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, Satoru Kakizaki, Naoto Saito, Yuya Nakano, Sachi Nakano, Yoichi Hazama, Sachiko Yoshida, Yoko Hachisu, Yoshiki Tanaka, Kenji Kashiwabara, Teruo Yoshinaga, Hiroki Tojima, Atsushi Naganuma and Toshio Uraoka

Abstract:
Aim 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.
Conclusions 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

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...
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 (SPPARa) (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.

Figure 1. Patient selection. HTG: hypertriglyceridemia, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis

Methods

Patients

Sixty-five MAFLD patients visited Gunma Saiseikai Maebashi Hospital (Maebashi, Gunma, 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 creatinine 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
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^{11}/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^{11}/L)]×100. The fatty liver index (20) was calculated as e^{0.953×\log_{10} (TG [mg/dL])+0.139×\log_{10} (\gamma-GTP [U/L])+0.053×\log_{10} (\text{waist circumference [cm]}-15.745). NAFLD fibrosis score (21) was calculated as −1.675+0.037×\log_{10} (years)+0.094×\log_{10} (\text{BMI (kg/m}^2)+1.13×\log_{10} (\text{IFG/diabetes (yes=1, no=0)})+0.99×\log_{10} (\text{ALT (U/L)})−0.013×\log_{10} (\text{platelet (10}^{11}/L))−0.66×\log_{10} (\text{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 liver stiffness measurement (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/m². 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.

Table 1. Patient Characteristics.

|                          | n=10 |
|--------------------------|------|
| Age (years)              | 66.0 (53.8-74.8) |
| Males, n (%)             | 5 (50.0) |
| BMI (kg/m²)              | 27.3 (24.6-30.0) |
| BMI (kg/m²)>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.
When the parameters at baseline and 6 months were compared, 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 decreased 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

| 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/m²) | 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 (×10³/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 aminotransferase 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.
difference between the values at baseline and 6 months ($p = 0.011$). 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 ($p = 0.028$;
Discussion

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

The authors state that they have no Conflict of Interest (COI).

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