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AUTOIMMUNE, CHOLESTATIC, AND BILIARY DISEASES (S GORDON AND C BOWLUS, SECTION EDITORS)

The Role of Fibrates in Primary Biliary Cholangitis

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Abstract

Purpose of Review Ursodeoxycholic acid (UDCA) is recognized worldwide as the standard of care of primary biliary cholangitis (PBC). Obeticholic acid and fibrates have recently shown the potential to further improve the biochemical markers of PBC. The purpose of this review is to discuss more specifically the role of fibrates in PBC.

Recent Findings The BEZURSO trial (Phase 3 Study of Bezafibrate in Combination With Ursodeoxycholic Acid in Primary Biliary Cholangitis) is the first ever placebo-controlled trial of a fibrate in PBC. In this 24-month study, second-line use of bezafibrate in addition to continued UDCA resulted in a rate of complete biochemical response significantly higher than that achieved with placebo and UDCA. This effect was associated with a parallel improvement in symptoms and surrogate markers of fibrosis. Studies aiming to determine the effect of bezafibrate on long-term outcomes are still needed.

Summary Bezafibrate (probably fibrates in general) should be considered as a second-line therapy of PBC in patients with incomplete response to or intolerance of UDCA.

Keywords Primary biliary cholangitis (PBC) · Fibrates · Bezafibrate · Fenofibrate · Peroxisome proliferator-activated receptor (PPAR) · Clinical trial

Introduction

Primary biliary cholangitis (previously known as primary biliary cirrhosis, PBC) is a progressive cholestatic liver disease that, if untreated, ultimately leads towards cirrhosis, liver failure, and premature death [1]. PBC mainly affects middle-aged women and is characteristically associated with lesions of granulomatous, non-suppurative destructive cholangitis of small bile ducts, and detection in the serum of specific autoantibodies, mostly antimitochondrial antibodies. Inflammation and cholestasis, a defect in biliary secretion leading to the accumulation of toxic bile acids within the liver, are the main driving factors of the disease. To date, however, only anticholestatic drugs have shown the potential to treat PBC, where classical or new generation anti-inflammatory drugs have failed [2].

Ursodeoxycholic acid (UDCA), a natural hydrophilic tertiary bile acid with choleretic properties, was the first anticholestatic agent to demonstrate efficiency in a phase 3 trial [3]. Accumulated evidence regarding its long-term efficacy and safety has made UDCA the only first-line treatment still recommended in PBC [4]. However, it is now clear that not all patients respond equally to UDCA and that those, approximately a third, who do not reach an adequate biochemical response are at high risk of disease progression [5–7]. Furthermore, poor tolerance to UDCA (diarrhea, abdominal pain) is reported in up to 9% of patients [8]. Two other categories of anticholestatic drugs, namely, obeticholic acid (OCA) and fibrates, were shown to be of specific interest in these situations, either in combination with UDCA or as a monotherapy [9••, 10, 11••, 12]. The purpose of this article is to review the role of fibrates in the therapeutic management of PBC.

This article is part of the Topical Collection on *Autoimmune, Cholestatic, and Biliary Diseases*

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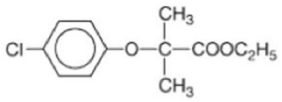
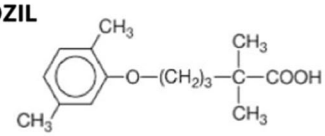
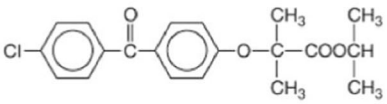
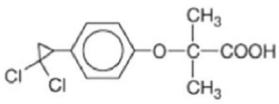
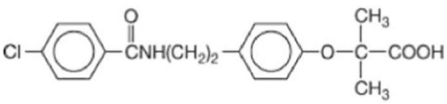
Fibrates: General Points

Fibrates are an old class of lipid-lowering agents, the first representative of which, clofibrate, was discovered in 1962 after that a marked fall in serum lipids was observed in a few French farmers intoxicated by phenyl-ethyl-acetic acid, a pesticide related to this family of compounds [13, 14]. While clofibrate was withdrawn in 2002, fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil are still available for use (Table 1). Fibrates increase fatty acid oxidation and accordingly are associated with a reduction in very low-density lipoprotein (VLDL) production and a parallel increase in high-density lipoprotein (HDL) concentrations in plasma [15]. This is associated with a reduction in serum levels of triglycerides, a (moderate) decline in LDL-cholesterol- and a (slight) increase in HDL-cholesterol levels. These outcomes, together with inherent anti-inflammatory effects of fibrates, contribute to reduce the development of atherosclerosis [16]. Fibrate derivatives exert their effects mainly through peroxisome proliferator-activator receptor (PPAR)-α agonistic properties. PPARs are members of the nuclear receptor family. They are distributed in three subtypes of transcription factors designated PPAR-α, PPAR-δ, and PPAR-γ, the former isoform of which is the most strongly expressed in the liver [17]. Fibrates are major PPAR-α ligands, but some compounds can exhibit additional affinities for PPAR-δ and PPAR-γ. This is particularly true for bezafibrate, which is a pan-PPAR agonist.

Once absorbed, fibrates are metabolized into active acid derivatives that are extensively bound to serum albumin for transport. These metabolites, which are not dependent on the cytochrome P450 system for clearance, are predominantly excreted in the urine, but fibrate derivatives are also detected

Table 1 Fibrates: main compounds and receptor binding affinities

LIGANDS	RECEPTORS		
	PPAR- α	PPAR- γ	PPAR- δ
CLOFIBRATE 	++++	+	-
GEMFIBROZIL 	++++	+	-
FENOFIBRATE 	++++	+	-
CIPROFIBRATE 	++++	+	-
BEZAFIBRATE 	++++	+++	+++

in the bile [18]. Most side effects related to fibrates concern potential toxicity on muscle, kidney, and liver. Rhabdomyolysis is a very rare event (combination with statin is classically discouraged), but muscle pain is a relatively common side effect. An increase in serum creatinine level is classically described. Its mechanism, which remains unclear, may involve renal hemodynamic changes or an increased release of creatinine by muscle [19]. This increase is typically mild and reversible after drug discontinuation, and no evidence for an increased risk of end-stage kidney disease has emerged from long-term studies [20–22]. Mild and transient elevation in transaminases is occasionally described in the first weeks of treatment, resolving even with continuation of the drug. Transaminase elevation above three times normal can occur in 3 to 5%. Real cases of acute hepatocellular or mixed, autoimmune-like hepatitis have anecdotally been reported [23, 24]. Finally, fibrates enhance cholesterol excretion into the bile and may consequently increase the risk of cholelithiasis [25].

Fibrates in PBC: Clinical Studies

First Reports

Clofibrate had been recognized in the 1960s for its ability to reduce the serum levels of alkaline phosphatase (ALP), but this specific property of fibrates remained largely ignored before being rediscovered in the 1990s [26, 27]. In 1999, Iwasaki et al. reported for the first time the results of an open-labeled study of bezafibrate in patients with PBC suggesting that this drug, either in combination with UDCA or alone, was safe in patients with this disease and able to decrease, or even normalize ALP and IgM levels, as well as to improve related symptoms [28]. Since then, numerous unblinded, small-sized controlled studies, first conducted in Japan and then afterwards in Western countries, have consistently confirmed these results either with bezafibrate or with fenofibrate [12, 29–37]. However, no data from placebo-controlled trials had been made available until 2017 (see next chapter on the Phase 3 study of Bezafibrate in Combination with Ursodeoxycholic Acid in Primary Biliary Cholangitis (BEZURSO) [38]. It is noteworthy that fibrates, when given as a monotherapy, have beneficial effects on ALP levels comparable in magnitude to those observed with UDCA [12]. Nowadays, it can be estimated that more than 800 patients have been exposed to bezafibrate or fenofibrate in phase 2 or 3 controlled studies. Meta-analyses of phase 2 trials have confirmed the beneficial effects of fibrates on major biochemical markers of the disease, including total bilirubin, ALP, gamma-glutamyltranspeptidase (GGT), alanine aminotransferase (ALT), and IgM levels, but have failed to detect a difference in mortality, liver-related morbidity, or adverse events because of the limited size and duration of studies [39–42]. Recent data have further endorsed that partial or complete relief of itch can be reached in a significant proportion of patients with this symptom [36, 43•]. For all the above-mentioned reasons, thousands of patients around the world, notably in Japan where bezafibrate is recommended as a second-line therapy [44], are currently being treated off-label with fibrates, most often in association with UDCA. However, potential concerns remain regarding the effects of fibrates on histological progression [45], and on long-term clinical outcomes and safety, especially long-term kidney toxicity and possible worsening of liver failure in advanced cirrhotic disease [34, 37, 46]. In addition, up to 22% of patients in retrospective studies were reported to have discontinued fibrates because of side effects, mainly myalgias and abdominal pain [37]. Finally, patients with advanced fibrosis and/or severe cholestasis were shown to be less responsive to fibrate add-on therapy and to be still at risk of disease progression [43•].

BEZURSO Trial

The BEZURSO trial (Phase 3 Study of Bezafibrate in Combination with Ursodeoxycholic Acid in Primary Biliary Cholangitis, NCT01654731) is the first and currently the only available placebo-controlled trial having addressed the efficacy and safety of a fibrate in patients with PBC [11••]. This non-industrial study randomly assigned 100 patients who had had an inadequate biochemical response to UDCA according to the Paris-2 criteria [47] (i.e., ALP or aspartate aminotransferase (AST) levels > 1.5 times the upper limit of normal range (xULN), or elevated total bilirubin) to receive bezafibrate at a daily dose of 400 mg (50 patients), or placebo (50 patients), in addition to continued treatment with UDCA for 24 months. Patients with decompensated cirrhosis or a total bilirubin level > 3 mg/dL and those with typical features of autoimmune hepatitis at baseline were non-eligible. The primary endpoint was the percentage of patients achieving a complete biochemical response as defined by normal levels of bilirubin, ALP, aminotransferases, albumin, and prothrombin index (a derived measure of prothrombin time) at 24 months.

The main results of the BEZURSO trial are summarized in Table 2. Half of the patients enrolled were at an advanced stage of the disease according to the histological stage (Ludwig's stage III–IV) or liver-stiffness measurement (> 9.6 kPa). Two patients (4%) in the bezafibrate group and 6 (12%) in the placebo group withdrew from the trial. The primary endpoint was achieved in 31% of the patients in the bezafibrate group and 0% in the placebo group ($p < 0.001$). At 24 months, normal levels of ALP were observed in 67% of the patients in the bezafibrate group and in 2% in the placebo group ($p < 0.001$). Changes in total bilirubin, ALP, GGT, and transaminases were consistent with the result of the primary endpoint, as were changes in pruritus, fatigue, and non-invasive markers of liver fibrosis

Table 2 Bezafibrate vs. placebo in addition to continued UDCA in patients with primary biliary cholangitis and an inadequate response to UDCA (main results of the BEZURSO trial)

Outcomes	Event rates		At 24 months		
	Bezafibrate	Placebo	ABI (95% CI)	RBI (95% CI)	NNT (95% CI)
Complete response	31%	0%	31% (18 to 45)	2900% (84 to 48,757)	3.5 (2.4 to 6.2)
Normal ALP level	67%	2%	65% (51 to 79)	2730% (304 to 19,733)	1.5 (1.3 to 2.0)
Paris-2 response	70%	10%	60% (44 to 76)	630% (182 to 1792)	1.7 (1.3 to 2.3)
	Median change from baseline		Difference in change from baseline (95% CI)		
Total bilirubin level	− 14%	18%	− 32% (− 47 to − 18)		
ALP level	− 60%	0%	− 59% (− 71 to − 47)		
GGT level	− 38%	7%	− 45% (− 65 to − 25)		
ALT level	− 36%	0%	− 35% (− 56 to − 14)		
AST level	− 8%	8%	− 14% (− 29 to 0)		
C4 bile acid level	− 70%	0%	− 90% (− 178 to − 2)		
Itch intensity score	− 100%	4%	− 95% (− 241 to 50)		
Worsened fatigue	8%	36%	− 28% (− 47 to − 8)		
Liver stiffness	− 15%	22%	− 36% (− 64 to − 8)		
ELF score	− 1%	3%	− 4% (− 8 to − 1)		

ABI absolute benefit increase, *RBI* relative benefit increase, *NNT* number needed to treat, *CI* confidence interval

(including liver stiffness and Enhanced Liver Fibrosis score). Levels of IgM decreased by 21% in the bezafibrate group and in 2% in the placebo group, but the difference did not reach the level of significance. Patients with portal hypertension or high ALP levels at baseline were less likely to achieve an adequate response to bezafibrate. Despite improvement in biochemistries, symptoms, and surrogate markers of fibrosis in the bezafibrate group, the number of liver-related complications did not differ between treatment arms (two in each arm), thus indicating the need for longer studies to determine the effect of bezafibrate on clinical outcomes.

Regarding safety and side effects, the incidence rates of serious and non-serious adverse events were similar between treatment groups. The percentage of patients with myalgia was higher in the bezafibrate group (20%) than in the placebo group (10%) although the difference was not significant. A 5% significant increase in serum creatinine level at 24 months was observed in the bezafibrate group as compared to the placebo group. One patient in the bezafibrate group, who had a history of diabetes and hypertension, had a decrease in the estimated glomerular filtration rate (eGFR) < 60 mL/min. Four patients (three in the bezafibrate group and one in the placebo group) had an increase in ALT levels > 5 times the upper limit of the normal range occurring within the first 6 months of trial. This led to a discontinuation of the active drug or placebo in three patients (two in the bezafibrate group and one in the placebo group). All cases 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). No increase in the risk of cholelithiasis was reported in the bezafibrate group.

Fibrates in PBC: Mechanisms of Action

Fibrates in PBC probably act through different mechanisms commonly shared across all members of the PPAR-α agonists' class (Fig. 1). Some mechanisms, however, may differ depending on the fibrate concerned, with special care to bezafibrate and its additional affinities for the other two PPAR isoforms, PPAR-δ and PPAR-γ. It is important to note that PPAR-α is highly and mostly expressed in hepatocytes, while PPAR-δ and PPAR-γ are present at a lower level in the liver, equally distributed in hepatocytes, cholangiocytes, Kupffer cells, and stellate cells for PPAR-δ, and mainly restricted to Kupffer cells for PPAR-γ [17, 48]. Three main mechanisms have been suggested to account for the beneficial effects of fibrates in PBC, including the reduction of bile acid overload in liver cells, the increase of phospholipid excretion into the bile, and the inhibition of pro-inflammatory agents within the liver and biliary tree [49•]. Together, these effects would contribute to reduce cholestasis and inflammation, the two driving forces of the disease. Fibrates, indeed, repress by approximately 60% the activity of cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid biosynthesis, thus reducing the production of bile acids in hepatocytes [50, 51]. The results of the BEZURSO trial support this finding with a 70% reduction in the serum level of C4 bile

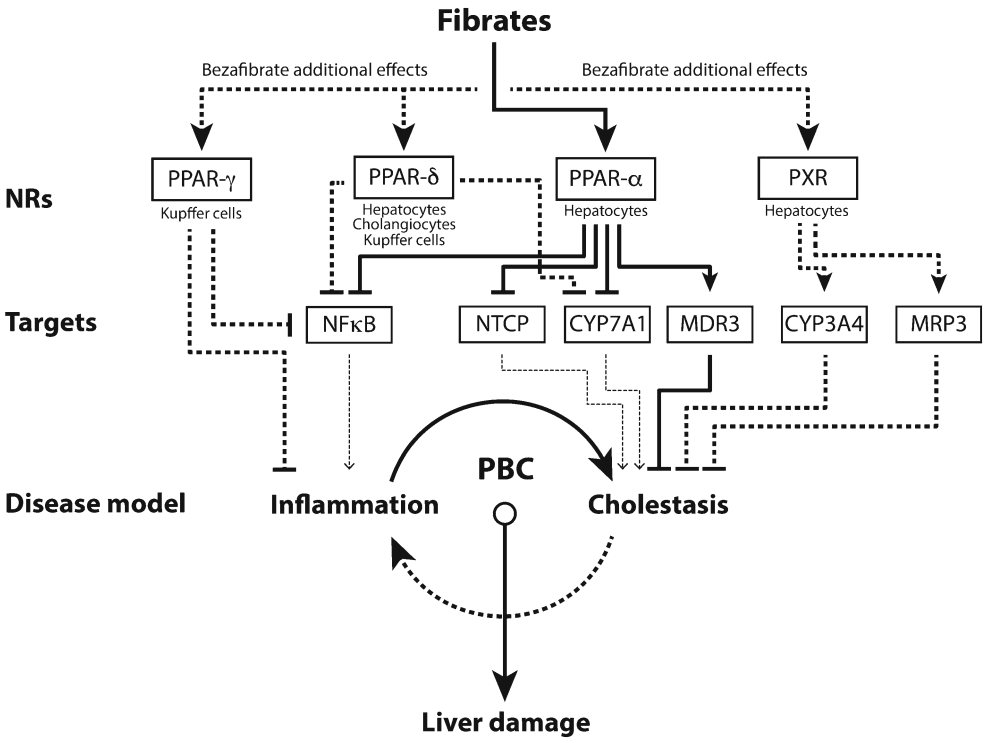


Fig. 1 Mechanisms through which fibrates are likely to exert beneficial effects in PBC. Thick plain lines illustrate PPAR-α-mediated effects. Thick doted lines illustrate additional effects of the pan-PPARs/PXR agonist bezafibrate. NR: nuclear receptor

acid precursor in the bezafibrate group as compared with no change in the placebo group (Table 2) [11••]. PPAR-α agonists also reduce the uptake of bile acids in hepatocytes by inhibiting the expression of the basolateral transporter sodium-taurocholate-cotransporting polypeptide [52]. There is also *in vitro* evidence that bezafibrate, in addition to its known effects on PPARs, might induce the genes targeted by the pregnane X receptor (PXR), notably those involved in bile acid detoxification as CYP3A4, thus potentially acting as a dual PPAR/PXR agonist [52]. PPAR-α agonists also enhance the biliary output of phospholipids through transcriptional induction of the phospholipid-flippase multidrug resistance protein 3 (MDR3) [53], the consequence of which is a better protection of the hepatocytes and cholangiocytes from membrane damage caused by accumulation of toxic bile acids. Fibrates have inherent anti-inflammatory effects [54]. These effects are mediated by PPAR-α transrepression of NF-κB signaling [55, 56]. Fibrates are therefore able to inhibit pro-inflammatory genes, and experimental models have shown that they can prevent liver inflammation [57]. As a result of its pan-PPAR properties, bezafibrate may further benefit from a broader range of therapeutic effects, including PPAR-δ- and PPAR-γ-specific anti-inflammatory actions [58, 59]. Seladelpar, a selective PPAR-δ agonist, has recently shown encouraging biochemical effects in patients with PBC [60], thus suggesting that the beneficial effects bezafibrate in PBC may partly be achieved through the activation of PPAR-δ.

Fibrates in PBC: Pending Questions

New steps are certainly needed to achieve a better understanding of the actual impact of fibrates on PBC. We have learned from the BEZURSO trial that 2 years of treatment with bezafibrate, in combination with UDCA, in patients with an incomplete response to the latter drug, improve the symptoms and major biochemical markers of the disease while preventing progression in liver stiffness [11••]. Whether these effects are able to translate into a lower rate of cirrhosis development and ultimately into a better prognosis remains unknown. Longer and larger placebo-controlled trials are needed to solve this question, but these studies seem unlikely to be developed in the future without the support of industry for an old class of genericable, inexpensive drugs. The Globe and UK-PBC risk models applied to the BEZURSO data anticipated a 58% (95% CI: 44–73%) and 51% (95% CI: 32–71%) reduction, respectively in the 10-year risk of death or liver transplantation in bezafibrate- vs. placebo-treated patients [11••]. Long-term side effects and safety of fibrates in PBC require prospective longitudinal studies with a special attention paid to kidney and to cirrhotic patients.

Other pending questions include the strategic positioning of fibrates with respect to OCA in the management of patients with PBC and incomplete response or intolerance to UDCA, as well as the potential synergy of fibrates with OCA in treating PBC. There is currently no available data providing direct comparison between these two drug regimens. Unlike OCA, bezafibrate is still off-label for use in PBC. However, the comparison of the

efficacy, safety, side-effect, and cost profiles of the two drugs, when taken together, is rather in favor of bezafibrate. Bezafibrate is furthermore the only one of the two therapies with a proven beneficial effect on PBC-validated surrogate markers of liver fibrosis. Fibrates, at last, are available in many countries in which OCA is not obtainable. Therefore, treating PBC with fibrates (preferably bezafibrate) as second-line use, either in addition to (inadequate response) or in substitution of (intolerance) UDCA, might reasonably be advocated, followed by OCA as a third-line option if available in case of incomplete response to or poor tolerance of fibrates. In patients with poor response to either dual (UDCA-OCA or UDCA-fibrates) therapy, pilot studies of triple (UDCA-OCA-fibrates) therapy are required to assess the potential synergy of OCA with fibrates. Finally, UDCA and fibrate combo therapy as first-line use in treatment-naive patients would deserve further consideration in future clinical trials.

Conclusions

We have now three major players in PBC treatment, namely, UDCA as a standard of care, followed by OCA and off-label use of bezafibrate as second-line options. Bezafibrate, or fibrates in general, has shown the potential to reduce symptoms and biochemical features of cholestasis in PBC, either in association with UDCA or alone. In patients with an incomplete response to UDCA, add-on therapy with bezafibrate further prevents progression in surrogate markers of fibrosis. Myalgia is a common but generally well-tolerated side effect of fibrates. Serum creatinine should be monitored during treatment, as should be transaminases more specifically within the first 6 months of treatment. Long-term outcomes of fibrates in patients with PBC require further evaluation.

Compliance with Ethical Standards

Conflicts of Interest The author reports receiving consulting fees from Intercept and Inventiva, grant support from Arrow Génériques (rAF 13.022_BeZUrSO_P100109_N°VAL 2013/2011-078-02), Intercept and French Ministry of Health(PHRC 2010 (BEZURSO; P100109), and fees for teaching from GlaxoSmithKline.

Human and Animal Rights Statement All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Informed Consent Informed consent was obtained in all participants in the BEZURSO trial.

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- •• Of major importance

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