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FRONTIER

Acetyl-CoA carboxylase inhibitors in non-alcoholic steatohepatitis: Is there a benefit?

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Abstract

De novo lipogenesis (DNL) plays an important role in the pathogenesis of hepatic steatosis and also appears to be implicated in hepatic inflammation and fibrosis. Accordingly, the inhibition of acetyl-CoA carboxylase, which catalyzes the rate-limiting step of DNL, might represent a useful approach in the management of patients with nonalcoholic fatty liver disease (NAFLD). Animal studies and preliminary data in patients with NAFLD consistently showed an improvement in steatosis with the use of these agents. However, effects on fibrosis were variable and an increase in plasma triglyceride levels was observed. Therefore, more long-term studies are needed to clarify the role of these agents in NAFLD and to determine their risk/benefit profile.

Key Words: Acetyl-CoA carboxylase inhibitors; Non-alcoholic steatohepatitis; Fibrosis; Steatosis; Firsocostat

Core Tip: Acetyl-CoA carboxylase inhibitors suppress de novo lipogenesis resulting in improvement in hepatic steatosis in both animal models and in patients with nonalcoholic fatty liver disease. However, the effects of these agents on hepatic fibrosis are inconsistent and they increase plasma triglyceride levels, casting doubt on their risk/benefit profile.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the commonest chronic liver disease in high-income countries, affecting 17%-46% of the general population[1]. NAFLD includes non-alcoholic fatty liver, characterized by isolated hepatic steatosis, and non-alcoholic steatohepatitis (NASH), where variable degrees of hepatic inflammation and fibrosis coexist with steatosis[2]. NASH is associated with increased risk for cirrhosis, hepatocellular cancer (HCC) and cardiovascular disease[3,4]. Diet and exercise, aiming at weight loss, is the cornerstone of management of NAFLD, but only a minority of patients achieves and maintains weight loss > 5%, which is essential for improvement in liver histology[2,5]. Several pharmacological agents have been evaluated in patients with NAFLD but none is currently licensed for use in this disease[2]. Therefore, there is an unmet need for safe and effective treatments in patients with NASH.

NON-ALCOHOLIC FATTY LIVER DISEASE

The pathogenesis of NASH is complex and multiple pathways, including insulin resistance, inflammation, oxidative stress and apoptosis are implicated[6]. De novo lipogenesis (DNL), defined as the synthesis of fatty acids from non-lipid sources, is pivotal in the development and progression of NASH. DNL is increased in patients with NAFLD and appears to be responsible for up to 38% of intrahepatic triglyceride content in this population[7]. In addition to its contribution to the development of hepatic steatosis, DNL also promotes fibrosis by activating hepatic stellate cells (HSC), which are the principal contributors to liver fibrosis[8,9]. Acetyl-CoA carboxylase (ACC) catalyzes the ATP-dependent carboxylation of acetyl-coenzyme A (CoA) to form malonyl-CoA, which is the rate-limiting and key regulatory step in DNL[10]. ACC exists as two isoenzymes that are encoded by two different genes; ACC1 is cytosolic whereas ACC2 is located at the mitochondrial membrane[10].

Given the central role of ACC in DNL and the implication of the latter in the pathogenesis of NAFLD, ACC might represent an attractive therapeutic target in this disease. Indeed, early studies showed that liver-specific, genetic inactivation of ACC protects against the development of hepatic steatosis[11,12]. More recently, several orally available, liver-specific, dual ACC1/ACC2 inhibitors have been developed and are being evaluated in the management of NAFLD (Table 1). Perhaps the most promising is firsocostat, formerly known as GS-0976. In mice with NASH, this agent improved hepatic steatosis and also reduced hepatic inflammation[13,14]. However, an increase in serum triglyceride, glucose and insulin levels as well in total body fat mass was observed[13,14]. In another study, a structural analog of GS-0976 reduced hepatic steatosis and hepatic insulin resistance in high-fructose-fed rats[15]. However, a 30%-130% increase in plasma triglyceride levels was again observed, which was attributed to an increase in very low density lipoprotein production and a decrease in triglyceride clearance by lipoprotein lipase[15]. Other ACC inhibitors also showed promise in ameliorating hepatic steatosis in rodent models of NASH. ND-630 reduced hepatic steatosis in Zucker diabetic fatty rats[16]. In addition, PF-05221304 not only improved liver steatosis in a rat model of NASH but also reduced hepatic inflammation[17].

In addition to the reduction in hepatic steatosis, ACC inhibition also appears to ameliorate hepatic fibrosis (Table 1), which is the strongest predictor of mortality in NASH[18-20]. In recent studies, firsocostat and a structural analog of this agent inhibited the activation of HSCs and reduced hepatic fibrosis both *in vitro* and in animal models of NASH[9,13,14]. PF-05221304 also prevented the activation of primary HSCs to myofibroblasts *in vitro* and reduced fibrosis in choline-deficient, high-fat-fed rats[17]. In contrast, MK-4074 did not affect fibrosis in a rat model of NASH, suggesting that the effect of ACC inhibition on fibrosis might be agent-specific [21]. On the other hand, another liver-specific, dual ACC1/ACC2 inhibitor, ND-654,

Table 1 Major findings of preclinical and clinical studies that evaluated the effects of acetyl-CoA carboxylase inhibitors in non-alcoholic steatohepatitis

Population	ACC inhibitor	Major findings	Ref.
Mice with NASH	Firsocostat (GS-0976)	↓ Hepatic steatosis, inflammation and fibrosis	[13, 14]
High-fructose-fed rats	A structural analog of firsocostat	↓ Hepatic steatosis; ↓ hepatic insulin resistance	[15]
Zucker diabetic fatty rats	ND-630	↓ Hepatic steatosis	[16]
Rat model of NASH	PF-05221304	↓ Hepatic steatosis, inflammation and fibrosis	[17]
Rat model of NASH	MK-4074	No effect on hepatic fibrosis	[21]
Rat model of NASH	ND-654	↓ Hepatic steatosis; Delayed progression of hepatocellular cancer	[22]
10 patients with NASH	Firsocostat	↓ Hepatic steatosis and fibrosis	[23]
126 patients with NASH	Firsocostat	↓ Hepatic steatosis and tissue inhibitor of metalloproteinase-1 levels	[24]
392 patients with NASH and bridging fibrosis or compensated cirrhosis (F3-F4)	Firsocostat	↓ Hepatic steatosis and stiffness	[25]
Healthy subjects	PF-05221304	Dose-dependent suppression of de novo lipogenesis	[26]
Overweight and/or obese adult males	ND-630	Suppression of de novo lipogenesis	[27]
30 patients with non-alcoholic fatty liver	MK-4074	↓ Hepatic steatosis	[28]

not only reduced hepatic steatosis but also delayed the progression of HCC in a rat model[22].

Preliminary studies suggest that ACC inhibition might also be effective in patients with NAFLD (Table 1). In a pilot, open-label, prospective study in 10 patients with NASH, administration of firsocostat for 12 wk reduced hepatic steatosis, assessed with magnetic resonance imaging (MRI), and fibrosis, assessed with both magnetic resonance elastography (MRE) and serum levels of tissue inhibitor of metalloproteinase 1 (TIMP-1)[23]. However, serum alanine aminotransferase levels did not change[23]. In a phase 2, randomized study in 126 patients with NASH, treatment with GS-0976 for 12 wk reduced hepatic steatosis, assessed with MRI, and TIMP-1 Levels more than placebo[24]. However, changes in MRE-measured liver stiffness did not differ among groups and an 11%-13% increase in serum triglyceride levels was observed in patients treated with GS-0976[24]. In a larger, phase 2b, randomized trial in 392 patients with NASH and bridging fibrosis or compensated cirrhosis (F3-F4), the incidence of the primary endpoint (a ≥ 1-stage improvement in fibrosis without worsening of NASH) did not differ between firsocostat and placebo[25]. However, firsocostat improved steatosis, increased the proportion of patients with ≥ 1-grade improvement in liver histology and improved liver stiffness evaluated by transient elastography and the Enhanced Liver Fibrosis Test compared with placebo[25]. Notably, serum glucose and insulin levels as well as body weight did not change in patients treated with firsocostat [25]. On the other hand, a mean increase in serum triglyceride levels by 42 mg/dL was observed in the firsocostat group[25].

Other ACC inhibitors also showed promising results in pilot clinical studies (Table 1). In healthy subjects, PF-05221304 dose-dependently suppressed DNL and was well-tolerated[26]. With doses yielding ≥ 90% DNL inhibition, asymptomatic increases in serum triglyceride levels and declines in platelet count occurred but these were not observed at ≤ 80% DNL inhibition[26]. A single dose of ND-630 was also shown to suppress DNL in overweight and/or obese but otherwise healthy adult males and was well tolerated[27]. Finally, in a randomized study in 30 patients with NAFL, treatment with MK-4074 for 4 wk decreased hepatic fat more than pioglitazone and placebo[28]. However, a 2-fold increase in plasma triglyceride levels was observed in patients treated with MK-4074 and not in the other groups[28]. It was shown that inhibition of ACC results in reduced intrahepatic content of polyunsaturated fatty acids, which in turn activates sterol regulatory element-binding protein-1c that increases hepatic production of very low density lipoprotein and therefore plasma triglyceride levels[28].

CONCLUSION

In conclusion, ACC inhibitors appear to represent a promising tool for ameliorating hepatic steatosis. The effect of these agents on hepatic fibrosis is less consistent and more studies are needed to assess their impact on NASH. In addition, given the high cardiovascular risk of patients with NASH, the increase in triglyceride levels during treatment with ACC inhibitors is a cause of concern and should be also be factored in the decision to administer them in this population.

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