【 ORIGINAL ARTICLE 】

Impact of Pemafibrate in Patients with Hypertriglyceridemia and Metabolic Dysfunction-associated Fatty Liver Disease Pathologically Diagnosed with Non-alcoholic Steatohepatitis: A Retrospective, Single-arm Study

Takeshi Hatanaka [1], Satoru Kakizaki [2,3], Naoto Saito [1], Yuya Nakano [1], Sachi Nakano [1],
Yoichi Hazama [1], Sachiko Yoshida [1], Yoko Hachisu [1], Yoshiki Tanaka [1], Kenji Kashiwabara [4],
Teruo Yoshinaga [1], Hiroki Tojima [3], Atsushi Naganuma [5] and Toshio Uraoka [3]

Abstract:
Objective   The therapeutic effect of pemafibrate on metabolic dysfunction-associated fatty liver disease (MAFLD) remains unknown. This retrospective, single-arm study investigated the efficacy and safety of pemafibrate in MAFLD patients with hypertriglyceridemia.
Methods   A total of 10 patients who received pemafibrate (oral, 0.1 mg, twice a day) at Gunma Saiseikai Maebashi Hospital between September 2018 and September 2019 were included. All patients underwent a liver biopsy, and the disease grade and stage were pathologically assessed based on the FLIP algorithm.
Results   The median age was 66.0 (53.8-74.8) years old, and 5 patients (50.0%) were men. All patients were diagnosed with non-alcoholic steatohepatitis (NASH). The fasting and non-fasting triglyceride (TG) levels were 175 (149-247) mg/dL and 228 (169-335) mg/dL, respectively. The AST and ALT values at 6 months were significantly lower than at baseline [AST: 28.0 (22.0-33.8) U/L vs. 43.5 (24.0-55.0) U/L, p=0.008, ALT: 23.0 (14.8-26.5) U/L vs. 51.5 (23.0-65.3) U/L, p=0.005, respectively], especially in NASH patients with significant activity and advanced fibrosis (p=0.040 and 0.014, respectively). Fasting TG levels were significantly lower and HDL-C levels significantly higher at 6 months than at baseline (p=0.005 and 0.032, respectively). At six months, FIB-4, the aspartate aminotransferase-to-platelet ratio index, and the macrophage galactose-specific lectin-2 binding protein glycosylation isomer level were significantly improved compared with baseline (p=0.041, 0.005 and 0.005, respectively). Treatment-related adverse events were not observed.
Conclusion   Pemafibrate treatment may be safe and effective for MAFLD patients with hypertriglyceridemia.

Key words: pemafibrate, metabolic dysfunction-associated fatty liver disease, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is an increasing cause of liver disease worldwide and is associated with metabolic disease, such as hypertension, obesity, diabetes mellitus and hyperlipidemia (1-3). Non-alcoholic steatohepatitis (NASH), which is a severe form of NAFLD, increases

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MAFLD (n = 65)
   │
   ├──────► Without HTG (n = 44)
   │
MAFLD with HTG (n = 21)
   │
   ├──────► Lack of biopsy specimen (n = 10)
   │
MAFLD with HTG assessed by liver biopsy (n = 11)
   │
   ├──────► Lifestyle intervention alone (n = 1)
   │
MAFLD with HTG  treated with pemafibrate (n = 10)
   │
Analyzed
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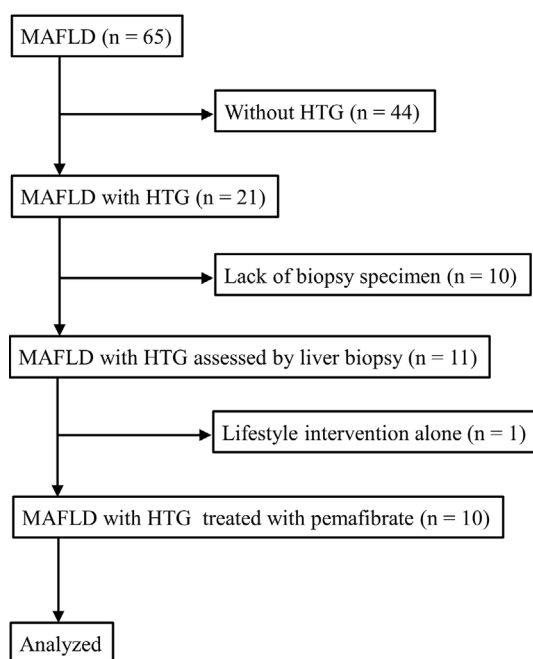
Figure 1.   Patient selection. HTG: hypertriglyceridemia, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis

the risk of cirrhosis, liver failure and hepatocellular carcinoma (4, 5). A previous study showed that a decreased alanine aminotransferase (ALT) level was correlated with histological improvement (6). Accordingly, the management of ALT plays an important role in preventing the progression of NASH, possibly resulting in a reduction in mortality. However, at present, evidence-based pharmacotherapy for NAFLD remains to be established (4, 5).

In 2020, the concept of metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed by a panel of international experts (7). The diagnostic criteria of MAFLD were the presence of hepatic steatosis in addition to one of the following three items: overweight/obesity, the presence of type 2 diabetes mellitus and evidence of metabolic dysregulation, such as hypertension and hypertriglyceridemia (7). A cross-sectional study (8) showed that the clinical feature of MAFLD were an increased body mass index (BMI), a poor metabolic profile (hypertension, diabetes mellitus) and elevated liver enzymes compared to NAFLD. Another study (9) reported that MAFLD patients had a higher BMI and greater waist circumference, a worse metabolic profile, higher liver enzyme levels and worse fibrosis scores than NAFLD patients. These studies indicated that MAFLD patients comprised a more homogenous cohort associated with a risk of advanced hepatic fibrosis than NAFLD (8, 9). Accordingly, the establishment of effective pharmacotherapies for MAFLD patients has been expected.

Pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) (10), shows efficacy on low triglyceride (TG) levels and elevated high-density lipoprotein cholesterol (HDL-C) levels when administered as monotherapy (11) or in combination with statins (12, 13) and has been approved for the treatment of hypertriglyceridemia in Japan. Pemafibrate also helps manage decreased aspartate aminotransferase (AST) and ALT levels and sustains the kidney function compared with fenofibrate (14). However, its efficacy and safety for patients with MAFLD, especially in cases with biopsy-proven NASH, remain unclear.

The present study therefore investigated the effects of 24-week pemafibrate treatment on the lipid profiles and liver function in patients with hypertriglyceridemia and MAFLD who were pathologically diagnosed with NASH.

Materials and Methods

Patients

Sixty-five MAFLD patients visited Gunma Saiseikai Maebashi Hospital (Maebashi, Japan) from September 2018 to September 2019. Of these patients, those without hypertriglyceridemia (n=44), those who did not receive a liver biopsy (n=10) and those who were treated with lifestyle intervention alone (n=1) were excluded. Accordingly, a total of 10 pemafibrate-treated patients with hypertriglyceridemia and MAFLD assessed by a liver biopsy were included in this retrospective, single-arm study (Fig. 1).

The fatty liver was diagnosed based on the findings of ultrasonography, such as increased liver echogenicity, liver-kidney contrast and poor visualization of deep hepatic parenchyma. The diagnosis of MAFLD was made based on a previous report (7), as the authors mentioned above. None of the 10 patients had significant alcohol consumption (i.e., a habitual alcohol intake of ≥30 g/day for men and ≥20 g/day for women) (4, 15). Other concomitant liver diseases, such as viral infection and autoimmune hepatitis, were not found in any of these patients. The pathological diagnosis, including the determination of the grade and stage, was performed by one pathologist according to the FLIP algorithm based on the SAF score (16). Hypertriglyceridemia was also diagnosed based on a fasting TG concentration of ≥150 mg/dL or a non-fasting TG concentration of ≥175 mg/dL (17).

This study was approved by the institutional of Gunma Saiseikai Maebashi Hospital, and the requirement for informed consent was waived because of the retrospective nature of the study.

Pemafibrate treatment and follow-up

Before pemafibrate treatment, the authors confirmed that the patients had a well-preserved liver function (not Child-Pugh class B or C) and did not have evidence of hepatocellular carcinoma, gallstones or renal impairment (serum creatine concentration ≥2.5 mg/dL). All patients received pemafibrate (oral, 0.1 mg, twice a day) and visited the outpatient clinic every 2-8 weeks. Biochemical parameters, including the hepatic function, lipid metabolism and renal function, were measured every one to two months. All patients received pemafibrate treatment for at least six months. The

Table 1. Patient Characteristics.

	n=10
Age (years)	66.0 (53.8-74.8)
Males, n (%)	5 (50.0)
BMI (kg/m^2)	27.3 (24.6-30.0)
BMI (kg/m^2) >25, n (%)	7 (70.0)
Waist circumference (cm)	96 (90-101)
Metabolic diseases	
Hypertension, n (%)	7 (70.0)
Diabetes mellitus, n (%)	1 (10.0)
Fasting TG (mg/dL)	175 (149-247)
Non-fasting TG (mg/dL)	228 (169-335)
Fatty liver index	73.0 (50.0-90.0)
NAFLD fibrosis score	-1.33 (-2.20 to -0.39)
Pathological diagnosis	
NASH, n (%)	10 (100.0)
Grade 1 / 2 / 3, n (%)	4 (40.0) / 6 (60.0) / 0 (0.0)
Stage 1 / 2 / 3 / 4, n (%)	4 (40.0) / 0 (0.0) / 4 (40.0) / 2 (20.0)
NAS	4 (2-5)
NASH+NAS of ≥4, n (%)	6 (60.0)
NASH+NAS of ≥4+F2≥2, n (%)	4 (40.0)

Continuous parameters are expressed as the median (IQR).

BMI: body mass index, IQR: interquartile range, NAFLD: non-alcoholic fatty liver disease, NAS: non-alcoholic fatty liver disease activity score, NASH: non-alcoholic steatohepatitis, TG: triglyceride

liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), as determined by transient elastography (FibroScan; ECHOSENS, Paris, France), and the macrophage galactose-specific lectin-2 binding protein glycosylation isomer (M2BPGi) level were measured at baseline and six months.

Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0. Pemafibrate therapy was continued until the appearance of unacceptable serious AEs.

Statistical analyses

Continuous parameters were expressed as the median [interquartile range (IQR)], and categorical parameters were expressed as the number (percentage). Wilcoxon's signed-rank test was used to compare continuous values at baseline and six months. Data on the changes in the liver function were analyzed with the Friedman test, with Bonferroni's test used for post-hoc comparisons. P values of <0.05 were considered to indicate statistical significance. FIB-4 was calculated using the following formula (18): age (year)×AST (U/L)/platelet count (×10^9/L)×[ALT (U/L)]$^{1/2}$. The aspartate aminotransferase-to-platelet ratio index (APRI) (19) was calculated as [AST (U/L)/upper limit of normal/platelet count (×10^9/L)]×100. The fatty liver index (20) was calculated as e^x/(1+e^x), where X=0.953×Log$_e$[TG (mg/dL)]+0.139×BMI (kg/m^2)+0.718×Log$_e$[γ-GTP (U/L)]+0.053×waist circumference (cm)-15.745. NAFLD fibrosis score (21) was calculated as -1.675+0.037×age (years)+0.094×BMI (kg/m^2)+1.13 ×IFG/diabetes (yes=1, no=0)+0.99×AST (U/L)/ALT (U/L)

ratio-0.013×platelet (10^9/L)-0.66×albumin (g/dL). Cases of NASH with a NAFLD activity score (NAS) of ≥4+F2 were defined as NASH with significant activity and advanced fibrosis. An unreliable LSM was defined as an IQR-to-median ratio of >30% or a success rate of <60%.

All statistical comparisons were carried out with the IBM Statistical Package for the Social Sciences software program (version 24, IBM SPSS 24; IBM, New York, USA).

Results

The patient characteristics are summarized in Table 1. The median age was 66.0 (53.8-74.8) years old, and 5 patients (50.0%) were men. The median BMI was 27.3 (24.6-30.0) kg/m^2. There were 7 (70.0%) patients with hypertension and 1 (10.0%) with diabetes mellitus. The fasting TG and non-fasting TG levels were 175 (149-247) mg/dL and 228 (169-335) mg/dL, respectively. Eight (80.0%) and 7 patients (70.0%) had fasting TG levels of >150 mg/dL and non-fasting TG levels of >175 mg/dL, respectively. The median waist circumference was 96 (90-101) cm. The median fatty liver index and NAFLD fibrosis score was calculated to be 73.0 (50.0-90.0) and -1.33 (−2.20 to -0.39), respectively.

The grade and stage were classified as follows: grade 1, n =4 (40.0%); grade 2, n=6 (60.0%); and grade 3, n=0 (0.0%); stage 1, n=4 (40.0%); stage 2, n=0 (0.0%); stage 3, n=4 (40.0%); stage 4, n=2 (20.0%). The median NAS was 4 (2-5). There were 6 patients (60.0%) with NASH+NAS≥4 and 4 (40.0%) with NASH+NAS≥4+F2≥2.

When the parameters at baseline and 6 months were com-

Table 2. **Changes in Measured Variables at Baseline and 6 Months (n=10).**

Variables	Baseline	6 months	p value
Body weight	71.0 (58.9-85.7)	69.5 (57.1-84.0)	0.110
BMI (kg/m^2)	27.3 (24.6-30.0)	26.0 (23.8-31.0)	0.110
AST (U/L)	43.5 (24.0-55.0)	28.0 (22.0-33.8)	0.008
ALT (U/L)	51.5 (27.0-65.3)	23.0 (14.8-26.5)	0.005
ALP (U/L)	285 (224-429)	186 (126-231)	0.005
γ-GTP (U/L)	40.0 (35.0-84.0)	23.0 (18.5-40.5)	0.005
Fasting TG (mg/dL)	175 (149-247)	93 (69-145)	0.005
LDL-C (mg/dL)	107 (81-135)	108 (91-129)	0.72
HDL-C (mg/dL)	46 (36-60)	51 (41-61)	0.032
Creatinine	0.72 (0.62-0.87)	0.74 (0.59-0.93)	0.92
eGFR	71.9 (57.5-80.7)	76.4 (58.2-81.2)	0.92
Platelet count (×10^4/μL)	19.0 (15.6-22.2)	21.0 (18.9-26.4)	0.047
FIB-4	2.26 (1.07-3.12)	2.08 (0.97-2.67)	0.041
APRI	0.58 (0.43-1.01)	0.39 (0.30-0.54)	0.005
M2BPGi (C.O.I)	1.06 (0.83-1.32)	0.65 (0.49-0.95)	0.005
CAP (dB/m)*	274 (224-319)	261 (216-316)	0.77
LSM (kPa)*	6.7 (4.9-9.6)	5.5 (5.2-8.7)	0.20

Data are expressed as the median (IQR).
*One patient was excluded because of IQR/median >30.
ALP: alkaline phosphatase, ALT: alanine aminotransferase, APRI: aspartate amino-transferase to platelet ratio index, AST: aspartate aminotransferase, BMI: body mass index, CAP: controlled attenuation parameter, eGFR: estimated glomerular filtration rate, γ-GTP: γ-glutamyl transpeptidase, HDL-C: high-density lipoprotein cholesterol, IQR: interquartile range, LDL-C: low-density lipoprotein cholesterol, LSM: liver stiffness measurement, M2BPGi: macrophage galactose-specific lectin-2 binding protein glycosylation isomer, TG: triglyceride

pared, the levels of AST, ALT, alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GTP) were all significantly reduced (p=0.008, 0.005, 0.005 and 0.005, respectively). The median body weight was reduced from 71.0 (58.9-85.7) kg at baseline to 69.5 (57.1-84.0) kg at 6 months, which was equivalent to a weight change rate of -3.69% (-4.45% to 0.12%), without statistical significance (p=0.110). The median BMI numerically decreased from 27.3 (24.6-30.0) at baseline to 26.0 (23.8-31.0) at 6 months (p=0.110). The fasting TG level was significantly lower and the HDL-C level significantly higher at 6 months than at baseline (p= 0.005 and 0.032, respectively). The platelet count at 6 months was also significantly higher than that at baseline (p =0.047). Regarding liver fibrosis markers, the FIB-4, APRI and M2BPGi values at 6 months were significantly higher than those at baseline (p=0.041, 0.005 and 0.005, respectively). In the analysis of the LSM, 1 patient was excluded because of an IQR/median >30. There were no significant differences between the LSMs at baseline and at 6 months (p=0.20). This information is shown in Table 2.

The AST values were reduced at 3 times points in all patients [43.5 (24.0-55.0) U/L at baseline, 36.0 (22.8-44.5) U/L at 3 months, 28.0 (22.0-33.8) U/L at 6 months]; the difference was statistically significant (p=0.010). The post-hoc analysis showed that the difference between the values at baseline and 6 months was statistically significant (p=0.011; Fig. 2a). In addition, the ALT value also significantly de-

creased from 51.5 (31.0-65.0) U/L at baseline to 32.0 (15.0-39.0) U/L at 3 months to 23.0 (15.0-26.0) U/L at 6 months (p=0.002), with a significant difference noted between the values at baseline and 6 months in the post-hoc analysis (p= 0.002; Fig. 2b). In NASH patients with significant activity and advanced fibrosis (n=4), the AST value significantly improved from 56.0 (42.8-60.3) U/L at baseline to 42.5 (38.0-46.3) U/L at 3 months and 28.0 (27.3-34.0) U/L at 6 months (p=0.039). Statistical significance was observed between baseline and 6 months (p=0.040; Fig. 2c). The value of ALT also significantly decreased from 59.0 (51.5-65.8) U/L at baseline to 33.5 (30.5-38.0) U/L at 3 months and 23.0 (19.0-25.5) U/L at 6 months (p=0.018). There were significant differences between the values at baseline and 6 months. (p=0.014; Fig. 2d). In the NASH patients without significant activity or advanced fibrosis (n=6), the AST value showed a numerical decrease from 33.5 (23.5-46.3) U/ L at baseline to 27.0 (20.5-37.8) U/L at 3 months and 26.5 (21.3-35.6) U/L at 6 months (p=0.16; Fig. 2e). The ALT value also showed a numerical decrease from 38.5 (14.3-70.3) U/L at baseline to 23.5 (12.8-53.3) U/L at 3 months and 19.5 (13.3-42.5) U/L at 6 months (p=0.065; Fig. 2f).

Regarding liver fibrosis markers, the FIB-4 significantly decreased from 2.26 (1.07-3.12) at baseline to 2.18 (1.01-2.75) at 3 months and 2.08 (0.97-2.67) at 6 months (p= 0.014; Fig. 3a). The post-hoc analysis revealed a significant difference between the values at baseline and 6 months (p=
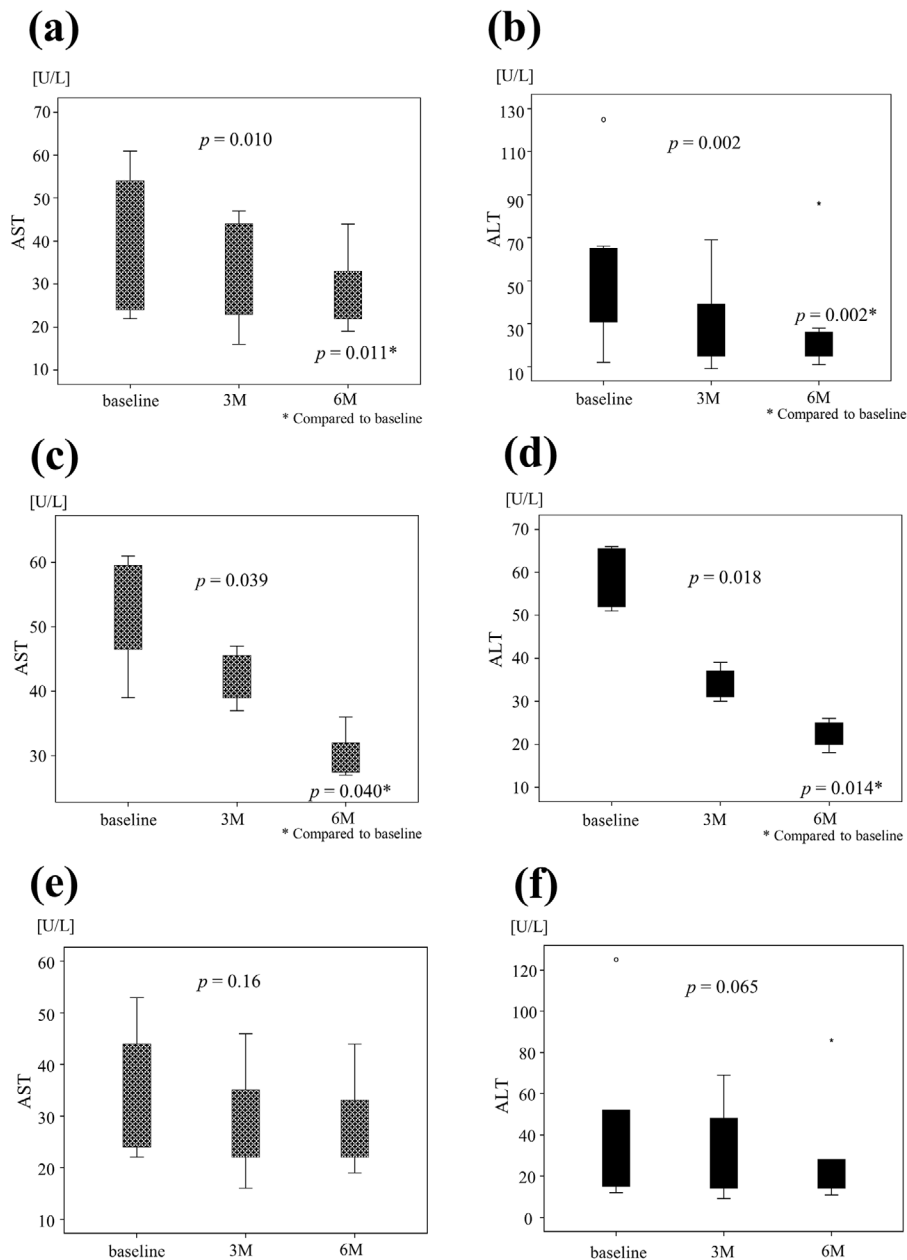
Figure 2. Change in the transaminase levels at baseline, 3 months and 6 months. (a) AST levels in all patients, (b) ALT levels in all patients, (c) AST levels in NASH patients with significant activity and advanced fibrosis, (d) ALT levels in NASH patients with significant activity and advanced fibrosis, (e) AST levels in NASH patients without significant activity or advanced fibrosis, (f) ALT levels in NASH patients without significant activity or advanced fibrosis. ALT: alanine aminotransferase, AST: aspartate aminotransferase, NASH: non-alcoholic steatohepatitis

0.011). Furthermore, the M2BPGi significantly improved from 1.06 (0.83-1.32) at baseline to 0.58 (0.41-1.09) at 3 months and 0.65 (0.49-0.95) at 6 months (p=0.002). There were significant differences between the values at baseline and 3 months (p=0.011) and at baseline and 6 months (p=0.005) in the post-hoc analysis (Fig. 3b). In NASH patients with significant activity and advanced fibrosis, the FIB-4 numerically decreased from 2.43 (1.26-3.20) at baseline to 2.35 (1.37-2.82) at 3 months and 1.86 (1.15-2.59) at 6 months (p=0.105; Fig. 3c). The M2BPGi also numerically reduced from 1.13 (0.64-1.33) at baseline to 0.79 (0.45-

1.36) at 3 months and 0.75 (0.54-0.90) at 6 months (p=0.17; Fig. 3d). In the NASH patients without significant activity or advanced fibrosis, the FIB-4 numerically decreased from 2.26 (1.01-3.03) at baseline to 2.08 (0.80-2.76) at 3 months and 2.23 (0.83-2.67) at 6 months (p=0.115; Fig. 3e). The M2BPGi significantly decreased from 1.07 (0.83-1.31) at baseline to 0.53 (0.39-1.09) at 3 months and 0.62 (0.42-1.04) at 6 months (p=0.007). The post-hoc analysis revealed significant differences between the values at baseline and 3 months (p=0.028) and at baseline and 6 months (p=0.028; Fig. 3f).
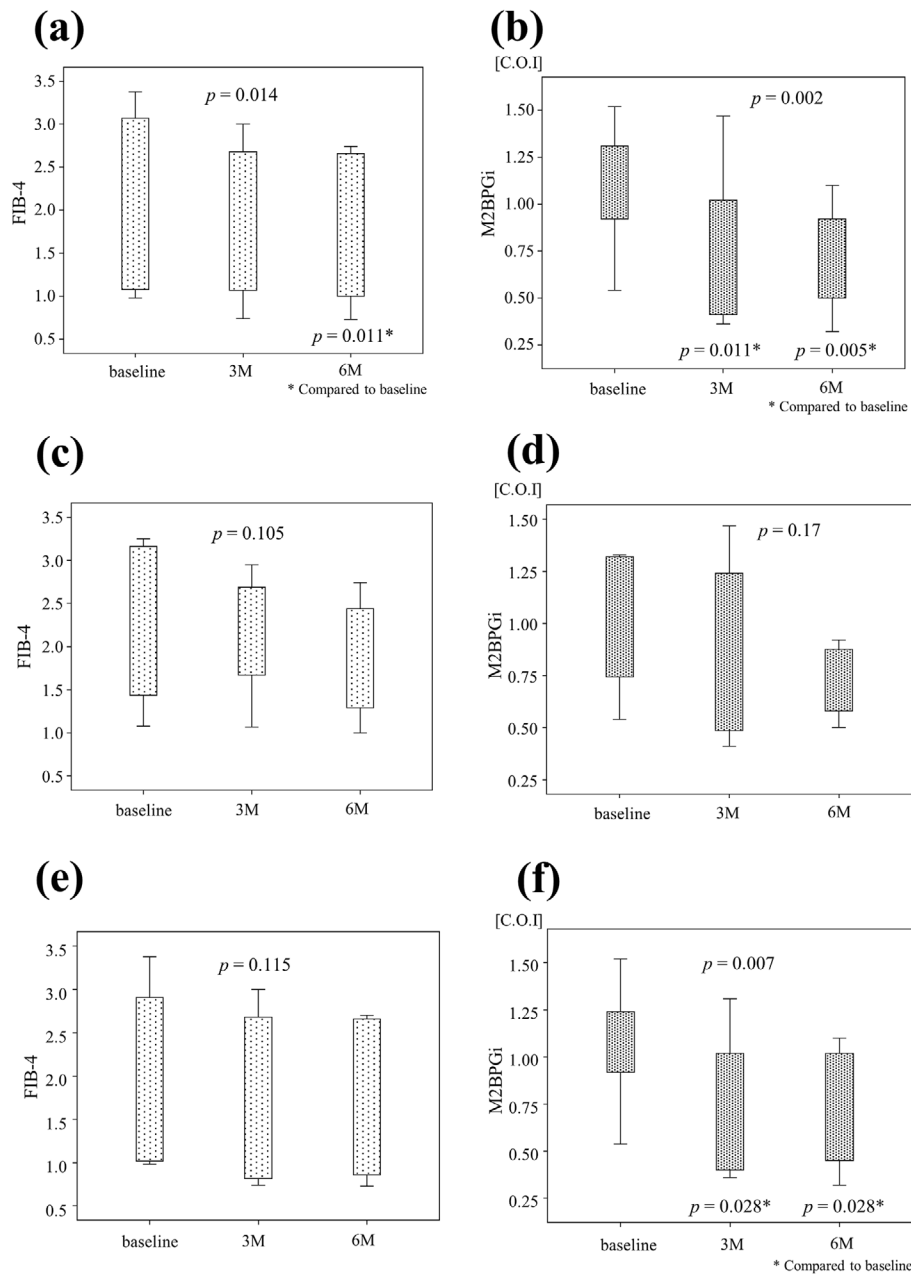
Figure 3. Change in the FIB-4 and M2BPGi values at baseline, 3 months and 6 months. (a) FIB-4 values in all patients, (b) M2BPGi values in all patients, (c) FIB-4 values in NASH patients with significant activity and advanced fibrosis, (d) M2BPGi values in NASH patients with significant activity and advanced fibrosis, (e) FIB-4 values in NASH patients without significant activity or advanced fibrosis, (f) M2BPGi values in NASH patients without significant activity or advanced fibrosis. M2BPGi: macrophage galactose-specific lectin-2 binding protein glycosylation isomer, NASH: non-alcoholic steatohepatitis

No AEs, including muscle pain, elevated creatinine kinase and renal impairment, were observed during pemafibrate treatment. All patients were able to continue to receive pemafibrate treatment without a dose reduction or discontinuation due to AEs.

Discussion

The authors found that 24-week pemafibrate treatment influenced the lipid profile, liver function and results of tran-

sient elastography in patients with hypertriglyceridemia and MAFLD who were pathologically diagnosed with NASH. The major finding of the current study is that the AST and ALT values were significantly reduced during treatment, without any AEs. While a favorable effect on the liver function was previously reported (14), the efficacy and safety of pemafibrate in the treatment of MAFLD remains to be clarified. The current findings suggest the potential efficacy and safety of pemafibrate in patients with hypertriglyceridemia and MAFLD. To our knowledge, this is the first report on

the effects of pemafibrate treatment in patients with MAFLD who were pathologically diagnosed with NASH. Furthermore, the present results also showed that the transaminase levels dramatically improved in biopsy-proven NASH patients with significant activity and advanced fibrosis.

A single-arm prospective study reported by Seko et al. (22) showed that the levels of transaminase, γ-GTP and fasting TG at baseline were significantly reduced and that HDL cholesterol and the platelet count were significantly elevated in comparison to the values at 12 weeks in 20 patients with NAFLD. Another retrospective study (23) showed that the transaminase and γ-GTP levels were decreased in patients with fatty liver disease who were treated with pemafibrate. The results of the previous studies were considered to be consistent with the present results.

The present results also showed that the transaminase level improved without a significant reduction in body weight or CAP, which is thought to constitute a non-invasive assessment of steatosis in NAFLD and MAFLD patients. However, the mechanism involved is unclear, as transaminase values are generally reduced via a reduction in body weight and steatosis in the liver. Indeed, among 20 MAFLD patients with hypertriglyceridemia (21 MAFLD patients with hypertriglyceridemia visited our hospital, but 1 was missing CAP data) with a median CAP of 290, the ALT value was higher in the patients with CAP≥290 than in those with CAP<290 [72 (30-118) vs. 51 (38-66) U/L]. One possible reason was that pemafibrate ameliorated the histological activity (ballooning and NAS) without affecting the accumulation of TG in the liver of a mouse model of NASH (24). Pemafibrate increased the number of lipid droplets and reduced the median lipid drop area, resulting in an improvement in macrovesicular steatosis (24), which was associated with the development of lobular inflammation and fibrosis (25).

In the present study, FIB-4, APRI and M2BPGi values were significantly reduced during pemafibrate treatment, seeming to suggest histological improvement. However, the FIB-4 and APRI values probably decreased because of the increase in the platelet count and the reduction of AST and ALT levels. Namely, changes in the transaminase level and platelet count, which are used in the determination of the FIB-4 and APRI values, might have resulted in the decrease in the FIB-4 and APRI values. Furthermore, in addition to liver fibrosis, the M2BPGi value might reflect other factors, including liver inflammation, liver damage and hepatocyte regeneration (26). Accordingly, the reduction in the M2BPGi value might have resulted from the improvement in liver inflammation. A further study is warranted to investigate whether or not pemafibrate is associated with histological improvement in NASH patients.

Liver fibrosis is strongly associated with liver-related mortality and the overall survival in NAFLD patients (27, 28), and inflammation plays a central role in progression to advanced fibrosis (29). Recently, Newsome et al. (30) proposed that NASH patients with significant activity and advanced fibrosis could be candidates for anti-inflammatory pharmacotherapy. Patients with inflammation can benefit from anti-inflammatory drugs, while the response to these drugs might be limited in patients with fibrosis but no or minimal inflammation (30). Given this background, the authors explored the changes in the transaminase levels of NASH patients with significant activity and advanced fibrosis and found a remarkable improvement in their transaminase levels. Further studies are needed to determine the indication for pemafibrate in NASH patients with hypertriglyceridemia.

In Japan, hypertriglyceridemia is diagnosed based on a fasting TG concentration of ≥150 mg/dL alone. When the fasting and non-fasting TG levels were compared, minor increases (+26 mg/dL) in plasma triglycerides were seen (17). Thus, the cut-off point for the non-fasting TG level was proposed to be 175 mg/dL (17). In addition, non-fasting TG had been shown to be equivalent to fasting TG for predicting cardiovascular disease (31). Accordingly, the authors adapted the criteria of a fasting TG concentration of ≥150 mg/dL or a non-fasting TG concentration of ≥175 mg/dL in the current study (17).

Although a significant difference was not observed, a median weight loss (WL) of 3.7% was obtained in the present study, which seemed to affect the present results. According to a previous study (32), the improvement in NAS was limited in patients with a WL of <5%, while those with a WL of 7% achieved a remarkable decrease in NAS (change in NAS from baseline: -0.89±0.13 vs. -3.89±0.29, respectively). Accordingly, the authors suspect that pemafibrate treatment exerted a marked influence on the present results.

Several limitations associated with the present study warrant mention. First, the study population was relatively small, and the current study represented a retrospective, single-arm experience. Second, the observation period was relatively short. Third, the histological findings were evaluated by a single pathologist. A previous study reported that interobserver variation existed in the interpretation of NAFLD histology (33). To minimize this bias, the authors used the FLIP algorithm, which is based on the SAF score, in order to decrease interobserver variation (16).

In conclusion, pemafibrate can be safe and effective treatment for patients with hypertriglyceridemia and MAFLD, especially for biopsy-proven NASH patients.

References

1. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med **346**: 1221-1231, 2002.
2. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology **64**: 73-84, 2016.

3. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther **34**: 274-285, 2011.

4. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology **67**: 328-357, 2018.

5. Watanabe S, Hashimoto E, Ikejima K, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. J Gastroenterol **50**: 364-377, 2015.

6. Hoofnagle JH, Van Natta ML, Kleiner DE, et al. Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther **38**: 134-143, 2013.

7. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol **73**: 202-209, 2020.

8. Lin S, Huang J, Wang M, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int **40**: 2082-2089, 2020.

9. Yamamura S, Eslam M, Kawaguchi T, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int **40**: 3018-3030, 2020.

10. Fruchart JC. Selective peroxisome proliferator-activated receptor alpha modulators (SPPARMalpha): the next generation of peroxisome proliferator-activated receptor alpha-agonists. Cardiovasc Diabetol **12**: 82, 2013.

11. Ishibashi S, Yamashita S, Arai H, et al. Effects of K-877, a novel selective PPARα modulator (SPPARMα), in dyslipidaemic patients: a randomized, double blind, active- and placebo-controlled, phase 2 trial. Atherosclerosis **249**: 36-43, 2016.

12. Arai H, Yamashita S, Yokote K, Araki E, Suganami H, Ishibashi S. Efficacy and safety of K-877, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), in combination with statin treatment: two randomised, double-blind, placebo-controlled clinical trials in patients with dyslipidaemia. Atherosclerosis **261**: 144-152, 2017.

13. Araki E, Yamashita S, Arai H, et al. Effects of pemafibrate, a novel selective PPARα modulator, on lipid and glucose metabolism in patients with type 2 diabetes and hypertriglyceridemia: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care **41**: 538-546, 2018.

14. Ishibashi S, Arai H, Yokote K, Araki E, Suganami H, Yamashita S. Efficacy and safety of pemafibrate (K-877), a selective peroxisome proliferator-activated receptor alpha modulator, in patients with dyslipidemia: results from a 24-week, randomized, double blind, active-controlled, phase 3 trial. J Clin Lipidol **12**: 173-184, 2018.

15. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol **64**: 1388-1402, 2016.

16. Bedossa P. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology **60**: 565-575, 2014.

17. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J **37**: 1944-1958, 2016.

18. Sumida Y, Yoneda M, Hyogo H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. BMC Gastroenterol **12**: 2, 2012.

19. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology **38**: 518-526, 2003.

20. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol **6**: 33, 2006.

21. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology **45**: 846-854, 2007.

22. Seko Y, Yamaguchi K, Umemura A, et al. Effect of pemafibrate on fatty acid levels and liver enzymes in non-alcoholic fatty liver disease patients with dyslipidemia: a single-arm, pilot study. Hepatol Res **50**: 1328-1336, 2020.

23. Ikeda S, Sugihara T, Hoshino Y, et al. Pemafibrate dramatically ameliorated the values of liver function tests and fibrosis marker in patients with non-alcoholic fatty liver disease. Yonago Acta Med **63**: 188-197, 2020.

24. Sasaki Y, Asahiyama M, Tanaka T, et al. Pemafibrate, a selective PPARα modulator, prevents non-alcoholic steatohepatitis development without reducing the hepatic triglyceride content. Sci Rep **10**: 7818, 2020.

25. Saponaro C, Gaggini M, Carli F, Gastaldelli A. The subtle balance between lipolysis and lipogenesis: a critical point in metabolic homeostasis. Nutrients **7**: 9453-9474, 2015.

26. Shirabe K, Bekki Y, Gantumur D, et al. Mac-2 binding protein glycan isomer (M2BPGi) is a new serum biomarker for assessing liver fibrosis: more than a biomarker of liver fibrosis. J Gastroenterol **53**: 819-826, 2018.

27. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology **61**: 1547-1554, 2015.

28. Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology **53**: 1874-1882, 2011.

29. Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. J Hepatol **51**: 371-379, 2009.

30. Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol **5**: 362-373, 2020.

31. White KT, Moorthy MV, Akinkuolie AO, et al. Identifying an optimal cutpoint for the diagnosis of hypertriglyceridemia in the nonfasting state. Clin Chem **61**: 1156-1163, 2015.

32. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology **149**: 367-378.e5; quiz e14-15, 2015.

33. Gawrieh S, Knoedler DM, Saeian K, Wallace JR, Komorowski RA. Effects of interventions on intra- and interobserver agreement on interpretation of nonalcoholic fatty liver disease histology. Ann Diagn Pathol **15**: 19-24, 2011.