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Original paper

Pemafibrate decreases markers of hepatic inflammation in patients with non-alcoholic fatty liver disease

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Abstract

Aim of the study: Non-alcoholic fatty liver disease (NAFLD) is frequently complicated by dyslipidemia and is considered to be a hepatic manifestation of metabolic syndrome. Pemafibrate is a novel selective peroxisome proliferator-activated receptor-α modulator. There are no reports of the clinical effects of pemafibrate in patients with NAFLD. The aim of this study is to determine the effect of pemafibrate on patients with NAFLD.

Material and methods: This is an observational study of patients with NAFLD complicated by dyslipidemia treated with pemafibrate for three months. Patient medical records were retrospectively reviewed.

Results: Thirty-eight patients were included, and all patients had dyslipidemia without diabetes. Changes in parameters after three months of pemafibrate therapy were evaluated. Weight was not significantly changed. Alanine aminotransferase, a marker of hepatic inflammation, significantly improved. Remarkably, alkaline phosphatase and γ-glutamyl transpeptidase decreased in all patients. The albumin-bilirubin score, a marker of hepatic function, improved due to significant elevation of serum albumin and decrease in total bilirubin. Lipid profiles including high-density lipoprotein cholesterol and triglycerides significantly decreased. Low-density lipoprotein cholesterol did not significantly change. The NAFLD fibrosis score significantly improved, but the FIB-4 index did not significantly change.

Conclusions: Three months of pemafibrate treatment of patients with NAFLD improves markers of hepatic inflammation, function and fibrosis. This is the first clinical study evaluating the effect of pemafibrate in patients with NAFLD.

Key words: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, pemafibrate, dyslipidemia, hepatitis.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is frequently complicated by dyslipidemia and is considered to be a hepatic manifestation of metabolic syndrome. NAFLD is the most common cause of chronic liver disease and its incidence is increasing worldwide [1]. NAFLD is roughly classified into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NASH has the potential to progress to hepatic fibrosis and hepatocellular carcinoma. Controlling hepatic inflammation is the key to preventing liver-related mortality due to NASH. Undoubtedly, lifestyle modifications such as exercise, weight control and calorie restriction are the first-line treatments, but it is very difficult for patients to maintain adequate weight loss. Although pioglitazone and vitamin E are suggested as a treatment for NASH, there are no definite medications [2].

Pemafibrate, a novel selective peroxisome proliferator-activated receptor-α modulator (SPPARMα), was released in 2018 in Japan as the first site in the world. It is believed to decrease triglyceride levels by upregulating peroxisome proliferator-activated receptor-α (PPARα) activity. An international joint clinical trial has been started to evaluate the effect of pemafibrate on the incidence of cardiovascular events [3]. Pemafibrate results in greater improvement in liver function in a rodent model of NASH compared to fenofibrate [4]. Although a phase II trial demonstrated significant improvements in hepatobiliary enzymes and lipid profiles, the diagnosis of NAFLD was not established [5]. There are no reports of the clinical effect of pemafibrate in patients with NAFLD. The aim of this study is to clarify the effect of pemafibrate on patients with NAFLD.

Material and methods

Study population and retrospective review

This is an observational study of patients with NAFLD who started treatment with pemafibrate from June 2019 to January 2020. Medical records were retrospectively reviewed and the following data abstracted: age, gender, smoking habits, alcohol use, medications, background diseases, height, weight and laboratory findings.

The inclusion criteria for this study include: 1) NAFLD diagnosed by abdominal ultrasound, 2) hypertriglyceridemia treated with pemafibrate, 3) continued elevation of alanine aminotransferase (ALT) > 30 for more than three months before starting pemafibrate, 4) negative hepatitis B surface antigen and hepatitis C virus antibody tests, 5) normal serum immunoglobulin-G level, 6) alcohol consumption < 30 g/day in males and < 20 g/day in females. The exclusion criteria include: 1) severe chronic kidney disease (serum creatinine > 2.5 mg/dl), 2) history of using pemafibrate or 3) patients who stopped pemafibrate treatment within three months. The Institutional Review Board approved this retrospective review.

Evaluation of the liver

Serum ALT levels were used to assess hepatic inflammation, because serum ALT is validated as a marker for the progression of hepatic fibrosis in patients with NASH [6, 7]. The albumin-bilirubin (ALBI) score was used to evaluate hepatic function [8]. To assess hepatic fibrosis, we used the FIB-4 index and NAFLD fibrosis score [9, 10]. Changes in these parameters were calculated with the following formula: value at three months – value before starting treatment.

Statistical analysis

Changes in parameters were evaluated with the Wilcoxon rank-sum test. Spearman's rank correlation coefficient was used to assess the association between variables. StatFlex 7.0 software (Artech Co., Ltd., Osaka, Japan) was used for statistical analyses.

Results

Baseline characteristics

Thirty-eight patients were included after excluding three patients who were not compliant with taking pemafibrate 0.1 mg twice daily for three months. Dose escalation of pemafibrate was not performed in all patients. All patients had dyslipidemia, and 29 patients were previously treated with statins and/or ezetimibe for more than six months (Table 1). All patients were neither diagnosed with diabetes mellitus nor treated with anti-diabetes medications, and hemoglobin A1c levels were confirmed to be less than 6.5%. There was no concomitant use of ursodeoxycholic acid or tocopherol. No serious adverse events have been observed.

Changes in hepatic and lipid profiles

Changes in the study parameters after three months of pemafibrate therapy are shown in Table 2. Weight was not significantly changed and ALT significantly decreased. Remarkably, alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GTP) decreased in all patients. Platelet counts significantly increased and the ALBI score, a marker of hepatic function, significantly decreased due to elevation of serum albumin

Table 1. Baseline characteristics of patients treated with pemafibrate

Variables	*N* = 38
Age (years), mean ±SE	57.1 ±2.2
Gender (male), *n* (%)	22 (58)
Currently using tobacco, *n* (%)	2 (5)
Complications treated with medications, *n* (%)	
Hypertension	16 (42)
Gastroesophageal reflux disease	13 (34)
Hyperuricemia	3 (8)
Diabetes mellitus	0 (0)
Combination use, *n* (%)	
Statins	27 (71)
Ezetimibe	10 (26)
Angiotensin II receptor blockers	11 (29)
Eicosapentaenoic acid/docosahexaenoic acid	1 (3)

Table 2. Changes in clinical parameters after a three-month course of pemafibrate therapy

Variables	Baseline	3 months	*P*-value
Weight (kg), mean ±SE	74.7 ±2.6	74.4 ±2.6	0.261
Body mass index	28.1 ±0.6	28.1 ±0.6	0.225
AST (U/l)	49.1 ±3.7	41.6 ±2.8	0.028
ALT (U/l)	63.9 ±3.6	41.6 ±3.6	< 0.001
ALP (U/l)	301 ±23	204 ±18	< 0.001
γ-GTP (U/l)	76.8 ±11.8	37.5 ±6.3	< 0.001
Platelet count ($\times 10^4$/μl)	25.2 ±0.6	27.7 ±0.8	< 0.001
Estimated GFR (ml/min/1.73 m^2)	77.2 ±2.7	76.1 ±2.9	0.130
LDL cholesterol (mg/dl)	98.3 ±4.4	93.4 ±4.1	0.086
HDL cholesterol (mg/dl)	51.7 ±2.3	54.3 ±2.0	0.016
Triglyceride (mg/dl)	171 ±34	115 ±18	< 0.001
Total bilirubin (mg/dl)	0.95 ±0.05	0.77 ±0.03	< 0.001
Serum albumin (g/dl)	4.3 ±0.1	4.5 ±0.1	0.001
ALBI score	−2.90 ±0.04	−3.07 ±0.03	< 0.001
FIB-4 index	1.51 ±0.16	1.47 ±0.12	0.500
NAFLD fibrosis score	−2.27 ±0.18	−2.38 ±0.18	0.009

SE – standard error, AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, γ-GTP – γ-glutamyl transpeptidase, GFR – glomerular filtration rate, LDL – lowdensity lipoprotein, HDL – highdensity lipoprotein, ALBI – albumin-bilirubin, NAFLD – non-alcoholic fatty liver disease

and a decrease in total bilirubin level. The lipid profiles including high-density lipoprotein (HDL) cholesterol and triglycerides improved. However, low-density lipoprotein (LDL) cholesterol levels did not change significantly. Regarding markers for hepatic fibrosis, the NAFLD fibrosis score was significantly improved, but the FIB-4 index did not significantly change.

Correlation analysis

We next investigated the association of changes in hepatic markers with other parameters (Table 3). Regarding hepatic inflammation, changes in serum ALT levels significantly correlated with changes in aspartate aminotransferase (AST), γ-GTP and triglyceride levels. The change in ALBI score significantly correlated with changes in ALP level.

Discussion

This retrospective observational study shows improvement in markers of hepatic inflammation, function and fibrosis after three months of pemafibrate treatment in patients with NAFLD. NAFLD is frequently associated with dyslipidemia, and the most common cause of death in patients with NAFLD is cardiovascular disease, followed by liver-related diseases [11]. To improve the long-term outcomes in patients with NAFLD, it is important to control both hepatic and lipid profiles. To the best of our knowledge, this is the first clinical study to report the effect of pemafibrate effect in patients with NAFLD.

In a Japanese phase II study, pemafibrate administration decreased serum ALT levels [5]. However, the diagnosis of NAFLD was not established in that trial. There were significantly fewer adverse events related to hepatobiliary enzyme elevation than in patients receiving placebo or fenofibrate [12]. There are no clinical studies to date that report the clinical effects of pemafibrate in patients with NAFLD. We first reported an improvement in markers of hepatic inflammation, function and fibrosis in patients with NAFLD without diminution of renal function. Unlike the previous phase II trial [5], both AST and ALT significantly decreased during pemafibrate therapy in this study.

Patients with NAFLD have a higher risk of having a reduced platelet count compared with people without NAFLD [13]. Recently, the effect of platelets on hepatic regeneration and suppression of fibrosis has been reported in a murine model [14]. The platelet counts were significantly elevated at three months in this study, which may be related to improved hepatic function. The definitive cause of platelet count elevation is unclear, but elevated thrombopoietin or improvements in hypersplenism may influence this result.

Interestingly, pemafibrate also improved the ALBI score in these patients. The ALBI score is calculated using serum total bilirubin and albumin levels. Despite the lack of a conclusive explanation, maintained amelioration of hepatic inflammation may lead to improved hepatic function. Since pemafibrate reduces hepatocyte ballooning as well as hepatocyte inflammation/fibrosis in a murine model [4], pemafibrate might relieve compression of small bile ducts due to ballooning and inflammation. The extent of improvement of hepatic fibrosis in this short-term study is not clear. Although NAFLD fibrosis score and platelet count significantly improved, the FIB-4 index did not change. To evaluate hepatic fibrosis, a long-term study is essential.

PPARα, a therapeutic target of pemafibrate, in hepatocytes plays an important role in enhancing mitochondrial β-oxidation and decreasing obesity-induced hepatic inflammation [15]. PPARα knock-out mice develop hepatic inflammation, steatosis and carcino-

Table 3. Association of changes in hepatic markers of inflammation/function with other parameters

Parameters changed during treatment	ΔALT		ΔALBI score	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
ΔWeight (kg)	0.131	0.430	0.078	0.640
ΔBody mass index	0.127	0.444	0.099	0.550
ΔAST (U/l)	**0.904**	**< 0.001**	0.043	0.796
ΔALT (U/l)	–	–	0.105	0.529
ΔALP (U/l)	0.306	0.061	**0.334**	**0.040**
Δγ-GTP (U/l)	**0.595**	**< 0.001**	0.275	0.093
ΔPlatelets (× 10^4/μl)	–0.148	0.373	0.223	0.178
ΔEstimated GFR (ml/min/1.73 m^2)	0.050	0.762	0.022	0.894
ΔLDL cholesterol (mg/dl)	0.279	0.089	0.258	0.117
ΔHDL cholesterol (mg/dl)	–0.138	0.406	–0.141	0.396
ΔTriglyceride (mg/dl)	**0.379**	**0.018**	0.177	0.286
ΔTotal bilirubin (mg/dl)	0.101	0.544	–	–
ΔSerum albumin (g/dl)	–0.017	0.981	–	–
ΔALBI score	0.105	0.529	–	–
ΔFIB-4 index	–	–	–0.285	0.082
ΔNAFLD fibrosis score	–	–	0.060	0.717

AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, γ-GTP – γ-glutamyl transpeptidase, GFR – glomerular filtration rate, LDL – low-density lipoprotein, HDL– high-density lipoprotein, ALBI – albumin-bilirubin, NAFLD – non-alcoholic fatty liver disease. Statistically significant changes (p < 0.05) are shown in a bold font.

genesis [16, 17]. However, classical fibrates such as fenofibrate and bezafibrate adversely affect hepatic function, and do not have adequate benefit to be used for the treatment of patients with NAFLD. PPARα gene expression is negatively proportionate to the severity of NASH, and histological improvement is associated with PPARα gene expression [18]. Considering the systemic expression of PPARα, pemafibrate may promote lipid catabolism in brown adipose tissue and muscle as well as the liver [19]. Pemafibrate with higher selectivity for PPARα than fenofibrate/bezafibrate has a beneficial effect on NAFLD that was reported in a murine model [4]. This high selectivity may contribute to the development of fewer adverse effects including hepatic and renal damage. Activated PPARα due to pemafibrate increases lipoprotein lipase activity, leading to decreased triglyceride and increase HDL cholesterol levels. It also increases cellular fatty acid uptake and β-oxidation in the liver [20]. In this study, there was a significant positive correlation between changes in ALT and triglyceride levels. PPARα activation itself or a metabolic pathway via decreased triglycerides may improve hepatocyte inflammation. Activated PPARα increases catabolism and decreases fat accumulation in the liver by enhancing β-oxidation. Therefore, PPARα is a promising therapeutic target for NAFLD.

There are some acknowledged limitations to this study. First, this is a retrospective single center study without a control group. Second, the study period may be too short to demonstrate an improvement in hepatic fibrosis. Third, histopathological evaluation of the liver was not performed. Fourth, concomitant use of statins and/or ezetimibe may bias these results. Fifth, exercise during the study period was not evaluated, although weight was not significantly changed. Sixth, a small number of treated patients was included.

In conclusion, three months of pemafibrate treatment in patients with NAFLD without diabetes significantly improves markers of hepatic inflammation, function and fibrosis. Pemafibrate is effective to control hepatic inflammation in patients with NAFLD in the short term. Further long-term studies are necessary to evaluate an improvement in hepatic fibrosis.

Disclosure

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