Treatment Strategies for Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

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KEYWORDS

• NAFLD • NASH • Treatment • Clinical trials • Nonantifibrotics

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) have been increasingly recognized as global health problems.
- Treatment strategies have been focusing on patients with more advanced liver disease.
- Lifestyle modification and vitamin E treatment are effective in the treatment of NAFLD; other treatment options are not approved and not based on strong evidence.
- New agents are mainly targeting oxidative stress, inflammation, apoptosis, peroxisome proliferator-activated receptor family, insulin resistance, bile acid metabolism, farnesoid X receptor, and lipid metabolism.
- Phase II and III studies are underway, targeting different points of NAFLD and NASH pathogenesis, which will help in developing personalized treatment options.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease in adults.[1,2] With the increasing obesity rates all over the world, the global prevalence of NAFLD has increased sharply and now it is affecting one-fourth of the general population in the United States and the rest of the world.[3]

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NAFLD covers a wide variety of conditions, from nonalcoholic steatohepatitis (NASH) to non-NASH NAFLD which encompasses steatosis alone. Although it is still debated, NASH subjects are primarily at an increased risk of developing fibrosis, cirrhosis, and hepatocellular carcinoma.[4] In fact, NASH is currently the second most common indication for liver transplantation and estimated to be the leading indication in the next 1 to 2 decades.[5] NAFLD is correlated intricately with insulin resistance and obesity, and because of strong associations with type 2 diabetes, hypertension, and dyslipidemia, it has been regarded as the hepatic manifestation of the metabolic syndrome.[3] Some NAFLD subjects are lean.[6] In fact, the majority of NAFLD subjects from rural areas of India and potentially other Asian countries have lean NAFLD.[7] In addition to the clinical impact, NAFLD has important economic impact on the society.[8] Finally, NAFLD and its advanced stages impairs patients' health-related quality of life, with a negative impact on patients' experience.[9]

Pathophysiologic Target for the Treatment of Nonalcoholic Steatohepatitis

Given its potentially progressive nature, NASH subjects are candidates for treatment protocols. In fact, the most appropriate subjects with NASH that should be the focus of clinical trials are those NASH subjects with significant fibrosis.[10] In this context, treatment strategies have targeted the accumulation of fat in the liver, or pathways that lead to liver cell injury and ultimately hepatic fibrosis. Additionally, other treatment strategies have targeted hepatic fibrosis with agents that have potential antifibrotic effects.[11]

Accumulation of lipid in hepatocytes causes fatty infiltration and there are various pathways that can lead to hepatic steatosis. These pathways include increased free fatty acid supply to hepatocytes as a major mechanism for steatosis. In fact, this process can occur either from increased intake of fat in the diet or increased lipolysis in the adipose tissue leading to higher amounts of lipids transferring to liver as well as increased de novo hepatic lipogenesis, decreased free fatty acid oxidation, and decreased very low density lipoprotein secretion in the liver.[12] Triglycerides are the major type of lipids stored in the liver of patients with NAFLD. The accumulation of triglycerides in hepatocytes is not always considered a pathologic condition. However, the accumulation of free fatty acids, especially in the mitochondria, may lead to the formation of reactive oxygen species and tumor necrosis factor (TNF)-α, which can further mediate liver damage.[13] These factors are the important elements of "multiple hit" hypothesis, which has been used to explain the pathogenesis of progression of NAFLD. According to this theory, insulin resistance represents the first hit. Because of the hyperinsulinemia, hepatic lipogenesis increases and lipolysis in the adipose tissue cannot be suppressed properly, both of which cause an increased efflux of free fatty acids from the adipose tissue to liver. In this context, hepatocytes become more susceptible to further harmful events, which represents the other multiple hits, including oxidative stress from reactive oxygen species, the TNF-α pathway, activation of the transforming growth factor-β pathway (a profibrogenic event), increased and dysregulated hepatocyte apoptosis, stellate cell activation, and dysregulation of adipocytokines.[14] All these insults result in recruitment of immune cells to damaged areas, which leads to further hepatocyte injury and worsening of inflammation.

Owing to the various mechanisms that contribute to the development of NAFLD and NASH, the number of strategies and treatment targets continue to grow. Although the first step in NAFLD treatment has been lifestyle modification with diet and exercise, other promising pharmacologic agents are emerging. **Table 1** shows the currently available effective treatment options for NAFLD and NASH.