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Efficacy and safety of pemafibrate in patients with chronic kidney disease

A retrospective study

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Abstract

Hypertriglyceridemia and chronic kidney disease (CKD) are known risk factors for cardiovascular disease. However, treatment with statins, which control low-density lipoprotein cholesterol levels, increases the risk of estimated glomerular filtration rate (eGFR) reduction. Although conventional fibrates, such as bezafibrate (Beza-F) and fenofibrate (Feno-F), are the mainstay for hypertriglyceridemia treatment, they may be associated with a risk of increased serum creatinine level and renal dysfunction. Pemafibrate (Pema) is pharmacologically defined as a selective peroxisomal proliferator-activated receptor α modulator which is excreted in bile and not likely to cause renal dysfunction. We evaluated the efficacy and safety of switching from Beza-F or Feno-F to Pema in CKD patients with hypertriglyceridemia. We recruited 47 CKD patients with hypertriglyceridemia who were receiving Beza-F, Feno-F, or eicosapentaenoic acid (EPA) but were switched to Pema from 2018 to 2021. A retrospective analysis of renal function and lipid profiles was performed before and 24 weeks after switching. CKD patients switching from EPA to Pema were used as study control. The effect of Pema on hypertriglyceridemia was equivalent to that of Beza-F or Feno-F. However, after switching to Pema, eGFR showed a marked average improvement of 10.2 mL/min/1.73 m^2 ($P < .001$). Improvement in eGFR and levels of N-acetyl-β-D-glucosaminidase and β-2-microglobulin was observed only in cases of switching from Beza-F or Feno-F but not from EPA. Although Beza-F and Feno-F are useful medications for the treatment of hypertriglyceridemia, these are associated with a high risk of renal dysfunction. We also found that the deterioration in eGFR due to Beza-F or Feno-F is reversible with drug withdrawal and may not increase the risk for long-term renal dysfunction. We suggest that Pema may be an effective and safe treatment for hypertriglyceridemia in CKD patients.

Abbreviations: Beza-F = bezafibrate, CKD = chronic kidney disease, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, EPA = eicosapentaenoic acid, Feno-F = fenofibrate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NAG = urinary N-acetyl-β-D-glucosaminidase, Pema = pemafibrate, sCr = serum creatinine, TG = triglyceride, UA = uric acid, β2MG = β-2-microglobulin.

Keywords: bezafibrate, EPA, fenofibrate, pemafibrate, renal injury

1. Introduction

Chronic kidney disease (CKD) is a serious public health problem, and its frequency and prevalence are increasing worldwide. CKD has an increased risk for cardiovascular disease (CVD), morbidity, and mortality. Although hyperglycemia and hypertension are the main risk factors for CKD development and progression, dyslipidemia is a common complication of CKD and is associated with a decline in glomerular filtration rate (GFR).[1] Moreover, dyslipidemia is known to be an important risk factor for CVD.[2] Additionally, high low-density lipoprotein cholesterol (LDL-C), high triglyceride (TG), and low

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Juntendo University Hospital (protocol code: E21-0033-U01; date of approval: 2021/8/20). Informed consent was specified on the hospital home page, and the requirement for written informed consent was waived.

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high-density lipoprotein cholesterol (HDL-C) are well-established risk factors for CVD.[2] According to the current evidence, lipid-lowering medications are effective in reducing CVD mortality and morbidity. Recent studies suggest that these medications may have a beneficial effect in CKD patients.[3]

Several studies have demonstrated an association between high TG level and CVD risk. A meta-analysis study showed that the TG level is a strong and independent predictor of CVD risk,[4] and the association between high TG levels and CVD risk is independent of LDL-C levels. Notably, additional treatment with fibrate for high TG was associated with reduced CVD risk independent of the LDL-C level among patients treated with statins.[5,6]

Bezafibrate (Beza-F) and fenofibrate (Feno-F) are highly effective in lowering plasma TG levels and moderately effective in raising HDL-C. In addition to lowering plasma TG levels, Feno-F significantly reduced serum uric acid (UA).[7] Moreover, treatment with Feno-F significantly improved arterial endothelial function.[8] Furthermore, a few studies have reported an increase in serum creatinine (sCr) during fibrate therapy.[9] Although the cause of renal dysfunction by fibrate is not well understood, clinicians should be aware of the incidence of fibrate-induced renal dysfunction.[10]

Pemafibrate (Pema) was first approved in Japan in 2017 and is pharmacologically defined as a selective peroxisomal proliferator-activated receptor α modulator. Pema rarely causes adverse effects and is likely to be safe even in CKD patients owing to its biliary mode of excretion.[11,12] However, it remains unclear if Pema is safe and efficient in CKD patients. Therefore, we assessed the efficacy and safety of Pema in CKD patients with hypertriglyceridemia who had switched from Beza-F or Feno-F to Pema.

2. Methods

2.1. Study population and design

We applied a case-crossover study design and recruited CKD patients with hypertriglyceridemia who received Beza-F, Feno-F (conventional fibrate), or eicosapentaenoic acid (EPA, 1.8 g/day) at Juntendo University Hospital, Tokyo, Japan, from January 2018 to December 2021. The conventional fibrate or EPA was switched to Pema (0.2 mg/day), and a retrospective analysis of renal function and lipid profiles was performed after 24 weeks. To assess the dose effect of Beza-F and Feno-F on renal function, we chose all patients who were treated with Beza-F (400 or 200 mg/day) and Feno-F (160 or 106 mg/day). Moreover, patients treated with EPA which is also prescribed for hypertriglyceridemia were used as a control. We excluded patients who changed existing treatments such as statins and renin-angiotensin inhibitors during the 24 week-study period.

2.2. Measurements

Clinical and laboratory data were collected immediately before and 24 weeks after the switchover to Pema. The laboratory parameters measured included renal function and lipid profiles such as sCr, estimated estimated glomerular filtration rate (eGFR), urinary N-acetyl-β-D-glucosaminidase (NAG), β-2-microglobulin (β2MG), and serum levels of TG, HDL-C, LDL-C, and UA.

2.3. Statistical analysis

Data are expressed as mean ± standard deviation. Comparisons between groups were performed using the Mann–Whitney *U* test. Spearman's correlation analysis was used to analyze the correlation between 2 variables. Statistical significance was defined as $P < .05$. Statistical analyses were performed using the GraphPad Prism software ver.8.0 (GraphPad Software, San Diego, CA).

3. Results

3.1. Improvement of dyslipidemia by Pema was equivalent to that by Feno-F or Beza-F

Clinical and laboratory data obtained immediately before the switchover to Pema are shown in Table 1. There were no significant differences in renal function and lipid profiles for each treatment group, except for serum TG, which was higher in the Pema group than in the Feno-F and Beza-F treatment groups. Primary diseases of CKD in each treatment groups were shown in Supplemental Table S1, Supplemental Digital Content, http://links.lww.com/MD/I417. Serum TG levels increased in the high dose Beza-F group (400 mg/day) and significantly decreased in the EPA group after switchover to Pema (Fig. 1A, $P < .001$). Additionally, serum levels of HDL-C and LDL-C were not significantly different between before and after the switchover (Fig. 1B and C).

3.2. Feno-F treatment group showed a significant increase in serum UA levels after the switchover

Serum UA levels significantly increased only in the Feno-F group, but not in the Beza-F or EPA groups, after the switchover to Pema (Fig. 2, $P < .001$).

3.3. Treatment with Pema improved both eGFR and tubular damage marker levels in CKD patients administered with Feno-F or Beza-F

In the Feno-F or Beza-F groups, sCr levels significantly decreased after switching to Pema (Fig. 3A, $P < .001$) and eGFR showed an average improvement of 10.2 mL/min/1.73 m^2 (Fig. 3B, $P < .001$). Significant improvement in eGFR was observed only in cases of switchover to Pema from Beza-F or Feno-F, but not EPA (Fig. 3C). Moreover, urinary NAG and β2MG levels tended to decline after the switchover from Feno-F and Beza-F groups (Fig. 3D and E) but did not change significantly in the EPA

Table 1

Baseline clinical parameters before switch to pemafibrate.

basic treatment	number	age	gender	sCr (mg/dL)	eGFR (mL/min/1.73m2)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	UA (mg/dL)
Fenofibrate 160 mg	8	64.5 ± 9.2	M5, F3	1.03 ± 0.37	58.7 ± 28.3	146.4 ± 81.5	53.9 ± 9.7	115.8 ± 38.9	4.7 ± 0.7
Fenofibrate 106 mg	10	67.8 ± 8.5	M7, F3	0.99 ± 0.27	59.2 ± 12.6	147.6 ± 59.8	53.6 ± 11.0	119.4 ± 21.5	5.7 ± 0.8
Bezafibrate 400 mg	7	60.0 ± 14.4	M5, F2	1.00 ± 0.23	57.4 ± 13.4	139.0 ± 34.4	46.0 ± 8.3	121.0 ± 15.1	5.7 ± 0.9
Bezafibrate 200 mg	11	56.7 ± 16.2	M8, F3	1.13 ± 0.19	52.4 ± 16.9	147.3 ± 56.1	56.8 ± 21.2	107.5 ± 31.5	5.8 ± 1.0
EPA 1.8 g	11	58.8 ± 15.2	M7, F4	0.96 ± 0.38	65.5 ± 20.8	327.4 ± 201.1	48.3 ± 9.4	100.5 ± 26.8	5.4 ± 0.7

eGFR = estimated glomerular filtration rate, EPA = eicosapentaenoic acid, F = female, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, M = male, sCr = serum creatinine, TG = triglyceride, UA = uric acid.

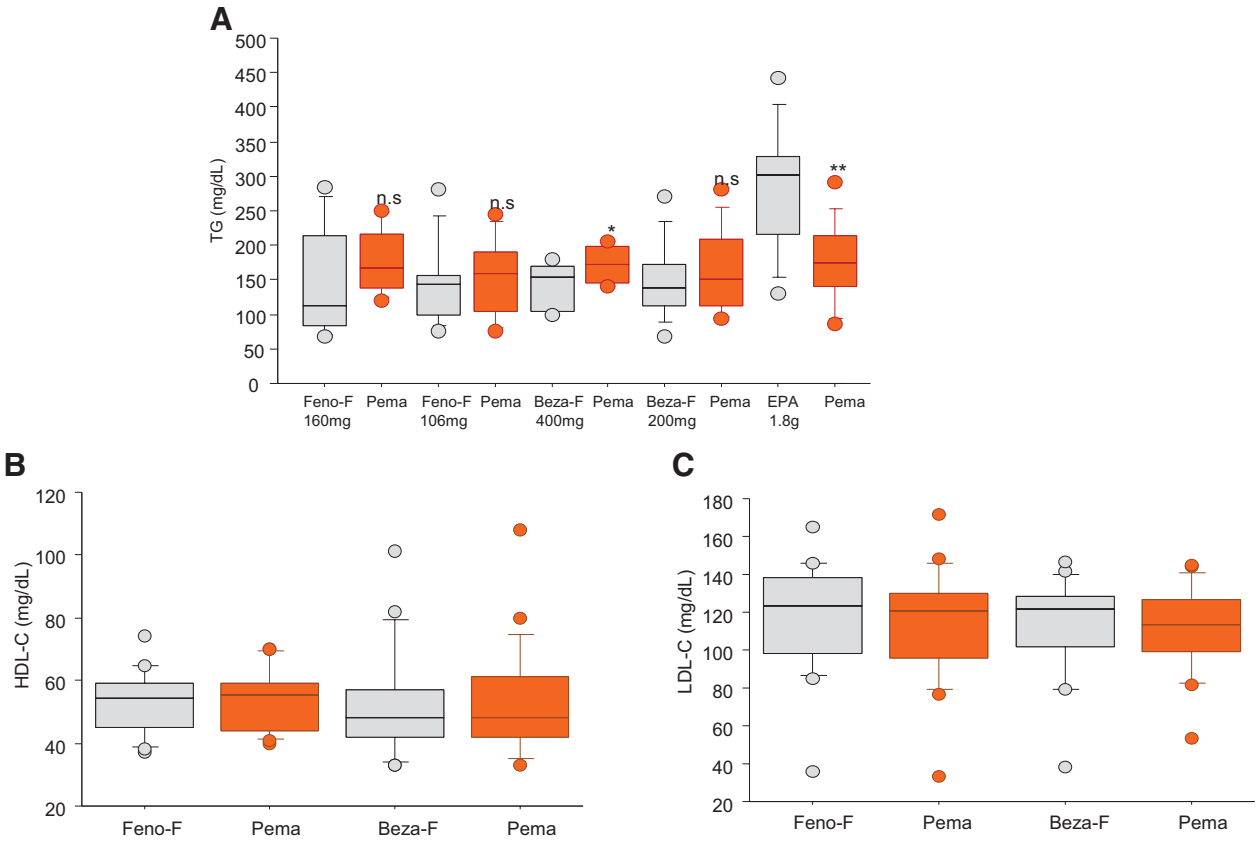

Figure 1. Effect of pemafibrate on dyslipidemia was similar to that of fenofibrate or bezafibrate. (A) Serum TG levels were not significantly changed after switchover from Beza-F or Feno-F to Pema. The effect of EPA on hypertriglyceridemia was lower than that of Pema ($P < .001$). (B and C) Levels of serum HDL-C and LDL-C were not significantly changed after switchover from Beza-F or Feno-F to Pema. $^{**}P < .001$, Beza-F = bezafibrate, EPA = eicosapentaenoic acid, Feno-F = fenofibrate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, n.s. = not significant, Pema = pemafibrate, TG = triglycerides.

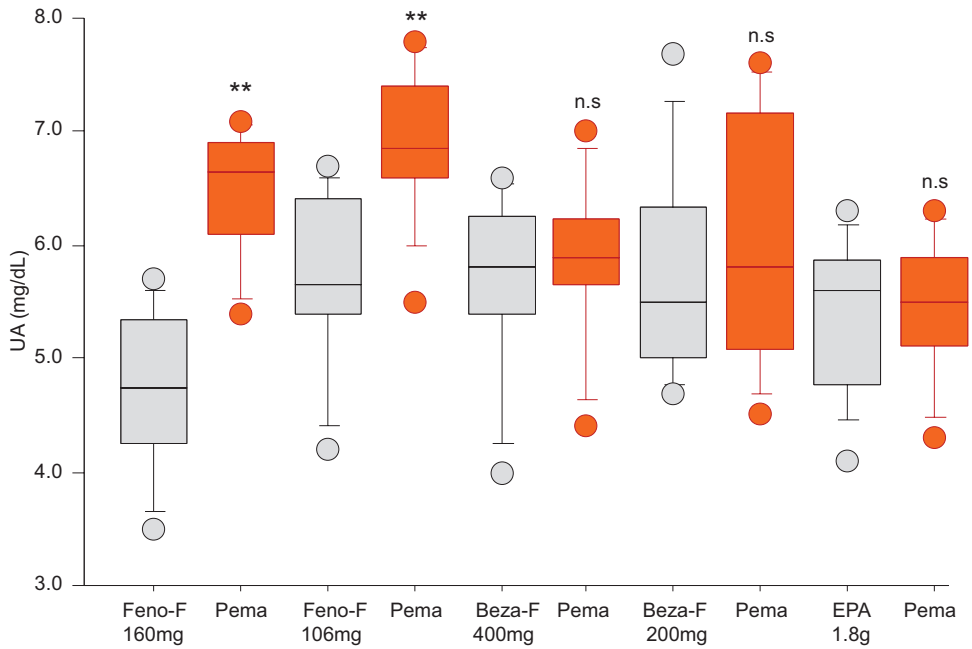

Figure 2. Effect of fibrates on serum uric acid. The fenofibrate treatment group showed a significant increase in serum uric acid levels after the switchover to pemafibrate ($P < .001$). $^{**}P < .001$, n.s. = not significant.

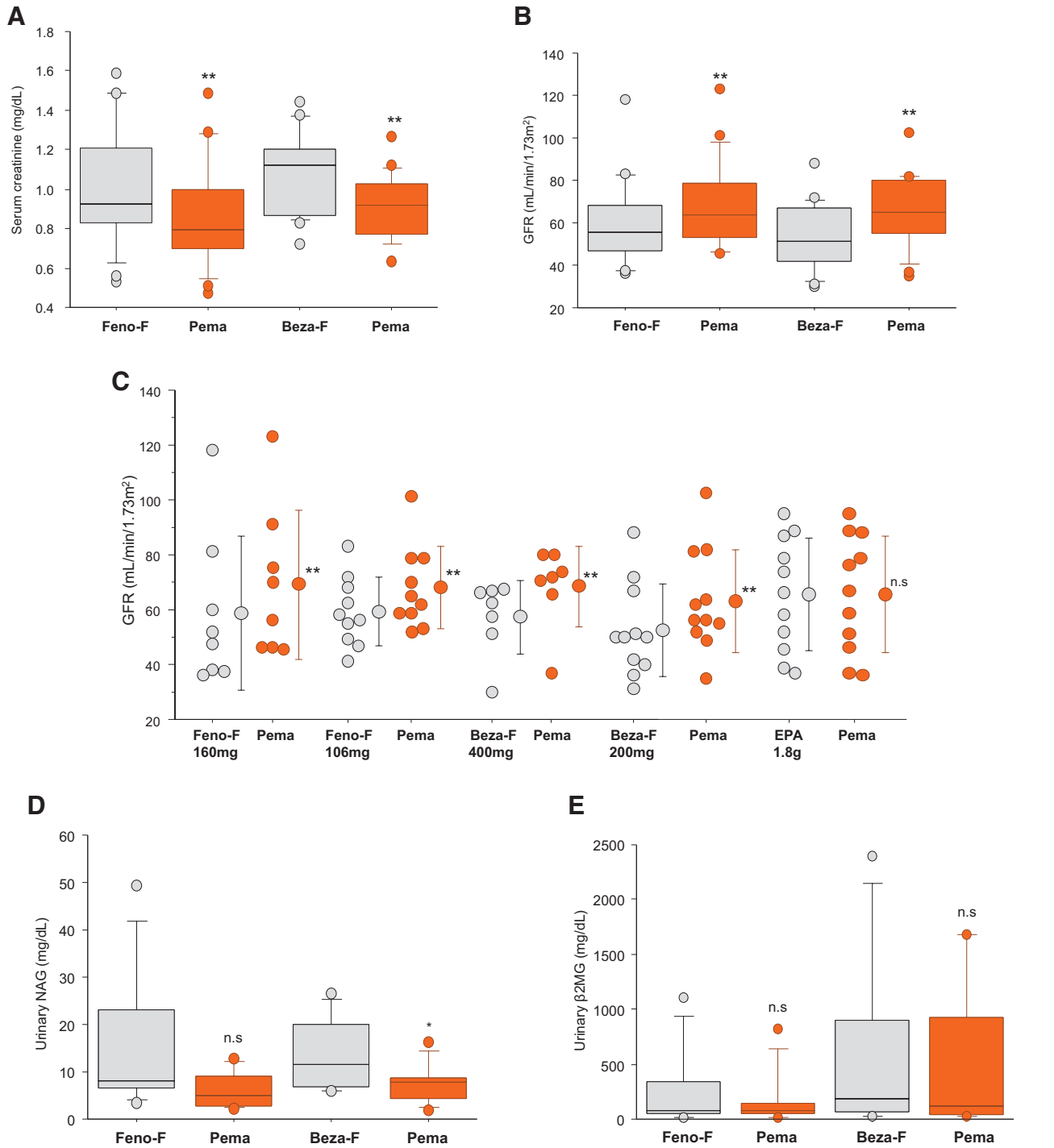

Figure 3. Changes in renal function after the switchover from Beza-F or Feno-F to Pema. (A) In the Feno-F or Beza-F treatment groups, serum creatinine levels significantly decreased after switching to Pema ($P < .001$). (B) eGFR showed a significant improvement after the switchover to Pema ($P < .001$). (C) Improvement in eGFR was observed only in cases of switchover from Beza-F or Feno-F ($P < .001$). In patients with the switchover from EPA to Pema, the level of eGFR did not change significantly. (D and E) Urinary NAG and β2MG tended to decline in Feno-F and Beza-F groups after the switchover to Pema. *$P < .01$. Beza-F = bezafibrate, eGFR = estimated glomerular filtration rate, EPA = eicosapentaenoic acid, Feno-F = fenofibrate, β2MG = β-2-microglobulin, NAG = urinary N-acetyl-β-D-glucosaminidase, n.s. = not significant, Pema = pemafibrate, TG = triglycerides.

group. There was no significant elevation of creatine kinase levels in patients treated with Beza-F or Feno-F.

4. Discussion

A high level of serum LDL-C is an established CVD risk factor. However, even after treatment with statin to reduce LDL-C levels, a CVD risk of 70% remains.[13] Additionally, hypertriglyceridemia is a known risk factor for CVD and may be a potential therapeutic target for further risk reduction.[5] A recent study indicated that hypertriglyceridemia (>150 mg/dL) increased the risk of eGFR reduction, even though LDL-C levels were well-controlled.[14] Another study suggested that long-term TG control was critical in delaying the decline in renal function in the early stages of diabetic kidney disease.[15]

Conventional fibrates, such as Beza-F and Feno-F, are effective in lowering plasma TG levels and increasing HDL-C levels. Moreover, Feno-F significantly reduced serum UA and further lowered plasma TG levels.[7] However, a few reports suggested that conventional fibrates may be associated with the risk of increased sCr levels.[9,10] In the present study, we confirmed that both Beza-F and Feno-F induced eGFR reduction even when administered at low doses.

Excretion of Beza-F and Feno-F is nearly completely renal (95%), whereas Pema is mainly excreted in the bile. Beza-F and Feno-F cause renal damage by accumulating in the kidney and causing rhabdomyolysis, which is considered as a negative effect of fibrates. Zingerman et al suggested that fibrates may induce the renal function deterioration by inhibiting enzyme cyclooxygenase-2 and reducing the production of vasodilatory prostaglandins, resulting in a decrease in intraglomerular pressure due to constriction of afferent arterioles.[16] Hottelart et al suggested that fibrates increase the production of creatinine, thereby increasing both serum and urine creatinine levels.[17] Alternatively, fibrates may injure the proximal tubules.[18] Our results showed that urinary NAG and β2MG levels tended to decline after the switchover to Pema in the Feno-F and Beza-F groups, but not in the EPA group (Fig. 3D and E). However, it remains unclear whether Pema exhibits renoprotective properties.

There are major differences between Pema and Beza-F or Feno-F. Pema is primarily excreted in the bile. It is pharmacologically defined as a selective peroxisomal proliferator-activated receptor α modulator.[19] Although Feno-F or Beza-F has a certain effect on liver function, there are no significant differences in liver function after switchover from Feno-F or Beza-F to Pema (Supplemental Table S2, Supplemental Digital Content, http://links.lww.com/MD/I418). Recently, Aomura et al[20] reported that in a fatty acid overload nephropathy model, Pema activated renal fatty acid metabolism, decreased renal free fatty acid content and oxidative stress, and improved tubular damage.

Meanwhile, it is notewothy that Feno-F can reduce serum UA, and the level of UA increases after the switchover to Pema (Fig. 2). However, hyperuricemia has a certain effect on renal dysfunction. In fact, additional urate-lowering medicine was necessary in several cases switchover from Feno-F to Pema. It is necessary to check the level of serum UA in case switchover from Feno-F to Pema.

Although the mechanism for fibrate-induced deterioration of renal function is unclear, our results showed a recovery in eGFR levels after the switchover to Pema. Thus, the deterioration in eGFR due to Beza-F or Feno-F is reversible with drug withdrawal and may not increase the risk for long-term renal dysfunction.

This study has several limitations. First, the patient sample may not be representative because it was derived from only 2 hospitals. Moreover, the study was retrospective and therefore, prone to selection bias. Second, the duration of the treatment period with Pema was approximately 24 weeks, which is a relatively short duration for evaluating a chronic disease and a risk of cardiovascular events. Therefore, a prolonged study period is necessary to investigate the risk-to-benefit ratio.

5. Conclusions

This study shows that Pema, Beza-F, and Feno-F exert similar effects in controlling hypertriglyceridemia. Although Beza-F and Feno-F may cause reversible renal injuries in CKD patients, Pema was shown to be safe in CKD patients.

Author contributions

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