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Review Article

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Abstract

Non-alcoholic Steatohepatitis (NASH) is emerging as a leading cause of cirrhosis worldwide. Weight reduction through lifestyle modification is accepted first line treatment for these patients. Histological improvement in high-risk patient is the primary target of pharmacotherapy in NASH patients. Even though currently many drugs are available for these high-risk patients, none of them has been approved USA Food and Drug Administration (FDA) until now. Among these, vitamin E and pioglitazone has been approved by AASLD (American Association for the Study of Liver Diseases) in selected group of patients. There are more than a dozen drug targeting different pathways in NASH patient currently in phase 2 and 3 trails. Here we briefly review the currently available drugs and future of pharmacotherapy in NASH patients.

Keywords: - NAFLD, Chronic liver disease, Insulin resistance, metabolic syndrome, Liver fibrosis.

Introduction

The global epidemic of obesity has led to an increasing prevalence of non-alcoholic fatty liver disease (NAFLD) worldwide. Non-alcoholic steatohepatitis (NASH) is the inflammatory subtype of NAFLD and is associated with disease progression to cirrhosis and its complications [1]. NASH is strongly associated with insulin resistance and other metabolic risk factors like central obesity, dyslipidemia, and type 2 diabetes mellitus (DM) [2]. NASH patients with intermediate or advanced fibrosis are at risk of progression to cirrhosis and liver-related mortality. NASH is emerging as a major cause of chronic liver disease and an indication for liver transplantation in the USA.

Currently, lifestyle modification comprising diet and exercise is the standard of care for NASH. Although weight reduction by ~10% reverses steatosis and fibrosis, most patients fail to achieve or maintain it. Weight loss through medications, bariatric surgery, and bariatric endoscopic procedures have shown limited success, but they are still not endorsed by any clinical societies as the standard of care. Hence, fibrosis reversal or preventing its progression is the principal target of pharmacological therapy in NASH. At present, there is no US Food and Drug Administration (FDA) approved drug for the treatment of NASH.

Currently, there are four main targets for pharmacotherapy in NASH [3, 4]. First group of drugs targeting hepatic fat accumulation (Pioglitazone, Saroglitazar, Elafibranor), bile acid farnesoid X receptor axis (Obeticholic acid), de novo lipogenesis inhibitors (Aramchol), incretins (Liraglutide) and fibroblast growth factor (FGF-21) analogues. The second group is targeting oxidative stress like antioxidants (Vitamin E), tumour necrosis factor-alpha pathway (Emricasan), and immune modulators (Amlexanox). The third group includes anti-obesity medication like Orlistat and the fourth group includes antifibrotics like Simtuzumab.

For the last two decades, several pharmacological agents have undergone clinical trials in NASH with inconsistent benefits. Pharmacotherapies

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with thiazolidinediones and vitamin E showed some benefit in a selective group of patients. Due to heterogeneous data (study design), inconsistent outcome targets (e.g., histology) and lack of long-term benefit and safety have limited their widespread use. In this context, multiple novel pharmacological agents are undergoing clinical trials for NASH. In this short review, we are summarizing currently available medications and the status of future pharmacotherapies (agents in phase 2 and 3 trials) in patients with NASH.

Current pharmacotherapy

Even though there are no FDA-approved drugs for NASH, many drugs are in clinical use in these patients with limited success (Table 1).

Table 1: Currently available pharmacotherapy

Drug	Mechanism of action	Trial/Result	Adverse effects/Long-term safety	Current status
Vitamin E	antioxidant	PIVENS trial 800 IU/day Improvement in NASH (43% vs 19%)	Haemorrhagic stroke, prostate cancer on long-term use	Can be considered in nondiabetic and non-cirrhotic biopsy-proven NASH
Pioglitazone	Insulin sensitizers (PPAR-γ agonist)	Meta-analysis showed improvement in steatosis (RR 2.03) inflammation (RR 1.71) and improvement in fibrosis (RR 1.38)	Weight gain Congestive heart failure Increased bone loss in postmenopausal women Myocardial infarction Bladder cancer	Can be considered in only selective diabetic patients with biopsy-proven NASH
Statins	Lipid-lowering effect Anti-inflammatory Antioxidant	Improvement in Steatosis, steatohepatitis, and fibrosis	No RCTs Safe for chronic liver disease. Hepatitis (Rare)	Recommended only NASH with dyslipidemia
Metformin	Improves insulin resistance	Improves liver enzymes. No improvement in liver histology	Lactic acidosis	Not recommended for treatment of NASH
Saroglitazar	PPAR α/γ agonist	Improvement in liver enzymes, liver imaging	Gastritis Asthenia	NASH with DM and dyslipidemia
Obeticholic acid	Farnesoid X receptor agonist Improves hepatic gluconeogenesis, and lipid synthesis improves insulin sensitivity	REGENERATE trial 25 mg daily. Reduction in fibrosis, NASH activity	Pruritus Dyslipidemia	Promising drug FDA approval pending
Pentoxifylline	Phosphodiesterase inhibitor Anti-TNF-α	Improves liver enzymes, and inflammation. No effect on steatosis/ fibrosis	Gastritis	Not recommended

Vitamin E - As oxidative stress is one of the mechanisms of hepatocyte injury; antioxidants are one of the initial therapeutic targets. At present American Association for the Study of Liver diseases (AASLD) and the European Association for the Study of Liver (EASL) guideline recommends vitamin E usage in patients with biopsy-proven NASH without cirrhosis and diabetes after discussing the benefit and risk [2]. In the PIVEN trial, where patients were randomized to 800 IU/day of vitamin E or placebo for 96 weeks, patients showed improvement in steatosis (p=0.005), lobular inflammation (p=0.02), and resolution of NASH (43% vs 19%) compared to placebo [5]. This study did not show any improvement in fibrosis. There is limited data on patients with cirrhosis and diabetes mellitus. Subsequent study has raised some concern regarding increased risk of overall

Metadoxine	Antioxidant antifibrotic	Improvement in hepatic steatosis. No improvement in liver enzymes/histology	Minor gastrointestinal (GI) side effects	Not recommended
Ursodeoxycholic acid (UDCA)	hepatoprotective	Improvement in liver enzymes. No effect on liver histology	GI side effects	Not recommended

mortality, increased incidence of prostate cancer, and haemorrhagic strokes on long-term use [2, 6].

Pioglitazone- Peroxisome proliferator-activated receptor (PPAR) γ agonists like pioglitazone and rosiglitazone have been shown to improve hepatic steatosis. Pioglitazone has shown consistent results in an improvement in inflammatory score in patients with NASH with DM, but limited benefit in improvement in fibrosis. A recent meta-analysis showed consistent improvement in steatosis (RR 2.03) and inflammation (RR 1.71) with improvement in fibrosis (RR 1.38) [7]. The major limitation of using pioglitazone is weight gain (average 4.4 kg) which makes it less acceptable to both patient and physician. It should be used with caution in patients with heart failure and post-menopausal women due to the risk of increased bone loss. In addition, safety concerns remain about myocardial infarction and bladder cancer.

Statin- Apart from lipid lower effects, statin also has antioxidant and anti-inflammatory effects. Several studies showed statin may improve liver enzymes and histology, but no Randomized Control Trials (RCTs) with histologic endpoints have been conducted. Despite their safety in chronic liver disease, statins are underutilized in NASH patients [8].At present statins are not recommended for the treatment of NASH without dyslipidemia.

Metformin- Metformin has shown improvement in insulin resistance, liver enzymes, and liver histology with a satisfactory safety profile in several studies. However, a recent meta-analysis concluded that metformin did not improve liver histology [9]. At present; it is not recommended as first-line therapy for the treatment of NASH in patients without diabetes.

Saroglitazar- A dual PPAR α/γ agonist, approved for diabetic dyslipidemia, favourably modulates lipid and glucose metabolism. At a dose of 4 mg/day, it has a favourable reduction in triglyceride, liver enzymes, and fatty liver imaging (liver stiffness measurement and controlled attenuation parameters) [10]. The most common side effects reported are gastritis and asthenia. It is a promising drug for diabetic NASH and was recently approved by the Drug Controller General of India (DCGI). Further results of RCTs are awaited and their usage in patients without diabetes and dyslipidemia has to be established.

Obeticholic acid- A synthetic lipophilic ethyl derivative of chenodeoxycholic acid (farnesoid X receptor agonist), on activation reduces hepatic gluconeogenesis and hepatic lipid synthesis, resulting in improvement in insulin sensitivity. In the interim analysis of the phase 3 trial (REGENERATE), 25 mg of Obeticholic acid has shown a significant reduction in fibrosis and NASH disease activity [11].However, pruritus and dyslipidemia are major side effects. Further data on efficacy and safety is awaited and FDA approval is still pending.

Pentoxifylline- A phosphodiesterase inhibitor with anti-tumour necrosis factor-α (TNF-α) activity has shown a significant reduction in liver enzymes, and inflammation without any impact on steatosis and fibrosis [12]. Thus, its usefulness is not yet established and is not recommended for routine usage.

Metadoxine- Metadoxine (pyridoxine-L-2-pyrrolidone-5 carboxylate) is an antioxidant (a source of glutathione) that affects adipocyte differentiation, limiting hepatic lipid accumulation and antifibrotic effect. It has been studied in alcoholic steatohepatitis. Its use in NASH is not yet established, as studies did not show any improvement in liver enzymes and histology, even though it showed improvement in liver steatosis assessed by ultrasound [13].

Ursodeoxycholic acid (UDCA)- Even though commonly prescribed in clinical practice, studies revealed inconsistent and disappointing results. UDCA is currently not recommended for the treatment of NASH by AASLD or any other associations.

Future pharmacotherapy

As the burden of NASH and related chronic liver diseases are increasing and with limited efficacy and safety of currently available treatment options, several pharmacological agents are in phase 2 and 3 trials (Table 2) [3]. **Drugs in phase 3 trials**

Table 2: Drugs in phase 2 and 3 trials

Elafibranor- Elafibranor (GFT505) is dual PPAR-α and δ agonist that improves insulin resistance and lipid metabolism through α receptor action and acts as an anti-inflammatory by decreasing macrophage activation by δ receptor action. In the phase 2b (GOLDEN 505) trial, 120 mg of Elafibranor showed improvement in NASH score without worsening fibrosis compared to 80 mg of Elafibranor or placebo [14].However, in the phase 3 trial (RESOLVE-IT), Elafibranor failed to meet the primary endpoint in the interim analysis.

Selonsertib- Selonsertib (GS-4997) is an oral apoptosis signal-regulating kinase 1(ASK-1) that has been shown in a phase 2 RCT to effectively reduce

Phase 3 trial				
Product name	**Mechanism of action**	**Study Name/design**	**Primary endpoint**	**Current status**
Elafibranor	PPAR-α/δ agonist	RESOLVE-IT Randomized double-blind placebo-controlled	Histologic improvement-NASH resolution without worsening of fibrosis	Interim analysis failed to achieve primary endpoints
Selonsertib	Apoptosis Signal-regulating Kinase (ASK-1) inhibitor	STELLAR 3 STELLAR 4 Randomized double-blind placebo-controlled	Fibrosis regression ≥1 Event-free survival	Interim analysis failed to achieve primary endpoints
Cenicriviroc	CCR2/CCR5 inhibitor	AURORA	Fibrosis regression	No decrease in NASH score. Final result awaited
Resmetirom	Thyroid hormone beta-agonist	MAESTRO-NASH MAESTRO-NAFLD	Resolution of NASH Adverse drug reaction	Results are pending
Aramchol	Stearoyl- CoA desaturase 1 modulator	ARMOR Obese/overweight Type 2 DM/prediabetes	Reduction in NASH score Fibrosis improvement/no worsening	Results are pending
Phase 2 trial				
NGM282	Fibroblast growth factor-19 analogue	F1-F3 fibrosis in biopsy	Reduction in NASH score with improvement/no worsening of fibrosis	Improvement in NASH score, fibrosis, and fat content on imaging
BMS-986036	Pegylated analogue of FGF-21	Phase 2 double-blind trial, biopsy-proven NASH	Reduction in hepatic fat content	Improvement in steatosis (MRI)
Emricasan	Pan-caspase inhibitor	Phase 2a trial	Improvement in fibrosis without worsening NASH	No improvement in fibrosis
Semaglutide	GLP-1 analogue	Phase 2a multicentre study	Resolution of NASH without worsening fibrosis	Improvement in NASH score, no change in fibrosis
Liraglutide	GLP-1 analogue	LEAN trial Placebo-controlled RCT	NASH resolution without worsening of fibrosis	NASH resolution without worsening fibrosis

hepatic fibrosis at a dose of 18 mg/day [15]. The early result of the phase 3 trial (STELLAR 3 and 4) has not shown any significant benefit compared to the placebo. This is likely to be a negative trial as the drug targets a late and redundant step in NASH pathogenesis.

Cenicriviroc- Cenicriviroc (CVC) is an oral dual CCR2/CCR5 inhibitor that has shown anti-inflammatory and antifibrotic properties in animal models through the reduction of C-C chemokines. In a phase 2 RCT (CENTAUR), cenicriviroc in a dose of 150 mg/day for one year has shown improvement in fibrosis compared to placebo (20% vs 10%) [16]. AURORA (phase 3 trial), targeting patients with F2-F3 fibrosis, is currently ongoing to measure fibrosis improvement and liver-related clinical outcomes.

Resmetirom- Resmetirom is an oral thyroid hormone beta-agonist that improves NASH by increasing hepatic fat metabolism and reducing lipotoxicity. In the phase 2 placebo-controlled trial, Resmetirom 80 mg/day showed improved NASH score but not at the fibrosis stage at week 36 [17]. There were no major side effects except diarrhoea and nausea.

Currently, a phase 3 clinical trial (MAESTRO-NASH and MAESTRO-NAFLD) is recruiting NASH/NAFLD patients. In the MAESTRO-NASH trial, the primary focus is NASH resolution in biopsy-proven NASH. In the MAESTRO-NAFLD trial, the primary focus is on adverse drug reactions. Both studies will also assess its effect on low-density lipoprotein cholesterol (LDL-c).

Aramchol- Arachidyl Amido Cholanoic Acid (Aramchol) is an oral stearoyl coenzyme- A desaturase 1 (SCD-1) modulator. SCD-1 is a key enzyme in hepatic lipogenesis. Aramchol causes down-regulation of SCD-1 leading to a decrease in adiposity, liver fatty acids, and a decrease in fibrosis by decreasing collagen production.

In a phase 2b trial (ARREST), overweight or obese patients (BMI > 25 kg/m2) with prediabetes or diabetes patients have enrolled in Aramchol 600 mg, 400 mg, or placebo [18]. Patients in both treatment groups achieved a reduction in liver fat (47% vs 24.4%) and liver enzymes compared to the placebo. A phase 3 trial (ARMOR) enrolling NASH patients with stage 2 and 3 fibrosis who are overweight or obese and prediabetes or type 2 DM is currently recruiting patients. The primary objective is the reduction in the NASH score with no worsening or improvement of fibrosis score of >1.

Drugs in phase 2 trials

There are more than two dozen phase 2 trials currently recruiting NASH patients with fibrosis in search of a novel pharmacotherapy agent (Table 2). Among these, only a few have published results which are discussed below.

NGM282- This is a fibroblast growth factor-19 (FGF-19) analogue and acts by inhibiting de novo bile acid synthesis and insulin-like effects on carbohydrate metabolism. In phase 2 trials 3 and 6 mg/day subcutaneous doses have been shown to decrease hepatic content [19]. No information on phase 2b or 3 trial is available right now.

BMS-986036- It is a pegylated analogue of FGF-21 and has a beneficial effect on insulin sensitivity, and lipid and fibrotic markers in diabetic patients. In a mouse model, it has been shown to decrease hepatic steatosis, NAS, and fibrosis. A phase 2 randomized double-blind trial showed improvement in steatosis (using MRI) [20]. Currently, no phase 2b or 3 trials are ongoing with this agent.

Emricasan- Emricasan is a pan-caspase inhibitor, which has been shown to decrease portal hypertension by blocking apoptotic and inflammatory caspase activation. In the phase 2a trial, it showed a significant decrease in hepatic venous pressure gradient (HVPG). However, in a randomized placebo-controlled trial, it failed to show any benefit in liver histology and fibrosis [21].

Combination therapy- The percentage of NASH patients achieving histological improvement to monotherapy is less than 50%, leaving a substantial proportion of patients without effective treatment. This may be due to the complex pathophysiology of NASH, driven by metabolic overload leading to stress on hepatocytes, resulting in cell damage, inflammation, and fibrosis. This led to the concept of combination therapy to improve the success rate. A few logical combinations include a drug

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with a metabolic mechanism of action and a drug with an anti-inflammatory or antifibrotic mechanism of action [22-24]. Few ongoing trials using combination therapy in NASH are listed in Table 3. Combination therapy may be overlapping (combination from beginning to end of treatment) or addition (second drug added when the effect of the first drug declines or is insufficient).

Table 3: Combination therapy

Study name	Combination	Study population	Endpoint	Results
CONTROL [23] Phase 2 NCT02633956	Obeticholic acid + Atorvastatin	NASH F1-F3 F4 no decompensation	LDL cholesterol Safety, Tolerability	Improvement in LDL Safe
TANDEM [24] Phase 2 NCT03517540	Tropifexor + Cenicriviroc	NASH F2/F3	Adverse effects Improvement in fibrosis and resolution of NASH	Results are pending
ELIVATE Phase 2 NCT04065841	Tropifexor + Licoglifozin	NASH F2/F3	Resolution of NASH with improvement/no worsening of fibrosis	Results are pending
Proof of concept study Phase 2 NCT02781584	Cilofexor +Firsocostat/ Selonsertib	NASH F2/F3	Treatment-emergent adverse events/ laboratory abnormalities	Results are pending
ATLAS Phase 2 NCT03449446	Cilofexor +Firsocostat/ Selonsertib	NASH F3/F4	Adverse events Treatment-emergent laboratory abnormalities One stage improvement in fibrosis without worsening NASH	Results are pending
Phase 2 NCT03987074	Cilofexor +Semaglutide/ Firsocostat	NASH F2/F3	Treatment-emergent adverse events/ laboratory abnormalities	Results are pending
Phase 2A NCT03776175	PF-05221304, ACC inhibitor + PF-06865571, DGAT2 inhibitor	NAFLD	Steatosis (MRI) Safety	Results are pending

Conclusion

As currently available drugs have limited success and to date, there is no FDA-approved drug in the management of NASH, this review provides the potential for the drugs in the pipeline and future therapeutic options in NASH. Even though clinical trial results of Obeticholic acid and Saroglitazar are encouraging, a substantial proportion of patients remain without effective treatment. This means future therapy may involve the combination of drugs targeting two or more mechanisms of action, as NASH is a heterogeneous disease with a diverse mechanisms. The treatment goal of pharmacotherapy in NASH is to prevent the progression of advanced liver disease including cirrhosis and hepatocellular carcinoma (HCC). Pharmacotherapy should be combined with lifestyle modification and management of co-morbidity, as cardiovascular disease remains the leading cause of mortality in NAFLD patients.

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