New Medications in the Treatment of Nonalcoholic Steatohepatitis

Scot Walker¹

Abstract

Nonalcoholic fatty liver disease, an accumulation of fat in the liver, is estimated to occur in almost 1 in 5 adults. With 2 of the most common risk factors being obesity and diabetes, its prevalence is growing. Nonalcoholic steatohepatitis is a more severe form of nonalcoholic fatty liver disease. There are currently no approved drugs to treat nonalcoholic steatohepatitis, but several drugs are being developed to treat this disease.

Keywords

formulary management/P&T, drug information, gastrointestinal disorders

Epidemiology

Nonalcoholic fatty liver disease (NAFLD) is an accumulation of fat in the liver (hepatic steatosis). NAFLD without inflammation is nonalcoholic fatty liver (NAFL), while the presence of inflammation indicates nonalcoholic steatohepatitis (NASH).¹ An examination of data from National Health and Nutrition Examination Survey (NHANES) suggests an increase of NAFLD to an estimated prevalence of 19%, representing almost 29 million adult patients. The most common risk factors include diabetes, metabolic syndrome, dyslipidemia, and obesity. NAFLD is also more prevalent in male patients and Mexican Americans.² An analysis of the economic impact of NAFLD estimated an annual cost of \$103 billion. If societal costs are included, the total is estimated to be \$292 billion. However, this analysis used a higher prevalence than the NHANES analysis.³ Outpatient treatment of NAFLD patients is estimated to be \$9,011, while hospitalized patients have an average cost of \$36,289. About one-third of NAFLD patients have fibrosis progression with NASH patients progressing twice as fast as NAFL patients (7 vs 14 years).⁴

Current Treatment

There are currently no approved drugs to treat NAFLD or NASH. It is estimated that 11% of patients with hepatic steatosis may be at high risk for hepatic fibrosis. Treatment for NASH currently consists of weight loss through diet and exercise. Weight loss was shown to decrease steatosis. A 7% to 10% decrease in weight has been shown to improve the NAFLD activity score.⁵ Bariatric surgery may also be considered for weight loss in noncirrhotic patients. Patients are

advised to avoid heavy use of alcohol. The effect of low or moderate alcohol use is unknown. The most recent guidelines from the American Association for the Study of Liver Diseases (AASLD) states that NAFLD patients are at a higher risk for cardiovascular complications. Therefore, statins are recommended to lower hyperlipidemia in NAFLD. Statins can also be used in patients with NASH without decompensated cirrhosis. Pioglitazone and vitamin E can be used in patients with biopsy-proven NASH to improve liver histology. Vitamin E should not be used in diabetic patients with NASH, NASH cirrhosis, or cryptogenic cirrhosis. Neither drug should be used in patients with NAFLD without liver biopsy.⁶

New Treatment Options

With no approved drugs and limitations with current treatments, there has been an increase in the development of therapies for NASH. While many drugs are in early stages of development, a few are in mid to late stages (Table 1). These drugs are for the treatment of NAFLD that has progressed to NASH. There are currently no drugs in late-stage development to prevent NASH from developing in high-risk NAFLD patients. Some drugs target a reduction in liver fat, while other drugs target liver pathology such as fibrosis or inflammation.

¹Prescribe Right, LLC, Wildwood, MO, USA

Corresponding Author:

Scot Walker, Chief Executive Officer, Prescribe Right, LLC, 1602 Westglen Farms Dr, Wildwood, MO 63011, USA.
Email: scot.walker@prescriberight.com

Table 1. New Treatment Options.

Generic name	Sponsor	Drug class	Efficacy summary
Phase III drugs			
Aramchol	Galmed	Fatty acid /bile acid conjugate	In a 3-month, 60 NAFLD patient, phase II trial, aramchol reduced liver fat compared with placebo. ⁷
Cenicriviroc	Allergan	CCR2/CCR5 inhibitor	Allergan announced that in a 2-year, 289-patient trial, cenicriviroc did not decrease inflammation or liver cell damage in NASH patients compared with placebo.
Elafibranor	Genfit	PPAR agonist	Genfit announced that in a 52-week, 276-patient, phase II trial, elafibranor did not resolve NASH without fibrosis worsening compared with placebo.
Selonsertib	Gilead	ASK1 Inhibitor	In a 24-week, 72-patient, phase II trial, selonsertib demonstrated improvements in liver fibrosis. The addition of simtuzumab did not improve results. ⁸
Phase II drugs			
Emricasan	Novartis, Conatus	Caspase inhibitor	Conatus announced that in an 86-patient, phase II trial, emricasan decreased progression of MELD scores and improved Child-Pugh scores in patients with NASH cirrhosis.
GS-0976	Gilead	Acetyl-CoA carboxylase inhibitor	Gilead announced that in a 126-patient, phase II trial, 48% of NASH patients treated with a high dose of GS-0976 had a reduction in liver fat, compared with 15% with placebo. GS-0976 patients also had larger reduction in TIMP-I, but there was no difference with placebo in liver stiffness, serum ALT, or PIII-NP.
NGM282	NGM Biopharmaceuticals	FGF19 analog	NGM Biopharmaceuticals announced that in an 82-patient, 12-week, phase II trial, patients treated with NGM282 had a 10%-12% reduction in liver fat compared with placebo. 34% of patients reached normal levels of liver fat content.

Source. Information adapted from the Prescribe Right Pharmaceutical Pipeline Tracker database.⁹

Note. NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; CCR2 = C-C chemokine receptor type 2; CCR5 = C-C chemokine receptor type 5; PPAR = peroxisome proliferator-activated receptor agonist; ASK1 = apoptosis signal-regulating kinase 1; MELD = model for end-stage liver disease; Acetyl-CoA = acetyl coenzyme A; TIMP-I = tissue inhibitor of metalloproteinase I; ALT = alanine transaminase; PIII-NP = amino terminal propeptide of type III procollagen; FGF19 = fibroblast growth factor 19.

Author's Note

Information is summarized from selected materials; additional information may be available from other sources. Due to the preapproval nature of the information, non-peer-reviewed data may be utilized. The information provided is meant to provide a way to assess the development status of a new drug and should not be used in making patient care decisions.

Declaration of Conflicting Interests

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