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Longitudinal outcomes of obeticholic acid therapy in ursodiol-nonresponsive primary biliary cholangitis: Stratifying the impact of add-on fibrates in real-world practice

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Summary

Background: Suboptimal response to ursodeoxycholic acid occurs in 40% of primary biliary cholangitis (PBC) patients, affecting survival. Achieving a deep response (normalisation of alkaline phosphatase [ALP] and bilirubin ≤0.6 upper limit of normal) improves survival. Yet, the long-term effectiveness of second-line treatments remains uncertain.

Aims: To evaluate the long-term effectiveness of obeticholic acid (OCA) ± fibrates. Focusing on biochemical response (ALP ≤1.67 times the upper limit of normal, with a decrease of at least 15% from baseline and normal bilirubin levels), normalisation of ALP, deep response and biochemical remission (deep response plus aminotransferase normalisation).

Methods: We conducted a longitudinal, observational, multicentre study involving ursodeoxyccholic acid non-responsive PBC patients (Paris-II criteria) from Spain and Portugal who received OCA ± fibrates.

Results: Of 255 patients, median follow-up was 35.1 months (IQR: 20.2–53). The biochemical response in the whole cohort was 47.2%, 61.4% and 68.6% at 12, 24 and 36 months. GLOBE-PBC and 5-year UK-PBC scores improved ($p < 0.001$). Triple therapy (ursodeoxycholic acid plus OCA plus fibrates) had significantly higher response rates than dual therapy ($p = 0.001$), including ALP normalisation, deep response and

[Correction added on 7 May 2024, after first online publication: The spelling of S. Rodríguez-Tajes' surname has been corrected in this version.]

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For affiliations refer to page 1613.

biochemical remission ($p<0.001$). In multivariate analysis, triple therapy remained independently associated with biochemical response ($p=0.024$), alkaline phosphatase normalisation, deep response and biochemical remission ($p<0.001$). Adverse effects occurred in 41.2% of cases, leading to 18.8% discontinuing OCA. Out of 55 patients with cirrhosis, 12 developed decompensation. All with baseline portal hypertension.

Conclusion: Triple therapy was superior in achieving therapeutic goals in UDCA-nonresponsive PBC. Decompensation was linked to pre-existing portal hypertension.

1 | INTRODUCTION

Patients with PBC who respond to UDCA have survival rates similar to those of healthy individuals.[1,2] However, persistent elevation of alkaline phosphatase (ALP) and serum bilirubin after 1 year of UDCA treatment is associated with worse transplant-free survival (TFS).[3,4] Several scoring systems, including GLOBE-PBC and UK PBC, are used to assess risk in PBC patients.[5,6] Timely evaluation of inadequate responses at 1 year, as well as assessment of liver fibrosis is crucial for considering second-line treatment options[7–10] Obeticholic acid (OCA), a novel therapy for PBC non-responders to UDCA, activates the nuclear farnesoid X receptor (FXR), leading to beneficial effects like down-regulating bile acid synthesis and inhibiting NF-KB activation in murine models.[11] The POISE trial demonstrated liver biochemical improvement with OCA compared to placebo in UDCA non-responders.[12] Additionally, fenofibrate, a predominant PPAR-α agonist and bezafibrate, a pan-PPAR agonist, have anti-cholestatic properties.[13] In a placebo-controlled trial involving UDCA suboptimal responders, bezafibrate significantly improved liver biochemistry.[14]

Due to the low prevalence of PBC and its long natural history, conducting prospective studies or clinical trials to compare treatment outcomes can be challenging. Real-world data analysis, including surrogate prognosis markers from second-line treatments of PBC, can provide valuable insights on long-term outcomes.[4–6] Although clinical trials have assessed the efficacy of OCA and bezafibrate,[12,14] there remains a knowledge gap regarding their long-term effectiveness, including ALP normalisation, deep response (normalisation of ALP and bilirubin ≤0.6 upper limit of normal) and biochemical remission (deep response plus aminotransferases normalisation), all of which have been linked to better TFS and OS.[15] Furthermore, in two recent studies in large international cohorts treated with UDCA, elevation of ALP in the setting of a normal GLOBE-PBC score or response according to Paris II criteria was associated with worse liver TFS,[16] especially in younger patients with more advanced liver fibrosis,[17] indicating the need for second-line therapy.

Therefore, this study aimed to assess the long-term effectiveness of OCA-based second-line therapy and subsequently fibrates in a subset of patients as a triple therapy in PBC patients who did not respond to UDCA treatment as per the Paris II criteria.

2 | METHODS

2.1 | Patients and design

This is an observational, cohort study, with prospective data collection and periodic retrospective analysis at 3 and 6 months from the start and then every 6 months. The extended study expanded the IBER-PBC cohort,[18] with an extended follow-up period which is now of 35.1 months (IQR 20.2–53), including 255 consecutive UDCA non-responders (per Paris II Criteria) from 24 institutions in Spain and Portugal (Paris II response is a prerequisite for the public health system to accept funding for second-line treatments in both countries). Recruitment started in September 2016, was approved by Institutional Research Boards and ended in March 2023. Patients were diagnosed with PBC based on intrahepatic cholestasis (elevation of ALP and GGT, gamma-glutamyl-transferase levels after ruling out extrahepatic bile duct obstruction) and a positive AMA (antimitochondrial antibodies) at a titre ≥1:80. If AMA was negative, patients were included if GP210 and/or SP100 antibodies were positive or if a suggestive liver biopsy indicated PBC. Assessment at each visit included blood count, liver biochemistry and the continuous scores (GLOBE PBC and UK-PBC) at baseline and during subsequent visits. The biochemical responses were assessed initially at 3 and 6 months and then at 12, 24 and 36 months.

There was no predefined consensus on the timing for initiating triple therapy or on the criteria for deeming dual therapy ineffective, and the decision to initiate triple therapy was made by each investigator at various times throughout the study (Figure S1) based on biochemical criteria. These criteria typically included ALP persisting at 1.5 times the upper limit of normal, with the remaining cases based on difficult-to-manage pruritus. The initiation of fibrates marked time zero for triple therapy.

Diagnosis of cirrhosis was made by liver biopsy, baseline VCTE value ≥16.9 kPa or by ultrasound (nodular liver surface plus at least one of the following criteria: splenomegaly or increased portal vein size), esophago-gastric varices or thrombocytopenia (100×10^9/L).

All patients received either OCA or OCA + fibrates, with the latter administered after OCA therapy. The dosage of OCA throughout the study is recorded in Table S2. The dose of bezafibrate remained constant during the study at 400 mg/day and that of fenofibrate at 160 mg/day in extended-release tablets/day. Treatment tolerance

and adverse effects were monitored at each visit. The severity of pruritus at baseline and during follow-up was evaluated using the verbal rating scale (VRS), which assigns a score of 0 for absence of pruritus, 1 for mild pruritus, 2 for moderate and 3 for severe. The VRS has been shown to have a strong correlation with visual analogue scales.[19]

Hepatic decompensation was defined as either an acute onset (including upper GI haemorrhage, ascites grade 2–3, hepatic encephalopathy or sepsis) or progressive onset (ascites, hepatic encephalopathy or jaundice).[20]

2.2 | Inclusion criteria

Consecutive patients with PBC with insufficient response to UDCA after 1 year of treatment according to the Paris II criteria[9] who initiated treatment with OCA in each participating centre.

2.3 | Exclusion criteria

Decompensated patients at baseline, previously transplanted patients or pregnancy, patients with overlap syndromes and patients previously treated with UDCA plus fibrates.

2.4 | Endpoints

Primary endpoints were to assess the long-term effect of treatment on:

1. Biochemical response (reduction of ALP level 1.67 times the upper limit of the normal range, with decrease of at least a 15% from baseline and a normal bilirubin level).
2. Normalisation of ALP, deep response (normalisation of ALP and bilirubin ≤0.6 ULN) and biochemical remission, which includes deep response plus normalisation of ALT and AST.

Secondary end-points were:

1. Assessment of the effect on GLOBE-PBC and UK-PBC scores.
2. Impact on pruritus and safety.

2.5 | Statistical analysis

We used linear mixed and generalised linear mixed models for analysing longitudinal data, with an unstructured covariance matrix. Results present estimated differences from baseline in dual therapy and the additional effect of triple therapy, along with 95% confidence intervals (CI95%).[21] Biochemical response, ALP normalisation, deep response and biochemical remission were assessed at 12, 24 and 36 months using the cumulative incidence function, considering discontinuation as a competing event. To analyse associated factors, subhazard ratios (sHRs) were determined using competing-risk regression models. Subjects were censored at their last follow-up date, with fibrates being considered a time-varying covariate. Liver-related survival and liver-related event-free survival were estimated using the Kaplan–Meier function. In the multivariate analysis, adjusting covariates included age, cirrhosis, baseline pruritus, baseline OCA dose, ALP and bilirubin levels. Statistical analysis was conducted using SPSS 17 and STATA 17 software.

3 | RESULTS

3.1 | Baseline clinical and demographic features

For the final analysis, the IBER-PBC cohort comprised 255 patients who met the selection criteria for the study (Figure S1). Among them, 90% were female and 83.3% tested positive for AMA, while 55.6% tested positive for ANA. The mean age at OCA initiation was 57.4 (SD 10.3) years (Table 1). Of the 43 patients with negative AMA results, 20 tested positive for GP210 or SP100 antibodies, while 23 had compatible liver biopsy findings. Cirrhosis was diagnosed in 55 patients (21.4% of the cohort). The median follow-up for dual therapy was 35.1 (IQR 20.2–53; Table 1). Among all patients, 57 received concomitant fibrates following OCA initiation (48 bezafibrate, 9 fenofibrate), mainly due to the ineffectiveness of dual therapy (43 cases) and pruritus (14 cases; Table 1). The median time to fibrate initiation was 18 months (IQR 7.8–30.6; Table 1). Baseline pruritus was present in 107 individuals (40.1% of the cohort) and pruritus was significantly more frequent in patients who initiated triple therapy (Table 1).

3.2 | Biochemical response

A total of 185 patients achieved biochemical response over time: 47.2%, 61.4% and 68.6% at 12, 24 and 36 months, respectively (Figure 1A). Univariate analysis showed a significant association between biochemical response and triple therapy, lower levels of ALP and bilirubin, the absence of cirrhosis and lower GLOBE and UK-PBC scores (Table S1). At multivariate analysis, lower ALP and bilirubin levels, baseline pruritus and triple therapy remained significantly associated with biochemical response (adjusted sHR = 1.67, 95% CI: 1.07–2.6, $p = 0.024$; Table 3).

There was a significant reduction over time in ALP, GGT, and aminotransferases with dual therapy ($p < 0.001$; Table 2). Triple therapy led to additional decreases in ALP (0.84 ULN, 95% CI: 0.63–1.04, $p < 0.001$) and GGT (1.01 ULN, 95% CI: 0.32–1.7, $p = 0.004$; Table 2, Figure 2); however, it had no effect on aminotransferases. Bilirubin values did not significantly change.

Serum albumin levels increased significantly over time ($p = 0.033$), but no significant effect was observed with triple therapy. There was

TABLE 1 Baseline clinical and demographic characteristics.

	Total (*N* = 255)	No fibrates (*N* = 198)	Fibrates added (*N* = 57)	Univariate *p*-value
Age (years), mean (SD)	57.4 (10.3)	58 (9.9)	55.3 (11.3)	0.101
Years since diagnosis, median (IQR)	6.6 (2.5–12.7)	6.9 (2.7–13.6)	5.1 (2.1–10.8)	0.058
Females, *N* (%)	233 (90.7%)	181 (91.4%)	51 (89.5%)	0.652
Diabetes mellitus (DM), *N* (%)	24 (9.3%)	19 (9.6%)	5 (8.8%)	0.851
AMA+, *N* (%)	214 (83.3%)	167 (84.3%)	45 (78.9%)	0.338
ANA+, *N* (%)	143 (55.6%)	112 (56.6%)	31 (54.4%)	0.770
Cirrhosis CPT A5-A6, *N* (%)	55 (21.4%)	46 (23.2%)	9 (15.8%)	0.229
Oesophageal varices, *N* (%)	27 (10.5%)	23 (11.6%)	4 (7%)	0.320
Other autoimmune diseases, *N* (%)	73 (28.4%)	57 (28.8%)	15 (26.3%)	0.715
Liver biopsy, *N* (%)	120 (47.1%)	96 (48.5%)	24 (42.1%)	0.395
Fibrosis Stage (METAVIR), *N* (%)				
F0–1	49 (49.5%)	39 (50.6%)	10 (45.5%)	0.638
F2	26 (26.3%)	21 (27.3%)	5 (22.7%)	
F3–4	24 (24.2%)	17 (22.1%)	7 (31.8%)	
Pruritus	103 (40.1%)	70 (35.4%)	33 (57.9%)	**0.002**
Fibrates added	57 (22.4%)			
Bezafibrate	48 (84.2%)		48 (84.2%)	
Fenofibrate	9 (15.8%)		9 (15.8%)	
Reason add-on fibrates, *N* (%)				
Non response	43 (75.4%)		43 (75.4%)	
Pruritus	14 (24.6%)		14 (24.6%)	
Months to fibrates, median (IQR)	18 (7.8–30.6)		18 (7.8–30.6)	
Baseline OCA dose ≥5 mg, *N* (%)	243 (94.6%)	186 (93.9%)	55 (96.5%)	0.742
Baseline OCA dose, median (IQR)	5 (5–5)	5 (5–5)	5 (5–5)	0.446
ALP ×ULN, median (IQR)	2.1 (1.8–2.9)	2 (1.7–2.7)	2.5 (2–3.7)	**0.000**
ALT ×ULN, median (IQR)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	1.3 (0.9–2.1)	0.095
AST ×ULN, median (IQR)	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.1 (0.9–2.1)	0.563
GGT ×ULN, median (IQR)	3.9 (2.2–7.1)	3.5 (2.2–6.8)	5 (2.9–8)	0.085
Bilirubin ×ULN, median (IQR)	0.6 (0.4–0.8)	0.6 (0.5–0.8)	0.5 (0.4–0.9)	0.750
Platelets ×LLN, median (IQR)	1.66 (1.23–2.1)	1.59 (1.18–2.07)	1.83 (1.38–2.41)	**0.017**
Albumin ×LLN, median (IQR)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.947
IgM, mg/dL, median (IQR)	296 (159.5–423.5)	309 (158.5–433.3)	254 (163–400.3)	0.344
Cholesterol, mg/dL, median (IQR)	220 (189.8–249)	216 (186.5–243.5)	242 (205–275)	**0.001**
Triglycerides, mg/dL, median (IQR)	98 (72–131.5)	97 (71–131)	101 (74.5–141.3)	0.650
MELD, median (IQR)	6 (6–7)	6 (6–7)	6 (6–7)	0.313
TE, kPa, median (IQR)	7.6 (5.8–11.5)	8 (5.6–11.8)	6.8 (6–9.7)	0.476
GLOBE-score, median (IQR)	0.2 (−0.5–0.8)	0.2 (−0.4–0.7)	−0.1 (−0.5–0.8)	0.571
PBC GLOBE 3y, median (IQR)	95.8 (92.8–97.9)	95.6 (93–97.7)	96.8 (92.4–98)	0.587
PBC GLOBE 5y, median (IQR)	92.5 (87.4–96.2)	92.3 (87.9–95.8)	94.2 (86.8–96.4)	0.581
PBC GLOBE 10y, median (IQR)	81.2 (69.6–90.1)	80.6 (70.5–89.2)	85.2 (68.3–90.5)	0.570

(Continues)

TABLE 1 (Continued)

	Total (*N* = 255)	No fibrates (*N* = 198)	Fibrates added (*N* = 57)	Univariate *p*-value
UK PBC 5y, median (IQR)	1.5 (0.9–2.8)	1.5 (0.8–2.8)	1.4 (0.9–2.6)	0.994
UK PBC 10y, median (IQR)	4.8 (2.8–9)	4.9 (2.7–9.1)	4.5 (2.8–8.6)	0.997
Months of follow up since OCA initiation, median (IQR)	35.1 (20.2–53)	33 (19.1–51.3)	39.8 (26.1–58.9)	**0.017**

Abbreviations: IQR, Q1–Q3; SD, standard deviation; TE, transient elastography.

The values in bold are those that reached statistical significance in the univariate analysis.

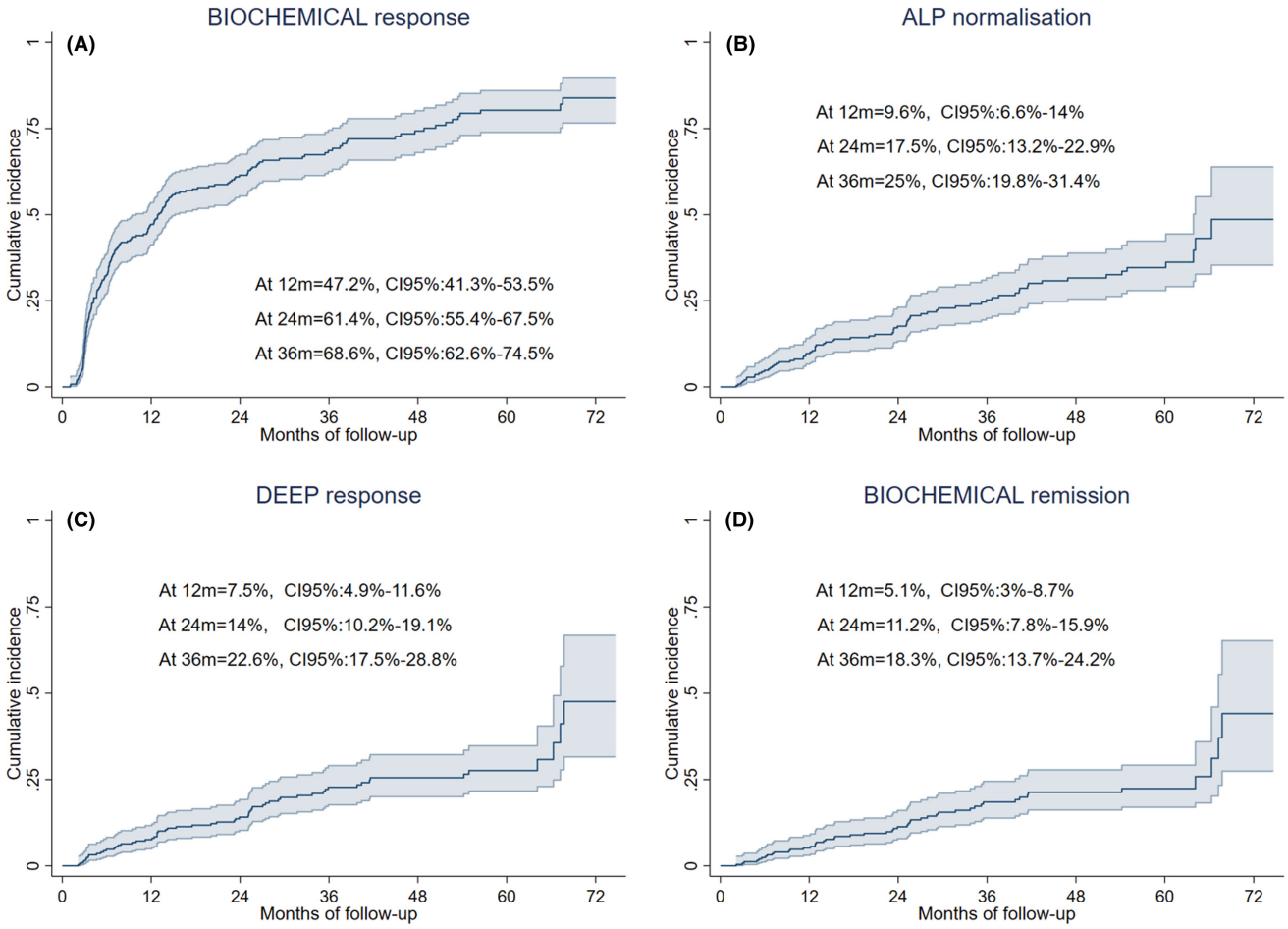

FIGURE 1 Cumulative incidence function of biochemical response, ALP normalisation, deep response and biochemical remission. (A) Cumulative incidence function of biochemical response in the whole population. (B) Cumulative incidence function of Alkaline Phosphatase normalisation in the whole population. (C) Cumulative incidence function of deep-response in the whole population. (D) Cumulative incidene function of biochemical remission in the whole population.

a small yet significant increase in creatinine levels at 48 months of 0.05 mg/dL (0.02–0.08) with dual therapy and 0.07 mg/dL (0.03–0.11) with triple therapy (Table 2).

IgM, total serum cholesterol and triglyceride levels decreased over time, with a significant effect of triple therapy on cholesterol reduction (17.9 mg/dL, 95% CI: 7.39–28.36, $p = 0.001$; Table 2).

There was a significant improvement in the GLOBE-PBC risk score ($p < 0.001$), with triple therapy associated with a 0.37-point reduction compared to dual therapy (95% CI: 0.25–0.48, $p < 0.001$), and in the UK-PBC risk score at 5 years ($p = 0.009$), although triple therapy did not show a significant effect (Table 2).

The MELD score and transient elastography (TE) results remained stable over time ($p = 0.727$; Table 2).

3.3 | ALP normalisation, deep response and biochemical remission

The cumulative incidence of ALP normalisation at 12, 24 and 36 months was 9.6%, 17.5% and 25.2%; 7.5%, 14% and 22.6% for deep response; and 5.1%, 11.2% and 18.3% for biochemical remission (Figure 1B–D), with a higher response rate observed in the triple

TABLE 2 Therapy effect on biochemical values, continuous scoring systems, MELD and liver stiffness over time.

			Dual therapy effect			Triple therapy additional effect			
	Time effect	Months	Difference from baseline	CI95%		Triple therapy effect	*p*-value	CI95%	
ALP ×ULN	<0.001	12	−0.74	−0.85	−0.63	−0.84	**<0.001**	−1.04	−0.63
		24	−0.80	−0.92	−0.67				
		36	−0.86	−1.01	−0.72				
ALT ×ULN	<0.001	12	−0.61	−0.74	−0.49	0.00	0.978	−0.20	0.21
		24	−0.64	−0.78	−0.50				
		36	−0.66	−0.81	−0.50				
AST ×ULN	<0.001	12	−0.42	−0.54	−0.31	0.11	0.253	−0.08	0.30
		24	−0.48	−0.60	−0.35				
		36	−0.46	−0.60	−0.32				
GGT ×ULN	<0.001	12	−2.70	−3.08	−2.33	−1.01	**0.004**	−1.70	−0.32
		24	−2.97	−3.40	−2.55				
		36	−3.11	−3.59	−2.63				
Bilirubin ×ULN	0.102	12	−0.03	−0.07	0.01	−0.03	0.452	−0.11	0.05
		24	−0.06	−0.10	−0.01				
		36	−0.02	−0.07	0.03				
Platelets ×LLN	<0.001	12	−0.11	−0.15	−0.07	0.13	**0.001**	0.05	0.21
		24	−0.11	−0.16	−0.07				
		36	−0.13	−0.18	−0.08				
Albumin ×LLN	0.033	12	0.01	0.00	0.02	0.00	0.816	−0.02	0.02
		24	0.01	0.00	0.02				
		36	0.02	0.01	0.04				
Creatinine (mg/dL)	0.007	12	0.00	−0.02	0.02	0.03	0.165	−0.01	0.06
		24	0.02	−0.01	0.04				
		36	0.01	−0.01	0.04				
IgM (mg/dL)	<0.001	12	−72.42	−94.83	−50.00	−23.73	0.248	−64.03	16.57
		24	−89.49	−115.23	−63.76				
		36	−97.89	−125.86	−69.91				
Cholesterol (mg/dL)	<0.001	12	−15.91	−21.85	−9.96	−17.88	**0.001**	−28.36	−7.39
		24	−20.69	−27.51	−13.87				
		36	−22.57	−30.10	−15.04				
Triglycerides (mg/dL)	0.006	12	−9.97	−15.86	−4.08	−1.39	0.791	−11.69	8.90
		24	−6.31	−13.09	0.48				
		36	−9.96	−17.37	−2.55				
GLOBE-PBC	<0.001	12	−0.12	−0.19	−0.06	−0.37	**<0.001**	−0.48	−0.25
		24	−0.19	−0.26	−0.12				
		36	−0.20	−0.28	−0.12				
UK PBC 5y	0.009	12	−0.44	−0.75	−0.14	0.15	0.62	−0.44	0.74
		24	−0.58	−0.93	−0.23				
		36	−0.31	−0.70	0.09				
MELD	0.727	12	0.01	−0.14	0.17	0.12	0.409	−0.17	0.42
		24	−0.10	−0.28	0.09				
		36	−0.07	−0.27	0.13				
TE	0.321	12	0.92	−0.18	2.01	−0.16	0.878	−2.24	1.91
		24	−0.65	−2.07	0.77				
		36	0.07	−1.38	1.53				

Note: Mixed models analysis, with adjustment for age and cirrhosis.

The values in bold are those that reached statistical significance in the mixed models analysis, with adjustement for age and cirrhosis.

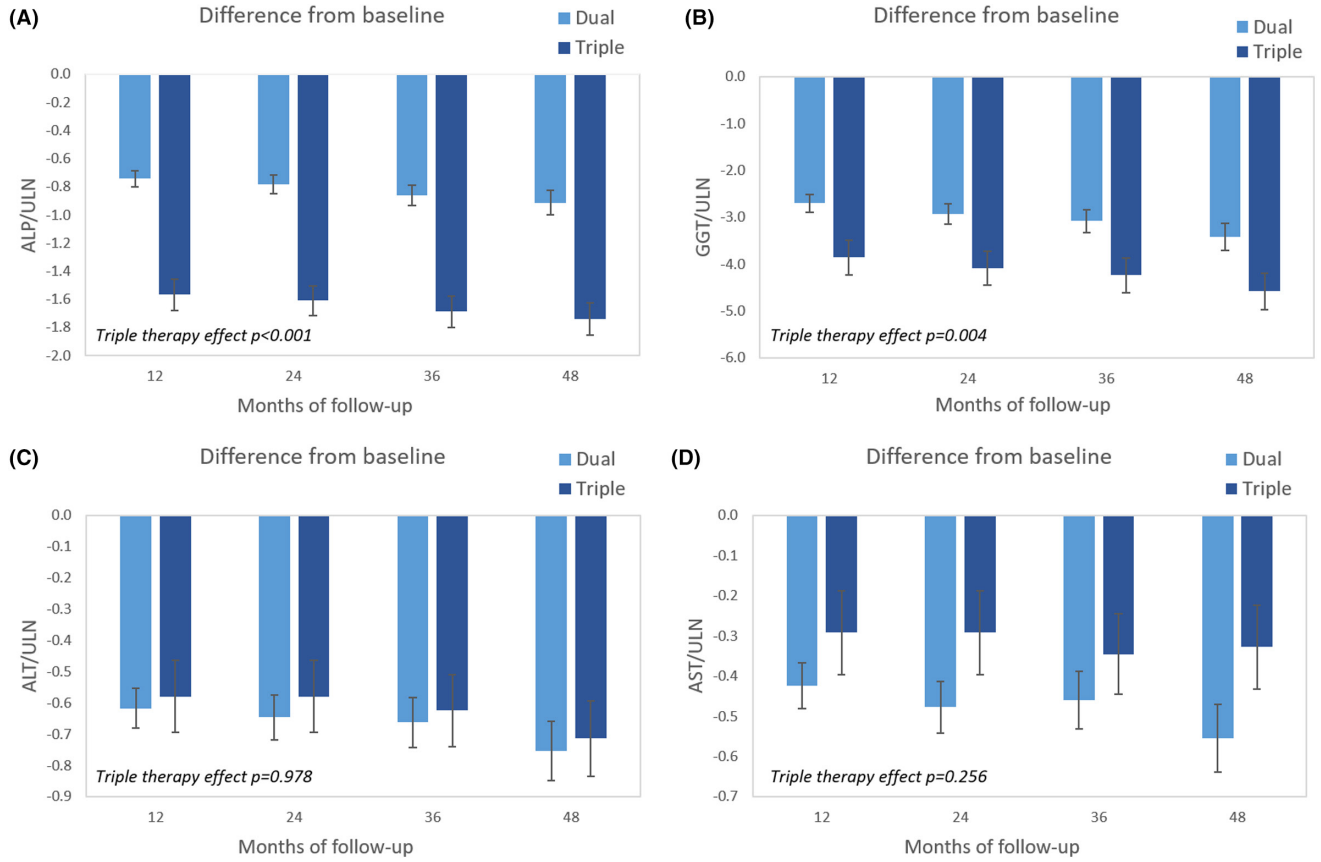

FIGURE 2 Triple therapy effect on ALP, GGT, ALT and AST over time. Estimated differences from baseline with standard errors (bars). (A) Reduction of Alkaline Phosphatase from baseline over time in dual and triple therapy. (B) Reduction of Gamma-Glutamyl-Transferase from baseline over time in dual and triple therapy. (C) Reduction of Alanine Aminotranferase from baseline over time in dual and triple therapy. (D) Reduction of Aspartate Aminotransferase from baseline over time in dual and triple therapy.

therapy group (Figure 3B–D). In univariate analysis, cirrhosis, ALP, bilirubin, GLOBE-PBC and UK-PBC scores were associated with response (Table S2).The adjusted effect of triple therapy was statistically significant across all criteria (Table 3).

3.4 | Effect on pruritus

At baseline, 103 patients (40.1%) experienced pruritus, of whom 23 (8%) experienced grade pruritus 2–3 as assessed by the VRS. The prevalence of grade 2–3 pruritus increased to 9% at 12 months of treatment, then decreased to 6% at 24 months and to 4.4% at 36 months (not significant) without a reduction in the OCA dosage. Within the subgroup receiving triple therapy, 7 cases (13.2%) presented with grade 2–3 pruritus at baseline, with 5 of these cases improving following the initiation of fibrates. Among patients on triple therapy without baseline pruritus, 10 developed grade 2–3 pruritus during OCA treatment, and of these cases, 7 cases showed improvement with the initiation of fibrates.

3.5 | Safety and tolerability

Adverse effects were observed in 41.2% of cases, primarily mild (as shown in Table S3); however, OCA was discontinued in 48 patients (18.8%). Reasons for discontinuation included: 12 cases of pruritus, eight cases of non-response, six cases of ascites development, four cases of non-adherence, three cases of oesophageal variceal bleeding, three cases of OCA intolerance, three cases of pregnancy, two cases of non-specific cutaneous lesions and one case each of liver transplantation, arthralgia, diarrhoea, heart failure and worsening of liver biochemistry, warnings and restriction recommendations issued by regulatory agencies.

No significant differences were observed in OCA discontinuation rates between dual and triple therapy (20.3% vs. 13.8%, $p=0.265$). Among the 55 patients with cirrhosis CPT-A5-6, 12 experienced decompensation. It is noteworthy that all these patients exhibited clinically significant portal hypertension (CSPH) at baseline, as evidenced by the presence of oesophageal varices.

Three patients died from liver-related diseases, and four underwent transplantation. Liver-related survival at 3 years was 98.9% (95% CI 95.6%–99.7%), which was comparable to the GLOBE survival baseline estimate (median 96%; IQR: 93%–98%). Furthermore, two patients without cirrhosis experienced decompensation: one case of oesophageal variceal bleeding secondary to pre-sinusoidal portal hypertension due to nodular regenerative hyperplasia and one case of ascites. One additional patient developed hepatocellular carcinoma without a diagnosis of cirrhosis at baseline. Liver event-free survival at 3 years was 94.6% (95% CI 90.6%–96.9%). Three

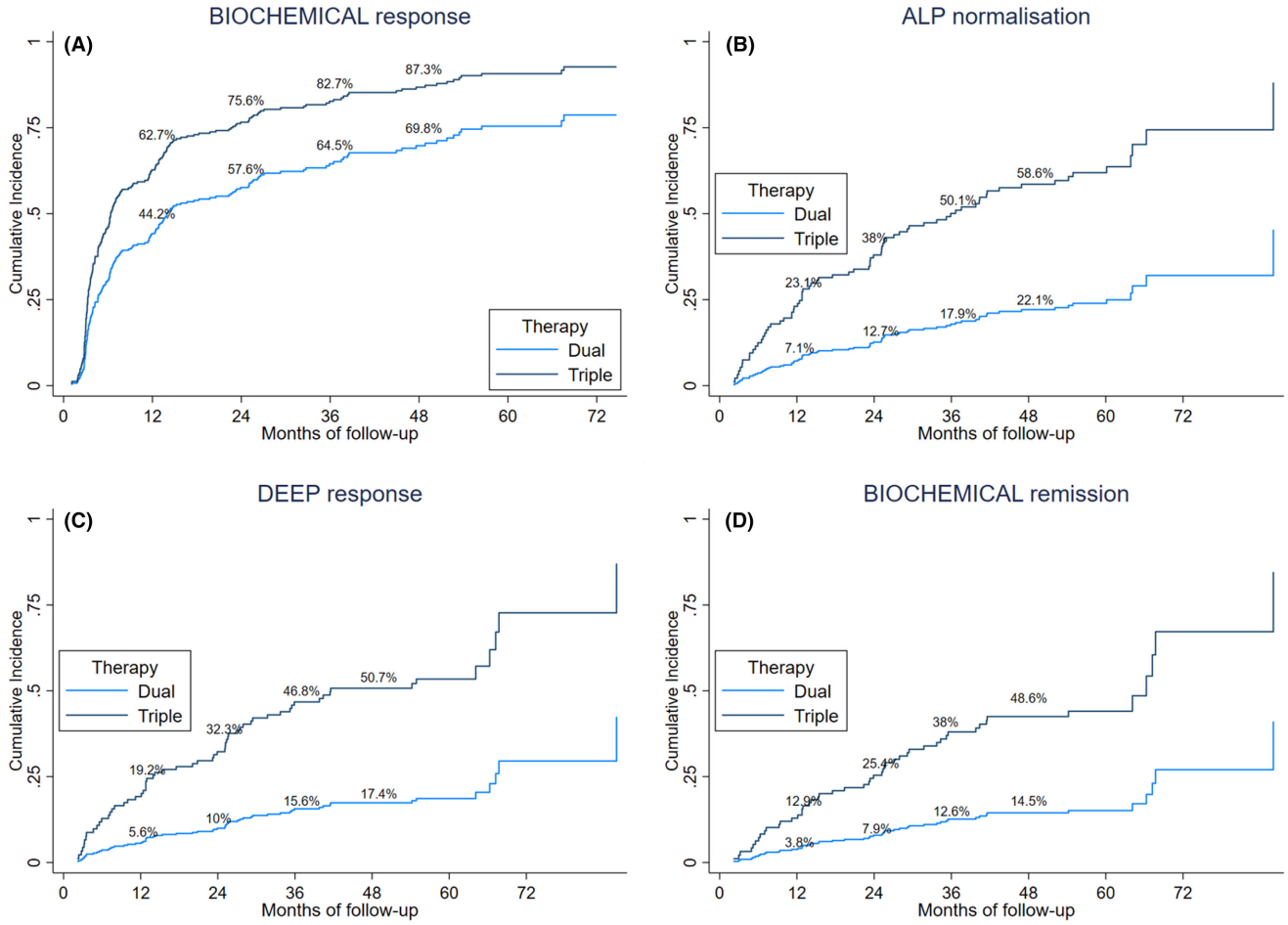

FIGURE 3 Cumulative incidence function of biochemical response (A), ALP normalisation (B), Deep-response (C) and biochemical remission (D).

deaths unrelated to liver disease occurred (lung cancer, COVID-19 pneumonia and heart failure).

4 | DISCUSSION

Randomised clinical trials (RCT) serve as the gold standard for assessing drug efficacy and safety, yet they may not accurately represent the heterogeneity of patient populations in real-world clinical practice, commonly involving patients with compromised health status, adherence difficulties and a higher prevalence of comorbidities, particularly in older populations. Moreover, RCTs may have insufficient follow-up duration to detect long-term effects and safety issues associated with chronic therapy. Integrating real-world populations into research significantly improves external validity, highlighting its importance as a relevant source of information.[22–25] This observational study provides data on the long-term effects of therapeutic interventions in real practice.

This study shows an improvement in surrogate biochemical markers related with outcomes in PBC; specifically, there was a decrease in ALP and GGT. The reduction of ALP and GGT was more pronounced in the subgroup receiving triple therapy without further reduction of triple therapy on aminotransferases. These findings align with those of a recent observational study.[26]

The rate of biochemical response in the dual therapy group at 1 year was 44.2%, slightly lower than that achieved in the POISE trial.[12] The rate of biochemical response with triple therapy significantly increased this response at 12 months to 62.7%. The cumulative biochemical response, deep response and biochemical remission were all lower in patients with cirrhosis at the univariate analysis, consistent with previous results.[27] However, in the adjusted analysis, only a lower degree of cholestasis as reflected by the absence of baseline pruritus, lower levels of ALP and bilirubin and triple therapy remained associated with responses. The reason for the association of baseline pruritus with a lower response does not seem to be linked to a reduction in OCA dosage, as it increased throughout the study; therefore, it may be related to the degree of cholestasis as suggested by the association, with levels of ALP and bilirubin.

The association of triple therapy with a positive response in all biochemical primary endpoints underscores the importance of this treatment approach in optimising therapeutic outcomes. Notably, this augmented response with triple therapy, although the subgroup is only 25% of the whole cohort, maintained statistical significance across all primary endpoints in the multivariate analysis, providing a

TABLE 3 Adjusted triple therapy effect in biochemical response, ALP normalisation, deep response and biochemical remission.

	sHR	CI95%		*p*-value
Biochemical response				
Triple therapy	1.67	1.07	2.60	**0.024**
Cirrhosis	0.76	0.48	1.19	0.228
Age at OCA start	1.00	0.98	1.01	0.8
Baseline OCA Dose	1.00	0.81	1.22	0.969
Baseline pruritus	0.64	0.46	0.90	**0.009**
Alkaline phosphatase (/ULN)	0.84	0.72	0.98	**0.028**
Total bilirubin (/ULN)	0.52	0.34	0.80	**0.002**
ALP normalisation				
Triple therapy	4.31	2.52	7.35	**<0.001**
Cirrhosis	1.61	0.79	3.30	0.191
Age at OCA start	0.99	0.97	1.02	0.685
Baseline OCA Dose	0.91	0.70	1.20	0.504
Baseline pruritus	0.50	0.29	0.86	**0.013**
Alkaline phosphatase (/ULN)	0.62	0.46	0.84	**0.002**
Total bilirubin (/ULN)	0.38	0.15	0.94	**0.036**
Deep response				
Triple therapy	4.16	2.37	7.30	**<0.001**
Cirrhosis	0.78	0.33	1.82	0.564
Age at OCA start	0.99	0.97	1.02	0.699
Baseline OCA Dose	1.08	0.75	1.55	0.693
Baseline pruritus	0.35	0.18	0.67	**0.002**
Alkaline phosphatase (/ULN)	0.62	0.45	0.85	**0.003**
Total bilirubin (/ULN)	0.22	0.06	0.87	**0.031**
Biochemical remission				
Triple therapy	3.77	2.09	6.78	**<0.001**
Cirrhosis	0.65	0.24	1.79	0.404
Age at OCA start	1.01	0.98	1.04	0.554
Baseline OCA Dose	0.97	0.66	1.41	0.869
Baseline pruritus	0.38	0.19	0.78	**0.008**
Alkaline phosphatase (/ULN)	0.59	0.39	0.90	**0.014**
Total bilirubin (/ULN)	0.08	0.02	0.29	**<0.001**

Note: Sub-hazard ratio (sHR) estimated by time-dependent competing risk regression multivariate models.

The values in bold are those that reached statistical significance.
Sub-hazard ratio (sHR) estimated by time-dependent competing risk regression multivariate models.

robust indication of effectiveness. The observation of a cumulative incidence of responses over time suggests the importance of sustained therapeutic intervention and the potential long-term benefits of this treatment strategy. However, the low rate of response even with triple therapy at stringent biochemical end-points highlights the need for incorporating new treatments with positive results in Phase III trials[28,29] and others in earlier phases of development.[30,31] Future therapies may entail that individualised approach, considering patient age, non-invasive determination of fibrosis stage and the degree of cholestasis.[7,17,32]

There was a significant favourable effect on GLOBE-PBC and UK-PBC scores, in the case of GLOBE-PBC but not of UK-PBC, this improvement was enhanced by triple therapy. While neither scoring system has been specifically validated in OCA-treated recent analyses indicate their applicability in this context.[33] A recent propensity score-matching analysis indicated that OCA-treated patients in the POISE trial had longer compared to two historical external cohorts (GLOBE and UK-PBC).[34]

There was a small but significant increase in serum albumin in dual therapy with no significant effect of triple therapy. This finding is noteworthy considering the lack of evidence supporting a beneficial effect of UDCA on serum albumin levels in patients with PBC.[35] A recent large international dataset machine-learning-based analysis identified a subgroup with serum albumin levels at least 1.2 times the lower limit of normal as having the best prognosis, highlighting the potential clinical significance of serum albumin in PBC management.[36]

Clinical trials have shown the efficacy of bezafibrate and fenofibrate in patients with PBC with an incomplete response to UDCA.[14,37] Moreover, retrospective cohort analyses from Japan have shown that UDCA in combination with bezafibrate improved GLOBE and UK-PBC scores and long-term prognosis compared with UDCA alone.[38,39] Recent studies have shown that add-on fibrates to UDCA + OCA further improve biochemical response,[40,41] suggesting potential synergistic effects by targeting different mechanisms.[42]

Pruritus was the main reason for the discontinuation of our study. However, the introduction of fibrates appeared beneficial, improving pruritus, regardless of whether it was pre-existing or OCA-induced. These observations confirm fibrates as a valuable adjunctive treatment for pruritus management in cholestatic patients.[43] Nonetheless, the high discontinuation rate emphasises the need for more tolerable second-line drugs to enhance adherence and effectiveness.[44]

Unexpectedly, serum creatinine levels increased minimally but significantly in the dual therapy group and further increased in patients receiving triple therapy. Although this increase did not reach significance, it is a well-known class effect of fibrates with no long-term influence on renal function.[45]

Liver stiffness remained unchanged with long-term treatment, consistent with observations from the POISE trial, which showed no variation in non-invasively assessed fibrosis at 12 months.[12] In addition, there were no changes with triple therapy.

All 12 patients with cirrhosis who decompensated had CSPH, as evidenced by the presence of oesophageal varices. Recent research indicates that advanced PBC disease, rather than OCA and fibrates, is associated with an increased risk of decompensation. Moreover, positive responses to OCA and fibrates are shown to reduce the risk of decompensation.[46] CSPH is considered the primary driver of decompensation in patients with cirrhosis.[47] A recent retrospective analysis of a PBC cohort indicates that CSPH may occur early in PBC and is associated with an increased risk for subsequent

decompensation and mortality.[48] Outside of this scenario, the administration of second-line treatment appears to be safe for the subgroup of patients with compensated cirrhosis.

There were no significant differences in the rate of discontinuation of OCA and fibrates, which is consistent with recent findings from the British Cohort of second line therapies in PBC.[49]

Some limitations of this study should be noted, particularly the retrospective analysis and the relatively small sample size of the subgroup receiving triple therapy, which hinders a comprehensive safety analysis of fibrates specifically in patients with cirrhosis.

These long-term, real-world results show a significant improvement in biochemical surrogate markers of PBC outcomes, including the GLOBE-PBC and UK-PBC scoring systems. Triple therapy outperformed dual therapy in biochemical response, including stringent biochemical markers and GLOBE-PBC.

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E. Gómez: Visualization; investigation. **J. L. Montero:** Visualization; investigation. **E. Molina:** Investigation; visualization. **L. García-Buey:** Investigation; visualization. **M. Casado:** Investigation; visualization. **J. Fuentes:** Investigation; visualization. **M. A. Simón:** Investigation; visualization. **A. Díaz-González:** Investigation; visualization. **F. Jorquera:** Investigation; visualization. **R. M. Morillas:** Investigation; visualization. **J. Presa:** Investigation; visualization. **M. Berenguer:** Investigation; visualization. **M. I. Conde:** Investigation; visualization. **A. Olveira:** Investigation; visualization. **G. Macedo:** Investigation; visualization. **I. Garrido:** Investigation; visualization. **M. Hernández-Guerra:** Visualization; investigation. **I. Olivas:** Investigation; visualization. **S. Rodríguez-Tajes:** Investigation; visualization. **M. Londoño:** Investigation; visualization. **J. M. Sousa:** Investigation; visualization. **J. Ampuero:** Investigation; visualization; conceptualization. **E. Romero-González:** Visualization; investigation. **Sh. González-Padilla:** Investigation; visualization. **D. Escudero-García:** Investigation; visualization. **A. Carvalho:** Investigation; visualization. **A. Santos:** Investigation; visualization. **M. L. Gutiérrez:** Investigation; visualization. **E. Pérez-Fernández:** Methodology; formal analysis; supervision; data curation; visualization; writing – review and editing; software. **L. Aburruza:** Investigation; visualization. **J. Uriz:** Investigation; visualization. **D. Gomes:** Visualization; investigation. **J. Martínez-González:** Investigation; visualization. **L. Santos:** Investigation; visualization. **A. Albillos:** Visualization; investigation. **C. M. Fernández-Rodríguez:** Conceptualization; investigation; funding acquisition; visualization; methodology; data curation; writing – original draft; supervision; validation; writing – review and editing; project administration; software.

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SUPPORTING INFORMATION

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