



Nonalcoholic steatohepatitis: A new research and development frontier in chronic liver disease

AUTHORS

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The treatment landscape for chronic liver diseases is evolving rapidly as advances in therapy for chronic hepatitis C (HCV) and chronic hepatitis B (HBV) infection have led to significant improvements in our ability to cure or control these diseases, respectively. Gilead Sciences, which has developed and commercialized several therapies for patients infected with HCV and HBV, is building on its experience in these liver diseases to address another condition in which patients face major unmet medical need: nonalcoholic steatohepatitis (NASH).

Nonalcoholic fatty liver disease (NAFLD) affects an estimated 83 million people in the United States¹. NASH is a more serious, progressive and chronic form of NAFLD². NAFLD, which is characterized by the presence of hepatic steatosis alone, is unlikely to progress or cause complications of advanced liver disease. On the contrary, patients with NASH also have hepatic inflammation, liver cell injury and variable degrees of fibrosis². Patients with advanced fibrosis due to NASH, defined as those with bridging fibrosis or cirrhosis, are at the highest risk of serious, often life-threatening and costly complications, including decompensated liver disease, liver cancer, the need for transplantation and death^{3,4}. In one study⁵ patients with compensated cirrhosis due to NASH had an almost 20% probability of liver-related complications or mortality over two years of follow-up. Due to the risk of these complications and their accompanying morbidity and mortality, patients with NASH and advanced fibrosis have the greatest unmet need and would benefit most from novel therapies that halt and/or reverse the progression of liver fibrosis.

NASH is most common in people with diabetes mellitus, people who are overweight

or obese or those with other related disorders². Individuals with NASH may be asymptomatic or have non-specific symptoms. As such, NASH is frequently diagnosed during evaluations for abnormal liver tests identified as part of routine testing or from an incidental finding of hepatic steatosis on abdominal imaging².

The noninvasive differentiation of NASH from simple steatosis is challenging but necessary due to the potential for NASH to progress to advanced fibrosis and related complications². At present, liver biopsy is the only reliable means of differentiating these conditions, but the procedure is limited by invasiveness, cost, availability, sampling error and the potential for complications². Due to its frequently asymptomatic nature and the lack of an accurate, simple screening test, NASH often remains undiagnosed until a patient has progressed to cirrhosis and has developed clinical complications². To overcome these challenges, efforts are ongoing to develop accurate noninvasive methods that will allow physicians to diagnose and monitor the progression of NASH without the need for liver biopsy.

Prevalence of NASH and its impact

NASH is common globally, with a prevalence of approximately 1.5–6% of the population⁶. In the United States, more than 600,000 incident cases of NASH are predicted annually⁴. The prevalence of advanced fibrosis due to NASH has doubled in the United States during the past two decades and is expected to grow further as obesity and diabetes rates rise⁷.

Between 30–40% of people with NASH are also expected to develop liver fibrosis, which is the most important factor driving outcomes in this condition². In a meta-analysis published this year⁸ that included cohorts of patients

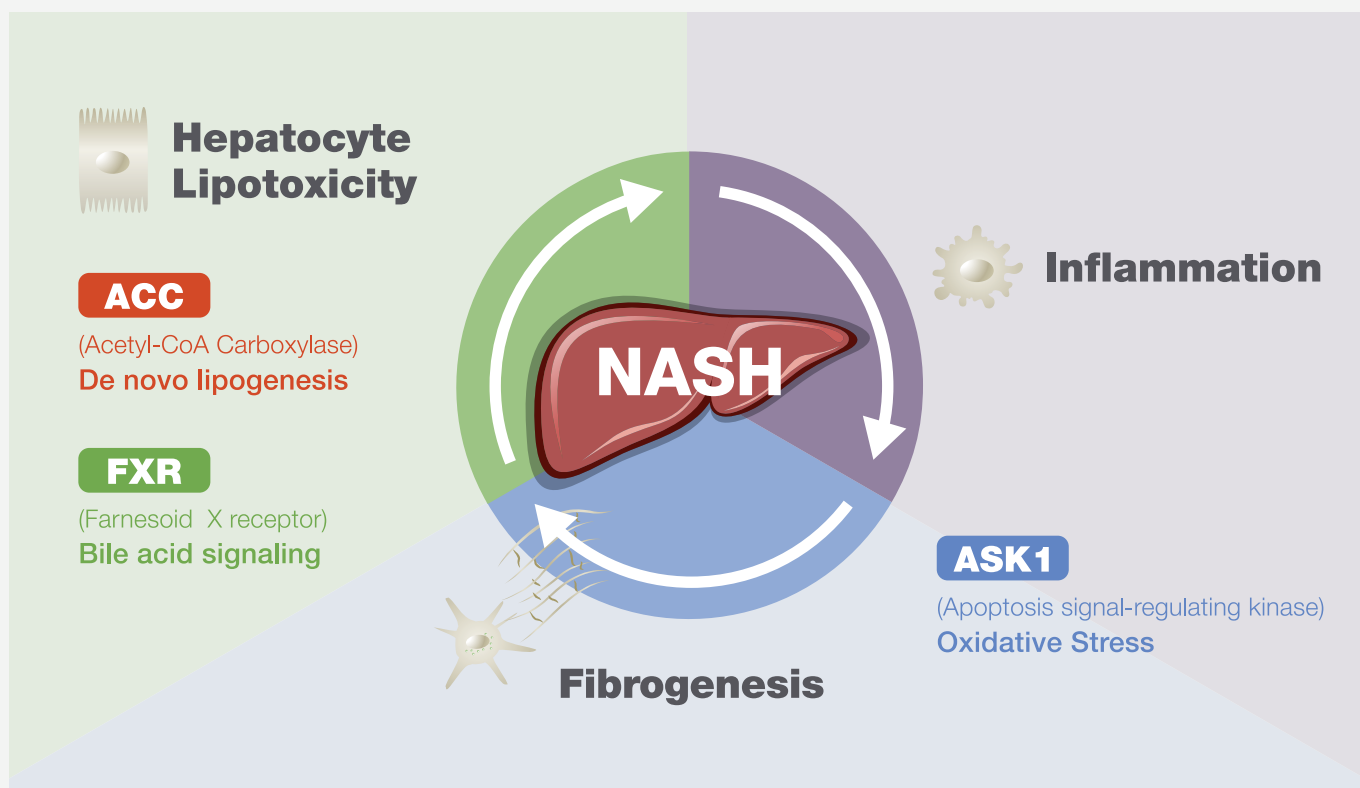


Figure 1 | Pathways driving advanced nonalcoholic steatohepatitis. Hepatocyte lipotoxicity, inflammation and fibrogenesis each contribute to the pathogenesis of nonalcoholic steatohepatitis (NASH) and represent opportunities for pharmacological intervention. Potential therapeutic targets include Acetyl-CoA carboxylase (ACC), which catalyzes the first step in *de novo* lipogenesis and inhibits the breakdown of fat in the liver through beta oxidation; farnesoid X receptor (FXR), a nuclear hormone receptor that regulates bile acid synthesis and affects hepatic lipid and glucose metabolism; and apoptosis signal-regulating kinase 1 (ASK1), which regulates signaling for hepatic inflammation and fibrosis in settings of oxidative stress.

with NAFLD (including NASH), the risk of all-cause and liver-related mortality increased exponentially as the stage of fibrosis increased from stage 0 (no fibrosis) to stage 4 (cirrhosis).

In keeping with the increasing prevalence and severity of NASH, morbidity due to this condition is also rising. As such, the number of patients with NASH awaiting liver transplantation in the United States has increased three-fold in the past decade, and by 2020 NASH-related decompensated cirrhosis is expected to become the leading indication for liver transplantation^{2,9}.

Targeting pathways driving advanced NASH

Gilead is exploring several investigational therapies for the treatment of NASH in patients with advanced fibrosis, who are at the highest risk of liver-related complications. Multiple Phase 2 and Phase 3 clinical trials are in progress, with additional trials in planning stages.

Our research is focused on several biological pathways associated with NASH pathogenesis, namely hepatocyte lipotoxicity,

inflammation and fibrogenesis (**Figure 1**). Drugs in development include an inhibitor of apoptosis signal-regulating kinase 1 (ASK1), a selective farnesoid X receptor (FXR) agonist and an inhibitor of Acetyl-CoA carboxylase (ACC). Due to the heterogeneity of patients with NASH and the multiple mechanisms involved in its pathogenesis, a combination of agents may hold the greatest promise for halting and reversing NASH disease progression.

ASK1

ASK1 is activated by oxidative stress, which is characteristic of NASH and associated with its pathogenesis^{10,11}. ASK1 mediates activation of p38 and JNK MAP kinase pathways in hepatic cells, which in turn promotes hepatocyte apoptosis, inflammation and fibrosis^{10,11}. The ASK1 pathway has been shown to be elevated in the livers of patients with NASH and is positively correlated with fibrosis stage^{10,12}.

FXR

FXR is a nuclear hormone receptor that is highly expressed in the gastrointestinal tract, liver and kidneys¹³. FXR is the primary regulator of

bile acid homeostasis and also plays important roles in glucose and lipid metabolism¹³. Patients with NASH have elevated serum levels of bile acids; bile acid accumulation in the liver can promote hepatocyte cell death, inflammation and fibrosis^{14,15}. FXR activation in the intestine produces fibroblast growth factor 19 (FGF19), an important hormone that signals the liver to decrease bile acid synthesis, increase bile acid export, reduce *de novo* lipogenesis (DNL) and increase beta oxidation of fatty acids¹⁶.

ACC

ACC catalyzes the first and rate-limiting step in DNL¹⁷. In NASH, DNL is elevated¹⁸. In hepatocytes, DNL supports steatosis and formation of lipotoxic signaling molecules¹⁹. In other cell types, including inflammatory cells such as macrophages, DNL has been implicated in cell activation²⁰. ACC also inhibits the breakdown of fat in the liver through mitochondrial beta oxidation¹⁷. The critical roles of ACC in fatty acid metabolism (both synthesis and breakdown), generation of lipotoxic mediators and cellular activation make it an important element of NASH pathogenesis.

Working towards a better future for patients with nonalcoholic steatohepatitis

The need for safe and effective therapies for patients with NASH, particularly those with advanced fibrosis, is clear due to their high risk of liver-related complications. Deeper understanding of the biological pathways implicated in the pathogenesis of NASH has enabled scientists to discover and now evaluate drugs with promise to slow and potentially reverse the progression of fibrosis, even in late-stage disease.

While research and development of safe and effective therapies for NASH is essential, new medicines alone will not be sufficient to stem the toll of this disease. Efforts aimed at building awareness of NASH among both the public and medical community are paramount so that at-risk individuals can be screened and, if diagnosed, can take the appropriate steps to reduce the risk of disease progression. These efforts would be expected to have significant benefits for patients who may otherwise face life-altering and potentially deadly complications, including liver failure and liver cancer. We are optimistic that research now underway within Gilead and elsewhere across the global hepatology community will lead to the development of effective and much needed therapies.

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