

Current and emerging pharmacological therapy for non-alcoholic fatty liver disease

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Abstract

The main treatment of patients with non-alcoholic fatty liver disease (NAFLD) is life style modification including weight reduction and dietary regimen.

Majority of patients are safely treated with this management and pharmacologic interventions are not recommended. However, a subgroup of NAFLD patients with non-alcoholic steatohepatitis (NASH) who cannot achieve goals of life style modification may need pharmacological therapy. One major obstacle is measurement of histological outcome by liver biopsy which is an invasive method and is not recommended routinely in these patients. Several medications, mainly targeting baseline mechanism of NAFLD, have been investigated in clinical trials for treatment of NASH with promising results. At present, only pioglitazone acting as insulin sensitizing agent and vitamin E as an antioxidant have been recommended for treatment of NASH by international guidelines. Lipid lowering agents including statins and fibrates, pentoxifylline, angiotensin receptor blockers, ursodeoxycholic acid, probiotics and synbiotics are current agents with beneficial effects for treatment of NASH but have not been approved yet. Several emerging medications are in development for treatment of NASH. Obeticholic acid, liraglutide, elafibranor, cenicriviroc and aramchol have been tested in clinical trials or are completing trials. Here in, current and upcoming medications with promising results in clinical trial for treatment of NAFLD were reviewed.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Vitamin E; Pioglitazone; Pharmacological therapy; Obeticholic acid

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Core tip: Non-alcoholic fatty liver disease (NAFLD) is an increasing liver disease worldwide. However, most of patients are treated with life style modification including weight loss and dietary regimen. Pharmacologic therapy may be indicated in a group of patients with non-alcoholic steatohepatitis. Here in, the current and emerging medications for treatment of NAFLD was reviewed briefly with regard of their beneficial effects

on histological outcomes.

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INTRODUCTION

Prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing and NAFLD is probably the most common cause of abnormal liver enzymes worldwide^[1]. The spectrum of NAFLD is ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and liver cirrhosis^[2]. While simple steatosis is generally considered a benign condition, it may gradually progress to NASH, liver cirrhosis and eventually hepatocellular carcinoma (HCC)^[3]. This has been resulted in significant attention of physicians and health care providers toward detection and treatment of NAFLD in recent years.

NASH has been estimated to affect 2%-5% of western population and is associated with 10-fold increase in liver related mortality^[4]. In addition to steatosis, NASH is defined by cellular injury and inflammation that may eventuate in liver fibrosis^[5]. Hepatocellular injury and fibrosis in NASH is mainly a result of free fatty acid lipotoxicity mediated by Kupffer and hepatic stellate cells causing collagen deposition^[6].

The main treatment of NAFLD is life style modification including exercise and weight loss. It has been suggested that more than 7% weight reduction sustained for 48 wk may cause significant improvement in histology of NASH^[7]. However, some patients will not achieve goals of lifestyle modification or cannot maintain them for long term period. On the other hand, there are patients with advanced liver disease needing targeted therapy. Most experts suggest pharmacologic therapy for NASH only in individuals with advanced disease or those at high risk of liver cirrhosis^[8]. No drug has been approved specifically for treatment of NAFLD yet, however, some drugs are now routinely prescribed or are under trial. Here in, current medications and future drug candidates for treatment of NAFLD are briefly reviewed (Table 1).

DISCUSSION

Pathogenesis of NAFLD

The pathogenesis of NAFLD is complex including multiple environmental and genetic factors. High calorie dietary regimens rich in carbohydrates and saturated fatty acids causing weight gain; are probably the most important environmental factor. The significant rising

prevalence of NAFLD in recent years is attributed to change in life style especially dietary regimen^[9]. Insulin resistance (IR) and metabolic syndrome are central in pathogenesis of NAFLD. Several other mechanistic pathways involved in pathogenesis of NAFLD finally result in IR. Metabolic derangements and IR in NAFLD are mediated by dysregulation of metabolic pathways which are naturally regulated by nuclear receptors such as peroxisome proliferator-activated receptors (PPARs), farnesoid X receptors (FXRs) and liver X receptors (LXRs)^[10]. Nuclear receptors have been targeted for production of drugs with beneficial effects in NAFLD.

Lipotoxicity, defined as fat induced injury to hepatocytes, oxidative stress, mediated by hypoxia-inducible transcription factors-1 α and 2 α , and chronic inflammation, through several cytokines and chemokines, are also involved in initiation and progression of NAFLD^[11]. These are other targets for medical therapy in NAFLD.

Genetic predisposition to NAFLD has been described in some studies. Patatin-like phospholipase domain containing-3 (PNPLA3) is a gene responsible for encoding a lipase acting for clearance of lipid droplets from the hepatocytes^[12]. Loss of function mutation of PNPLA3 results in hepatocytes injury and steatohepatitis. The other important genetic factor is loss of function mutation in trans-membrane 6 superfamily member 2 (*TM6SF2*) gene that is a predisposing risk for NAFLD^[13]. Alteration of adipocytokines and micronutrients^[14], thyroid hormone abnormalities^[15], and vitamin D deficiency^[16] are other proposed contributing factors in pathogenesis of NAFLD. Understanding pathogenesis and epidemiology of NAFLD may help clinicians for estimation of more precise burden of disease in population. While surveillance strategies applied to all individuals is not cost-effective, screening may be suggested for high risk groups such as those with metabolic syndrome, diabetes mellitus and hypertension^[17].

Insulin sensitizer

Since the main defined mechanism for NAFLD is IR, drugs targeting IR have been implemented as treatment of NAFLD. Peroxisome proliferator-activated receptor (PPAR)- γ is a nuclear receptor and a member of PPAR superfamily that is expressed exclusively in adipose tissue and involved in glucose metabolism and lipogenesis^[18]. Thiazolidinediones, agonists of PPAR- γ , are primarily used for treatment of diabetes mellitus and act by improvement of insulin sensitivity^[19]. Thiazolidinediones also have anti-inflammatory, anti-fibrotic properties and increase serum adiponectin level^[20-22]. The largest clinical trial investigating the effect of thiazolidinedions in NASH patients, PIVENS trial, randomized 247 patients with biopsy proven NASH to receive pioglitazone (30 mg/d), vitamin E (800 IU/d) or placebo for 96 wk^[23]. This study showed that

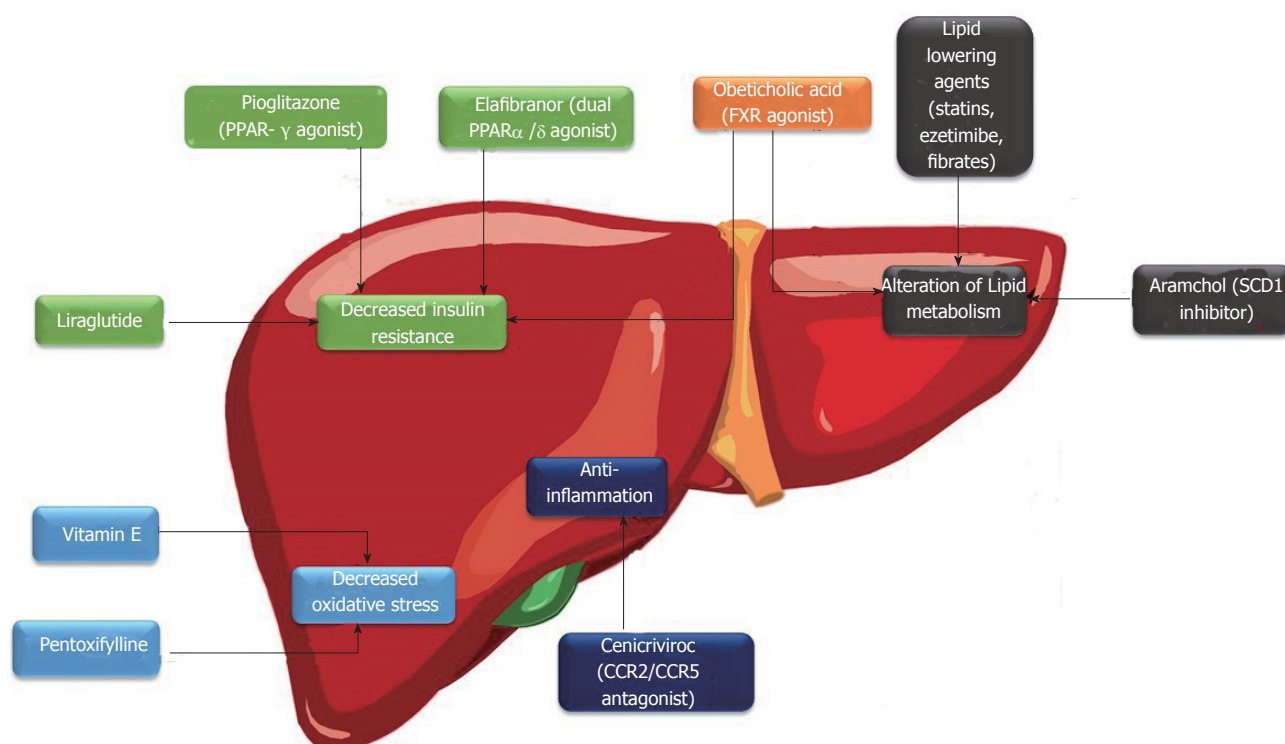


Figure 1 Current and emerging drugs for non- alcoholic fatty liver disease and their mechanism of action. PPAR: Peroxisome proliferator-activated receptor; SCD1: Stearoyl CoA desaturase-1; FXR: Farnesoid X receptor.

Table 1 Current medications that have been used for treatment of non- alcoholic fatty liver disease

Medication	Mechanism	Effect on histology	Recommended by AASLD/EASL
Pioglitazone	PPAR- γ	Improvement of steatosis, lobular inflammation and ballooning	Yes
Vitamin E	Anti-oxidant	Improvement of hepatocyte ballooning	Yes
Metformin	Amelioration of IR	No beneficial effect	No
Statins	HMG-CO A reductase inhibition	No beneficial effects	No
Ezetimibe	Inhibition of cholesterol absorption	Improvement of hepatocyte ballooning	No
Fibrates	PPAR- α	Improvement of hepatocyte ballooning	No
Pentoxifylline	Inhibition of TNF- α and anti-oxidants	Improvement of inflammation and ballooning	No
Losartan	ARB	Improvement of steatosis, lobular inflammation, ballooning and fibrosis	No
UDCA	Prevention of apoptosis/inflammation	Lacking data	No
Synbiotic and probiotics	Modulation of gut microbiota	Lacking data	No

PPAR- γ : Peroxisome proliferator-activated receptor- γ ; HMG-CO A: Hydroxyl-methyl-glutaryl-coenzyme A reductase; ARB: Angiotensin receptor blockers; UDCA: Ursodeoxycholic acid; AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of Liver.

pioglitazone could improve steatosis and histological alterations in patients with definite NASH in their liver biopsies. FLIRT trial showed improvement of steatosis and serum aminotransferase level by rosiglitazone in patients with NASH^[24]. However, use of rosiglitazone has been prohibited in Europe and highly restricted in United States based on FDA concerns regarding increase in cardiovascular side effects with this drug^[25]. Some studies showed beneficial effects of thiazolidinediones in amelioration of hepatic fibrosis^[17,26]. American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of Liver (EASL) have suggested use of pioglitazone for treatment of patients with NASH^[27,28].

It should be noted that beneficial effects of thiazolidinediones are abrogated after discontinuation and NASH is returned in liver biopsies^[29]. Other limitation of thiazolidinediones, restricting their widespread application, is their side effects including weight gain, increased bone loss and fracture risk, deterioration of heart failure and increased risk of bladder cancer with pioglitazone^[30-32].

Metformin

Metformin is used to treat type II diabetes acting through amelioration of IR by decreasing hepatic gluconeogenesis and triglyceride production^[33]. Metformin is no longer considered as a treatment for

Table 2 Emerging medications for treatment of non- alcoholic fatty liver disease

Medication	Mechanism	Histology benefit
Obeticholic acid	Farnesoid X receptor agonist	Improvement of steatosis, lobular inflammation, ballooning and fibrosis
Aramchol	Inhibition of SCD1	Lacking data
Elafibranor	PPAR α/δ agonist	Improvement of steatosis and fibrosis
Cenicriviroc	Inhibition of CCR2/CCR5	Lacking data
Liraglutide	Glucagon-like peptide-1 agonist	Improvements in steatosis and hepatocyte ballooning

SCD1: Stearoyl CoA desaturase-1; PPAR: Peroxisome proliferator-activated receptor.

NAFLD. While it had some promising results in animal studies, both pediatric and adult clinical trials failed to demonstrate histological improvement of NASH in human by metformin^[34]. AASLD and EASL guidelines do not recommend metformin as a treatment for NAFLD at present^[27,28].

Anti-oxidants

Oxidative stress has a major role in NASH pathogenesis especially activation of hepatic stellate cells (HSCs) and promoting liver fibrosis^[35]. Vitamin E is a fat soluble anti-oxidant that is capable of repairing oxidizing radicals and prevent lipid peroxidation^[36]. Vitamin E regulates PPAR and transforming growth factor- β 1 (TGF- β 1) pathways and is involved in inflammation, apoptosis and fibrosis process^[37,38]. Vitamin E has been tested in clinical trials to evaluate its efficacy in treatment of patients with NASH. Vitamin E with a dose of 800 IU/d compared to placebo for treatment of patients with NASH in PIVENS trial. After 96 wk of therapy, amelioration of hepatic steatosis, lobular inflammation and hepatocyte ballooning were seen in vitamin E treated group^[23]. However, no improvement of fibrosis was observed. The Treatment of NAFLD in Children (TONIC) trial is a randomized trial allocating 800 IU/d vitamin E and metformin (1 g/d) to children with NAFLD. Vitamin E resulted in improvement of hepatocyte ballooning but failed to improve hepatic inflammation, fibrosis and steatosis^[39]. Based on promising results of these studies, AASLD and EASL have suggested use of vitamin E for treatment of non-diabetic, non-cirrhotic patients with NASH^[27,28]. Safety profile of vitamin E is still controversial. Vitamin E treatment was associated with an increase in all cause related mortality in a meta-analysis^[40]. Some studies also showed an increase in hemorrhagic stroke and prostate cancer with high doses and long term use of vitamin E respectively^[41,42]. Therefore, it is better to individualize use of vitamin E for treatment of NASH based on these cautions. Medications against NAFLD and their mechanisms of action were outlined in Figure 1.

Lipid lowering agents

NAFLD is considered the hepatic manifestation of metabolic syndrome. Many patients with NAFLD have features of metabolic syndrome including diabetes

mellitus, dyslipidemia and obesity. Accumulation of free cholesterol in hepatocytes have been also suggested in pathogenesis of NAFLD^[43]. Statins that inhibit hydroxyl-methyl-glutaryl-coenzyme A reductase are widely used as cholesterol lowering agents and can be theoretically useful in patients with NAFLD^[44]. Athyros *et al*^[45] showed that daily atorvastatin use can improve liver enzymes and reduce cardiovascular morbidity in patients with mild to moderate abnormal liver tests. In an animal model of NASH, simvastatin was associated with amelioration of liver fibrosis by inhibition of hepatic stellate cells *via* nitric oxide synthase pathway^[46]. However, simvastatin therapy was not associated with improvement of liver enzymes, hepatic steatosis and fibrosis in a group of patients with biopsy proven NASH^[47]. In a retrospective cohort, statin use was associated with decreased risk of advanced fibrosis in patients at risk for NASH^[48]. While there are concerns about risk of using statins in patients with chronic liver disease^[49], most recent studies showed that statins are generally safe in patients with NAFLD^[50]. Since most of patients with NAFLD have components of metabolic syndrome such as dyslipidemia and DM II, statin use may be considered in this group of patients.

Ezetimibe is a cholesterol absorption inhibitor that is used for treatment of patients with elevated cholesterol level. In a mice model of hepatic steatosis induced by high fat diet, ezetimibe therapy prevented hepatic steatosis and decreased hepatic insulin resistance^[51]. In MOZART trial, ezetimibe could not significantly reduce hepatic steatosis as assessed by magnetic resonance imaging-derived proton density fat fraction^[52]. In a meta-analysis of 6 studies, Nakeda *et al*^[53] reported that ezetimibe therapy resulted in improvement of liver enzymes and hepatocyte ballooning in patients with NAFLD. Colesvelam is a bile acid sequestrant that is used clinically to decrease low density lipoprotein (LDL). A placebo controlled clinical trial showed that colesvelam was associated with increased liver fat in patients with NASH as assessed by magnetic resonance imaging and magnetic resonance spectroscopy^[54].

Fibrates are activator of peroxisome proliferator-activated receptor alpha (PPAR- α) that are used as anti-hyperlipidemic agents and mainly decrease serum triglyceride level. Fibrates also improve insulin resistance, stimulate oxidation of fatty acids and have

anti-inflammatory effects^[55]. In an animal model of NAFLD, fibrates therapy was associated with resolution of hepatic steatosis, steatohepatitis and fibrosis^[56]. A pilot trial showed improvement of metabolic syndrome and glucose metabolism by fenofibrate in patients with NAFLD but with only minimal effects on liver histology^[57]. Co-treatment with pentoxifylline plus fenofibrate was effective in reduction of liver stiffness and markers of liver fibrosis in patients with NAFLD^[58].

Pentoxifylline

Pentoxifylline is an inhibitor of tumor necrosis factor- α (TNF- α) with anti-oxidant properties that initially was known to be effective in treatment of alcoholic hepatitis^[59]. Most animal models suggested beneficial effects of pentoxifylline in reducing liver enzymes and hepatic inflammation^[60,61]. In a randomized placebo trial, pentoxifylline significantly improved liver fibrosis and decreased NAFLD activity score^[62]. They also showed that beneficial effects of pentoxifylline in NASH are mediated by decreasing free-radical-mediated lipid oxidation^[63]. Satapathy *et al*^[64] showed that 12 mo pentoxifylline therapy was associated with biochemical and histological improvement in patients with NASH. Two meta-analysis reported beneficial effects of pentoxifylline in terms of reduction of liver enzymes and improvement of histology in NASH patients^[65,66]. However, long-term safety and efficacy of pentoxifylline in patients with NASH needs to be investigated as there are some reports of aggravation of fatty liver in mice by pentoxifylline therapy^[67].

Angiotensin receptor blockers

Angiotensin II receptor blockers are a group of medications widely used for treatment of hypertension. Angiotensin II probably promotes liver fibrosis via activation of transforming growth factor- β (TGF- β) and toll-like receptor-4 signaling^[68,69]. In a series of 7 patients with NASH, 48 mo therapy with an angiotensin II receptor blocker, losartan (50 mg/d), resulted in amelioration of necro-inflammatory response and improvement of hepatic fibrosis^[70]. These beneficial effects was reported to be mediated *via* inhibition of HSC in this group of patients^[71]. Fogari *et al*^[72] reported that combination of simvastatin and losartan improved hepatic steatosis indices and decreased visceral adipose tissue diameter. In FANTASY trial, telmisartan therapy for 12 mo was associated with decreased serum free fatty acid levels without significant improvement in liver enzymes^[73]. Addition of losartan to rosiglitazone had no extra histological benefit than rosiglitazone alone in patients with NASH^[74]. In a rat model of type II diabetes, valsartan could reduce hepatic fibrosis and steatosis correlated with reduction of tissue expression of TNF- α and monocyte chemoattractant protein-1 (MCP-1)^[75]. Further studies are needed to confirm therapeutic role of angiotensin II receptor blockers in treatment of NAFLD.

Ursodeoxycholic acid

It has been postulated that ursodeoxycholic acid (UDCA) may prevent progression of NAFLD because of anti-inflammatory and anti-apoptotic properties^[76]. In a randomized placebo controlled trial, Ratziu *et al*^[77] showed that high dose UDCA was effective in improvement of serum aminotransferase and markers of liver fibrosis in patients with biopsy proven NASH. A systematic review of 12 trials reported beneficial effects of UDCA for treatment of NASH^[78]. However, UDCA is not currently recommended for treatment of NASH in international guidelines due to lacking of well-designed large randomized trials and lack of evidence about histological benefits.

Synbiotics and probiotics

Probiotics are live, human origin, non-pathogenic microorganisms with beneficial effects when consumed adequately. Prebiotics are not live microorganisms but chemicals causing growth of microorganisms. Nutritional supplements composed of probiotics and prebiotics are called synbiotics^[79]. The role of gut microbiota has been confirmed in pathogenesis of insulin resistance and NAFLD^[80]. Therefore, modulation of gut microbiota using probiotics and synbiotics has been suggested as a treatment option in NAFLD. Several studies with different preparations of probiotics have been conducted among NAFLD patients. A meta-analysis of 4 randomized trials reported that probiotics had beneficial effects on liver enzymes, lipid profile and improved insulin resistance in patients with NAFLD/NASH^[81]. A double blind randomized clinical trial showed that Synbiotic + life style modification including physical activity and dietary regimen was superior to life style modification alone in treatment of patients with NAFLD^[82]. Beneficial effects of synbiotics was also confirmed in lean NAFLD^[83]. Despite promising results, data regarding histologic benefits of synbiotics and probiotics is lacking. Larger studies are needed to further elucidate the issue.

EMERGING PHARMACOLOGICAL OPTIONS

Obeticholic acid

Farnesoid X receptor (FXR) is a nuclear receptor which is expressed in the liver and is involved in bile acid synthesis. Binding of bile acids to FXR results in down-regulation of bile acid synthesis, hepatic lipogenesis, hepatic gluconeogenesis and improved peripheral insulin sensitivity^[84]. FXR activation resulted in prevention of weight gain and decreased liver/muscle fat deposition and hepatic steatosis in obese rats^[85]. Obeticholic acid (OCA) is a synthetic bile acid derivatives that acts as agonist of FXR and has been shown to be capable of reduction of hepatic steatosis in mice^[86]. In a randomized double blind placebo controlled trial, 25 mg or 50 mg OCA was

given to patients with type II diabetes and NAFLD for 6 wk. After completion of the study, OCA group had significant reduction in liver enzymes and markers of liver fibrosis compared to those in placebo group. However, the histologic features were not evaluated in this study^[87]. FLINT trial is a multi-central randomized trial reporting improvement of histological features of NASH with 25 mg daily OCA for 72 h^[88]. An unfavorable outcome was a rise in total cholesterol and LDL cholesterol accompanied by a fall in HDL cholesterol^[88]. OCA seems to be a promising agent to be included in treatment of NASH in future.

Aramchol

Aramchol is a conjugate molecule composed of two components, cholic and arachidonic acid, which is primarily used for treatment of cholesterol gallstone^[89]. Aramchol is an inhibitor of stearoyl CoA desaturase-1 (SCD1) an enzyme which is involved in lipid metabolism and hepatic insulin resistance^[89,90]. Administration of 100 or 300 mg aramchol for 3 mo in patients with NAFLD resulted in decreased liver fat content without significant improvement of liver enzymes^[91]. Larger clinical trials are needed to further elucidate the role of this agent in treatment of NAFLD.

Elafibranor

Peroxisome proliferator-activated receptor alpha (PPAR- α) is a member of PPAR superfamily that is expressed in adipose tissue, liver, skeletal muscle, heart and is involved in regulation of lipid and glucose metabolism. PPAR- α gene expression has been shown to have negative correlation with severity of NASH and visceral adiposity in patients with NAFLD^[92]. Activation of another PPAR, PPAR- δ , is associated with improvement of insulin resistance, increase in oxidation of fatty acids and decrease in hepatic gluconeogenesis^[93]. Elafibranor, a dual agonist of PPAR α/δ , has improved lipid profile and reduced hepatic fat in animal studies^[94]. In a cross-over randomized trial, 80 mg daily administration of elafibranor in obese subjects was associated with improvement of hepatic and peripheral insulin resistance^[95]. A recent randomized clinical trial showed that daily oral 120 mg elafibranor for 52 wk was associated with improvement of hepatic steatosis and fibrosis in patients with NASH in a dose dependent manner. Elafibranor therapy was also associated with improvement of systemic inflammation, lipid/glucose profiles and liver enzymes when compared to the placebo group^[96]. Authors reported a reversible rise in serum creatinine in elafibranor group, otherwise, the drug was well-tolerated. Elafibranor may be considered as a candidate for treatment of patients with NASH after completion of ongoing phase III trial.

Cenicriviroc

Overexpression of inflammatory chemokines CCL2

(MCP-1) and CCL5 (RANTES) have been established in patients with NASH leading to worsening of hepatic inflammation and fibrosis^[97]. CCR2 and CCR5 are chemokine receptors for CCL2 and CCL5 that are inhibited by cenicriviroc. Anti-fibrotic properties of cenicriviroc have been approved in thioacetamide model of hepatic fibrosis in mice^[98]. CENTAUR is an ongoing randomized clinical trial evaluating efficacy of cenicriviroc in patients with NASH and hepatic fibrosis^[99].

Liraglutide

Liraglutide is an incretin mimetic that acts as an agonist of glucagon-like peptide-1 receptor and was primarily used for treatment of type II diabetes. In animal model, liraglutide therapy was associated with amelioration of hepatic steatosis in mice fed with high fat/high fructose^[100]. In Wistar rats, liraglutide therapy improved insulin resistance and hepatic steatosis by activation of AMP-activated protein kinase^[101]. In a randomized trial, addition of liraglutide to insulin glargine was not superior to insulin glargine alone in improvement of glycemia and hepatic steatosis^[102]. In a small randomized trial, 1.8 mg liraglutide administered subcutaneously was effective in improvement of histological features in patients with NASH^[103]. Table 2 outlined new emerging medications for NAFLD.

CONCLUSION

Several medications including thiazolidindiones, metformin, vitamin E, statins, pentoxifylline, losartan, ursodeoxycholic acid, probiotics and synbiotics have been applied for treatment of NAFLD/NASH with promising but conflicting results. Future candidate medications for this purpose with ongoing or completing clinical trials are OCA, elafibranor, aramchol, cenicriviroc and liraglutide targeting different underlying mechanisms in NASH. Some of them may have beneficial effects on histological features of NAFLD/NASH.

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