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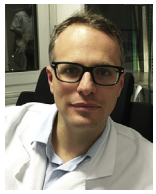
Perspectives on Treatment for Nonalcoholic Steatohepatitis

Guillaume Lassailly[1,2,3] Robert Caiazzo[4,5,6] François Pattou[4,5,6] Philippe Mathurin[1,2,3]

[1]Lille Inflammation Research International Center, University of Lille; [2]Inserm U995; [3]Service des Maladies de l'Appareil Digestif, Centre Hospitalier Régional Universitaire (CHRU); [4]European Genomic Institue for Diabetes (EGID); [5]Inserm U1190; [6]Service de Chirurgie Endocrinienne, CHRU, Lille, France

It is important to provide treatment to patients with nonalcoholic steatohepatitis (NASH) because one third of patients with the metabolic syndrome die of liver disease. Basic research studies have elucidated mechanisms of NASH pathogenesis, which could lead to therapeutic targets. Health agencies have confirmed strategies for the optimal management of NASH and approved new drugs and treatments, which urgently are needed. The US Food and Drug Administration recently endorsed end points for NASH therapy. The reversal of NASH with no evidence of progression to advanced fibrosis has been defined as the end point for phase 2b and phase 3 trials in patients with NASH and early stage fibrosis. Although a decrease in the nonalcoholic fatty liver disease activity score could serve as an end point in clinical trials, it is not clear whether patients with lower scores have a lower risk of progression to advanced fibrosis. End points for clinical trials of patients with NASH cirrhosis currently are based on model for end-stage liver disease and Child–Pugh–Turcotte scores, as well as the hepatic venous pressure gradient. Different strategies are being explored to reduce liver diseases that are linked to a sedentary lifestyle, overeating, and genetic factors. In association with insulin resistance and deregulation of the lipid metabolism (accumulation of lipotoxins that promote hepatic lipogenesis, adipose tissue lipolysis, and impaired β-oxidation), these factors could increase the risk of liver steatosis with necroinflammatory lesions and fibrosis. We review the pathogenic mechanisms of NASH and therapeutic options, as well as strategies that are being developed for the treatment of injury to the liver and other organs.

Keywords: Steatohepatitis; treatment.

The optimal treatment for nonalcoholic steatohepatitis (NASH) would reduce liver-related mortality, metabolic comorbidities, and the risk of cardiovascular events. Research aimed at achieving these goals has received a large amount of support because NASH has been declared a public health issue by public health authorities. The endorsement of therapeutic end points for NASH by the US Food and Drug Administration (FDA) was important and facilitates the development of new agents. The reversal or resolution of NASH, defined as the disappearance of necroinflammatory features (hepatocyte ballooning and portal inflammation) in histologic analysis, along with an absence of evidence for disease progression to advanced fibrosis, has been recognized as the end point for phase 2b and phase 3 trials of patients with NASH and early stage fibrosis.[1] Although a decrease in the nonalcoholic fatty liver disease (NAFLD) activity score (NAS) could be used as an end point in clinical trials, studies are needed to determine whether patients with lower scores have a reduced risk for progression to advanced fibrosis. End points for clinical trials of patients with NASH and cirrhosis currently are based on model for end-stage liver disease and Child–Pugh–Turcotte scores, as well as the hepatic venous pressure gradient.[1] These new approaches provide a foundation to develop treatments for NAFLD.

New therapeutic targets must be identified that can lead to the development of agents to reduce disease progression in patients with NASH. To limit liver-related complications, these agents should target one of the several pathways in the complex process of liver injury in patients with NASH. These are likely to involve agents that modify the metabolic profile because accumulation of hepatic fat and liver injury are associated with insulin resistance.[2] We review the roles of weight loss, insulin sensitization, lipid metabolism, oxidative stress, fibrosis, inflammation, and the intestinal microbiota in the development and treatment of NASH (Table 1).

Abbreviations used in this paper: **ASBT, apical sodium-dependent bile acid transporter; CB1, Cannabinoid 1; CCR, chemokine (C-C motif) receptor 2; EPA, eicosapentaenoic acid; FDA, Food and Drug Administration; GLP1, glucagon-like peptide-1; IL, interleukin; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; NPC1L1, Niemann–Pick C1–like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; PRKCE, protein kinase C epsilon; PUFA, polyunsaturated fatty acid; TNF, tumor necrosis factor.**

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MANAGEMENT

Table 1. Agents Available or in Development for the Treatment of NASH or NAFLD

Drugs and therapy	Action	Phase of development	Histologic impact	Pros and cons	References
Weight loss					
Lifestyle	Reduces insulin resistance and cardiovascular risk; lipid profile reduces oxidative stress	Recommended as first-line treatment	Depends on the level of weight loss: ■ >3%–5%: reduces steatosis ■ >7%–9%: reduces necroinflammation ■ ≥10%: reduces fibrosis	Only 10% of patients reach the 10% weight loss threshold required for an effect, and risk weight gain relapse	6, 7, 56
Bariatric surgery	Induces sustained weight loss for up to at least 10 y; increases insulin resistance and cardiovascular risk	Cohort studies	Reverses NASH in 85% of patients Reduces steatosis, necroinflammation, and fibrosis	Recommended for patients with morbid obesity Postoperative morbidity limits applicability to patients with body mass index $\leq$ 35 kg/m^2	37–39
Insulin sensitizers					
Pioglitazone	PPARγ agonist, lipid homeostasis, inflammation, and cell differentiation	Phase 2 completed	Improves ■ steatosis ■ necroinflammation ■ fibrosis	Pros: effective for patients with NASH Cons: weight gain, risk of congestive heart failure (no effect on mortality), and bladder cancer	59, 61
Liraglutide	GLP1 agonist, promotes satiation, weight loss, reduces insulin resistance	Phase 3	Reduces ■ steatosis ■ necroinflammation No worsening of fibrosis ■ resolution of NASH	Pros: marketed for patients with diabetes, safety seems acceptable Cons: gastrointestinal side effects, requires subcutaneous administration	26
Agents with multiple targets					
GFT505/elfibranor	PPARα and PPARδ agonist; reduces insulin resistance, inflammation, and fibrosis; improves lipid metabolism	Phase 3	Reduces ■ steatosis ■ necroinflammation ■ fibrosis Reverses NASH[a]	120 mg/day reduces histologic features of NASH	65
Obeticholic acid	FXR agonist, increases energy homeostasis and lipid metabolism; reduces insulin resistance, inflammation, and fibrotic pathways	Phase 3	Reduces ■ steatosis ■ necroinflammation ■ fibrosis ■ NAS without worsening of fibrosis	Pros: reduces histologic features in NASH Cons: side effects, with 20% of patients developing pruritus	72,73
Agents that alter lipid metabolism					
Aramchol	Inhibition of stearoyl coenzyme A desaturase 1	Phase 2	Decrease fat amount, no effects on NASH	No effects on NASH, only preliminary results available	83
Anti-oxidants					
Vitamin E	Tocopherol, anti-oxidative stress	Phase 2 completed	Significant effects on ■ steatosis ■ necroinflammation ■ NAS	Pros: recommended as first-line pharmacologic therapy Cons: no data from patients with diabetes or cirrhosis; concerns for long-term use	61