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Title

Effectiveness and tolerability of bezafibrate in primary biliary cholangitis – a nationwide real-world study

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Author contributions

Study concept and design: MH, AM, RdV, EW, UB, JD, FC, BH, BV, MK, SM, RV, HF, JV, TG, CP. Data acquisition: all authors. Data Analysis: MH, AM, EW. Data Interpretation: MH, AM, RdV, UB. Drafting manuscript: MH, AM, RdV. Critical revision for important intellectual content and final approval: all authors.

Data availability statement

Since this is a multicenter study involving 71 centers where data is shared, the generated dataset is not openly available to researchers outside the study team. Please contact the corresponding author to inquire about the possibilities of collaboration.

List of abbreviations

AST, aspartate aminotransferase; ALP, serum alkaline phosphatase; ALT, alanine aminotransferase ; AMA, anti-mitochondrial antibodies; CI, confidence interval; DPCS, Dutch PBC Cohort Study; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; IQR, inter quartile range; ITT, intention to treat; LSM, Liver stiffness measurement ; LLN, Lower limit of normal; OR, Odds ratio; PBC, Primary Biliary Cholangitis; PPARs, peroxisome proliferator-activated receptors; TB, Total Bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

ABSTRACT

Introduction: Off-label bezafibrate is increasingly used for primary biliary cholangitis (PBC) following randomized evidence of clinical efficacy. Evaluate the real-world experience with bezafibrate in PBC in relation to tolerability, response and long-term outcome.

Methods: All patients initiating off-label bezafibrate in the Dutch PBC Cohort Study (DPCS) – a retrospective cohort study– were evaluated. Biochemical changes (Δ) during the first year of treatment were assessed, expressed in upper limits of normal (ULN). Dichotomous response was evaluated with the Paris II criteria and normal alkaline phosphatase (ALP).

Results: In total, 317 individuals (290 [91.5%] females) initiated bezafibrate therapy. Median baseline ALP was 2.30 (IQR 1.52–3.36) and median TB 0.58 (IQR 0.41–0.92). At 12 months, the cumulative cessation rate was 24.6% (95%CI 19.7–29.5); the minimal cessation rate due to side effects was 12.9%. The overall on-treatment median ΔALP and ΔTB at 12 months were -1.00xULN (IQR -1.50 to -0.49) and -0.06xULN (IQR -0.20 to 0.05). Normal ALP increased from 6% at baseline to 40% at one year, and Paris II fulfilment from 19% to 48% (p<0.001 both). The ΔALP at one year was 0.83 (IQR -1.25 to -0.53) in complete responders and -1.16 (IQR -2.34 to -0.45) in incomplete responders (p=0.078). Multivariable logistic regression showed that ALP (OR 0.52, 95%CI 0.34 – 0.80) and AST (OR 0.22, 95%CI 0.10 – 0.51) were negatively associated with the Paris II response. Ln(ALP in ULN) during bezafibrate treatment were associated with decompensation, liver transplantation or death (HR 3.29, 95%CI 1.76-6.16, p<0.001).

Discussion: In this real-world nationwide study, the one-year fibrate discontinuation rate was substantial. However off-label use of bezafibrate was associated with reductions in the biochemical markers of cholestasis in PBC, which were associated with clinical outcome in this setting of second line therapy.

Study Highlights

What is already known

- Bezafibrate for patients with primary biliary cholangitis resulted in higher complete biochemical response rates in a randomized clinical trial setting compared to placebo.

What is new

- This real-world nation-wide cohort shows that bezafibrate was associated with an improvement of the biochemical markers of cholestasis. Patients with an incomplete response to bezafibrate also showed marked reduction of their ALP level.
- Higher ALP levels during bezafibrate therapy were associated with a statistically significantly higher risk of liver decompensation, liver transplantation or death.
- The confirmation of the association between ALP and clinical outcome in the setting of bezafibrate therapy is important for policy makers who decide on approval and reimbursement of new PBC drugs.

MANUSCRIPT BODY

1. INTRODUCTION

Primary biliary cholangitis (PBC) is a rare, chronic and progressive immune-mediated cholestatic liver disease (1, 2). Over time, PBC can progress to biliary cirrhosis, at which stage patients may develop complications of portal hypertension and hepatocellular carcinoma (HCC) with the risk of liver-related death. Without treatment, the life expectancy of individuals with PBC is substantially impaired(3). Ursodeoxycholic acid (UDCA) improves alkaline phosphatase (ALP), which has been associated with prognosis in UDCA monotherapy (4, 5). In addition, UDCA delays the progression of hepatic fibrosis in PBC and improves the long-term survival (6, 7). Lifelong use of UDCA in a dose of 13-15 mg/kg/day is thus recommended as standard treatment for PBC (5, 8).

Patients with an impaired clinical outcome despite UDCA, usually identified by various dichotomous response criteria, would benefit from second line therapy (9). Obeticholic acid (OCA) was shown to improve liver-related biochemistry and, potentially, hepatic fibrosis and clinical outcome, but was recently withdrawn from the European and US markets (10-13). Phase 3 trials showed seladelpar and elafibranor, both selective peroxisome proliferator-activated receptor (PPAR) agonists, to improve cholestasis as well (14, 15). However, reimbursement and availability of these treatment options varies. Off-label bezafibrate has gained momentum after two recent academic trials indicated that this pan-PPAR agonist reduces ALP and improves cholestatic pruritus (16, 17). A small non-controlled study with paired liver biopsies suggested that five years of add-on bezafibrate therapy decreased hepatic fibrosis (18). In addition, a retrospective Japanese cohort study showed that UDCA-bezafibrate combination therapy was associated with a lower risk of liver transplantation (LT) and mortality, compared to UDCA alone (19).There remain, however, concerns on the safety and tolerability with non-licensed fibrate treatment, also because high-risk individuals may have been underrepresented in clinical trials. Real-world studies are important to improve our understanding of the risks and benefits of bezafibrate in PBC (14, 15, 20). Therefore, the objective of

this nationwide Dutch cohort study was to assess the biochemical efficacy, tolerability and clinical outcome with off-label PPAR agonist therapy.

2. METHODS

Study Design

All identifiable patients with an established diagnosis of PBC according to international clinical practice guidelines (8, 21) in the Netherlands, from 1990 onwards, were registered in the Dutch PBC Cohort Study (DPCS). For patients with chronic cholestasis who tested negative for antimitochondrial antibodies (AMA), diagnosis was based on alternative PBC-specific antibodies (gp210 and sp100) or liver histology. The DPCS is a nationwide, multicenter, retrospective cohort study, conducted in all 71 Dutch Hospitals (of which seven academic centers). All clinical data were collected up to the last available patient visit at the time of data collection in the participating center (ranging from January 2019 to February 2023). The method of systematic case finding has been described previously (22). For the current study, all consecutive patients with an established diagnosis with PBC who initiated a PPAR agonist during follow-up were included; no exclusion criteria were specified. Since almost all participants in the study were treated with bezafibrate, the further analyses and discussion will primarily address and mention bezafibrate.

Data collection and clinical definitions

Clinical data was systematically collected within electronic case report forms. For the current study, type, dosage, and the start date and stop date of fibrates were recorded, along with the UDCA treatment history. If obtainable, the reason for fibrate discontinuation was recorded. Presence of PBC-AIH overlap was defined according to Paris criteria (23). Presence of cirrhosis was based on liver stiffness measurement (LSM) result ≥ 15 kPa as determined by FibroScan^{R}, or histological evaluation (defined as a METAVIR score F4 and/or Scheuer and Ludwig Classification Stage IV) (24-26), up to

one year after bezafibrate initiation. When no liver biopsy or LSM was performed, cirrhosis was considered as present in case of radiological signs of advanced liver disease in combination with splenomegaly, thrombocytopenia, hypoalbuminemia, prolonged prothrombin time, gastro-esophageal varices or ascites. Liver-related laboratory measurements were registered prior to bezafibrate initiation and during follow-up thereafter. All laboratory results are expressed as times the upper limit of normal (xULN) or times the lower limit of normal (xLLN), according to the reference values in the local laboratory/hospital.

Biochemical efficacy

Biochemical measurements closest to the start of fibrates were used as baseline (median time between laboratory results and start of bezafibrate was 13 days [IQR 3-45]). Measurements closest to 12 months (minimum nine months, maximum 18 months) were used to assess the biochemical response after one year of bezafibrate therapy. For on-treatment biochemical analyses during the first year, subjects were eligible if they had continuously received bezafibrate. An available case approach was used. The number of observations included in each analysis is specified in the respective tables. The Paris II criteria (ALP and aspartate aminotransferase [AST] <1.5 x ULN and normal total bilirubin [TB]) were used for dichotomous response evaluation. Dichotomous response rates are presented separately for the on-treatment cohort and for the intention to treat (ITT) cohort. In the on-treatment assessment, the response rate describes the biochemical response among those who actively used bezafibrate at time of laboratory assessment. Thus, patient who stopped bezafibrate prior to an available laboratory result were excluded. In the ITT analysis, all patient who started BZF were included and their biochemistry after one year (closest laboratory value to 12 months, within the range from 9-18 months) was used independent of whether bezafibrate was of was not stopped before that time.

Clinical outcome

The clinical events which were collected during follow-up included liver decompensation (defined as either ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy and/or hepatorenal syndrome), LT or death. These were combined in a composite endpoint defined as clinical disease progression, to which the first event contributed. In cases of uncertainty concerning hepatic decompensation, cases were systematically reviewed by the medical research team to ensure consistency and reliability of the endpoint adjudication. Data from all three LT centers in the Netherlands were included and mortality data (registered through administrative records in the Netherlands) is generally linked to digital hospital information systems.

Statistical analyses

Patients' characteristics were described using means with standard deviation (SD) for normally distributed data and medians with interquartile ranges (IQR) for non-normally distributed data. Categorical variables are presented as counts and proportions. To compare continuous data of independent groups, Student's t and Mann-Whitney-U tests were used for normally and non-normally distributed data, respectively. The Chi-Square test was used to examine differences in categorical variables between two or more independent groups.

The biochemical evolution during bezafibrate treatment was explored and visualized using linear mixed models with natural cubic splines. To facilitate interpretation, effect plots were generated showing the expected biochemical values (transformed back to their original scale) with their corresponding 95% confidence intervals over the initial 18 months.

Logistic regression was performed to explore associations between baseline factors and the biochemical response according to the Paris II criteria at 12 months of treatment. All on-treatment available laboratory results after one year were included in complete case analyses. Odds ratios (OR) with 95% confidence intervals (CI) were reported. Cumulative discontinuation rates and rates of clinical disease progression (adjusted for age) were assessed by Kaplan-Meier estimator and Cox

proportional hazard regression analyses. To optimize the power of our primary analyses, time zero in survival analyses was defined as the date of the first ALP measurement after 90 days of treatment, as the BEZURSO trial indicated a maximized ALP decline with bezafibrate after 3 months with stable ALP levels thereafter (16). The ALP level (in ULN) was log-transformed using the natural logarithm and included as a continuous covariate in the Cox proportional hazards models. A (mean)age-adjusted cubic spline function was applied to visualize the relation between ALP and the estimated hazard of clinical disease progression. Sensitivity analyses for the association between ALP and outcome were performed: (1) with adjustment for cirrhosis at baseline, (2) in a subgroup of patients with time zero as the date of the ALP measurement between 9-18 months of treatment, (3) with censoring of patients at the time of fibrate discontinuation during follow-up, and (4) for the subgroup of patients without concomitant immunosuppressive drugs.

Although generally contra-indicated, 9 patients with cirrhosis had hepatic decompensation events prior to initiation of bezafibrate. These cases were included in the biochemical analyses but excluded from the survival analyses on clinical disease progression.

All statistical tests were two-sided at a significance level of 0.05. Statistical analyses were performed with the SPSS, version 28, software (Chicago, IL) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Ethics

The study was conducted in accordance with the Declaration of Helsinki guidelines and the principles of good clinical practice and approved by the Medical Ethical Committee of the coordinating center, the Erasmus University Medical Center in Rotterdam, The Netherlands (MEC-2019-0009).

3. RESULTS

Characteristics of patients initiating fibrate therapy

Overall, 317 individuals initiated fibrate therapy during follow-up. Except for seven (ciprofibrate n=5 [1.6%], gemfibrozil n=2 [0.6%]), all received bezafibrate (n=310, 97.8%) in a dose of 400mg once daily. Table 1 describes the baseline characteristics. Patients were mostly women (n=290, 91.5%), with a median age at start of treatment of 55.3 years (IQR 48.4-64.4). Fibrates were used as monotherapy in nine (2.8%) patients, of whom eight were intolerant to UDCA and one was reluctant to use UDCA. Recipients of combination treatment with UDCA (n=308; 97.2%) had a median UDCA treatment duration of 7.4 years (IQR 2.2-12.7) before fibrate therapy was added. Thirty individuals (9.7%) had less than one year of UDCA treatment at the time bezafibrate was initiated. Fifty-seven (18.0%) subjects had cirrhosis. The median ALP and TB at bezafibrate initiation were 2.30xULN (IQR 1.53-3.35) and 0.58xULN (IQR 0.41-0.93), respectively.

Fibrates were prescribed at least once in 61 (85.9%) of the 71 Dutch hospitals. Notably, 144 (45.4%) individuals who received fibrates were managed in one of the seven academic centers. The first bezafibrate treatment was started in 2008, with increase in the use of off-label bezafibrate therapy from 2015 onwards (p=0.026, Figure S1).

The median follow-up duration among the 317 individuals was 30.4 (IQR 18.0-50.4) months, of whom 241 (76.0%) were treated for at least nine months at the time of the last data collection

Discontinuation of bezafibrate treatment

During the current follow-up, 76 individuals discontinued PPAR agonist therapy in the first year of treatment (74/76 [97.4%] were on bezafibrate, Table 2). Almost half of these patients (36/76, 47.4%) stopped within the first 3 months of treatment. The cumulative discontinuation rates at 6 and 12 months were 15.6% (95%CI 11.7–19.5) and 24.6% (95%CI 19.7–29.5), respectively. After the first year of bezafibrate therapy, an additional 33 (10.4%) individuals discontinued treatment. These patients stopped bezafibrate treatment after a median duration of 19.3 (IQR 16.0 – 31.5) months. Table 2 describes the reasons for bezafibrate discontinuation in relation to the timing of treatment cessation. The reason for discontinuation was known for 82 of the 109 (75%) patients who stopped fibrate therapy. Side effects were the most frequent cause (47/82, 57%), including elevation of liver enzymes in three subjects and elevation of creatinine in six subjects. The creatinine increase was completely reversible in all individuals after bezafibrate discontinuation; the difference in creatinine level between the post-cessation follow-up measurement and the baseline measurement ranged from -31 to +6 µmol/L. The cumulative discontinuation rate at 12 months due to side-effects was the minimally 12.9% (95%CI 9.0-16.8%) and maximally 18.6% (95%CI 14.1-23.1) considering there were patients for whom the reason for discontinuation was not known.

At 6 months, the cumulative discontinuation rates did not significantly differ for subgroups of age (12.2% [95%CI 7.9-16.5] vs. 21.4% [95%CI 13.4-29.4] for <62 and ≥62 years, log-rank x^2=2.79, p=0.095), cirrhosis status (14.3% [95%CI 10.0-18.6] vs. 19.4% [95%CI 9.2-29.6] for non-cirrhosis vs. cirrhosis, log-rank x^2=3.35, p=0.060), or type of center(22.5% [95%CI 15.2%-28.8%] vs. 27.8% [95% 20.4 - 35.2%], for non-academic vs. academic center, log-rank x^2=0.96, p=0.328). Also for subgroups based on baseline ALP (17.0% [95%CI 11.3–22.7] vs. 14.5% [95%CI 10.7-18.3] for ALP ≤1.67 vs. >1.67xULN, log-rank x^2=0.31, p=0.578) or TB (17.0% [95%CI 11.1–22.9] vs. 13.6% [95%CI 7.5–19.7], for normal vs. abnormal bilirubin, log-rank x^2=1.71, p=0.191) the cumulative discontinuation rates did not differ significantly.

Of the 109 people who discontinued bezafibrate treatment during the entire follow-up, PPAR agonists had been re-initiated in 31 individuals during the registered follow-up. Twenty-two (71.0%) of these 31 patients had continued treatment up to the last known follow-up date, leaving 86 of 317 patients without PPAR agonists (27.1%) at the end of follow-up.

Biochemical changes during the first year of bezafibrate therapy

Figure 1 shows the estimated evolution of the liver-related biochemical parameters and creatinine based on all available on-treatment laboratory values during the first 18 months of bezafibrate therapy. The linear mixed models indicated a steep decline in both ALP and gamma-glutamyltransferase (GGT) during the first months of treatment, which is maintained thereafter. Even though the median baseline TB was 0.58 (IQR 0.41-0.93), with 223 (79.6%) individuals having a normal TB, there was a small gradual decrease in TB during the first year of therapy. The transaminases showed a different pattern of response, with a more profound and rapid decline for alanine aminotransferase (ALT), as compared to AST.

The median ΔALP and ΔTB were -1.00xULN (IQR -1.50 to -0.49) and -0.06xULN (IQR -0.20 to 0.05), with a median percentage change of -48.9% and -11.1% from baseline, respectively ($p<0.001$ for both). Table 3 shows the deltas and percentage changes of the other liver-related enzymes ($p<0.005$ for all). The creatinine value increased from 66 µmol/L (IQR 59-77) at start of bezafibrate therapy to 71 µmol/L (IQR 61-81) at 12 months ($p<0.001$) among the 117 subjects with paired measurements. Thirty-nine (33.3%) of these 117 subjects had no elevation of creatinine at 12 months.

At 12 months of therapy, 89/182 (48.9%) individuals met the dichotomous Paris II criteria and 80/201 (39.8%) had a normal ALP. In those with baseline and follow-up data, the percentage of patients fulfilling the Paris II criteria increased from 19.3% to 47.8%. The percentage of patients with normal ALP increased from 6.1%% to 39.8% ($p<0.001$ for both). In the intention-to-treat analysis,

100/236 (42.4%) met the Paris II criteria and 88/253 (34.8%) had normal ALP at 12 months. The results according to the other dichotomous response criteria are presented in Figure 2.

Factors associated with biochemical response

Univariable logistic regression analyses, showed that cirrhosis, treatment in an academic care center and higher baseline AST, ALT, GGT, ALP, and TB were negatively associated with fulfilling Paris II response at 12 months (Table 4). In multivariable analysis, adjusted for age, cirrhosis and TB at start of bezafibrate therapy, baseline ALP (aOR 0.52 (95%CI (0.34–0.80), p=0.003) and baseline AST (aOR 0.22, 95%CI 0.10-0.51, p<0.001) remained associated with the Paris II response (Table 4). Treatment in an academic center was not associated with biochemical response if added to the multivariable mode (aOR 0.84, 95% CI 0.34-2.06, p=0.706).

On-treatment biochemical changes stratified for baseline values

Subjects were categorized into three groups according to baseline ALP level; a low (ALP ≤1.67 xULN; n=62), medium (1.67-3.0 xULN; n=75) and high group (≥3.0 xULN; n=60). All three groups showed a marked decline of the ALP level during the first year of treatment (p<0.001 for all). The percentage ALP change in the low, medium and high baseline ALP group were -40.9%, -50.8% and -50.9%, respectively (p=0.011). There was a more profound difference in the absolute median ΔALP among the 3 groups: -0.54 (IQR -0.69 to -0.28), -1.15 (IQR -1.33 to -0.79), and -2.21 (IQR -3.55 to -1.10), respectively (p<0.001, for all comparisons, Figure 3). In contrast, dichotomous response rates reduced with higher ALP at baseline: 83.6%, 54.7% and 10.2%, respectively, for Paris II criteria (p<0.001), and 75.8%, 40.0% and 3.3%, respectively, for normal ALP (p<0.001). Albeit not statistically significant, patients with PBC who did not fulfil Paris II criteria at 12 months had a stronger absolute ALP reduction (ΔALP -1.16 [IQR -2.34 to -0.45]) as opposed to patients who did
(-0.83 [IQR -1.25 to -0.53], p=0.078).

When categorizing patients according to their baseline TB level, the ΔTB after one year of treatment in patients with a baseline TB ≤0.6xULN (n= 92) was 0.00xULN (IQR -0.09 to 0.05) versus -0.18 xULN (IQR-0.35 to 0.00) in those with a baseline TB >0.6 xULN (n=78) (*p*<0.001, Figure 3).

On treatment biochemical changes in individuals with cirrhosis

On-treatment biochemical changes could be assessed in 45 individuals with cirrhosis. At baseline, these subjects had higher median age (62.0 [IQR 54.5-69.6] vs. 54.3 [IQR 47.9-63.4]), with higher serum TB (0.88 [IQR 0.59-1.60] vs. 0.53 [IQR 0.41-0.82]), higher AST (1.84 [1.26-2.52] vs. 1.37 [0.97-2.14]) and lower platelet count (170 [IQR 120-259] vs. 274 [IQR 238-328]) versus those without cirrhosis (p<0.05 for all). Among patients with cirrhosis the median ΔALP was -0.75 (IQR -1.44 to -0.31), the median ΔTB was -0.06 (IQR -0.27 to 0.03) and median ΔAST was -0.17 (IQR -0.57 to 0.17). This did not differ from the ΔALP of -1.03 (IQR -1.57 to -0.52), ΔTB of -0.06 (IQR -0.18 to 0.05) and ΔAST of -0.07 (IQR -0.43 to 0.13) among patients without cirrhosis (p>0.1 for all). At 12 months, the on-treatment response rate according to the Paris II criteria was lower in subjects with cirrhosis (11/34, 32.4%) than in subjects without cirrhosis (78/148, 52.7%, p=0.032). There was no statistically significant difference in the proportion of subjects with normal ALP at 12 months (12/36 [33.3%] vs. 68/165 [41.2%], p=0.382).

On treatment ALP levels in relation to clinical outcome

In total, 25 patients experienced clinical disease progression after bezafibrate initiation. Adjusted for age, on-treatment Ln ALP (in ULN) was associated clinical disease progression (aHR 3.29, 95%CI 1.76-6.16, p<0.001) (Figure 4), as were Ln TB (aHR 7.82, 95%CI 3.99-15.32, p<0.001) and Ln AST (aHR 7.26, 95% CI 2.72-19.37, p<0.001). Sensitivity analyses showed a stable association between Ln ALP and clinical outcome. The aHR of Ln ALP for clinical disease progression was 3.11 (95%CI 1.67–5.79) if further adjusted for cirrhosis at bezafibrate initiation, 2.62 (95%CI 1.14-6.03, p=0.024) in case patients were censored at the time of bezafibrate discontinuation, 6.17 (95%CI 2.23-16.2, p<0.001)

based on the on-treatment ALP between 9 and 18 months, and 2.95 (95% CI 1.41-6.16, p=0.004) in case patients with concomitant immunosuppressive drugs were excluded.

Fulfilment of Paris-2 at one year of bezafibrate therapy was statistically significantly associated with clinical disease progression (aHR 0.15, 95%CI 0.03-0.68, p=0.014).

4. DISCUSSION

In this real-world nationwide cohort in the Netherlands, bezafibrate therapy was associated with a reduction in ALP, AST, and TB levels. These key biochemical markers in PBC have a well-documented relation to the long-term clinical outcome of UDCA monotherapy. Unlike the relative decline, the absolute decline in ALP with bezafibrate therapy depended strongly on its baseline level. Patients with high ALP levels at baseline showed the strongest absolute reduction at one year. This is an important finding as the overall dichotomous response rate of 45% according to the Paris II criteria was inversely related to the baseline ALP levels. Patients who did not fulfil the Paris II criteria showed at least a similar - if not a stronger - absolute ALP decline after one year of bezafibrate therapy. This demonstrates that patients with PBC who are classified as incomplete responders based on dichotomous response criteria still benefit from add-on bezafibrate therapy. These results thus challenge the dichotomous evaluation of the biochemical response to anti-cholestatic therapy, both in daily practice as well as within clinical trials. The finding that higher ALP levels during bezafibrate therapy were associated with worse clinical outcome further highlights the importance of our biochemical results. Confirming this association between ALP and clinical outcome in the setting of combination therapy is also important to support the surrogacy of this biochemical parameter of cholestasis, both for patients, physicians and policymakers. It further indicates that a subset of patients may indeed need more than two drugs with distinct mechanisms of action to optimize their long-term clinical outcome.

Considering the promising biochemical improvements, it is unfortunate that the cumulative bezafibrate discontinuation rate at one year of follow-up was as high as 25%. The main documented reason to stop bezafibrate therapy was side effects, predominantly related to gastrointestinal symptoms and myalgia. Based on our results, the minimal cumulative one-year discontinuation rate due to side effects was 12.9%, but this could be as high as 19.6% as the reason for discontinuation was missing for a quarter of the patients. The stopping rate in our real-world study was higher than in the previously described trials (14% in a 2-year trial) (16, 27). It was similar, however, to the cumulative one-year stopping rate of 25.9% among UK patients with PBC who were treated with fibrates outside the clinical trial setting (28). Extending bezafibrate treatment to non-academic centers did not appear to explain this finding, as our cohort showed comparable discontinuation rates between both types of centers. Still, when evaluating the discontinuation rate in our study, it should be noted that this concerns the earliest experiences in the Netherlands, starting from the first documented prescription in 2008. It was only recently, however, that more substantial evidence to support the clinical benefit of PPAR agonism emerged (16, 18, 19, 29). These insights may impact both the physicians' and patients' willingness to continue PPAR agonist therapy, which could potentially reduce premature discontinuation of PPAR agonist therapy today. It is also important to emphasize that a substantial number of patients were able to successfully restart bezafibrate therapy. This may be explained by individuals which initially started bezafibrate as a temporary treatment for itch, by more vigorous symptom management during re-treatment and/or increased patient and physician awareness. The largest study on bezafibrate in PBC to date, which was performed in Japan where there is longer experience with bezafibrate, reported a 6% rate of permanent discontinuation (19). Future prospective efforts with patient-reported outcomes are needed to better assess drug-related side effects during bezafibrate in a real-world setting. At present, both the pros and cons of off-label use of bezafibrate should be discussed with individuals in need of second-line treatment today (5, 8). Most patients were able to remain on long-term bezafibrate treatment which can improve their level of pruritus, liver-related biochemistry and,

potentially, liver histology and clinical outcome (18, 19). New, more selective PPAR agonists, have now broadened the therapeutic armamentarium. Their real-world safety, tolerability and efficacy, as well as their position next to bezafibrate, should be explored.

After one year of treatment, bezafibrate use was associated with an almost 50% reduction in ALP. This is in line with results in both clinical trial (-60%) and real-world (-57%) setting (16, 28). With a linear mixed model analysis we confirmed that ALP declines within the first months of fibrate therapy, with a sustained response thereafter (16). An important and timely finding was that higher on-treatment levels of ALP were associated with an increased risk of liver decompensation, transplant or death. More support for the surrogacy of ALP in the setting of second line therapy is important for policymakers who need to decide on market access and reimbursement of newly developed PBC drugs, especially considering the (insurmountable) difficulties of long-term trials on clinical endpoints (30). While our time-to-event analyses had power constrained due to a limited number of clinical events, the results are in line with current understanding of the prognostic relevance of ALP in PBC. Despite stable results in a variety of sensitivity analyses, our findings will need further confirmation in more comprehensive multivariate analyses.

Despite relatively low TB levels at baseline, we observed an overall median decline in TB of 11% at one year. This is similar to the decline of TB in the BEZURSO trial (14%) (16). However, TB levels only went down in the subgroup of patients with a baseline TB >0.6 xULN. This is relevant as the prognosis among UDCA-treated patients with PBC starts to deteriorate from this TB level onwards (31). A real-world study conducted in the UK did not find a relevant decrease in TB with fibrate therapy (28). This negative finding remained in their subgroup of patients with a TB >0.6 xULN at the start of therapy. Whether the impact on TB differs according to the type of PPAR agonist is currently unclear.

The difference in the AST and ALT response to bezafibrate therapy was an interesting finding. Both in our study and the BEZURSO trial the reduction of ALT (-25% and -36%, respectively) was stronger than the reduction in AST (-6% and -8%, respectively) (16). This difference was also

observed with other PPAR agonists which are currently in development for PBC (32, 33). There is no strong liver-related hypothesis for this difference in response, and therefore also extrahepatic sources of AST should be considered. Of note, PPAR agonists have been associated with (mostly mild) myopathy (34).

Our results advocate to evaluate of add-on bezafibrate therapy on a continuous biochemical scale. There was a trend for a larger absolute decline in ALP among individuals who did not meet the Paris II criteria after approximately one year of therapy as compared to those who did. These incomplete responders had higher ALP levels at baseline, and thus a higher risk of unfavorable outcome. As results, bezafibrate prevents more cases with clinical disease progression among patients with an incomplete response (35).

The real-world setting of this study, in all treatment centers in the Netherlands, provides valuable insights. The retrospective nature of the study, however, entails limitations. This includes the non-protocolled follow-up, which results in missing data on, for instance, the reason for treatment initiation or discontinuation, and biochemical parameters. Information on the argumentation for a clinical decision is not systematically recorded by the treating physician, and could thus not be retrieved through medical chart review. Also, patient-reported outcome measures (such as pruritus) are also not structurally assessed in daily clinical practice. The retrospective design with irregular follow-up further forced a time-window for biochemical response assessment, but this may not have a great impact on the representability of our results considering the BEZURSO trial indicated a maximum decline in ALP as early as 3 months, with stable ALP levels thereafter (16). Our mixed linear model analyses on the biochemical parameters also supports our methodology. At last, there may be bias because the experience with fibrate therapy was limited during the early phase of this study's inclusion period. Yet, the similarities with the results in clinical trials are reassuring with respect to the reliability of these data.

In conclusion, in this nationwide real-world study, bezafibrate use was associated with improvements of the biochemical markers of cholestasis and liver injury, which are also linked to

clinical outcome in this setting of add-on bezafibrate therapy. As the reduction in ALP was more prominent in patients who did not fulfil the standard dichotomous response criteria, it is important to assess the response to therapy on a continuous scale as well. The relatively high bezafibrate discontinuation rate indicates, however, that there is a need to optimize educative efforts for patients and their treating physicians and to improve PPAR agonist treatment strategies.

FIGURE LEGENDS

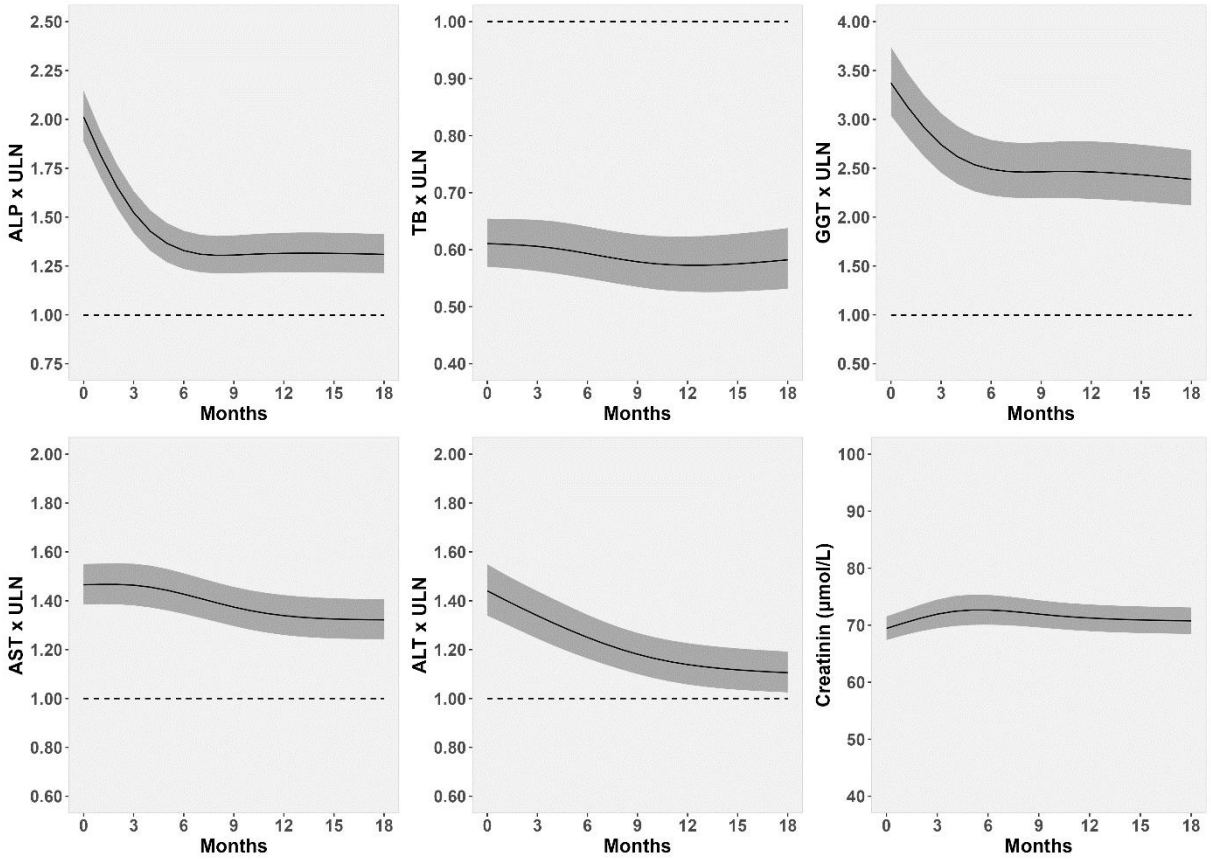

Figure 1. Biochemistry during bezafibrate treatment

The biochemical evolution over time during bezafibrate treatment was explored and visualized using linear mixed models. The dynamics are presented for (a) ALP, (b) TB, (c) GGT, (d) AST, (e) ALT, and (f) creatinine. The models were fitted on all (on-treatment) laboratory measurements collected from start of bezafibrate treatment until a maximum of 18 months thereafter. Dashed lines show the ULN for each biochemical parameter, except for creatinine. Biochemical parameters were transformed using the natural logarithm. To facilitate interpretation, we generated effects plots showing the expected biochemical values (transformed back to their original scale times the ULN) with their corresponding 95% confidence intervals over time. Non-linearity of the trajectories was modelled using natural cubic splines (3 degrees of freedom). For patients who stopped bezafibrate therapy during follow-up, the on-treatment laboratory data were included up to the point of treatment cessation.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma Glutamyl Transferase; TB, Total bilirubin; ULN, upper limit of normal.

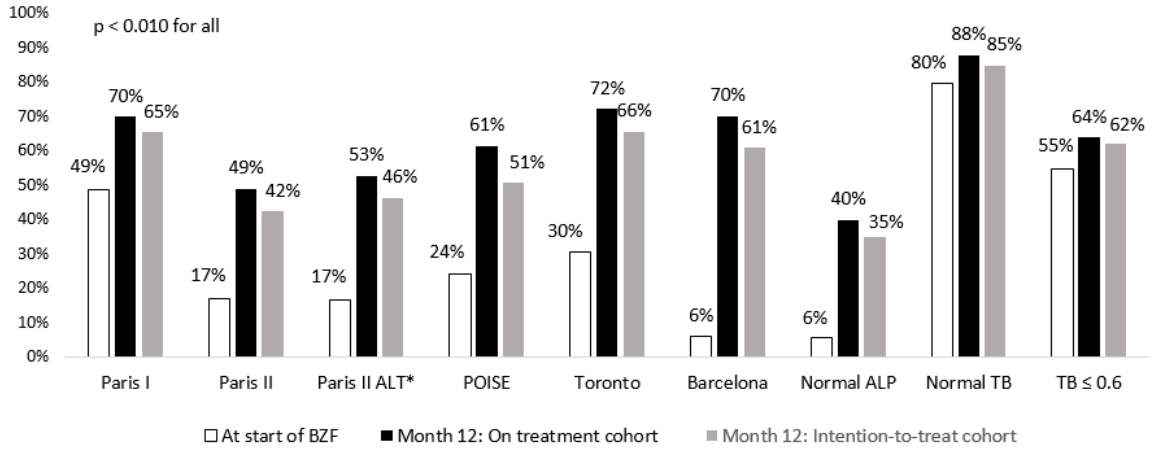

Figure 2. Dichotomous response rates to bezafibrate therapy at 12 months

*Paris II response with ALT instead of AST. P < 0.010 for all comparisons at start of treatment vs. on treatment cohort, and at start of treatment vs. intention-to-treat cohort. Rates (%) of dichotomous response to bezafibrate therapy according to various dichotomous response criteria, separately presented at start of treatment, for the on-treatment cohort at 12 months of treatment and intention-to-treat cohort irrespective of treatment status at 12 months. Treatment response criteria according to Paris I (ALP≤3x ULN, AST≤2xULN, and TB≤ULN), Paris II (ALP≤1.5xULN, AST≤1.5xULN, and TB≤ULN), Paris II ALT (ALP≤1.5xULN, ALT≤1.5xULN (instead of AST), and TB≤ULN), POISE (ALP≤1.67xULN, ALP decrease >15%, and TB≤ULN) , Toronto (ALP ≤1.67xULN), Barcelona (ALP decrease of 40% or normal ALP), Normal ALP, Normal TB, TB≤0.6xULN. Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TB, Total bilirubin; ULN, upper limit of normal.

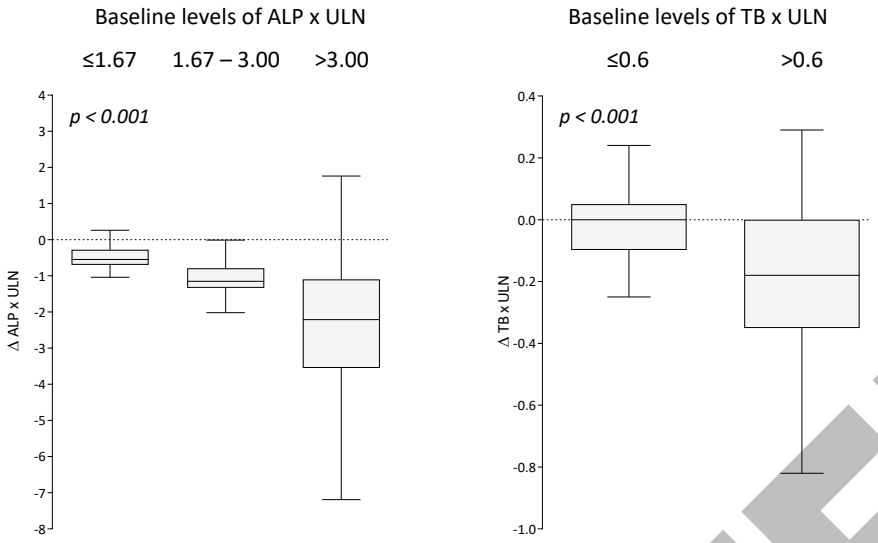

Figure 3. Median changes in ALP and TB during stratified for baseline levels

Median differences are presented with Tukey Whiskers. The cut-offs for ALP were based on distribution of ALP (approximately the 33rd and 67th percentiles) and set according to the POISE and Paris I criteria: ≤1.67xULN (n=62), 1.67-3.00 (n=75), ≥3.0xULN (n=60). The cut-off for bilirubin was based on median value and, for interpretation purposes, fixed at the below-normal bilirubin cut-off (0.6xULN) (≤0.6 [n=92] vs. >0.6 [n=78]). These analyses included patients with on-treatment values at 12 months of follow-up. Statistical analyses were performed using the Kruskal-Wallis test for ALP ($p < 0.001$) and the Mann Whitney U test for bilirubin ($p < 0.001$).

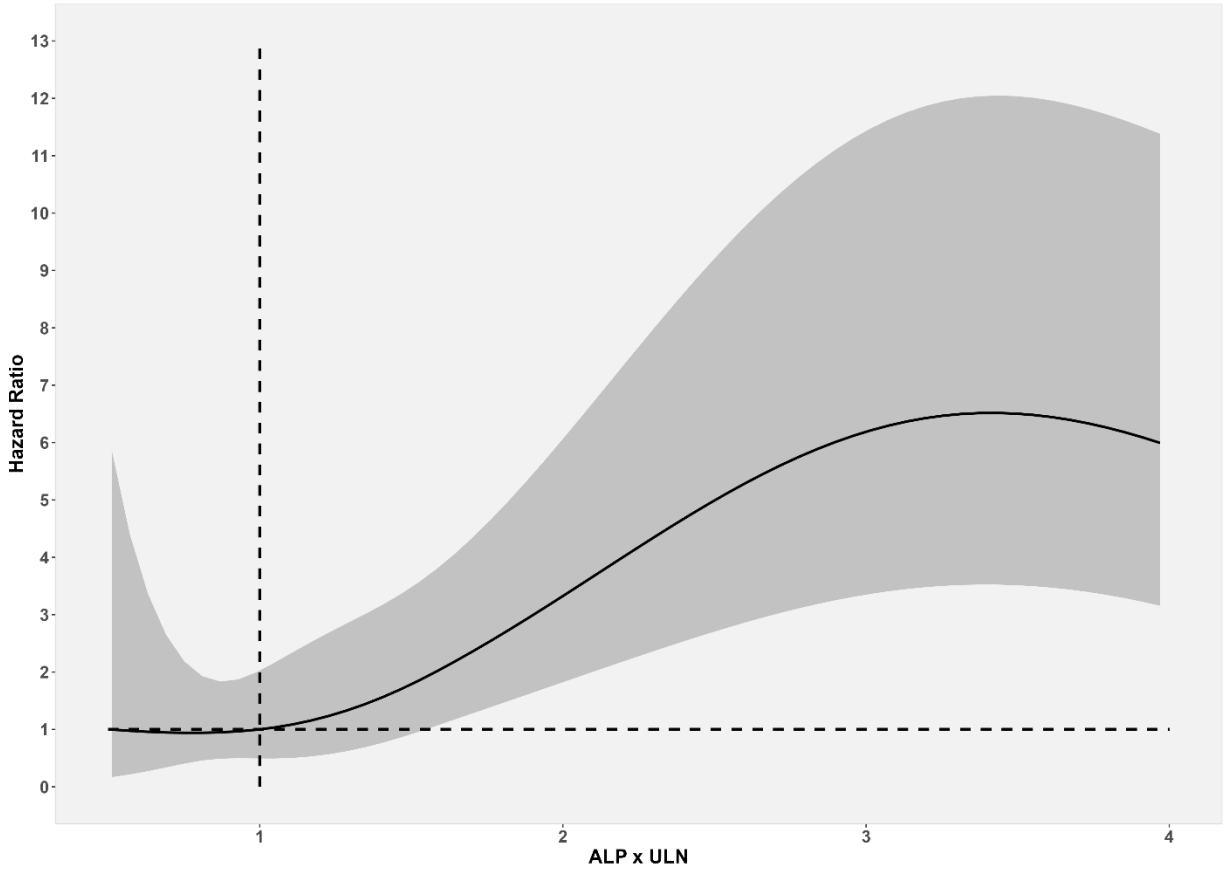

Figure 4. The age-adjusted hazard of liver decompensation, liver transplant or death according to the ALP level during fibrate therapy.

Hazard ratios were estimated by applying a cubic spline function of alkaline phosphatase (3 degrees of freedom) for a patient with a mean age of 55 years old. Two hundred twenty-two patients with on-bezafibrate-treatment ALP levels were included for this analysis.

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Patient and public involvement

The Dutch Patient Liver Association was involved in the development of the Dutch PBC Cohort study.

Collaborators of the Dutch PBC Study Group:

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Table 1. Cohort characteristics

	Initiation Cohort (*n* = 317)
Age at diagnosis, years*	47.5 (10.5)
Age at start bezafibrate, years†	55.3 (48.4 – 64.4)
Female, n (%)	290 (91.5)
AMA positive, n (%)	278 (88.3)
Calendar year of initiation†	2019 (2017 – 2020)
Type of PPAR agonist, n (%)	
Bezafibrate	310 (97.8)
Ciprofibrate	5 (1.6)
Gemfibrozil	2 (0.6)
Add-on therapy to UDCA, n (%)	308 (97.2)
Years of UDCA treatment†	7.3 (2.2 – 12.4)
UDCA dose mg/kg/day†	14.5 (12.9 – 16.2)
Liver stiffness kPa†	8.5 (6.2 – 15.0)
Cirrhosis, n (%)	57 (18.0)
Prior decompensation event[§]	9 (2.8)
PBC-AIH overlap, n (%)‡	18 (5.7)
Co-administered medication, n (%)	36 (11.4)
Azathioprine	12 (3.8)
Prednisone	18 (5.6)
Budesonide	10 (3.2)
Mycophenolate mofetil	4 (1.3)
Obeticholic acid	2 (0.6)
Serum TB (ULN)†	0.58 (0.41 – 0.92)
Serum ALP (ULN)†	2.30 (1.52 – 3.36)
Serum AST (ULN)†	1.41 (1.00 – 2.17)
Serum ALT (ULN)†	1.44 (0.94 – 2.37)
Serum GGT (ULN)†	3.87 (2.20 – 6.41)
Serum albumin (LLN)†	1.14 (1.06 – 1.25)
Platelet count (x10^9/L)†	262 (208 – 318)
Creatinine (µmol/L)†	66 (59 – 78)
Paris II Response[¶], n(%)	46/269 (17.1)

AMA status was available for 315/317 (99.4%) patients. UDCA dose in mg/kg/day was available for 291 (94.5%) of the 308 patients who used UDCA, due to missing weight in 17 patients using UDCA. Liver stiffness measurements at baseline (one year prior up to one year after initiation) were available for 153 (48.3%) patients. Baseline TB was missing for 37 (11.7%) patients, ALP for 8 (2.5%), AST for 27 (8.5%), ALT for 10 (3.2%), GGT for 15 (4.7%), albumin for 110 (35%), platelet count for 94 (30%) and creatinine for 105 (33%).
Abbreviations: AIH, Autoimmune Hepatitis; ALP, Alkaline Phosphatase; ALT, Alanine Transferase; AMA, Antimitochondrial Antibodies; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; LLN, lower limit of normal; PBC, Primary Biliary Cholangitis; PPAR, peroxisome proliferator-activated receptor; TB, Total Bilirubin; UDCA, Ursodeoxycholic Acid; ULN, upper limit of normal.
*Data are expressed as mean and standard deviation
†Data are expressed as median and interquartile range
[§] Defined as either ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy and/or hepatorenal syndrome
‡According to the Paris criteria (23).
[¶] ALP and AST <1.5xULN and normal TB

Table 2. Reasons for terminating bezafibrate treatment categorized by timing of discontinuation

	Timing of Discontinuation			Overall
	0-6 months	6-12 months	>12 months	
	(n=49)	(n=27)	(n=33)	(n=109)
Reason for discontinuation				
Any adverse event*	27 (55.1)	11 (40.7)	9 (27.2)	47 (43.1)
Myalgia	5 (10.2)	3 (11.1)	4 (12.1)	14 (12.8)
Gastrointestinal complaints	6 (12.2)	2 (7.4)	2 (6.1)	10 (9.2)
Elevation of creatinine[#]	2 (4.1)	4 (14.8)	0 (0.0)	6 (5.5)
Elevation liver enzymes	2 (4.1)	1 (3.7)	1 (3.0)	3 (3.7)
Skin lesions	2 (2.7)	0 (0.0)	3 (6.9)	3 (3.1)
Other (palpitations, malaise, headache)	7 (14.2)	0 (0.0)	1 (0.3)	8 (7.3)
Not specified	10 (20.4)	1 (3.7)	1 (3.0)	12 (11.0)
Patient's initiative (non-specified)	5 (10.2)	3 (11.1)	3 (9.1)	11 (10.1)
No effect on biochemistry	1 (2.0)	2 (7.4)	4 (12.1)	7 (6.4)
No effect on pruritus	2 (4.1)	2 (7.4)	0 (0.0)	4 (3.7)
Trial participation	1 (2.0)	1 (3.7)	1 (3.0)	3 (2.8)
Disease progression	0 (0.0)	0 (0.0)	2 (6.1)	2 (1.8)
Other	1 (2.0)	2 (7.4)	5 (15.2)	8 (7.3)
Unknown	12 (24.5)	6 (22.2)	9 (27.3)	27 (24.8)

The numbers of patients who discontinued bezafibrate treatment are categorized by reason for discontinuation and timing of discontinuation, and are presented as absolute numbers and percentage (%).
*Number of patients who ceased treatment due to any adverse event; patients may have discontinued for multiple side effects.
[#] The creatinine increase was completely reversible in all individuals after bezafibrate discontinuation; the difference in creatinine level between the post-cessation follow-up measurement and the baseline measurement ranged from -31 to +6 µmol/L.

Table 3. Assessment of biochemical changes at 12 months of treatment

n	Obs.*	Month 0†	Month 12†	*p* value‡	*Median delta*†	*Median % change*†
TB (ULN)	170	0.58 (0.42 – 0.88)	0.50 (0.35 - 0.82)	<0.001	-0.06 (-0.20 to 0.05)	-11.1% (-29.4% to +12.5%)
ALP (ULN)	197	2.22 (1.50 - 3.35)	1.15 (0.78 - 1.84)	<0.001	-1.00 (-1.50 to -0.49)	-48.9% (-59.4% to -29.4%)
AST (ULN)	183	1.42 (1.00 - 2.20)	1.29 (0.94 - 1.87)	0.002	-0.08 (-0.43 to 0.13)	-6.3% (-24.3% to +12.2%)
ALT (ULN)	196	1.44 (1.00 - 2.35)	1.12 (0.73 - 1.84)	<0.001	-0.29 (-0.76 to 0.00)	-24.5% (-40.4% to +0.00%)
GGT (ULN)	193	4.86 (2.34 - 6.21)	2.43 (1.25 - 4.46)	<0.001	-1.14 (-2.29 to -0.24)	-37.8% (-54.6% to -10.4%)
Albumin (LLN)	132	1.14 (1.06 - 1.26)	1.16 (1.06 - 1.26)	0.476	0.00 (-0.03 to 0.06)	0.0% (-3.0% to +5.0%)
Platelet count (x10³/mm³)	109	255 (210 - 298)	269 (211 – 313)	0.321	1 (-18 to 29)	-0.4% (-6.3% to +11.5%)
Creatinine (umol/L)	117	66 (59 - 77)	71 (61 - 81)	<0.001	4 (-2 to 11)	+6.08% (-2.7% to +16.6%)

*only patients with on-treatment biochemical lab works are included for these analyses.

† Data is expressed as median with interquartile range (IQR)

‡ Wilcoxon signed Rank test Month 0 vs Month 12Abbreviations: ALP, Alkaline Phosphatase; ALT, Alanine Transferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; IQR, Interquartile Range; LLN, lower limit of normal; ULN, upper limit of normal; TB, total bilirubin.

Table 4. Factors associated with Paris II response after one year of bezafibrate treatment

		Univariable		Multivariable	
	Obs.	**Odds ratio**	***p* value**	**Odds ratio**	***p* value**
Female Sex	182	0.82 (0.29 – 2.38)	0.720		
Age at start bezafibrate	182	1.04 (1.01 – 1.07)	0.007	1.01 (0.97 – 1.06)	0.637
Age at PBC diagnosis	182	1.05 (1.01 – 1.09)	0.006		
Duration PBC (per year)	182	1.01 (0.97 – 1.05)	0.661		
nAMA Negative	180	0.84 (0.31 – 2.27)	0.726		
Treatment in tertiary center	182	0.47 (0.26 – 0.84)	0.012		
Cirrhosis at start of bezafibrate	182	0.42 (0.19 – 0.96)	0.039	0.44 (0.14 – 1.38)	0.124
Baseline AST (per ULN)	172	0.10 (0.05 – 0.20)	<0.001	0.22 (0.10 – 0.51)	<0.001
Baseline ALT (per ULN)	177	0.38 (0.26 – 0.57)	<0.001		
Baseline GGT (per ULN)	175	0.82 (0.74 – 0.91)	<0.001		
Baseline ALP (per ULN)	178	0.32 (0.22 – 0.47)	<0.001	0.52 (0.34 – 0.80)	0.003
Baseline TB (per ULN)	165	0.12 (0.05 – 0.32)	<0.001	0.56 (0.19 – 1.72)	0.313
Platelet Count (per $10x10^9$/L)	128	1.02 (0.99 – 1.06)	0.242		
Creatinine (per 10 umol/L)	130	1.13 (0.92 – 1.39)	0.251		
Baseline Albumin (per 0.1xLLN)	122	1.13 (0.87 – 1.46)	0.367		

Response to bezafibrate evaluated according to the Paris II criteria in the biochemical on-treatment cohort. Odds ratios are presented with 95% Confidence intervals. Abbreviations: ALP, Alkaline Phosphatase; ALT, Alanine Transferase; AMA, Antimitochondrial Antibodies; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; PBC, Primary Biliary Cholangitis; TB, total bilirubin.

Supplementary Figure 1---http://links.lww.com/AJG/D839

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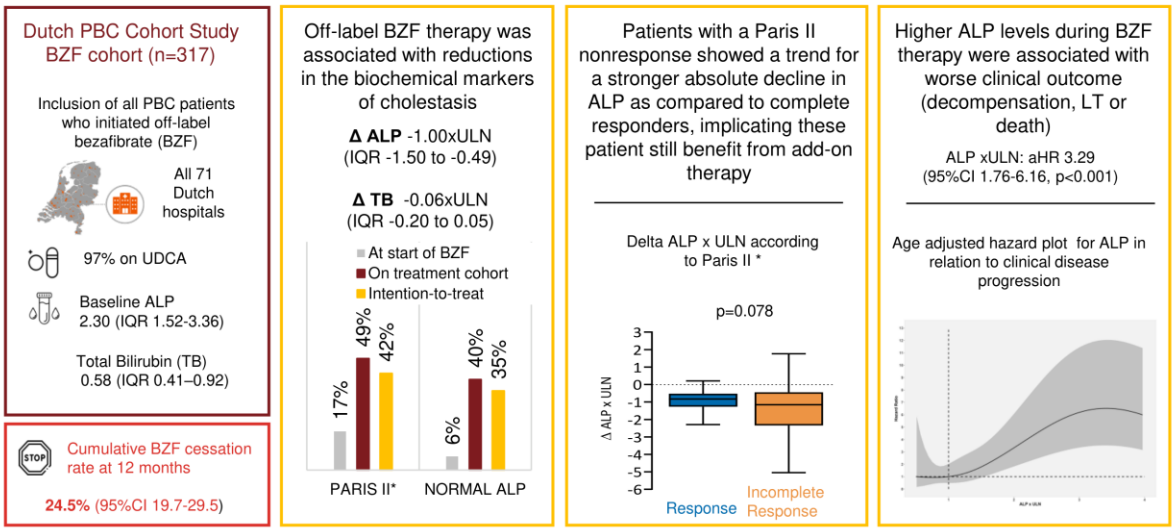
Effectiveness and tolerability of BZF in PBC

a nationwide real-world study



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