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Statins, Fibrates, and Other Peroxisome Proliferator-Activated Receptor Agonists for the Treatment of Cholestatic Liver Diseases

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Abstract: Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune cholestatic liver diseases that commonly result in the need for liver transplantation. The lack of an effective therapy for PSC remains a largely unmet need in hepatology, and although the majority of patients with PBC will have an adequate response to ursodeoxycholic acid and/or obeticholic acid, there is a need for treatment among patients who do not respond completely to these therapies. Investigations of statins, fibrates, and other peroxisome proliferator-activated receptor (PPAR) agonists suggest clinical benefit with some of these agents. Statins have recently been suggested to improve outcomes in patients with PSC but have not demonstrated benefit in patients with PBC, whereas fibrates and newer PPAR agonists appear to improve biochemical markers linked to better clinical outcomes in patients with PBC. Further research is needed to fully understand the clinical efficacy of these agents in the treatment of PBC and PSC.

Cholestatic liver diseases include various disease states that result in the disruption of bile flow out of the hepatobiliary system. These disease states include primary biliary cholangitis (PBC, previously known as primary biliary cirrhosis) and primary sclerosing cholangitis (PSC). Although both are inflammatory autoimmune diseases that target biliary epithelial cells and commonly progress to cirrhosis if left untreated, they affect different population groups and stem from different underlying disease pathologies. PBC primarily affects women over the age of 50 years, whereas PSC is most common in young men with inflammatory bowel disease (IBD). PSC can be further subdivided into small duct and large duct PSC, with large duct PSC frequently progressing to liver failure and small duct PSC generally following a more benign course. For treatment purposes, the key difference between PBC and PSC is the response to ursodeoxycholic acid (UDCA). The majority of PBC patients respond to UDCA, with improved clinical outcomes and laboratory

values.[1] However, between 39% and 67% of patients have an incomplete response, for which obeticholic acid (Ocaliva, Intercept Pharmaceuticals) has been approved.[2] Conversely, there are currently no medications that have been proven to be effective for the treatment of PSC. Due to the need for additional therapeutic options for treatment of these diseases, investigations have turned to drugs that alter liver metabolic processes, including statins, fibrates, and other peroxisome proliferator-activated receptor (PPAR) agonists.

The rationale for using statins to treat PBC and PSC stems from effects on both inflammation and cholestasis. Statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, have been suggested to have potential in preventing cirrhosis by limiting the production of geranylgeranyl-pyrophosphate, an activator of the contractile and nitric oxide inhibitor proteins Rho kinase and RhoA. In rodents, RhoA was significantly elevated in animals with cirrhosis, and levels of nitric oxide synthase increased in rats with bile duct ligation when treated with atorvastatin.[3] Statins also possess anti-inflammatory properties, although through an unknown mechanism. Current hypotheses include decreasing interferon γ–induced major histocompatibility complex class II (MHC-II) expression on endothelial cells, with atorvastatin appearing to decrease MHC-II expression the most.[4] Further, the effects of statins on bile acid metabolism, transport, and detoxification through PPARα and pregnane X receptor/sterol X receptor agonist activity could improve cholestasis.[5]

PPAR agonists are nuclear hormone receptors that bind fatty acids and fatty acid–derived molecules to regulate many metabolic pathways. Three PPAR isotypes, α, β/δ, and γ, are found in humans and differ in distribution, ligand activation, and metabolic regulatory pathways. PPARα is the primary receptor expressed in hepatocytes and enhances fatty acid and triglyceride metabolism, whereas PPARγ is essential for adipocyte differentiation and is the target of insulin-sensitizing thiazolidinediones. PPARβ/δ and γ are involved in energy use.[6] These receptors are targeted by numerous drugs, including fenofibrate (α), bezafibrate (α, β/δ, γ), pemafibrate (α), elafibranor (α, β/δ; Genfit), and seladelpar (β/δ; CymaBay Therapeutics).[7]

A potential role of PPAR agonists in cholestatic disease was supported by the finding that biliary epithelial cells in patients with PBC have decreased expression of PPARγ due to inhibition of PPARγ gene expression and increased degradation caused by elevated levels of the type 1 T helper cell–type cytokine.[8] In addition, a lack of PPARα, which can regulate bile acid synthesis, results in enhanced liver damage from bile acid exposure.[9] The effects of PPAR activation on cholestatic liver diseases appear to be mediated by several mechanisms. Activation of PPARα upregulates *MDR3*, reduces interleukin-1–induced C-reactive protein expression on hepatocytes, and inhibits nuclear factor kappa beta activity by inducing expression of IκBα. PPARδ activation can activate PPARγ coactivator 1α, which increases farnesoid X receptor activity, the target of obeticholic acid. Fibrates can also upregulate bile acid efflux transporters and the intestinal bile acid transporter. In murine studies, PPARγ agonists decreased inflammation in biliary epithelial cells.[10,11]

Primary Biliary Cholangitis

Statins in Primary Biliary Cholangitis

Interest in statins as a treatment option for PBC began in 1993 when 2 patients with PBC who were treated with pravastatin had decreased cholic acid and chenodeoxycholic acid levels and improved serum alkaline phosphatase (ALP) levels, and liver biopsy showed improvement in 1 patient and inhibited progression in the other. The patients also reported improvement in pruritus and xanthomas.[12] Subsequently, Cash and colleagues investigated the effects of simvastatin on PBC in a randomized trial of 21 patients treated with 20 mg of the drug or placebo for 1 year (Table 1).[13] The primary focus was determining the changes in endothelial function, antioxidant status, and vascular compliance, which was measured with pulse wave analysis and velocity. There was no difference in measured outcomes between the treatment groups.[13] Stanca and colleagues[4] found no beneficial effect of atorvastatin on ALP or γ-glutamyltransferase (GGT) levels in their retrospective study of 15 patients. Prospective studies by Stojakovic and colleagues found ALP levels increased with statin treatment, but no changes were reported in the levels of C-reactive protein, GGT, alanine aminotransferase (ALT), or aspartate aminotransferase (AST).[14,15] Conversely, a nonrandomized prospective study found beneficial biochemical effects of statins in PBC, including improvements in levels of ALP, GGT, and serum immunoglobulin M, but no change in levels of AST or ALT.[16]

Discrepancies in results from studies investigating statin effects may be explained by variation in anti-inflammatory or vascular effects of different statins and differences in the patient populations, including responsiveness to UDCA and stages of disease, the latter of which is of particular importance because endothelial dysfunction and inflammation may not be responsive to statins in late-stage disease.[17]

Fibrates in Primary Biliary Cholangitis

Decreased PPAR activity plays a role in PBC pathogenesis, and PPAR agonists serve as a new potential therapeutic

Table 1. Statins in Primary Biliary Cholangitis

Reference	Year	Drug	Study Design	Sample Size	Results	
					ALP Levels	Other Endpoints
Cash et al[13]	2013	Simvastatin	Randomized, single-blind, placebo-controlled trial	21	NS	No significant change in ALT, AST, GGT, total bilirubin, or CRP levels
Stanca et al[4]	2008	Atorvastatin	Retrospective cohort	15	NS	No significant change in ALT, AST, GGT, or total bilirubin levels
Stojakovic et al[14]	2007	Atorvastatin	Nonrandomized, single-blind trial	18	↑	No significant change in ALT, AST, GGT, total bilirubin, CRP, or IgM levels
Ritzel et al[16]	2002	Simvastatin	Nonrandomized, prospective trial	6	↓	Significant decrease in GGT and serum IgM levels. No significant change in AST or ALT levels

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, γ-glutamyltransferase; Ig, immunoglobulin; NS, not significant.

target. Since the 1999 pilot study by Iwasaki and colleagues suggested that there may be benefit to bezafibrate treatment in PBC, many studies have shown favorable effects, leading bezafibrate to being recognized as second-line therapy for PBC in Japan and Europe (Table 2).[18,19] These studies primarily involve observational prospective and retrospective cohort studies with some recent randomized, controlled trials.

The most significant study supporting the use of bezafibrate for PBC was a double-blind, randomized, controlled study of 100 PBC patients treated with either 400 mg of bezafibrate per day or placebo for 2 years.[20] Patients were required to have an inadequate biochemical response to UDCA, and outcome measures included biochemical response, liver stiffness, and histologic improvement at the end of treatment. Complete normalization of ALP and aminotransferase levels was achieved in 31% of patients receiving bezafibrate compared to 0% of patients receiving placebo. Liver stiffness decreased by 15% in the treatment group and increased by 22% in the placebo group. Liver biopsy histology results were available for 28 patients before and after treatment but did not differ significantly. These results are similar to biochemical improvements observed in other open-label trials.[21-23] An added benefit of bezafibrate, and likely other PPAR agonists, has been improvement in pruritus in patients with PBC who have moderate to severe itch.[24]

Evidence on the efficacy of other fibrates, including fenofibrate and pemafibrate, is limited. Cheung and colleagues retrospectively analyzed 120 patients treated with fenofibrate for a median of 11 months.[25] ALP levels decreased significantly in patients treated with fenofibrate compared to patients receiving only UDCA therapy. Treatment success measured by the Toronto criteria for biochemical improvement (ALP ≤1.67 × the upper limit of normal [ULN]) was met by 41% of patients treated with fenofibrate compared to 7% in the UDCA group. ALT and AST levels also improved in patients treated with fenofibrate. A smaller retrospective study found similar effects but observed no improvement in the UK-PBC risk score.[26] Similarly, a meta-analysis of trials with fenofibrate found biochemical benefits, with no significant difference in pruritus when compared to UDCA.[27] Data on pemafibrate are limited to a small retrospective cohort of 7 patients with PBC treated with 0.1 mg of pemafibrate twice daily for 3 months. ALP levels significantly decreased 3 months following the addition of pemafibrate therapy to UDCA treatment; the decrease in GGT levels was nonsignificant.[28]

Despite the data on the potential efficacy of bezafibrate and fenofibrate in PBC, concerns about safety and adverse effects, including hepatotoxicity and myositis, persist. Elevations in serum creatinine are a well-documented effect of PPAR agonists and appear to be related to either increased production of creatinine rather than a change in glomerular filtration rate or downregulation of prostaglandins in the kidney causing decreased vasodilation with no effect on renal tubular function.[29] In 50 patients treated with bezafibrate in a study by Corpechot and colleagues, creatinine increased by 5% in the treatment group and decreased by 3% in the placebo group, and 1 bezafibrate-treated patient developed stage 3 chronic kidney disease.[20] In addition, 20% of patients in the treatment group experienced myalgias compared to 10% in the placebo group, with 1 patient in the bezafibrate group developing rhabdomyolysis,

Table 2. Fibrates and Other PPAR Agonists in Primary Biliary Cholangitis

Reference	Year	Drug(s)	Study Design	Sample Size	Results	
					ALP Levels	Other Endpoints
Honda et al[44]	2019	Bezafibrate	Retrospective cohort	118	↓	Significant decrease in total bilirubin, albumin, GGT, ALT, and AST levels, and in GLOBE and UK-PBC scores
Corpechot et al[20]	2018	Bezafibrate	Randomized, double-blind, placebo-controlled trial	100	↓	Significant decrease in liver stiffness and GGT levels but no change in liver histology
Hosonuma et al[23]	2015	Bezafibrate	Randomized, open-label, controlled trial	27	↓	Significant decrease in Mayo risk score, but not in AST, total bilirubin, or albumin levels
Iwasaki et al[22]	2008	Bezafibrate	Randomized, open-label, controlled trial	67	↓	Significant decrease in GGT, ALT, and IgM levels
Itakura et al[21]	2004	Bezafibrate	Randomized, open-label, crossover trial	16	↓	Significant decrease in GGT levels
Jörn et al[30]	2019	Elafibranor	Randomized, double-blind, placebo-controlled trial	45	↓	Significant decrease in GGT, IgM, and C4 levels
Duan et al[45]	2018	Fenofibrate	Retrospective cohort	39	↓	No significant change in GLOBE or UK-PBC scores
Cheung et al[25]	2016	Fenofibrate	Retrospective cohort	120	↓	Significant decrease in percent of patients meeting Toronto criteria and increase in transplant-free survival, but no change in INR, AST, ALT, total bilirubin, or albumin levels
Hegade et al[26]	2016	Fenofibrate	Retrospective cohort	23	↓	No significant change in UK-PBC scores
Han et al[46]	2012	Fenofibrate	Nonrandomized, open-label trial	22	↓	Significant decrease in GGT levels but not in ALT or AST levels
Levy et al[47]	2011	Fenofibrate	Nonrandomized, open-label trial	20	↓	Significant decrease in AST and IgM levels
Liberopoulos et al[48]	2010	Fenofibrate	Randomized, open-label, controlled trial	10	↓	Significant decrease in ALT and GGT levels
Walker et al[49]	2009	Fenofibrate	Retrospective cohort	16	↓	Significant decrease in IgM levels
Ohira et al[50]	2002	Fenofibrate	Retrospective cohort	7	NS	No significant change in GGT or IgM levels
Chung et al[51]	2019	Fenofibrate and bezafibrate	Retrospective cohort	87	↓	Significant decrease in GGT levels, cirrhosis, and GLOBE and UK-PBC scores
Dohmen et al[52]	2013	Fenofibrate and bezafibrate	Nonrandomized, open-label trial	14	↓	Significant decrease in GGT and IgM levels
Joshita et al[28]	2019	Pemafibrate	Retrospective cohort	7	↓	No significant change in GGT, ALT, or AST levels
Bowlus et al[32]	2018	Seladelpar	Randomized, open-label trial	119	↓	Significant decrease in ALT levels
Jones et al[31]	2017	Seladelpar	Randomized, double-blind, placebo-controlled trial	41	↓	Significant increase in ALT levels and reduction in C4 levels

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7α-Hydroxy-4-cholesten-3-one; GGT, γ-glutamyltransferase; Ig, immunoglobulin; INR, international normalized ratio; NS, not significant; PPAR, peroxisome proliferator-activated receptor.

which resolved with discontinuation. Skeletal muscle and creatinine side effects from fibrates may be linked, as the increase in creatinine may be partially responsible for the hypercreatinemia.[29] Four patients in the study (3 receiving bezafibrate and 1 receiving placebo) developed ALT levels 5 times the ULN. Levels returned to normal within 3 months of drug discontinuation, with 2 patients requiring glucocorticoids.[20]

Novel Peroxisome Proliferator-Activated Receptor Agonists in Primary Biliary Cholangitis

Novel PPAR agonists being developed for use in PBC are elafibranor, a PPARα/δ agonist, and seladelpar, a PPARδ agonist. In a phase 2b, 12-week trial of PBC patients with inadequate response to UDCA treated with placebo, 80 mg of elafibranor daily, or 120 mg of elafibranor daily, there was a significant decrease in ALP levels for patients receiving either dose of the drug. ALP levels decreased by 48% and 41% in patients treated with 80 mg and 120 mg, respectively, and increased by 3% in patients given placebo.[7,30] In an initial phase 2 study of seladelpar testing 50 mg and 200 mg daily—doses previously shown to be well-tolerated for other indications—seladelpar reduced ALP levels; however, 3 patients treated with seladelpar experienced ALT increases greater than 5 times the ULN, which resolved 2 to 4 weeks after drug discontinuation.[31] In a subsequent phase 2 study of seladelpar in doses of 5 mg, 10 mg, or 5 mg followed by 10 mg for 12 weeks, ALT elevations were not observed and, in fact, transaminases decreased by 31% and 33% in the 5-mg-to-10-mg and 10-mg groups, respectively.[32] In addition, ALP levels decreased by 47% and 46%, respectively, with 59% and 71% of patients achieving an ALP level below 1.67 times the ULN. Despite the evidence of biochemical improvement, further development of seladelpar has been placed on hold due to atypical histologic findings, including interface hepatitis with or without biliary injury, in a clinical trial of doses ranging from 10 to 50 mg daily for nonalcoholic steatohepatitis. Importantly, there was no biochemical evidence of hepatotoxicity in these patients, and it remains unclear if this is a unique property of seladelpar or a class effect.

Primary Sclerosing Cholangitis

Unlike PBC, PSC does not currently have validated medical treatment options. UDCA can improve liver biochemistries in patients with PSC but does not improve long-term outcomes (Table 3).[33] While antibiotics such as vancomycin and metronidazole have shown promising results in case series and small clinical trials, neither have enough supporting data to be considered validated treatment options at this time, leaving liver transplantation as the only treatment option.[34,35] This gap in therapy and the potential efficacy of treatments in PBC have prompted exploration of statins and fibrates as treatments for PSC.

Statins in Primary Sclerosing Cholangitis

The evidence of potential efficacy of statins in PSC is limited to a single retrospective cohort study of Swedish PSC patients in national databases.[36] The cohort included 2194 patients but was limited to patients with comorbid IBD. Use of statins correlated with a significant decrease in all-cause mortality, death or liver transplantation, and adverse liver events. However, when including only patients who received at least 2 statin dispensations, only death or liver transplantation remained significant. Other limitations of this study included the absence of the specified type of statin used and exclusion of PSC patients without IBD. In addition, confounders such as advanced liver disease, which may have bias against the use of statins, were not accounted for.

Fibrates in Primary Sclerosing Cholangitis

Although the literature on fibrate use in PSC is relatively greater than that on statin use, it remains limited. Interest developed after the publication of case reports from Japan of decreased ALP and GGT levels with bezafibrate treatment.[37,38] These case reports were followed by several small prospective studies. The first included 7 PSC patients treated with 400 mg of bezafibrate twice daily, 6 of whom were receiving UDCA prior to and during the study.[39] In 3 patients, bezafibrate was effective in improving levels of ALP, GGT, AST, and ALT after 3 and 6 months of treatment. There was no notable improvement among the other 4 patients, and 2 cases of worsening liver biochemistries were noted after 6 months. After 26 months of treatment, patients who were not responding at 6 months remained nonresponsive. In a second study, 11 PSC patients, of whom 8 were taking UDCA, were treated with 200 mg of bezafibrate twice daily for 12 weeks.[40] At the end of the 12-week period, all patients had improvement in GGT and ALP levels, while only 7 patients had improvement in ALT and AST levels. Efficacy, defined as improvement in ALP, GGT, AST, and ALT levels, was reached by 64% of study participants. In a retrospective review of 25 PSC patients (including 11 in the previously mentioned studies) in Japan treated with 200 mg of bezafibrate twice daily, 75% of Child-Pugh class A PSC patients responded to bezafibrate compared to 0% with Child-Pugh class B.[41] Factors not associated with response included age at onset of illness, disease duration, or concomitant IBD. Patients in whom bezafibrate was added to UDCA due to inadequate response to UDCA had lower rates of response. If patients did not respond within 3 months,

Table 3. Statins and PPAR Agonists in Primary Sclerosing Cholangitis

Reference	Year	Drug(s)	Study Design	Sample Size	Results	
					ALP Levels	Other Endpoints
Mizuno et al[40]	2015	Bezafibrate	Nonrandomized, open-label trial	15	↓	Significant decrease in ALT levels
Mizuno et al[39]	2010	Bezafibrate	Retrospective cohort	7	↓	Decrease in ALT, GGT, and AST levels
Stokkeland et al[36]	2019	Statins	Retrospective cohort	404	ND	Significant decrease in liver-related death or transplantation
Lemoinne et al[42]	2018	Fibrates	Retrospective cohort	20	↓	Significant decrease in levels of ALT but not in GGT, AST, total bilirubin, albumin, prothrombin time, IgG, IgM, or platelet count
Abdalla et al[43]	2019	Fenofibrate	Nonrandomized, open-label trial	8	↓	Significant decrease in levels of ALT but not in AST, total bilirubin, prothrombin time, or albumin

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; Ig, immunoglobulin; ND, not determined; PPAR, peroxisome proliferator-activated receptor.

they were unlikely to respond with a longer duration of therapy.

Experience with either bezafibrate or fenofibrate for PSC outside of Japan is limited. Fourteen patients in Paris were treated with 200 mg per day of fenofibrate, and 6 patients in Barcelona were treated with 400 mg per day of bezafibrate.[42] All patients had received treatment with UDCA for at least 1 year before study participation with an incomplete response, defined as ALP values remaining greater than 1.5 times the ULN. Treatment duration varied, with a median of 1.56 years. Five patients discontinued treatment with either bezafibrate or fenofibrate due to worsening of liver symptoms, including 2 cases of acute cholangitis and 3 of worsening cholestasis. After 3 months of treatment, 8 patients had ALP values less than 1.5 times the ULN, with 2 patients having values less than 1 times the ULN. However, no significant changes were observed in ALT or AST levels. No difference was noted between patients receiving fenofibrate compared to bezafibrate. Of note, pruritus improved in 7 of the 8 patients reporting the symptom before treatment. Outside of this report is a single prospective, open-label study of 160 mg of fenofibrate in 8 PSC patients.[43] After 6 months of treatment, ALP values decreased significantly, with a median decrease of 47%, which subsequently increased within 9 weeks of fenofibrate discontinuation. There was also a significant decrease in ALT levels, but no significant change in levels of AST, albumin, prothrombin time, or total bilirubin. Investigators also evaluated liver elastography in 4 patients before and after treatment and found a mild, nonsignificant decrease.

Conclusion

Despite progress in developing therapies for PBC and PSC, unmet needs remain. Repurposing old drugs (statins and fibrates) or drugs that never made it to market for their original indication (small-molecule PPAR agonists) for new indications such as PBC and PSC is an appealing strategy that is not dependent upon the expense of initial target discovery and drug development. While there may be benefits from statin therapy, studies in PBC have not shown promising results. Further studies of statins, and particularly PPAR agonists, in PSC through well-conducted clinical trials are needed to determine if these approaches have clinical benefit before they can be recommended for use in clinical practice. In contrast, data on fibrates and PPAR agonists for PBC are becoming well established and entering clinical practice, with newer agents likely to be available in the near future. However, understanding their unique safety profiles in cholestasis as well as in advanced liver disease will be critical to optimizing their use.

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