

Pharmacologic Management of Non-Alcoholic Fatty Liver Disease

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a common complex chronic liver disease that encompasses a spectrum of disease from simple steatosis to non-alcoholic steatohepatitis (NASH). NASH has the potential to progress to advanced fibrosis and cirrhosis and is associated with increased morbidity and mortality. Currently, there are no definitive universally accepted treatment options available for NASH. Most pharmacological agents that have been investigated are limited by inconsistent efficacy or side effects. We reviewed the current literature on the principle drugs that have been tested for NAFLD in the adult population, with special emphasis on clinical data and safety profiles.

Methods: A comprehensive PUBMED/MEDLINE search was conducted to identify principal therapeutic intervention studies for NAFLD, from which a summary of the studies were formulated in this review.

Results: A variety of studies, including retrospective, open-label and randomised controlled trials were reviewed in terms of clinical efficacy and side effect profiles. In addition to the most commonly studied therapeutic agents (insulin sensitizers, vitamin E, pentoxifylline, UDCA, PUFA, statins and ezetimibe), emerging pharmacologic agents showing potential efficacy in NAFLD were also explored.

Conclusion: Based on risk-benefit profiles, pentoxifylline seems to have the best treatment outcomes currently, with significant improvement in histology while having minimal tolerable side effects. Further clinical research is warranted to understand and improve our repertoire of treatment options, including potential combination therapy, towards this complex disease.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, with disease prevalence of approximately 35% [1,2]. It represents a clinico-pathologic disease entity ranging from simple steatosis (SS), which has a relatively benign course to non-alcoholic steatohepatitis (NASH), where hepatic steatosis is accompanied by significant necroinflammation, hepatocyte injury (ballooning) with or without fibrosis [3]. Patients with NASH are at risk of disease progression and complications; 38% of patients with NASH will have progression of fibrosis in 5 years and 20% will develop cirrhosis over 10 years [4]. In addition, relative to SS or the general population, patients with NASH are at risk of increased mortality, particularly liver related or cardiovascular related mortality [5-7]. Indeed, NAFLD is anticipated to become the leading cause of liver transplantation in the near future [8]. Consequently, there is a pressing need to address this disease in terms of effective and safe treatment options. However, 34 years after the first description by Ludwig et al. [9], NAFLD remains a difficult disease to manage, with no universally accepted pharmacologic treatment options currently available. Lifestyle modification involving diet restriction, weight loss and exercise is often suggested as the first line therapy for NAFLD, but is difficult to maintain on a long term basis. As such, pharmacologic options are then indicated. We reviewed the current literature on the principle drugs that have been tested for NAFLD in the adult population, with special emphasis on clinical efficacy and safety profiles.

Insulin sensitizers

Given that insulin resistance (IR) plays a dominant role in the pathogenesis of NAFLD, insulin sensitizers have been extensively explored as treatment options, the principle agents being metformin and thiazolidinediones (TZD).

Metformin

Metformin is a biguanide widely used in clinical practice and has been used since the 1950s, but only gained FDA approval in 1994 [10]. It is the first line oral therapy agent for the treatment of type 2 diabetes mellitus (DM), as recommended by American and European diabetes association [11]. Metformin improves insulin sensitivity via inhibition of gluconeogenesis, stimulating glucose uptake in muscles, inhibiting adipose tissue lipolysis and augmenting hepatic fatty acid oxidation [12]. Animal studies first demonstrated the reversal of hepatic steatosis, liver inflammation and ALT abnormalities with metformin [13,14]. Among the first non-randomised clinical trials, Marchesini observed that metformin improved aminotransaminases [15]. Subsequent studies supported the beneficial role of metformin on liver biochemistry and metabolic profiles, but effect of metformin on liver histology remained limited and inconsistent [16]. In particular, metformin did not show improvement of liver histology in randomised trials [16]. As summarised in Table 1, thirteen studies involving metformin in NAFLD have been performed, with variable effects seen in liver enzymes, metabolic parameters and liver histology. Several meta-analyses have also been conducted. Rakoski et al. observed that metformin had no beneficial pooled effects on liver histology, ALT

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Reference	Intervention	Sample size	Duration	Liver enzymes	Histology	Other endpoints
Marchesini [15]	Met	20	4 mths	↓ALT	NA	↓IR, ↓ Liver Volume
Nair [96]	Met	15	12 mths	Transient ↓ALT,AST	Improved	
Uygun [97]	Met vs Diet	36	6 mths	↓ALT, AST	Not improved	↓IR
Bugianesi [98]	Met vs Diet	110	12 mths	Not improved	Improved	↓IR, ↑% of normal ALT
Duseja [99]	Met vs Diet	50	6 mths	↓ALT	NA	
De Oliveria [100]	Met + NAC	20	6 mths	↓ALT	Improved	↓IR
Idilman [101]	Met vs Diet/Ex	74	12 mths	Not improved	Not improved	↓IR, ↓BMI
Loomba [102]	Met	28	12 mths	↓ALT	Improved	↓IR, ↓ weight
Haukeland [103]	Met Vs plac	48	6 mths	Not improved	Not improved	↓weight, ↓lipids
Garinis [104]	Met vs Diet	50	6 mths	Not improved	NA	↓IR, ↓BMI, ↑adiponectin
Shields [105]	Met vs LM	19	12 mths	Not improved	Not improved	
Shargorodsky [106]	Met vs plac	63	12 mths	Not improved	NA	↓ arterial stiffness, ↑adiponectin
Sofer [107]	Met vs plac	63	4 mths	Not improved	NA	↓Vascular stiffness

Met: Metformin, Vit E: Vitamin E, NAC: N Acetylcysteine, Ex: Exercise, Plac: Placebo, LM: Lifestyle Modification, mths: Months, NA: Not Assessed, IR: Insulin Resistance, BMI: Body Mass Index.

Table 1: Studies of Metformin in adult NAFLD patients.

Reference	Intervention	Sample size	Duration	Liver enzymes	Histology	Other endpoints
Caldwell [108]	Troglitazone	10	6 mths	↓ALT	Not improved	-
Neuschwander [24]	Rosiglitazone	30	48 wks	↓ALT, AST	Improvement	↓IR, ↓BMI
Promrat [109]	Pioglitazone	18	48 wks	↓ALT	Improvement	↓hepatic fat, wt gain
Sanyal [110]	Pioglitazone+Vit E vs Vit E	20	6 mths	No improvement	Improvement	↓IR, ↓FFA
Belfort [111]	Pioglitazone vs plac	55	6 mths	↓ALT, AST	Improvement	↓IR, ↓hepatic fat
Aithal [112]	Pioglitazone vs plac	74	12 mths	↓ALT, AST	Improvement	↓IR, ↓GGT, ↓Ferritin, wt gain
Idilman [101]	Rosiglitazone vs Diet/Ex	74	48 wks	No improvement	Not improved	↓IR
Ratziu [25]	Rosiglitazone vs plac	63	12 mths	↓ALT	Improvement	↓IR, ↑adiponectin, wt gain
Sanyal [29]	Pioglitazone vs plac	274	24 mths	↓ALT, AST	Improvement	↓IR, wt gain

Vit E: vitamin E, plac: placebo, Ex: exercise, mths: months, IR: insulin resistance, BMI: body mass index, wt: weight, FFA: free fatty acid

Table 2: Studies of thiazolidinediones (TZDs) in adult NAFLD patients.

or body mass index (BMI) [17]. In the meta-analysis by Musso et al. involving 671 patients and 11 randomised control trials, metformin did not improve liver histology but significantly reduced body weight, waist circumference and metabolic parameters compared to placebo [18]. Another meta-analysis by Li et al. with 9 studies and 417 patients reported that metformin improved aminotransaminases, IR and BMI, but not liver histology [19]. Current guidelines do not recommend metformin as a treatment for NAFLD [3]. However, it can be used to treat type 2 DM in patients with NAFLD. Metformin is safe and not associated with hepatotoxicity. Furthermore, it does not cause weight gain, an important aspect while managing NAFLD, and is generally well tolerated, with gastrointestinal side effects being most common, but usually not requiring treatment discontinuation. An additional consideration is the potential anti-tumour effect of metformin. With emerging data suggesting the development of hepatocellular carcinoma (HCC) in the context of NAFLD with or without cirrhosis [20, 21], the inverse association seen between HCC risk and long term metformin therapy takes on additional importance [22].

Thiazolidinediones

Thiazolidinediones (TZDs) are agonists to peroxisomal proliferator-activated receptor (PPAR) γ , which decrease hepatic lipogenesis, improve insulin sensitivity both centrally and peripherally, and stimulate hepatic fatty acid oxidation while augmenting adiponectin levels [23]. They include troglitazone (which has since been removed due to hepatotoxicity potential), rosiglitazone and pioglitazone. Rosiglitazone was associated with decreased liver aminotransferases, improved steatosis, ballooning and inflammation but had no effect on fibrosis [24]. The FLIRT trial confirmed the effect of rosiglitazone on liver aminotransferase and steatosis, but also did not demonstrate improvement on fibrosis [25]. Furthermore, extension of treatment

with rosiglitazone did not improve liver histology [26]. Other studies have focused on pioglitazones, which also reported efficacy in improving aminotransaminases but variable effects on liver histology [27,28]. In the landmark PIVENS trial with the largest number of NAFLD patients in a treatment trial, pioglitazone was associated with decreased aminotransaminases, reduction of hepatic steatosis and lobular inflammation, but not fibrosis. However, the histological improvements did not attain the prespecified level of significance for primary histological outcome [29]. The principal trials of TZDs in NAFLD are illustrated in Table 2. Meta-analysis of studies evaluating TZDs in NAFLD show consistently that TZDs improved steatosis, ballooning and inflammation [17,18,30,31], while only one meta-analysis showed improvement in fibrosis [31]. Improvement in fibrosis was also seen in another meta-analysis when trials focusing specifically on pioglitazones were analysed [30]. However, the drawbacks of TZD therapy are also considerable. The beneficial effects of TZDs are not maintained with discontinuation of therapy, suggesting the need for continued long term therapy [32]. In addition, the safety of sustained TZD use has also been questioned. Increased risk of edema [33] and heart failure [34] have been reported with TZD usage. An increased risk of cardiovascular events was seen with rosiglitazone [35] but not with pioglitazone [36] leading to restrictions on the usage of rosiglitazone in clinical practice. Other pertinent considerations include weight gain [average weight gain of 4.4 kg [31], bone loss with increased risk of fractures [37] and increased risk of bladder cancers [38]. Consequently, there are reservations in recommending TZDs as a major therapeutic option.

Antioxidants & cytoprotective agents

Antioxidants: Oxidative stress and accompanying

proinflammatory cytokines have been recognised as an important aspect of NASH pathogenesis. Hence, several studies of antioxidants have been conducted in NAFLD, with the most commonly studied antioxidant agent being vitamin E. Multiple studies of vitamin E either alone or in combination with other agents have been performed with generally beneficial results Table 3. The largest trial was the PIVENS trial with 247 non-diabetic NASH patients, which showed that 800 IU of vitamin E improved aminotransaminases, hepatic steatosis and inflammation, but had no effect on fibrosis [29]. A separate randomised controlled study demonstrated that a combination of vitamin E and C improved histological fibrosis scores but not histological inflammation or ALT [39]. Of concern, however, high dose vitamin E (400 iu or more) has been implicated in increased all-cause mortality in one meta-analysis [40], which was not observed in other meta-analysis [41,42]. Furthermore, a separate meta-analysis observed that vitamin E might be associated with increased risk for hemorrhagic stroke [43], while the SELECT trial suggested an increased incidence of prostate cancer in healthy men taking 400 iu of vitamin E daily over 7 years [44]. Accordingly, the enthusiasm for vitamin E has been tempered by concerns over safety with long term use of vitamin E. Nevertheless, vitamin E can still be considered as a treatment option in non-diabetic patients with NASH, as suggested by the guidelines of the American Association for the Study of Liver Diseases (3).

Pentoxifylline: Pentoxifylline is a non-selective phosphodiesterase inhibitor with anti-inflammatory properties via TNF- α inhibition. Few randomised, placebo controlled trials on patients with NASH have been conducted, most with favourable results Table 3. In a small pilot study, Lee et al. found that while aminotransaminases improved with pentoxifylline, there was no effect on the inflammatory markers -TNF- α and IL-6. However, this study was limited by a small sample size and short duration of treatment [45]. A separate trial found no significant benefit of pentoxifylline on aminotransaminases or liver histology [46]. In contrast, Zein et al. found that pentoxifylline improved NAFLD activity scores, steatosis, inflammation and fibrosis, but not ballooning [47]. A recent meta-analysis of 5 randomised trials found that pentoxifylline reduced aminotransaminases, steatosis, inflammation and fibrosis [48]. In terms of safety profile, only minor side effects were reported with pentoxifylline. These include nausea, emesis, headaches and abdominal cramps, which did not usually require treatment discontinuation [46,47].

Polyunsaturated fatty acids: N-3 polyunsaturated fatty acids (PUFA) are essential fatty acids that can only be derived from exogenous sources. Some data suggest that a low dietary intake of PUFA may have a role in NAFLD pathogenesis [49]. In addition, PUFA has been shown

to improve hypertension, dyslipidemia and cardiovascular disease [50], diseases closely related to NAFLD [51]. PUFA act by regulating gene transcription factors involved in hepatic lipid metabolism [52] which have down-stream effects of increased insulin sensitivity, inhibition of hepatic lipogenesis, increased fatty acid oxidation and reduction of pro-inflammatory cytokines [53]. Various studies using a range of PUFA dosages, composition of the PUFA and duration of treatment have not found consistent results in the context of NAFLD Table 4 [53]. More importantly, most of the studies did not evaluate histological endpoints of treatment. Among the first trials, Capanni et al. found that PUFA improved liver aminotransaminases, metabolic profiles and hepatic steatosis on imaging [54]. Other studies have provided collaborative observations [53]. A meta-analysis of 9 trials and 355 patients found that there were beneficial changes in hepatic steatosis but less convincing evidence of improvement in aminotransaminases with PUFA therapy [55]. Two recent randomised controlled trials which provided histological outcome measures did not demonstrate improved liver histology, but in fact suggested worsening of insulin resistance with PUFA therapy in one trial [56,57]. More studies are required before PUFA can be recommended as a treatment option in NAFLD.

Ursodeoxycholic acid (UDCA): UDCA is a naturally occurring hydrophilic bile acid originally approved for treatment of primary biliary cirrhosis. It acts through alteration of the bile acid pool, immune modulation and reduction of oxidative stress [58]. Several studies exploring effects of UDCA monotherapy or in combination with other agents have reported improvement in aminotransaminases predominantly, with less convincing efficacy in histology Table 4 [49]. Initial UDCA monotherapy at a dose of 13-15 mg/kg did not show any efficacy on aminotransaminases or liver histology [59] while higher dose UDCA monotherapy (28-35 mg/kg) improved aminotransaminases and serum markers of fibrosis (Fibrotest), but no histologic endpoints were evaluated [60]. In combination with vitamin E, UDCA also showed mainly improvement of aminotransaminases [61,62]. In a recent meta-analysis of 3 studies involving 385 subjects, UDCA did not demonstrate any biochemical benefits in NASH. In addition, while there was improvement of lobular inflammation, there was also a suggestion that fibrosis may increase with UDCA [63]. While UDCA is generally well tolerated, with only minor gastrointestinal side effects observed, based on the limited evidence of drug efficacy, UDCA is generally not recommended in NAFLD [27,64].

Lipid lowering agents

Lipotoxicity, which is the hepatic accumulation of lipid molecules

Reference	Intervention	Sample size	Duration	Liver enzymes	Histology	Other endpoints
Yakaryilmaz [113]	Vit E	9	24 wks	↓ALT, AST	Improvement	↓IR
Bugianesi [98]	Vit E vs Diet	110	12 mths	Not improved	NA	
Sanyal [29]	Vit E vs Plac	274	24 mths	↓ALT, AST	Improvement	
Pietu [62]	Vit E+UDCA	101	4 years	↓ALT, AST	Improvement	
Dufour [61]	Vit E+UDCA vs plac	48	24 mths	↓ALT, AST	Improvement	
Harrison [39]	Vit E+C vs plac	49	6 mths	Not improved	Improvement	
Foster [114]	Vit E/Vit C/Atorvastatin vs plac	1005	4 years	NA	NA	Reduced steatosis on CT
Satapathy [115]	Pentoxifylline	18	6 mths	↓ALT, AST	NA	↓IR, ↓TNF α , ↓fatigue
Satapathy [116]	Pentoxifylline	9	12 mths	↓ALT, AST	Improvement	
Lee [45]	Pentoxifylline vs plac	11	3 mths	↓AST	NA	
Van Wagner [46]	Pentoxifylline vs plac	30	12 mths	Not improved	Not improved	
Zein [47]	Pentoxifylline vs plac	55	12 mths	↓ALT	Improvement	

Vit E: vitamin E, plac: placebo, UDCA: ursodeoxycholic acid, wks: weeks, mths: months, NA: not assessed, IR: insulin resistance, TNF α : tumor necrosis factor α

Table 3: Studies of Vitamin E and Pentoxifylline in adult NAFLD patients.

Reference	Intervention	Sample size	Duration	Liver enzymes	Histology	Other endpoints
Capanni [54]	n-3 PUFA	56	12 mths	↓ALT, AST	NA	↓TG, ↓FG, improved LET and DPI
Spadaro [117]	n-3 PUFA + diet vs diet	40	6 mths	↓ALT	NA	↓TG, ↓TNF α, ↓IR, ↓liver fat on US
Zhu [118]	n-3 PUFA vs plac	144	24 wks	↓ALT	NA	↓TG, ↓LDL, ↓liver fat on US
Tanaka [119]	EPA	23	12 mths	↓ALT, AST	Improved	↓TChol, ↓liver fat on US
Sofi [120]	n-3 PUFA + diet vs diet	11	12 mths	↓ALT, AST	NA	↓TG, ↑HDL, ↑adiponectin
Vega [121]	n-3 PUFA	22	8 wks	NA	NA	↓TG
Cussions [122]	n-3 PUFA vs plac	25	8 wks	Not improved	NA	↓TG, ↓BP, ↓liver fat on MRS
Dasarathy [56]	n-3 PUFA vs plac	37	48 wks	Not improved	Not improved	↑IR
Sanyal [57]	EPA vs plac	243	12 mths	Not improved	Not improved	↓TG
Mendez-S [123]	UDCA vs plac	27	6 wks	Not improved	NA	
Lindor [59]	UDCA vs plac	166	2 years	Not improved	Not improved	
Leuschner [124]	UDCA vs plac	185	18 mths	Not improved	Not improved	↓GGT
Ratziu [60]	UDCA vs plac	126	12 mths	↓ALT, AST	NA	↓GGT, ↓IR, ↓FibroTest

Plac: Placebo, Mths: Months, Wks: Weeks, NA: Not Assessed, TG: Triglyceride, FG: Fasting Glucose, LET: Liver Echo Texture, DPI: Doppler Perfusion Index, TNF α: Tumor Necrosis Factorα, IR: Insulin Resistance, US: Ultrasound, HDL: High Density Lipoprotein, BP: Blood Pressure, MRS: Magnetic Resonance Spectroscopy, GGT: Gamma Glutamyl Transferase.

Table 4: Studies of PUFA and UDCA in adult NAFLD patients.

Reference	Intervention	Sample size	Duration	Liver enzymes	Histology	Other endpoints
Nelson [72]	Simvastatin vs plac	16	6 mths	↓ALT	Not improved	
Abel [125]	Simvastatin+Eze vs simvastatin	45	6 mths	↓ALT,AST	NA	
Rallidis [126]	Pravastatin	5	6 mths	↓ALT	Improved	↓TChol
Lewis [127]	Pravastatin vs plac	291	36 wks	↓ALT	NA	↓TChol, ↓LDL, ↓TG
Hyogo [128]	Atorvastatin	31	24 mths	↓ALT,AST	Improved	↓TChol, ↓LDL, ↓TG, ↑HDL
Gomez-D [129]	Atorvastatin	25	12 mths	↓ALT,AST	NA	↓TChol
Athyros [74]	Atorvastatin vs no statin	437	36 mths	↓ALT,AST	NA	↓cardiovascular events
Kimura [130]	Atorvastatin	43	12 mths	↓ALT,AST	Improved	Improved lipids, ↓AGEs
Antonopoulos[131]	Rosuvastatin	23	8 mths	↓ALT,AST	NA	↓GGT, Improved lipids
Nakahara [132]	Rosuvastatin	19	24 mths	Not improved	Improved	↓TChol, ↓LDL
Ekstedt [73]	Variable statins vs no statins	68	10-16yrs	Not improved	Improved	↑frequency of DM

Eze: Ezetimibe, Plac: Placebo, Mths: Months, Wks: Weeks, Yrs: Years, NA: Not Assessed, TChol: Total Cholesterol, LDL: Low Density Lipoprotein, TG: Triglyceride, HDL: High Density Lipoprotein, AGE: Advanced Glycation Endproducts, GGT: Gamma Glutamyl Transferase, DM: Diabetes Mellitus

Table 5: Statins in adult NAFLD patients.

Reference	Intervention	Sample size	Duration	Liver enzymes	Histology	Other endpoints
Yoneda [77]	Ezetimibe	10	6 mths	↓ALT,AST	Improved	↓LDL, ↓CRP, ↓type IV collagen 7S
Chan [133]	Ezetimibe + diet vs diet	10	16 wks	Not improved	NA	↓IHTG, Improved lipids, ↓CRP, ↓IL-6
Park [76]	Ezetimibe	45	24 mths	↓ALT	Improved	↓IR, ↓CRP, Improved lipids
Takeshita [78]	Ezetimibe vs plac	32	6 mths	Not improved	Improved	↓TChol, ↑HbA1C

NA: Not Assessed, LDL: Low Density Lipoprotein, CRP: High Sensitivity C-reactive Protein, IHTG: Intrahepatic Triglyceride, IL-6: Interleukin-6, IR: Insulin Resistance, TChol: Total Cholesterol

Table 6: Ezetimibe in adult NAFLD patients.

that lead to inflammatory damage of hepatocytes, has emerged as an important mechanism in the pathogenesis of hepatic steatosis, steatohepatitis and fibrosis [65]. Therefore, lipid lowering therapy may improve liver disease by improving lipid profile and lowering lipotoxicity [66].

Statins: Statins are potent lipid lowering agents via their inhibition of hydroxymethylglutaryl-coenzyme A reductase. Besides lowering cardiovascular risk, statins also have immunomodulatory, antioxidative, anti-thrombotic and anti-inflammatory properties [67,68]. Traditionally, the concerns that statins can induce aminotransaminase elevations had limited the use of statins in liver disease. However, several studies have demonstrated the safety of statin use in NAFLD [69,70]. Moreover, several studies reported improvement in liver aminotransaminases or hepatic steatosis on imaging Table 5 [71]. In the only randomised placebo controlled trial with post treatment histology, Nelson et al. found that simvastatin did not improve aminotransaminases or histological features of NASH [72]. On the other hand, fibrosis was less frequently seen in patients

taking statins in another study that explored changes in liver histology over time [73]. In addition, data from the post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study provide a compelling argument to use statins in NAFLD; statins were well tolerated, improved aminotransaminases and reduced risk of cardiovascular events [74]. As such, statins can be recommended for treatment of dyslipidemia in NAFLD patients, but not as a specific treatment of NAFLD.

Ezetimibe: Ezetimibe inhibits dietary cholesterol absorption from the intestinal lumen via inhibition of the sterol transporter, Niemann-Pick C1-like 1 (NPC1L1) protein, consequently leading to reduced serum cholesterol levels [75]. Studies have explored ezetimibe monotherapy or in combination with other agents such as statins and acarbose, which in general, showed improvement in aminotransaminases and lipid profile Table 6 [75]. Two pilot open labelled trials demonstrated that ezetimibe improved insulin resistance, lipid profile, aminotransaminases and inflammatory markers, while also extending benefits to steatosis, necroinflammation, ballooning

and NAS on histology. However, there was no significant effect on fibrosis [76,77]. A subsequent and only RCT to date that evaluated ezetimibe in NAFLD with post treatment histology reported significant improvement in histological ballooning and fibrosis from baseline, but there were no significant histological differences compared to placebo. In addition, ezetimibe worsen HbA1c levels [78]. Further studies are warranted to evaluate ezetimibe in NAFLD.

Emerging Drug Therapies

A variety of new therapeutic agents targeting various aspects of pathogenesis in NAFLD are currently emerging. Novel antidiabetic agents target the Glucagon-like peptide-1 (GLP-1) incretin pathway which regulate blood glucose by stimulation of insulin release, improve hepatic fatty acid oxidation and insulin sensitivity [79]. They include GLP-1 analogues (exenatide, liraglutide) and dipeptidyl peptidase (DPP) IV inhibitors (sitagliptin, vildagliptin, saxagliptin) which prevent the rapid degradation of GLP-1 [28]. A small open labelled case series found that exenatide improved grade of ballooning and fibrosis score in 4 out of 8 diabetic patients with NASH, accompanied by significant improvement in weight loss, diabetic profile and aminotransaminase [80]. A separate study found that liraglutide improved BMI, aminotransferases and APRI (AST to platelet ratio index) score, a surrogate non-invasive marker of hepatic fibrosis [81]. Two other studies investigated the use of sitagliptin, demonstrating beneficial effects ranging from reduction in BMI, aminotransferases, ballooning and NASH scores [82,83]. Another agent of increasing interest in NAFLD is the Farnesoid X receptor (FXR) agonist. Obeticholic acid (OCA) is a semisynthetic FXR agonist which can modulate hepatic lipogenesis, steatosis and insulin resistance, in addition to inhibiting inflammatory and fibrogenic responses [84]. A pilot study demonstrated that OCA was well tolerated, improved insulin sensitivity, aminotransaminases and markers of inflammation/fibrosis in diabetic subjects with NASH [85]. The Farnesoid X Receptor Ligand Obeticholic Acid in NASH treatment (FLINT) trial conducted by the NASH clinical research network investigating the use of OCA in NASH patients had recently ended and published results are currently being eagerly awaited. Another exciting agent in development is the lysyl oxidase-like-2 (LOXL-2) inhibitor monoclonal antibody, simtuzumab, which is an anti-fibrotic agent currently being investigated in NASH patients with advanced fibrosis/cirrhosis [49,86]. There have been a number of many other pharmacological agents with potential benefits in NAFLD. However, there are extremely limited data on the efficacy of these agents that prevent a reliable review or recommendation for their clinical use. These would include probiotics [87-89], S-Adenosylmethionine (SAME) supplements [90,91], α -lipoic acid [92,93] and milk thistle/silybin [94,95]. Other investigatory agents can also be found at the national institute of health website: <http://clinicaltrials.gov>.

Conclusion

NAFLD is an increasingly prevalent disease with potentially severe outcomes, yet current treatment approaches remain much to be desired. At present, no drug has universally been accepted for the treatment of NAFLD, as evidenced by the myriad of approaches explored. Most therapeutic agents do not show clear consistent efficacy or are limited by side effect profiles. Balancing these two aspects, pentoxifylline seems to have the best treatment outcomes with significant improvement in histology while having minimal tolerable side effects. Further clinical research is warranted to understand and improve our repertoire of treatment options towards this complex disease.

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