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**Combination of fibrates with obeticholic acid is able to normalize biochemical liver tests in patients with difficult-to-treat primary biliary cholangitis**

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**The full affiliations of the authors within the PPAROCA Study Group are available in the Appendix**

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Authors contributions: CC, study designer, coordinating investigator, data acquisition, data analysis and interpretation, drafting manuscript; PAS, OC: data acquisition, data analysis and interpretation, drafting manuscript, critical revision; LL, FC: statistical analysis, data interpretation, critical revision; Remaining authors: data acquisition, critical revision.

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**SUMMARY**

BACKGROUND

Obeticholic acid (OCA) and fibrates are second-line therapies for patients with primary biliary cholangitis (PBC) with an inadequate response to ursodeoxycholic acid (UDCA).

AIM

To know whether OCA and fibrates, administered together in combination with UDCA, have additive beneficial effects in patients with difficult-to-treat PBC.

METHODS

PBC patients treated for ≥ 3 months with UDCA, OCA, and fibrates (bezafibrate or fenofibrate) due to failure of either second-line therapy were included in a multicenter, uncontrolled retrospective cohort study. Changes in biochemical liver tests and pruritus were analyzed using a generalized linear mixed-effect model.

RESULTS

Among 58 patients included, half received OCA as second-line and fibrates as third-line therapy (Group OCA-Fibrate) while the other half had the inverse therapeutic sequence (Group Fibrate-OCA). The mean duration of triple therapy was 11 months (range 3-26). Compared to dual therapy, triple therapy was associated with a significant gain in ALP reduction: 22% per first year (95%CI 12%-31%), an effect that was stronger in OCA-Fibrate than in Fibrate-OCA group. Triple therapy was associated with a 3.4 (95%CI 1.4-8.2) odds ratio (OR) of reaching normal ALP and with a significant decrease in GGT, ALT, AST, and total bilirubin. The ORs of achieving the Paris-2 and Toronto criteria of adequate biochemical

response were 6.8 (95%CI 2.8-16.7) and 9.2 (95%CI 3.4-25.1), respectively. Finally, triple therapy significantly improved pruritus in OCA-Fibrate but not Fibrate-OCA group.

CONCLUSIONS

Triple therapy with UDCA, OCA and fibrates is able to normalize biochemical liver tests and improve pruritus in patients with difficult-to-treat PBC.

## 1. INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic, progressive cholestatic liver disease exposing patients to a risk of cirrhosis and premature death from liver failure or hepatocellular carcinoma.[1] Ursodeoxycholic acid (UDCA), the standard-of-care treatment for this condition, improves liver transplantation (LT)-free survival.[2-5] However, approximately one third of patients, who presents with an inadequate biochemical response to UDCA, are still exposed to increased mortality or potential need for LT.[6-8] These high-risk PBC patients are in needs for additional therapies.

Two second-line therapies, namely obeticholic acid (OCA) and fibrates, administrated in association with UDCA, have shown additive biochemical effects in PBC, though their long-term benefit has yet to be proven.[9] OCA, a selective Farnesoid-X receptor (FXR) agonist, is currently the only drug officially approved in patients with resistance or intolerance to UDCA. OCA has shown efficacy on key biochemical markers of PBC, but has been associated with pruritus and potential risk of liver injury in patients with most advanced disease.[10-12] Fibrates are peroxisome proliferator-activated receptors (PPAR)-$\alpha$ agonists. Bezafibrate (BZF), a pan-PPAR agonist, has shown beneficial effects on both symptoms and biochemical features of high-risk PBC patients, while fenofibrate (FNF), a selective PPAR-$\alpha$ agonist, has comparable effects.[13-16] Most frequent side-effects of fibrates are myalgias and increased creatinine level.

Inadequate response to second-line therapies with either OCA of fibrates has been reported in a varying percentage of high-risk PBC patients. The POISE's primary endpoint was unreached in approximately half of OCA-exposed patients during the POISE trial.[10] In the BEZURSO trial, 69% of the BZF-treated patients did not reach complete biochemical response, but 70% achieved a good response according to Paris-2 criteria.[14] These data suggest that 30%

to 50% of UDCA poor-responders do not adequately respond to second-line therapies with OCA or fibrates. These hard-to-treat patients, who represent 10% to 15% of all PBC patients, are in needs for optimized treatment.

As OCA and fibrates have different pharmacological targets, their combination in addition to UDCA (i.e. triple therapy) may have additive or even synergistic effects. Little is known about the effects of this triple combination in PBC. A recent report of 11 Belgian patients who had failed to respond to OCA suggests that BZF add-on therapy may reduce ALP and bilirubin levels and mitigate OCA-induced pruritus.[17] Herein, we report a study of 58 high-risk PBC patients who had not adequately responded to OCA (n=29) or fibrates (n=29) dual therapy and were afterwards treated with the triple association of UDCA, OCA and fibrates. In this study, we analyzed the comparative effects of triple and dual therapies on biochemical liver tests and pruritus in all patients and according to the therapeutic sequence.

## 2. PATIENTS AND METHODS

This multicenter, retrospective cohort study, conducted from January to December 2019, was thought as a proof-of-concept study designed to assess the potential additive effects of triple therapy with UDCA, OCA and fibrates in patients with PBC who previously failed to achieve adequate response to either dual therapy, namely UDCA and OCA or UDCA and fibrates combinations. The treatment sequence was left to the discretion of each clinician. The study received approvals from the institution review board of each participating center.

### 2.1. Patients

To be eligible, the patients had to meet the following criteria: 1) diagnosis of PBC according to established criteria; 2) failure to achieve an adequate biochemical response to ≥ 12-month UDCA therapy (13-15 mg/kg/d) based on Paris-2 criteria (namely ALP and AST ≤ 1.5 times the upper limit of the normal range (xULN) with a normal bilirubin level) as minimal common failure definition;[18] 3) subsequent failure to achieve an adequate biochemical response to ≥ 3-month dual therapy with UDCA (13-15 mg/kg/d) and OCA (5 to 10 mg/d) or UDCA (13-15 mg/kg/d) and fibrates (BZF 200 to 400 mg/d or FNF 100 to 200 mg/d) using Paris-2 criteria as minimal common failure definition;[18] 4) treatment with ≥ 3-month triple therapy including UDCA (13-15 mg/kg/d), OCA (5 to 10 mg/d) and fibrates (BZF 200 to 400 mg/d or FNF 100 to 200 mg/d). A minimal 3 months of dual and triple therapy was required since this period of time was considered sufficient to assess biochemical response.[10,14] Patients with autoimmune hepatitis (AIH) overlap syndrome diagnosed based on the Paris criteria were not excluded provided that steroids or immunosuppressive drugs had been started at least 6 months before second-line therapy and remained stable during follow-up.[19]

Ineligibility criteria included duration of triple therapy < 3 months, missing starting dates of drugs and insufficient follow-up data, decompensated or Child-Pugh class B or C cirrhosis at any time before triple therapy, patients on the waiting list for LT, and any medication susceptible to influence biochemical liver tests (in particular corticosteroids or immunosuppressive drugs) introduced during or within the 3 months preceding triple therapy.

**2.2. Data collection**

For each patient included, the following baseline and follow-up variables were retrospectively collected: date of birth, gender, date of PBC diagnosis, weight at diagnosis,

date of UDCA initiation, dose of UDCA, features of AIH overlap syndrome and related treatments (date of initiation, dose), date of OCA initiation, dose of OCA, date of fibrates initiation, dose of fibrates, presence of pruritus, 0-10 itch intensity score, presence of myalgia, serum levels of total bilirubin, ALP, GGT, AST, ALT, Albumin, IgM, platelets, creatinine, and total cholesterol, and liver stiffness measurement (LSM) as assessed by vibration-controlled transient elastography (Fibroscan, Echosens, France). The serum activity of liver enzymes was normalized and expressed as a multiple of ULN. Time-dependent variables were assigned to real dates and collected at the following key time-points of treatment sequence: 1) UDCA initiation; 2) dual therapy initiation; 3) 6-month dual therapy; 4) triple therapy initiation; 5) 3-month triple therapy; and 6) last follow-up available under triple therapy. Cirrhosis was defined by at least one of the following criteria: histological stage 4, LSM > 16 kPa, FIB-4 score > 3.25, or platelet count < $150x10^9$/L. Adequate biochemical response was defined based on the Paris-2 (see above) and modified Toronto (ALP ≤ 1.67 xULN and normal bilirubin) criteria.[8,18]

**2.3. Outcomes**

The primary outcome was relative change in serum ALP level. The key secondary outcome was serum ALP level normalization. Other secondary outcomes included relative changes in serum levels of total bilirubin, GGT, AST, ALT, albumin, IgM, platelets, creatinine, and total cholesterol, LSM, itch intensity score, and pruritus and biochemical response rates. Treatment discontinuation was used as an indicator of safety and tolerance.

**2.4. Statistical analysis**

Based on the therapeutic sequence, patients were categorized in 2 groups. 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. The characteristics of the two groups were compared at the time of dual therapy initiation using the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables. Continuous variables were expressed as median and interquartile range (IQR) and categorical variables as absolute number and percentage (%).

Differences between triple and dual therapies in all patients and by treatment group were assessed using a generalized linear mixed-effects model (GLMM) to account for clustering due to repeated observation from the same patient, as repeated measures within a patient are correlated. All data from all participants were included in the analysis, as GLMM allows for unbalanced and missing data. To deal with non-normal distributions of variables, data were log transformed before being processed. The model was adjusted for within-subject random effects, age, gender, and UDCA dose. Because of collinearity between therapeutic groups and doses of second- or third-line drugs, and the limited number of explanatory variables allowed due to the small size of the studied population, complementary adjustment for OCA and fibrates doses was not possible. For each variable tested under triple vs. dual therapy, results were expressed as mean relative change (for continuous variables) or mean odds ratio (OR) (for categorical variables) per unit of time (year) and corresponding 95% confidence interval. For all results, a sensitivity analysis excluding patients with features of AIH overlap syndrome was performed. Box plots (for continuous variables) and 100% stacked bar graphs (for categorical variables) were generated to represent outcomes graphically. All tests were two-tailed, and data analysis was performed with a significance level of $p<0.05$ for all

statistical comparisons. All statistical models were verified based on residual plots. Data were analyzed using R version 3.6.1.

## 3. RESULTS

In total, 58 eligible patients from 19 centers across 7 Western countries were included in this retrospective cohort study (their distributions by center and country are shown in Appendix, Tables S1 and S2). The 11 Belgian patients previously reported in the literature participated in this study.[17] All patients had previously failed to adequately respond to standard UDCA, then to a second-line option (OCA or fibrates) in combination with UDCA. All had subsequently been exposed to triple therapy with UDCA, OCA and fibrates for a minimal period of 3 months. They consisted of 29 patients who received OCA as second-line therapy then fibrates as third-line therapy (Group OCA-Fibrate) and 29 others who experienced the inverse therapeutic sequence, namely fibrates as second-line therapy then OCA as third-line therapy (Group Fibrate-OCA). The distributions of groups by center and of fibrates type (BZF, FNF) between groups are shown in Appendix (Tables S3 and S4, respectively), as are the numbers of patients assessed in the adjusted GLMM by variable tested and group (Table S5).

### 3.1. Baseline characteristics, follow-up, and drug doses

The patient characteristics by group at baseline of second-line therapy are shown in **Table 1**. As expected, patients were mainly women of 50 years old exhibiting significant persisting clinical and/or biochemical features of cholestasis despite UDCA therapy (median ALP level: 2.7 xULN; pruritus 59%). The median LSM was 9.9 kPa (range 4.2 to 48.0) and 22%

of patients had proven or predicted cirrhosis. The median duration of prior UDCA therapy was 4.1 years (range 1.0 to 24.8). The dose of UDCA was 15.4 (4.0) mg/kg/d (range 7.6 to 24.6). Eleven (19%) patients were considered to have features of PBC-AIH overlap syndrome. All of them had stable doses of corticosteroids and immunosuppressive drugs at the time of inclusion. Treatment groups were comparable except for a younger age and higher GGT and transaminases levels in Group Fibrate-OCA compared to Group OCA-Fibrate. These differences may be related to a greater proportion of patients with PBC-AIH overlap syndrome in Group Fibrate-OCA (28%) than in Group OCA-Fibrate (10%).

Total follow-up from UDCA initiation was 8.6 (10.7) years (range 1.9 to 27.5). Total duration of dual therapy was 2.8 (4.3) years (range 0.3 to 9.8) and that of triple therapy was 0.8 (0.6) years (mean 11 months; range 3 to 26 months). Neither the complete follow-up nor the durations of dual and triple therapies differed between groups (Appendix, Table S6).

Over the combination treatment period (dual then triple therapy), the daily dose of OCA was 5 (5) mg (range 1.7 to 10) in Group OCA-Fibrate and 5 (1.25) mg (range 0.7 to 10) in Group Fibrate-OCA. In Group Fibrate-OCA, the daily dose of fibrates was 400 (0) mg (range 200 to 400) for BZF and 180 (40) mg (range 160 to 200) for FNF, while in Group OCA-Fibrate it was 400 (0) mg (range 200 to 400) and 160 (55) mg (range 72.5 to 200), respectively. Dose adjustments according to treatment and group are shown in Appendix (Table S7).

### 3.2. Primary outcome

The mean changes in serum ALP level were compared between dual and triple therapies in all patients and by group. Compared to dual therapy, the gain in ALP reduction associated with triple therapy on the entire population was 22% per year (95%CI 12% to 31%; $p<0.001$).

When assessed by group, triple therapy-associated reduction in ALP level was significantly higher in Group OCA-Fibrate: 42% per year (95%CI 29% to 53%; p<0.001) than in Group Fibrate-OCA: 11% per year (95%CI -3% to 23%; p=0.1). The box plots of ALP levels at baseline of dual therapy, baseline of triple therapy, and last follow-up under triple therapy are shown in **Figure 1**. The effect of triple therapy on ALP level was detectable as early as month 3 (Appendix, Figure S1). The results were unchanged after the exclusion of patients with features of AIH overlap syndrome (Appendix, Table S8).

### 3.3. Secondary outcomes

The likelihood of reaching a complete normalization of ALP level (key secondary outcome) was assessed in all patients and by group. Compared to dual therapy, triple therapy on the entire population was associated with an OR of 3.4 per year (95%CI 1.4 to 8.2; p<0.01) of achieving ALP normalization. When assessed by group, triple therapy-associated likelihood of ALP normalization was significantly higher in Group OCA-Fibrate: 13.2 per year (95%CI 2.9 to 60.1; p<0.001) than in group Fibrate-OCA: 1.7 per year (95%CI 0.6 to 5.3; p=0.3). The 100% stacked bar graph of normal vs abnormal ALP levels at key time points of the study period is shown in **Figure 2**. These results were unchanged after the exclusion of patients with features of AIH overlap syndrome (Appendix, Table S9).

The mean changes in serum levels of total bilirubin, GGT, AST, ALT, albumin, IgM, platelets, cholesterol, and creatinine, and LSM were compared between dual and triple therapies in all patients and by group. Compared to dual therapy, triple therapy on the entire population was associated with a significant reduction gain in total bilirubin (12% per year; 95%CI 4% to 20%; p<0.01), GGT (36% per year; 95%CI 24% to 46%; p<0.001), AST (13% per

year; 95%CI 3% to 21%; p<0.01) and ALT (21% per year; 95%CI 10% to 30%; p<0.001). The box plots of these liver tests at the key time points of the study period are shown in **Figure 3**. On the entire population, triple therapy was associated with an OR of achieving normal levels of GGT, ALT, and AST of 1.6 per year (95%CI 1.2 to 2.0; p<0.001), 2.3 per year (95%CI 1.1 to 5.0; p<0.05), and 1.6 per year (95%CI 0.7 to 3.8; p=0.2), respectively. When assessed by group, the reduction gains in these liver tests were greater in Group Fibrate-OCA than in Group OCA-Fibrate (Appendix, Figure S2). No significant changes vs dual therapy were observed within the first year of triple therapy in albumin, IgM, platelets, cholesterol, creatinine, and LSM (Appendix, Table S10). Results were unchanged after the exclusion of patients with features of AIH overlap syndrome (Appendix, Table S11).

The likelihood of reaching an adequate biochemical response was then assessed. On the entire cohort, triple therapy was associated with an OR of reaching an adequate biochemical response of 6.8 per year (95% CI 2.8 – 16.7; p<0.001) for the Paris-2 criteria and 9.2 (95% CI 3.4 – 25.1; p<0.001) for the Toronto criteria. When assessed by group, these ORs remained highly significant in each group but were consistently higher in Group OCA-Fibrate than in Group Fibrate-OCA (Appendix, Table S12).

Compared to dual therapy, the mean change following triple therapy in itch intensity score was not significant when assessed on the entire population: mean gain reduction 13% per year (95%CI -58% to 52%; p=0.7). However, when assessed by group, triple therapy was associated with a significant reduction in itch intensity score in Group OCA-Fibrate: mean gain reduction 72% per year (95%CI 24% to 90%; p<0.05), whereas it did not in Group Fibrate-OCA: mean reduction gain -49% per year (95%CI -210% to 28%; p=0.3). When pruritus was considered as a binary variable (absent vs present), the OR of having no pruritus under triple vs dual therapy was 2.5 per year (95%CI 0.9 to 6.9; p=0.08) on the entire population. When

assessed by group, the OR was 9.9 per year (95%CI 1.5 to 67.1; $p<0.05$) in Group OCA-Fibrate and 1.4 per year (95%CI 0.4 to 4.9; $p=0.6$) in Group Fibrate-OCA. The 100% stacked bar graph of absent vs present pruritus at the key time points of the study period is shown in **Figure 4**. These results were unchanged after the exclusion of patients with features of AIH overlap syndrome (Appendix, Table S13).

Myalgias were reported in 2 (3%) patients. In both cases, this symptom preceded fibrates introduction. At the end of the study period, no patients had discontinued triple therapy.

## 4. DISCUSSION

In this proof-of-concept, multicenter, retrospective cohort study of patients with high-risk PBC who had previously failed to respond to UDCA therapy as well as to a combination of UDCA with OCA or fibrates (dual therapy), we showed that triple therapy with UDCA, OCA, and fibrates has the potential to improve and even normalize the biochemical and clinical features of the disease, a finding that supports additive or synergistic effects of FXR and PPAR agonists in the treatment of PBC.

The main result of this study is that triple therapy, when compared to dual therapy, was associated with a significant reduction in ALP and bilirubin levels, two of the main prognostic factors that predict long-term survival in PBC.[20] It has been shown that bilirubin within the normal range and normalization of ALP should be the goals of treatment for improved survival in PBC.[21] In the present study, the likelihood with triple therapy of ALP normalization was, on average, multiplied by a factor of 3 compared to dual therapy. In addition, the probabilities of achieving normal levels of GGT or ALT were significantly higher with triple than dual therapy.

Finally, the likelihood with triple therapy of achieving an adequate biochemical response as defined by the Paris-2 or Toronto criteria was significantly increased as compared to dual therapy. Pending prospective controlled studies, these data support the use of triple therapy in patients with difficult-to-treat PBC.

Another important finding from our study is that fibrates, when added to OCA and UDCA (Group OCA-Fibrate), led to a significant improvement of pruritus with a 10 times increased probability of having no itch than with OCA and UDCA. This result is in accordance with the known beneficial effect of fibrates on PBC-associated pruritus.[14,15,22] It suggests that the association of fibrates with OCA, irrespective of its long-term potentiating effects on PBC, could be particularly relevant in order to mitigate the side-effects of OCA.[17]

The comparison of therapeutic sequences between OCA and fibrates (Group OCA-Fibrate vs Group Fibrate-OCA) revealed differences in biochemical responses that could reflect drug-specific mechanisms. Although the small size of our study does not allow for definite conclusion, it appears from the present data that fibrates are more efficient than OCA in reducing ALP level, whereas OCA could have stronger effects than fibrates on GGT and transaminases. These results suggest that fibrates and OCA have different impact on the mechanisms that concomitantly lead to PBC, including liver inflammation and cholestasis, and may explain their additive beneficial effects.

We did not use a matched control group for the comparison of triple therapy with dual therapy. Instead, the patients were their own controls and we applied a linear mixed-effects model to control for within-subject autocorrelations. We adjusted the model for confounding factors, including age, gender, and UDCA dose, because these factors have been shown to influence biochemical response in PBC.[23,24] We could not adjust for OCA and fibrates doses.

However, we assume these covariates would have had only little impact on results since few changes in dosage occurred during the study. Our results were expressed as relative changes per year. These rates, which were used for comparison purposes, cannot pretend to reflect the actual kinetics of biochemical liver tests, which mostly vary within the first 3 to 6 months of additional therapy before they stabilize. The use of a piecewise linear mixed-effects model may improve data modeling.

The main limitation of this retrospective study concerns the evaluation of tolerance and safety. By selecting patients who had been treated with triple therapy for at least 3 months, we have *de facto* excluded those who had experienced early intolerance to this combination, as well as those who had previously discontinued one of both dual therapies. Unfortunately, we did not collect safety data in those excluded patients, so we were unable to estimate the actual percentage of patients with PBC who had been given triple therapy and had well tolerated it. None of the patients included had discontinued triple therapy during a follow-up of up to 26 months. Longer and larger studies are needed to better assess the safety and side-effects of triple therapy in PBC.

In conclusion, in patients with high-risk PBC who previously failed to one of both second-line therapy with OCA or fibrates, triple therapy combining UDCA, OCA, and fibrates has the potential to improve and even normalize serum levels of ALP, GGT, transaminases, and total bilirubin. Furthermore, addition of fibrates to OCA increases the percentage of PBC patients with no pruritus. Clinical trials aiming to assess the efficacy and safety of triple therapy in patients with high-risk PBC are warranted.

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**Table 1.** Characteristics of patients at baseline of dual therapy.

| | Group OCA-Fibrate (n=29) | Group Fibrate-OCA (n=29) | P-value |
|---|---|---|---|
| Age (yrs) | 51.8 (16.6) | 46.0 (13.5) | < 0.05 |
| Female gender | 25 (86%) | 27 (93%) | 0.67 |
| Disease duration (yrs) | 5.0 (10.0) | 4.0 (10.0) | 0.39 |
| UDCA (mg/kg/d) | 14.9 (4.2) | 15.6 (3.9) | 0.44 |
| PBC-AIH overlap | 3 (10%) | 8 (28%) | 0.18 |
| Pruritus | 16 (55%) | 17 (63%) | 0.60 |
| Total bilirubin (mg/dL) | 0.6 (0.5) | 0.7 (0.8) | 0.30 |
| ALP (xULN) | 2.6 (0.9) | 3.0 (1.3) | 0.65 |
| GGT (xULN) | 5.0 (4.5) | 8.2 (10.1) | < 0.01 |
| AST (xULN) | 1.5 (1.0) | 1.8 (1.0) | 0.05 |
| ALT (xULN) | 1.5 (1.0) | 2.1 (2.0) | 0.05 |
| Albumin (g/L) | 43.0 (3.8) | 41.0 (4.5) | 0.96 |
| IgM (g/L) | 4.0 (3.1) | 4.5 (4.2) | 0.85 |
| Platelets (G/L) | 252 (115) | 243 (96) | 0.98 |
| Cholesterol (g/L) | 2.4 (0.8) | 2.9 (0.6) | 0.09 |
| Creatinine (mg/dL) | 0.7 (0.1) | 0.7 (0.2) | 0.51 |
| LSM (kPa) | 10.9 (6.5) | 8.4 (7.6) | 0.59 |
| Cirrhosis | 6 (21%) | 7 (24%) | 0.75 |

Variables are expressed as median (IQR). Group OCA-Fibrate: patients who received OCA as second-line therapy and fibrates as third-line therapy. Group Fibrate-OCA: patients who received fibrates as second-line therapy and OCA as third-line therapy. P-values are those for the Mann-Whitney test for continuous variables or the Fisher's exact test for categorical variables.

## FIGURE LEGENDS

**Figure 1.** Box plots of alkaline phosphatase level at the key time points of the study period (baseline of dual therapy, baseline of triple therapy, and last follow-up under triple therapy) in the entire population (panel A) and each group (panel B).

P-values are those for the adjusted generalized linear mixed-effects model comparing changes per unit of time in ALP level between dual and triple therapies.

The horizontal line in each box represents the median, the top and bottom of the boxes the interquartile range, and the whiskers the lowest and highest values with deviation < 1.5 times the interquartile range from first and third quartile, respectively.

**Figure 2.** 100 percent stacked bar graph of normal vs abnormal alkaline phosphatase levels at the key time points of the study period (baseline of dual therapy, baseline of triple therapy, and last follow-up under triple therapy) in the entire population (panel A) and each group (panel B).

P-values are those for the adjusted generalized linear mixed-effects model comparing odds ratios per unit of time of achieving normal ALP level between dual and triple therapies.

**Figure 3.** Box plots of total bilirubin (panel A), GGT (panel B), AST (panel C), and ALT (panel D) levels at the key time points of the study period (baseline of dual therapy, baseline of triple therapy, and last follow-up under triple therapy) in the entire population.

P-values are those for the adjusted generalized linear mixed-effects model comparing changes per unit of time in total bilirubin, GGT, AST, or ALT levels between dual and triple therapies.

The horizontal line in each box represents the median, the top and bottom of the boxes the interquartile range, and the whiskers the lowest and highest values with deviation < 1.5 times the interquartile range from first and third quartile, respectively.

**Figure 4.** 100 percent stacked bar graph of absent vs present pruritus at the key time points of the study period (baseline of dual therapy, baseline of triple therapy, and last follow-up under triple therapy) in the entire population (panel A) and each group (panel B).

P-values are those for the adjusted generalized linear mixed-effects model comparing odds ratios per unit of time of having no pruritus between dual and triple therapies.

**APPENDIX**

# Combination of fibrates with obeticholic acid is able to normalize biochemical liver tests in patients with difficult-to-treat primary biliary cholangitis

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**Table S1.** Distribution of patients by center.

| Participating centers | No. of eligible patients |
|---|---|
| Saint-Antoine University Hospital, Paris (ERN Rare-Liver) | 14 |
| University Hospitals KU, Leuven (ERN Rare-Liver) | 11 |
| University Hospital of Leipzig | 4 |
| San Gerardo University Hospital, Monza (ERN Rare-Liver) | 4 |
| La Tronche University Hospital, Grenoble | 3 |
| University Hospitals of Birmingham (ERN Rare-Liver) | 3 |
| University Hospital of Padova (ERN Rare-Liver) | 3 |
| Intercommunal Hospital of Creteil | 2 |
| Rangueil University Hospital, Toulouse (internal medicine) | 2 |
| University Medical Center, Hamburg (ERN Rare-Liver) | 2 |
| University Hospital of Reims | 2 |
| Edouard Herriot University Hospital, Lyon | 1 |
| Regional Medical Center, Orléans | 1 |
| University Hospital of Poitiers | 1 |
| University Hospital of Besançon | 1 |
| Beaujon University Hospital, Clichy | 1 |
| Rangueil University Hospital, Toulouse (hepatology) | 1 |
| University Hospitals of Barcelona (ERN Rare-Liver) | 1 |
| University of Miami Miller School of Medicine | 1 |
| University Hospital of Nice | 0 |
| University Hospital of Montpellier | 0 |

**Table S2.** Distribution of patients by country.

| Participating countries | No. of eligible patients |
|---|---|
| France | 29 |
| Belgium | 11 |
| Italy | 7 |
| Germany | 6 |
| United Kingdom | 3 |
| Spain | 1 |
| United States of America | 1 |

**Table S3.** Distribution of groups by center.

| Participating centers | Group OCA-Fibrate | Group Fibrate-OCA |
|---|---|---|
| Saint-Antoine University Hospital, Paris | 1 | 13 |
| University Hospitals KU, Leuven | 11 | 0 |
| University Hospital of Leipzig | 0 | 4 |
| San Gerardo University Hospital, Monza | 1 | 3 |
| La Tronche University Hospital, Grenoble | 2 | 1 |
| University Hospitals of Birmingham | 3 | 0 |
| University Hospital of Padova | 3 | 0 |
| Intercommunal Hospital of Creteil | 2 | 0 |
| Rangueil University Hospital, Toulouse (internal medicine) | 2 | 0 |
| University Medical Center, Hamburg | 1 | 1 |
| University Hospital of Reims | 1 | 1 |
| Edouard Herriot University Hospital, Lyon | 0 | 1 |
| Regional Medical Center, Orléans | 0 | 1 |
| University Hospital of Poitiers | 0 | 1 |
| University Hospital of Besançon | 0 | 1 |
| Beaujon University Hospital, Clichy | 0 | 1 |
| Rangueil University Hospital, Toulouse (hepatology) | 1 | 0 |
| University Hospitals of Barcelona | 0 | 1 |
| University of Miami Miller School of Medicine | 1 | 0 |

OCA, obeticholic acid.

**Table S4.** Distribution of bezafibrate and fenofibrate by group.

| Type of fibrates | Group OCA-Fibrate | Group Fibrate-OCA |
|---|---|---|
| Bezafibrate only | 24 | 23 |
| Fenofibrate only | 4 | 3 |
| Bezafibrate or Fenofibrate* | 1 | 3 |

* A few patients received both drugs consecutively. OCA, obeticholic acid.

**Table S5.** Numbers of patients assessed in the adjusted generalized linear mixed-effects model by variable tested and group.

| Variable | Entire cohort | Group OCA-Fibrate | Group Fibrate-OCA |
|---|---|---|---|
| Pruritus | 55 | 28* | 27 |
| Total bilirubin | 55 | 28 | 27 |
| ALP | 55 | 28 | 27 |
| GGT | 54 | 27 | 27 |
| AST | 55 | 28 | 27 |
| ALT | 55 | 28 | 27 |
| Paris-2 criteria | 55 | 28 | 27 |
| Toronto criteria | 55 | 28 | 27 |
| Albumin | 49 | 26 | 23 |
| IgM | 25 | 12 | 13 |
| Platelets | 27 | 14 | 13 |
| Cholesterol | 28 | 14 | 14 |
| Creatinine | 29 | 15 | 14 |
| LSM | 51 | 24 | 27 |

* For each variable tested, the model was adjusted for age, sex, and UDCA dose. One patient in the OCA-Fibrate group and 2 in the Fibrate-OCA group had to be excluded from the analysis because of unavailable data on UDCA dose.

OCA, obeticholic acid; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgM, immunoglobulin M; LSM, liver stiffness measurement.

**Table S6.** Total follow-up and durations of dual therapy and triple therapy on the entire population and by group.

| | **Group OCA-Fibrate** | **Group Fibrate-OCA** | **P-value** |
|---|---|---|---|
| Total follow-up (yrs) | 9.6 (12.2) | 8.2 (9.0) | 0.35 |
| Dual therapy (yrs) | 4.8 (5.1) | 2.4 (3.1) | 0.41 |
| Triple therapy (yrs) | 0.9 (0.5) | 0.8 (0.9) | 0.31 |

Data are expressed as median (IQR). P-values are those for the Mann-Whitney test.

**Table S7.** Dose adjustments during dual and triple therapies (shown are the numbers of patients with increased, decreased, or unchanged dose).

| | Group OCA-Fibrate | | | Group Fibrate-OCA | | |
|---|---|---|---|---|---|---|
| | Increased | Decreased | Unchanged | Increased | Decreased | Unchanged |
| **Dual therapy** | | | | | | |
| OCA | 3 | 5 | 21 | n/a | n/a | n/a |
| Fibrates | n/a | n/a | n/a | 0 | 0 | 29 |
| **Triple therapy** | | | | | | |
| OCA | 0 | 0 | 29 | 6 | 1 | 22 |
| Fibrates | 0 | 2 | 27 | 0 | 0 | 29 |

N/A, non-applicable. OCA, obeticholic acid.

**Table S8.** Reduction gain per year in alkaline phosphatase level under triple vs. dual therapy as estimated on the entire cohort and by group after the exclusion of patients with features of AIH overlap syndrome.

| | Reduction gain in ALP | 95% confidence interval | P-value |
|---|---|---|---|
| Entire cohort | 26% | 14% – 37% | < 0.001 |
| Group OCA-Fibrate | 43% | 30% – 54% | < 0.001 |
| Group Fibrate-OCA | 8% | -15% – 25% | 0.474 |

P-values are those for the adjusted generalized linear mixed-effects model comparing triple vs. dual therapy.

**Table S9.** Odds ratio per year of having normal alkaline phosphatase level under triple vs. dual therapy as estimated on the entire cohort and by group after the exclusion of patients with features of AIH overlap syndrome.

| | Odd ratios of normal ALP | 95% confidence interval | P-value |
|---|---|---|---|
| Entire cohort | 4.0 | 1.4 – 11.3 | 0.008 |
| Group OCA-Fibrate | 9.1 | 2.1 – 39.4 | 0.003 |
| Group Fibrate-OCA | 1.7 | 0.4 – 7.9 | 0.486 |

ALP, alkaline phosphatase. P-values are those for the adjusted generalized linear mixed-effects model comparing triple vs. dual therapy.

**Table S10.** Relative change per year under triple vs. dual therapy in serum levels of albumin, IgM, platelets, cholesterol, and creatinine, and in liver stiffness measurement as estimated on the entire population.

| | Relative change | 95% confidence interval | P-value |
|---|---|---|---|
| Albumin | -1% | -3% – 1% | 0.43 |
| IgM | 9% | -19% – 49% | 0.54 |
| Platelets | -7% | -15% – 2% | 0.11 |
| Cholesterol | -8% | -17% – 4% | 0.18 |
| Creatinine | -4% | -10% – 2% | 0.19 |
| LSM | 2% | -16% – 25% | 0.81 |

LSM: liver stiffness measurement as assessed by vibration-controlled transient elastography (Fibroscan). P-values are those for the adjusted generalized linear mixed-effects model comparing triple vs. dual therapy.

**Table S11.** Reduction gain per year in secondary outcomes under triple vs. dual therapy as estimated on the entire cohort after the exclusion of patients with features of AIH overlap syndrome.

| | Reduction gain | 95% confidence interval | P-value |
|---|---|---|---|
| Bilirubin | 13% | 4% – 22% | 0.008 |
| GGT | 30% | 14% – 43% | < 0.001 |
| AST | 13% | 1% – 24% | 0.029 |
| ALT | 25% | 12% – 36% | < 0.001 |
| Albumin | -1% | -2% – 4% | 0.460 |
| IgM | -1% | -36% – 60% | 0.976 |
| Platelets | 5% | -5% – 15% | 0.332 |
| Cholesterol | 4% | -9% – 16% | 0.534 |
| Creatinine | 6% | -1% – 12% | 0.107 |
| LSM | -2% | -32% – 20% | 0.868 |

P-values are those for the adjusted generalized linear mixed-effects model comparing triple vs. dual therapy.

**Table S12.** Odds ratio per year of reaching an adequate biochemical response under triple vs. dual therapy as estimated on the entire cohort and by group.

| | **OR (95% CI) of reaching adequate response** | | | |
|---|---|---|---|---|
| | Paris-2 criteria | P-value | Toronto criteria | P-value |
| Entire cohort | 6.8 (2.8 – 16.7) | <0.001 | 9.2 (3.4 – 25.1) | <0.001 |
| Group OCA-Fibrate | 12.7 (2.7 – 58.7) | 0.001 | 30.7 (4.7 – 199.6) | <0.001 |
| Group Fibrate-OCA | 5.3 (1.8 – 15.8) | 0.003 | 5.8 (1.8 – 18.9) | |

**Table S13.** Reduction gain per year in itch intensity score and odds ratio of having no pruritus under triple vs. dual therapy as estimated on the entire cohort and by group after the exclusion of patients with features of AIH overlap syndrome.

| | **Reduction gain in itch** | **95% confidence interval** | **P-value** |
|---|---|---|---|
| Entire cohort | 36% | -34% – 69% | 0.234 |
| Group OCA-Fibrate | 72% | 21% – 90% | 0.016 |
| Group Fibrate-OCA | -36% | -278% – 51% | 0.553 |
| | **Odds ratio of no pruritus** | **95% confidence interval** | **P-value** |
| Entire cohort | 2.2 | 0.7 – 7.1 | 0.187 |
| Group OCA-Fibrate | 9.1 | 1.3 – 50.0 | 0.026 |
| Group Fibrate-OCA | 0.7 | 0.1 – 4.0 | 0.714 |

P-values are those for the adjusted generalized linear mixed-effects model comparing triple vs. dual therapy.

**Figure S1.** Box plots of alkaline phosphatase level at different time points of the study period (baseline of dual therapy, 6-month dual therapy, baseline of triple therapy, 3-month triple therapy, and last follow-up under triple therapy) in the entire population (panel A) and each group (panel B).

The triple therapy-associated reduction gain in ALP level (compared to dual therapy) was detectable as early as month 3. The horizontal line in each box represents the median, the top and bottom of the boxes the interquartile range, and I bars 1.5 times the interquartile range.

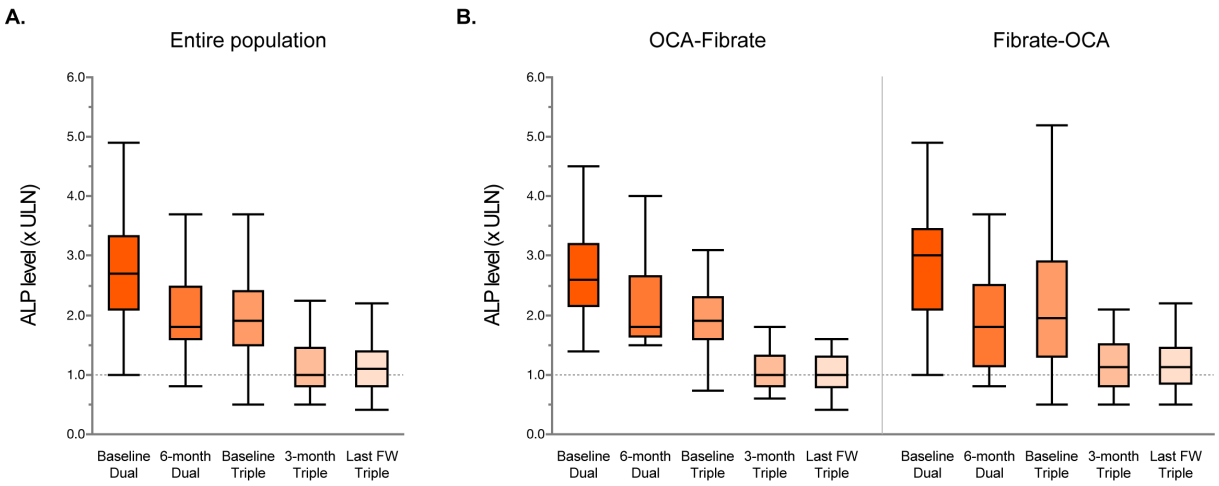

**Figure S2.** Box plots of total bilirubin (panel A), GGT (panel B), AST (panel C), and ALT (panel D) levels in each therapeutic group at the key time points of the study period (baseline dual therapy, baseline triple therapy, and last-follow up triple therapy).

The horizontal line in each box represents the median, the top and bottom of the boxes the interquartile range, and I bars 1.5 times the interquartile range. P-values are those for the adjusted generalized linear mixed-effects model.