ORIGINAL ARTICLE

A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis

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ABSTRACT

BACKGROUND

Patients with primary biliary cholangitis who have an inadequate response to therapy with ursodeoxycholic acid are at high risk for disease progression. Fibrates, which are agonists of peroxisome proliferator–activated receptors, in combination with ursodeoxycholic acid, have shown potential benefit in patients with this condition.

METHODS

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

RESULTS

The primary outcome occurred in 31% of the patients assigned to bezafibrate and in 0% assigned to placebo (difference, 31 percentage points; 95% confidence interval, 10 to 50; P<0.001). Normal levels of alkaline phosphatase were observed in 67% of the patients in the bezafibrate group and in 2% in the placebo group. Results regarding changes in pruritus, fatigue, and noninvasive measures of liver fibrosis, including liver stiffness and Enhanced Liver Fibrosis score, were consistent with the results of the primary outcome. Two patients in each group had complications from end-stage liver disease. The creatinine level increased 5% from baseline in the bezafibrate group and decreased 3% in the placebo group. Myalgia occurred in 20% of the patients in the bezafibrate group and in 10% in the placebo group.

CONCLUSIONS

Among patients with primary biliary cholangitis who had had an inadequate response to ursodeoxycholic acid alone, treatment with bezafibrate in addition to ursodeoxycholic acid resulted in a rate of complete biochemical response that was significantly higher than the rate with placebo and ursodeoxycholic acid therapy. (Funded by Programme Hospitalier de Recherche Clinique and Arrow Génériques; BEZURSO ClinicalTrials.gov number, NCT01654731.)

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Primary biliary cholangitis is a progressive liver disease of unknown cause that affects primarily women older than 30 years of age. 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 toward cirrhosis and liver failure.[1] Ursodeoxycholic acid, a hydrophilic bile acid with choleretic and liver-protective properties, is currently the standard first-line therapy for primary biliary cholangitis.[2,3] Treatment with ursodeoxycholic acid decreases the levels of the biochemical markers of cholestasis and extends the time to liver transplantation.[4,5] However, long-term survival remains limited in patients who have an incomplete biochemical response.[6-8] Additional therapeutic options are therefore needed in patients who have an inadequate response to ursodeoxycholic acid.

The combination of obeticholic acid, a selective agonist of the farnesoid X receptor, with ursodeoxycholic acid has recently been shown to decrease the levels of the biochemical markers of cholestasis in patients with primary biliary cholangitis who have had an inadequate response to ursodeoxycholic acid.[9,10] In these studies, however, obeticholic acid was associated with higher rates of severe pruritus than placebo.[10] Alternatively, treatment with ursodeoxycholic acid and fibrates, which are agonists of peroxisome proliferator–activated receptors (PPARs), has the potential both to improve biochemical measures and to reduce the symptoms of primary biliary cholangitis.[11-14] The aim of the BEZURSO trial (Bezafibrate in Combination with Ursodeoxycholic Acid in Primary Biliary Cholangitis [formerly known as primary biliary cirrhosis]) was to assess the efficacy, safety, and adverse-event profile of bezafibrate, a pan-PPAR agonist, in patients with primary biliary cholangitis who, despite treatment with ursodeoxycholic acid, have continued to have clinically significant abnormalities in biochemical liver measures.

Methods

Participants

Patients 18 years of age or older who had received a diagnosis of primary biliary cholangitis according to established criteria[2] were recruited at 21 centers throughout France. At the time of enrollment, all the patients were being treated with ursodeoxycholic acid at a dose of 13 to 15 mg per kilogram of body weight per day. Patients were eligible if they had had an inadequate biochemical response to ursodeoxycholic acid, defined according to the Paris 2 criteria[15] (i.e., a serum level of alkaline phosphatase or aspartate aminotransferase >1.5 times the upper limit of the normal range or an abnormal total bilirubin level) after 6 months or more of treatment; however, patients with a total bilirubin level above 50 μmol per liter (3 mg per deciliter) were excluded. Patients with typical features of autoimmune hepatitis were also excluded from the trial. All patients provided written informed consent.

Trial Oversight and Design

The protocol, available with the full text of 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 the fidelity of the trial to the protocol and for the completeness and accuracy of the data and analyses.

The trial was designed as a two-group, randomized, double-blind, placebo-controlled trial. Centralized balanced-block randomization (blocks of 4) was computer-generated without stratification according to center. Patients were randomly assigned, in a 1:1 ratio, to receive once-daily oral placebo or bezafibrate at a dose of 400 mg; patients in both groups received ursodeoxycholic acid therapy. Follow-up assessments were performed every 3 months for 24 months. Ultrasonography of the liver and liver-stiffness measurement were performed at baseline, at 12 months, and at 24 months. Liver stiffness was assessed with the use of vibration-controlled transient elastography (FibroScan, Echosens); liver stiffness correlates with histologic fibrosis and is a prognostic factor in primary biliary cholangitis.[16] A measurement of liver stiffness less than 6 kPa is considered to be normal.

Outcomes

The primary outcome was the percentage of patients with a complete biochemical response, which was defined as normal serum levels of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin,

and albumin, as well as a normal prothrombin index (the patient's prothrombin time expressed as a percentage of the normal value) at 24 months.

Secondary outcomes included the percentage of patients with a response, as defined above, at various time points during the trial; the percentage of patients with a normal alkaline phosphatase level at 24 months; changes in serum levels of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin, albumin, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, and changes in the prothrombin index and platelet count; the percentage of patients with an adequate biochemical response at 24 months as defined by the Barcelona,[6] Paris 1,[7] Paris 2, Rotterdam,[17] and Toronto[8] criteria, as well as by the GLOBE score[18] (see the Supplementary Appendix, available at NEJM.org); changes in pruritus intensity on a visual-analogue scale (scores range from 0 to 10, with 0 indicating no itch and 10 indicating the worst itch imaginable)[19]; changes with respect to fatigue (absent, intermittent, or continuous); changes in quality of life (as assessed with the use of the Nottingham Health Profile, which measures well-being in six areas of life, with scores in each part ranging from 0 to 100, and higher scores indicating worse quality of life)[20]; and changes in liver stiffness. Secondary outcomes also included changes in the Enhanced Liver Fibrosis score (a validated measure of liver fibrosis that is based on the serum levels of hyaluronic acid, procollagen type III N-terminal peptide, and tissue inhibitor of metalloproteinase 1),[21] development of portal hypertension (defined as meeting at least one of the following criteria: ascites, esophageal or gastric varices, ultrasonographic signs of portal hypertension, platelet count <150,000 per cubic millimeter, or a liver-stiffness measurement of >20 kPa), and survival without liver transplantation or liver complications (which were defined as ascites, variceal bleeding, hepatic encephalopathy, or a doubling of total bilirubin level to >50 μmol per liter).

Post hoc exploratory outcomes included changes in serum levels of total and endogenous bile acids, ursodeoxycholic acid, 7α-hydroxy-4-cholesten-3-one (C4, a bile acid precursor), IgM, IgG, high-sensitivity C-reactive protein, tumor necrosis factor α (TNF-α), and interleukin-12; projected survival estimated according to the GLOBE score (which is used to predict the risk of liver transplantation and death from any cause) and the UK-PBC risk score (which is used to predict the risk of liver transplantation and death from liver-related causes)[22]; and predictive factors of inadequate response (see the Supplementary Appendix).

SAFETY REPORTS

Safety was assessed by investigators at each patient visit on the basis of clinical examination, blood tests, and patient-reported symptoms. All serious adverse events were reported to Assistance Publique–Hôpitaux de Paris within the first 24 hours after onset and were closely monitored. Adverse events were summarized according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 20.0, system organ class; the MedDRA preferred term; severity; and causal relationship as assessed by the investigators.

STATISTICAL ANALYSIS

On the basis of the results of a 2-year, open-label pilot study involving 38 patients followed at Saint-Antoine Hospital in Paris who received combination therapy with ursodeoxycholic acid (13 to 15 mg per kilogram of body weight per day) and fibrates (400 mg per day of bezafibrate or 200 mg per day of fenofibrate) (unpublished data), we expected a rate of complete biochemical response of 40% in the bezafibrate group and 10% in the placebo group. We chose bezafibrate, a pan-PPAR agonist, because its effects in primary biliary cholangitis are better documented. Assuming a 17% loss to follow-up, we calculated that 100 patients would need to be enrolled for the study to have 90% power, at a two-sided significance level of 5%.

Analyses were performed at the end of the trial in the intention-to-treat population, which included all patients who underwent randomization; patients were unaware of their group assignments. Multiple imputation was performed to replace missing data on biochemical measures that were used to assess the primary outcome; however, the primary outcome as reported here was analyzed without multiple imputation. We used the chi-square test to compare groups and to estimate the difference in response rates

(with the 95% confidence interval). Sensitivity analyses were performed with the use of no imputation, the last-observation-carried-forward method, and the worst-case-scenario method. Quantitative data are expressed as means with standard deviations or medians and interquartile ranges when appropriate and as percent means (with 95% confidence intervals) for the differences between the bezafibrate and placebo groups. Piecewise linear mixed-effects models were used to explore some critical measures over time after log transformation, with consideration of random effects for time and patient. Breakpoints in the piecewise linear function (segmented regression) were not prespecified. Logistic-regression analysis was used to study the predictive factors of inadequate biochemical response. All tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. No adjustment for multiple comparisons was planned, and 95% confidence intervals, without P values, are reported for the secondary outcomes and exploratory analyses. A total of 44 tests were conducted for secondary outcomes. Given the large number of tests conducted, the 95% confidence intervals may not be reproducible. Analyses were performed with SAS software, version 9.3 (SAS Institute). Additional details are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

A total of 100 patients (50 in each group) were enrolled during the period from September 2012 through December 2014 (Fig. S1 in the Supplementary Appendix). The characteristics of the patients did not differ between the groups at baseline (Table 1). Overall, 95% of the patients were white women, and the mean (±SD) age was 53±10 years. Clinically significant pruritus (a score of ≥3 on the visual-analogue scale) was reported in 40% of the patients, and 58% reported intermittent or continuous fatigue. A total of 54% of the patients were at an advanced stage of disease, according to histologic findings (Ludwig stage 3 or 4, with stages ranging from 1 to 4; stage 3 indicates bridging fibrosis, and stage 4 cirrhosis[23]) or liver-stiffness measurement (>9.6 kPa).

TRIAL AND DRUG DISCONTINUATION

Overall, 92 patients (92%) completed the trial. Two patients (4%) in the bezafibrate group and 6 (12%) in the placebo group withdrew from the trial. Temporary or permanent discontinuation of the active drug or placebo occurred in 13 patients in the placebo group and in 7 patients in the bezafibrate group; discontinuation of ursodeoxycholic acid occurred in 4 patients in the placebo group and in 2 patients in the bezafibrate group.

PRIMARY OUTCOME

The primary outcome was reached in 31% of the patients in the bezafibrate group and in 0% in the placebo group (difference, 31 percentage points; 95% confidence interval [CI], 10 to 50; P<0.001). In an analysis that used multiple imputation for missing data, the primary outcome was reached in 30% of the patients in the bezafibrate group and in 1% in the placebo group (difference, 29 percentage points; 95% CI, 16 to 43; P<0.001). The conclusion remained unchanged in sensitivity analyses (Table S1 in the Supplementary Appendix). The rate of complete biochemical response in the bezafibrate group increased progressively until month 15, when it reached a plateau of 30 to 35% (Fig. 1).

SECONDARY OUTCOMES

Biochemical Measures

The specific changes in the levels of total bilirubin, alkaline phosphatase, γ-glutamyltransferase, alanine aminotransferase, albumin, total cholesterol, and low-density lipoprotein cholesterol, and in the platelet count were consistent with results for the primary outcome (Fig. 2 and Table 2). At 24 months, 31 patients (67%) in the bezafibrate group and 1 patient (2%) in the placebo group had normal alkaline phosphatase levels (difference, 65 percentage points; 95% CI, 47 to 79). A 60% median reduction from baseline in alkaline phosphatase level was observed in the bezafibrate group at 3 months. A similar rapid reduction in γ-glutamyltransferase level was observed among patients in the bezafibrate group. These results were confirmed in longitudinal analyses. The level of total bilirubin decreased 14% from baseline in the bezafibrate group and increased 18% in the placebo group. Among patients with

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Bezafibrate Group (N=50)	Placebo Group (N=50)
Age — yr	53±9	53±11
Age at diagnosis — yr†	46±7	49±11
Female sex — no. (%)	49 (98)	46 (92)
White race — no. (%)‡	47 (94)	48 (96)
Median ursodeoxycholic acid dose (IQR) — mg/kg/day	15 (13–16)	15 (14–16)
Fatigue — no. (%)§	29 (58)	29 (58)
Clinically significant pruritus — no. (%)¶	16 (32)	24 (48)
Total bilirubin — μmol/liter	14.0±7.6	12.6±6.8
Median alkaline phosphatase (IQR) — U/liter‖	244 (211–308)	242 (186–344)
Median aspartate aminotransferase (IQR) — U/liter	44 (33–57)	45 (33–64)
Median alanine aminotransferase (IQR) — U/liter	55 (37–73)	53 (34–72)
Median γ-glutamyltransferase (IQR) — U/liter	162 (112–240)	164 (100–273)
Albumin — g/liter**	41.3±3.6	41.9±2.7
Prothrombin index — %††	105±12	104±15
Platelet count — per mm^3‡‡	252,000±70,540	266,340±73,480
Total cholesterol — mmol/liter§§	6.4±1.4	6.7±1.3
Liver stiffness — kPa¶¶	12.8±12.6	11.4±7.9
Advanced disease — no. (%)‖‖	28 (56)	26 (52)
Disease stage — no./total no. (%)***		
Stage 1	13/47 (28)	18/49 (37)
Stage 2	14/47 (30)	14/49 (29)
Stage 3	11/47 (23)	6/49 (12)
Stage 4	9/47 (19)	11/49 (22)

* Plus–minus values are means ±SD. There were no significant ($P<0.05$) differences between groups in the characteristics at baseline. To convert the values for bilirubin to milligrams per deciliter, divide by 17.1. To convert the values for cholesterol to milligrams per deciliter, divide by 0.0259.

† Data were missing for one patient in the bezafibrate group and one patient in the placebo group.

‡ Race was reported by investigators according to a standardized nomenclature.

§ Fatigue was defined as the presence of continuous or intermittent fatigue, as reported by the patient. Data were missing for one patient in the placebo group.

¶ Clinically significant pruritus was defined as a score of 3.0 or more on a visual-analogue scale (scores range from 0 to 10, with 0 indicating no itch and 10 indicating the worst itch imaginable).

‖ Data were missing for one patient in the placebo group.

** Data were missing for two patients in the bezafibrate group and three patients in the placebo group.

†† Data were missing for two patients in the bezafibrate group. The prothrombin index is the patient's prothrombin time expressed as a percentage of the normal value.

‡‡ Data were missing for two patients in the bezafibrate group.

§§ Data were missing for two patients in the bezafibrate group and two patients in the placebo group.

¶¶ Liver stiffness was determined with the use of vibration-controlled transient elastography (FibroScan, Echosens). On the basis of research by Corpechot et al.,[16] liver stiffness in patients with primary biliary cholangitis 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. Data were missing for six patients in the bezafibrate group and five patients in the placebo group.

‖‖ Advanced disease was defined as a liver stiffness greater than 9.6 kPa or Ludwig histologic stage 3 or 4.[23]

*** Disease stage was defined according to Ludwig histologic stage when available or with the use of FibroScan, according to the thresholds given above. Data were missing for three patients in the bezafibrate group and one patient in the placebo group.

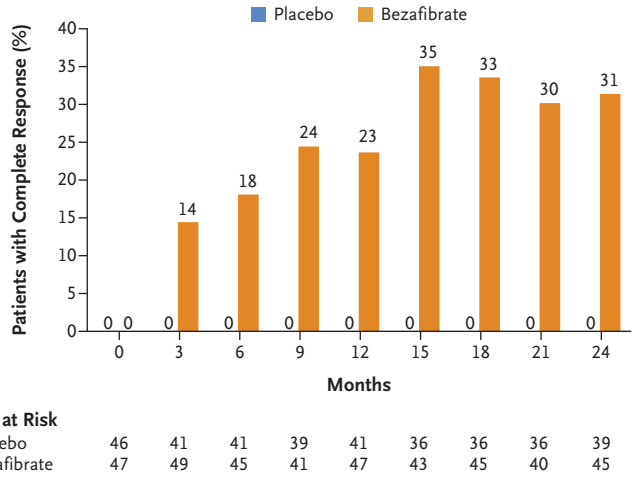

Figure 1. Percentage of Patients with a Complete Biochemical Response According to Time and Trial Group.

Shown are the percentages of patients with available data who had a complete biochemical response, defined as normal serum levels of total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and albumin, and a normal prothrombin index (the patient's prothrombin time expressed as a percentage of the normal value). Bezafibrate and placebo were administered with standard-of-care ursodeoxycholic acid. No patients in the placebo group had a complete biochemical response.

cirrhosis, no significant increase in total bilirubin was observed in the bezafibrate group as compared with the placebo group. Alanine aminotransferase levels in the bezafibrate group decreased progressively. Three months after the end of trial (i.e., at the end of the washout period), levels of total bilirubin, alkaline phosphatase, γ-glutamyltransferase, and aminotransferases worsened in the bezafibrate group but not in the placebo group. Additional information is provided in the Supplementary Appendix.

Prespecified Biochemical Responses

The rates of adequate biochemical response as defined according to established criteria (Barcelona, Paris 1 and Paris 2, Rotterdam, Toronto, and GLOBE score) were significantly higher in the bezafibrate group than in the placebo group, except in the case of the Rotterdam criteria, since response according to the Rotterdam criteria can be evaluated only in late-stage disease. Data are provided in Table S7 in the Supplementary Appendix.

Patient-Reported Outcomes

Changes in pruritus intensity were consistent with results of the primary outcome, as were changes with respect to fatigue. No significant differences between the groups were found in the quality-of-life scores (Fig. S5 and Tables S8 and S9 in the Supplementary Appendix).

Noninvasive Measures of Fibrosis

Liver stiffness at 24 months decreased 15% from baseline in the bezafibrate group and increased 22% in the placebo group (difference, −36 percentage points; 95% CI, −64 to −8) (Fig. 2D). Changes in Enhanced Liver Fibrosis scores were consistent with this result (difference, −4 percentage points; 95% CI, −8 to −1) (Table S10 in the Supplementary Appendix).

Liver Histologic Results

Histologic data were available for 59 patients at baseline (30 patients in the bezafibrate group and 29 patients in the placebo group) and for 51 patients at 24 months (26 patients in the bezafibrate group and 25 patients in the placebo group), but only 28 patients had available data at both time points. In this subgroup, changes in histologic stage, fibrosis stage, and activity grade did not differ significantly between the groups.

Clinical Outcomes

Features of portal hypertension developed in 19 patients, with no significant difference between the groups (20% in the bezafibrate group and 18% in the placebo group). Four patients, 2 in each group, had liver complications: in the bezafibrate group, 1 patient underwent a liver transplantation and 1 was placed on a waiting list for transplantation; in the placebo group, ascites developed in 1 patient, and the total bilirubin level doubled to more than 50 μmol per liter in 1 patient. No patients died.

POST HOC ANALYSES

At baseline, serum levels of total and endogenous bile acids, ursodeoxycholic acid, and C4 (a marker of bile acid synthesis) did not differ significantly between the groups. Changes in C4 levels were consistent with the results of the primary outcome. Changes in total and endogenous bile acid levels did not differ significantly between groups, but the proportion of endogenous bile

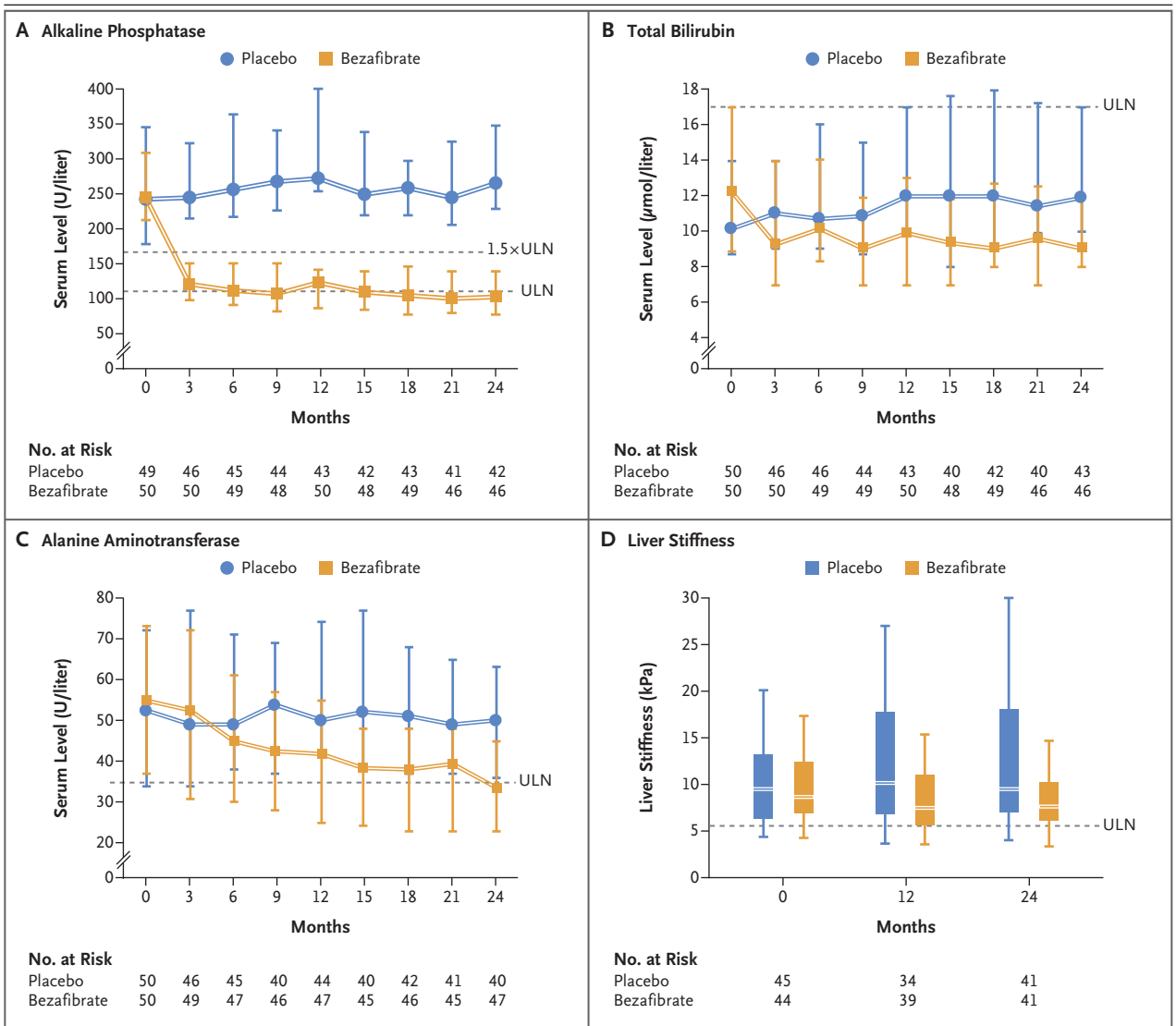

Figure 2. Alkaline Phosphatase, Total Bilirubin, and Alanine Aminotransferase Levels, and Liver Stiffness According to Time and Trial Group.
Shown are the median values of alkaline phosphatase, total bilirubin, alanine aminotransferase, and liver stiffness at each time point of the trial period. I bars in Panels A, B, and C indicate interquartile ranges. In Panel D, 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. Bezafibrate and placebo were administered with standard-of-care ursodeoxycholic acid. ULN denotes upper limit of the normal range.

acid within the bile acid pool decreased significantly with bezafibrate.

In a post hoc analysis of markers of immunity and inflammation, conducted in a subgroup of patients with available data, changes in serum IgM and IgG levels did not differ significantly between the groups. No significant between-group differences were found with respect to changes in the serum levels of high-sensitivity C-reactive protein, TNF-α, or interleukin-12.

The factors that were independently associated with an inadequate biochemical response to bezafibrate were features of portal hypertension and alkaline phosphatase level. The threshold of alkaline phosphatase that best predicted an inadequate biochemical response was a level more

Table 2. Relative Changes from Baseline to 24 Months in Biochemical Measures.*

Measure	Bezafibrate Group (N=50)		Placebo Group (N=50)		Difference (95% CI)
	Missing Values	Median Change from Baseline	Missing Values	Median Change from Baseline	
	no. (%)	*% (IQR)*	*no. (%)*	*% (IQR)*	*percentage points*
Total bilirubin	4 (8)	–14 (–33 to 6)	7 (14)	18 (0 to 40)	–32 (–47 to –18)
Alkaline phosphatase	4 (8)	–60 (–66 to –46)	8 (16)	0 (–14 to 20)	–59 (–71 to –47)
γ-Glutamyltransferase	4 (8)	–38 (–59 to –24)	7 (14)	7 (–14 to 51)	–45 (–65 to –25)
Aspartate aminotransferase	4 (8)	–8 (–30 to 3)	7 (14)	8 (–17 to 26)	–14 (–29 to 0)
Alanine aminotransferase	4 (8)	–36 (–53 to –14)	7 (14)	0 (–24 to 31)	–35 (–56 to –14)
Albumin	7 (14)	0 (–4 to 7)	12 (24)	–3 (–7 to 3)	3 (–1 to 8)
Platelet count	4 (8)	2 (–8 to 11)	8 (16)	–2 (–16 to 4)	3 (–5 to 12)
Prothrombin index	6 (12)	–2 (–5 to 0)	7 (14)	0 (–8 to 2)	1 (0 to 2)
Total cholesterol	8 (16)	–16 (–24 to –9)	11 (22)	0 (–9 to 7)	–16 (–23 to –9)
Low-density lipoprotein cholesterol	19 (38)	–23 (–31 to –14)	13 (26)	2 (–13 to 12)	–26 (–36 to –16)
High-density lipoprotein cholesterol	16 (32)	–2 (–13 to 10)	13 (26)	–4 (–10 to 5)	1 (–9 to 11)

* Bezafibrate and placebo were administered with standard-of-care ursodeoxycholic acid. IQR denotes interquartile range.

than 2.53 times the upper limit of the normal range.

In a post hoc analysis of prognostic scores, the application of the GLOBE and UK-PBC risk scores at baseline, at 12 months, and at 24 months showed significantly lower predicted rates of liver transplantation and death at 5, 10, and 15 years in the bezafibrate group than in the placebo group. (Additional information on post hoc analyses is provided in Figs. S6 through S8 and Tables S11 through S13 in the Supplementary Appendix.)

SAFETY AND ADVERSE EVENTS

Overall, 424 adverse events were reported in 88 patients (49% in the bezafibrate group and 51% in the placebo group). A total of 39 serious adverse events (9%) were reported in 26 patients (14 patients in the bezafibrate group and 12 patients in the placebo group) (Table 3, and Table S14 in the Supplementary Appendix).

Creatinine levels increased 5% in the bezafibrate group and decreased 3% in the placebo group from baseline (difference, 7 percentage points; 95% CI, –1 to 15). This difference was noticeable at month 3 and remained mostly stable during the rest of the trial (Fig. S9 in the Supplementary Appendix). One patient in the bezafibrate group (who had a history of diabetes and hypertension) had a decrease in the estimated glomerular filtration rate (eGFR) to less than 60 ml per minute (indicating stage 3 chronic kidney disease). A total of 10 patients (4 in the bezafibrate group and 6 in the placebo group) had stage 2 chronic kidney disease (eGFR ≥60 and <90 ml per minute) at 24 months.

Four patients had an increase in aminotransferase levels that was more than 5 times the upper limit of the normal range (three patients in the bezafibrate group and one in the placebo group). This led to a permanent discontinuation of the active drug or placebo in three patients (two in the bezafibrate group and one in the placebo group). All cases of elevated aminotransferase levels in the bezafibrate group resolved within 3 months, either spontaneously (in one patient) or after glucocorticoid administration (two patients, in whom liver histologic features at baseline were suggestive of associated autoimmune hepatitis).

Myalgia was reported in 20% of the patients in the bezafibrate group and in 10% in the placebo group. Moderate, asymptomatic rhabdomyolysis developed at 3 months in one patient in

the bezafibrate group, who concomitantly received statin therapy; the rhabdomyolysis resolved after discontinuation of bezafibrate.

DISCUSSION

In this randomized trial, we found that among patients with primary biliary cholangitis who had had an inadequate response to ursodeoxycholic acid, approximately one third of the patients in the bezafibrate group, as compared with no patients 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 with respect to pruritus, fatigue, and noninvasive measures of liver fibrosis were consistent with this result. Patients were selected on the basis of Paris 2 criteria,[15] which have been recognized as relevant predictors of clinical outcomes in several independent populations of patients with primary biliary cholangitis.[24,25]

In the current trial, bezafibrate was associated with a rapid and sustained decrease in alkaline phosphatase level and a parallel decrease in total bilirubin, the two most important prognostic indicators in primary biliary cholangitis.[25] Despite initial concerns,[26] we did not observe an increase in bilirubin level in patients with cirrhotic liver disease who were treated with bezafibrate.

These changes in the bezafibrate group were accompanied by a decrease in liver stiffness and Enhanced Liver Fibrosis score, two markers of liver fibrosis that are prognostic factors in primary biliary cholangitis.[16,21] However, our histologic data were too limited to determine whether these changes were related to an effective reduction in liver fibrosis and hepatic inflammation.

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

Portal hypertension and a high alkaline phosphatase level at baseline were identified 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 the serum creatinine level. This is a known effect of PPAR-α agonists.[27-29] Its mechanism may involve renal hemodynamic changes or an increased creatinine release by muscle.[30] Stage 3 chronic kidney disease developed during treatment with bezafibrate in one patient in this trial, who had diabetes and hypertension. As a precaution, bezafibrate use should be evaluated taking kidney function into consideration, especially in patients with diabetes, hypertension, or any known renal disease.

Various mechanisms may lead to the therapeutic effects described above.[31,32] Our results suggest that bezafibrate acts in part through specific anticholestatic properties such as the inhibition of bile acid synthesis and consequent reduction in endogenous bile acid overload.[33] Previous findings have suggested a suppressive effect of fibrates on immune response.[13,34] We found no significant changes in IgM, high-sensitivity C-reactive protein, TNF-α, or interleukin-12 serum levels, but suppression of intrahepatic proinflammatory cytokines is highly plausible.[35] Finally, the PPAR-δ agonistic effects of beza-

Table 3. Incidence of Adverse Events Occurring in 10% or More of Patients and All Serious Adverse Events.*

Event	Bezafibrate Group (N=50)	Placebo Group (N=50)
	no. of patients with event (%)	
Any adverse event	43 (86)	45 (90)
Arthralgia	7 (14)	11 (22)
Myalgia	10 (20)	5 (10)
Nasopharyngitis	9 (18)	10 (20)
Bronchitis	4 (8)	9 (18)
Depressive mood	7 (14)	8 (16)
Abdominal pain	7 (14)	6 (12)
Pruritus	4 (8)	7 (14)
Diarrhea	1 (2)	6 (12)
Flulike syndrome	5 (10)	5 (10)
Any serious adverse event	14 (28)	12 (24)
Aminotransferase level >5x ULN	3 (6)	1 (2)
Creatine kinase level >5x ULN	1 (2)	0
Creatinine increase with worsening stage of chronic kidney disease	1 (2)	0

* Shown are the numbers of patients with at least one reported event. A list of all serious adverse events is provided in the Supplementary Appendix. Bezafibrate and placebo were administered with standard-of-care ursodeoxycholic acid. ULN denotes upper limit of the normal range.

fibrate may be considered specifically because seladelpar, a selective PPAR-δ agonist, has recently been shown to improve measures of cholestasis in patients with primary biliary cholangitis.[36]

In conclusion, in patients with primary biliary cholangitis who had had an inadequate response to ursodeoxycholic acid, add-on therapy with bezafibrate for 24 months resulted in a higher rate of complete biochemical response than ursodeoxycholic acid therapy plus placebo. Parallel changes in patient-reported outcomes and noninvasive measures of liver fibrosis were consistent with this effect. Bezafibrate was associated with an increase in creatinine level. Longer and larger studies are needed to assess the effects of bezafibrate on clinical outcomes.

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APPENDIX

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