Effects of pemafibrate on primary biliary cholangitis with dyslipidemia

Mayumi Yamaguchi¹ | Takeharu Asano² | Takahiro Arisaka³ | Hirosato Mashima² | Atsushi Irisawa³ | Masaya Tamano¹

¹Department of Gastroenterology, Dokkyo Medical University Saitama Medical Center, Minami-Koshigaya, Koshigaya, Japan
²Department of Gastroenterology, Jichi Medical University Saitama Medical Center, Amanuma, Omiya-ku, Japan
³Department of Gastroenterology, Dokkyo Medical University, Kitakobayashi, Mibu, Japan

Correspondence
Masaya Tamano, Department of Gastroenterology, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minami-Koshigaya, Koshigaya, Saitama 343-8555, Japan.
Email: mstamano@dokkyomed.ac.jp

Abstract

Aim: The purpose of this study was to examine the effect of pemafibrate (PEM) in primary biliary cholangitis (PBC) patients with dyslipidemia.

Methods: Patients who were diagnosed with PBC between June 2018 and December 31, 2020 were included in the study if they also had dyslipidemia and their alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) levels remained above the normal range despite taking 600 mg/day ursodeoxycholic acid (UDCA) for at least 6 months. Patients who were treated with UDCA alone were administered PEM as an add-on (PEM-add group), and patients who were treated with UDCA and bezafibrate (BEZ) for at least 6 months were given PEM instead of BEZ (PEM-switch group). Clinical parameters were compared in all patients, and the levels of ALP, GGT, the estimated glomerular filtration rate (eGFR), and creatinine (Cr) were compared between the PEM-add and PEM-switch groups. Improvement in cholangitis was also evaluated.

Results: In the PEM-add group, both ALP and GGT improved in 40 of 46 patients (87.0%). In the PEM-switch group, both ALP and GGT improved in 15 of 29 patients (51.7%). In the PEM-switch group, however, significant improvement was seen in eGFR and Cr.

Conclusions: Administration of PEM is effective in PBC patients with dyslipidemia who are refractory to UDCA monotherapy. In patients using both UDCA and BEZ, there was an advantage in switching to PEM if they had renal damage; however, improvement of ALP and GGT occurred in about 50%.

Keywords
bezafibrate, dyslipidemia, pemafibrate, primary biliary cholangitis, ursodeoxycholic acid

Abbreviations: ALP, alkaline phosphatase; BEZ, bezafibrate; Cr, creatinine; eGFR, estimated glomerular filtration rate; FEN, fenofibrate; GGT, gamma-glutamyl transferase; PBC, primary biliary cholangitis; PEM, pemafibrate; PPAR, proliferator-activated receptor.
INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by cholestasis and chronic inflammation, and it can progress to cirrhosis. There are currently no treatment options that result in complete remission, and ursodeoxycholic acid (UDCA) is considered the first-line therapy. UDCA is effective in over 80% of PBC patients, because it results in not only serologic improvements, but it also prolongs survival and time to liver transplant. Patients who respond poorly to UDCA are treated with fibrates. Fibrates include bezafibrate (BEZ) and fenofibrate (FEN); however, only BEZ is used for liver diseases in Japan because FEN is contraindicated in this patient population.

Pemafibrate (PEM) is a novel drug for the treatment of dyslipidemia known to have an anti-inflammatory effect on hepatocytes; it binds to peroxisome proliferator-activated receptor α (PPARα) and regulates the expression of target genes to reduce the concentration of plasma triglycerides (TGs) and increase high-density lipoprotein (HDL) cholesterol levels. Pemafibrate is a novel fibrate that was recently developed, and it is a highly potent ligand of PPARα that effectively reduces TGs. The purpose of this study was to examine the effect of PEM in PBC patients with dyslipidemia.

METHODS

This study was reviewed and approved by the Ethics Committee of each institution (approval IDs: 2099, S21-014, and R-45-4); it conformed to the ethical guidelines of the 2008 Declaration of Helsinki. This was a retrospective, observational study conducted after posting information about the study on the hospital’s website.

Patients

Patients who were diagnosed with PBC between June 2018 and December 31, 2020 were included in the study if they also had dyslipidemia and their alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) levels remained above the normal range despite taking 600 mg/day UDCA for at least 6 months. The diagnosis of PBC and the definition of symptomatic patients were according to the Japan Society of Hepatology guidelines. Dyslipidemia was defined as having either a fasting low-density lipoprotein (LDL) cholesterol level ≥140 mg/dl or a TG level ≥150 mg/dl. Patients were excluded if only their LDL level was elevated and if they had not undergone any prior treatment for dyslipidemia. Patients were excluded if they had hepatitis B, hepatitis C, malignant disease, cholelithiasis, obstructive jaundice, or severe liver dysfunction.

Patients who were treated with UDCA alone were administered PEM (0.2 mg/day) as an add-on (PEM-add group), and patients who were treated with UDCA and BEZ (400 mg/day) for at least 6 months were administered PEM (0.2 mg/day) instead of BEZ (PEM-switch group). The switch from BEZ to PEM was made based on the decision of a primary physician after obtaining the patient’s informed consent. Similar to PEG-added group, patients with normal ALP and GGT were excluded in PEG-switched group. The following clinical parameters were compared in all patients, and the levels of ALP, GGT, and the estimated glomerular filtration rate (eGFR) were compared between the PEM-add and PEM-switch groups.

Clinical parameters

Clinical parameters before and 3 months after the administration of PEM were compared. Clinical parameters included the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, γ-glutamyltransferase (GGT), total bilirubin (T-Bil), serum albumin (Alb), eGFR, creatinine (Cr), total cholesterol (T-cho), TGs, HDL cholesterol (HDL), LDL cholesterol, white blood cells, hemoglobin (Hb), platelets (Plts), and prothrombin activity (PT%).

Defining improvements in cholangitis

Changes in the ALP level were evaluated based on the criteria developed by Parés et al. and improvements in ALP were defined as having a normal ALP level or achieving ≥40% improvement compared to pre-PEM (Barcelona criteria). Changes in the GGT level were evaluated based on the criteria developed by Azemoto et al., and improvements in GGT were defined as having a normal GGT level or reduction rate of GGT above the upper limit of normal more than 70% (Ehime criteria). Cholangitis was considered to have improved if both ALP and GGT improvement criteria were met. In this study, histological diagnosis of the liver was not performed, so elevations in ALP and GGT are considered cholangitis for convenience. This is a unique evaluation in this study.

Patients who did not meet these criteria were considered to have no improvements in cholangitis.

Statistical analysis

Continuous data for biochemical examinations are expressed as means ± standard deviation (SD). The paired Wilcoxon test and chi-squared test were used to test for differences in each parameter before and after the start of treatment. The non-paired Wilcoxon test was used to test for differences in each parameter between PEM-add group and PEM-switch group at the time of administration. Values of p < 0.05 were considered significant.

RESULTS

Figure 1 shows the patient selection process. A total of 318 patients were diagnosed with PBC during the study period. Twelve of 318 patients were on watchful waiting without any treatment. A total of
Eighty-five patients were treated with the combination of UDCA and bezafibrate (BEZ), and 29 of them underwent the switch from BEZ to PEM (PEM-switch group). Figure 1 shows the changes in eGFR before and 3 months after the administration of PEM in the PEM-add and PEM-switch groups. Prior to the administration of PEM, eGFR was lower in the PEM-switch group (68.2 ± 23.1 ml/min) that was previously administered BEZ compared with the PEM-add group (72.5 ± 20.5 ml/min); however, the difference was not significant (Table 1: p = 0.5495). Three months after the administration of PEM, there was an increasing trend in eGFR to 73.9 ± 19.0 ml/min (p = 0.1015) in the PEM-add group and a significant increase to 73.2 ± 21.8 ml/min (p = 0.0034) in the PEM-switch group.

Figure 4 shows the changes in ALT, ALP, GGT, eGFR, or Cr (p = 0.2786, p = 0.3090, p = 0.1223, p = 0.5495, p = 0.3549). T-Bil, Alb, Plts, and PT% were within the normal ranges in both groups, and none of the patients had clinical disease progression.

Table 2 shows the clinical parameters pre- and 3 months post-PEM administration in the PEM-add group. The levels of ALP and GGT were significantly decreased, from 445.8 ± 236.5 to 269.0 ± 121.4 U/L (p < 0.0001) and from 99.5 ± 113.3 to 55.8 ± 72.7 U/L (p < 0.0001), respectively. As seen in Figure 2, ALP and the GGT are improved in most patients of PEM-add group 3 months after the administration of PEM.

Although the level of AST did not decrease significantly (p = 0.1982), there was a significant decrease in the levels of ALT (p = 0.035). The levels of T-cho, TG, and LDL were significantly decreased (p < 0.0001, p < 0.0001, p < 0.0001), and the levels of Alb and Plts were significantly increased (p = 0.0033, p < 0.0001).

Table 3 shows the clinical parameters pre- and 3 months post-PEM administration in the PEM-switch group. The levels of GGT were significantly decreased, from 137.5 ± 169.0 U/L (p = 0.0360). The levels of ALP were decreased from 462.1 ± 460.1 to 398.1 ± 348.7 U/L, but not significantly (p = 0.1546). As seen in Figure 3, there were a few cases in the PEM-switch group that showed gradual increases in ALP and GGT levels 3 months after the administration of PEM. The TG level was significantly decreased (p = 0.0117), but the T-cho and LDL levels were not decreased significantly (p = 0.0871, p = 0.0635).

Table 4 summarizes improvements in the levels of ALP and GGT and cholangitis in the PEM-add and PEM-switch groups. The ALP level improved in 91.3% (42/46) and 65.5% (19/29) of patients in the PEM-add and PEM-switch groups, respectively. Similarly, the GGT level improved in 93.5% (43/46) and 55.2% (16/29) of patients in the PEM-add and PEM-switch groups, respectively. Lastly, cholangitis improved in 87.0% (40/46) and 51.7% (15/29) of patients in the PEM-add and PEM-switch groups, respectively.
Acid cytotoxicity.

The bile acid ratio (PC/BA ratio) is a particularly critical indicator of bile phospholipids. In other words, the phosphatidylcholine/hydrophobic dissolution of mixed micelles that bile acid forms with cholesterol and epithelium, bile pH control by bicarbonate ion, and the formation and from hydrophobic acid by the presence of mucin that covers the component of bile and is highly cytotoxic. The bile duct is protected against cholestasis of unknown cause. Hydrophobic bile acid is the main cause of biliary cirrhosis; however, it is not yet approved in Japan, and there are issues with regards to its cost-benefit, since UDCA is much more expensive than UDCA. Moreover, OCA has been associated with a risk of gallstone formation.

DISCUSSION

Primary biliary cholangitis is characterized by the presence of chronic cholestasis of unknown cause. Hydrophobic bile acid is the main component of bile and is highly cytotoxic. The bile duct is protected from hydrophobic acid by the presence of mucin that covers the epithelium, bile pH control by bicarbonate ion, and the formation and dissolution of mixed micelles that bile acid forms with cholesterol and phospholipids. In other words, the phosphatidylcholine/hydrophobic bile acid ratio (PC/BA ratio) is a particularly critical indicator of bile acid cytotoxicity.10,11

Prolonged cholestasis results in a decreased PC/BA ratio, leading to separation of hydrophobic bile acid into bile.12 This causes damage to the epithelial cells of the bile duct, and this may lead to the development of chronic, non-suppurative, destructive cholangitis.

Ursodeoxycholic acid is hydrophilic bile acid that has a cellular protective effect. Ursodeoxycholic acid normally represents a small percentage of the bile acid pool; however, when administered orally in a continuous manner, it effectively replaces hydrophobic bile acid and improves the PC/BA ratio to minimize damage to the epithelial cells of the bile duct.12 In European and American guidelines, a daily UDCA dose of 13.15 mg/kg is recommended; however, in Japan, a daily dose of 600 mg is recommended irrespective of body weight. Many studies suggest that the effect of UDCA should be evaluated between 6 months and 1 year after the start of the treatment.8,9 Thus, in the present study, only PBC patients who had been on 600 mg/day UDCA for at least 6 months and still had elevated levels of ALT and GGT above the normal range were included.

Obeticholic acid (OCA) is currently being developed as an alternative treatment for PBC patients who do not respond to UDCA. Obeticholic acid binds to farnesoid X receptor, to which bile acid acts as a ligand, and reduces overexposure to bile acid. Obeticholic acid was shown to be effective in the Phase 3 Study of OCA in Patients with Primary Biliary Cirrhosis (POISE), and it was subsequently approved for use in 2016 by the Food and Drug Administration in the United States. However, it is not yet approved in Japan, and there are issues with regards to its cost-benefit, since OCA is much more expensive than UDCA. Moreover, OCA has been associated with a risk of gallstone formation.14

### Table 1

|                        | PEM-add group (n = 46) | PEM-switch group (n = 29) | p value |
|------------------------|------------------------|--------------------------|---------|
| Age (y)                | 64.0 ± 11.9 (21–87)    | 64.2 ± 11.6 (42–82)      | 0.9479  |
| Symptomatic/Asymptomatic | 12/34              | 16/13                    | 0.2390  |
| Sex (male/female)      | 2/44                  | 4/25                     | 0.7090  |
| AST (U/L)              | 32.7 ± 26.5 (8–162)    | 44.0 ± 41.0 (20–237)      | 0.143   |
| ALT (U/L)              | 32.8 ± 42.1 (8–278)    | 35.2 ± 34.6 (12–184)      | 0.2786  |
| ALP (U/L)              | 445.8 ± 236.5 (144–1575) | 462.1 ± 460.1 (107–2676) | 0.3090  |
| GGT (U/L)              | 99.5 ± 113.3 (14–682)  | 163.7 ± 241.3 (12–1276)  | 0.1223  |
| T-Bil (mg/dl)          | 0.8 ± 0.4 (0.4–2.3)    | 0.8 ± 0.4 (0.3–1.8)       | 0.5034  |
| Alb (g/dl)             | 4.1 ± 0.4 (3.0–4.9)    | 4.1 ± 0.46 (2.8–5.0)      | 0.6336  |
| eGFR (ml/min)          | 72.5 ± 20.5 (18.7–138.5) | 68.2 ± 23.1 (24.4–133.6) | 0.5495  |
| Cr (mg/dl)             | 0.69 ± 0.24 (0.43–2.07) | 0.78 ± 0.30 (0.45–1.60)  | 0.3549  |
| T-cho (mg/dl)          | 217.7 ± 40.8 (126–304) | 223.4 ± 65.7 (111–427)    | 0.8654  |
| TG (mg/dl)             | 152.9 ± 82.2 (47–426)  | 105.7 ± 56.0 (47–290)     | 0.0054  |
| HDL (mg/dl)            | 65.6 ± 18.7 (26–112)   | 74.5 ± 43.6 (32–197)      | 0.9334  |
| LDL (mg/dl)            | 125.9 ± 34.7 (56–197)  | 119.0 ± 31.4 (64–178)     | 0.4267  |
| WBC (10³/μl)           | 5.7 ± 1.8 (2.1–13.6)   | 5.7 ± 1.5 (3.5–9.3)       | 0.8575  |
| Hb (g/dl)              | 13.3 ± 1.4 (10.2–17.4) | 12.1 ± 1.6 (9.2–15.3)     | 0.0010  |
| Plts (10³/μl)          | 22.7 ± 5.9 (8.4–33.3)  | 26.1 ± 9.9 (7.7–47.8)     | 0.1305  |
| PT (%)                 | 109.3 ± 22.2 (35.6–155.8) | 105.6 ± 19.2 (52.3–144.8) | 0.4723  |

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; Hb, hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Plts, platelets; PT%, prothrombin time %; T-Bil, total bilirubin; T-cho, total cholesterol; TG, triglycerides; WBC, white blood cells.
TABLE 2 Changes in the biochemical parameters from before to 3 months after the administration of pemafibrate (PEM) in the PEM-add group (n = 46)

| Parameter        | Pre-PEM     | 3 months post-PEM | p value |
|------------------|-------------|-------------------|---------|
| AST (U/L)        | 32.7 ± 26.5 | 32.8 ± 23.9       | 0.1982  |
| ALT (U/L)        | 32.8 ± 42.1 | 25.8 ± 18.5       | 0.0305  |
| ALP (U/L)        | 445.8 ± 236.5 | 269.0 ± 121.4 | <0.0001 |
| GGT (U/L)        | 99.5 ± 113.3 | 55.8 ± 72.7       | <0.0001 |
| T-Bil (mg/dl)    | 0.8 ± 0.4   | 0.7 ± 0.4         | <0.0001 |
| Alb (g/dl)       | 4.1 ± 0.4   | 4.3 ± 0.5         | 0.0033  |
| eGFR (ml/min)    | 72.5 ± 20.5 | 73.9 ± 19.0       | 0.1015  |
| Cr (mg/dl)       | 0.69 ± 0.24 | 0.64 ± 0.21       | 0.0540  |
| T-cho (mg/dl)    | 217.7 ± 40.8 | 190.5 ± 35.5     | <0.0001 |
| TG (mg/dl)       | 152.9 ± 82.2 | 91.3 ± 41.6       | <0.0001 |
| HDL (mg/dl)      | 65.6 ± 18.7 | 71.0 ± 15.0       | 0.0081  |
| LDL (mg/dl)      | 125.9 ± 34.7 | 108.0 ± 30.5     | <0.0001 |
| WBC (10^3/µl)    | 5.7 ± 1.8   | 5.6 ± 1.9         | 0.1318  |
| Hb (g/dl)        | 133.4 ± 1.4 | 130.0 ± 1.4       | 0.0007  |
| Plts (10^5/µl)   | 22.7 ± 5.9  | 24.9 ± 6.9        | <0.0001 |
| PT (%)           | 109.3 ± 22.2 | 108.0 ± 25.1      | 0.1694  |

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; Hb, hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Plts, platelets; PT%, prothrombin time %; T-Bil, total bilirubin; T-cho, total cholesterol; TG, triglycerides; WBC, white blood cells.

TABLE 3 Changes in the biochemical parameters from before to 3 months after the administration of pemafibrate (PEM) in the PEM-switch group (n = 29)

| Parameter        | Pre-PEM     | 3 months post-PEM | p value |
|------------------|-------------|-------------------|---------|
| AST (U/L)        | 44.0 ± 41.0 | 42.0 ± 31.0       | 0.4545  |
| ALT (U/L)        | 35.2 ± 34.6 | 35.3 ± 31.4       | 0.2581  |
| ALP (U/L)        | 462.1 ± 460.1 | 398.1 ± 348.7   | 0.1546  |
| GGT (U/L)        | 163.7 ± 241.3 | 137.5 ± 169.0   | 0.0360  |
| T-Bil (mg/dl)    | 0.8 ± 0.4   | 0.8 ± 0.5         | 0.1101  |
| Alb (g/dl)       | 4.1 ± 0.46  | 4.0 ± 0.6         | 0.3187  |
| eGFR (ml/min)    | 68.2 ± 23.1 | 73.2 ± 21.8       | 0.0034  |
| Cr (mg/dl)       | 0.78 ± 0.30 | 0.72 ± 0.29       | 0.0041  |
| T-cho (mg/dl)    | 223.4 ± 65.7 | 211.2 ± 60.5     | 0.0871  |
| TG (mg/dl)       | 105.7 ± 56.0 | 90.5 ± 45.3       | 0.0117  |
| HDL (mg/dl)      | 74.5 ± 43.6 | 74.4 ± 33.0       | 0.1571  |
| LDL (mg/dl)      | 119.0 ± 31.4 | 112.3 ± 35.7     | 0.0635  |
| WBC (10^3/µl)    | 5.7 ± 1.5   | 5.5 ± 1.6         | 0.1214  |
| Hb (g/dl)        | 12.1 ± 1.6  | 12.2 ± 1.6        | 0.2124  |
| Plts (10^5/µl)   | 26.1 ± 9.9  | 26.3 ± 10.5       | 0.4195  |
| PT (%)           | 105.6 ± 19.2 | 102.8 ± 20.6      | 0.0111  |

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; Hb, hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Plts, platelets; PT%, prothrombin time %; T-Bil, total bilirubin; T-cho, total cholesterol; TG, triglycerides; WBC, white blood cells.

FIGURE 2 Changes in alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels in the PEM-add group. The levels of ALP and GGT decrease significantly, 445.8 ± 236.5 to 269.0 ± 121.4 U/L (p < 0.0001) and from 99.5 ± 113.3 to 55.8 ± 72.7 U/L (p < 0.0001)
Bezafibrate is one of the fibrates that activate PPARα, which is a nuclear receptor protein expressed in organs such as the liver. Fibrates block the activation of NF-κB via activation of PPARα, lower the expression of IL-1 and IL-6, and may inhibit inflammatory and immune responses.15,16 Fibrates also facilitate the expression of multidrug resistance gene 3 (mdr3), a transport element in the ATP-dependent bile secretion system that exists in bile duct membranes.17 Increases in mdr3 protein facilitate the secretion of biliary phospholipids, facilitate the inactivation of hydrophobic bile acids by micellization, and protect hepatic cells and bile duct epithelium.17,18

Thus, UDCA reduces the denominator of the PC/BA ratio, whereas BEZ increases the numerator, and the epithelial damage of the bile duct in PBC patients is improved.

In PBC patients who are resistant to UDCA monotherapy, the combination of UDCA and BEZ was shown to be effective in improving liver function, as well as histologically defined liver fibrosis.16,19-21 A retrospective cohort study also demonstrated that the combination of UDCA and BEZ reduced the need for liver transplant and the liver-related mortality rate.4

Similarly, the combination of UDCA with FEN, which is another PPARα agonist, was also shown to have a major impact on improving
TABLE 4 Improvement of alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and cholangitis in the pefibrate (PEM)-add group and the PEM-switch group

|                   | PEM-add group | PEM-switch group |
|-------------------|---------------|-----------------|
| ALP               | 42/46 (91.3%) | 19/29 (65.5%)   |
| GGT               | 43/46 (93.5%) | 16/29 (55.2%)   |
| Cholangitis       | 40/46 (87.0%) | 15/29 (51.7%)   |

Abbreviations: ALP, Alkaline phosphatase; GGT, gamma-glutamyltransferase.

Though the levels of ALP and GGT decreased in patients who were switched from BEZ to PEM, there was no significant change in ALP. In the present study, the ALP and GGT levels of patients in the PEM-switch group showed an effect similar to that of BEZ.

This could be attributed to the fact that PEM is a selective PPARα agonist, whereas BEZ is a pan-PPAR agonist. Bezafibrate activates both PPARα and PPARδ, and seladelpar, a selective PPARδ agonist, was shown to improve cholestasis in PBC patients. Thus, the effect of BEZ on cholestasis is elicited by its action on both PPARα and PPARδ. On the other hand, PEM does not act on PPARδ, despite having a greater effect on PPARα activation than BEZ.

Recently, a dual peroxisome proliferator-activated receptor (PPAR) alpha/gamma agonist, aleglitazar, has been reported in a meta-analysis to increase the incidence of hypoglycemia, gastrointestinal hemorrhage, bone fracture, heart failure, cardiovascular death, and malignancy in patients with type 2 diabetes mellitus. However, it has been reported that with long-term administration of PEM in patients with type 2 diabetes, there was no difference in adverse events compared with administration of placebo. To examine the effect of PEM administration on cardiovascular events, the PROMINENT study is currently underway in 24 countries.

In an animal model, dual PPAR alpha/gamma activation was also reported to cause cardiac dysfunction via inhibition of the SIRT-PGC1 alpha axis. At the same time, in a basic study using PEM, it was confirmed in a cardiac ischemia reperfusion injury model that the size of infarcts shrank with the administration of PEM compared with an untreated group. As to the reason, decreased oxidative stress, decreased myocardial apoptosis, decreased mitochondrial dysfunction, and inhibition of NF-κB signaling from PEM were shown to be implicated.

As seen in Table 5, the PEM-effective group within the PEM-switch group had 15 patients, nearly the same as the 14 patients in the PEM-resistant group. A comparison of baseline parameters showed significant differences in AST, GGT, T-cho, and HDL.
Therefore, it may be that an effect from PEM is also obtained when the effect of previously administered BEZ was larger. Since significant differences were not observed in T-Bil, Alb, Plt, or PT% between the two groups, it was conjectured that there were no differences due to reserve liver function.

As shown in Table 2, T-cho, TG, and LDL were significantly decreased and HDL was significantly increased in the PEM-add group. This is thought to show the efficacy of PEM in patients who have not yet been treated with fibrates. At the same time, whereas significant changes were seen in Alb and Plt, they were only slight changes within the reference range, and the clinical implications are unclear. As shown in Table 3, a significant decrease in TG was also seen in the PEM-switch group, suggesting that the action of decreasing TG is more powerful with PEM than with BEZ.

Unlike other fibrates, PEM can be combined with statins and does not affect kidney function. It is well known that BEZ is excreted by the kidneys and can reduce renal function. In addition, since FEN is excreted by the kidneys, attention is necessary when it is given to patients with renal dysfunction. On the other hand, PEM is excreted by the liver. The switch to PEM from BEZ or FEN has recently been reported to recover renal function in the treatment for PBC.

Thus, it has the potential to become one of the treatment options for PBC. In the present study, the switch from BEZ to PEM led to a significant improvement in eGFR and Cr. The combination of UDCA and BEZ is a common treatment for PBC. In patients in whom high ALP and GGT levels and renal damage are seen with combination BEZ, there is thought to be an advantage in switching from BEZ to PEM. When switching to PEM, however, it should be fully understood that it will be ineffective in about half of patients.

It is important to note, however, that PEM is contraindicated in patients with severe liver dysfunction and gallstones, since it acts on liver metabolism and bile secretion, and that insurance coverage for its use in Japan is limited to those with dyslipidemia. Insurance coverage must be respected in PBC patients, as in others.

In conclusion, the administration of PEM in PBC patients with dyslipidemia who responded poorly to UDCA was shown to be effective in improving ALP and GGT levels. In particular, PEM may be considered for second-line treatment if treatment with UDCA alone for over 6 months is ineffective. Since PEM is a selective PPAR-α modulator, it does not act on PPAR5. The switch from BEZ may worsen cholangitis, so the decision to switch should be made carefully in some limited cases, such as those with kidney dysfunction.

---

**TABLE 5** Comparison between the pemafibrate (PEM)-effective group and the PEM-resistant group within the PEM-switch group at baseline

|                      | PEM-effective group (n = 15) | PEM-resistant group (n = 14) | p value |
|----------------------|------------------------------|-----------------------------|---------|
| Age (y)              | 62.8 ± 12.2 (45–79)          | 65.5 ± 11.2 (42–82)         | 0.5263  |
| Symptomatic/Asymptomatic | 9/6                      | 7/7                        | 0.2390  |
| Sex (male/female)    | 1/14                        | 3/11                       | 0.7090  |
| AST (U/L)            | 31.1 ± 9.3 (21–53)          | 57.9 ± 56.0 (20–237)       | 0.0422  |
| ALT (U/L)            | 26.9 ± 14.2 (12–70)         | 46.4 ± 45.9 (12–184)       | 0.0731  |
| ALP (U/L)            | 362.5 ± 188.1 (1.7–757)     | 568.7 ± 627.8 (135–2676)   | 0.2948  |
| GGT (U/L)            | 95.5 ± 135.5 (12–564)       | 236.8 ± 342.5 (44–1276)    | 0.0028  |
| T-Bil (mg/dl)        | 0.8 ± 0.4 (0.3–1.7)         | 0.7 ± 0.4 (0.3–1.8)        | 0.3708  |
| Alb (g/dl)           | 4.2 ± 0.7 (2.8–5.0)         | 4.0 ± 0.5 (2.8–4.6)        | 0.5735  |
| eGFR (ml/min)        | 62.9 ± 20.5 (24.4–89.6)     | 74.0 ± 25.1 (24.6–133.6)   | 0.3593  |
| Cr (mg/dl)           | 0.81 ± 0.32 (0.49–1.59)     | 0.74 ± 0.29 (0.45–1.60)    | 0.4847  |
| T-cho (mg/dl)        | 192.9 ± 42.6 (111–264)      | 256.2 ± 71.6 (180–427)     | 0.0272  |
| TG (mg/dl)           | 109.7 ± 68.1 (49–290)       | 101.4 ± 41.6 (47–181)      | 0.9652  |
| HDL (mg/dl)          | 50.7 ± 12.8 (32–64)         | 42.4 ± 50.6 (46–197)       | 0.0426  |
| LDL (mg/dl)          | 114.3 ± 27.9 (64–162)       | 123.9 ± 35.2 (67–178)      | 0.4320  |
| WBC (10^3/μl)        | 5.5 ± 1.5 (3.5–9.3)         | 5.9 ± 1.6 (3.5–9.3)        | 0.2947  |
| Hb (g/dl)            | 11.8 ± 1.0 (9.7–13.4)       | 12.5 ± 1.9 (9.2–15.3)      | 0.1622  |
| Plts (10^3/μl)       | 24.6 ± 8.4 (7.7–35.7)       | 22.7 ± 11.4 (11.8–47.8)    | 0.6625  |
| PT (%)               | 100.4 ± 20.0 (52.3–126.8)   | 114.7 ± 17.7 (91.0–144.8)  | 0.2791  |

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; Hb, hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Plts, platelets; PT%, prothrombin time %; T-Bil, total bilirubin; T-cho, total cholesterol; TG, triglycerides; WBC, white blood cells.
ACKNOWLEDGMENTS
The authors would like to thank the institutions that participated in the
working group and everyone who helped collect clinical data. This
work did not receive any grants from funding agencies in the public,
commercial, or not-for-profit sectors.

CONFLICT OF INTEREST
All authors declare no conflict of interest.

REFERENCES
1. European Association for the Study of the Liver. EASL Clinical
Practice Guidelines: the diagnosis and management of patients with
primary biliary cholangitis. J Hepatol. 2017 Jul;67:145–72.
2. Guidelines for the management of primary biliary cirrhosis: the
Intractable Hepatobiliary Disease Study Group supported by the
Ministry of Health, Labour and Welfare of Japan. Hepatol Res. 2014
Jan;44(Suppl 1):71–90.
3. Hazan R, Tur-Kaspa R. Bezafibrate treatment of primary biliary
cirrhosis following incomplete response to ursodeoxycholic acid. J
Clin Gastroenterol. 2010 May-Jun;44:371–3.
4. Honda A, Tanaka A, Kaneko T, Komori A, Abe M, Inao M, et al.
Bezafibrate improves GLOBE and UK-PBC scores and long-term
outcomes in patients with primary biliary cholangitis. Hepatology.
2019 Dec;70:2035–46.
5. Ishibashi S, Yamashita S, Arai H, Araki E, Yokote K, Suganami H, et al.
Effects of K-877, a novel selective PPARα modulator (SPPARα), in
dyslipidemic patients: a randomized, double blind, active- and
placebo-controlled, phase 2 trial. Atherosclerosis. 2016
Jun;249:36–43.
6. Fruchart JC. Selective peroxisome proliferator-activated receptor α
modulators (SPPARMα): the next generation of peroxisome
proliferator-activated receptor α-agonists. Cardiovasc Diabetol.
2013 May 31;12:82.
7. Ishibashi S, Arai H, Yokote K, Araki E, Suganami H, Yamashita S.
Efficacy and safety of pemafibrate (K-877), a selective peroxisome
proliferator-activated receptor α modulator, in patients with dysli-
pidemia: results from a 24-week, randomized, double blind, active-
controlled, phase 3 trial. J Clin Lipidol. 2018 Jan-Feb;12:173–84.
8. Parés A, Caballería L, Rodrés J. Excellent long-term survival in pa-
tients with primary biliary cirrhosis and biochemical response to
ursodeoxycholic acid. Gastroenterology. 2006 Mar;130:715–20.
9. Azemoto N, Kumagai T, Abe M, Konishi I, Matsuura B, Hiaya Y, et al.
Biochemical response to ursodeoxycholic acid predicts long-term
outcome in Japanese patients with primary biliary cirrhosis. Hepa-
tol Res. 2011 Apr;41:310–17.
10. Maillet de Buy Wenniger LJ, Hohenester S, Maroni L, Van Vliet SJ,
Oude Elferink RP, Beuers U. The cholangiocyte glycoalkyl stabilizes
the “Biliary HCO3 Umbrella”: an integrated line of defense against
toxic bile acids. Dig Dis. 2013;33:397–407.
11. Hofmann AF. Bile acid secretion, bile flow and biliary lipid secretion
in humans. Hepatology. 1990 Sep;12:175–22S. Discussion S-55.
12. Ishizaki K, Imada T, Tsurufuji M. Hepatoprotective bile acid “ursode-
oxycholic acid (UDCA)” property and difference as bile acids.
Hepatol Res. 2005 Oct;33:174–7.
13. Samur S, Klebanoff M, Banken R, Pratt DS, Chapman R, Ollendorf
DA, et al. Long-term clinical impact and cost-effectiveness of obe-
ticholic acid for the treatment of primary biliary cholangitis. Hepat-
ology. 2017 Mar;65:920–8.
14. Al-Dury S, Wahlström A, Panzitt K, Thorell A, Stålman M, Trauner
M, et al. Obeticholic acid may increase the risk of gallstone forma-
tion in susceptible patients. J Hepatol. 2019 Nov;71:986–91.
15. Schoonjans K, Staels B, Auwerx J. Role of the peroxisome
proliferator-activated receptor (PPAR) in mediating the effects of
fibrates and fatty acids on gene expression. J Lipid Res. 1996
May;37:907–25.
16. Honda A, Ikemoto T, Nakamura M, Miyazaki T, Iwamoto J, Hirayama
T, et al. Anticholestatic effects of bezafibrate in patients with pri-
mary biliary cirrhosis treated with ursodeoxycholic acid. Hepatology.
2013 May;57:1931–41.
17. Chianale J, Volrath W, Wielandt AM, Amigo L, Rigotti A, Nervi F,
et al. Fibrates induce mdr2 gene expression and biliary phospho-
lipid secretion in the mouse. Biochem. J. 1996 Mar 15;314(Pt
3):781–6.
18. Smit JJ, Schinkel AH, Ouwe Elferink RP, Groen AK, Wagenaar E, van
Deemter L, et al. Homozygous disruption of the murine mdr2 P-
glycoprotein gene leads to a complete absence of phospholipid
from bile and to liver disease. Cell. 1993 Nov 5;75:451–62.
19. Corpechot C, Chazouillères O, Rousseau A, Le Gruyer A, Haber-
setzer F, Mathurin P, et al. A placebo-controlled trial of bezafibrate
in primary biliary cholangitis. N Engl J Med. 2018
Jun 7;378:2171–81.
20. Iwasaki S, Ohira H, Nishiguchi S, Zeniya M, Kaneko S, Onji M, et al.
The efficacy of ursodeoxycholic acid and bezafibrate combination
therapy for primary biliary cirrhosis: a prospective, multicenter
study. Hepatol Res. 2008 Jun;38:557–64.
21. Itakura J, Izumi N, Nishimura Y, Inoue K, Ueda K, Nakanishi H, et al.
Prospective randomized crossover trial of combination therapy with
bezafibrate and UDCA for primary biliary cirrhosis. Hepatol Res.
2004 Aug;29:216–22.
22. Cheung AC, Lapointe-Shaw L, Kowgier M, Meza-Cardona J,
Hirschfield GM, Janssen HL, et al. Combined ursodeoxycholic acid
(UDCA) and fenofibrate in primary biliary cholangitis patients with
incomplete UDCA response may improve outcomes. Aliment Phar-
macol Ther. 2016 Jan;43:283–93.
23. Grigorian AY, Mardini HE, Corpechot C, Poupin R, Levy C. Fenofi-
brate is effective adjunctive therapy in the treatment of primary
biliary cirrhosis: a meta-analysis. Clin Res Hepatol Gastroenterol.
2015 Jun;39:296–306.
24. Levy C, Peter JA, Nelson DR, Keach J, Petz J, Cabrera R, et al. Pilot
study: fenofibrate for patients with primary biliary cirrhosis and an
incomplete response to ursodeoxycholic acid. Aliment Pharmacol
Ther. 2011 Jan;33:235–42.
25. Yamashita S, Masuda D, Matsuzawa Y. Pemafibrate, a new selective
PPARα modulator: drug concept and its clinical applications for
dyslipidemia and metabolic diseases. Curr Atherosclerosis Rep.
2020 Jan 23;22:5.
26. Liu ZM, Hu M, Chan P, Tomlinson B. Early investigational drugs
targeting PPAR-α for the treatment of metabolic disease. Expt
Opin Invest Drugs. 2015 May;24:611–21.
27. Sasaki Y, Asahiya M, Tanaka T, Yamamoto S, Murakami K, Kamiya
W, et al. Pemafibrate, a selective PPARα modulator, prevents non-
alcoholic steatohepatitis development without reducing the hepatic
triglyceride content. Sci Rep. 2020 May 8;10:7818.
28. Honda Y, Kessoku T, Ogawa Y, Tomono W, Imajo K, Fujita K, et al.
Pemafibrate, a novel selective peroxisome proliferator-activated
receptor alpha modulator, improves the pathogenesis in a rodent
model of nonalcoholic steatohepatitis. Sci Rep. 2017 Feb
14;7:42477.
29. Joshita S, Umemura T, Yamashita Y, Sugiuira A, Yamazaki T, Fujimori
N, et al. Biochemical and plasma lipid responses to pemafibrate in
patients with primary biliary cholangitis. Hepatol Res. 2019
Oct;49:1236–43.
30. Jones D, Boudes PF, Swain MG, Bovilus CL, Galambos MR, Bacon
BR, et al. Seladelpar (MBX-8025), a selective PPAR-δ agonist, in
patients with primary biliary cholangitis with an inadequate
response to ursodeoxycholic acid: a double-blind, randomised,
placebo-controlled, phase 2, proof-of-concept study. Lancet Gas-
troenterol Hepatol. 2017 Oct;2:716–26.
31. Han CL, Qu CZ. Cardiovascular risk and safety evaluation of a dual peroxisome proliferator-activated receptor-alpha/gamma agonist, aleglitazar, in patients with type 2 diabetes: a meta-analysis. J Cardiovasc Pharmacol. 2020 Apr;75:351–7.
32. Araki E, Yamashita S, Arai H, Yokote K, Satoh J, Inoguchi T, et al. Efficacy and safety of pemafibrate in people with type 2 diabetes and elevated triglyceride levels: 52-week data from the PROVIDE study. Diabetes Obes Metabol. 2019 Jul;21:1737–44.
33. Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, et al. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (PROMINENT) study. Am Heart J. 2018 Dec;206:80–93.
34. Kalliora C, Kyriazis ID, Oka SI, Lieu MJ, Yue Y, Area-Gomez E, et al. Dual peroxisome-proliferator-activated-receptor-α/γ activation inhibits SIRT1-PGC1α axis and causes cardiac dysfunction. JCI Insight. 2019 Aug 8.
35. Li W, Xu J, Guo X, Xia X, Sun Y. Pemafibrate suppresses oxidative stress and apoptosis under cardiomyocyte ischemia-reperfusion injury in type 1 diabetes mellitus. Exp Ther Med. 2021 Apr;21:331.
36. Yamashita S, Arai H, Yokote K, Araki E, Matsushita M, Nojima T, et al. Efficacy and safety of pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα); pooled analysis of phase 2 and 3 studies in dyslipidemic patients with or without statin combination. Int J Mol Sci. 2019 Nov 6;20:5537–64.
37. Yamashita S, Masuda D, Matsuzawa Y. Clinical applications of a novel selective PPARα modulator, pemafibrate, in dyslipidemia and metabolic diseases. J Atherosclerosis Thromb. 2019 May;1:26:389–402.
38. Dohmen K, Onohara SY, Harada S. Effects of switching from fenofibrate to pemafibrate for asymptomatic primary biliary cholangitis. Korean J Gastroenterol. 2021 Oct 25;78:227–34.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Yamaguchi M, Asano T, Arisaka T, Mashima H, Irisawa A, Tamano M. Effects of pemafibrate on primary biliary cholangitis with dyslipidemia. Hepatol Res. 2022;52(6):522–31. https://doi.org/10.1111/hepr.13747