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PHARMACOLOGICAL APPROACHES FOR NONALCOHOLIC FATTY LIVER DISEASE

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Abstract

Background and aims: *Nonalcoholic fatty liver disease (NAFDL) is a multifactorial condition with a wide spectrum of histological severities, from asymptomatic hepatic steatosis to nonalcoholic steatohepatitis (NASH) with or without fibrosis. NAFLD is highly common and potentially serious in children and adolescents and affects approximately one third of the general population. It is closely associated with obesity, insulin resistance and dyslipidemia. NASH is a histological diagnosis and has a great significance because it can progress to cirrhosis, liver failure, and hepatocellular carcinoma (HCC), and is associated with both increased cardiovascular and liver related mortality. The purpose of this review is to summarize the evidence for current potential therapies of NAFLD.* ***Material and Methods:*** *We searched MEDLINE from 2010 to the present to identify the pharmacological approaches for NAFLD.* ***Results and conclusions:*** *NAFLD may be a new risk factor for extrahepatic diseases such as cardiovascular disease (CVD), chronic kidney disease (CKD), colorectal cancer, type 2 diabetes mellitus (T2DM) and osteoporosis. Currently there is no specific targeted treatment for NAFLD/NASH.*

key words: *nonalcoholic fatty liver disease, insulin sensitizers, incretin-based therapies, farnesoid X receptor agonists, caspase inhibition.*

Background and aims

Chronic liver diseases constitute the fifth most frequent cause of death in the European Union [1]. Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in the United States and Western countries [2,3]. It is associated with obesity, type 2 diabetes mellitus (T2DM), insulin resistance, and the accumulation of triglycerides in hepatocytes [4]. NAFLD includes a wide spectrum of diseases ranging from hepatic steatosis to nonalcoholic steatohepatitis (NASH), which has a great significance because it can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC), in some patients [5,6]. Liver fibrosis and ultimately cirrhosis, it is common to all end-stage chronic liver diseases [7]. Fibrosis is characterized by a several times increase of the extracellular matrix comprising collagen,

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glycoproteins, proteoglycans sulphate and hyaluronan and also changes in the microstructure of collagen, glycoproteins and proteoglycans [1].

Many different pathways were described for the pathogenesis of NAFLD (fig. 1) [8]. All require further elucidation, but each of them can be target of novel therapies [9].

The importance of treatment for NAFLD is strongly related with its complications. Currently, there is no approved treatment for NAFLD/NASH but interventions that improve the metabolic profile of patients (obesity, dyslipidemia, insulin-resistance and diabetes control) might be useful [10].

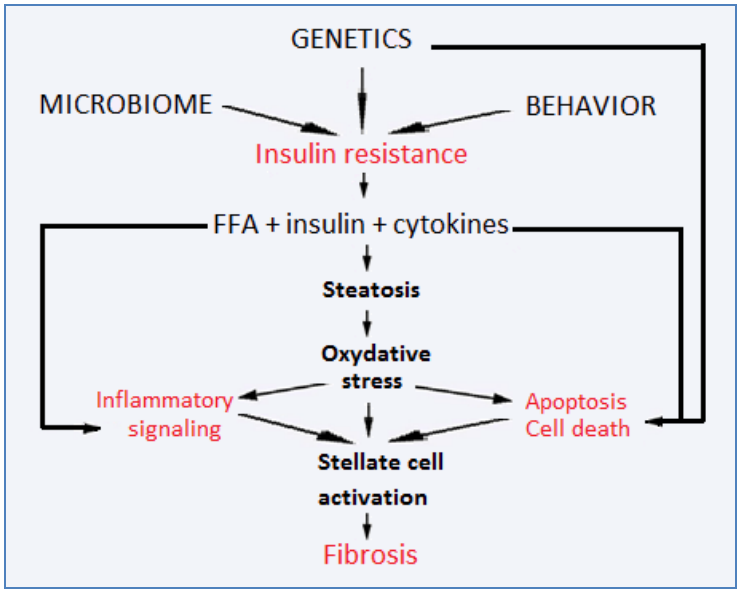

Figure 1. *Pathogenetic pathways of NAFLD - potential target for therapy. (Adapted after [8])*

Anti-hyperglycemic drugs

Insulin sensitizers

Thiazolidinediones (TZDs) (troglitazone, rosiglitazone, and pioglitazone) are a class of peroxisome proliferator activated receptor γ (PPARγ) agonists, that have a significant effect on insulin sensitivity in insulin resistant states and in type 2 diabetes mellitus, as well as in patients with NAFLD/NASH [11].

(TZDs) are notable for the ability to cause differentiation of pluripotent stem cells into adipocytes [12]. Glitazones improve insulin resistance and promote differentiation of insulin resistant large pre-adipocytes into small, proliferative, insulin sensitive adipocytes. PPARγ agonists also exert anti-inflammatory effects on Kupffer cells, which might be indicative of direct hepatoprotective effects [8]. Thus, TZDs are probably the best pharmacologic option for subjects with NAFLD [13].

Pioglitazone is the best studied drug in NASH. The randomized controlled trials reported a beneficial effect of pioglitazone on liver histology, although the advantage was limited for fibrosis. In another randomized controlled trial, administration of 30 or 45 mg/d of pioglitazone induced significant improvements in serum aminotransferases levels and liver histology (steatosis, inflammation, ballooning) compared with placebo in NASH patients [14].

Incretin-Based Therapies

Glucagon like peptide-1 (GLP-1) is a naturally existing incretin hormone with a potent blood-glucose reducing action only during hyperglycemia since it induces insulin secretion

and reduces glucagon secretion in a glucose-dependent manner [15]. In Ohki *et al* study, that included 126 patients who were clinically diagnosed with NAFLD and T2DM, the aspartate aminotransferase to platelet ratio *index* (APRI) was significantly improved in the liraglutide group and pioglitazone group but not in the sitagliptin group [16]. Armstrong *et al* showed a significant histological benefit in 52 patients with biopsy-proven NASH, treated with liraglutide 1.8 mg per day for 48 weeks. NASH resolution occurred in 39% of patients treated with liraglutide compared to 9% with placebo, and less patients treated with liraglutide experienced worsening of fibrosis [17].

Lipid-lowering medications

NAFLD is strongly associated with obesity and dyslipidemia. Statins (HMG-CoA reductase inhibitors) are among the most-prescribed classes of medications and increasing numbers of patients have received statins in recent decades in all developed countries [18]. Statins have anti-inflammatory, anti-oxidant and antithrombotic effects that are independent of their lipid-lowering activity. Since in NAFLD and NASH inflammation and oxidative stress play an important pathogenetic role, statins have been proposed for the treatment of these conditions [19].

Statins decrease lipid levels both peripherally and viscerally, specifically in the liver but the efficacy of statins for NAFLD/NASH has not been fully validated [20]. In a randomized controlled trial, atorvastatin (20 mg/d) combined with antioxidants (vitamin C and E) was effective in reducing the risk of hepatic steatosis by 71% after 4 years of active therapy in individuals with NAFLD at baseline [21]. Although some studies have reported decreased serum aminotransferases or a reduction in steatosis evidenced by imaging methods, most studies have shown no evidence of liver histology improvement [22].

Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs)

ACE-I and ARBs induced vasodilation increases the delivery of glucose and insulin to insulin-sensitive tissues and improves blood flow in the pancreas, promoting insulin secretion [23]. The beneficial effects of ARBs on insulin resistance could also be related to the selective stimulation of peroxisome proliferator-activated receptors γ (PPAR-γ).

Furthermore, clinical trials have showed the ability of renin-angiotensin system (RAS) inhibition to prevent new-onset of diabetes mellitus. A meta-analysis by Al-Mallah *et al* [24] including 100.848 patients, reported that there was a 20% reduction in the incidence of new onset T2DM with the use of ACE-I and ARBs. Despite the encouraging evidence from animal studies, data from human studies about the use of ACE-I and ARBs in NAFLD/NASH, are limited and contradictory [24].

Microbiomes

The data on microbiota sustain the hypothesis that differences in gut microbiota profile may have an impact on the liver, on the background of obesity and insulin resistance [25]. Probiotics have been proposed as a treatment option because their modulating effect on the gut flora could influence the gut-liver axis. Several studies have suggested the important role of gut-derived bacterial products in the pathogenesis of steatosis, inflammation and fibrosis, all NASH-associated features [26,27]. A recent meta-analysis that included 134 patients with NAFLD/NASH from 14 randomised controlled trials (RCTs), showed probiotic therapy significantly decreased liver aminotransferases, total-cholesterol level, TNF-α

and improve insulin resistance in NAFLD patients. Of the four RCTs included in this meta-analysis, the studied probiotics included *Lactobacillus*, *Bifidobacterium* and *Streptococcus* [28].

Probiotics are safe, cheap and have no known long-term adverse effects, as well as in the management of NASH probiotic supplementation appears to be attractive.

Anti-oxidants and cytoprotective drugs

Vitamin E is a well-known antioxidant that prevents the propagation of free radicals. In the large PIVENS trial, 247 subjects were randomized to receive RRR-α-tocopherol 800 IU/day versus pioglitazone 30 mg/day versus placebo over 96 weeks. There was a significant improvement of hepatocellular ballooning and steatosis, without significant improvement in fibrosis score [14]. However, vitamin E use is associated with adverse effects, including risk of hemorrhagic stroke, bladder cancer and prostate cancer [29].

Pentoxifyllin is a non-selective phosphor-diesterase inhibitor, which it was shown that affecting multiple steps in the cytokine pathway by direct or indirect inhibition of TNF-α [30].

In two small studies with associated liver biopsies in patients with NASH, one study was negative, and in the other there was a poor improvement in steatosis, lobular inflammation and fibrosis [22]. Thus, Zein *et al* reported that administration of pentoxifyllin (1200 mg/d) for 12 months improved histological features of NASH (steatosis, lobular inflammation, and fibrosis) compared to placebo [31]. Baniasadi *et al* suggest that pentoxifyllin administration does not significantly help in the treatment of patients with NASH [32]. A meta-analysis carried out by Du Juan *et al* showed that pentoxifyllin therapy improved liver function and histological changes in patients with NAFLD/NASH [33]. It is necessary to examine the current state of beneficial effect of the treatment with pentoxifyllin in patients with NAFLD or NASH, and also generating hypotheses for future research.

New areas of interest

Farnesoid X receptor agonists- Obeticholic acid (OCA)

Farnesoid X receptor (FXR) activated by natural or synthetic ligands, was described mainly as a regulator of bile acid synthesis, and, more recently, as a regulator of the gut-liver axis in the fed state [34]. Activation of FXR improves hepatic steatosis, inflammation and fibrogenesis in NAFLD. Obeticholic acid (OCA) is a synthetic farnesoid X receptor (FXR) agonist, and in animal models of NAFLD/NASH, has been shown to increase hepatic insulin sensitivity and reduce gluconeogenesis, with amelioration of hepatic steatosis [35].

In the recently published FLINT clinical trial, Neuschwander-Tetri *et al.* studied NASH patients treated with OCA for 72 weeks and showed improvement of histological hepatic steatosis, inflammation, and fibrosis vs. placebo [36].

Caspase inhibition (GS-9450, Emricasan)

A Phase 2 randomized, placebo-controlled study investigating the safety, tolerability, and activity of multiple oral doses of GS-9450 was performed in 124 patients with NASH. Study design included five parallel treatment groups: placebo or GS-9450 1 mg, 5 mg, 10 mg, or 40 mg administered orally once daily for 4 weeks. On completion of treatment, subjects entered a 4-week follow-up period. The results of this study showed significant decreases in alanine aminotransferase (ALT) levels and smaller non-statistically significant reductions in aspartat

aminotransferase (AST) and CK-18 fragments in patients with NASH. This finding suggests that reducing apoptosis may be a valuable therapeutic strategy in patients with NASH [37].

Emricasan (IDN-6556) is an irreversible pancaspase protease inhibitor that is orally administered. In animal models, hepatic fibrosis and liver damage were reduced by emricasan. In a double- blind, placebo-controlled, study that included 105 patients treated with emricasan for 14 days, significantly reduced ALT and AST levels were observed [9].

Conclusion

Elucidating the pathogenesis pathways of NASH could result in a new generation of effective therapies with minimal side effects. The development of novel pharmacotherapies will be complicated because of the multifactorial pathogenesis of NAFLD, the heterogeneity of the patients, the imprecision of disease staging techniques, and the tendency of spontaneous disease regression in many patients, likely related to the improvement of metabolic control.

There is a lack of consensus regarding the most appropriate pharmacotherapy for this disease. Current approaches to the management of NAFLD and NASH are often suboptimal. There has been an increased effort to develop antifibrotic agents to treat patients with NASH and significant fibrosis to reduce progression to end-stage disease. There is a clinical need for an effective treatment, and evidence from animal studies suggests that the liver injury from NAFLD may be reversible. More clinical and preclinical studies on potential drugs are needed to improve treatment for NAFLD/NASH, which is an increasingly prevalent disease.

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