts to retrieve missing data. This study was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Research Board of the initiating centre (Birmingham; CARMS 14238), with individual participating hospital approval in accordance with local regulations.

Data presentation and statistical analysis

Data are presented using the median and interquartile range for continuous variables. Liver enzymes are expressed as ratios to the ULN, as previously described.[4–6,9,12,13] The nonparametric Mann-Whitney *U* test was used to determine whether significant differences existed between groups, whereas the Wilcoxon signed-rank test was applied to analyze differences from baseline to 3, 6, and 12 months within treatment groups. Nominal data are presented as absolute values (percentages in parenthesis), and differences compared by the Fisher exact test.

Exploratory analysis was conducted to determine the predictors of response to second-line treatment at 12 months (logistic regression). Univariate and multivariable regression models were also fit to assess the impact of individual covariates on the instantaneous rate of clinical events during follow-up. Covariates having a P value of $\leq .1$ in univariate analysis were fed into subsequent multivariable models. A P value of $< .05$ in a 2-sided test was deemed statistically significant. In the event a baseline covariate was of particular interest, yet the P value was $> .1$ on univariate analysis, separate multivariable regression analyses were performed, forcing the variable into the model. This was in parallel to evaluating potential moderator effects of the covariate, through analysis of statistical interaction terms with other baseline variables. Analyses were conducted using SPSS Statistics v24.0 (SPSS Inc, Chicago, IL).

Given differences in baseline characteristics between treatment groups, propensity score matching was also performed, using the model detailed in Supplementary Table 2, resulting in matched groups as described in Supplementary Table 3. The nearest-neighbor method of propensity score matching was implemented in R using the package "MatchIt," specifying a calliper of 0.1 and a 1:1 ratio when selecting patients from the 2 treatment groups.[14] Baselines variables that were significantly different in distribution between treatment groups were included in the propensity score model, with sequential addition and testing of other covariates to improve the balance of the resulting matched dataset. Balance was assessed through calculation of standardized mean differences for all measured baseline variables. Following this, assessment of drug efficacy was validated on the matched dataset.

Patient and public involvement

The overarching goal for this study was to capture on-treatment biochemical responses following 12 months of second-line therapy. On discussion with the Birmingham PBC Patient Group, it was also suggested that data relating to earlier timepoints be measured (as early signals of therapeutic efficacy), alongside baseline and on-treatment pruritus behavior at interval clinic visits (described above), and that we address potential safety concerns relating to drug-induced liver injury reported by the United States Food and Drug Administration.[15] The study was also presented to the PBC Foundation (an international organization committed to supporting people living with PBC) to obtain further perspective and comments, and to ensure findings can be translated and disseminated to the broader patient community. In collaboration, a lay abstract will be published and made available to the patient population through the periodical 'PBC Bear Facts,' along with a nontechnical summary of study findings. Additionally, the longer-term experiences of second-line therapy will continue to be studied and presented, together with a full breakdown of potential side effects and details of putative drug-induced hepatotoxicity.

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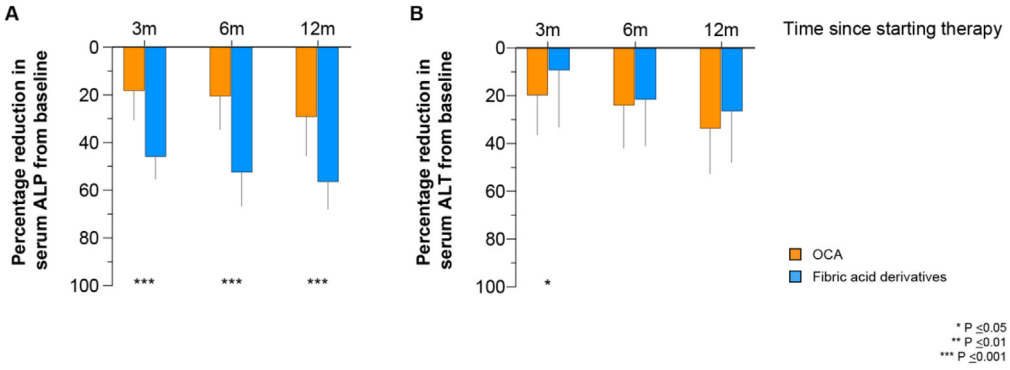
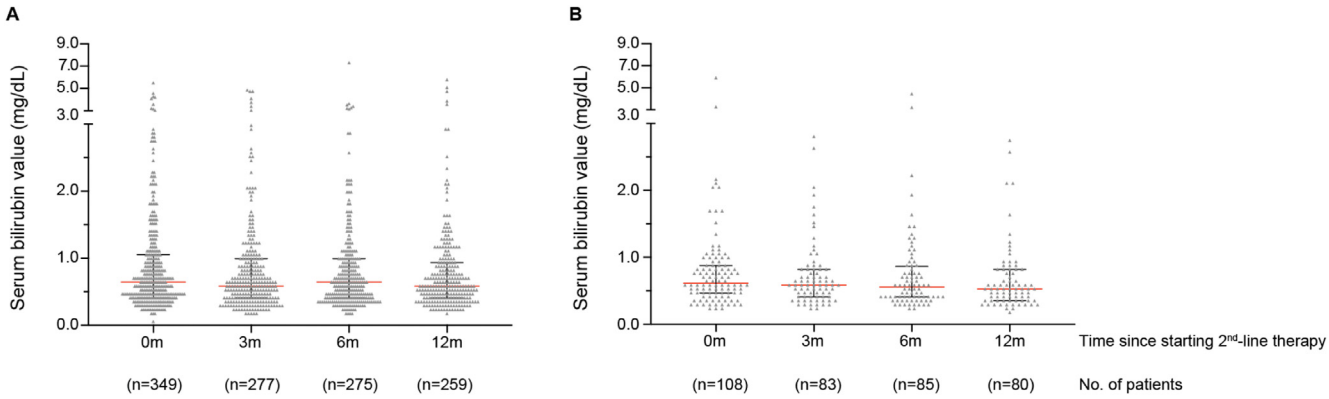
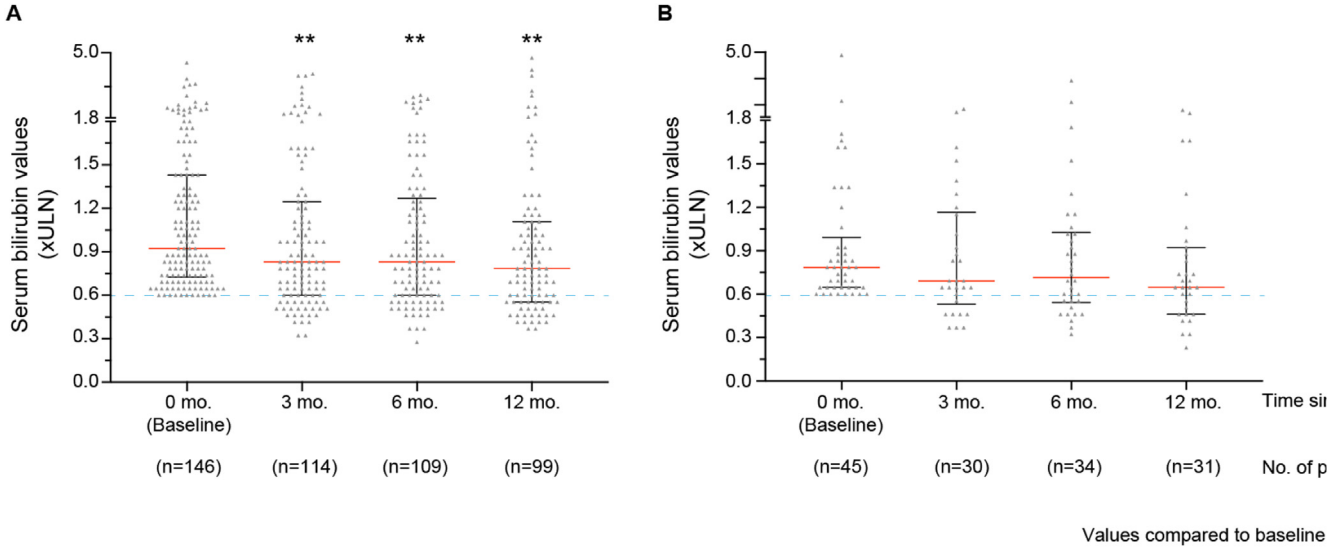


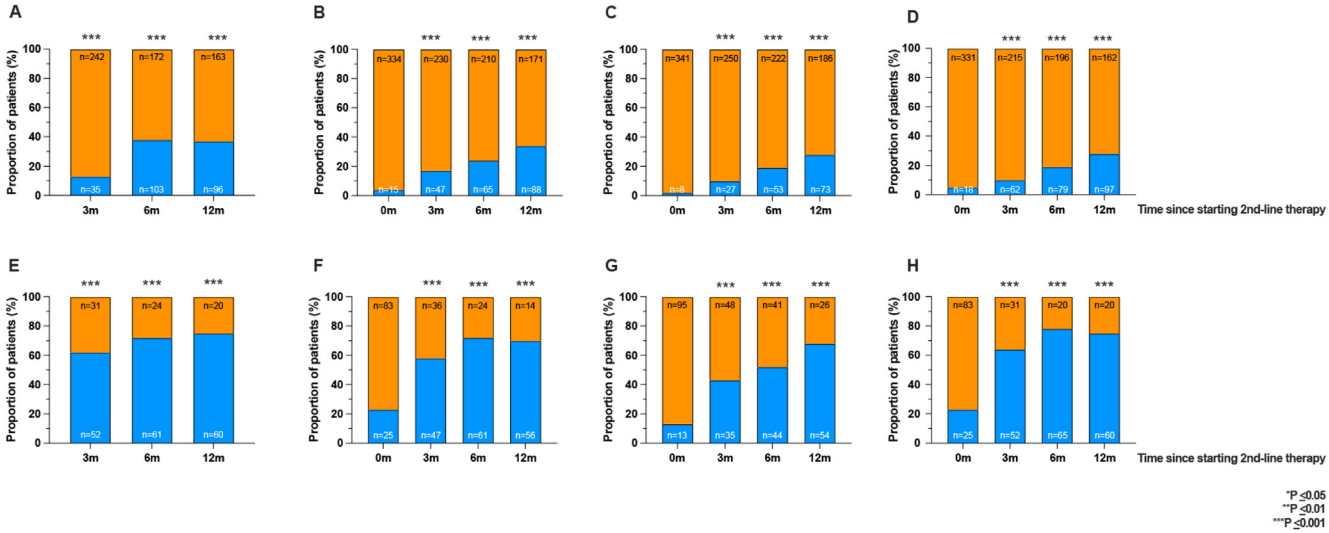
Supplementary Figure 1. Magnitude of ALP and ALT changes stratified by treatment group. Percentage reductions in serum ALP (*A*) and ALT (*B*) are presented relative to baseline values, following 3, 6, and 12 months of therapy. *Asterisks* indicate comparisons between treatment groups taken at indicative timepoints (Mann-Whitney *U* test).



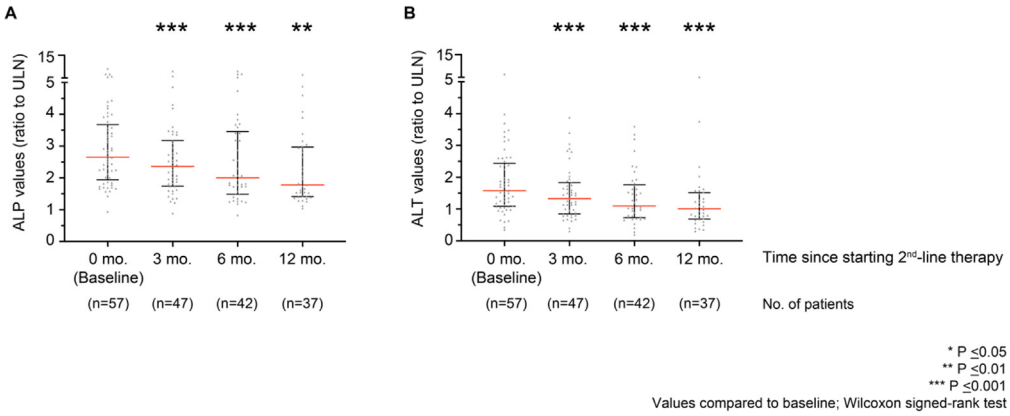
Supplementary Figure 2. On-treatment changes in serum bilirubin. Serum bilirubin values are presented for the OCA (*A*) and fibric acid derivative (*B*) groups, respectively, at baseline and following 3, 6, and 12 months of therapy. Values expressed in mg/dL, with *red lines* indicating the median, and black whiskers indicating the interquartile range. The number of patients on therapy indicate the number having the indicated blood tests at the specified timepoints. n = 43 and n = 21 patients in the OCA group and n = 16 and n = 8 in the fibric acid derivative group did not have blood tests performed at 3 and 6 months, respectively, but continued therapy until month 12.



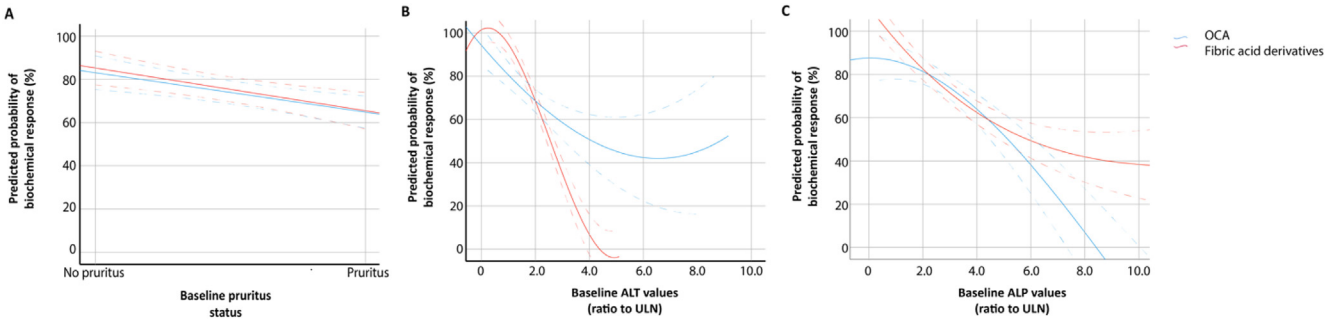
Supplementary Figure 3. On-treatment changes in serum bilirubin among patients with baseline values >0.6 × ULN. Serum bilirubin values presented for the OCA (*A*) and fibric acid (*B*) treatment groups, respectively, at baseline and following 3, 6, and 12 months of therapy, specifically among those with baseline bilirubin values above 0.6 × ULN. *Red lines* indicate median values, and *black whiskers* the interquartile range. Asterisks indicate significant *P* values when comparing serum values from matched patient data at specific timepoints with readings taken at baseline (Wilcoxon signed-rank test).



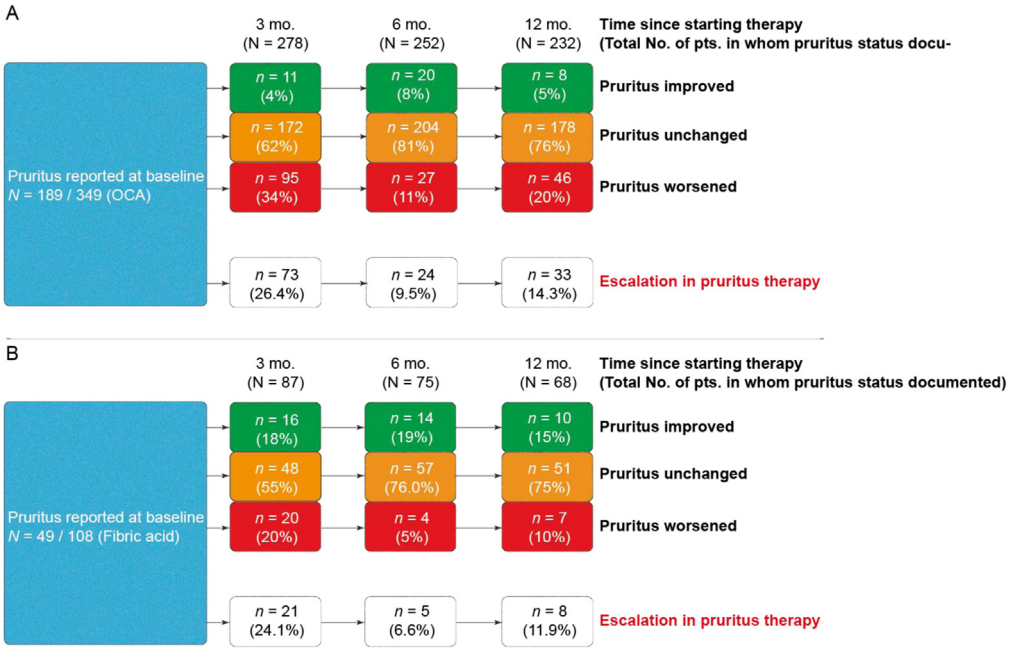
Supplementary Figure 4. Biochemical response rates according to variant criteria. Biochemical response rates are shown for patients under therapy with OCA (**A** to **D)** and fibric acid derivatives (**E** to **H)**, indicating the number of patients meeting response/non-response criteria at baseline, 3-, 6- and 12-months, respectively. Biochemical response criteria are presented according to the Barcelona criteria (**A** and **E**), POISE criteria (**B** and **F**), Paris II criteria (**C** and **G**), and Toronto criteria (**D** and **H**). Asterisks indicate data comparing serum values from matched patient data at specific timepoints with readings taken at baseline (Fisher's exact test).



Supplementary Figure 5. Biochemical changes in patients with cirrhosis treated with OCA. Serum ALP and ALT values are presented for patients with cirrhosis under OCA therapy (*A* and *B*), at baseline and following 3, 6, and 12 months of therapy. Values expressed as a ratio to the ULN range, with *red lines* indicating the median and *black whiskers* indicating the inter-quartile range. Asterisks indicate data comparisons between matched patient data at specific timepoints to readings taken at baseline (Wilcoxon signed-rank test).



Supplementary Figure 6. Interaction terms between treatment group and predicted probability of treatment response; propensity-score matched group only. The predicted probability of attaining biochemical response at 12 months is shown according to treatment with OCA (*blue*) and fibric acid derivatives (*red*), in the propensity score-matched cohort. Statistical interactions are shown with baseline pruritus status (*A* – not significant), baseline ALT values (*B*), and baseline ALP values (*C*). Estimated probabilities have been adjusted for age at starting second-line therapy, use of concomitant UDCA, presence of cirrhosis, and baseline bilirubin. Predicted probabilities in (*B*) and (*C*) have been estimated with cubic spline function. *Solid lines* indicate the estimated probability, and *broken lines* the 95% confidence intervals.



Supplementary Figure 7. Impact of second-line therapy on pruritus over time. Pruritus behavior (for those with pre-existing itch) over the course of treatment is shown for patients under treatment for OCA (*A*) and fibric acid derivatives (*B*). During the course of treatment, the proportion of patients requiring an escalation in pruritus therapy (or initiation of anti-pruritus therapy de novo) during the course of treatment was 31.8% vs 23.2% (25/108), in the OCA and fibric acid derivative group, respectively; $P = .613$.

Supplementary Table 1. Baseline Patient Characteristics

	Overall	OCA[a]	Fibric acid derivatives[b]	
	(N = 457)	(n = 349)	(n = 108)	*P* value
Female sex	413 (90.4)	318 (91.1)	95 (88.0)	.33
Age at PBC diagnosis, *y*	47 (41–54)	47 (41–53)	48 (42–57)	.23
Age at starting second-line therapy, *y*	56 (49–63)	55 (48–63)	56.5 (50–60)	.29
AMA-positive	411 (92.8)	315 (93.5)	98 (90.7)	.34
IgG	14 (11.4–17)	14 (11.4.–17.0)	13 (11.2–14.3)	.033
IgM	3.7 (2.3–5.8)	3.8 (2.4–5.8)	3.4 (2.2–5.6)	.21
UDCA treated	400 (88.3)	302 (87.5)	98 (90.7)	.37
History of pruritus[d]	238 (52.5)	189 (54.8)	49 (45.4)	.09
On anti-pruritus therapy	170	130	40	.97
Laboratory values (continuous)				
ALT[e]	1.43 (1.00–2.15)	1.44 (1.05–2.22)	1.38 (0.85–2.05)	.12
ALP[e]	2.74 (1.99–3.78)	2.89 (2.11–.3.95) (n=345)	2.27 (1.69–3.30)	< .001
Bilirubin	0.54 (0.35–0.85)	0.55 (0.35–0.90)	0.53 (0.40–0.75)	.49
	40 (37–44)	41 (37–45) (n = 336)	39 (35.3–44) (n = 108)	.023
Albumin	40 (37–44)	41 (37–45)	39 (35–44)	.023
Platelet count	265 (206.75–324)	262 (206–321) (n = 336)	281.4 (211–331.25) (n = 98)	.18
Creatinine	63.5 (56–74)	64 (57–75)	62 (54.5–70.0)	.042
Laboratory values (categorical)				
ALT >1 × ULN	338 (74.9)	264 (77)	73 (68.2)	.07
AST >1 × ULN	164 (73)	153 (73.2)	12 (70.6)	.815
ALP >1.5 × ULN	426 (93.2)	336 (97.4)	90 (83.3)	< .001
ALP >1.67 × ULN	407 (89.1)	324 (93.9)	83 (76.9)	< .001
ALP >2 × ULN	336 (73.5)	274 (79.4)	62 (57.4)	< .001
ALP >3 × ULN	200 (43.8)	162 (47.0)	38 (35.2)	.032
Bilirubin >1 × ULN	89 (19.7)	76 (22.1)	13 (12)	.022
UK-PBC risk scores				
5 years	1.6 (0.7–4.1)	1.69 (0.7–4.4)	1.4 (0.7–3.1)	.31
10 years	5.4 (2.5–13.0)	5.56 (2.5–14.1)	4.8 (2.5–9.9)	.31
15 years	9.8 (4.5–22.9)	10.1 (4.5–24. 6)	8.7 (4.6–17. 7)	.31
Biochemical non-responders (Paris)	268 (59.2)	219 (63.5)	49 (45.4)	.001
Liver cirrhosis[c]	66 (14.6)	57 (16.5)	9 (8.3)	.035
Child Pugh A	51 (11.2)	45 (12.9)	6 (5.6)	.05
Child Pugh B	15 (3.3)	12 (3.4)	2 (1.9)	.06
Splenomegaly[f]	68 (26.1)	58 (30.7)	10 (13.9)	.006
Liver stiffness	9 (6.8–13.6)	9.50 (7.05–14)	7.1 (5.45–10.98)	.002
Liver stiffness readings >9.6 kPa	110	96	14	

Note: Continuous data expressed as median (interquartile range) and categorical data as raw numbers (percentages).
ALP, Alkaline phosphatase; ALT, alanine transaminase; AMA, Anti-mitochondrial antibody; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN; upper limit of normal.
[a]Starting dosages of OCA: n = 34 patients commenced on 5 mg once a week; n = 4, 5 mg twice weekly, n = 23, 5 mg every other day, and the remainder on 5 mg once a day.
[b]Starting dosages of bezafibrate: n = 3 commenced on 200 mg once a day, n = 3 on 600 mg once a day, and the remainder on 400 mg daily. For fenofibrate, n = 8 commenced on 160 mg once a day; n = 3 on 134 mg once a day; n = 1 on 130 mg once a day, and the remainder on 200 mg daily.
[c]Thirty-four individuals with cirrhosis were started on 5 mg once a day of OCA, n = 3 on 5 mg every other day, n = 19 on 5 mg once weekly and n = 2 on 5 mg twice weekly.
[d]n = 4 patients in the OCA group did not have baseline pruritus data documented; elastography readings not available in n = 156 and n = 62 patients in the OCA and fibric acid groups, respectively.
[e]Serum ALT and ALP values denote readings relative to the laboratory ULN.
[f]Denotes a spleen length >12.5 cm.

Supplementary Table 2. Summary of the Logistic Regression Model Used to Calculate Propensity Scores Prior to Matching

Variable	Coefficient	*P*-value
(Interception)	0.71	.059
Baseline ALT values	−0.15	.576
Baseline ALP values	−0.55	.073
Baseline bilirubin	−0.20	.586
Cirrhosis = Y	−0.82	.053
POISE criteria already met = Y	−1.39	.001

Note: A multivariable model with baseline 5 covariates (serum ALT, serum ALP, serum bilirubin, cirrhosis, POISE criteria) and treatment group as the dependent variable was fitted to the data as part of the propensity score-matching process within the "matchit" function in the R package "MatchIt." The coefficients of these 5 covariates in the fitted model and *P* values representing the significance of each covariate are shown. Stepwise variable selection is based on covariates that were significantly different between treatment groups at baseline; other covariates beyond those shown were not included because their inclusion did not improve the balance of the resulting matched dataset. Overall balance was assessed through calculation of standardized mean differences for all measured baseline variables.

ALP, Alkaline phosphatase; ALT, alanine transaminase; POISE, PBC OCA International Study of Efficacy.

Supplementary Table 3. Patient Characteristics Following Propensity Score Matching

	OCA (n = 95)	Fibric acid derivatives (n = 95)	*P* value	Standardized mean differences
Female sex	90 (94.7)	83 (87.4)	.08	0.26
Age at diagnosis, *y*	48 (40.9–53.9)	48 (41–55)	.96	0.007
Age at starting second-line therapy, *y*	55 (48–61)	56 (48–66)	.50	0.08
AMA-positive	82 (88.2)	84 (89.4)	.79	0.03
UDCA treated	80 (84.2)	85 (89.5)	.28	0.15
History of pruritus	49 (51.6)	45 (47.4)	.56	0.08
On anti-pruritus therapy	30 (31.6)	41 (43.2)	.09	0.24
Laboratory values (continuous)[a]				
ALT	1.33 (0.93–1.85)	1.48 (0.85–2.15)	.45	0.10
ALP	2.38 (1.84–3.74)	2.48 (1.85–3.42)	.94	0.07
Bilirubin	10 (7–16)	11 (8–16)	.45	0.05
Albumin	41 (38–44)	39 (35–44)	.07	0.25
Platelet count	264 (209.75–329)	283 (212–335)	.29	0.14
Creatinine	63 (56.5–75.5)	62 (54–70.5)	.19	0.10
Laboratory values (categorical)				
ALT or AST >1 × ULN	66 (69.5)	67 (70.5)	.87	0.02
ALP >1.5 × ULN	88 (92.6)	85 (89.5)	.45	0.11
ALP >1.67 × ULN	81 (85.3)	82 (86.3)	.84	0.03
ALP >2 × ULN	61 (64.2)	62 (65.3)	.88	0.02
ALP >3 × ULN	36 (37.9)	37 (38.9)	.88	0.02
Bilirubin >ULN	13 (13.7)	13 (13.7)	1.00	<0.01
Bilirubin >2 × ULN	4 (4.2)	2 (2.1)	.41	0.12
Bilirubin >50 micromol/L	1 (1.1)	1 (1.1)	1.00	<0.01
Bilirubin >100 micromol/L	0	1 (1.1)	.31	0.15
UK-PBC score				
5 years	1.31 (0.58–3.16)	1.46 (0.82–3.33)	.42	0.04
10 years	4.35 (1.95–10.2)	4.83 (2.72–10.74)	.42	0.02
15 years	7.94 (3.60–18.15)	8.81 (5.00–19.06)	.42	0.02
Liver cirrhosis	14 (14.7)	8 (8.4)	.17	0.03
Child Pugh A	10(10.5)	6 (6.3)	.51	0.06
Child Pugh B	3 (3.2)	2 (2.1)	.51	0.02
Splenomegaly	14 (27.5)	9 (14.8)	.09	0.18
Liver stiffness[b]	9.6 (7–14)	7.8 (5.8–12.8)	.15	0.20
No. completing follow-up[c]				
3 months.	85 (89.5)	88 (92.6)	.52	0.19
6 months	81 (85.3)	81 (86.2)	.76	0.17
12 months	69 (72.6)	67 (70.5)	.69	0.18

Note: Continuous data expressed as median (interquartile range) and categorical data as raw numbers (percentages).
Note: Propensity score matching was used to create OCA and fibric acid derivative groups, which were not significantly different with respect to baseline characteristics. The nearest-neighbour method of propensity score matching was implemented in R using the package "MatchIt," specifying a calliper of 0.1. Balance was assessed through calculation of standardized mean differences. *P* values > .05 indicate no significant differences between groups.
Note: Starting dosages of OCA included 4 patients commenced on 5 mg once a week, 2 patients on 5 mg twice weekly, 3 patients on 5 mg every other day, and 86 patients on 5 mg once daily. For fibric acid derivatives, 54 patients were commenced on fenofibrate and 40 on bezafibrate.
ALP, Alkaline phosphatase; ALT, alanine transaminase; AMA, Anti-mitochondrial antibody; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN; upper limit of normal.
[a]Serum ALT and ALP values denote readings relative to the laboratory ULN.
[b]Denotes liver stiffness obtained through transient elastography.
[c]Patients discontinuing therapy at 3, 6, and 12 months include n = 9, n = 13, n = 23 and n = 7, n = 11, and n = 24 for the OCA and fibrates groups, respectively.

Supplementary Table 4A. Biochemical Response Rates in the Intent-to-treat Population at 12 Months

	OCA, %	Fibric acid derivatives, %	*P* value
Paris-I criteria	52.4	59.2	.12
Paris-II criteria	20.9	50	< .001
Toronto criteria	27.7	55.5	.003
POISE criteria	25.2	51.8	< .001
Barcelona criteria	30.6	46.3	< .001

OCA, Obeticholic acid; POISE, PBC OCA International Study of Efficacy.

Supplementary Table 4B. Biochemical Response Rates in Propensity Score-matched Groups at 12 Months

	OCA, %	Fibric acid derivatives, %	*P* value
Paris-I criteria	79.7	77.1	.71
Paris-II criteria	31.9	63.8	< .001
Toronto criteria	46.4	71.4	.003
POISE criteria	45.6	67.1	.01
Barcelona criteria	30.6	79.3	< .001

OCA, Obeticholic acid; POISE, PBC OCA International Study of Efficacy.

Supplementary Table 5. Twelve-month Biochemical Response Rates in High-risk Groups[a]

Baseline stratifier	OCA group, n/N at 12 months (%)	Fibric acid group, n/N at 12 months (%)	*P* value between treatment groups
Cirrhosis	21/37 (57)	4/7 (57)	.99
Liver stiffness >9.6 kPa	50/72 (70)	6/8 (75)	.74
Biochemical nonresponder to UDCA alone (Paris)	92/161 (57)	20/33 (61)	.71
ALP >1.5 × ULN	180/253 (71)	52/67 (77)	.29
ALP >1.67 × ULN	88/155 (56)	19/31 (61)	.69
ALP >2 × ULN	141/208 (68)	33/45 (73)	.69
Bilirubin >ULN	10/45 (22)	3/8 (37)	.35

ALP, Alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
[a]Data presented for the intent-to-treat patient population.

Supplementary Table 6. Baseline Predictors of Response to Second-line Therapy Across the Nationwide PBC Cohort

	OR (95% CI)	*P* value
Univariate analysis		
Female sex	1.42 (0.64–3.16)	.39
Age at diagnosis (per year inc)	1.03 (1.00–1.06)	.009
Age at starting second-line therapy	1.05 (1.02–1.08)	< .001
AMA-positive	0.37 (0.11–1.26)	.112
IgG	0.93 (0.86–1.02)	.16
IgM	0.98 (0.88–1.09)	.76
UDCA treated vs non-treated	2.77 (1.35–5.72)	.006
History of pruritus	0.35 (0.21–0.59)	< .001
Baseline laboratory values		
ALT	0.97 (0.97–0.98)	< .001
ALP	0.99 (0.99–0.99)	< .001
Bilirubin	0.87 (0.85–0.91)	< .001
Albumin	1.02 (0.97–1.07)	.36
Platelet count	1.00 (1.00–1.00)	.11
Creatinine	1.00 (0.99–1.00)	.87
Cirrhosis	0.40 (0.21–0.78)	.007
Spleen length, *cm*	0.86 (0.72–1.03)	.09
Splenomegaly	0.47 (0.23–0.95)	.03
Liver stiffness	0.98 (0.95–1.02)	.38
Treatment group[a]	0.62 (0.34–1.14)	.12
Treatment initiated at a transplant unit	0.76 (0.42–1.39)	.37
Multivariable analysis[b]		
Age at starting second-line therapy	1.04 (1.00–1.08)	.023
UDCA treated vs non-treated	3.14 (1.18–8.36)	.022
History of pruritus	0.40 (0.21–0.77)	.006
Baseline laboratory values		
ALT	0.69 (0.48–0.98)	.038
ALP	0.67 (0.54–0.84)	< .001
Bilirubin	0.89 (0.86–0.93)	< .001
Cirrhosis	0.61 (0.24–1.52)	.29
Multivariable analysis including treatment group forced in as a covariate[c]		
Age at starting second-line therapy	1.04 (1.00–1.08)	.026
UDCA treated vs non-treated	3.17 (1.19–8.41)	.021
History of pruritus	0.41 (0.21–0.79)	.008
Baseline laboratory values		
ALT	0.68 (0.48–0.97)	.033
ALP	0.68 (0.55–0.84)	< .001
Bilirubin	0.89 (0.86–0.93)	< .001
Treatment group[a]	1.38 (0.61–3.10)	.44
Cirrhosis	0.62 (0.25–1.56)	.31

ALP, Alkaline phosphatase; ALT, alanine transaminase; AMA, anti-mitochondrial antibody; CI, confidence interval; OCA, obeticholic acid; OR, odds ratio; PAC, percentage accuracy classification; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid

[a]Treatment group: OCA vs fibric acid derivatives.

[b]Model PAC 83.3%.

[c]Model PAC 83.3%.

Supplementary Table 7. Multivariable Analysis: Assessment of Statistical Interaction Terms According to Treatment Group

	OR (95% CI)	*P* value
Including treatment group by pruritus as an interaction term[a]		
Age at starting second-line therapy	1.04 (1.00–1.08)	.024
UDCA treated vs non-treated	4.31 (1.56–11.92)	.005
History of pruritus	0.23 (0.11–0.52)	< .001
Baseline laboratory values		
ALT	0.71 (0.49–1.01)	.056
ALP	0.67 (0.54–0.83)	< .001
Bilirubin	0.88 (0.84–0.93)	< .001
Treatment group (OCA vs fibric acid derivatives)	0.39 (0.13–1.23)	.11
Cirrhosis	0.66 (0.26–1.68)	.385
Treatment group (OCA vs fibric acid derivatives) × history of pruritus[c]	11.79 (2.10–66.28)	.005
Including treatment group by baseline ALT values as an interaction term[b]		
Age at starting second-line therapy	1.04 (1.00–1.07)	.037
UDCA treated vs non-treated	3.94 (1.46–10.62)	.007
History of pruritus	0.36 (0.18–0.71)	.003
Baseline laboratory values		
ALT	0.92 (0.61–1.38)	.671
ALP	0.65 (0.52–0.82)	< .001
Bilirubin	0.90 (0.86–0.93)	< .001
Treatment group (OCA vs fibric acid derivatives)	36.40 (2.28–581.32)	.011
Cirrhosis	0.53 (0.21–1.34)	.181
Treatment group (OCA vs fibric acid derivatives) × baseline ALT values	0.20 (0.06–0.70)	.012
Including treatment group by baseline ALP values as an interaction term[c]		
Age at starting second-line therapy	1.04 (1.00–1.08)	.027
UDCA treated vs non-treated	3.05 (1.12–8.30)	.029
History of pruritus	0.41 (0.21–0.80)	.009
Baseline laboratory values		
ALT	0.71 (0.50–1.02)	.064
ALP	0.57 (0.43–0.75)	< .001
Bilirubin	0.89 (0.85–0.93)	< .001
Treatment group (OCA vs fibric acid derivatives)	0.38 (0.092–1.59)	.187
Cirrhosis	0.58 (0.23–1.49)	.260
Treatment group (OCA vs fibric acid derivatives) × baseline ALP values	1.46 (1.03–2.07)	.031
Including treatment group by age at starting second-line therapy as an interaction term[d]		
Age at starting second-line therapy	1.03 (0.99–1.07)	.105
UDCA treated vs non-treated	3.25 (1.22–8.68)	.019
History of pruritus	0.40 (0.21–0.78)	.007
Baseline laboratory values		
ALT	0.69 (0.49–0.99)	.044
ALP	0.67 (0.54–0.83)	< .001
Bilirubin	0.89 (0.85–0.93)	< .001
Treatment group (OCA vs fibric acid derivatives)	0.14 (0.001–13.39)	.40
Cirrhosis	0.60 (0.24–1.50)	.272
Treatment group × age at starting second-line therapy	1.04 (0.96–1.13)	.322
Including treatment group by concomitant UDCA as an interaction term[d]		
Age at starting second-line therapy	1.04 (1.00–1.08)	.026
UDCA treated vs. non-treated	3.01 (0.98–9.20)	.054
History of pruritus	0.41 (0.21–0.80)	.009
Baseline laboratory values		
ALT	0.68 (0.47–0.97)	< .001
ALP	0.68 (0.55–0.84)	< .001
Bilirubin	0.89 (0.86–0.93)	< .001
Treatment group (OCA vs fibric acid derivatives)	1.13 (0.13–9.95)	.911
Cirrhosis	0.62 (0.25–1.57)	.313
Treatment group (OCA vs fibric acid derivatives) × concomitant UDCA treated	1.26 (0.12–13.33)	.848
Including treatment group by baseline bilirubin as an interaction term[d]		
Age at starting second-line therapy	1.04 (1.00–1.07)	.028
UDCA treated vs non-treated	3.18 (1.20–8.44)	.020
History of pruritus	0.41 (0.21–0.79)	.007
Baseline laboratory values		
ALT	0.68 (0.48–0.97)	.033

Supplementary Table 7. Continued

	OR (95% CI)	*P* value
ALP	0.68 (0.55–0.84)	< .001
Bilirubin	0.89 (0.85–0.94)	< .001
Treatment group (OCA vs fibric acid derivatives)	1.17 (0.21–6.50)	.859
Cirrhosis	0.62 (0.25–1.56)	.308
Treatment group (OCA vs fibric acid derivatives) × baseline bilirubin	1.01 (0.92–1.12)	.829
Including treatment group by cirrhosis as an interaction term[d]		
Age at starting second-line therapy	1/04 (1.00–1.08)	.026
UDCA treated vs non-treated	3.15 (1.18–8.40)	.022
History of pruritus	0.41 (0.21–0.79)	.007
Baseline laboratory values		
ALT	0.68 (0.47–0.97)	.031
ALP	0.68 (0.55–0.85)	.001
Bilirubin	0.89 (0.86–0.93)	< .001
Treatment group (OCA vs fibric acid derivatives)	1.46 (0.60–3.53)	.406
Cirrhosis	0.66 (0.24–1.76)	.404
Treatment group (OCA vs. fibric acid derivatives) × cirrhosis	0.70 (0.07–7.03)	.759

ALP, Alkaline phosphatase; ALT, alanine transaminase; CI, confidence interval; OCA, obeticholic acid; OR, odds ratio; PAC, percentage accuracy classification; UDCA, ursodeoxycholic acid
[a]Model PAC 83.6%.
[b]Model PAC 84.2%.
[c]Model PAC 82.4%.
[d]Model PAC 83.3%.

Supplementary Table 8. Reasons for Drug Discontinuation During the Course of the Study

	OCA, n	Fibric acid derivatives, n
Myalgia	0	2
Elevated creatinine	0	1
Deterioration in liver biochemistry	6	3
Decompensation	5	0
Transplant assessment	5	1
Worsening pruritus	29	0
Miscellaneous intolerances[a]	25	13
Patient non-compliance	0	1
Non-response	7	2

OCA, Obeticholic acid.
[a]Includes gastrointestinal side effects (diarrhea, cramps, nausea, vomiting, abdominal pain), elevated creatinine, light-headedness, dizziness, and headache.