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Fibrates as Adjuvant Therapy for Chronic Cholestatic Liver Disease: Its Time Has Come

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In 1993, the effects of fibrates in lowering serum alkaline phosphatase (ALP) was shown for bezafibrate (BF) to be the result of hepatic, rather than bone or intestinal, isoenzymes.¹ These initial observations led to the suggestion that fibrates might be beneficial for patients with an elevated ALP and cholestatic liver disease. Since then, several dozen case reports and pilot studies have demonstrated the efficacy of fibrates in reducing serum biomarkers of cholestasis and liver function abnormalities in patients with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) and incomplete responses to ursodeoxycholic acid (UDCA) monotherapy (Tables 1 and 2).

Yet, despite the growing number of these observational studies, the mechanism(s) by which fibrates reduce biochemical markers of cholestasis, and whether fibrate therapy improves survival in these disorders, remains unclear. The study of Honda et al.² in the current issue of *Hepatology* seeks to address the first of these issues. Their findings confirm that adjunct therapy with BF reduces ALP levels in adult patients with PBC who experienced an incomplete response to UDCA, and they further suggest that BF acts as a dual peroxisome proliferator-activated receptor (PPAR) and pregnane X receptor (PXR) agonist. These results are of interest, because fibrates are attracting increased attention as adjunct therapy for chronic cholestatic liver diseases. Nevertheless, this study raises several questions regarding the appropriate patient population for this therapy, the dosage of UDCA, as well as which fibrate to use, because BF is not U.S. Food and Drug Administration (FDA) approved.

BF is a fibric-acid derivative and clinically used as a hypolipidemic agent to lower serum triglyceride (TG) levels, primarily through PPAR activation. Often, it has been referred to as a “PPAR- α ” agonist; however, BF activates all three isoforms of human PPAR, specifically PPAR- α , PPAR- δ , and PPAR- γ , at similar concentrations (i.e., 50, 20, and 60 μ M, respectively).³ Thus, the term “pan-PPAR” agonist is a more-accurate descriptive. In the United States, fenofibrate (FF) and gemfibrozil, PPAR- α -selective agonists, are the fibric-acid derivatives that are FDA approved and clinically used for treatment of hyperlipidemia. Recently, pilot studies in patients with PBC refractory to UDCA monotherapy demonstrated that FF also reduced biochemical features and symptoms of cholestasis.^{4–9}

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Honda et al. currently report the effects and assess the mechanisms of adjunct BF as an anticholestatic agent in 19 adults with early-stage PBC and compare their response to UDCA (600 and 10–13 mg/kg/day) monotherapy. Three months of combination therapy with BF (400 mg/day) led to a significant reduction in serum biliary enzymes, cholesterol, and TGs as well as modulation of PPAR- α and PXR target genes, including an up-regulation of the adenosine-triphosphate-binding cassette subfamily G transporters, ABCG5 and ABCG8. Although BF improved biochemical tests, the dose of UDCA was only 10–13 mg/kg/day and thus would be considered subtherapeutic. A recent study proposes that candidates requiring new therapeutic approaches should be limited to patients with ALP >1.5 times the upper limit of normal only after incompletely responding to optimal doses of UDCA of 13–15 mg/kg/day.¹⁰ Based on these criteria, it is possible that an increase of UDCA to 15 mg/kg/day might have provided adequate therapy in this particular patient cohort, particularly because the histological stage of fibrosis was only 1–2.

Nevertheless, combination therapy improved biochemical manifestations of cholestasis in these patients. To explain possible mechanisms by which BF works, Honda et al. treated DPX2 cells, a derivative of the HepG2 cell line, which expresses PXR, with BF and compared the response to cells treated with rifampicin, a PXR agonist. High-dose BF (200 μ M) activated PXR; however, GW4064 (3–30 μ M), a farnesoid X receptor (FXR) agonist, also increased PXR activity similar to, if not greater than, BF, suggesting FXR involvement in PXR regulation. It is noteworthy that BF at 10 μ M, which corresponds to plasma concentration of 400 mg/day in these patients, did not activate PXR. Thus, the conclusion that BF is a dual PPAR and PXR agonist, which is based on cytochrome P450 (CYP)3A4 messenger RNA (mRNA) and activity data at supratherapeutic doses, requires more study. Moreover, the possibility of coordinated regulation of PXR by PPAR isoforms as well as by FXR and the liver X receptor (LXR) should also be considered, especially because PXR can be activated by a variety of substrates, including troglitazone,¹¹ a PPAR- γ agonist.¹² Reduction of TG levels are an expected action of fibrates, as well as the down-regulation of CYP7A1 and CYP27A1 expression. Interestingly, Nakajima et al. showed that low-dose BF reduced TGs¹³ and cholesterol¹⁴ by a PPAR- α -independent mechanism, supporting the notion that BF-mediated actions are concentration dependent and may partially occur by coordinated actions of PPAR (i.e. PPAR- δ and/or PPAR- γ , FXR, and LXR). More evidence of coordinated actions by these nuclear receptors is the finding that up-regulation of ABCG5 mRNA in human liver by BF was PPAR α independent and occurred by LXR.¹⁵ Although Honda et al.'s study begins to shed light on the molecular mechanisms behind BF's clinical effects, more work is clearly needed.

Lastly, the reduced serum concentrations of chenodeoxycholic acid and deoxycholic acid and, to a lesser extent, cholic acid and lithocholic acid, are attributed to an inhibitory effect of BF on *de novo* bile-acid synthesis; however, one could argue that these effects are the result of increased glucuronidation by up-regulation of UDP-glucuronosyltransferase subfamily 1A and 2B isoenzymes, known targets of PPAR- α and LXR- α agonists.¹⁶ Further investigation into the effects of BF on cholesterol synthesis and bile-acid metabolism would help to clarify this issue.

Although questions of whether BF directly coregulates PXR and PPARs remain, the benefits of using a drug, such as fibrates with multiple targets that regulate bile-transporter expression and inflammation, for the treatment of cholestasis seem promising. Larger, multicenter, prospective, double-blind studies of fibrates plus UDCA are clearly needed in patients with PBC and PSC, as also recently noted by others.¹⁷ Fibrates are well tolerated clinically and there is more than sufficient evidence, including the present study of Honda et al., to demonstrate therapeutic efficacy for patients with PBC and, possibly, PSC. Their modes of action within the hepatocyte are undoubtedly multifactorial and are likely to account for the positive effects on liver function.

Abbreviations

ABC	adenosine-triphosphate-binding cassette
ALP	alkaline phosphatase
BF	bezafibrate
CYP	cytochrome P450
FDA	U.S. Food and Drug Administration
FF	fenofibrate
FXR	farnesoid X receptor
LXR	liver X receptor
mRNA	messenger RNA
PBC	primary biliary cirrhosis
PPAR	peroxisome proliferator-activated receptor
PSC	primary sclerosing cholangitis
PXR	pregnane X receptor
TGs	triglycerides
UDCA	ursodeoxycholic acid

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Summary of Prospective Clinical Studies Testing the Efficacy of Bezafibrate as Adjunct Therapy in Patients With Chronic Cholestatic Liver Disease Not Responding Adequately to UDCA Monotherapy

Table 1

Author (Reference)	Daily BF Dose	Daily UDCA Dose	UDCA (n), UDCA+BF (n) (Diagnosis)	Bezafibrate Safety	Therapeutic Outcomes of Adjunct Bezafibrate
Nakai et al. ¹⁸	400 mg	600 mg	13, 10 (PBC)	No side effects	↓ ALP, γ-GTP, and IgM
Kanda et al. ¹⁹	400 mg	600 mg	11, 11 (PBC)	Polydipsia (n = 1), resolved w/o therapy interruption	↓ ALP and pruritis
Ohmoto et al. ^{20,21}	400 mg	600 mg	11, 6 (PBC) ²⁰ 10, 10 (PBC) ²¹	Not reported	↓ serum markers of hepatic fibrosis ²⁰ ; ↓ ALP, γ-GTP, ALT, IgM, pruritis, and fatigue ²¹
Kita et al. ²²	400 mg	600 mg	17, 22 (PBC), 4, 6 (PSC)	No side effects	↓ ALP, γ-GTP, ALT, IgM, and pruritis (in PSC)
Hazzan and Tur-Kaspa ²³	400 mg	900–1,500 mg	8, 8 (PBC)	Not reported	↓ ALP and γ-GTP
Takeuchi et al. ²⁴	400 mg	600 mg (12–15 mg/kg)	22, 15 (PBC)	No side effects	↓ ALP, IgM, cholesterol, and TGs
Iwasaki et al. ²⁵	400 mg	600 mg	Study 1: 25, 20* Study 2: 10, 12 (PBC)	Study 1: abdominal pain (n = 2), resolved; Study 2: ↑ serum creatine phosphokinase, resolved w/o therapy interruption	↓ ALP, γ-GTP, and IgM (no significant difference between treatment in Study 1); ↓ cholesterol and TGs
Nagasaka et al. ²⁶	5 mg/kg	None	0, 3 (PFIC-1)	No side effects	↓ pruritis, total bilirubin and bile acids, ALT, AST, and TGs

Abbreviation: γ-GTP, gamma-glutamyl transferase; IgM, immunoglobulin M; w/o, without; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PFIC-1, progressive familial intrahepatic cholestasis type 1.

* Study 1 compared UDCA monotherapy to BF monotherapy.

Summary of Prospective Clinical Studies Testing the Efficacy of Fenofibrate as Adjunct Therapy in Patients With Chronic Cholestatic Liver Disease Not Responding Adequately to UDCA Monotherapy

Table 2

Author (Reference)	Daily FF dose	Daily UDCA dose	UDCA (n), UDCA+ FF (n) (diagnosis)	Fenofibrate Safety	Therapeutic Outcomes of Adjunct Fenofibrate
Ohira et al. ⁷	150–200 mg	600–900 mg	7, 7 (PBC)	No side effects	↓ ALP, γ-GTP, IgM, pruritis, and fatigue
Dohmen et al. ⁴	< 60 kg: 100 mg; > 60 kg: 150 mg	600 mg	9, 9 (PBC)	No side effects	↓ ALP, γ-GTP, IgM, and AMA
Levy et al. ⁶	160 mg	13–15 mg/kg	20, 20 (PBC)	Heartburn (n = 2): study withdrawal	↓ ALP, IgM, AST, TGs, and serum cytokines
Han et al. ⁵	200 mg	13–15 mg/kg	22, 22 (PBC)	Pruritis (n = 1): interruption, symptoms resolved, then FF restarted	↓ ALP, γ-GTP, ALT, AST, cholesterol, and TGs
Liberopoulos et al. ⁹	200 mg	600 mg	4, 6 (PBC)	No side effects	↓ ALP, γ-GTP, ALT, cholesterol and TGs

Abbreviations: γ-GTP, gamma-glutamyl transferase; IgM, immunoglobulin M; AMA, antimitochondrial antibodies; AST, aspartate aminotransferase; ALT, alanine aminotransferase.