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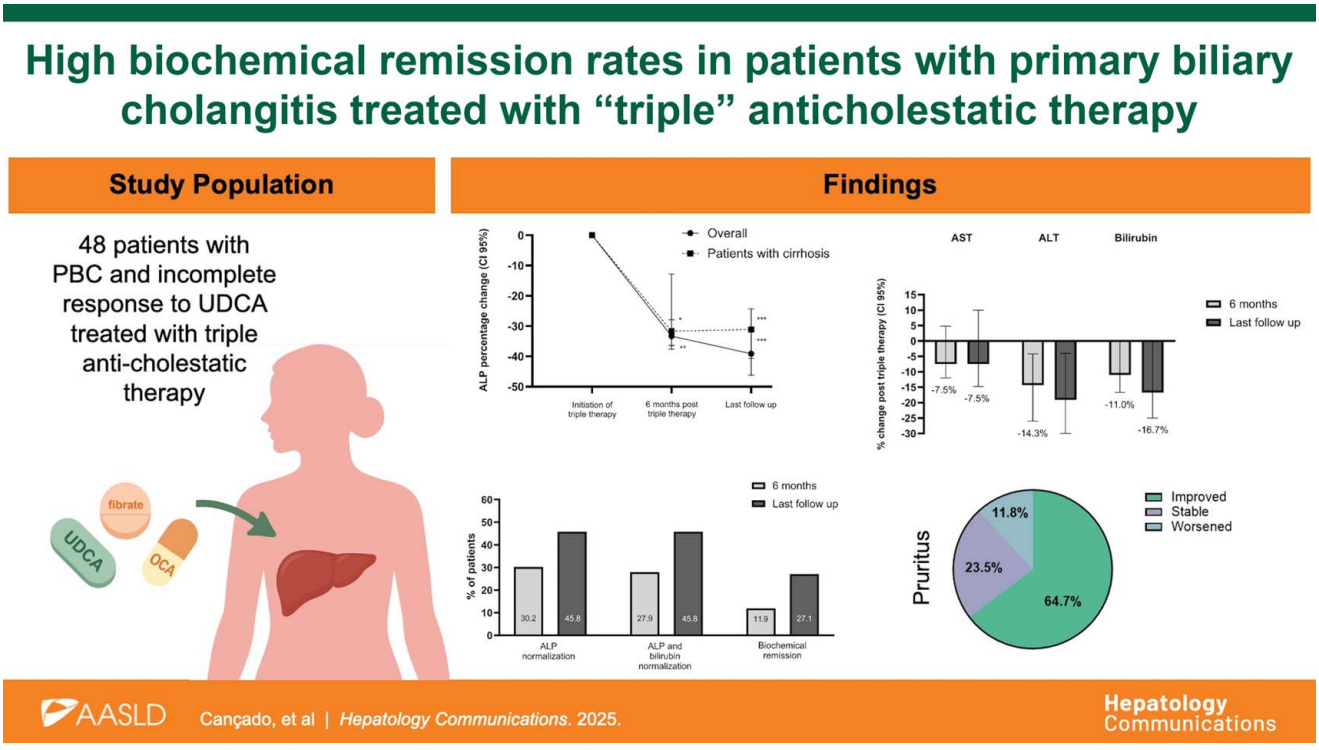
VISUAL ABSTRACT



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ORIGINAL ARTICLE

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High biochemical remission rates in patients with primary biliary cholangitis treated with "triple" anticholestatic therapy

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Abstract

Background: Treatment goals in primary biliary cholangitis (PBC) are increasingly aspirational, aiming for normal serum liver tests. One of the add-on therapies to ursodeoxycholic acid (UDCA) is with the approved farnesoid X receptor (FXR) agonist obeticholic acid (OCA), alongside off-label use of fibrates (peroxisome proliferator-activated receptor [PPARs]). We report our experience of synergistic FXR-PPAR-UDCA combination therapy in PBC.

Methods: A review of patients with PBC seen between July 2022 and July 2023 was performed across the autoimmune liver disease programme at the Toronto Centre for Liver Disease. Univariate and multivariate analyses were performed.

Results: Four hundred seventy patients with PBC were seen, of which 71% were treated with UDCA only, 7% UDCA-OCA, 11.3% UDCA-fibrates, and 10.6% UDCA-OCA-fibrates. Among 50 patients on triple therapy, 82% had OCA as the first add-on therapy. Most patients (92%) received bezafibrate, while 8% had fenofibrate. Forty-eight patients were included in the final analysis. The mean follow-up time after triple therapy was 17.4 months. Triple therapy demonstrated median ALP reductions after 6 months of 33.3% (95% CI: 27.9%–37.6%) and 39.1% (95% CI: 30.7%–46.2%) at the last follow up; 30.2% of the patients had a normal serum ALP at 6 months, while 11.9% had normal ALP, AST, ALT, and bilirubin. Subgroup analysis of 28 patients followed for at least 12 months showed a 44.7% (95% CI: 33.3%–50.9%) median reduction in ALP. Liver stiffness remained relatively stable throughout the follow-up. Out of 34 patients with self-reported pruritus before

Abbreviations: AMA, anti-mitochondrial antibodies; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; TCLD, Toronto Centre for Liver Disease; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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triple therapy, 64.7% reported improvement, 11.8% worsened, and 23.5% had no change in itching intensity. On multivariable analysis, only older age at diagnosis (OR = 1.12; 95% CI: 1.02–1.22) positively impacted ALP normalization.

Conclusions: Our data confirm that FXR-PPAR-UDCA triple therapy significantly improves ALP with normalization for 30% of patients with PBC at 6 months.

Keywords: fibrates, incomplete responders, obeticholic acid, treatment, ursodeoxycholic acid

INTRODUCTION

Primary biliary cholangitis (PBC) is a relatively rare cholestatic disease characterized by a chronic and progressive immune-mediated granulomatous lymphocytic cholangitis.[1] Unchecked, this results in progressive biliary fibrosis.[2] Ursodeoxycholic acid (UDCA) remains first-line therapy and has been shown to improve transplant-free survival.[3–5] However, up to 40% of the patients will not respond completely to UDCA based on liver biochemistry and may benefit from add-on therapies.[4] This is premised on the concept of biochemical response predicting disease progression over time, with a variety of on-treatment response criteria stratifying disease progression risk.[6–9] Previous studies have demonstrated that normalization of ALP and bilirubin is associated with a significantly lower risk for liver transplantation or death.[8] Furthermore, even patients with an adequate response to UDCA according to the Paris-2 criteria, but with a persistent ALP elevation between 1.1 and 1.5× the upper limit of normal (ULN), remain at risk of poor outcome compared with patients with a deep response.[9] Therefore, treatment goals in PBC are increasingly aspirational, aiming for normal serum liver tests, especially ALP and bilirubin.

Currently, add-on therapy to UDCA is with the conditionally approved farnesoid X receptor (FXR) agonist obeticholic acid (OCA), alongside off-label use of fibric acid derivatives (peroxisome proliferator-activated receptor [PPAR] agonists).[10,11] While in the United States, fibrates remain infrequently used off-label, 2 new PPAR agonists— elafibranor and seladelpar—have recently received accelerated approval from the FDA.[12,13] FXR activation has been shown to inhibit the transcription of CYP7A1, stimulate the bile salt export pump, regulate bile acids through enterohepatic circulation, and increase the secretion of fibroblast growth factor-19, thereby modulating bile acid metabolism.[14–16] Synergistic to the FGF19-FXR pathway, PPARs are key factors in controlling the bile acid detoxification by regulating specific genes that are responsible for bile acid production, metabolism, and transportation, such as those related to CYP7A1, uridine 5′-diphospho-glucuronosyltransferases, MDR3, BSEP, etc.[17–19] In this way, FXR and PPAR agonist therapies have potential mechanistic alignment that supports considering their use together. Furthermore, while OCA has been associated with higher rates of severe pruritus, fibrates have the potential to decrease itching.[20–25]

In this study, we utilize comprehensive electronic medical records to report our current experience of synergistic FXR-PPAR-UDCA combination therapy, from a representative PBC-focused program. We demonstrate a high rate of ALP normalization among a large population of “triple” therapy–treated patients with PBC, supporting the emerging goal of adopting care pathways in the management of patients with PBC that target normal serum liver tests alongside improved quality of life.

METHODS

Study population

Adult patients (≥18 y old) with an established clinical diagnosis of PBC seen in the Toronto Centre for Liver Disease between July 1, 2022, and July 1, 2023, were identified through an extended electronic medical records database search. Patients with autoimmune hepatitis overlap syndrome were excluded. All patients with PBC simultaneously treated with UDCA, OCA, and fibrates (bezafibrate or fenofibrate) for at least 3 months were included. At the time of enrollment, all the patients were being treated with UDCA at a dose of 13–15 mg per kilogram of body weight per day. OCA and fibrate dose adjustments and sequencing were made at the discretion of the most responsible hepatologist.

Definitions

PBC was confirmed as per AASLD guidelines with patients fulfilling at least 2 of the following diagnostic

criteria: (i) positive serology for anti-mitochondrial antibodies (AMA) or other specific autoantibodies, including sp100 or gp210, if AMA-negative; (ii) persistent increase of the serum ALP levels; and (iii) liver histology compatible with PBC.[26,27] Liver histology specimens were available for all patients with AMA-negative-PBC. A clinical diagnosis of liver cirrhosis was defined as 1 or more of the following: (a) imaging (eg, surface nodularity, caudate hypertrophy, splenomegaly, and collateral circulation); (b) clinical features of portal hypertension (eg, gastroesophageal varices, ascites, and platelet count $< 150{,}000/mm^3$); (c) histological evaluation with fibrosis stage 4; and (d) liver stiffness by transient elastography higher than 16.9 kPa. Total follow-up time at the Toronto Centre for Liver Disease (TCLD) was defined as the difference between the date of the first appointment at TCLD and the date of the last visit. Pruritus improvement was defined as a subjective, patient-reported reduction in itch intensity (eg, from severe to moderate or mild) following initiation of triple therapy. Autoimmune hepatitis-PBC overlap syndrome, used as an exclusion criterion, was defined by the presence of a combination of biochemical, serological, and/or histological features consistent with autoimmune hepatitis as defined by Paris criteria,[28] or by the concomitant use of immunosuppressive therapy. Liver stiffness measurement > 9.6 kPa was used as a cutoff to define higher risk of adverse outcomes (liver decompensation, liver transplantation, or death) as described by Corpechot et al.[29]

Data collection

Demographical, clinical, and biochemical data were retrieved by electronic chart review. For each patient included, the following baseline and follow-up variables were retrospectively collected: date of birth, sex, date of PBC diagnosis, date of UDCA, OCA, and fibrate initiation, date of the last of follow-up; liver histology; AMA, anti-sp100, anti-gp210, and anti-nuclear antibody status; serum liver and renal biochemistry (ALP, ALT, AST, GGT, bilirubin, albumin, and creatinine); OCA and fibrate doses at 6 months and at the last follow-up; presence of cirrhosis (at diagnosis and at the moment triple therapy was started); liver stiffness measurement as assessed by vibration controlled transient elastography (FibroScan) up to 6 months before, after 12 months, and last available after triple therapy; patient-reported pruritus; and adverse effects after triple therapy. Time-dependent variables were collected at the following time points: (a) immediately before dual therapy initiation; (b) immediately before triple therapy initiation; (c) 6 months after triple therapy; (d) 12 months after triple therapy; and (e) at the last follow-up available under triple therapy.

All study procedures were conducted in accordance with the ethical standards of the Helsinki Declaration. This study was approved by the institutional research board at the University Health Network.

Outcomes

The primary outcome was the relative change in serum ALP level at 6 months after triple therapy initiation and at the last available follow-up. Secondary outcomes were relative change in ALP at 12 months, relative changes in total bilirubin, ALT, and AST; relative changes in creatinine; normalization of ALP; normalization of ALP, AST, ALT, and bilirubin, hereafter defined as biochemical remission; and qualitative patient-reported change in pruritus intensity. Treatment discontinuation and adverse effects were used as indicators of safety and tolerance.

Statistical analysis

Demographic and clinical information were described using median and IQR for continuous variables and absolute frequency and percentage for categorical variables. Before analysis, missing data were handled using pairwise deletion. Continuous variable distributions were assessed for normality using the Shapiro-Wilk test. For nonparametric distributions, median percentage changes were calculated for paired data, and 95% CIs were estimated using 10,000 bootstrap replicates. For group comparisons (univariate analysis), we used the paired Student t test or the Wilcoxon signed-rank test for continuous variables and the chi-squared test (or the Fisher exact test in the case of a small sample size) for categorical variables. For therapeutic sequence analysis, patients were divided into 2 subgroups. Group OCA-Fibrate included patients who received OCA as second-line therapy and fibrates as third-line therapy, whereas Group Fibrate-OCA included patients treated with fibrates as second-line therapy and OCA as third-line therapy. Multivariate analysis involved performing logistic regression to assess the association between the proportion of ALP normalization and the patients' demographic and clinical variables. All tests are 2-tailed, with statistical significance set at a threshold of p value < 0.05. The statistical analysis was conducted using R version 4.3.0.

RESULTS

Study population and treatment

In total, 470 prevalent patients with PBC were seen over the 1-year inclusion period, of which 71% were treated with UDCA only, 7% UDCA and OCA, 11.3% UDCA

and fibrate, and 10.6% UDCA, OCA, and fibrate (Figure 1). Among 50 patients on triple therapy (86% female, median age at diagnosis 43.5 [14.6] y, median age at dual therapy 51.1 y [11.2], median age at triple therapy 53.6 y [13.0], 96% AMA positive, and 36% cirrhotic), 82% had OCA as the first add-on therapy. Total follow-up time at TCLD was 4.10 (IQR: 3.2) years. Most patients (92%) received bezafibrate, while 8% had fenofibrate. Median interval between first-line and third-line initiation was 4.5 years, and median time between second-line and third-line therapy was 1.8 years. The median follow-up time after triple therapy was 17.4 months (range: 3–58.1). At the last available follow-up, 54.2% were on OCA 10 mg daily, and 70.8% bezafibrate 400 mg daily (Figure 2). ALP ratio (ALP divided by ULN) before triple therapy initiation was 1.73 × ULN (IQR: 0.9). Liver stiffness was measured in 31 patients before triple therapy (median 7.6 kPa [5.6–10.2 kPa]) and was higher than 9.6 kPa in 35% of them. During follow-up, 35 patients (70%) had a liver biopsy, 34.3% with advanced fibrosis (7 with fibrosis grade 3 and 5 with fibrosis grade 4). All patients had previously failed to adequately respond to both UDCA monotherapy and a second-line option (OCA or fibrates) in combination with UDCA. Baseline patient characteristics are shown in Table 1.

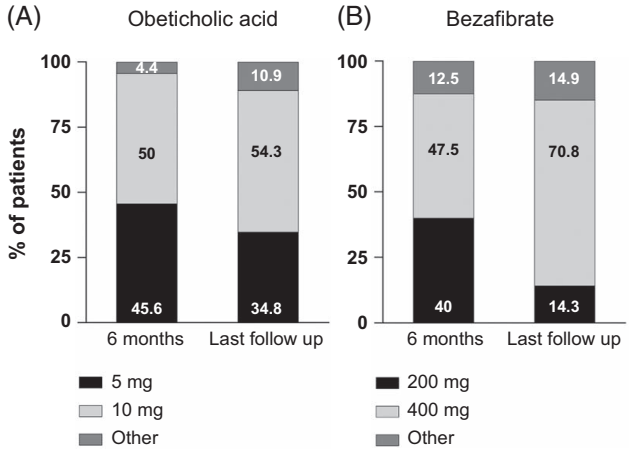

FIGURE 2 (A) Obeticholic acid and (B) bezafibrate daily dose over time.

Triple therapy significantly reduces ALP in patients with and without cirrhosis

Biochemical data after triple therapy were available for 43 patients at 6 months and 48 patients at the last follow-up, 18 of them with cirrhosis (37.5%). Patients on triple therapy demonstrated median ALP reductions after 6 months of 33.3% (95% CI: 27.9%–37.6%; $p = < 0.0001$ compared with dual therapy) and 39.1% (95% CI: 30.7%–46.2%; $p = 0.001$ compared with 6 mo after triple therapy) at the last follow-up (Figure 3A). ALP ratio at 6 months was 1.18 × ULN (IQR: 0.66) and 1.09 × ULN (IQR: 0.6) at the last follow-up. Patients with cirrhosis showed similar results: −31.7% (95% CI 12.8%–36.4%; $p < 0.0001$ compared with dual therapy) median ALP reduction at 6 months and −31.1% (95% CI: 24.3%–40.6%; $p = 0.29$ compared with 6 mo after triple therapy) at the last follow-up. Subgroup analysis of 28 patients

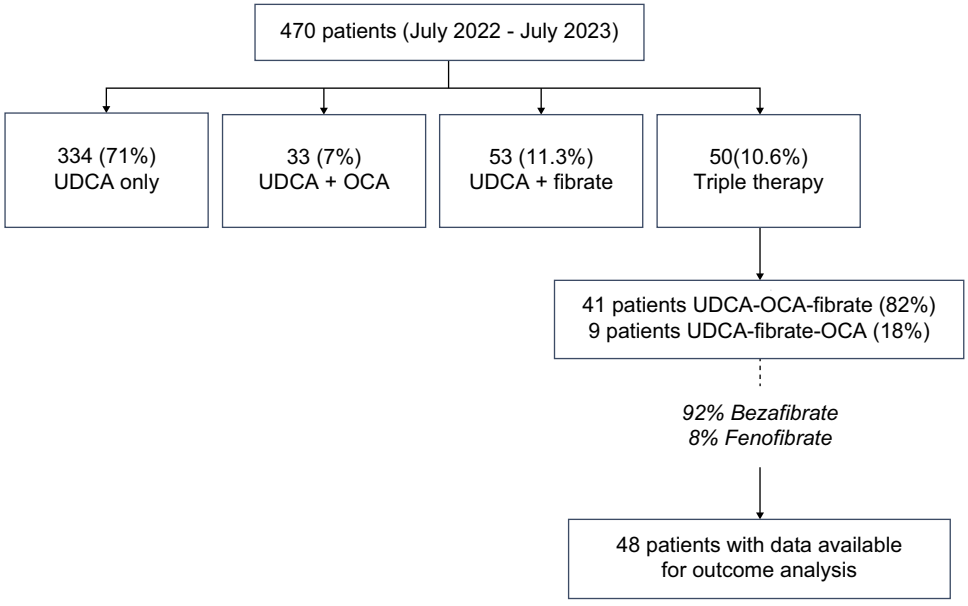

FIGURE 1 Flowchart—PBC treatment in TCLD autoimmune liver clinics. Abbreviations: OCA, obeticholic acid; PBC, primary biliary cholangitis; TCLD, Toronto Centre for Liver Disease; UDCA, ursodeoxycholic acid.

TABLE 1 Demographics, clinical, and biochemical characteristics of the cohort

Variable (n = 50)	Results
Age at diagnosis (y), median (IQR)	43.5 (14.6)
Age at first visit to TCLD (y), median (IQR)	50.6 (14.5)
Female sex, n (%)	43 (86)
AMA-positive patients, n (%)	48 (96)
Cirrhosis at the time of triple therapy, n (%)	18 (36)
Sequencing, n (%)	
OCA-fibrate	41 (82)
Fibrate-OCA	9 (18)
Liver tests pre-triple therapy, median (IQR)[a]	
ALP (U/L)	396.5 (282.5)
GGT (U/L)	169 (216.5)
AST (U/L)	58 (44.3)
ALT (U/L)	58 (77)
Bilirubin (μmol/L)	12 (9)

[a]Some laboratory parameters were not available for all patients. Data were available for: ALT (n = 49); bilirubin (n = 49); and GGT (n = 27).
Abbreviations: AMA, anti-mitochondrial antibody; OCA, obeticholic acid; TCLD, Toronto Centre for Liver Disease.

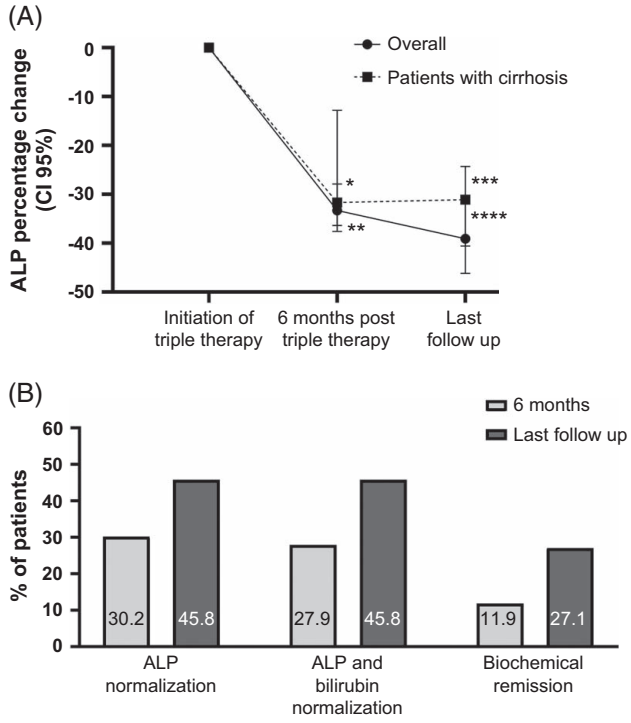

FIGURE 3 Triple therapy is associated with biochemical improvement at 6 months and the last follow-up. (A) Overall, ALP reduction was 39.1%, while patients with cirrhosis had a reduction of 31.1%. Bars = 95% CI. *Difference between ALP levels before the initiation of triple therapy and 6 months after treatment among patients with cirrhosis (n = 18); $p < 0.0001$. **Overall difference between ALP levels before the initiation of triple therapy and 6 months after treatment (n = 48); $p < 0.0001$.***Difference between ALP levels at 6 months of triple therapy and the last follow-up among patients with cirrhosis (n = 18); $p < 0.29$. ****Overall difference between ALP levels at 6 months of triple therapy and the last follow-up (n = 48); $p < 0.001$. (B) Percentage of patients with ALP normalization, ALP, and bilirubin normalization and biochemical remission.

followed for at least 12 months showed a median 44.7% [95% CI: 33.3%–50.9%, $p < 0.0001$] reduction in ALP.

Triple therapy is associated with high rates of ALP normalization and biochemical remission

Complete normalization of ALP level was observed in 30.2% of the patients at 6 months and 45.8% at the last follow-up. Similarly, 31.2% of the patients with cirrhosis normalized ALP at 6 months and 38.9% at the last follow-up. The OR of achieving ALP normalization was not statistically different between OCA-fibrate and fibrate-OCA sequences at 6 months. However, the OCA-fibrate sequence was more effective when we consider ALP at the last follow-up (OR = 11.67, 95% CI [1.8-229.5]; $p = 0.03$), compared with the fibrate-OCA sequence. ALP and bilirubin normalization were observed in 27.9% and 45.8% of the patients at 6 months and at the last follow-up, respectively. Bilirubin levels $< 0.6 \times$ ULN were observed in 77% of patients at 6 months and in all patients at the last follow-up. Overall, 11.9% and 27.1% of the patients normalized ALP, AST, ALT and bilirubin at 6 months and at the last follow-up, respectively, achieving biochemical remission (Figure 3B). Among patients with cirrhosis, none reached biochemical remission at 6 months, while 16.7% normalized their liver tests at the last follow-up. Median liver stiffness at 12 months (n = 13) and last available after triple therapy (n = 46) was 7.7 kPa (6.0–9.35, $p = 0.99$ compared with liver stiffness measurement before treatment) and 8.0 kPa (5.9–13.5, $p = 0.99$ compared with liver stiffness measurement before treatment), respectively (Supplemental Figure S1, Supplemental Digital Content 1, http://links.lww.com/HC9/C108).

Triple therapy does not significantly change AST, but improves ALT

Compared with dual therapy, triple therapy was associated with a reduction in total bilirubin (−11% [95% CI: −16.7%, 0.0%; $p = 0.0004$] at 6 mo and −16.7% [95% CI: −25.0%, 0.0%; $p = 0.01$] at the last follow-up), and ALT (-14.3% [95% CI: −26.0%, −4.2%; $p = 0.015$] at 6 mo and −19.1% [95% CI: −32.0%, −4.0%; $p = 0.005$] at the last follow-up). AST decreased at 6 months (−7.5% [95% CI: −12.0%, 4.8%; $p = 0.41$]) and the last follow-up (−7.5% [95% CI: −14.8%, 10.0%; $p = 0.35$]) (Supplemental Figure S2, Supplemental

TABLE 2 Older age at diagnosis positively impacted ALP normalization

Variable	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Male sex	1.57 (0.30, 8.91)	0.59		
Age at diagnosis	**1.08 (1.01, 1.17)**	**0.03**	**1.12 (1.02, 1.22)**	**0.02**
Time to triple therapy	1.00 (0.99, 1.00)	0.44		
Cirrhosis pre-triple therapy	0.65 (0.19, 2.20)	0.49		
Fibrate dose	1.00 (0.99, 1.00)	0.54		
OCA dose	1.11 (0.90, 1.37)	0.35		
ALP pre-triple therapy	**0.37 (0.11, 0.87)**	**0.05**	0.39 (0.12, 1.25)	0.11
Bilirubin pre-triple therapy	1.01 (0.92, 1.11)	0.85		

Bold values are statistical significance.
Abbreviation: OCA, Obeticholic acid.

Digital Content 1, http://links.lww.com/HC9/C108). Creatinine did not change significantly over time ($p = 0.18$).

Older age at diagnosis positively impacted ALP normalization at the last follow-up

On univariate analysis, age at diagnosis (OR = 1.08; 95% CI [1.01–1.17]; $p = 0.03$) and ALP ratio before triple therapy initiation (OR = 0.37; 95% CI [0.11–0.87]; $p = 0.05$) influenced ALP normalization. However, on multivariable analysis, only older age at diagnosis (OR = 1.12; 95% CI [1.02, 1.22]; $p = 0.02$) positively impacted ALP normalization at the last follow-up (Table 2). We could not identify any predictors of ALP normalization at 6 months.

Adverse effects and self-reported pruritus

Out of 34 patients with self-reported pruritus before triple therapy, 64.7% reported improvement, 11.8% worsened, and 23.5% had no change in itching intensity (Figure 4). Muscle cramps and abdominal pain were reported by 1 patient each. Four patients increased transaminases during the follow-up, but improved after fibrate dose reduction. At the end of the study period, only 1 patient discontinued triple therapy.

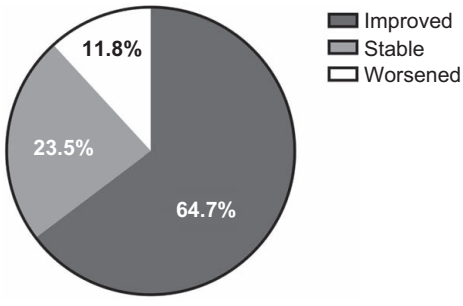

FIGURE 4 Triple therapy associated with better subjective pruritus control.

DISCUSSION

We sought to highlight the current goal-driven practice for managing PBC in our program. We reviewed the clinical course of all patients on maximal PBC therapy over the period of 1 year and report on 48 high-risk patients who had previously failed to respond to UDCA and second-line therapies. We demonstrate that the combination of UDCA, an FXR agonist (OCA), and fibrates significantly decreased ALP values, with more than 30% of patients reaching normalization.

Although different published criteria, either dichotomous or continuous, are currently used to define response to UDCA and offer prognostic information, recent analysis from the Global PBC study group demonstrated that normalization of ALP and bilirubin is independently associated with higher transplant-free survival.[8] It has also been shown that even among patients with PBC who attained an adequate response to UDCA according to Paris-2 criteria, there is a complication-free survival gain with ALP normalization.[9] In this way, therapy goals are increasingly driven by risk stratification and individualized approach, establishing a new paradigm to achieve normal serum liver tests, improve quality of life, and prevent end-stage liver disease.[11] In our study, 27.9% of the patients normalized both ALP and bilirubin at 6 months of triple therapy, while 11.9% of patients achieved biochemical remission, supporting the synergistic effects of FXR and PPAR agonists in the treatment of PBC with incomplete response to UDCA monotherapy. Our data further support the findings recently reported by the IBER-PBC cohort on triple therapy for patients with PBC with incomplete response to UDCA treated with OCA and subsequently with fibrates.[30] Although we cannot draw definite conclusions, the relative stability in liver stiffness during follow-up is also reassuring. Furthermore, we demonstrated that the likelihood with triple therapy of achieving an adequate biochemical response correlates with patient age at diagnosis, which has also been shown to predict response to UDCA therapy.[31–36]

When we compared the treatment sequences involving add-on drugs, specifically the OCA-Fibrate group versus

the Fibrate-OCA group, we identified that the OCA-fibrate sequence seems to be more effective in attaining biochemical response in the long term. This finding has also been reported by Soret et al,[37] although drug-specific additive mechanisms are still unclear. This may be related to the fact that fibrates have been shown to be more efficient in reducing ALP levels.[10,38] Alternatively, by alleviating pruritus, fibrates may facilitate better tolerance and allow for higher dosing of OCA. In our case, the small size of our cohort precludes a definite conclusion, but a future meta-analysis may help to clarify this issue.

Another noteworthy finding is the reduction in patient-reported pruritus intensity in 64% of the individuals when fibrates are introduced alongside OCA and UDCA. Similarly, Soret et al[37] have shown a significant reduction in itch intensity score of up to 72% per year after triple therapy. This finding implies that combining fibrates with OCA, regardless of their potential long-term synergistic effects on PBC, could also be particularly valuable in diminishing the adverse effects of OCA, leading to better tolerance of higher OCA doses and finally to better liver test results. In our study, 54% of the patients were receiving OCA 10mg daily at the last follow-up, a higher proportion than previously reported in real-world studies with OCA as second-line therapy.

Similar to other studies, we have also shown a small, but statistically significant, improvement in serum ALT levels after triple therapy.[37] In fact, in clinical trials, values of ALT decreased 21%–35% with OCA and 36% with bezafibrate.[20,23] By contrast, in a real-world study from the United Kingdom, the proportion of patients attaining complete normalization in serum ALT significantly increased over time under OCA therapy, but not following treatment with fibrates, when used as second-line drugs.[10]

The main limitation of this study, besides its retrospective design, is the evaluation of tolerance and adverse effects. By including only patients already on triple therapy, we excluded patients who had experienced early intolerance to this combination or who had already discontinued one of the drugs. In our cohort, only 1 patient stopped triple therapy due to an adverse effect (muscle cramp). Creatinine remained stable throughout the follow-up. An ongoing clinical trial testing triple therapy as a second-line treatment for PBC will better address this issue in the future.

In conclusion, we report a large real-world off-label experience of synergistic FXR-PPAR agonist therapy, alongside UDCA in patients with PBC at high risk of disease progression. We demonstrate clinically meaningful rates of improvement in ALP values and ALP normalization in up to 30.2% of patients. As aspirational goals for the care of patients with PBC move toward liver test normalization, adjunctive therapy appears promising.

AUTHOR CONTRIBUTIONS

Guilherme G.L. Cançado: conceptualization; acquisition of data; writing—original draft; and writing—review and editing. Bo Chen: data analysis. Madeline Cameron: acquisition of data. Inbal Houri: acquisition of data. Kristel K. Leung: acquisition of data. Aliya F. Gulamhusein: acquisition of data and writing—review and editing. Bettina Hansen: interpretation of data and writing—review and editing. Gideon M. Hirschfield: conceptualization; acquisition of data; interpretation of data; and writing—review & editing.

FUNDING INFORMATION

No direct support was provided for manuscript preparation.

CONFLICTS OF INTEREST

Guilherme G.L. Cançado has received a research grant from Ipsen. Aliya F. Gulamhusein has consulted for Advanz, Cymabay, and Gilead. Bettina Hansen has consulted for and received grants from Calliditas, CymaBay, and Intercept. She consults for Albireo, Enyo, Eiger, Ipsen, and Mirum. Gideon M. Hirschfield has consulted for Ipsen, GSK, Kowa, Mirum, Pliant, Gilead, Cymabay, Intercept, Advanz, and Dr. Falk. The remaining authors have no conflicts to report.

ETHICS STATEMENT

This study was approved by the institutional research board at the University Health Network.

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