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EDITORIAL

Role of ezetimibe in non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) encompasses a histological spectrum ranging from simple steatosis to steatohepatitis, advanced fibrosis and inflammatory changes. Ezetimibe inhibits cholesterol absorption from the intestinal lumen into enterocytes. The molecular target of ezetimibe is the sterol transporter Niemann-Pick C1-like 1 protein (NPC1L1). Human NPC1L1 is abundantly expressed in the liver and may facilitate the hepatic accumulation of cholesterol. Ezetimibe exerts beneficial effects on several metabolic variables. Ezetimibe treatment attenuates hepatic steatosis and is beneficial in terms of NAFLD biochemical markers. The combination of ezetimibe with other interventions may also be beneficial in NAFLD patients. Our group investigated the ezetimibe-orlistat combination treatment in overweight and obese patients with hypercholesterolemia, with beneficial effects on NAFLD biochemical markers. These results are promising for patients with NAFLD, who usually have increased cardiovascular disease risk and need a multifactorial treatment. However, it should be mentioned that most results are from animal studies and, although modest elevation of liver function tests may raise the suspicion of NAFLD, none of these tests are sensitive to establish the diagnosis of NAFLD with great accuracy.

Key words: Ezetimibe; Non-alcoholic fatty liver disease; Hypolipidemic treatment; Insulin resistance; Acarbose; Orlistat

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries. NAFLD encompasses a histological spectrum ranging from simple steatosis to steatohepatitis, advanced fibrosis and inflammatory changes[1,2]. Furthermore, NAFLD is associated with peripheral and hepatic insulin resistance and many of the features defining the metabolic syndrome[3,4]. Furthermore, it was shown that being overweight and obese may result to fibrotic and inflammatory hepatic injury, an effect mediated in part by insulin resistance[5].

ROLE OF EZETIMIBE IN NAFLD

Ezetimibe belongs to a class of hypolipidemic agents, the cholesterol absorption inhibitors, which inhibit cholesterol absorption from the intestinal lumen into enterocytes[6]. The molecular target of ezetimibe is the sterol transporter Niemann-Pick C1-like 1 protein (NPC1L1)[7,8]. Besides its low-density lipoprotein cholesterol (LDL-C) lowering effect, ezetimibe exerts beneficial effects on several other

metabolic variables[9]. Of interest, human NPC1L1 is also abundantly expressed in the liver and may facilitate the hepatic accumulation of cholesterol[10].

Ezetimibe treatment appears to attenuate hepatic steatosis[11]. Jia *et al*[12] fed NPC1L1 knockout (L1-KO) mice and their wild-type controls for 24 wk with a high-fat diet and found that a high-fat diet did not cause fatty liver. L1-KO mice were completely protected against high-fat diet-induced hyperinsulinemia under both fed and fasted states and during glucose challenge. Furthermore, hepatic fatty acid synthesis and levels of mRNAs for lipogenic genes were substantially reduced in L1-KO mice[12]. Inhibition of NPC1L1 by ezetimibe in Zucker Obese Fatty rats improved hepatic insulin signaling as well as hepatic steatosis[13]. Hence, NPC1L1 contributes to hepatic insulin resistance through cholesterol accumulation and its inhibition could be a potential therapeutic target of hepatic insulin resistance[13].

Ezetimibe administration in humans has also been beneficial in terms of NAFLD biochemical markers[14], including fatty acid concentration[15]. In a study, long-term ezetimibe treatment (24 mo) was given in 45 patients with newly diagnosed liver biopsy-proven NAFLD (Table 1)[16]. Ezetimibe significantly improved visceral fat area [from (155.9 ± 38.9) to (146.5 ± 34.8) cm^2, $P < 0.05$), fasting insulin [from (10.9 ± 5.6) to (9.4 ± 5.1) mU/L, $P < 0.05$], homeostasis model assessment [HOMA, from (3.04 ± 1.17) to (2.62 ± 1.24), $P < 0.05$], the concentration of triglycerides [from (168 ± 94) to (138 ± 88) mg/dL, $P < 0.05$], total cholesterol [from (228 ± 44) to (194 ± 36) mg/dL, $P < 0.01$), LDL-C [from (136 ± 33) to (114 ± 31) mg/dL, $P < 0.05$), as well as the mean levels of small LDL and very small LDL [from (37.9 ± 5.4) to (33.2 ± 5.1) mg/dL, $P < 0.05$ and from (23.8 ± 4.8) to (18.6 ± 2.8) mg/dL, $P < 0.01$, respectively]. Ezetimibe also significantly lowered serum alanine aminotransferase [ALT, from (62 ± 25) to (49 ± 23) IU/L, $P < 0.01$] and high-sensitivity C-reactive protein [hsCRP, from (883 ± 408) to (685 ± 377) μg/L, $P < 0.05$] levels. The histological features of steatosis grade ($P = 0.0003$), necroinflammatory grade ($P = 0.0456$), ballooning score ($P = 0.0253$) and NAFLD activity score ($P = 0.0007$) were significantly improved compared with baseline.

ROLE OF DRUG COMBINATIONS INCLUDING EZETIMIBE IN NAFLD

Ezetimibe in the setting of hyperlipidemia is usually given combined with other hypolipidemic drugs[6], which leads to complementary results in terms of cardiovascular disease risk factors due to the different mechanisms of action. The combination of ezetimibe with other interventions seems to be beneficial in NAFLD patients. For example, compared with weight loss alone, the administration of ezetimibe plus weight loss in 25 obese subjects significantly decreased intrahepatic triglyceride content (-18%), as well as plasma hsCRP (-53%), interleukin-6 (-24%), LDL-C (-18%), and campesterol (-59%) concentration (all $P < 0.05$)[17]. Furthermore, combined treatment of ezetimibe with insulin-sensitizing agents had greater effect on hepatic fat content and lipid peroxidation compared to monotherapy in the methionine choline-deficient diet rat model of NAFLD[18]. Interestingly, the combination of ezetimibe and acarbose for 24 wk reduced steatosis, inflammation and fibrosis in the liver, compared with long-term monotherapy with either drug, in a high-fat diet-induced NAFLD mouse model (C57BL/6J mice)[19]. The combination treatment also significantly increased the expression of microsomal triglyceride transfer protein and peroxisome proliferators-activated receptor-alpha1 in the liver, compared with either monotherapy.

Table 1 Effects of ezetimibe, alone or combined with other drugs, in non-alcoholic fatty liver disease-related variables in humans

Drug (s)	Parameter
Ezetimibe[16]	↓Visceral fat area ↓HOMA ↓Triglycerides, ↓total cholesterol, ↓LDL-C ↓ALT ↓hsCRP ↓Steatosis grade and NAFLD activity score
Ezetimibe plus weight loss[17]	↓Intrahepatic triglyceride content ↓hsCRP ↓Interleukin-6 ↓LDL-C
Ezetimibe plus orlistat[20-22]	↓Body mass index and waist circumference ↓Total cholesterol and triglycerides ↓HOMA ↓ALT, AST, γGT

NAFLD: Non-alcoholic fatty liver disease; HOMA: Homeostasis model assessment; LDL-C: Low density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γGT: γ-glutamyl-transpeptidase; hsCRP: High sensitivity C-reactive protein.

Our group investigated the ezetimibe-orlistat combination treatment in 88 overweight and obese patients with hypercholesterolemia, who were randomised to ezetimibe (group E), orlistat (group O) and their combination (group OE)[20-22]. We observed significant within-group changes in body mass index, waist circumference and body weight, which were significantly greater in groups receiving orlistat. We also observed significantly greater reductions in total cholesterol, triglycerides and apolipoprotein B levels in the combination group compared with monotherapy groups. Parameters of carbohydrate metabolism were significantly improved in groups receiving orlistat (i.e. in groups that lost weight) compared with the ezetimibe group. The activities of ALT (-16% in group O, -18% in group E, -14% on group OE, all $P < 0.05$) and gamma-glutamyl-transpeptidase (gGT, -15% in group O, -11% in group E, -25% in group OE, all $P < 0.05$) were improved in all treatment groups, whereas aspartate aminotransferase activity improved only in the combination group (-17%, $P < 0.05$).

CONCLUSION

These results are promising for patients with NAFLD, who usually have increased cardiovascular disease risk and need a multifactorial treatment. However, it should be mentioned that, although modest elevation of liver function tests may raise the suspicion of NAFLD, none of these tests are sensitive to establish the diagnosis of NAFLD with great accuracy[23]. Minimal requirement of any form of NAFLD resolution should be a lower fibrosis score. Furthermore, most results are given by animal studies which do not always correspond to human physiology.

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