Emerging Therapies for Nonalcoholic Fatty Liver Disease

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KEYWORDS

• Nonalcoholic fatty liver disease • FXR agonists • Insulin sensitizers • PPAR agonists • Antifibrotic agents

KEY POINTS

- There is a large unmet need for new therapeutics for patients with nonalcoholic steatohepatitis (NASH). No treatment to date has shown efficacy in greater than 50% of patients.
- The ideal treatment of NASH should improve liver histology and cardiovascular outcomes and have good tolerability and an excellent safety profile.
- Because insulin resistance is central to the pathogenesis of NASH, many new NASH drugs have insulin sensitization as one of their primary modes of action; however, other drug classes are emerging.
- There has been an increased effort to develop antifibrotic agents to treat patients with NASH complicated by significant fibrosis to reduce progression to end-stage disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the developed world, with prevalence estimates varying from 25% to 40% across different countries.[1,2] In the United States, the estimated prevalence is about 20% to 30%.[3] At present there are no drug therapies that have been approved for the treatment of nonalcoholic steatohepatitis (NASH) by the US Food and Drug Administration. Among drugs studied to date, few have achieved an efficacy of greater than 50%, highlighting the great need for new therapeutics for patients with NASH.

Current clinical practice guidelines recommend that only patients with biopsy-confirmed NASH, those with any degree of fibrosis, or those with both should be considered for liver-directed therapy.[2] This group is at greatest risk of liver-related

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complications with progressive disease and likely to benefit most from effective therapy. An added complexity in treatment of NASH is the recognition that it represents a multifaceted condition with variable coexisting metabolic complications. The ideal therapy would effectively reverse the liver injury and fibrosis and improve, or at least have no negative impact on, other metabolic parameters or cardiovascular comorbidities. In addition, the ideal therapy should have good tolerability and an excellent safety profile with longer-term use, because many drugs may need to be used for years to obtain the desired clinical benefits.

Although changes on liver biopsy are used to define NASH and identify patients who are candidates for therapy, these histologic manifestations of disease represent the result of multiple different but interrelated pathogenetic pathways (Fig. 1), which are likely of variable importance in each individual. Looking to the future, it can be envisioned that therapy will be individualized, with specific metabolic and liver disease profiles treated with specific types of medications. Combinations of drugs working in complimentary or synergistic ways are likely to be the future of effective NASH therapy.

CHALLENGES IN DRUG DEVELOPMENT FOR NONALCOHOLIC STEATOHEPATITIS

Multiplicity of Pathways to Liver Injury

There are multiple different pathways described for the pathogenesis of NAFLD and each of them can be a potential target of the therapy (Table 1). It is also likely that more than 1 target is involved in the disease development and progression (Fig. 2). There is not a perfect animal model to study NAFLD. Many of the pharmacologic agents showing promise in animal models fail to show benefits in humans with NASH.[4] Clinical trials currently underway in patients with NASH are summarized in Table 2.

Defining Study End Points

The common primary outcomes used in NASH studies are either resolution of steatohepatitis with no worsening of fibrosis or a minimum of 2-point improvement in NASH activity score (NAS), with at least a 1-point improvement in more than 1 category and no worsening of fibrosis. Primary outcomes used in current randomized controlled trials in NASH are shown in Table 3.

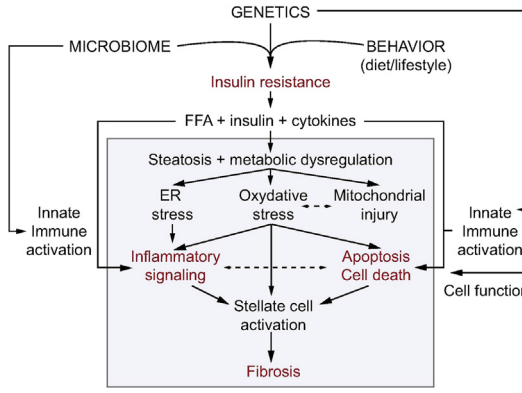

Fig. 1. Pathogenetic pathways for NASH highlighting potential targets for NASH. ER, endoplasmic reticulum; FFA, free fatty acid. (*From* Ratziu V, Goodman Z, Sanyal A. Current efforts and trends in the treatment of NASH. J Hepatol 2015;62(1 Suppl):S66; with permission.)