Effect of pemafibrate, a novel selective peroxisome proliferator-activated receptor- α modulator (SPPARM α), on urinary protein excretion in IgA nephropathy with hypertriglyceridemia

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Abstract

Lipid abnormalities, including hypertriglyceridemia, are one of the most common comorbidities in patients with chronic kidney disease (CKD) and are independently associated with disease progression. However, it remains uncertain whether treatment for hypertriglyceridemia has favorable effects on the clinical course of IgA nephropathy (IgAN). Pemafibrate is a novel selective peroxisome proliferator-activated receptor- α modulator and may be distinct from conventional fibrates in terms of its pharmacological activity and hepatic and renal safety. A recent clinical study demonstrated that pemafibrate was safe and effective for correcting pro-atherogenic lipid abnormalities in CKD patients with a wide range of renal insufficiency. However, the effect of pemafibrate on renal function in patients with IgAN and hypertriglyceridemia has not been verified. This paper is the first to show that 12 months of pemafibrate (0.1 mg daily) administration in three drug-naïve and mild IgAN patients with variable renal dysfunction and histopathology proven IgAN decreased serum triglyceride level and excretion of urinary protein and liver-type fatty acid-binding protein with no change in estimated glomerular filtration rate (eGFR). These findings suggest that pemafibrate is safe and effective for correcting hypertriglyceridemia and decreasing urinary protein excretion without changing eGFR and blood pressure levels in mild IgAN patients with hypertriglyceridemia.

Keywords Pemafibrate · Selective peroxisome proliferator-activated receptor- α modulator (SPPARM α) · IgA nephropathy · Urinary protein excretion

Introduction

Hyperlipidemia is one of the most prevalent comorbidities in patients with chronic kidney disease (CKD) and is independently associated with its progression, and hypertriglyceridemia is also a known risk factor for progression of CKD [1]. Lipid accumulation and lipotoxicity in kidney tissue is likely to induce renal impairment, emphasizing the clinical importance of careful management of hyperlipidemia in the care of CKD.

Previous randomized-controlled clinical trials demonstrated that conventional fenofibrate therapy attenuated urinary protein excretion and delayed estimated glomerular filtration rate (eGFR) loss in patients with type 2 diabetes [2]. However, it has yet to be determined whether treatment for hypertriglyceridemia affects the clinical course of nephropathies other than diabetic nephropathy. In particular, little is known about the renal effect of such treatment in patients with IgA nephropathy (IgAN), a major cause of CKD with approximately 40% of patients with the disorder progressing to end-stage renal disease (ESRD).

Conventional fibrates are excreted via the kidney and therefore their use has been restricted in patients with renal insufficiency due to concerns over possible over-accumulation and adverse side effects, such as rhabdomyolysis. Pemafibrate is a novel selective peroxisome proliferator-activated receptor- α (PPAR α) modulator (SPPARM α) that is excreted predominantly via the liver [3]. Novel SPPARM α

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agents may be distinct from conventional fibrates in terms of their pharmacological activity and hepatic and renal safety. This suggests that they may have multiple pharmacological actions. In a phase III trial, 52 weeks of pemafibrate treatment in hypertriglyceridemia patients with a broad range of impaired renal function was proven to be safe and effective for improving lipid abnormalities [4]. Furthermore, an experimental study in *db/db* mice showed pemafibrate treatment attenuated urinary albumin excretion and ameliorated the pathological features of diabetic nephropathy [5], indicating a renoprotective effect that may possibly occur in other types of nephropathy, including IgAN. This paper is the first report on the effects of 12 months of treatment with pemafibrate on proteinuria in three IgAN patients with mild, moderate, or severe renal dysfunction.

Case report

Case 1: 35-year-old male, body mass index (BMI) 21.4 kg/m², blood pressure (BP) 120/76 mm Hg, serum creatinine 0.70 mg/dL, eGFR 103.3 mL/min/1.73m², urinary protein excretion 88.8 mg/g.crea, and triglyceride 198 mg/dL. Case 2: 40-year-old female, BMI 21.9 kg/m², BP 122/78 mm Hg, serum creatinine 1.10 mg/dL, eGFR 44.8 mL/min/1.73m², urinary protein excretion 156.8 mg/g.crea, and triglyceride 228 mg/dL. Case 3: 50-year-old male, BMI 19.8 kg/m², BP 118/80 mm Hg, serum creatinine 1.90 mg/dL, eGFR 31.3 mL/min/1.73m², urinary protein excretion 212.8 mg/dL, and triglyceride 330 mg/dL. All blood and urine samples were collected at 8:00 am under fasting conditions at the hospital. The background laboratory data before pemafibrate administration are summarized in Table 1.

The three patients had no previous history other than IgAN and hypertriglyceridemia, and had not been taking other medications, including antihypertensives and lipid-lowering agents. Based on the patients' backgrounds and laboratory data, skilled nephrologists excluded other systemic and/or renal diseases, including diabetes. Then, three people had been diagnosed with IgAN by histopathological examination of a renal biopsy that showed IgA deposition in glomeruli in all three cases (Fig. 1). The severity of glomerular and tubulointerstitial changes in case 3 appeared to be higher than those in case 1 and 2, however, all three patients showed a relatively low histological grade (Table 2) based on the clinicohistological classification of Study Group Special IgA Nephropathy [6] and the MEST-C Oxford classification [7].

We recommended the standard therapies for IgAN patients, such as renin–angiotensin–aldosterone system (RAAS) inhibitors, tonsillectomy, and steroids, however, all three patients refused these therapies unfortunately. They seemed to worry about the side effects of these therapies,

Table 1 Background laboratory data

	Case 1 (35 yr, male)	Case 2 (40 yr, female)	Case 3 (50 yr, male)
Triglyceride (mg/dL)	198	228	330
LDL-C (mg/dL)	132	130	126
HDL-C (mg/dL)	66	60	58
Urinary protein excretion (mg/g.crea)	88.8	156.8	212.8
Serum creatinine (mg/dL)	0.70	1.10	1.90
eGFR (mL/min/1.73m ²)	103.3	44.8	31.3
Urinary L-FABP (μg/g.crea)	18.2	22.8	44.6
IgG (mg/dL)	1200	1340	1260
IgA (mg/dL)	320	360	310
IgM (mg/dL)	88	110	122
C3 (mg/dL)	100	110	98
C4 (mg/dL)	22.0	28.0	26.5
CH50 (U/mL)	40	36	38

LDL-C low-density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol; *eGFR* estimated glomerular filtration rate; *L-FABP* liver-type fatty acid-binding protein

hospitalization, and economical problem. In addition, their histological and clinical grades of IgAN were low (Table 2). While, they accepted a medication only for hypertriglyceridemia, possibly due to its simplicity of clinical use. Therefore, we initiated pemafibrate (0.1 mg/day), which is known to be safe for renal insufficient patients [4], with the consent of patients, and continued for 12 months.

Pemafibrate treatment clearly decreased triglyceride levels in the three patients (Fig. 2a). Compared to baseline, pemafibrate reduced fasting triglyceride levels by 57% in case 1, 56% in case 2, and 65% in case 3. On the other hand, low-density lipoprotein and high-density lipoprotein cholesterol levels did not change during the 12-month treatment period. Urinary protein excretion also gradually decreased during the observation period and reached < 100 mg/g.crea (Fig. 2b). Twelve months of pemafibrate treatment reduced urinary protein excretion by 43% in case 1, 54% in case 2, and 58% in case 3. In addition, urinary liver-type fatty acid-binding protein (L-FABP) levels decreased gradually in the three patients (30% in case 1, 37% in case 2, and 55% in case 3; Fig. 2c). In contrast, eGFR showed no obvious change during the 12-month period in the three patients (Fig. 2d). Both systolic and diastolic blood pressures also showed no obvious changes during the period (Fig. 2e, f). Furthermore, no adverse effects, including hepatic disorders and rhabdomyolysis, were observed during the period of pemafibrate treatment. After the observation period, the three patients hoped to continue taking pemafibrate without the need for standard treatment options for IgAN, such as RAAS inhibitors, steroids, and a tonsillectomy.

Fig. 1 Histopathology of the renal biopsies. PAS staining $\times 100$, immunofluorescence for IgA staining $\times 400$. **a** Case 1, **b** Case 2, and **c** Case 3. Detailed histological findings are shown in Table 2

Table 2 Detailed histological findings and clinical grade

	Number of total glomeruli	Rate of global sclerosis (%)	Rate of segmental lesion (%)	Rate of crescents (%)	MEST-C score	Histological grade	Clinical grade
Case 1	30	3.3	6.7	0	M0, E0, S0, T0, and C0	I-C	I
Case 2	32	6.1	9.4	0	M0, E0, S0, T0, and C0	I-C	I
Case 3	33	12.1	15.2	3.0	M0, E0, S1, T1, and C0	II-A/C	I

Fig. 2 Changes in laboratory parameters and blood pressures over the 12 month treatment period with pemafibrate. **a** Triglyceride, **b** urinary protein excretion, **c** urinary L-FABP, **d** eGFR, and **e** systolicand **f** diastolic blood pressures. eGFR, estimated glomerular filtration rate; L-FABP, liver-type fatty acid-binding protein

Discussion

This case series is the first report that 12 months of pemafibrate treatment reduced serum triglyceride levels and urinary protein excretion and L-FABP without changing eGFR, in three drug-naïve IgAN patients with low clinical grade, but declined eGFR, and hypertriglyceridemia.

Because therapy-mediated reduction in urinary protein excretion is known to be associated with an improved prognosis in IgAN [8, 9], pemafibrate has potential to become a novel and safe therapeutic approach in those mild IgAN patients and hypertriglyceridemia.

Elevated levels of serum cholesterol and triglyceride are associated with the incidence and progression of CKD and a greater decline in eGFR [1]. There is also evidence that

conventional fenofibrate attenuates renal impairment and delays the progression of nephropathy in patients with diabetes [2]. However, another fibrate, gemfibrozil, has been reported to have no clinically relevant effect on renal function in patients with coronary artery disease and CKD, relative to that observed with placebo [10]. Therefore, it remains controversial whether medication-mediated improvement of hypertriglyceridemia has favorable effects on renal function and prevents progression of nephropathy in patients with established CKD.

Recently, Yokote et al. [4] reported that pemafibrate, a novel SPPARM α , was safe and effective for correcting lipid abnormalities in a broad range of dyslipidemic patients with different levels of renal impairment. In that study, pemafibrate treatment for 52 weeks was proven to cause greater improvement of pro-atherogenic lipid abnormalities in a subgroup of patients with the lowest baseline eGFR (eGFR < 30 mL/min/1.73m²). Importantly, no changes in eGFR were observed throughout the observation period even in subgroups with a baseline eGFR < 60 mL/min/1.73m². Taken together, these findings provided evidence that pemafibrate was well tolerated and effective even in patients with CKD and ESRD. While the etiologies of the patients' renal impairment were not fully defined in the study, 37% and 53% of the participants had type 2 diabetes and hypertension, respectively.

In our case series of mild IgAN patients with low clinical grade, but declined eGFR, pemafibrate treatment was safe and well tolerated for 12 months, with no apparent changes in eGFR observed during the treatment period in any patient. Moreover, pemafibrate decreased urinary protein excretion, suggesting that the agent has renoprotective effects in mild IgAN patients. Due to safety concerns regarding renal impairment, a low dose of pemafibrate of 0.1 mg once daily was initiated and continued for 12 months in our three patients. Thus, our report may indicate a possibility that at least pemafibrate of 0.1 mg once daily becomes an alternative treatment in those patients without excess harm. It should be determined whether the usual dose of pemafibrate (0.2 mg twice daily) is also safe and more effective in attenuating urinary protein excretion in IgAN patients with renal insufficiency.

The underlying mechanisms of the apparent renoprotective effects of pemafibrate in CKD are not fully understood. PPAR α is known to be expressed widely along nephron segments, including glomerular and renal tubular cells [11]. Recently, Maki et al. [5] successfully demonstrated that pemafibrate administration in an experimental model of diabetic nephropathy attenuated albuminuria and ameliorated the pathological features of diabetic nephropathy by reducing renal lipid content and oxidative stress. Similarly, in our three cases urinary L-FABP concentration, a representative marker of excess oxidative stress in

the kidney, was decreased after 12 months of pemafibrate treatment. Furthermore, the reductions of proteinuria and L-FABP observed in the present cases were unlikely associated with changes in blood pressure. These findings suggest that pemafibrate has a direct renoprotective effect, at least in part, as a result of common mechanisms in CKD irrespective of etiology. Furthermore, experimental studies have shown that pemafibrate attenuated the arterial atherosclerotic burden as a consequence of an anti-inflammatory action by modulating lipid and energy metabolism [12]. Therefore, pemafibrate may have beneficial impacts on multi-organ/tissue, over and above its action of correcting lipid abnormalities.

In summary, this is the first report that 12 months of pemafibrate treatment in three drug-naïve patients with mild IgAN and hypertriglyceridemia was clinically safe and effective for decreasing urinary protein excretion without changing eGFR and blood pressure levels. However, since we had no control group, the findings in the present case report may be hypothesis-generating at this time. A placebo-controlled randomized clinical trial to investigate the safety and efficacy of pemafibrate in hypertriglyceridemia patients with mild to moderate renal impairment is now in progress (NCT03011450). In addition, the current cases exhibited a typical clinical characteristic of the early stage of IgAN with small amount of urinary protein excretion, and the reduction of proteinuria in these patients were marginal because of the lower levels of proteinuria at baseline. Accordingly, whether the effects of pemafibrate on hard-to-treat IgAN patients is still uncertain. Thus, the findings in the present case report are hypothesis-generating at this time, and further study is required to determine the optimal IgAN patients with hypertriglyceridemia who could potentially benefit from treatment with pemafibrate in a broad spectrum of IgAN patients. Further research is also warranted to test whether pemafibrate exerts a renoprotective effect in other types of CKD and nephropathy.

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Compliance with ethical standards

Conflict of interest AT has received a research grant from Glaxo-SmithKline. KN has received honoraria from Ono, Takeda, Daiichi Sankyo, Astellas, MSD, Boehringer Ingelheim, and Mitsubishi Tanabe; research grants from Asahi Kasei, Astellas, Boehringer Ingelheim, Mitsubishi Tanabe, Teijin, and Terumo; scholarship from Bayer, Takeda, Astellas, Daiichi Sankyo, Teijin, and Bristol-Myers Squibb. The remaining authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the participant included in the article.

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