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ORIGINAL ARTICLE

Effects of Switching from Fenofibrate to Pemafibrate for Asymptomatic Primary Biliary Cholangitis

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Background/Aims: The addition of a fibrate to ursodeoxycholic acid (UDCA) is the standard treatment for asymptomatic primary biliary cholangitis (aPBC) with an incomplete response to UDCA. Among the fibrates, bezafibrate and fenofibrate increase the serum creatinine level and reduce the estimated glomerular filtration rate (eGFR). Pemafibrate is an selective peroxisome proliferator-activated receptor alpha modulator (SPPARM-α) mainly metabolized by the liver that was recently approved to treat dyslipidemia. This study confirmed the changes in the biochemical markers after switching from fenofibrate to pemafibrate in aPBC patients.

Methods: This study examined the effects of switching treatment from fenofibrate to pemafibrate in 16 aPBC patients. The biological parameters of these patients were examined at the initiation of fenofibrate and after switching to pemafibrate, then at 24 and 48 weeks later, respectively.

Results: Among patients with aPBC treated with UDCA and fenofibrate, the ALP, GGT, and serum IgM levels decreased significantly ($p<0.0001$) over 48 weeks. On the other hand, serum creatinine levels increased significantly, and eGFR decreased significantly ($p<0.0001$). After switching to pemafibrate plus UDCA, patients with aPBC exhibited significantly lower serum creatinine levels ($p=0.007$) and significantly higher eGFR levels ($p=0.014$).

Conclusions: Pemafibrate has therapeutic efficacy for aPBC patients with an inadequate response to UDCA. Pemafibrate might be another option for aPBC patients given its beneficial effects on renal function, but larger, multicenter studies with a longer follow-up are needed. **(Korean J Gastroenterol 2021;78:227-234)**

Key Words: Primary biliary cholangitis; Pemafibrate; Bezafibrate; Fenofibrate; Glomerular filtration rate; Creatinine

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic, slowly progressing cholestatic autoimmune liver disease characterized by progressive inflammatory destruction of the interlobular bile duct, which eventually leads to cirrhosis and hepatic failure.[1] Originally called “primary biliary cirrhosis”, the name of the disorder was changed to PBC to describe it and its natural history more accurately.[2] Although the etiology of PBC has not been established, its onset is attributed to autoimmunity, primarily because of its association with autoantibodies, especially AMA, and elevated IgM levels.

Ursodeoxycholic acid (UDCA), which delays the development of fibrosis, is the only approved therapeutic agent for PBC. UDCA-responsive patients have a similar life expectancy as their age- and sex-matched controls.[3-6] On the other hand, not all patients exhibit a complete biochemical response to UDCA. Approximately 10-20% progress to cirrhosis or require liver transplantation, indicating a clear need for additional therapies.[7,8]

Fibrate, a fibric acid derivative used to treat hypercholesterolemia and hypertriglyceridemia, decreases the levels of the serum liver biochemical markers. Fibric acid derivatives appear to regulate cell proliferation and the expression levels

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of various lipids and proteins through the activation of peroxisome proliferator-activated receptor alpha (PPAR-α).[9-11] Therefore, fibric acid is considered a "PPAR-α agonist".

Bezafibrate activates all three isoforms of human PPAR (PPAR-α, PPAR-δ, and PPAR-γ) at similar concentrations (50, 20 and 60 μM, respectively).[12,13] Therefore, bezafibrate is described more accurately as a "pan-PPAR" agonist. On the other hand, fenofibrate exhibits stronger binding affinity to PPAR-α than bezafibrate.[12] Hence, fenofibrate is referred to as a "PPAR-α–selective" agonist.[13]

Both bezafibrate and fenofibrate lower the biliary liver enzyme levels in patients with PBC.[13-26] On the other hand, there are reports that the administration of bezafibrate or fenofibrate increases the serum creatinine levels and decreases the estimated glomerular filtration rate (eGFR).[27,28] The mechanism of fibrate-induced renal function impairment is unclear. One theory states that fibrates reduce the production of vasodilatory prostaglandins, which would lead to a change in the renal function in patients who experience a rise in the serum creatinine levels.[29] Hottelart et al.[30] reported that fenofibrate does not alter the glomerular filtration rate but increases creatininemia by increasing the net daily production of creatinine. Accordingly, there are concerns regarding the adverse effects of bezafibrate and fenofibrate on the kidneys because of their long-term use in treating PBC. Accordingly, additional therapeutic options are required.

Pemafibrate, a selective peroxisome proliferator-activated receptor alpha modulator (SPPARM-α), was recently approved for the treatment of dyslipidemia, a common comorbidity of PBC.[31,32] A phase III clinical trial showed that pemafibrate is superior to fenofibrate in terms of renal safety for patients with dyslipidemia.[32] Bezafibrate and fenofibrate are metabolized mainly by the kidneys, whereas pemafibrate is metabolized mainly by the liver.[33] Therefore, pemafibrate might not adversely affect renal function.

To the best of the authors' knowledge, there is only one published report on the biochemical effects of pemafibrate in patients with asymptomatic PBC (aPBC).[34] Therefore, this study examined the changes in the biochemical markers in patients with aPBC after switching from fenofibrate plus UDCA to pemafibrate plus UDCA.

SUBJECTS AND METHODS

1. Patients

From 2010-2018, 16 consecutive patients (14 females and two males) with aPBC treated with fenofibrate plus UDCA were recruited. PBC was diagnosed based on the JSH criteria.[35] This study enrolled 16 patients with aPBC treated with fenofibrate plus UDCA for at least 48 weeks (range 96-336 weeks). The inclusion criteria were as follows: 1) an established diagnosis of PBC made according to the published criteria,[36] including liver biochemical findings of cholestasis associated with PBC (i.e., elevated ALP and/or GGT), compatible serological parameters (i.e., AMA) and a compatible or diagnostic liver histology; 2) treatment with UDCA 13-15 mg/kg/day for at least 6 months; 3) persistent elevation of serum ALP greater than twice the upper limit of normal on two separate measurements.

Accordingly, two male and 14 female patients with aPBC who exhibited incomplete responses to UDCA for at least 6 months were evaluated. All 16 patients (60.9±13.1 years old) were given fenofibrate 80 mg/day in addition to their usual dose of UDCA (Table 1); this dosage was chosen based on a previous finding showing that it decreased the ALP and IgM levels.[15,24] For these 16 aPBC patients, a switch to pemafibrate plus UDCA was proposed considering reports of adverse events due to fenofibrate, which included an increased creatinine kinase level.[27,28] Pemafibrate 0.1 mg was administered orally twice daily (Table 2). All patients were negative for HBsAg and anti-HCV. Individuals with known cerebrovascular disease, hypertension, diabetes mellitus, cancer, renal disease, or thyroid disease were excluded. None of the patients had liver cirrhosis according to ultrasonography, fibroscan, or laboratory data. No patients had been treated with D-penicillamine, corticosteroids, colchicine, or immunosuppressive agents within the preceding 4 weeks. Liver biopsies were not required as per the inclusion criteria.

2. Methods

Laboratory tests for liver biochemical parameters, lipids, uric acid, serum creatinine, eGFR, and serum IgM levels, as well as complete blood cell counts, were performed at the initiation of fenofibrate administration (i.e., baseline) and at 24 and 48 weeks. Similarly, the abovementioned characteristics were compared at 24 and 48 weeks after the patients had

been switched to pemafibrate. The effects of adding pemafibrate to UDCA therapy were evaluated in accordance with the ethical guidelines of the Declaration of Helsinki, and the Chihaya Hospital Ethics Committee approved the study protocol.

3. Statistical analysis

All data are expressed as the mean±standard deviation (SD). Statistical comparisons were made using the Wilcoxon signed-rank test or the χ^2-test as appropriate. A p-value <0.05 was considered significant.

Table 1. Changes in the Biological Characteristics of Patients with aPBC at the Baseline, 24 Weeks and 48 Weeks after Treatment with Fenofibrate Plus UDCA

	Baseline	24 weeks	p-value (0w vs. 24w)	48 weeks	p-value (0w vs. 48w)
Biochemical marker	n=16				
Age (years)	60.9±13.1				
Male:female (n)	2:14				
TB (mg/dL)	0.6±0.2	0.6±0.2	0.062	0.5±0.2	0.011
ALP (U/L)	596±72	249±20	<0.0001	226±54	<0.0001
ALT (U/L)	50±31	22±8	<0.0001	20±18	<0.0001
GGT (U/L)	291±246	54±41	<0.0001	54±45	<0.0001
IgM (mg/dL)	325±291	186±142	<0.0001	171±124	<0.0001
LDL-C (mg/dL)	114±26	100±22	0.024	105±23	0.213
TG (mg/dL)	118±51	86±30	0.003	98±40	0.04
HDL-C (mg/dL)	70±22	73±19	0.553	72±18	0.462
UA (mg/dL)	5.0±1.2	4.0±1.0	<0.0001	4.2±1.2	<0.0001
Creatinine (mg/dL)	0.61±0.16	0.67±0.14	0.007	0.68±0.18	<0.0001
eGFR (mL/min/1.73 m^2)	87±29	74±15	0.005	76±24	<0.0001

Values are presented as mean±standard deviation.
aPBC, asymptomatic primary biliary cholangitis; UDCA, ursodeoxycholic acid; TB: total bilirubin, ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; IgM, immunoglobulin M; LDL-C, low density lipoprotein-cholesterol; TG: triglyceride, HDL-C, high density lipoprotein-cholesterol; UA: uric acid, eGFR: estimated glomerular filtration rate.

Table 2. Changes in the Biological Characteristics of Patients with aPBC at the Baseline, 24 Weeks and 48 Weeks after Switching from Fenofibrate Plus UDCA to Pemafibrate Plus UDCA

	Baseline	24 weeks	p-value (0w vs. 24w)	48 weeks	p-value (0w vs. 48w)
Biochemical marker	n=16				
Age (years)	64.9±14.0				
Male:female (n)	2:14				
TB (mg/dL)	0.6±0.2	0.5±0.2	0.008	0.5±0.2	0.025
ALP (U/L)	231±59	203±63	0.003	192±59	0.011
ALT (U/L)	20±7	21±8	0.749	19±9	0.21
GGT (U/L)	55±48	41±31	0.011	44±38	0.05
IgM (mg/dL)	180±139	172±141	0.426	171±159	0.417
LDL-C (mg/dL)	98±21	90±19	0.006	91±17	0.019
TG (mg/dL)	84±32	82±30	0.95	84±36	0.831
HDL-C (mg/dL)	75±14	63±11	<0.0001	66±12	0.001
UA (mg/dL)	4.5±1.1	5.4±1.4	0.002	5.5±1.4	<0.0001
Creatinine (mg/dL)	0.68±0.18	0.63±0.20	0.003	0.62±0.17	0.007
eGFR (mL/min/1.73 m^2)	74±20	82±30	0.004	81±19	0.014

Values are presented as mean±standard deviation.
aPBC, asymptomatic primary biliary cholangitis; UDCA, ursodeoxycholic acid; TB: total bilirubin, ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; IgM, immunoglobulin M; LDL-C, low density lipoprotein-cholesterol; TG: triglyceride, HDL-C, high density lipoprotein-cholesterol; UA: uric acid, eGFR: estimated glomerular filtration rate.

RESULTS

1. Changes in biochemical characteristics after treatment with fenofibrate plus UDCA

Table 1 lists the biochemical characteristics of patients with aPBC at the initiation of fenofibrate treatment and at 24 and 48 weeks. Compared to the baseline, at 48 weeks, fenofibrate plus UDCA decreased the serum levels of ALT (from 50±31 to 20±8 U/L), ALP (from 596±72 to 226±54 U/L), GGT (from 291±246 to 54±45 U/L), and IgM (from 325±291 to 171±124 mg/dL) (all p<0.0001; Table 1).

Similarly, the serum triglyceride (TG) and uric acid levels decreased significantly (from 118.0±51.0 to 98.0±40.0 mg/dL, p=0.04; from 5.0±1.2 to 4.2±1.2 mg/dL, respectively; both p<0.0001) in patients after initiating fenofibrate plus UDCA. The serum levels of LDL-cholesterol and HDL-cholesterol did not change significantly (from 114±26 to 105±23 mg/dL, p=0.213; from 70±22 to 72±18 mg/dL, p=0.462; respectively). On the other hand, after initiating fenofibrate plus UDCA, the serum levels of creatinine increased significantly (from 0.61±0.16 to 0.68±0.18 mg/dL, p<0.0001), whereas eGFR decreased significantly (from 87±29 to 76±24 mL/min/1.73 m^2, p<0.0001) (Figs. 1, 2). No adverse events were observed, such as transient elevation of the transaminase levels, rhabdomyolysis, or esophagitis or known adverse side effects of these drugs.

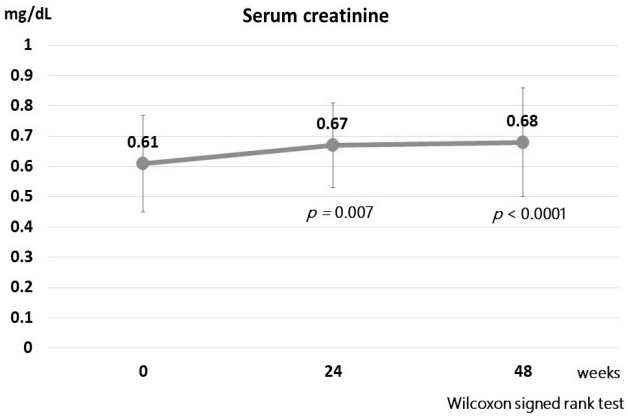

Fig. 1. Changes in the serum creatinine levels in patients with aPBC treated with fenofibrate plus UDCA. aPBC, asymptomatic primary biliary cholangitis; UDCA, ursodeoxycholic acid.

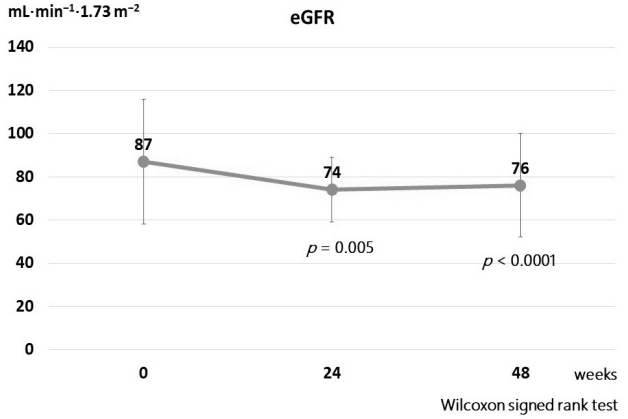

Fig. 2. Changes in the eGFR in patients with aPBC treated with fenofibrate plus UDCA. eGFR, estimated glomerular filtration rate; aPBC, asymptomatic primary biliary cholangitis; UDCA, ursodeoxycholic acid.

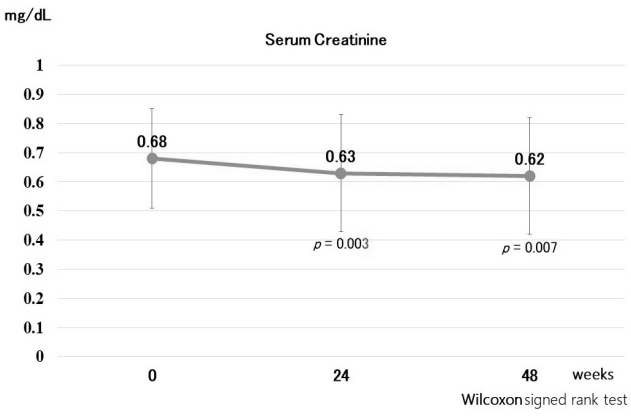

Fig. 3. Changes in the serum creatinine levels in patients with aPBC treated with pemafibrate plus UDCA after switching from fenofibrate plus UDCA. aPBC, asymptomatic primary biliary cholangitis; UDCA, ursodeoxycholic acid.

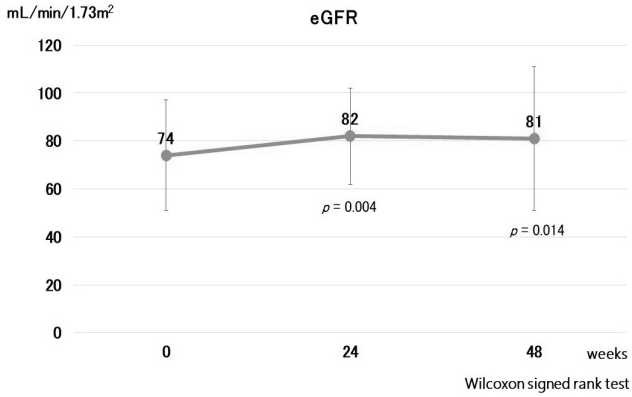

Fig. 4. Changes in the eGFR in patients with aPBC treated with pemafibrate plus UDCA after switching from fenofibrate plus UDCA. eGFR, estimated glomerular filtration rate; aPBC, asymptomatic primary biliary cholangitis; UDCA, ursodeoxycholic acid.

2. Changes in the biochemical characteristics after switching to pemafibrate plus UDCA

Table 2 lists the biochemical characteristics obtained when patients with aPBC switched from fenofibrate plus UDCA to pemafibrate plus UDCA and at 24 and 48 weeks. Serum ALT and IgM levels did not change significantly from the time of switching to pemafibrate to 48 weeks (from 20±7 to 19±9 U/L, p=0.21; from 180±139 to 171±159 mg/dL, p=0.417, respectively). The serum ALP levels decreased significantly from the baseline to 48 weeks (from 231±59 to 192±59 U/L, p=0.011), and serum GGT levels tended to decrease (from 55±48 to 44±38 U/L, p=0.05) (Table 2).

Furthermore, the serum TG levels did not change significantly (from 84±32 to 84±36 mg/dL, p=0.831) from the baseline to 48 weeks, whereas those of LDL-cholesterol and HDL-cholesterol decreased significantly (from 98±21 to 91±17 mg/dL, p=0.019; from 75±14 to 66±12 mg/dL, p=0.001, respectively). The AST, ALT, ALP, GGT, IgM, TG, LDL-cholesterol, and HDL-cholesterol levels were maintained within the normal ranges after switching from fenofibrate to pemafibrate. The uric acid levels increased significantly from the baseline to 48 weeks (from 4.5±1.1 to 5.5±1.4 mg/dL, p<0.0001). By contrast, the serum creatinine levels decreased significantly (from 0.68±0.20 to 0.62±0.17 mg/dL, p=0.007), while the eGFR levels increased significantly (from 74±20 to 81±19 mL/min/1.73 m^2, p=0.014) (Figs. 3, 4).

No adverse events, such as transient elevation of transaminase levels, rhabdomyolysis, esophagitis, or known adverse side effects of these drugs, were observed after switching to pemafibrate plus UDCA.

DISCUSSION

The present study demonstrated the efficacy of pemafibrate for 48 weeks in patients with aPBC who previously exhibited a complete response to fenofibrate and UDCA combination therapy.

Because patients with aPBC who exhibit an incomplete biochemical response to UDCA in the first 3 months generally have poor outcomes, a new therapeutic approach is needed for such cases.[37] Several studies in Japan reported that bezafibrate successfully lowers the levels of biliary liver enzymes in patients with PBC.[17-20] Hazzan and Tur-Kaspa[38], Lens et al.[39], and Corpechot et al.[40] reported that adding bezafibrate to UDCA is safe and improves the biochemical profiles of PBC patients of European descent significantly.

Compared to bezafibrate, fenofibrate has stronger and more specific affinity to PPAR-α.[12,13,24] On the other hand, only a few studies have investigated the effects of fenofibrate in patients with PBC.[13-16,21-24,41] In one study, fenofibrate plus UDCA for 6 months reduced liver biochemical parameters, such as ALT, GGT, and IgM, in seven patients with PBC.[14] In another study, fenofibrate reduced the serum levels of ALP and IgM in patients with aPBC.[15] Furthermore, Walker et al.[16] reported the first European experience with the administration of a fibric acid derivative in patients with PBC; both serum ALP and IgM levels decreased significantly, with 89% of patients exhibiting normalized serum ALP levels. In another pilot study, six patients with PBC treated with fenofibrate plus UDCA exhibited larger reductions in the ALP, GGT, and ALT levels compared to four patients with PBC treated with UDCA alone.[21] Similarly, Levy et al.[22] reported significant decreases in the ALP and IgM levels after 48 weeks of fenofibrate plus UDCA in 20 patients with PBC who had not responded to the treatment with UDCA alone. Han et al.[23] examined the effectiveness of fenofibrate plus UDCA for more than 1 year in 22 Chinese patients with PBC who exhibited a partial response to UDCA; they confirmed that the ALP, GGT, TG, AST, and ALT levels decreased with no obvious adverse effects. Hegade et al.[26] confirmed that long-term treatment with fenofibrate as an adjunct to UDCA safely and effectively improves ALP levels in patients with PBC. Although these studies demonstrate the biochemical effectiveness of fenofibrate, its histological efficacy has also been demonstrated.[42]

The proposed action mechanism of fibric acid derivatives in the context of PBC involves the regulation of cell proliferation and the expression of various lipids and proteins via the activation of PPAR-α.[9,11] Fibrates inhibit NF-κB activation via PPAR-α activation, which decreases interleukin-1 (IL-1) and IL-6 expression, potentially reducing the inflammatory and immune responses.[10,11] In addition to regulating proteins and lipids, the beneficial effects of fibrates on PBC might be due to cross-talk between PPAR-α and the bile acid-activated nuclear receptor, the farnesoid X receptor.[43] Pineda Torra et al.[43] showed that bile acid-activated farnesoid X receptor enhances PPAR-α transcription in human hepatic stellate cells. Furthermore, fibrates may facilitate the expression of mdr3 (multidrug resistance gene 3), a transport element of the

ATP-dependent bile secretion system found in the biliary membranes.[11,44-46] Accordingly, increased expression of mdr3-encoded proteins would lead to enhanced biliary phospholipid secretion and increased inactivation of hydrophobic bile acids via micellization, thereby protecting the hepatocytes and the biliary epithelium.

Although bezafibrate and fenofibrate are beneficial for aPBC, some reports have suggested that they can adversely affect the renal function.[27,28,40,47-50] In the FIELD Helsinki follow-up study, an investigation of the renal function after administering fenofibrate in 170 patients with type 2 diabetes revealed significantly higher serum creatinine levels ($p<0.001$) and reduced eGFR ($p<0.001$).[48] Regarding PBC, Duan et al.[51] reported that the serum creatinine levels and eGFR worsened in 26 cirrhotic and noncirrhotic patients with PBC after 2 years of treatment with fenofibrate plus UDCA. Arai et al.[50] reported that in patients with dyslipidemia, a treatment with fenofibrate dramatically increased and decreased the serum creatinine and eGFR levels, respectively, compared to the treatment with pemafibrate.

In the present study, all 16 patients exhibited normal ALT, ALP, GGT, and IgM levels after switching from fenofibrate to pemafibrate. Although the ALT and IgM levels were maintained within the normal ranges after switching to pemafibrate, the ALP levels decreased significantly (from 231±59 to 192±59 U/L, $p=0.011$), and the GGT levels tended to decrease (from 55±48 to 44±38 U/L, $p=0.05$). Joshita et al.[34] also reported that in four PBC cases, ALP and GGT levels decreased over 3 months after switching from bezafibrate to pemafibrate. Compared to bezafibrate and fenofibrate, pemafibrate might decrease the ALP and GGT levels to greater extents in patients with aPBC. In the present study, the uric acid levels increased significantly (from 4.5±1.1 to 5.5±1.4 mg/dL, $p<0.0001$) after switching from fenofibrate to pemafibrate. Fenofibrate decreases the serum levels of uric acid by increasing its urinary excretion through the inhibition of urate transporter 1.[52] Therefore, the uric acid levels increased after switching from fenofibrate to pemafibrate because pemafibrate does not inhibit urate transporter 1.

After switching from fenofibrate plus UDCA to pemafibrate plus UDCA, the serum creatinine levels in the aPBC patients decreased significantly (from 0.68±0.18 to 0.62±0.17 mg/dL, $p=0.007$) while eGFR increased significantly (from 74±20 to 81±19 mL/min/1.73 m^2, $p=0.014$). Regarding their excretion, 69.1% and 64% of bezafibrate and fenofibrate, respectively, are excreted in the urine.[33] Pemafibrate is excreted principally via the liver; only 14.5%, of which less than 0.5% is in the active form, is excreted via the kidneys into the urine.[33] Therefore, the long-term administration of pemafibrate for aPBC is theoretically safe.

In summary, patients with aPBC who switched from fenofibrate to pemafibrate exhibited a preserved renal function. Nevertheless, long-term follow-up of additional patients with aPBC will be required to confirm any advantages of pemafibrate, elucidate the effect of pemafibrate on aPBC, and determine its long-term biochemical efficacy.

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