Communication

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Pemafibrate Improves Alanine Aminotransferase Levels Independently of Its Lipid-Lowering Effect

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Abstract: AIM: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. Pemafibrate, a selective peroxisome proliferator-activated receptor α modulator (SPPARMα), has been reported to ameliorate liver function among patients with dyslipidemia. However, there are not many reports of the clinical effects of the pemafibrate. This study aims to summarize the experience of using pemafibrate and analyze the effects on liver function in patients with dyslipidemia. METHODS: One hundred twelve cases of hyperlipidemia receiving pemafibrate 0.2 mg/day were retrospectively enrolled in this study. Age, gender, BMI, complications, concomitant medications, serum parameters (TG, HDL-C, LDL-C, AST, ALT, γGTP, ALP, platelets, M2BPGi, Cre, eGFR, HbA1c, blood glucose level at any time) were investigated and evaluated. RESULTS: Pemafibrate administration significantly improved serum TG and HDL-C, but not in LDL-C. Serum AST, ALT, γGTP, and ALP were also significantly improved. The fib-4 index, a liver fibrosis score, did not change significantly, but M2-BPGi, an index of fibrosis, decreased significantly. No correlation was observed between each lipid parameter and ALT, and ALT decreased independently of the lipid parameters. Conclusions: As we expected, pemafibrate demonstrated a lipid-improving effect without adversely affecting hepatic and renal functions. An unexpected finding was the decrease in ALT that was independent of lipid parameters.

Keywords: pemafibrate; Non-alcoholic fatty liver disease (NAFLD); Alanine Aminotransferase; M2-BPGi; dyslipidemia; liver fibrosis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, and its incidence is increasing (1). NAFLD is frequently complicated by dyslipidemia, and in about 50 % of cases with hypertriglyceridemia (TG > 150 mg/dl) (2). Dietary, physical activity therapy, and weight loss associated with them are the first choices for the treatment of NAFLD, but it is very difficult to achieve improvement because weight management is left to the motivation of patient. In addition to weight loss, the next treatment that should be introduced is drug therapy. As a treatment method, Sodium-glucose cotransporter-2 (SGLT2) inhibitors, vitamin E, statins, Angiotensin-converting enzyme (ACE) inhibitors, and aldosterone receptor blockers have been proposed for NASH / NAFLD depending on complications, but there is currently no clear treatment method (3). Fibrate, peroxisome proliferator-activated receptor (PPAR)α agonist, raises HDL-C and reduces TG. But it is not selective and not high affinity ligand of PPARα Bezafibrate activates not only PPARα but also PPAR γ/β and is considered as a pan-PPAR agonist (4). On the other hand, pemafibrate (Kowa Company), a selective peroxisome proliferator-activated receptor (PPAR)-α modulator (SPPARMα), received the world's first approval in Japan as a therapeutic agent for dyslipidemia in 2018. It has a mechanism to lower TG more safely and efficiently by activating PPARα from a lower dose than conventional fibrates (5). Pemafibrate has been reported to suppress hepatic fat deposition in the

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rodent model of NASH compared to fenofibrate (6). Phase II trials have shown useful improvements not only in lipid profiles but also in hepatobiliary system parameters (7). From these points, there is a report recommending pemafibrate in the treatment of NAFLD (3). However, there are not many reports of the clinical effects of pemafibrate other than clinical trials. The purpose of this study is to summarize the experience of using pemafibrate and analyze what kind of patients are suitable for pemafibrate administration.

Methods

A retrospective observational study was conducted on dyslipidemia patients who received pemafibrate as outpatient treatment from April 2019 to April 2020. Cases were collected under the following conditions in the Department of Gastroenterology at our hospital (Kameda Daiichi Hospital). Age, gender, BMI, complications, concomitant medications, serum parameters (TG, HDL-C, LDL-C, AST, ALT, γGTP, ALP, platelets, M2BPGi, Creatinine, eGFR, HbA1c, blood glucose level at any time) were collected. These parameters were evaluated by non-fasting blood sampling, and the blood sampling time was unified as possible. Pre-administration data were obtained from the outpatient visit immediately before the administration of pemafibrate, and for post-administration data, the information from the last visit after the administration of pemafibrate was used. The present study was approved by the Ethical Committee of Kameda Daiichi Hospital (Institutional review board no. R3-2021, April 28, 2021) and consent to participate in the study was obtained using the opt-out method.

Liver function evaluation

The criteria for NAFLD was fat deposition on abdominal ultrasonography. The FIB-4 index was calculated to assess liver fibrosis (8). FIB-4 index was calculated using the following formula: age (year) x AST (U / L) / platelet count (x 10^9 / L) x [ALT (U / L)]$^{1/2}$. Since serum ALT has been evaluated as a marker for the progression of liver fibrosis in NASH patients (9, 10), the correlation between serum ALT and each parameter was examined.

Statistical analysis

Each item value is expressed as mean ± standard deviation (SD) or %. Comparison before and after administration was performed by paired t-test, and the significance level was 5 % on both sides. For correlation, the relationship between variables was evaluated using the Spearman correlation coefficient, and the significance level was set to 5%. For statistical analysis, Excel statistics and statistical analysis software EZR were used.

Ethical examination

The Institutional Review Board approved this retrospective review.

Results

1. Baseline (Table 1)

Table 1. Baseline characteristics of patients treated with pemafibrate.

Characteristics	N=112	Average ± SD
Age (years)　Mean (Range)	62.2	13.7
Males / Females	77	
BMI（kg/m²） Mean (Range)	25.4	4.2
Follow-up period (days) Mean (Range)	224.1	83.6

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Complications treated with medications		%
Liver disease(n)	90	80.4
NAFLD(n)	71	63.4
Hypertension(n)	54	48.2
Diabetes mellitus(n)	43	38.4
Concomitant medications(n)		%
Statin	51	45.5
Ezetimibe	5	4.5
EPA・DHA	0	0.0
SGLT2 inhibitor	31	27.7
DPP4 inhibitor	28	25.0
Metformin	16	14.3
ARB	16	14.3
UDCA	30	26.8
Vitamin E	23	20.5

This study included one hundred twelve sequential patients with hyperlipidemia receiving Pemafibrate 0.2 mg/day. The average administration period was 224.1± 83.6 days. 80 % had liver disease and 63.4 % were diagnosed with NAFLD which was treated with UDCA and vitamin E. The complication rates of lifestyle-related disease, hypertension, and diabetes were 48.2 % and 38.4 %, respectively, and SGLT2 inhibitors, DPP4 inhibitors, and metformin were administered as concomitant drugs. As therapeutic drugs for dyslipidemia, statins, and ezetimibe were administered in 45.5 % and 4.5 %, respectively. There were no cases of concomitant use of EPA preparations.

2. Pre and post-treatment (Table 2)

Table 2. Changes in clinical parameters before and after pemafibrate therapy.

Variables	Before	After	Change	P value
Weight(kg)	68.3±14.2 (98)	68.9±14.1 (106)	0.5±2.0 (98)	0.023
BMI(kg/m^2)	25.4 ±4.2 (78)	25.7±4.1 (87)	0.2±0.7 (78)	0.028
AST(IU/L)	36.1±32.1 (102)	27.8±17.0 (112)	−7.9±27.8 (102)	0.005
ALT(IU/L)	43.7±43.8 (102)	24.0±13.8 (112)	−18.9±40.6 (102)	<0.001
γ−GTP (IU/L)	93.8±210.2 (102)	44.3±129.3 (112)	−47.1±99.1 (102)	<0.001
ALP(IU/L)	253.0±88.9 (97)	164.8±53.7 (112)	−85.2±60.8 (97)	<0.001
Platelet count(×10^4/μl)	24.6±7.2 (105)	26.9±8.6 (112)	2.4±6.0 (105)	<0.001
fib−4 index	1.6±1.0 (98)	1.5±0.9 (112)	−0.1±0.5 (98)	0.257
M2BPGi	0.9±0.7 (36)	0.7±0.5 (90)	−0.1±0.2(36)	0.028
Triglyceride(mg/dl)	234.6±126.3 (112)	126.7±68.4 (112)	−107.9±111.0 (112)	<0.001
HDL−C(mg/dl)	52.6±12.9 (112)	55.7±11.6 (112)	3.1±9.7 (112)	0.001
LDL−C(direct)(mg/dl)	118.4±35.2 (112)	111.9±28.0 (112)	−6.4±36.2 (112)	0.064
Serum Cre(mg/dl)	0.8±0.2 (105)	0.8±0.2 (112)	0.0±0.1 (105)	0.570
eGFR(mL/min/1.73m^2)	73.0±15.2 (105)	73.1±15.5 (112)	−0.3±9.0 (105)	0.707
HbA1c(%)	6.5±1.0 (90)	6.4±1.0 (110)	0.0±0.7 (90)	0.874
Glucose(non−fasting)(mg/dl)	138.7±42.1 (91)	130.4±38.1 (110)	−6.5±42.7 (91)	0.153
Systolic blood pressure(mmHg)	133.8±15.4 (107)	138.8±16.2 (111)	4.4 ±15.5 (107)	0.004
Diastolic blood pressure(mmHg)	77.5±11.8 (107)	81.0±13.5 (111)	2.9±10.1 (107)	0.004
Uric acid(mg/dl)	5.4±1.4 (95)	5.3±1.3 (112)	−0.1±0.9 (95)	0.269

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Significantly improved lipid parameters of TG and HDL-C. There is no significant change in LDL-C. The hepatobiliary system parameters of AST, ALT, and ALP were significantly improved. The fib-4 index, which is a liver fibrosis score, did not change significantly. Body weight and platelets increased significantly. No significant changes were observed in renal and blood glucose parameters.

3. ALT correlation (Figures 1 and 2)

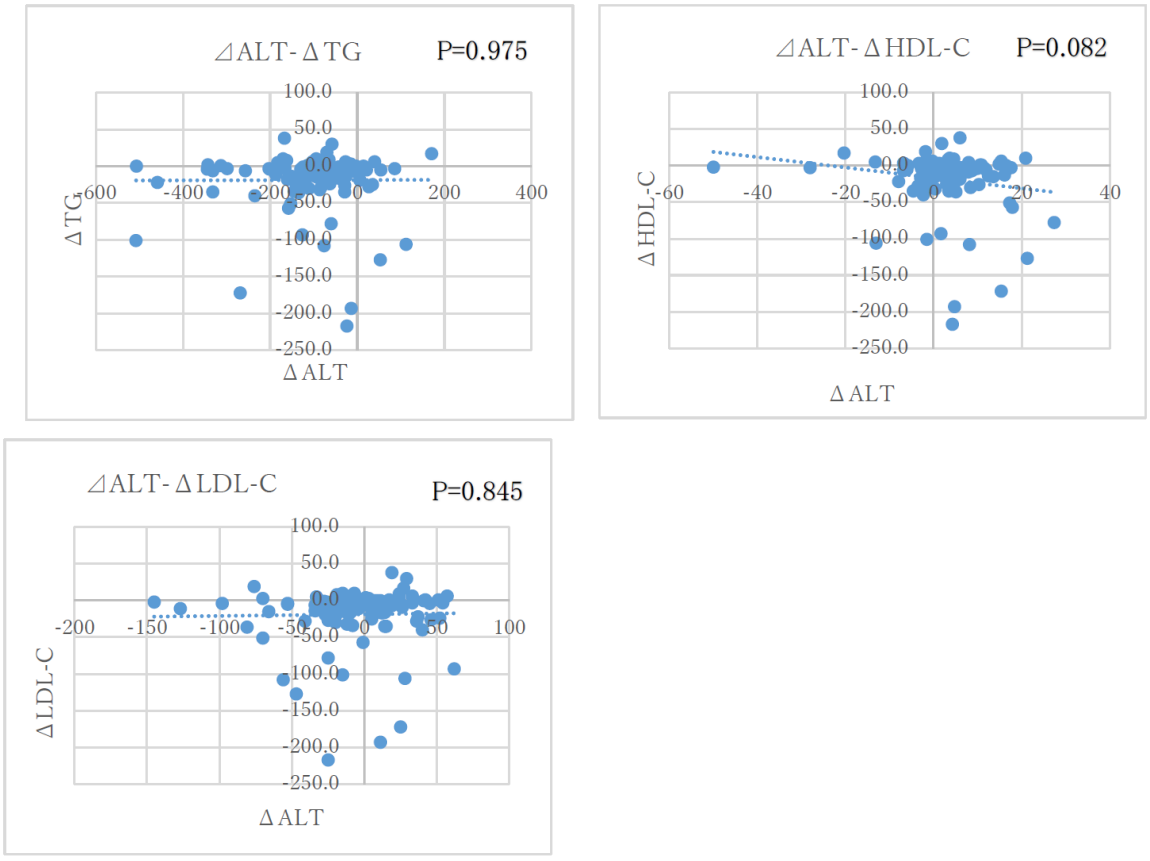
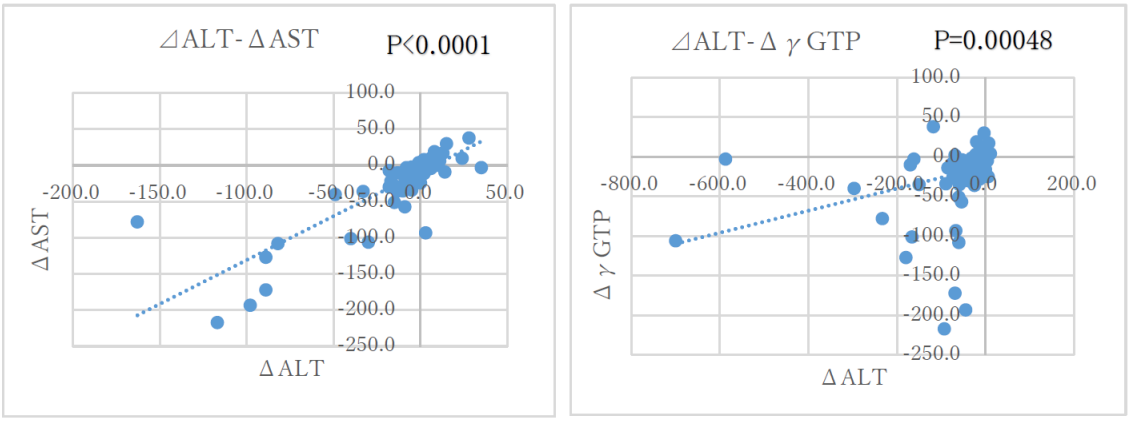


Figure 1. Association of changes ALT with lipids parameters.



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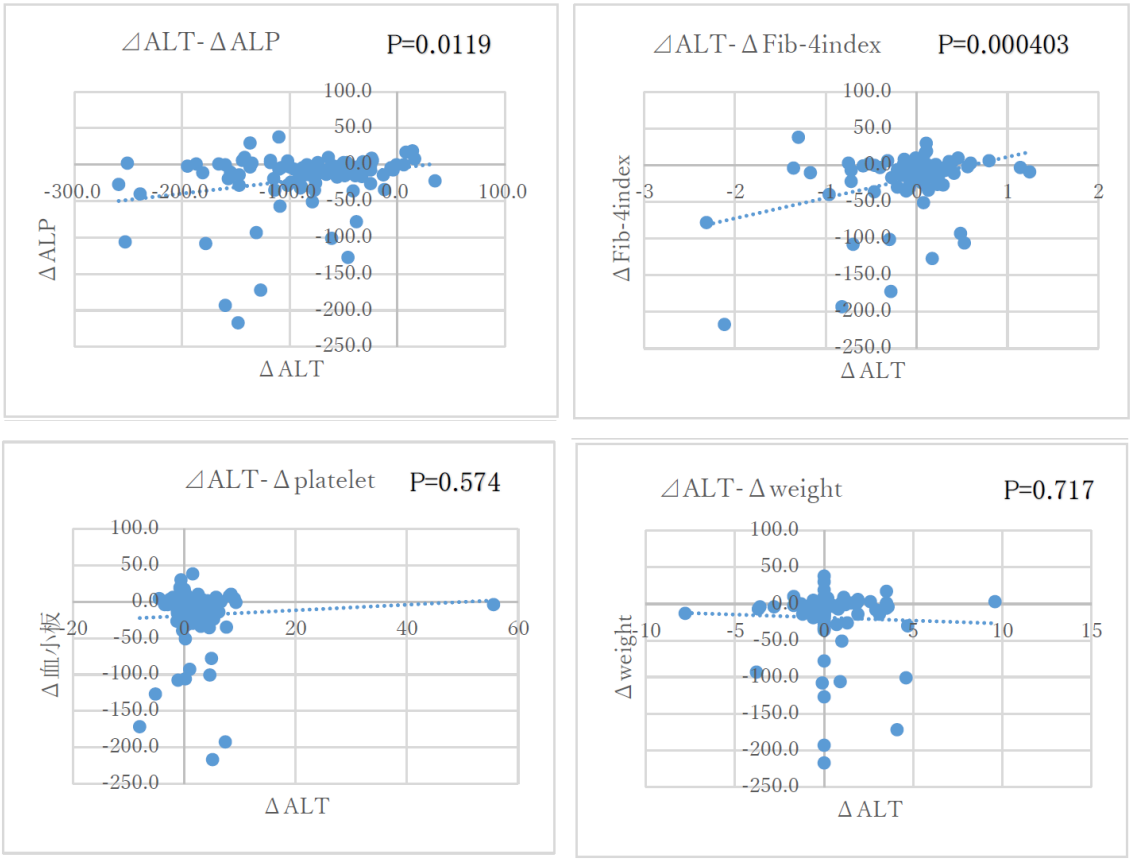

Figure 2. Association of changes ALT with other parameters.

The correlation between ΔALT and the degree of changes in lipid parameters (ΔTG, ΔHDL-C, ΔLDL-C) was examined. Correlation between ΔALT and ΔTG: Correlation coefficient r = 0.0319, P = 0.975, ALT and HDL-C: Correlation coefficient r = -0.173, P = 0.082, ΔALT and ΔLDL-C: Correlation coefficient r = 0.0196, P = 0.845, no correlation observed between each lipid parameter and ΔALT, and ΔALT decreased independently of the lipid parameters.

4. Safety information

No serious adverse events have been observed.

Discussion

In this study, significant improvement in lipid parameters and hepatobiliary parameters was observed in dyslipidemia patients who received pemafibrate. 64 % of these cases were complicated by NAFLD, suggesting a link between NAFLD and hyperlipidemia. Hypertriglyceridemia and NAFLD are related diseases in metabolic syndrome, and NAFLD is often associated with hyperlipidemia. The complication rate in this study is almost the same as the previous report that showed that about 50% of patients with TG > 150 mg / dl were complicated by NAFLD (2). Hypertriglyceridemia is also an exacerbating factor for cardiovascular events (11, 12). Cardiovascular disease is the most common cause of death in NAFLD patients (13). Therefore, treatment intervention for lipids parameters is considered to be a necessary treatment for improving the long-term prognosis of NAFLD patients. In Japanese phase II trial, the administration of pemafibrate reduced serum ALT levels in subjects with normal liver function (7). There were significantly fewer adverse events associated with elevated hepatobiliary enzymes than in patients receiving fenofibrate (14). In this study, AST and ALT are decreased, which is in agreement with the previous findings. Several clinical studies have reported the clinical effects of pemafibrate in patients with NAFLD, but they are limited (15, 16, 17). Since serum ALT has been evaluated as a marker for the progression of liver fibrosis in NASH patients (9, 10), we performed a correlation analysis between the degree of ALT changes and

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lipid parameters in this study. As a result, it was confirmed that ALT changes independently of lipid parameters. In addition, ALT was not correlated with body weight. Pemafibrate decreased collagen 1α1 and TNFα mRNA expression in the liver with NASH model mice (18). The improvement of liver fibrosis and inflammation by pemafibrate treatment might reduce the serum levels of ALT in the present study. Pemafibrate phase 2 study in NAFLD patients, not only with hypertriglyceridemia but also with non- hypertriglyceridemia, pemafibrate therapy significant reduced in serum ALT and liver stiffness (19). Therefore, these findings suggest that it might directly improve liver fibrosis and alleviate inflammation in liver not via triglycerides lowering effects. It is consistent with the improvement ALT levels independently of its lipid-lowering effects in the present study. The present study also showed the reduction in the biliary enzymes, γGTP and ALP. Fibrate activates PPARα and micellizes hydrophobic bile acids via the upregulation of the expression of multidrug resistance gene 3 (mdr3), a transporter related for secretion of biliary phospholipid in bile duct membranes (20, 21). According to the result, Fibrate may protect hepatic cells and bile duct epithelium. Therefore, it has been reported that the efficacy of pemafibrate treatment add on ursodeoxycholic acid in primary biliary cholangitis patients with dyslipidemia (22, 23).

This is a new finding that has never been reported before. PPARα knockout mice develop liver inflammation, steatosis, and carcinogenesis (24, 25). Therefore, PPARα is the key to improving fatty liver. Pemafibrate is a drug that promotes mitochondrial β-oxidation in hepatocytes and lowers lipid parameters, especially TG, by activating the nuclear receptor PPARα (26). Honda et al. reported that pemafibrate reduced hepatic fat, hepatocyte ballooning and hepatocyte inflammation / fibrosis (6). Sakai et al. also reported that pemafibrate suppressed hepatic inflammation. Increased hepatic lipid droplet number, and reduction of their size was observed in NASH model mice (27). Even in LDL knockout pigs that do not exhibit hyerglyceridemia, pemafibrate administration suppresses vasculitis (28). This is thought to be a direct effect on blood vessels. The ALT-lowering effect of pemafibrate in this study may also be contributed by a direct anti-inflammatory effect on the liver, and may have been caused by a mechanism different from the serum TG-lowering pathway. PPARα is an important factor for improving fatty liver, but conventional PPARα agonists, that is fibrates such as fenofibrate and bezafibrate adversely affect liver function and have little advantage in treating patients with NAFLD (5). Pemafibrate, which is more selective for PPARα than fenofibrate / bezafibrate, may have had beneficial effects on NAFLD reported in mouse models (6). This high selectivity may help reducing the occurrence of side effects such as liver and kidney damage. In this study, statins were prescribed in half of the cases during the observation period of 1 year or more, but there were no significant changes in renal markers. From the above points, it is considered that the risk of adverse effects on the kidneys is low.

Conclusion

Pemafibrate was expected to have a lipid-improving effect without adversely affecting hepatic and renal functions, and the decrease in ALT was independent of lipid parameters.

Limitation

There are several limitations in this study.

1. Single facility, retrospective observational study.
2. The pemafibrate administration period is not unified.
3. The control group has not been set.
4. No histopathological evaluation of the liver performed after administration.
5. There are quite a lot of concomitant medications, and pemafibrate alone cannot be evaluated. In particular, SGLT2 inhibitors and concomitant drugs such as statins and ezetimibe may greatly affect the effects of NAFLD.

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Disclosure of Ethical Statements: Approval of the research protocol: The present study was approved by the Ethical Committee of Kameda Daiichi Hospital (Institutional review board no. R3-2021, April 28, 2021) and consent to participate in the study was obtained using the opt-out method.

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Conflict of interest: S.T. receives research funding from Kowa company.

Ethics statement: The Institutional Review Board approved this retrospective review.

A list of abbreviations

ACE	Angiotensin-converting enzyme
NAFLD	Non-alcoholic fatty liver disease
SGLT2	Sodium-glucose cotransporter-2
SPPARMα	A selective peroxisome proliferator-activated receptor (PPAR)-α modulator

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