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Review article

Treatments of nonalcoholic fatty liver disease in adults who have no other illness: A Review article

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases. In the absence of treatment, NAFLD can damage the liver tissue and even have extra-hepatic complications. No therapeutic regimen has ever been approved for the treatment of this disease. A variety of clinical trials have been conducted in the field of NAFLD. Reviewing these trials is necessary to provide the most effective treatments. In this article, we aimed to review randomized controlled trials that evaluate the effects of pharmacological agents on NAFLD adults without other illness.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver disease with prevalence of 25.24% in the worldwide [1]. NAFLD includes a range of liver disorders from simple steatosis to nonalcoholic steatohepatitis (NASH). NASH can progress to cirrhosis and hepatocellular carcinoma that this has made NAFLD to the second cause of liver transplantation in United States [2]. Furthermore, NAFLD can increase the risk of extrahepatic diseases including type 2 diabetes mellitus, cardiovascular disease, and chronic kidney disease [3]. NASH is characterized by hepatic inflammation and hepatocellular damage, with or without fibrosis [4]. Liver biopsy is gold standard for definitive diagnosis of NASH. In quantifying hepatic fat content, advanced magnetic resonance imaging (MRI) techniques are better than liver histology [5]. Despite the high prevalence and unfavourable prognosis, there is currently no approved pharmacological therapy for NAFLD; therefore, an accurate review of NAFLD clinical trials is necessary. In this article, we reviewed randomized controlled trials that evaluate the effects of pharmacological agents on NAFLD adults without other illness and reported the most effective treatments for these patients.

Conventional approaches in NAFLD treatment

- Weight Loss

Weight loss at a rate of 0.5–1 kg per week is primarily recommended for overweight or obese NAFLD patients [6]. Weight reduction can improve elevated liver enzymes, hepatic histology, insulin resistance, and quality of life in patients with NAFLD [7–12]. Losing weight is possible through diet modification and increasing physical activity levels. Pharmacological treatments can be used for lose weight in those who fail to achieve target weight loss by lifestyle modification alone [6]. Fast weight loss due to worsening liver disease is not suggested at all [13]. If patients do not respond to pharmacological treatments, bariatric surgery is performed for weight loss [6]. In some patients undergoing bariatric surgery, after operation, liver fibrosis may worsen, for this reason liver function should be monitored regularly in follow-up [14].

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; MRI, magnetic resonance imaging; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; BMI, body mass index; WHR, waist to hip ratio; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; CT, computed tomography; FPG, fasting plasma glucose; ALP, alkaline phosphatase; UDCA, ursodeoxycholic acid; FXR, farnesoid X receptor; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; MRS, magnetic resonance spectroscopy; MRE, magnetic resonance elastography; PTX, pentoxyfylline; NAS, NAFLD activity score; PPAR, peroxisome proliferator-activated receptor.

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- Pharmacological Therapies

Pharmacological treatments studied in NAFLD trials are divided into two categories: Monotherapy and combination therapy. For more effective treatment of NAFLD, combination therapies were introduced. Some of these therapies routinely used to treat NAFLD. These treatments are targeting the mechanisms involved in causing NAFLD. The summary of these treatments has been shown in Table 1.

Vitamin E

Oxidative stress plays an important role in the pathogenesis of NAFLD [15]. Vitamin E is a fat-soluble vitamin that has high antioxidant capacity. Nutritional assessment of NAFLD patients indicated inadequate vitamin E intake in them [16]. In the PIVENS trial, taking 800 IU/day of vitamin E for 2 years in non-diabetic patients with NASH could significantly improve liver histology with the exception of fibrosis score compared to placebo; also this treatment could decrease serum aminotransferases levels, but not bilirubin, stronger than placebo. A rapid reduction in alanine aminotransferase (ALT) and aspartate aminotransferase levels (AST) was observed in the first 6 months of treatment and then remained stable. In this study, changes in anthropometric measurements, lipid profile, insulin resistance and quality of life did not differ between the two groups [17]. This improvement in liver histology and ALT levels was independent of weight loss; therefore, vitamin E can be beneficial even for those who cannot lose weight [18]. It has been seen that high doses of vitamin E (400 IU/day<) is associated with increased all-cause mortality [19]; so in order to

Table 1
Summary of agents studied in NAFLD.

Agent	Benefits	Adverse effects	Comments
Vitamin E	Improvement of serum aminotranferases and liver histology except of fibrosis	Increase in all-cause mortality at a dose of 800 IU/day	Suitable for patients who cannot lose weight; 400 IU/day is recommended; adding orlistat to vitamin E plus diet has no advantage over vitamin E plus diet alone; adding spironolactone to vitamin E can be more effective than vitamin E alone in improving insulin resistance and NAFLD- liver fat score
Pioglitazone	Improvement of serum aminotransferases, glycaemic control, and liver histology; increase in HDL	Weight gain	Recommended only for diabetic patients with NAFLD
Rosiglitazone	Normalization of ALT; improvement of insulin sensitivity and steatosis in liver biopsy	Weight gain; decrease in hemoglobin; increase in LDL	Recommended only for diabetic patients with NAFLD; adding metformin or losartan to this drug has no advantage over rosiglitazone alone
Metformin	Decrease in BMI, leptin, HbA1c, triglycerides, LDL, ALT, and ALP; increase in adiponectin and HDL; positive vascular effect	Negative effect on bone health in long-term use	In normalization of aminotransferases, it is more effective than vitamin E or diet
UDCA	Decrease in aminotransferases, FPG, HbA1c, insulin resistance, serum marker of fibrosis, and lobular inflammation in liver biopsy	–	It is similar to vitamin E in symptomatic improvement and decrease in ALT, NAFLD fibrosis score, and tolerability; combination therapy with UDCA plus vitamin E can be more effective than UDCA alone in reducing AST and NAS in liver biopsy
Obeticholic acid	Improvement of liver histology and hepatic steatosis as assessed by MRI-PDFF; decrease in aminotransferases, total bilirubin, and BMI	Increase in ALP and insulin resistance; worsening of lipid profile; pruritus	–
Colesevelam	–	Increase in liver fat as assessed by MRI-PDFF and MRS	–
Simvastatin	–	–	–
Probucol	Decrease in ALT	–	Its effect has only been evaluated on serum aminotransferases levels
Ezetimibe	Decrease in fibrosis and ballooning score in liver biopsy	Increase in HbA1c and hepatic long-chain fatty acids	It is ineffective in reducing liver fibrosis as assessed by MRE
Fenofibrate	–	–	Combination therapy with fenofibrate plus pentoxyfylline can be more effective than fenofibrate alone in reducing aminotransferases, insulin resistance, FPG, serum marker of fibrosis, liver stiffness as assessed by fibro-scan, and systemic inflammation
Pentoxyfylline	Improvement of liver histology except of hepatocellular ballooning	–	There is a conflict between studies on results of liver histology evaluation
Losartan	–	–	The study did not have enough sample size
Telmisartan	Improvement of liver histology except of hepatocellular ballooning	–	Placebo-controlled trial is warranted
Elafibranor	Improvement of liver enzymes, glucose profile, systemic inflammation, and liver histology without fibrosis worsening	Mild and reversible increase in serum creatinine	–
Orlistat	Decrease in FPG, aminotransferases, hepatic steatosis as assessed by ultrasound	–	Suitable for patients who cannot lose weight through lifestyle modification; liver biopsy or advanced MRI conduction is necessary
Rifaximin	Decrease in insulin resistance, aminotransferases, systemic inflammation, serum marker of apoptosis, and NAFLD-liver fat score	–	liver biopsy or advanced MRI conduction is necessary

NAFLD, nonalcoholic fatty liver disease; HDL, high density lipoprotein; ALT, alanine aminotransferase; LDL, low density lipoprotein; BMI, Body mass index; HbA1c, hemoglobin A1c; ALP, alkaline phosphatase; FPG, fasting plasma glucose; UDCA, ursodeoxycholic acid; AST; aspartate aminotransferase; NAS, NAFLD activity score; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; MRS, magnetic resonance spectroscopy; MRE, magnetic resonance elastography

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avoid this concern, vitamin E is recommended at a dose of 400 IU/-day for non-diabetic patients with NASH [6]. Further studies are needed to suggest this treatment for other NAFLD patients.

Thiazolidinediones

Insulin resistance has the most important role in the development of hepatic steatosis [20]. Thiazolidinediones, including pioglitazone and rosiglitazone, are insulin sensitizers. In non-diabetic NASH patients treated with standard diet (reduce 500 kcal/day) and exercise plus pioglitazone (30 mg/day) or placebo for 12 months, pioglitazone was superior to placebo in reduction of ALT, gamma-glutamyltransferase (GGT), and ferritin levels, but not in the change of bilirubin and albumin; also in comparison with placebo, pioglitazone could significantly improve hemoglobin A1c (HbA1c) and C-peptide levels, but no difference was observed in insulin resistance and adipokines levels between the groups. This treatment improved liver histology including hepatocellular injury, Mallory-Denk bodies, and fibrosis; however the change in steatosis, lobular inflammation, and portal inflammation was the same in both groups at the end of trial. In this study, pioglitazone did not play a role in improving lipid profile. The only reported adverse event was weight gain with pioglitazone, although the change in body mass index (BMI) and waist to hip ratio (WHR) was similar to placebo [21]. In the PIVENS trial, 2 years of taking pioglitazone at a dose of 30 mg/day could decrease liver enzymes, but not bilirubin levels, compared to placebo. In improvement of steatosis and lobular inflammation, pioglitazone was superior to placebo, but the change of hepatocellular ballooning did not differ between these. Pioglitazone was not effective than placebo in improving quality of life and lipid profile except in increasing high-density lipoprotein (HDL). This medication also decreased insulin resistance that this change was not significant compared to placebo. An increase in the anthropometric measurements, exception of waist circumference, observed in pioglitazone group more than placebo group [17].

Rosiglitazone is another member of thiazolidinediones. Consumption of rosiglitazone at a dose of 8 mg/day for 12 months (initiation with 4 mg/day and increasing to 8 mg/day after 30 days) in non-diabetic NASH patient, could normalize ALT levels and increase insulin sensitivity and adiponectin levels compared to placebo. Also, rosiglitazone was more effective than placebo in the improvement of steatosis, but not other liver histological features. In this study, rosiglitazone failed to significantly change in triglycerides, HDL, leptin, and HbA1c levels over placebo. The adverse events of rosiglitazone were weight gain, hemoglobin reduction, and rising total cholesterol and low-density lipoprotein (LDL) levels, which were considerable compared to placebo [22]. Continue treatment with rosiglitazone in this dose for another 2 years had not additional advantage over the first year and could only maintain insulin sensitivity and ALT levels [23].

Thiazolidinedions could not ameliorate lipid profile; consequently, it cannot have any cardiovascular protection effect. The administration of thiazolidinediones is associated with many adverse events. To achieve therapeutic goals, these medications should be taken for a long time. Discontinuance of these agents causes recurrence of the disease [24]. For the reasons mentioned, thiazolidinediones is only saved for diabetic patients with NASH and it is not recommended for other NAFLD patients.

Metformin

Metformin is another insulin sensitizer. In biopsy-proven NAFLD patients, 6 months treatment with 500 mg/day metformin (in body weight >90 kg, initiation with 500 mg/day and increasing every week to reach 2500 mg/day or 3000 mg/day) indicated significant reduction in body weight, BMI, total cholesterol, LDL as well as leptin and improving glycaemic control compared to placebo; but changes in HDL, triglycerides, insulin resistance, adiponectin, aminotransferases levels, and biochemical marker of inflammation were not statistically significant between the two groups. Change in hepatic histology and liver steatosis as assessed by computed tomography (CT) were the same in both groups [25]. Generally, the only benefit of this treatment in NAFLD patients is reducing body weight, BMI, and risk of cardiovascular events. Taking metformin at a dose of 850–1700 mg/day for 4 months had beneficial vascular effect and could significantly reduce fast plasma glucose (FPG), triglycerides, ALT, and alkaline phosphatase (ALP) as well as increase HDL and adiponectin levels in NAFLD patients; however, none of these changes were observed with placebo except FPG lowering. In this study, metformin was not effective in changing systolic and diastolic blood pressure, total cholesterol, LDL, AST levels, insulin resistance, and systemic inflammation. No information is available on the effect of this treatment on hepatic steatosis [26]. Consumption of metformin with this dose for an additional 8 months was only able to maintain positive vascular effect and elevated level of adiponectin and could significantly decrease insulin resistance compared to baseline [27]. In comparison with vitamin E or prescriptive diet, treatment of NAFLD patients with 2 g/day metformin for 12 months was able to normalize serum aminotransferases levels in comparison with 800 IU/-day vitamin E or weight-reducing diet. In this trial, metformin also reduced liver fat, necroinflammation, and fibrosis from baseline in liver biopsy [28].

It has been shown metformin can reduce bone metabolism markers; therefore, it may have a negative effect on bone health [29,30]. Therefore, it should be considered when consuming for long-term. Although metformin cannot improve liver histology compared to placebo, it can contribute to the protection of NAFLD patients from cardiovascular events and its use is recommended.

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) reduced the secretion of cholesterol from the liver and also reduces fraction reabsorption of cholesterol by intestines. UDCA intake at a dose of 10 mg/kg/day (divided into twice daily) for 3 months in NAFLD patients could significantly reduced aminotransferases levels, while the placebo was incapable of decline them. In this study, UDCA was not effective in modifying BMI and liver steatosis as assessed by CT [31]. Also, in NAFLD patients who received standard diet (1200 kcal/day), 1200 mg/day UDCA could decrease aminotransferases, FPG, total cholesterol levels, BMI, and hepatic steatosis as assessed by ultrasound in the course of 6 weeks; in comparison with placebo only changes in FPG and total cholesterol levels were statically significant [32]. In patients with NASH receiving 13–15 mg/kg/day UDCA for 2 years, changes of body weight, BMI, and liver biochemistry including hepatic enzymes, bilirubin, albumin levels, and prothrombin time as well as liver histology were not statically significant compared to placebo recipients [33]. Despite this therapeutic regimen, taking 23–28 mg/kg/day UDCA in three divided dose for 18 months, in patients with NASH, could significantly improve lobular inflammation and reduce GGT levels compared to placebo; however, the change in the levels of other liver enzymes, bilirubin, albumin, triglycerides, total cholesterol, FPG, iron as well as other features of liver histology did not differ between the groups at the end of intervention [34]. UDCA intake at a dose of 28–35 mg/kg/day (divided into three times daily) for 12 months could significantly normalize ALT level and reduce insulin resistance and serum fibrosis marker and also improve glycaemic control in NASH patients compared to placebo. UDCA in this dose was safe and well tolerated by patients [35]. Comparison of UDCA (300 mg twice

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daily for 13 months) and vitamin E (400 mg twice daily for 13 months) in NAFLD patients indicated that UDCA had no advantage over vitamin E in symptomatic improvement, reduction of ALT, NAFLD fibrosis score as calculated by formula, and tolerability [36].

Obeticholic acid

The farnesoid X receptor (FXR) is a member of nuclear receptors superfamily. Activation of this receptor by bile acids regulates the expression of genes involved in lipid and glucose homeostasis [37]. Obeticholic acid is a synthetic variant of the natural bile acid chenodeoxycholic acid, which acts by activating the FXR. Taking 25 mg/day of oral obeticholic acid for 18 months could significantly improve aminotransferases, total bilirubin levels, body weight, BMI, hepatic steatosis as assessed by a novel MRI technique, the-proton-density-fat-fraction (PDFF), and liver histology except portal inflammation in NASH patients compared with placebo; however, further studies are needed to clarify long-term benefits and safety of this medication. This treatment was not more effective than placebo in altering triglycerides and albumin levels, prothrombin time, glycaemic control, waist circumference, WHR, blood pressure as well as quality of life. ALP, other components of the lipid profile, insulin resistance were worse in obeticholic acid recipients than the placebo group. In this trial, 23% of patients in obeticholic acid group developed pruritus, while this figure was 6% in placebo group [38,39].

Colesevelam

Bile acid sequestrants can interrupt enterohepatic circulation of bile acids and increase conversion of hepatic cholesterol to bile acids. These agents increase plasma glucagon-like-peptide-1 levels, which stimulates pancreatic beta cells to release insulin [40]. Colesevelam is a bile acid sequestrant. In patients with NAFLD, another bile acid sequestrant, colestimide, was effective in reducing liver fat on CT imaging method [41]. Despite this finding, treatment with 3.75 g/day colesevelam for 6 months increased liver fat as assessed by MRI-PDFF as well as magnetic resonance spectroscopy (MRS) without any effect on liver histology in NASH patients [42].

Statins

Toxic lipids contribute to inflammation and insulin resistance in hepatocytes [43]. Lipid lowering drugs could affect NAFLD by reducing toxic lipids. Statins are lipid lowering drugs that inhibit 3-hydroxy-3-methyglutaryl-coenzyme A reductase. In the case of statins, randomized controlled trials are limited. A pilot study comparing simvastatin effects with placebo in NASH patient has indicated that reception of simvastatin 40 mg once daily for 12 months cannot be effective in decreasing BMI, liver enzymes, total cholesterol, LDL, and triglycerides levels and also cannot improve liver histology [44]. Therefore, monotherapy with simvastatin does not appear to be effective in treating NASH.

Probucol

Probucol is an anti-hyperlipidemic drug with strong antioxidant properties. Probucol effects have only been studied on serum aminotransferases levels. Compared to placebo, taking 500 mg/day of probucol for 6 months was able to reduce serum ALT levels in patients with NASH. Probucol also was effective in reducing AST levels in these patients, although this change was not statistically significant in comparison with placebo [45].

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor. In NAFLD patients, taking ezetimibe at a dose of 10 mg/day for 6 months could improve hepatic fibrosis and ballooning score. However, ezetimibe had higher proportion of adverse events including elevation in HbA1c and hepatic long-chain fatty acids [46]. In another trial, this treatment had no advantage over placebo in reducing liver fat as measured by MRI-PDFF, serum aminotransferases levels as well as improving liver histology and liver stiffness as assessed by magnetic resonance elastography (MRE) in patients with NASH [47].

Fenofibrate

In NAFLD patients, 200 mg/day fenofibrate for 8 weeks could not affect insulin sensitivity and intrahepatic triglyceride content measured by using MRS compared to placebo [48].

Pentoxyfylline

Several studies have confirmed the anti-inflammatory, antioxidant, and antifibrogenic effects of pentoxyfylline [49–53]. In patients with NASH, taking 400 mg pentoxyfylline (PTX) three times a day for 12 months could improve liver histology including steatosis, lobular inflammation, and NAFLD activity score (NAS) compared to placebo, but it was not able to be effective than placebo in improvement of hepatocellular ballooning; also the reduction of fibrosis was significant in comparison with placebo, but the number of patients with improvement was equal in both groups [54]. However, another study rejected these benefits of PTX [55]. Improvement in liver histology probably relates to the reduction of lipid oxidation by PTX [56]. These studies failed to demonstrate the superiority of PTX over placebo in changing aminotransferases, adipokines, inflammatory biomarkers as well as triglycerides levels, body weight, insulin resistance, and measurement of hepatocyte apoptosis [54,55]. The most important benefit of this regimen in patients with NASH is improving liver histology.

Angiotensin II receptor blockers

Angiotensin II plays a major role in the pathogenesis of hepatic fibrosis, insulin resistance, and also tissue iron deposition [57–59]. Losartan is an angiotensin II receptor blocker. Consumption of losartan at a dose of 50 mg once daily for 2 years in patients with NASH could not improve fibrosis in liver biopsy compared to placebo; of course this study failed to recruit an adequate sample size to prove the anti-fibrotic effect of losartan [60]. In another trial, taking 40–80 mg/day telmisartan plus lifestyle modification for 12 months could significantly improve all liver histology features in patients with NASH. However, in lifestyle modification group only hepatocyte ballooning improved, but fibrosis worsened [61].

Elafibranor

Elafibranor is an agonist of peroxisome proliferator-activated receptor (PPAR)-alpha and gamma. PPAR are nuclear receptors that play an important role in regulation of metabolic homeostasis, immune-inflammation, and differentiation. PPAR-gamma agonists like pioglitazone have many side effects. In a multicenter trial, elafibranor significantly improved liver histology without fibrosis worsening, liver enzyme, glucose profile, and markers of systemic inflammation compared to placebo. In this trial, elafibranor was administered to NASH patients at a dose of 120 mg/day for 13 months. The only adverse event that occurred in treatment

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group more than placebo group was a mild, reversible increase in serum creatinine [62].

Orlistat

Orlistat is a gastrointestinal lipase inhibitor used to treat obesity. In NAFLD patients, taking 120 mg of orlistat three times a day plus weight loss program (a diet containing 104.5 kJ/day and physical activity including 40 min of walking at a rate of 5–6 km/h) for 6 months could significantly reduce FPG, total cholesterol, and GGT levels; but in the placebo group, these changes was not considerable. Anthropometric measurements as well as ALT and AST levels decrease in both groups. Reduction of ALT level in orlistat group is two times higher than in the placebo group and occurs more quickly. The reduction in liver steatosis assessed by ultrasound was significant only in orlistat group. In this trial, orlistat had no effect on triglycerides and insulin resistance [63]. Its effect on liver histology is unknown. Orlistat is only suitable for patients who have not been able to reduce their body weight by lifestyle modification and is never recommended as a primary treatment for NAFLD [6].

Rifaximin

Gut microbiota plays an important role in the pathogenesis of NAFLD. Rifaximin is a nonabsorable antibiotic that acts against a broad spectrum of gut microbiota. In NASH patients, treatment with 1100 mg/day rifaximin for 6 months could significantly reduce insulin resistance, serum aminotranferases, endotoxin, proinflammatory cytokines, cytokeratin-18, and NAFLD-liver fat score from baseline; but no significant changes in lipid profile and BMI. At the end of trial, no changes in these variables were observed among placebo recipients [64].

Rosiglitazone plus metormin and rosiglitazone plus losartan

Forty-eight weeks of combination therapy with rosiglitazone (4 mg twice daily) plus metformin (500 mg twice daily) or rosiglitazone (4 mg twice daily) plus losartan (50 mg once daily) did not have any benefit on rosiglitazone (4 mg twice daily) alone in improving liver histology and serum aminotransferases in patients with NASH. Adding metformin could not prevent rosiglitazone weight gain [65].

Ursodeoxycholic acid plus vitamin E

In a clinical trial, NASH patients with elevated aminotransferases levels randomly assigned to one of the UDCA/vitamin E (12 mg/kg/day UDCA and 400 IU vitamin E twice a day for 2 years) or UDCA/placebo or Placebo/placebo groups. In UDCA plus vitamin E recipients, there was a significant reduction in ALT and AST levels as well as NAS in liver biopsy after the course of treatment. In UDCA/placebo group only ALT levels decreased. In placebo/placebo group no improvement occurred [66]. These results show that combination therapy with UDCA and vitamin E can be more effective than monotherapy with UDCA for the recovery of NASH.

Fenofibrate plus pentoxifylline

Taking 300 mg/day fenofibrate plus 1200 mg/day pentoxifylline for 6 months could significantly reduce serum aminotransferases, insulin resistance, FPG, direct and indirect biomarker of liver fibrosis, liver stiffness as assessed by fibro-scan, and proinflammatory cytokine compared to 300 mg/day fenofibrate alone. In this trial, lipid profile improved in both group and combination therapy did not have any benefits over fenofibrate alone in this case [67].

Orlistat plus vitamin E plus diet

In one clinical trial, it was shown that the addition of orlistat (120 mg three times a day) to vitamin E (800 IU/day) plus diet (1400 Kcal/day) for 9 months could not enhance weight loss or improve serum aminotransferases, liver histology, and insulin sensitivity compared vitamin E plus diet alone [68].

Spironolactone plus vitamin E

The rennin-angiotensin-aldosterone system plays an important role in the pathogenesis of insulin resistance and NAFLD [69,70]. In NAFLD patients, treatment with spironolactone (25 mg/day) plus vitamin E (400 IU/day) for 8 weeks could significantly reduce insulin resistance and NAFLD liver fat score as calculated by formula compared to vitamin E (400 IU/day) alone. At the end of trial, ALT-to-platelet ratio index, an index of fibrosis did not change [71,72].

Novel approaches in NAFLD treatment

New agents with strong experimental evidence are recently being studied in patients with NAFLD, and may provide a new approach in NAFLD treatment. The summary of these agents has been shown in Table 2.

Caspase inhibitor (GS-9450)

Apoptosis can lead to inflammation and fibrosis in liver disease. Caspases are a family of protease enzymes playing an essential role in apoptosis. GS-9450 is a selective caspase inhibitor that reduces hepatocyte apoptosis. In NASH patients, taking 40 mg/day GS-9450 for 4 weeks was able to reduce serum ALT levels from baseline compared to placebo. In this phase 2 trial, serum AST and caspase 3-cleaved cytokeratin-18 fragments levels also decreased in the treatment group, although these reductions were no statistically significant. No serious adverse events were reported during study [73].

Phosphodiesterase-4 inhibitor (ASP9831)

Cyclic adenosine monophosphate is a second messenger that mediates numerous signaling pathways resulting in suppression or inhibition inflammatory mediator release. Intracellular levels of cyclic adenosine monophosphate are modulated by phosphodiesterases [74]. ASP9831 is a phosphodiesterase-4 inhibitor that showed potent anti-inflammatory and antifibrotic effect in preclinical studies. In phase 2 trial, neither ASP9831 nor placebo could change serum aminotransferases, adiponectin, cytokeratin-18 levels, and systemic inflammation in NASH patients. In this trial ASP9831 was administrated at a dose of 50 mg or 100 mg twice daily for 3 months. Adverse events were mild and ASP9831 recipients experienced gastrointestinal disorders more than placebo group [75].

Anti-CD3 antibody (OKT3 monoclonal Antibody)

Anti-CD3 antibody regulates T cells and improves insulin resistance and liver damage in preclinical studies [76]. OKT3 monoclonal antibody is an anti-CD3 antibody. In a phase 2a trial, oral administration of OKT3 was well tolerated by patients with NASH. OKT3 was administered at a dose of 0.2 mg or 1 mg or 5 mg/day. After 30 days, immune-modulatory effects of OKT3 were observed in 1 mg and 5 mg/day OKT3 groups. In comparison with placebo,

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Table 2
Summary of new agent that are recently being studied in patients with NAFLD.

Agent	Action	Trial phase	Dose	Benefits	Adverse effects
GS-9450	Caspase inhibition	2 [73]	1, 5, 10 or 40 mg once daily-oral	Decrease in ALT in 40 mg once daily group	Mild
ASP9831	Phosphodiesterase-4 inhibition	2 [75]	50 or 100 mg twice daily-oral	–	Mild; gastrointestinal disorders was reported with ASP9831 more than placebo
OKT3	Anti-CD3 antibody	2a [77]	0.2, 1 or 5 mg/day-oral	Decrease in AST and FPG in all OKT3 groups; improvement of oral glucose tolerance test in 5 mg/day; immune-modulatory effects in 1 mg and 5 mg/day OKT3 groups	Mild; gastrointestinal disorders was reported with OKT3 more than placebo
Liraglutide	glucagon-like peptide 1 analogue	2 [78,79]	1.8 mg/day-oral	Decrease in BMI, LDL, leptin, ALT, hepatic *de novo* lipogenesis, and insulin resistance; improvement of liver histology; increase in adiponectin	Mild to moderate; gastrointestinal disorders was reported with liraglutide more than placebo
Oltipraz	Liver X recptor alpha inhibition	2 [81]	30 or 60 mg twice daily-oral	Decrease in BMI and liver fat as assessed by MRS in 60 mg twice daily group	Mild
Cenicriviroc	C–C chemokine receptor type 2 and 5 antagonist	2b [85]	150 mg once daily-oral	Improvement of systemic inflammation and fibrosis in liver biopsy	Mild to moderate; grade 4 uric acid elevation and asymptomatic grade 3 amylase elevations was reported with cenicriviroc more than placebo; grade 2 arrhythmia as a serious adverse event was reported
NGM282	Fibroblast growth factor 19 analogue	2 [88]	3 or 6 mg once daily-subcutaneous	Decrease in liver fat as assessed by MRI-PDFF	Mild; injection site reaction and gastrointestinal disorders was reported with NGM282 more than placebo
GS-0976	Acetyl-coenzyme A carboxylase inhibition	2 [89]	5 or 20 mg/day-oral	Improvement of liver biochemistry; Decrease in liver fat as assessed by MRI-PDFF and serum marker of fibrosis (ineffective on fibrosis as assessed by MRE)	Mild; asymptomatic hypertriglyceridemia was reported wit GS-0976 more than placebo
Pegbelfermin	PEGylated fibroblast growth factor 21 analogue	2a [91]	10 mg once daily or 20 mg once weekly-oral	Decrease in liver fat as assessed by MRI-PDFF	Mild; diarrhea and nausea was reported with pegbelfermin more than placebo
RO5093151	HSD11B1 inhibition	1b [93]	200 mg twice daily-oral	Decrease in liver fat as assessed by MRS	Mild; nervous system disorders was reported with RO5093151 more than placebo

ALT, alanine aminotransferase; FPG, fasting plasma glucose; BMI, body mass index; LDL, low density lipoprotein; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; MRE, magnetic resonance elastography; MRS, magnetic resonance spectroscopy.

AST and FPG decreased in all OKT3 groups. Oral glucose tolerance test significantly improved only in 5 mg/day OKT recipients [77].

Liraglutide

Liraglutide is a long-acting glucagon-like peptide 1 analogue. In a multicenter phase 2 trial, 1.8 mg /day liraglutide was able to reduce BMI, HbA1c, ALT, LDL, leptin, and adiponectin levels in NASH patients compared to placebo at a quarterly interval. In comparison with placebo, this treatment could significantly increase hepatic and adipose tissue insulin sensitivity and decrease hepatic *de novo* lipogenesis as well as improve liver histology [78,79]. In this trial, liraglutide was well tolerated by NASH patients; however, gastrointestinal disorders, as an adverse event, was more frequently in liraglutide group than placebo group [79].

Oltipraz

Liver X receptor alpha play an important role in regulating the expression of genes involved in lipid production [80]. Oltipraz has a potent antisteatotic effect by inhibiting the activity of liver X receptor alpha. In a multicenter phase 2 trial, oltipraz was administered to NAFLD patients at a dose of 30 mg or 60 mg twice daily for 6 months. At the end of the study, high-dose group showed significant decrease in liver content as measured by MRS as well as BMI in comparison with placebo recipients. There was no significant difference between study groups in changes of insulin resistance, liver enzymes, lipid profile, and cytokines from baseline. In this trial, the incidence of adverse events was similar in treatment groups and placebo group [81].

Cenicriviroc

Cenicriviroc is a dual antagonist of C–C chemokine receptor type 2 and 5. Blockade of these receptors may have anti-inflammatory and antifibrotic properties [82–84].In a phase 2b trial that was conducted in NASH patients with liver fibrosis, cenicriviroc could improve fibrosis without worsening of steatohepatitis and reduce systemic inflammation compared to placebo. Cenicriviroc was administered at a dose of 150 mg once daily for 2 years in this study. The safety and tolerability of cenicriviroc was similar to placebo [85].

Fibroblast growth factor 19 analogue (NGM282)

Fibroblast growth factor 19 is a hormone that regulates bile acid synthesis and glucose metabolism [86,87]. NGM282 is an analogue of this hormone. In a phase 2 study, patients with NASH were randomly assigned to receive 3 mg or 6 mg subcutaneous NGM282 or placebo once daily for 3 months. At the end of trial, NGM282 recipients showed a significant reduction in liver fat content as assessed by MRI-PDFF compared to placebo recipients. In this trial, adverse events were mild and injection site reactions, diarrhea, abdominal pain, and nausea occurred more frequently in NGM282 groups than placebo group [88].

Acetyl-coenzyme a carboxylase inhibitor (GS-0976)

Acetyl-coenzyme A carboxylase is a lipogenic hepatic enzyme. The effect of GS-0976, an inhibitor of this enzyme, was evaluated in patients with NASH. In a phase 2 study, GS-0976 was administered at a dose of 5 mg or 20 mg/day for 3 months. At the end of

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trial, only patients receiving 20 mg/day GS-0976 showed a significant decrease in hepatic steatosis as assessed by MRI-PDFF, plasma biomarker of fibrosis, and live biochemistry compared to placebo. MRE results did not differ between trial groups. GS-0976 was well tolerated, although increase serum triglycerides was reported in treatment groups [89].

Pegbelfermin

Fibroblast growth factor 21 is a pleiotropic hormone-like protein that plays an essential role in regulation of energy metabolism [87,90]. Pegbelfermin is a PEGylated human fibroblast growth factor 21 analogue. In a phase 2a trial, this agent was well tolerated and significantly reduced liver fat content as assessed by MRI-PDFF compared to placebo in patients with NASH. Pegbelfermin was administered at a dose of 10 mg once daily or 20 mg once week for 4 months. Adverse events that occurred during the study were mild and the most common events were diarrhea and nausea [91].

HSD11B1 inhibitor (RO5093151)

Cortisol plays an important role in the pathogenesis of metabolic syndrome [92]. HSD11B1 or cortisone reductase enzyme reduces cortisone to the active hormone cortisol. RO5093151 is a HSD11B1 inhibitor. In a multicenter phase 1b trial, treatment with RO5093151 at a dose of 200 mg twice daily for 3 months could significantly decrease mean liver fat content as assessed by MRS compared with placebo in NAFLD subjects. Nervous system disorders, as an adverse event, occurred more frequently in RO5093151 group than placebo group [93].

Conclusion

In addition to environmental factors, genetic also plays an important role in the development of NAFLD [94–96]. Interpatient variability in NAFLD prognosis limits the conclusion about effective pharmacotherapy. In adults with NAFLD, weight loss remains the first line of treatment. Weight loss concurrent with pharmacological treatments improves NAFLD more effective. The most effective NAFLD pharmacological therapies are those that improve liver histology and hepatic steatosis as assessed by advanced MRI techniques. However, the beneficial effects of these treatments should be balanced with the potential adverse events. In NAFLD patients, the risk of cardiovascular diseases is high. Cardiovascular diseases remain the main cause of death among these patients. Treatments that improve lipid profile and have positive vascular effects can be effective in reducing cardiovascular diseases risk. New agents currently in trial can provide the basis for targeted pharmacotherapy in NAFLD.

References

[1] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73–84.
[2] Bellentani S. The epidemiology of non-alcoholic fatty liver disease. Liver Int 2017;37:81–4.
[3] Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62(1):S47–64.
[4] Cholankeril G, Perumpail RB, Pham EA, Ahmed A, Harrison SA. Nonalcoholic fatty liver disease: epidemiology, natural history, and diagnostic challenges. Hepatology 2016;64(3):954.
[5] Noureddin M, Lam J, Peterson MR, Middleton M, Hamilton G, Le TA, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 2013;58(6):1930–40.
[6] Sheth SG, Chopra S, Lindor KD. Natural history and management of nonalcoholic fatty liver disease in adults. 2015.
[7] Hickman I, Jonsson J, Prins J, Ash S, Purdie D, Clouston A, et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. Gut 2004;53(3):413–9.
[8] Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. Hepatology 2004;39(6):1647–54.
[9] Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes 2005;54(3):603–8.
[10] Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51(1):121–9.
[11] Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol 2012;57(1):157–66.
[12] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149(2). pp. 367–78.e5.
[13] Andersen T, Gluud C, Franzmann M-B, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. J Hepatol 1991;12(2):224–9.
[14] Chavez-Tapia NC, Tellez-Avila FI, Barrientos-Gutierrez T, Mendez-Sanchez N, Lizardi-Cervera J, Uribe M. Bariatric surgery for non-alcoholic steatohepatitis in obese patients. Cochrane Database Syst Rev 2008;1.
[15] Masarone M, Rosato V, Dallio M, Gravina AG, Aglitti A, Loguercio C, et al. Role of oxidative stress in pathophysiology of nonalcoholic fatty liver disease. Oxid Med Cell Longevity 2018;2018:1–14. https://doi.org/10.1155/2018/9547613.
[16] Allard JP, Aghdassi E, Mohammed S, Raman M, Avand G, Arendt BM, et al. Nutritional assessment and hepatic fatty acid composition in non-alcoholic fatty liver disease (NAFLD): a cross-sectional study. J Hepatol 2008;48(2):300–7.
[17] Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362(18):1675–85.
[18] Hoofnagle J, Natta M, Kleiner D, Clark J, Kowdley K, Loomba R, et al. Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2013;38(2):134–43.
[19] Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142(1):37–46.
[20] Méndez-Sánchez N, Arrese M, Zamora-Valdés D, Uribe M. Current concepts in the pathogenesis of nonalcoholic fatty liver disease. Liver Int 2007;27(4):423–33.
[21] Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135(4):1176–84.
[22] Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. Gastroenterology 2008;135(1):100–10.
[23] Ratziu V, Charlotte F, Bernhardt C, Giral P, Halbron M, LeNaour G, et al. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: Results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. Hepatology 2010;51(2):445–53.
[24] Lutchman G, Modi A, Kleiner DE, Promrat K, Heller T, Ghany M, et al. The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. Hepatology 2007;46(2):424–9.
[25] Haukeland JW, Konopski Z, Eggesbø HB, von Volkmann HL, Raschpichler G, Bjøro K, et al. Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. Scand J Gastroenterol 2009;44(7):853–60.
[26] Sofer E, Boaz M, Matas Z, Mashavi M, Shargorodsky M. Treatment with insulin sensitizer metformin improves arterial properties, metabolic parameters, and liver function in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled trial. Metabolism 2011;60(9):1278–84.
[27] Shargorodsky M, Omelchenko E, Matas Z, Boaz M, Gavish D. Relation between augmentation index and adiponectin during one-year metformin treatment for nonalcoholic steatohepatosis: effects beyond glucose lowering?. Cardiovasc Diabetol 2012;11(1):61.
[28] Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol 2005;100(5):1082.
[29] Soifer E, Gavish D, Shargorodsky M. Does metformin treatment influence bone formation in patients with nonalcoholic fatty liver disease?. Horm Metab Res 2015;47(08):556–9.
[30] Sofer E, Shargorodsky M. Effect of metformin treatment on circulating osteoprotegerin in patients with nonalcoholic fatty liver disease. Hep Intl 2016;10(1):169–74.
[31] Santos V, Lanzoni VP, Szejnfeld J, Shigueoka D, Parise ER. A randomized double-blind study of the short-time treatment of obese patients with nonalcoholic fatty liver disease with ursodeoxycholic acid. Braz J Med Biol Res 2003;36(6):723–9.
[32] Méndez-Sánchez N, González V, Chávez-Tapia N, Ramos MH, Uribe M. Weight reduction and ursodeoxycholic acid in subjects with nonalcoholic fatty liver

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disease. A double-blind, placebo-controlled trial. Ann Hepatol 2004;3 (3):108–12.
[33] Lindor KD, Kowdley KV, Heathcote EJ, Harrison ME, Jorgensen R, Angulo P, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. Hepatology 2004;39(3):770–8.
[34] Leuschner UF, Lindenthal B, Herrmann G, Arnold JC, Rössle M, Cordes HJ, et al. High-dose ursodeoxycholic acid therapy for nonalcoholic steatohepatitis: a double-blind, randomized, placebo-controlled trial. Hepatology 2010;52 (2):472–9.
[35] Ratziu V, De Ledinghen V, Oberti F, Mathurin P, Wartelle-Bladou C, Renou C, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol 2011;54(5):1011–9.
[36] Parikh P, Ingle M, Patel J, Bhate P, Pandey V, Sawant P. An open-label randomized control study to compare the efficacy of vitamin e versus ursodeoxycholic acid in nondiabetic and noncirrhotic Indian NAFLD patients. Saudi J Gastroenterol 2016;22(3):192.
[37] Cariou B. The farnesoid X receptor (FXR) as a new target in non-alcoholic steatohepatitis. Diabetes Metab 2008;34(6):685–91.
[38] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385(9972):956–65.
[39] Middleton MS, Heba ER, Hooker CA, Bashir MR, Fowler KJ, Sandrasegaran K, et al. Agreement between magnetic resonance imaging proton density fat fraction measurements and pathologist-assigned steatosis grades of liver biopsies from adults with nonalcoholic steatohepatitis. Gastroenterology 2017;153(3):753–61.
[40] Hofmann AF. Bile acid sequestrants improve glycemic control in type 2 diabetes: A proposed mechanism implicating glucagon-like peptide 1 release. Hepatology 2011;53(5):1784.
[41] Taniai M, Hashimoto E, Tobari M, Yatsuji S, Haruta I, Tokushige K, et al. Treatment of nonalcoholic steatohepatitis with colestimide. Hepatol Res 2009;39(7):685–93.
[42] Le TA, Chen J, Changchien C, Peterson MR, Kono Y, Patton H, et al. Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. Hepatology 2012;56 (3):922–32.
[43] Nakamura S, Takamura T, Matsuzawa-Nagata N, Takayama H, Misu H, Noda H, et al. Palmitate induces insulin resistance in H4IIEC3 hepatocytes through reactive oxygen species produced by mitochondria. J Biol Chem 2009;284 (22):14809–18.
[44] Nelson A, Torres DM, Morgan AE, Fincke C, Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: a randomized placebo-controlled trial. J Clin Gastroenterol 2009;43(10):990–4.
[45] Merat S, Malekzadeh R, Sohrabi MR, Sotoudeh M, Rakhshani N, Sohrabpour AA, et al. Probucol in the treatment of non-alcoholic steatohepatitis: a double-blind randomized controlled study. J Hepatol 2003;38(4):414–8.
[46] Takeshita Y, Takamura T, Honda M, Kita Y, Zen Y, Kato K-i, et al. The effects of ezetimibe on non-alcoholic fatty liver disease and glucose metabolism: a randomised controlled trial. Diabetologia 2014;57(5):878–90.
[47] Loomba R, Sirlin CB, Ang B, Bettencourt R, Jain R, Salotti J, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). Hepatology 2015;61(4):1239–50.
[48] Fabbrini E, Mohammed BS, Korenblat KM, Magkos F, McCrea J, Patterson BW, et al. Effect of fenofibrate and niacin on intrahepatic triglyceride content, very low-density lipoprotein kinetics, and insulin action in obese subjects with nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2010;95 (6):2727–35.
[49] Koppe SW, Sahai A, Malladi P, Whitington PF, Green RM. Pentoxifylline attenuates steatohepatitis induced by the methionine choline deficient diet. J Hepatol 2004;41(4):592–8.
[50] Hernandez E, Correa A, Bucio L, Souza V, Kershenobich D, Gutierrez-Ruiz M. Pentoxifylline diminished acetaldehyde-induced collagen production in hepatic stellate cells by decreasing interleukin-6 expression. Pharmacol Res 2002;46(5):435–43.
[51] Balibrea JL, Arias-Diaz J, García C, Vara E. Effect of pentoxifylline and somatostatin on tumour necrosis factor production by human pulmonary macrophages. Circulatory Shock 1994;43(2):51–6.
[52] Kozaki KEH, Bermudez L, Keefe EB, So SK, Esquivel CO. Effects of pentoxifylline pretreatment on Kupffer cells in rat liver transplantation. Hepatology 1995;21 (4):1079–82.
[53] Romanelli RGCA, Carloni V, DeFranco R, Montalto P. Ceni E, al et. Effect of pentoxifylline on the degradation of procollagen type I produced by human hepatic stellate cells in response to transforming growth factor-β1. Br J Pharmacol 1997;122(6):1047–54.
[54] Zein CO, Yerian LM, Gogate P, Lopez R, Kirwan JP, Feldstein AE, et al. Pentoxifylline improves nonalcoholic steatohepatitis: a randomized placebo-controlled trial. Hepatology 2011;54(5):1610–9.
[55] Van Wagner LB, Koppe S, Brunt EM, Gottstein J, Gardikiotes K, Green RM, et al. Pentoxifylline for the treatment of non-alcoholic steatohepatitis: a randomized controlled trial. Ann Hepatol 2011;10(3):277–86.
[56] Zein CO, Lopez R, Fu X, Kirwan JP, Yerian LM, McCullough AJ, et al. Pentoxifylline decreases oxidized lipid products in nonalcoholic steatohepatitis: new evidence on the potential therapeutic mechanism. Hepatology 2012;56(4):1291–9.
[57] Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Noguchi R, Nakatani T, et al. Angiotensin-II type 1 receptor interaction is a major regulator for liver fibrosis development in rats. Hepatology 2001;34(4):745–50.
[58] Togashi N, Ura N, Higashiura K, Murakami H, Shimamoto K. The contribution of skeletal muscle tumor necrosis factor-α to insulin resistance and hypertension in fructose-fed rats. J Hypertens 2000;18(11):1605–10.
[59] Ishizaka N, Saito K, Mitani H, Yamazaki I, Sata M, Usui S-i, et al. Iron overload augments angiotensin II–induced cardiac fibrosis and promotes neointima formation. Circulation 2002;106(14):1840–6.
[60] McPherson S, Wilkinson N, Tiniakos D, Wilkinson J, Burt AD, McColl E, et al. A randomised controlled trial of losartan as an anti-fibrotic agent in non-alcoholic steatohepatitis. PLoS ONE 2017;12(4):e0175717.
[61] Alam S, Kabir J, Mustafa G, Gupta U, Hasan S, Alam A. Effect of telmisartan on histological activity and fibrosis of non-alcoholic steatohepatitis: a 1-year randomized control trial. Saudi J Gastroenterol 2016;22(1):69.
[62] Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an agonist of the peroxisome proliferator– activated receptor– α and– δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150(5). pp. 1147–59.e5.
[63] Zelber-Sagi S, Kessler A, Brazowsky E, Webb M, Lurie Y, Santo M, et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2006;4 (5):639–44.
[64] Abdel-Razik A, Mousa N, Shabana W, Refaey M, Elzehery R, Elhelaly R, et al. Rifaximin in nonalcoholic fatty liver disease: hit multiple targets with a single shot. Eur J Gastroenterol Hepatol 2018;30(10):1237–46.
[65] Torres DM, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of nonalcoholic steatohepatitis in humans: a 12-month randomized, prospective, open-label trial. Hepatology 2011;54(5):1631–9.
[66] Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, et al. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin e in nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2006;4(12):1537–43.
[67] El-Haggar SM, Mostafa TM. Comparative clinical study between the effect of fenofibrate alone and its combination with pentoxifylline on biochemical parameters and liver stiffness in patients with non-alcoholic fatty liver disease. Hep Intl 2015;9(3):471–9.
[68] Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: a randomized, prospective trial. Hepatology 2009;49(1):80–6.
[69] Hirose A, Ono M, Saibara T, Nozaki Y, Masuda K, Yoshioka A, et al. Angiotensin II type 1 receptor blocker inhibits fibrosis in rat nonalcoholic steatohepatitis. Hepatology 2007;45(6):1375–81.
[70] Giacchetti G, Sechi LA, Rilli S, Carey RM. The renin–angiotensin–aldosterone system, glucose metabolism and diabetes. Trends Endocrinol Metab 2005;16 (3):120–6.
[71] Polyzos SA, Kountouras J, Zafeiriadou E, Patsiaoura K, Katsiki E, Deretzi G, et al. Effect of spironolactone and vitamin E on serum metabolic parameters and insulin resistance in patients with nonalcoholic fatty liver disease. J Renin-Angiotensin-Aldosterone Syst 2011;12(4):498–503.
[72] Polyzos SA, Kountouras J, Mantzoros CS, Polymerou V, Katsinelos P. Effects of combined low-dose spironolactone plus vitamin E vs vitamin E monotherapy on insulin resistance, non-invasive indices of steatosis and fibrosis, and adipokine levels in non-alcoholic fatty liver disease: a randomized controlled trial. Diabetes Obes Metab 2017;19(12):1805–9.
[73] Ratziu V, Sheikh MY, Sanyal AJ, Lim JK, Conjeevaram H, Chalasani N, et al. A phase 2, randomized, double-blind, placebo-controlled study of GS-9450 in subjects with nonalcoholic steatohepatitis. Hepatology 2012;55(2):419–28.
[74] Dastidar SG, Rajagopal D, Ray A. Therapeutic benefit of PDE4 inhibitors in inflammatory diseases. Curr Opin Invest Drugs 2007;8(5):364.
[75] Ratziu V, Bedossa P, Francque SM, Larrey D, Aithal GP, Serfaty L, et al. Lack of efficacy of an inhibitor of PDE4 in phase 1 and 2 trials of patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2014;12(10). pp. 1724–30.e5.
[76] Ilan Y, Maron R, Tukpah A-M, Maioli TU, Murugaiyan G, Yang K, et al. Induction of regulatory T cells decreases adipose inflammation and alleviates insulin resistance in ob/ob mice. Proc Natl Acad Sci 2010;107(21):9765–70.
[77] Lalazar G, Mizrahi M, Turgeman I, Adar T, Ya'acov AB, Shabat Y, et al. Oral administration of OKT3 MAb to patients with NASH, promotes regulatory T-cell induction, and alleviates insulin resistance: results of a phase IIa blinded placebo-controlled trial. J Clin Immunol 2015;35(4):399–407.
[78] Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol 2016;64(2):399–408.
[79] Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387(10019):679–90.
[80] Hwahng SH, Ki SH, Bae EJ, Kim HE, Kim SG. Role of adenosine monophosphate-activated protein kinase–p70 ribosomal S6 kinase-1 pathway in repression of liver X receptor-alpha–dependent lipogenic gene induction and hepatic steatosis by a novel class of dithiolethiones. Hepatology 2009;49(6):1913–25.
[81] Kim W, Kim B, Lee J, Lee C, Yeon J, Chang M, et al. Randomised clinical trial: the efficacy and safety of oltipraz, a liver X receptor alpha-inhibitory dithiolethione in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2017;45(8):1073–83.

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[82] Mossanen JC, Krenkel O, Ergen C, Govaere O, Liepelt A, Puengel T, et al. Chemokine (C-C motif) receptor 2–positive monocytes aggravate the early phase of acetaminophen-induced acute liver injury. Hepatology 2016;64(5):1667–82.
[83] Friedman S, Sanyal A, Goodman Z, Lefebvre E, Gottwald M, Fischer L, et al. Efficacy and safety study of cenicriviroc for the treatment of non-alcoholic steatohepatitis in adult subjects with liver fibrosis: CENTAUR Phase 2b study design. Contemporary Clin Trials 2016;47:356–65.
[84] Marra F, Tacke F. Roles for chemokines in liver disease. Gastroenterology 2014;147(3). pp. 577–94.e1.
[85] Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology 2018;67(5):1754–67.
[86] Kliewer SA, Mangelsdorf DJ. Bile acids as hormones: the FXR-FGF15/19 pathway. Dig Dis 2015;33(3):327–31.
[87] Degirolamo C, Sabbà C, Moschetta A. Therapeutic potential of the endocrine fibroblast growth factors FGF19, FGF21 and FGF23. Nat Rev Drug Discovery 2016;15(1):51.
[88] Harrison SA, Rinella ME, Abdelmalek MF, Trotter JF, Paredes AH, Arnold HL, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2018;391(10126):1174–85.
[89] Loomba R, Kayali Z, Noureddin M, Ruane P, Lawitz EJ, Bennett M, et al. GS-0976 reduces hepatic steatosis and fibrosis markers in patients with nonalcoholic fatty liver disease. Gastroenterology 2018;155(5). pp. 1463–73.e6.
[90] Kharitonenkov A, Larsen P. FGF21 reloaded: challenges of a rapidly growing field. Trends Endocrinol Metab 2011;22(3):81–6.
[91] Sanyal A, Charles ED, Neuschwander-Tetri BA, Loomba R, Harrison SA, Abdelmalek MF, et al. Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial. The Lancet. 2018;392(10165):2705–17.
[92] Jeong I-K. The role of cortisol in the pathogenesis of the metabolic syndrome. Diab Metab J 2012;36(3):207–10.
[93] Stefan N, Ramsauer M, Jordan P, Nowotny B, Kantartzis K, Machann J, et al. Inhibition of 11β-HSD1 with RO5093151 for non-alcoholic fatty liver disease: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Diab Endocrinol 2014;2(5):406–16.
[94] Valenti L, Al-Serri A, Daly AK, Galmozzi E, Rametta R, Dongiovanni P, et al. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatology 2010;51(4):1209–17.
[95] Anstee QM, Day CP. The genetics of NAFLD. Nat Rev Gastroenterol Hepatol 2013;10(11):645.
[96] Liu Y-L, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JB, et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nat Commun 2014;5:4309.

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