The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis

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N Engl J Med 2018;378:2171-81.
DOI: 10.1056/NEJMoa1714519

RobotReviewer report

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Bezafibrato (Bezalip) per il trattamento della colangite biliare primaria.pdf	RCT	100	+	+	+	?

Characteristics of studies

Bezafibrato (Bezalip) per il trattamento della colangite biliare primaria.pdf

Population

1. 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.
2. 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 Œºmol per liter (3

	mg per deciliter) were excluded . 3. 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 adverseevent 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.
Intervention	1. 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. 2. 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. 3. 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.
Outcomes	1. 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, Œ≥-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. 2. 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. 3. 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, Bezafibr ate in Primary Biliary Cholangitis 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.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. Centralized balanced-block randomization (blocks of 4) was computer-generated without stratification according to center. 2. 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. 3. 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.
Allocation concealment	low	1. Centralized balanced-block randomization (blocks of 4) was computer-generated without stratification according to center. 2. 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. 3. The trial was designed as a two-group, randomized , double-blind, placebo-controlled trial.
Blinding of participants and personnel	low	1. The trial was designed as a two-group, randomized , double-blind, placebo-controlled trial. 2. 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. 3. 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.
Blinding of outcome assessment	high/unclear	1. 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. 2. We thank the patients and all the physicians who referred them to the participating centers; the staff at the Clinical Research Center of the East of Paris, Saint-Antoine University Hospital , for their logistic support; and Jacob Staal-Anderson for his contribution to the revision of an earlier version of the manu- script. 3. 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.