Pharmacological options for the nonalcoholic fatty liver disease (NAFLD)

Sang Hoon Park

Department of Internal Medicine, Hallym University Medical Center, Seoul, Korea

Introduction

Nonalcoholic fatty liver disease (NAFLD) is highly prevalent and the most clinically relevant subset, nonalcoholic steatohepatitis (NASH), has been known to have the potential to progress to cryptogenic cirrhosis and hepatocellular carcinoma. The proportion of patients with NAFLD who have NASH is still not entirely clear but might range from 10%-30%. Because bland hepatic steatosis is a benign process in the majority of patients, NASH is thought to be a separate disease with a different pathogenesis. More than ten years ago, Day and James presented a hypothesis so-called “two-hit” model, suggesting that after a first hit (hepatic steatosis), another hit (oxidant stress, pro-inflammatory cytokines) is needed to develop NASH. However, recently, some investigators propose a new model so-called “multiple parallel hits hypothesis” suggesting that many hits may act in parallel, finally resulting in liver inflammation. It may precede steatosis in NASH, as inflammatory events may lead to subsequent steatosis. Overall, the notion that insulin resistance and lipotoxicity (cellular injury due to metabolites of fatty acid) play a central role of liver inflammation in NAFLD is accepted by all. In this aspect, focuses have been made on combined treatment targeting multiple hits in the pathogenesis of NASH. Weight loss via lifestyle modification remains the most common and fundamental therapy advocated for reducing hepatic lipid in NAFLD. Even weight loss and physical activity continued to be the cornerstone of therapy in NAFLD, but reaching a long-term lifestyle modification is not free from difficulties. Pharmacologic treatment should be considered for patients with NAFLD/NASH unable to achieve or maintain lifestyle-induced weight loss. Unfortunately, there is no approved pharmacological therapy for NAFLD at this point. Thiazolidinediones (TZDs) improved steatosis, hepatocellular ballooning and inflammation and have been demonstrated to reduce the risk of fibrosis progression in several randomized-controlled trials (RCTs). In a large RCT, large dose of vitamin E improved all histological lesions except for fibrosis. Metformin had a beneficial effect on ALT, but did not improve liver histology compared with placebo. Higher doses (25-30 mg/kg) of ursodeoxycholic acid (UDCA) showed a modest benefit for ALT and lobular inflammation. Some lipid-lowering drugs (statins, ezetimibe) improved ALT and radiological steatosis. Here, we systemically reviewed the effect of current pharmacological treatments for the NAFLD.
Insulin sensitizers: thiazolidinediones (TZDs)

The main target of TZDs is PPAR-γ in adipose tissue. They reduce hepatic inflammation, improve insulin signaling in adipose tissue and liver, increase level of adiponectin, and collectively lead to improved liver histology in patients with NASH. TZDs are the only compounds that have consistently shown some benefits in patients with NASH and effects were independent of presence of diabetes, the implementation of lifestyle intervention, use of different drugs, dose or trial duration.14-22 Most studies have shown not only reduction of ALT levels but also improve steatosis and liver cell injury, including hepatocyte ballooning, inflammation and ultimately reduced the risk of fibrosis progression (Table 1).

Lutchman et al. suggested long-term treatment with TZDs is possibly necessary to maintain improvement in disease activity by showing that TZDs discontinuation resulted in worsening of ALT level and histologic evidence of liver injury.23 However, PIVENS and FLIRT-2 trials showed that prolonged treatment with TZDs may offer no additional histological benefit and also that metabolic improvement does not necessarily parallel histological improvement.19,20 Moreover, there has been considerable debate about long-term safety of TZDs regarding cardiovascular disease, bone loss, and bladder cancer.24-26 Concerns about cardiovascular safety led the Korea Food & Drug Administration (KFDA) and European Medicines Agency (EMA) to recommend withdrawal of rosiglitazone from clinical use. More recently, some European countries and FDA recommend not to use pioglitazone in patients with active bladder cancer and to use it with caution in patients with a prior history of bladder cancer until more definitive data become available.

Despite these problems, TZDs consistently improve steatosis, necro-inflammation, slow fibrosis progression and ameliorate glucose and lipid metabolism. Consequently, although further studies are warranted examining the role of TZDs, particularly focused on histological dose-responses, identifying factors for response, and duration of optimal therapy, we should be cautiously optimistic for the future of TZDs in the treatment of NASH.27 Long-term risks of bone frac-

Table 1. RCTs in NAFLD ranging from 6-24 months duration: TZDs

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>DM(%)</th>
<th>Intervention, dose</th>
<th>Comparators</th>
<th>Duration (month)</th>
<th>Resoibse</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanyal 2004</td>
<td>20</td>
<td>0%</td>
<td>Pio. 30 mg</td>
<td>Vit E</td>
<td>6</td>
<td>yes</td>
<td>Steatosis, inflammation</td>
</tr>
<tr>
<td>Belfort 2006</td>
<td>55</td>
<td>48%</td>
<td>Pio. 45 mg</td>
<td>Placebo</td>
<td>6</td>
<td>yes</td>
<td>Steatosis, inflammation</td>
</tr>
<tr>
<td>Ratziu 2008</td>
<td>63</td>
<td>31%</td>
<td>Rosi. 8 mg</td>
<td>Placebo</td>
<td>12</td>
<td>yes</td>
<td>Steatosis, mean NAS score</td>
</tr>
<tr>
<td>Aithal 2008</td>
<td>74</td>
<td>0%</td>
<td>Pio. 30 mg</td>
<td>Placebo</td>
<td>12</td>
<td>yes</td>
<td>Balloning</td>
</tr>
<tr>
<td>Idilman 2008</td>
<td>74</td>
<td>?</td>
<td>Rosi. 8 mg</td>
<td>Metformin/diet +excr</td>
<td>12</td>
<td>yes</td>
<td>Steatosis, inflammation</td>
</tr>
<tr>
<td>Sanyal 2010</td>
<td>247</td>
<td>0%</td>
<td>Pio. 30 mg</td>
<td>Vit E/placebo</td>
<td>24</td>
<td>yes</td>
<td>Steatosis, inflammation</td>
</tr>
<tr>
<td>Ratziu 2010</td>
<td>53</td>
<td>26%</td>
<td>Rosi. 8 mg</td>
<td>Placebo</td>
<td>24</td>
<td>yes</td>
<td>Steatosis</td>
</tr>
<tr>
<td>Omer 2010</td>
<td>64</td>
<td>70%</td>
<td>Rosi. 4 mg</td>
<td>Metformin</td>
<td>12</td>
<td>yes</td>
<td>Steatosis, inflammation</td>
</tr>
<tr>
<td>Torres 2011</td>
<td>137</td>
<td>16%</td>
<td>Rosi. 8 mg</td>
<td>Rosi+met/Rosi +losartan</td>
<td>12</td>
<td>yes</td>
<td>Steatosis, inflammation, fibrosis</td>
</tr>
</tbody>
</table>
turies, peripheral weight gain, and the potential to develop congestive heart failure, and bladder cancer by TZDs should be further investigated. Therefore, the risk-benefit ratio should be considered in each patient prior to initiating therapy with a TZD.

**Metformin**

Metformin decreases gastrointestinal glucose absorption and increases insulin sensitivity by increasing glucose uptake and hepatic AMP-kinase-mediated oxidative glucose and lipid metabolism.\textsuperscript{28,29} While, earlier uncontrolled studies indicated a possible benefit from its use in NASH, its ability to improve insulin sensitivity or liver histology has not been confirmed in more recent studies.\textsuperscript{30-32} Similarly, metformin added to rosiglitazone in the treatment of patients with NASH offered no advantage over TZD monotherapy.\textsuperscript{22}

In conclusion, although metformin is still considered as first-line therapy for the treatment of type 2 diabetes mellitus combined with NAFLD in clinical practice, there is no firm evidence that it significantly improve liver histology in NAFLD.

**Anti-oxidants: vitamin E**

The exact mechanism of action of vitamin E in patients with NAFLD remains unclear but is believed to be related to decreasing intracellular oxidative stress. Early pilot studies showed mixed results on liver histology, but its efficacy was shown in recent large RCTs.\textsuperscript{14,19,33,34} Higher doses of vitamin E showed modest improvement in hepatic steatosis, lobular inflammation, ballooning and the rate of NASH resolution (Table 2). Therapeutically, vitamin E is attractive because it likely targets intracellular pathways different from insulin sensitizers and offers an opportunity for combined treatment in NASH.\textsuperscript{12} However, the observation that long-term high dose vitamin E supplementation was associated with

### Table 2. Representative trials: Vitamin E for NASH

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Drug</th>
<th>Dose (IU)</th>
<th>Duration</th>
<th>Improved Histology or LFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison 2003</td>
<td>45</td>
<td>RCT</td>
<td>Vit E + Vit C vs. Placebo</td>
<td>1000 + 1000</td>
<td>6 M</td>
<td>Fibrosis, not inflammation</td>
</tr>
<tr>
<td>Sanyal 2004</td>
<td>20</td>
<td>Pilot</td>
<td>Vit E vs. Pio + Vit E</td>
<td>400</td>
<td>6 M</td>
<td>Steatosis, Ballooning (p=0.055)</td>
</tr>
<tr>
<td>Sanyal 2010</td>
<td>247</td>
<td>RCT</td>
<td>Vit E vs. Pio. vs. Placebo</td>
<td>800</td>
<td>2-yr</td>
<td>NAS, resolution of NASH</td>
</tr>
<tr>
<td>Lavine 2011</td>
<td>173</td>
<td>RCT</td>
<td>Vit E vs. Met. vs. Placebo</td>
<td>800</td>
<td>2-yr</td>
<td>Ballooning, NAS, Not LFT</td>
</tr>
</tbody>
</table>

### Table 3. Two Large RCTs: High dose UDCA for NASH

<table>
<thead>
<tr>
<th>study</th>
<th>n</th>
<th>Design</th>
<th>Dose (mg/kg)</th>
<th>Duration</th>
<th>Improved Histology or LFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuschner 2010</td>
<td>185</td>
<td>RCT</td>
<td>23-28</td>
<td>16 M</td>
<td>Lobular inflammation, GGT</td>
</tr>
<tr>
<td>Ratziu 2011</td>
<td>126</td>
<td>RCT</td>
<td>28-35</td>
<td>12 M</td>
<td>Serum fibrosis marker, ALT, IR index</td>
</tr>
</tbody>
</table>
increased all-cause mortality needs to be evaluated.\textsuperscript{35}

Despite this concern, vitamin E for the treatment of NASH is thought to be helpful in the near future.

**Cytoprotective agents: urosodeoxycholic acid (UDCA)**

UDCA is a naturally occurring bile acid, with an excellent safety profile and various mechanisms of action to the liver. The pharmacologic attributes, immunomodulatory functions and direct anti-apoptotic properties of UDCA may interfere with the progression of NAFLD.\textsuperscript{36} In several clinical trials, evaluating the efficacy of UDCA at usual doses (from 12 to 15 mg/kg per day) in patients with NASH, have yielded variable but generally good results.\textsuperscript{37,38} However, these promising initial results were not substantiated by a large RCT that enrolled 166 patients with NASH. The study showed no differences in liver function tests or histology between UDCA and placebo at the end of trial.\textsuperscript{39} Although this has dampened enthusiasm for UDCA as usual dose monotherapy, it is possible that higher dose of UDCA (more than 25 mg/kg per day) might have a beneficial effect just like in the treatment of primary sclerosing cholangitis. Accordingly, in two large RCTs, UDCA improve ALT, lobular inflammation and serum fibrosis markers (Table 3).\textsuperscript{40,41}

Consequently, higher doses of UDCA in NAFLD can be useful with excellent long-term safety profile in the near future.

**Lipid-lowering drugs: statins**

Statins competitively inhibit hepatic hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase, thereby decreasing cholesterol production and reducing serum cholesterol levels. The interest in the use of anti-hyperlipidemic drugs for NAFLD stems from the role of dyslipidemia in metabolic syndrome and its association with NAFLD. Although, the use of statins in patients with chronic liver disease has raised concerns about the potential for hepatotoxicity, its use is thought to be essentially safe in compensated liver disease considering the incidence of significant hepatotoxicity is exceedingly rare.\textsuperscript{42,43} Statins improved ALT and radiological steatosis in hyperlipidemic NAFLD patients in several studies.\textsuperscript{44,45} However, statins had no effect on post-treatment histology in a randomized-controlled trial.\textsuperscript{46}

In conclusion, statins are safe in NAFLD and needed to be considered in patients with dyslipidemia combined with NAFLD.

**Ezetimibe**

Ezetimibe is a selective and potent inhibitor of intestinal cholesterol absorption. It can effectively blocks intestinal absorption of dietary and biliary cholesterol by inhibiting the intestinal sterol influx transporter (Niemann-Pick C1-like 1 protein).\textsuperscript{47} Ezetimibe could prevent hepatic steatosis and also progression to NASH by reducing hepatic lipogenesis, hepatic apoptosis and cellular injury.\textsuperscript{48} Ezetimibe reduce hepatic steatosis, necro-inflammation and ballooning but not fibrosis in biopsy-proven NAFLD patients.\textsuperscript{49,50}
Anti-TNF-α agent: pentoxifylline

Tumor necrosis factor-α (TNF-α) is a well-known proinflammatory, proapoptotic cytokine that is activated as part of the innate immune system and has been implicated as a key player in the development of hepatic steatosis and steatohepatitis.\textsuperscript{51,52} Pentoxifylline inhibit the synthesis/release of TNF-α and its ability to inhibit TNF-α and eicosanoid-induced inflammatory responses has been well known.\textsuperscript{53} In addition, it may have hepatoprotective effects via increases hepatic glutathione levels. Prior small clinical trials have shown the promising efficacy of pentoxifylline for the treatment of NASH.\textsuperscript{54-56} Recently, one well-designed RCT demonstrated that pentoxifylline improves steatosis and lobular inflammation and can affect the progression of liver fibrosis in NASH.\textsuperscript{57} Pentoxifylline was overall well tolerated in patients with NASH.\textsuperscript{57,58}

Angiotensin receptor blockers: telmisartan, losartan

Renin-angiotensin system (RAS) is associated with not only hypertension but also modulation of insulin sensitivity, systemic inflammation, hepatic lipogenesis and fibrogenesis.\textsuperscript{59,60} Several small ARB trials focused on the treatment of hypertensive NAFLD patients.\textsuperscript{61,62} Losartan combined with simvastatin has been shown to improve radiologic steatosis, visceral adiposity, HOMA and CRP compared with amlodipine combined with simvastatin, despite similar blood pressure reduction, suggesting the beneficial effect of ARB on NAFLD.\textsuperscript{63} In a well-designed RCT on hypertensive NASH, telmisartan improved steatosis, necro-inflammation, fibrosis, HOMA, and TG more consistently than vlasartan.\textsuperscript{64} The difference in efficacy might result from the fact that the effects of telmisartan are driven not only through the angiotensin-1 receptor blockade, but also via its specific PPAR-γ modulation effect.

In conclusion, telmisartan/losartan may be a primary choice for the treatment of hypertension-associated NAFLD.

Other drugs

n-3 polyunsaturated fatty acid (n-3 PUFA),\textsuperscript{65} L-carnitine,\textsuperscript{66} probiotics,\textsuperscript{67} incretin GLP-1 analogues,\textsuperscript{68,69} semi-synthetic bile acids (Int-747), se-
selective caspase inhibitors (GS-9450), caffeine, green tea, garlic extract.

Conclusions

Pathogenesis of NAFLD is thought to involve complex interactions of multiple hits, including insulin resistance, lipotoxicity, oxidative stress, and various inflammatory cytokines. Lifestyle modification including, weight reduction and regular moderate-intensity aerobic exercise still remain cornerstone for the treatment of NAFLD. However, because long-term durability of achieved benefits and patients adherence to the above regimens is concern, diverse pharmacologic drugs should be considered for patients with NASH unable to achieve or maintain lifestyle-induced weight loss. Furthermore, pharmacologic treatment directed at the correction of concurrent baseline metabolic disorders (dyslipidemia, T2DM, hypertension) should be given as needed (Figure 1). However, the ideal treatment for NASH should be one that decreases overall mortality, including liver-related and cardiovascular deaths, while remaining safe, widely available, and relatively inexpensive. Unfortunately, there is no satisfactory pharmacologic option so far.

In conclusion, although there is not much evidence, pioglitazone, vitamin E, and higher dose UDCA has shown possible modest therapeutic efficacy and safety profile. Thus, we should continue to test these drugs to determine their long-term safety and efficacy through large scale studies.

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