A Placebo-controlled Trial of Bezafibrate in Primary Biliary Cholangitis

Christophe Corpechot, Olivier Chazouillères, Alexandra Rousseau, Antonia Le Gruyer, François Habersetzer, Philippe Mathurin, Odile Goria, Pascal Potier, Anne Minello, Christine Silvain, et al.

▶ To cite this version:

Christophe Corpechot, Olivier Chazouillères, Alexandra Rousseau, Antonia Le Gruyer, François Habersetzer, et al.. A Placebo-controlled Trial of Bezafibrate in Primary Biliary Cholangitis. New England Journal of Medicine, 2018. hal-03972495

HAL Id: hal-03972495

https://hal.sorbonne-universite.fr/hal-03972495

Submitted on 3 Feb 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

A Placebo-controlled Trial of Bezafibrate in Primary Biliary Cholangitis

Christophe Corpechot, M.D. (1,2), Olivier Chazouillères, M.D. (1,2), Alexandra Rousseau, Ph.D. (3), Antonia Le Gruyer, M.D. (4), François Habersetzer, M.D., Ph.D. (5), Philippe Mathurin, M.D., Ph.D. (6), Odile Goria, M.D. (7), Pascal Potier, M.D. (8), Anne Minello, M.D., Ph.D. (9), Christine Silvain, M.D. (10), Armand Abergel, M.D., Ph.D. (11), Maryline Debette-Gratien, M.D., Ph.D. (12), Dominique Larrey, M.D., Ph.D. (13), Olivier Roux, M.D. (14), Jean-Pierre Bronowicki, M.D., Ph.D. (15), Jérôme Boursier, M.D., Ph.D. (16), Victor de Ledhingen, M.D., Ph.D. (17), Alexandra Heurgue-Berlot, M.D. (18), Eric Nguyen-Khac, M.D., Ph.D. (19), Fabien Zoulim, M.D., Ph.D. (20), Isabelle Ollivier-Hourmand, M.D. (21), Jean-Pierre Zarski, M.D., Ph.D. (22), Gisèle Nkontchou, M.D. (23), Lydie Humbert (24), Dominique Rainteau, Ph.D. (24), Guillaume Lefèvre, Pharm. D., Ph.D. (25), Luc de Chaisemartin, Pharm. D., Ph.D. (26), Sylvie Chollet-Martin, M.D., Ph.D. (26), Farid Gaouar M.D. (1), Farid-Hakeem Admane (3), Tabassome Simon, M.D., Ph.D. (3, 27), Raoul Poupon, M.D. (1,2)

Affiliations:

1) Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, Hepatology and Gastroenterology Department, Saint-Antoine University Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France; 2) Inserm UMR_S938, Sorbonne University, Paris, France; 3) Department of Clinical Pharmacology and Clinical Research Platform of East of Paris, Assistance Publique - Hôpitaux de Paris, Paris, France; 4) Hepatology and Gastroenterology Department, Pontchaillou University Hospital, Rennes, France; 5) Hepatology and Gastroenterology Department, University Hospitals of Strasbourg, Strasbourg, France; 6) Hepatology and Gastroenterology Department, Claude Huriez

University Hospital, Lille, France; 7) Hepatology and Gastroenterology Department, Charles Nicolle University Hospital, Paris, France; 8) Hepatology and Gastroenterology Department, Orléans Hospital, Orléans, France; 9) Hepatology and Gastroenterology Department, Le Bocage University Hospital, Dijon, France; 10) Hepatology and Gastroenterology Department, University Hospital of Poitiers, Poitiers, France; 11) Hepatology and Gastroenterology Department, Estaing University Hospital, Clermont-Ferrand, France; 12) Hepatology and Gastroenterology Department, University Hospital of Limoges, Limoges, France; 13) Hepatology and Gastroenterology Department, St-Eloi University Hospital, Montpellier, France; 14) Hepatology Department, Beaujon University Hospital, Clichy, France; 15) Hepatology and Gastroenterology Department, Brabois University Hospital, Nancy, France; 16) Hepatology and Gastroenterology Department, University Hospital pf Angers, Angers, France; 17) Hepatology and Gastroenterology Department, Haut-Lévêque University Hospital, Pessac, France; 18) Hepatology and Gastroenterology Department, Robert Debré University Hospital, Reims, France; 19) Hepatology and Gastroenterology Department, University Hospital of Amiens, Amiens, France; 20) Hepatology and Gastroenterology Department, Croix-Rousse University Hospital, Lyon, France; 21) Hepatology and Gastroenterology Department, University Hospital of Caen, Caen, France; 22) Hepatology and Gastroenterology Department, Michallon University Hospital, Grenoble, France; 23) Hepatology and Gastroenterology Department, Jean Verdier University Hospital, Bondy, France; 24) Biochemistry Laboratory, Inserm U1057/UMR 7203, Paris, France; 25) Biochemistry laboratory, Tenon University Hospital, Paris, France; 26) Immunology Laboratory, Inserm UMR_S996, Bichat University Hospital, Paris, France; 27) Sorbonne University, Paris 6, Paris, France.

Key-words: Randomized controlled trial; PPAR agonist; Pruritus; Elastography; ELF score; UDCA; Inadequate response.

Word count: Abstract: 248; manuscript: 2792.

Number of Tables: 3.

Number of Figures: 2.

Conflict of interest: All the authors declare to have no conflict of interest in relation to this study.

Sponsorship and funding: This trial was promoted by the Assistance Publique – Hôpitaux de Paris, Paris, France and funded by a grant from Programme Hospitalier de Recherche Clinique (PHRC) 2010 (Ministry of Health) and from Arrow Génériques, Lyon, France.

Special acknowledgments: We are indebted to the patients and we thank all the physicians who referred them to the participating centers for their help in recruitment. We thank the Clinical Research Center of East of Paris (CRC-East), Saint-Antoine University Hospital (AP-HP), for its logistic support. We thank Jacob Staal-Anderson for his contribution to the revision of this article.

Corresponding author: Christophe Corpechot, MD. Reference center for inflammatory biliary diseases and autoimmune hepatitis, Saint-Antoine Hospital, 184 rue du faubourg Saint-Antoine, 75571 Paris, cedex 12, France. E-mail: christophe.corpechot@aphp.fr.

BACKGROUND

Patients with primary biliary cholangitis (PBC) who inadequately respond to ursodeoxycholic acid (UDCA) therapy are at high risk of disease progression. Fibrates, which are agonists of peroxisome proliferator-activated receptors, in combination with UDCA, have shown potential benefit in this condition.

METHODS

In this 24-month, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 100 patients who had an inadequate response to UDCA according to the Paris-2 criteria to receive bezafibrate, at a daily dose of 400 mg (n=50), or placebo (n=50), in addition to continued treatment with UDCA. The primary outcome was a complete biochemical response defined as normal levels at 24 months of all of the following: total bilirubin, alkaline phosphatase (ALP), aminotransferases, albumin, and prothrombin index.

RESULTS

The primary outcome occurred in 30% of patients with bezafibrate and 1% with placebo (difference [95%CI] = 29% [16% ; 43%]; $P < 0.001$). Normalization of ALP occurred in 67% of patients with bezafibrate and 2% with placebo. Changes in pruritus, fatigue, and non-invasive markers of liver fibrosis, including liver stiffness measurement and Enhanced Liver Fibrosis score, were consistent with the primary outcome. Two patients in each group experienced end-stage liver complications. Creatinine level increased 5% in the bezafibrate group and decreased 3% in the placebo group. Myalgia was experienced by 20% in bezafibrate and 10% in placebo group.

CONCLUSIONS

Bezafibrate administered with UDCA in patients with PBC who had inadequate response to UDCA alone resulted in a significantly higher rate of complete biochemical response than

placebo with UDCA. (Funded by the Assistance Publique–Hôpitaux de Paris with support from Arrow Génériques; BEZURSO ClinicalTrials.gov number, NCT01654731).

Primary biliary cholangitis (PBC) is a progressive liver disease of unknown cause that mainly affects women over the age of 30. It is characterized by serum autoantibodies, inflammation and destruction of small intrahepatic bile ducts, progressive cholestasis, a distinctive symptom of which is pruritus, and slow progression towards cirrhosis and liver failure.[1] Ursodeoxycholic acid (UDCA), a hydrophilic bile acid with choleretic and liver-protective properties, is currently the standard first-line therapy for PBC.[2,3] Treatment with UDCA improves biochemical markers of cholestasis and delays the time to liver transplantation.[4,5] However, long-term survival remains impaired in patients with incomplete biochemical response.[6-8] Additional therapeutic options are therefore needed in patients who have an inadequate response to UDCA.

Combination of obeticholic acid (OCA), a selective agonist of the farnesoid X receptor, with UDCA has recently been shown to decrease biochemical markers of cholestasis in patients with PBC who have inadequately responded to UDCA.[9,10] In these studies, however, OCA was associated with higher rates of severe pruritus than placebo.[10] Alternatively, association of UDCA with fibrates, that are agonists of peroxisome proliferator-activated receptors (PPAR), might have the potential to improve both biochemical parameters and symptoms of PBC.[11-14] The aim of the present trial was to assess the efficacy, safety, and adverse-event profile of bezafibrate, a pan-PPAR agonist, in patients with PBC who despite UDCA treatment continue to exhibit significant alteration in biochemical liver tests.

METHODS

Participants

Patients aged 18 or older who had been diagnosed with PBC according to established criteria[2] were recruited from 21 centers throughout France. All patients were treated with UDCA at a dose of 13-15 mg/kg/d. Entry criterion was an inadequate biochemical response to UDCA as defined by the Paris-2 criteria[15], i.e. a serum level of alkaline phosphatase (ALP) or aspartate aminotransferase (AST) > 1.5 times the upper limit of the normal range (ULN) or an abnormal total bilirubin level (< 50 µmole/L), assessed after 6 months of treatment or more. All patients gave written informed consent. The protocol, available with this article at nejm.org, was approved by the Committee for the Protection of Persons and the French National Agency for Medicines and Health Products Safety. The authors vouch for fidelity of this report to the protocol and for the completeness and accuracy of the data and data analyses.

Trial design

The study was designed as a 2-arm, randomized, double-blind, placebo-controlled trial. Centralized balanced block randomization (blocks of size 4) was computer generated without stratification by center. Patients were randomly assigned, in a 1:1 ratio, to receive once-daily oral placebo or bezafibrate at a dose of 400 mg in combination with UDCA therapy. They were followed-up every 3 months during 24 months. Ultrasound (US) of the liver and liver stiffness measurement were performed at baseline, 12, and 24 months. Liver stiffness measurement was assessed using vibration-controlled transient elastography

(Fibroscan, Echosens, France); liver stiffness measurements correlate with histological fibrosis and prognosis.[16]

Primary, secondary, and exploratory outcomes

The primary outcome was the percentage of patients with a complete biochemical response as defined by normal serum levels at 24 months of all of the following: ALP, AST, alanine aminotransferase (ALT), total bilirubin, albumin, and prothrombin index.

Secondary outcomes included the percentage of patients with the above-defined response at the different time points of the study, the percentage of patients with normal ALP at 24 months, changes in serum levels of ALP, AST, ALT, gammaglutamyl transpeptidase (GGT), total bilirubin, albumin, prothrombin index, total, high and low density lipoprotein (HDL, LDL) cholesterol, and platelets count, the percentage of patients with an adequate biochemical response at 24 months, changes in itch intensity score (0-10 visual analogue scale (VAS), 10 indicating worse itch),[17] fatigue (absent, intermittent, continuous) and quality of life (Nottingham Health Profile classified into 6 domains of well-being, each of which being scored from 0 (better) to 100 (worse)),[18] changes in liver stiffness measurement. Secondary outcomes also included changes in Enhanced Liver Fibrosis score (a validated measure of liver fibrosis based on the serum levels of hyaluronic acid, procollagen type III N-terminal peptide, and tissue inhibitor of metalloproteinase 1),[19] development of portal hypertension (defined as meeting at least one of the following criteria: ascites, esophageal or gastric varices, US signs of portal hypertension, platelet count < 150 G/L, or liver stiffness measurement > 20 kPa), and survival without liver transplantation or liver complications (defined as ascites, variceal bleeding, hepatic encephalopathy, or a doubling of total bilirubin level > 50 µmole/L).

Post-hoc exploratory outcomes included changes in serum levels of total and endogenous bile acids (BA), UDCA, 7α-hydroxy-4-cholesten-3-one (C4 bile acid precursor), immunoglobulins M (IgM) and G (IgG), high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor alpha (TNF-α), and interleukin 12 (IL-12), survival estimated according to the Globe and UK-PBC risk scores (see supplementary appendix), and predictive factors of inadequate response.

Safety reports

Adverse events were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class version 20.0, the MedDRA preferred term, severity and causal relationship as assessed by the investigators.

Statistical analysis

Based on the results of a 2-year, open-label pilot study of 38 patients followed at Saint-Antoine Hospital, Paris, France, treated with UDCA (13-15 mg/kg/d) and fibrates (bezafibrate 400 mg/d or fenofibrate 200 mg/d) combination therapy (unpublished data, available on request), we expected a rate of complete biochemical response of 40% in the bezafibrate group and 10% in the placebo group. We decided to opt for bezafibrate, a pan-PPAR agonist, because of better-documented effects and broader expected properties. Considering a 2-sided 5%-alpha risk and a 17% lost-to-follow-up rate, 100 patients were needed to achieve 90% statistical power.

Analyses were performed at the end of the trial on the intent-to-treat population (all randomized patients), and blinded to treatment allocation. Multiple imputation was performed to replace missing biochemical parameters used to assess the primary outcome. The difference in response rates and its 95% confidence interval (95%CI) were estimated and treatment groups were compared using chi-square test. Sensitivity analyses (no imputation, last observation carried forward and worst-case scenario methods) were performed. Quantitative data were expressed as mean and standard deviation (SD) or median and interquartile range when appropriate and mean difference between bezafibrate and placebo groups and 95% CI. Piecewise linear mixed-effects models were used to explore some critical parameters overtime after log-transformation, considering random effects for time and subject. Knots were not pre-specified. Logistic regression analysis was used to study the predictive factors of inadequate biochemical response. All tests were two-sided and a P-value < 0.05 indicated statistical significance. No adjustment for multiple comparisons was planned, and 95%CI, without p values, are reported for the secondary outcome and exploratory analyses. A total of 44 tests were conducted for secondary outcomes. Given the number of tests conducted, the 95%CI may not be reproducible. Analyses were performed using SAS version 9.3, SAS institute Inc., Cary, USA. See supplementary appendix for additional details.

RESULTS

Trial populations

One hundred patients (n=50 in each group) were enrolled between September 2012 and December 2014 (Fig. S1 in supplement appendix). Baseline characteristics of patients did not differ between groups (**Table 1**). Overall, 95% were female, mostly of Caucasian origin, with an average age of 53 ± 10 years. Forty percent of patients had significant (VAS ≥ 3) pruritus and 48% declared intermittent or continuous fatigue. Half (54%) was at an advanced stage of disease according to histology (Ludwig's stage 3 or 4) or liver stiffness measurement (> 9.6 kPa).

Study and drug discontinuation

A total of 92 (92%) patients completed the trial. Early termination of the study occurred in 2 (4%) patients in the bezafibrate group and 6 (12%) patients in the placebo group. Temporary or definitive cessation of the randomized treatment occurred in 13 patients in placebo vs. 7 patients in bezafibrate group; cessation of UDCA occurred in 4 patients in placebo vs. 2 patients in bezafibrate group.

Primary outcome

The primary outcome was achieved in 30% of patients in the bezafibrate group and 1% in the placebo group (difference [95%CI] = 29% [16% ; 43%]; $P < 0.001$). The conclusion remained unchanged in sensitivity analysis (Table S1 in supplement appendix). The rate of complete biochemical response in the bezafibrate group increased progressively during the first 15 months of treatment before reaching a plateau of 30-35% (**Fig. 1**).

Secondary outcomes

Biochemical parameters

The specific changes in total bilirubin, ALP, GGT, ALT, albumin, platelet count, and total cholesterol were consistent with the primary outcome (**Table 2**). At 24 months, 31 (67%) patients in the bezafibrate group and 1 (2%) patient in the placebo group had normal ALP levels (difference [95%CI] = 65% [47% ; 79%]). A 60% median reduction in ALP was observed in the bezafibrate group from month 3 (**Fig. 2A**). A similar rapid reduction in GGT was observed among bezafibrate users (Fig. S2 in supplement appendix). These results were confirmed in longitudinal analysis (Tables S2 and Table S3 in supplement appendix). Total bilirubin showed a 14% decrease in the bezafibrate group and a 18% increase in the placebo group (**Fig. 2B** and Table S4 in supplement appendix). The course of bilirubin in cirrhotic patients did not differ between groups. Aminotransferases in the bezafibrate group decreased progressively (**Fig. 2C** and Fig. S3 in supplement appendix; Tables S5 and Table S6 in supplement appendix). Three months after the end of study (washout period of allocated treatment), total bilirubin, ALP, GGT, and aminotransferases deteriorated in the bezafibrate but not the placebo group (Fig. S4 in supplement appendix).

Predefined biochemical responses

The rates of adequate biochemical response as defined by established criteria (Barcelona, Paris-1, Paris-2, Rotterdam, Toronto, and Globe score) were significantly higher in the bezafibrate than in the placebo group, except for the Rotterdam criteria that were expected to deteriorate only in late-stage disease (Table S7 in supplement appendix).

Patient-reported outcomes

Changes in itch intensity score were consistent with the primary outcome (Fig. S5 in supplement appendix), as were changes in fatigue status (Table S8 in supplement appendix). No differences were found in the quality-of-life scores (Table S9 in supplement appendix).

Noninvasive markers of fibrosis

Changes in liver stiffness measurement at 24 months showed a 15% decrease in the bezafibrate group and a 22% increase in the placebo group (difference [95%CI] = -48% [-82% ; -13%]; **Fig. 2D**). Changes in Enhanced Liver Fibrosis score were consistent with this result (difference [95%CI] = -4% [-8% ; -1%]; Table S10 in supplement appendix).

Liver histology

Histological data were available in 59 patients at baseline (bezafibrate: 30, placebo: 29) and 51 patients at 24 months (bezafibrate: 26, placebo: 25), but only 28 patients had available data at both time points. Among this subgroup, changes in histological stage, fibrosis stage, and activity grade did not differ between treatment arms.

Clinical outcomes

Nineteen patients developed features of portal hypertension with no difference between groups (20% in the bezafibrate vs. 18% in the placebo groups). Four patients, 2 in each group, experienced liver complications: one liver transplantation and one inscription on waiting list in the bezafibrate group, one ascites and one doubling of total bilirubin > 50 µmole/L in the placebo group. No patients died.

Post hoc analyses

Serum bile acids and C4 precursor

At baseline, serum levels of total and endogenous BA, UDCA, and C4 precursor (a marker of BA synthesis) did not differ between groups (Table S11 in supplement appendix). Changes in C4 precursor were consistent with the primary outcome (Fig. S6 in supplement appendix).

Changes in total and endogenous BA levels did not differ between groups, but the proportion of endogenous BA within the BA pool significantly decreased with bezafibrate (Table S12 in supplement appendix).

Markers of immunity and inflammation

In the subgroup of patients with available data, changes in serum IgM and IgG levels did not differ significantly between groups (Fig. S7A in supplement appendix). No difference was found in hs-CRP, TNF-α, and IL-12 serum level changes (Fig. S7B in supplement appendix).

Predictive factors of inadequate response

The factors that were independently associated with an inadequate biochemical response to bezafibrate were features of portal hypertension and ALP level (Table S13 in supplement appendix).

Prognostic scores

The application of the Globe and UK-PBC risk scores at baseline, 12 and 24 months showed a significant reduction in the predicted rates of liver transplantation and death in the bezafibrate vs. placebo group (Fig. S8 in supplement appendix).

Safety and side-effects

Overall, 424 adverse events were reported in 88 patients and were distributed as follows: 49% in bezafibrate, 51% in placebo group (**Table 3**).

A total of 39 (9%) serious adverse events (SAE) was reported in 26 patients, 14 patients in bezafibrate and 12 patients in placebo group (Table S14 in supplement appendix).

Creatinine levels increased 5% in the bezafibrate group and decreased 3% in the placebo group (difference [95%CI] = 11% [5% ; 18%]). This difference was noticeable at month 3 and remained stable during the study (Fig. S9 in supplement appendix). One patient in the bezafibrate group (with history of diabetes and hypertension) showed a decrease in estimated glomerular filtration rate (eGFR) to < 60 mL/min (stage 3 renal disease). Ten patients (4 in bezafibrate, 6 in placebo group) met stage 2 renal disease (eGFR ≥ 60 and < 90 mL/min) at 24 months.

Four patients experienced an increase in aminotransferases > 5 times the ULN, one in placebo and 3 in bezafibrate group. This led to a definitive cessation of allocated treatment in 3 patients (one in placebo, 2 in bezafibrate group). All cases in the bezafibrate group resolved within 3 months, either spontaneously (one patient) or after corticosteroids administration (2 patients in whom liver histology at baseline was suggestive of associated autoimmune hepatitis).

Myalgia was experienced by 20% in bezafibrate and 10% in placebo group. One patient in the bezafibrate group, who concomitantly received statin therapy, developed moderate, asymptomatic rhabdomyolysis at month 3 that resolved after treatment discontinuation.

DISCUSSION

In this randomized trial, we found that in patients with PBC who had inadequately responded to UDCA, approximately a third of the patients in the bezafibrate group, as compared to none in the placebo group, reached the primary outcome, i.e. normal levels of the main biochemical markers of the disease at 24 months. Parallel changes in pruritus, fatigue, and noninvasive markers of liver fibrosis were consistent with this result.

Patients were selected based on the Paris-2 criteria[15], which have been recognized as relevant predictors of clinical outcomes in several independent populations of PBC patients.[20,21]

In the present trial, bezafibrate was associated with a rapid and sustained fall in ALP level and a parallel decrease in total bilirubin, the 2 most important prognostic indicators in PBC.[21] Despite initial concerns,[22] we did not observe an increase in bilirubin level in cirrhotic patients who were treated with bezafibrate.

These changes were accompanied by a decrease in liver stiffness measurement and Enhanced Liver Fibrosis score, two markers of liver fibrosis and prognosis of PBC.[16,19] Our histological data, unfortunately, were too limited to determine if these changes were related to an effective reduction in liver fibrosis and hepatic inflammation.

The trial was not large or long enough to assess the effect of bezafibrate on hard outcomes. Larger trials will be required to assess effects on liver transplantation and mortality.

Portal hypertension and high ALP level were identified at baseline as independent predictors of treatment failure. Advanced cirrhosis and severe cholestasis should therefore be considered as potential limiting factors for adjunctive therapy with bezafibrate.

Bezafibrate was associated with a 5% increase in serum creatinine level. This is a known effect of PPAR-α agonists.[23-25] Its mechanism may involve renal haemodynamic changes or an increased creatinine release by muscle.[26] One patient in this trial, who had diabetes and hypertension, developed stage 3 renal disease during treatment with bezafibrate. As a precaution, bezafibrate use should be evaluated with regard to the kidney function, especially in patients with diabetes, hypertension, or any known renal disease.

Different mechanisms may lead to the therapeutic effects described above.[27,28] Our results support that bezafibrate acts in part through specific anticholestatic properties such as inhibition of BA synthesis and consequent reduction in endogenous BA overload.[29] Previous findings have suggested a suppressive effect of fibrates on immune response.[13,30] We found no significant changes in IgM, hs-CRP, TNF-α and IL-12 serum levels but suppression of intrahepatic pro-inflammatory cytokines is highly plausible.[31] Finally, the PPAR-δ agonistic effects of bezafibrate may be considered specifically as seladelpar, a selective PPAR-δ agonist, has recently been shown to improve markers of cholestasis in patients with PBC.[32]

In conclusion, in patients with PBC and inadequate response to UDCA, 24-month add-on therapy with bezafibrate achieved a higher rate of complete biochemical response than placebo. Parallel changes in patient-reported outcomes and non-invasive markers of liver fibrosis were consistent with this effect. Bezafibrate was associated with an increase in creatinine level. Longer and larger studies are required to assess the effects of bezafibrate on clinical outcomes.

REFERENCES

1. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. Lancet 2015;386:1565-75.
2. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145-72.
3. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. Hepatology 2009;50:291-308.
4. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. N Engl J Med 1991;324:1548-54.
5. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997;113:884-90.
6. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology 2006;130:715-20.
7. Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology 2008;48:871-7.
8. Kumagi T, Guindi M, Fischer SE, et al. Baseline Ductopenia and Treatment Response Predict Long-Term Histological Progression in Primary Biliary Cirrhosis. Am J Gastroenterol 2010;105:2186-94.
9. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic Acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic Acid. Gastroenterology 2015;148:751-61.
10. Nevens F, Andreone P, Mazzella G, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med 2016;375:631-43.
11. Nakai S, Masaki T, Kurokohchi K, Deguchi A, Nishioka M. Combination therapy of bezafibrate and ursodeoxycholic acid in primary biliary cirrhosis: a preliminary study. Am J Gastroenterol 2000;95:326-7.
12. Iwasaki S, Ohira H, Nishiguchi S, et al. The efficacy of ursodeoxycholic acid and bezafibrate combination therapy for primary biliary cirrhosis: A prospective, multicenter study. Hepatol Res 2008;38:557-64.
13. Levy C, Peter JA, Nelson DR, et al. Pilot study: fenofibrate for patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. Aliment Pharmacol Ther 2011;33:235-42.
14. Reig A, Sese P, Pares A. Effects of Bezafibrate on Outcome and Pruritus in Primary Biliary Cholangitis With Suboptimal Ursodeoxycholic Acid Response. Am J Gastroenterol 2018;113:49-55.
15. Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol 2011;55:1361-7.
16. Corpechot C, Carrat F, Poujol-Robert A, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology 2012;56:198-208.
17. Reich A, Heisig M, Phan NQ, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol 2012;92:497-501.
18. Poupon RE, Chretien Y, Chazouilleres O, Poupon R, Chwalow J. Quality of life in patients with primary biliary cirrhosis. Hepatology 2004;40:489-94.

19. Mayo MJ, Parkes J, Adams-Huet B, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. Hepatology 2008;48:1549-57.
20. Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic Acid. Gastroenterology 2013;144:560-9.
21. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147:1338-49.
22. Cheung AC, Lapointe-Shaw L, Kowgier M, et al. Combined ursodeoxycholic acid (UDCA) and fenofibrate in primary biliary cholangitis patients with incomplete UDCA response may improve outcomes. Aliment Pharmacol Ther 2016;43:283-93.
23. Zhao YY, Weir MA, Manno M, et al. New fibrate use and acute renal outcomes in elderly adults: a population-based study. Ann Intern Med 2012;156:560-9.
24. Ting RD, Keech AC, Drury PL, et al. Benefits and safety of long-term fenofibrate therapy in people with type 2 diabetes and renal impairment: the FIELD Study. Diabetes Care 2012;35:218-25.
25. Mychaleckyj JC, Craven T, Nayak U, et al. Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic participants. Diabetes Care 2012;35:1008-14.
26. Sica DA. Fibrate therapy and renal function. Curr Atheroscler Rep 2009;11:338-42.
27. Cuperus FJ, Halilbasic E, Trauner M. Fibrate treatment for primary biliary cirrhosis. Curr Opin Gastroenterol 2014;30:279-86.
28. Ghonem NS, Assis DN, Boyer JL. Fibrates and cholestasis. Hepatology 2015;62:635-43.
29. Honda A, Ikegami T, Nakamuta M, et al. Anticholestatic effects of bezafibrate in patients with primary biliary cirrhosis treated with ursodeoxycholic acid. Hepatology 2013;57:1931-41.
30. Dohmen K, Mizuta T, Nakamuta M, Shimohashi N, Ishibashi H, Yamamoto K. Fenofibrate for patients with asymptomatic primary biliary cirrhosis. World J Gastroenterol 2004;10:894-8.
31. Nagasawa T, Inada Y, Nakano S, et al. Effects of bezafibrate, PPAR pan-agonist, and GW501516, PPARdelta agonist, on development of steatohepatitis in mice fed a methionine- and choline-deficient diet. Eur J Pharmacol 2006;536:182-91.
32. Jones D, Boudes PF, Swain MG, et al. Seladelpar (MBX-8025), a selective PPAR-delta agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. Lancet Gastroenterol Hepatol 2017;2:716-26.

Table 1. Demographic and clinical characteristics of the patients at baseline.

Characteristic	Placebo group (n=50)	Bezafibrate group (n=50)
Age – yr.	53 ± 11	53 ± 9
Age at diagnosis – yr.	49 ± 11	46 ± 7
Female sex – no. (%)	46 (92)	49 (98)
Caucasian origin – no. (%)	48 (96)	47 (94)
UDCA daily dose – mg/kg	15 (14 – 16)	15 (13 – 16)
Fatigue – no. (%)	29 (58)	29 (58)
Significant pruritus – no. (%)	24 (48)	16 (32)
Total bilirubin – µmole/L	12.6 ± 6.8	14.0 ± 7.6
ALP – U/liter	242 (186 – 344)	244 (211 – 308)
AST – U/liter	45 (33 – 64)	44 (33 – 57)
ALT – U/liter	53 (34 – 72)	55 (37 – 73)
GGT – U/liter	164 (100 – 273)	162 (112 – 240)
Albumin – g/L	41.9 ± 2.7	41.3 ± 3.6
Prothrombin index – %	104 ± 15	105 ± 12
Platelet count – G/L	266 ± 74	252 ± 71
Total cholesterol – mmole/L	6.7 ± 1.3	6.4 ± 1.4
Liver stiffness measurement – kPa	11.4 ± 7.9	12.8 ± 12.6
Advanced disease – no. (%)	26 (52)	28 (56)
Disease stage:		
Stage 1 – no. (%)	18 (37)	13 (28)
Stage 2 – no. (%)	14 (29)	14 (30)
Stage 3 – no. (%)	6 (12)	11 (23)
Stage 4 – no. (%)	11 (22)	9 (19)

Data are preceded by the number (percentage) of missing values. Quantitative data are expressed as mean ± SD or median (25th percentile – 75th percentile) when appropriate. Categorical data are expressed as number (%). Fatigue was defined by continuous or intermittent fatigue as reported by patients. Significant pruritus was defined by itch intensity VAS of 3.0 or more. Liver stiffness measurement was determined by vibration-controlled transient elastography (Fibroscan, Echosens, Paris, France). On the basis of research by Corpechot et al.,[16] liver stiffness in patients with PBC was assessed as follows: fibrosis stage F0 was associated with a stiffness of 7.0 kPa or less, stage F1 with a stiffness of 7.1 to 8.6 kPa, stage F2 with a stiffness of 8.7 to 10.8 kPa, stage F3 with a stiffness of 10.9 to 16.0 kPa, and stage F4 with a stiffness of 16.1 kPa or more. Advanced disease was defined by liver stiffness measurement > 9.6 kPa or Ludwig's histological stage 3 or 4. Disease stage was defined by Ludwig's histological stage when available or by Fibroscan using the thresholds reported above. Values were missing for the following variables: age at diagnosis (1 patient placebo, 1 bezafibrate); fatigue (1, 0); ALP (1, 0); albumin (3, 2); prothrombin index (0, 2); platelet count (0, 2); total cholesterol (2, 2); liver stiffness measurement (5, 6); disease stage (1, 3). There were no significant (a p-value < 0.05 level) differences between groups for any of the above baseline characteristics.

Table 2. Relative changes from baseline to 24 months in biochemical parameters.

Parameter	Placebo group		Bezafibrate group		Mean difference [95%CI]
	Missing n (%)	% change	Missing n (%)	% change	
Total bilirubin	7 (14)	18 (0 ; 40)	4 (8)	-14 (-33 ; 6)	-26 [-46 ; -6]
ALP	8 (16)	0 (-14 ; 20)	4 (8)	-60 (-66 ; -46)	-59 [-70 ; -49]
GGT	7 (14)	7 (-14 ; 51)	4 (8)	-38 (-59 ; -24)	-71 [-114 ; -28]
AST	7 (14)	8 (-17 ; 26)	4 (8)	-8 (-30 ; 3)	-17 [-34 ; 1]
ALT	7 (14)	0 (-24 ; 31)	4 (8)	-36 (-53 ; -14)	-35 [-55 ; -16]
Albumin	12 (24)	-3 (-7 ; 3)	7 (14)	0 (-4 ; 7)	4 [0 ; 8]
Platelet count	8 (16)	-2 (-16 ; 4)	4 (8)	2 (-8 ; 11)	8 [1 ; 15]
PT index	7 (14)	0 (-8 ; 2)	6 (12)	-2 (-5 ; 0)	1 [-3 ; 4]
Total-C	11 (22)	0 (-9 ; 7)	8 (16)	-16 (-24 ; -9)	-16 [-22 ; -11]
LDL-C	13 (26)	2 (-13 ; 12)	19 (38)	-23 (-31 ; -14)	-26 [-34 ; -18]
HDL-C	13 (26)	-4 (-10 ; 5)	16 (32)	-2 (-13 ; 10)	-4 [-14 ; 5]

Relative changes are expressed as median percentage (25^{th} percentile – 75^{th} percentile). The mean differences between the bezafibrate and placebo groups are shown with corresponding 95% confidence intervals (CI). PT denotes Prothrombin. PT index expresses the % of normal plasma yielding the same PT time. Total-C denotes Total Cholesterol. LDL-C denotes Low-Density Lipoprotein-Cholesterol. HDL-C denotes High-Density Lipoprotein-Cholesterol. Bezafibrate and placebo were administered with standard-of-care UDCA.

Table 3. Incidence of adverse events of 10% or more and of all serious adverse events.

Event	Placebo group	Bezafibrate group
Any adverse events	45 (90)	43 (86)
Arthralgia	11 (22)	7 (14)
Myalgia	5 (10)	10 (20)
Nasopharyngitis	10 (20)	9 (18)
Bronchitis	9 (18)	4 (8)
Depressive mood	8 (16)	7 (14)
Abdominal pain	6 (12)	7 (14)
Pruritus	7 (14)	4 (8)
Diarrhea	6 (12)	1 (2)
Flu-like syndrome	5 (10)	5 (10)
Serious adverse events	12 (24)	14 (28)
Transaminase flare > 5 x ULN	1 (2)	3 (6)
Creatinine kinase flare > 5 x ULN	0 (0)	1 (2)
Creatinine increase with worsening of CKD	0 (0)	1 (2)

Shown are the numbers (percentage) of patients with at least one reported event. ULN denotes the upper limit of normal range. CKD denotes chronic kidney disease stage. All serious adverse events are listed in supplement appendix. Bezafibrate and placebo were administered with standard-of-care UDCA.

FIGURE LEGENDS

Figure 1. Percentage of patients with a complete biochemical response according to time and trial group.

The percentage of patients with a complete biochemical response, as defined by normal serum levels of total bilirubin, ALP, AST, ALT, albumin and prothrombin index, was estimated from available data at each time point of the trial period in both the placebo (blue columns) and bezafibrate (orange columns) groups. The number of patients with available data is shown at each time point for each group. Bezafibrate and placebo were administered with standard-of-care UDCA.

Figure 2. Alkaline phosphatase, total bilirubin, alanine aminotransferase, and liver stiffness measurement according to time and trial group.

The median values of phosphatase alkaline (**Panel A**), total bilirubin (**Panel B**), alanine aminotransferase (**Panel C**), and liver stiffness measurement (**Panel D**) are shown at each time point of the trial period in both the placebo (blue circles) and bezafibrate (orange squares) groups. Lower and upper error bars indicate the 25^{th} and 75^{th} percentiles, respectively. ULN denotes the upper limit of the normal range. The number of patients with available data is shown at each time point for each group. Bezafibrate and placebo were administered with standard-of-care UDCA.