Combination Therapy Using Pemafibrate and Dapagliflozin for Metabolic Dysfunction-associated Fatty Liver Disease

Teruhiko Imamura and Koichiro Kinugawa

Abstract:
Metabolic syndrome, including diabetes mellitus, obesity, and dyslipidemia, is associated with the development and progression of metabolic dysfunction-associated fatty liver disease. Therapeutic strategies, particularly optimal medical therapies, for treating metabolic dysfunction-associated fatty liver disease remain unestablished. We encountered a 37-year-old man with obesity (body mass index 39.0), metabolic dysfunction-associated fatty liver disease, and nephrotic syndrome due to obesity-related focal segmental glomerulosclerosis. Combination therapy using pemafibrate and dapagliflozin, together with body weight reduction, ameliorated his hypertriglyceridemia, hyperglycemia, hepatic injury, and proteinuria. Combination therapy using selective peroxisome proliferator-activated receptor \( \alpha \) modulator and sodium-glucose cotransporter 2 inhibitor, together with body weight reduction, might be a promising dual-medical strategy for ameliorating metabolic dysfunction-associated fatty liver disease.

Key words: PPAR, SGLT2 inhibitor, NASH, triglyceride


Introduction
Metabolic dysfunction-associated fatty liver disease (MAFLD) is a recently-proposed concept to more clearly identify high-risk cohorts of liver cirrhosis/liver cancer, beyond conventional non-alcoholic fatty liver disease (NAFLD) (1). MAFLD is based on evidence of hepatic steatosis in addition to one of the following three criteria: obesity, type 2 diabetes mellitus, or metabolic dysregulation, including hypertriglyceridemia (1). MAFLD does not consider the alcohol intake for its definition and would include the concept of NAFLD.

There is no established pharmacologic therapeutic strategy for MAFLD, and one of the suggested approaches is to encourage patients to reduce their body weight (2). Recently, an experimental study demonstrated that combination therapy using a selective peroxisome proliferator-activated receptor \( \alpha \) modulator (SPPARM\( \alpha \)) and sodium-glucose cotransporter 2 inhibitor (SGLT2 inhibitor) had the therapeutic potential to prevent the progression of NAFLD (3). In the clinical settings, monotherapy with a SPPARM\( \alpha \) or SGLT2 inhibitor is suggested to be partially effective in NAFLD patients, but the impact of their combination therapy has not yet been evaluated (4, 5). Furthermore, the clinical implication of these therapies for those with MAFLD, instead of NAFLD, remains unknown.

We encountered an obese patient with MAFLD that was ameliorated by combination therapy with a SPPARM\( \alpha \) and SGLT2 inhibitor.

Case Report

Before referral
A 37-year-old man consulted the previous institute for his proteinuria, hypertension, dyslipidemia, and impaired glucose intolerance, which had been suspected on annual medical examinations over the past 3 years. His body weight had remained around 98.0 kg for the past several years. He had no notable medical history. He had been drinking 20 g/day of alcohol for 16 years, except for the last 2 years, where he drank 10 g/day. Telmisartan 20 mg/day was initiated to treat his hypertension. Diabetic retinopathy was excluded.
Figure. Trends in laboratory data. Follow-up months were counted from the initiation of dapagliflozin.

Table: Laboratory Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 months</th>
<th>5 months</th>
<th>8 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>103</td>
<td>100</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>Abdominal circumference, cm</td>
<td>103</td>
<td>101</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Visceral fat area, cm²</td>
<td>128</td>
<td>122</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Lipid parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>458</td>
<td>289</td>
<td>392</td>
<td>217</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>47</td>
<td>53</td>
<td>46</td>
<td>50</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>121</td>
<td>147</td>
<td>127</td>
<td>149</td>
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<tr>
<td>Triglyceride/HDL cholesterol</td>
<td>9.7</td>
<td>5.5</td>
<td>8.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Triglyceride-rich lipoprotein-cholesterol, mg/dL</td>
<td>68</td>
<td>41</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td>Hepatology parameters</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>58</td>
<td>45</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>80</td>
<td>75</td>
<td>76</td>
<td>29</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/L</td>
<td>98</td>
<td>54</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase, IU/L</td>
<td>113</td>
<td>107</td>
<td>113</td>
<td>69</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>1.1</td>
<td>0.7</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>7.8</td>
<td>7.0</td>
<td>7.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Urine protein, g/g creatinine</td>
<td>3.77</td>
<td>3.43</td>
<td>3.20</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Seven months before his referral to our institute, dapagliflozin 10 mg/day was initiated (green bar in Figure). His body weight was 101 kg, and abdominal circumference was 103 cm. He stated that his body weight had further increased by 2-3 kg in the past year. The laboratory data, all of which were obtained in a fasting condition throughout this presentation, at baseline are displayed in Figure (0 month). His triglyceride level was 458 mg/dL, and hemoglobin A1c was 7.8%. Aspartate aminotransferase was 58 IU/L, and alanine aminotransferase was 80 IU/L. Urine protein was 3.77 g/g creatinine. Computed tomography indicated a fatty acid liver-to-spleen ratio of 0.69 Hounsfield units and visceral fat area of 128 cm². HBs antigen and HCV antibody were negative. Based on these findings, he was diagnosed with MAFLD. His fibrosis-4 index was 0.59, his fatty liver index was 98.10, and his hepatic steatosis index was 52.0 (6).

Three months following the initiation of dapagliflozin, triglyceride was 289 mg/dL, and hemoglobin A1c was 7.0% (3 months in Figure). Aspartate aminotransferase and alanine aminotransferase decreased slightly down to 45/75 IU/L. Urine protein remained at 3.43 g/g creatinine. He was referred to our institute for a further investigation and treatment.

On referral

The patient’s body height was 161 cm, and his body weight was 100 kg (body mass index 39.0 kg/m²). His blood pressure was 138/78 mmHg, and his pulse rate was 64 bpm. He had no peripheral edema.

His triglyceride level was 392 mg/dL, triglyceride/high-density lipoprotein (HDL)-cholesterol ratio was 8.5, and triglyceride-rich lipoprotein-cholesterol (calculated as total cholesterol - [HDL-cholesterol + low-density lipoprotein-cholesterol]), was 47 mg/dL (5 months in Figure). Hepatology data remained almost unchanged from the values at the previous institute. Hemoglobin A1c also remained unchanged at 7.0%. Pemafibrate 0.2 mg/day was initiated (blue bar in Figure). He was hospitalized for a renal biopsy, indicating obesity-related focal segmental glomerulosclerosis. We decided to continue treatment for his metabolic syndrome.

Following 3-month combination therapy using dapagliflozin and pemafibrate (8 months in Figure), the triglyceride level, triglyceride/HDL-cholesterol ratio, and triglyceride-rich lipoprotein-cholesterol level had decreased to 217 mg/dL, 4.3, and 36 mg/dL, respectively. His hepatology data further improved. Aspartate aminotransferase and alanine aminotransferase decreased to 37/29 IU/L. Urine protein improved to 1.13 g/g creatinine. His fibrosis-4 index was 0.56, his fatty liver index decreased to 93.30, and his hepatic steatosis index decreased to 46.3. His body weight had decreased partially to 97 kg. The liver-to-spleen ratio on computed tomography had improved to 0.82 Hounsfield units, and the visceral fat area had decreased slightly to 122 cm².

Discussion

An experimental study using a mouse model of NAFLD demonstrated that pemafibrate prevented NAFLD progression by reducing myeloid cell recruitment via interaction with liver sinusoidal endothelial cells without affecting the...
hepatic triglyceride accumulation (7). In a sub-analysis of a phase II trial, pemafibrate had the potential to decrease liver enzyme levels (8). The pan-peroxisome proliferator-activated receptor agonist Lanifibranor was recently demonstrated to improve NAFLD in a phase II trial (9). Experimental and clinical studies have shown that SGLT2 inhibitors improve hepatology and metabolic parameters while reducing the visceral fat area in patients with diabetes mellitus-related NAFLD (5).

Given these findings, the combination of pemafibrate and an SGLT2 inhibitor might theoretically exert a synergetic protective effect on the progression of MAFLD, a recently proposed concept that broadly covers fatty liver diseases beyond NAFLD and is more often associated with progression of liver fibrosis, development of malignancy, and cardiovascular events than is NAFLD. However, no studies have described the impact of combination therapy on NAFLD (and, of course, MAFLD), except for an experimental study using a NAFLD mouse model (3). In that study, a combination of pemafibrate and tofogliflozin, an SGLT2 inhibitor, synergistically ameliorated hepatic injury and prevented the progression of NAFLD and development of hepatocellular carcinoma.

We observed for the first time in real-world practice that dapagliflozin partially improved hepatology parameters, and the combination of pemafibrate and dapagliflozin further ameliorated hepatic injury in a patient with MAFLD. Given the nature of clinical observation, we cannot distinguish the impact of pemafibrate alone versus the combination of pemafibrate and dapagliflozin. Furthermore, we cannot exclude the impact of dietary restriction, although the patient failed to obey most of our recommendations, and body weight reduction was only slight. We diagnosed him with MAFLD clinically without a liver biopsy. The pathological impact of the combination therapy in patients with more progressed MAFLD accompanying hepatic fibrosis remains a future concern.

Several other lipid parameters were improved in this patient, probably by pemafibrate therapy, including the triglyceride/HDL-cholesterol ratio and triglyceride-rich lipoprotein-cholesterol, both of which are associated with incremental cardiovascular risk (10, 11). Proteinuria partially improved, probably due to partial body weight reduction (12) and pemafibrate administration via the activation and maintenance of renal fatty acid metabolism (13, 14).

We reported a patient with MAFLD whose hepatic injury was ameliorated by the combination of pemafibrate and dapagliflozin together with partial body weight reduction. Further randomized control trials are warranted to validate our findings and establish the optimum combination therapy regimen in patients with MAFLD.

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

References


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