An eBook on Diabetes

Chapter 2

Drug Pipelines in the Treatment of NASH

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Abstract

Nonalcoholic steatohepatitis (NASH) which is a more severe form of nonalcoholic fatty liver disease (NAFLD) can at least partly lead to cirrhosis, hepatocellular carcinoma (HCC), and hepatic failure. Liver transplantation is the only option for NASH cirrhosis at this time. By 2020, NASH is projected to overtake hepatitis C as the leading cause of liver transplants in the U.S. There are still no approved drugs for treating NASH. Although there are about 196 agents of investigational NASH therapies in various stages of development, we here mainly review phase 2/3 drug candidates in the pipeline for NASH. The NASH space across the seven major markets of the U.S., France, Germany, Italy, Spain, the UK, and Japan, is set to rise from $618 million in 2016 to around $25.3 billion by 2026. However, the fact that the race to develop an effective drug against NASH has reached the home stretch, with six drug candidates (obeticholic acid, elafibranor, selonsertib, cenicriviroc, resmetirom, and dapagliflozin) in phase 3 stage of the trial, is welcome news for patients. The very earliest a NASH drug could hit the market is 2021, assuming all goes well as planned.

Keywords: Farnesoid X receptor ligand; Peroxisome proliferator-activated receptor; Fibroblast growth factor; Apoptosis signaling kinase 1; Thyroid hormone receptor β agonist

Abbreviations: ACC: Acetyl-CoA carboxylase; ASK1: Apoptosis signaling kinase1; AE: Adverse event; ALT: Alanine aminotransferase; AMPK: Adenosine monophosphate-activated protein kinase; AST: Aspartate aminotransferase; CCR2/5: C-C motif chemokine receptor-2/5; CVC: Cenicriviroc; DPP-4: Dipeptidyl peptidase-4; FGF: Fibroblast growth factor; FXR: Farnesoid X receptor; GLP-1RA: Glucagon-like peptide receptor agonist; HCC: Hepatocellular carcinoma; LDL-C low-density lipoprotein cholesterol; MRE: Magnetic resonance elastography; MRI-PDFF: Magnetic resonance imaging-proton density fat fraction; NAFLD: Nonalcoholic fatty liver disease; NAS: Nonalcoholic fatty liver disease activity score; NASH: Nonalcoholic steatohepatitis; NASH CRN: NASH Clinical Research Network; OCA: Obeticholic acid; PPAR: Peroxisome proliferator-activated receptor; Pro-C3 neoepitope: specific N-terminal propeptide of type III collagen; SEL: Selonsertib; SGLT: Sodium glucose cotransporter; SIM: Simtuzumab; T2DM: Type 2 diabetes; THRβ: Thyroid hormone receptor β agonist

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease. One fourth of adult population is now suffering from NAFLD worldwide [1,2]. The incidence of nonalcoholic steatohepatitis (NASH) is a more severe form of NAFLD. NASH refers to liver inflammation due to fat buildup in the liver, has risen dramatically over the last two decades because of growing prevalence of obesity, metabolic syndrome, and type 2 diabetes (T2DM). Also called a "silent" liver disease, since the symptoms are not manifested in early stages, in some patients, NASH can also progress to fibrosis and cirrhosis over the years, with a high risk for liver failure and hepatocellular carcinoma (HCC). In early stages of NASH, patients generally feel well. However once the disease is more advanced or cirrhosis develops, they begin to experience symptoms such as fatigue, weight loss, and weakness. A person with cirrhosis experiences fluid retention, muscle wasting, bleeding from the intestines, and liver failure. NASH is rapidly becoming the leading cause for end-stage liver disease or liver transplantation [3]. In Japan, liver related diseases, such as cirrhosis and HCC, are now the 3rd leading causes of death in T2DM according a nationwide survey (2001-2010) [4]. It is estimated that the prevalence of diagnosed NASH will reach 45 billion US dollars by 2027 in US, Japan, England and EU 4 (France, Germany, Italy, and Spain). Lifestyle interventions such as dietary caloric restriction and exercise are currently the cornerstone of therapy for NASH, can be difficult to achieve and maintain, underscoring the dire need for pharmacotherapy. However, there are no approved pharmacotherapies for NASH. This review provides an overview of NASH agents currently in the pipeline under development.

2. Metabolic modulators

2.1. Peroxisome proliferator-activated receptor (PPAR) agonists

Since peroxisome proliferator-activated receptor (PPAR) has multiple functions,

PPAR agonists are now expected to be the most promising agent among a variety of NASH treatments [5].

2.1.1. PPARγ: First of all, pioglitazone (PPARγ agonist) show a statistically significant improvement in NASH compared to placebo [6-8]. However, pioglitazone has also several concerns for wide clinical use, such as increased risks at prostate or pancreas cancer, body weight gain, fluid retention, bone fracture in women, and increased cardiovascular events. INT131, which is a selective PPARγ modulator (SPPARMγ), is in the development for T2DM patients. INT131 demonstrated dose-dependent reductions in HbA1c, equivalent to 45 mg pioglitazone, but with less fluid accumulation and body weight gain [9]. Although no study with INT131 for the NASH treatment has been initiated, its agent will be expected in the future.

2.1.2. PPARα: There has been no studies proving efficacy of PPARα agonists, such as bezafibrate or fenofibrate which have been extensively used in the treatment of hypertriglyceridemia but have no impact in NASH. Pemafibrate (K-877, Parmodia™), a selective PPARα modulator (SPPARMα), was approved in Japan 2017. In Japan, phase 2, randomized double-blind placebo controlled trial (RDBPCT) decreased serum transaminase activities as well as lipid profiles in patients with dyslipidemia without increasing adverse effects (AEs) [10]. Pemafibrate, which improves liver pathology in diet-induced rodent model of NASH [11], will become a promising therapeutic agent for human NASH. In Japan, clinical phase 2 trial for the treatment of NAFLD/NASH with ≥ 10% on magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and ≥ 2.5 kPa on magnetic resonance elastography (MRE) is now ongoing. Primary endpoint is % change from baseline to week 24 in hepatic fat content by MRI-PDFF (NCT03350165). A major outcomes of study, PROMINENT (Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN diabetic patiENTs)study, will provide definitive evaluation of the role of pemafibrate for management of residual cardiovascular risk in T2DM patients with atherogenic dyslipidaemia despite statin therapy [12].

2.1.3. PPARδ: PPARδ, because of its presence in macrophages, has the additional effect of decreasing macrophage and Kuepfer cell activation and increasing fatty acid oxidation. Although a PPARβ/δ agonist (GW501516), was highly promising in initial trials, the drug may have been withdrawn due to safety concerns. A phase 2b of seladelpar (MBX8025) (CymaBay Therapeutics), a selective PPARδ (SPPARMδ) agonist, is now on going for patients with NASH (n=181, NCT03551522) or primary biliary cholangitis (PBC) (NCT03301506, NCT03602560). According to 12-week topline results for NASH, seladelpar (10mg/d, 20mg/d, and 50mg/d) significantly reduced hepatobiliary enzymes, lipid profiles , high sensitivity C-reactive protein and compared to placebo in spite of no significant reduction in liver fat content by MRI-PDFF (http://www.globenewswire.com/news-release/2019/06/11/1866763/0/en/CymaBay-Therapeutics-Reports-Topline-12-Week-Data-from-an-Ongoing-Phase-2b-Study-of-Seladelpar-in-Patients-with-Nonalcoholic-Steatohepatitis.html.).

2.2. Dual PPAR agonists

2.2.1. PPARα/γ agonist

India-based Zydus Cadila is evaluating once-daily oral experimental therapy saroglitazar magnesium in a phase 2 trial in NASH patients. Saroglitazar is a dual PPARα/γ agonist, approved for the treatment of dyslipidemia in diabetic patients in India [13]. In mice with choline-deficient high-fat diet-induced NASH, saroglitazar reduced hepatic steatosis, inflammation, ballooning and prevented development of fibrosis. It also reduced serum ALT, AST and expression of inflammatory and fibrosis biomarkers. In this model, the reduction in the overall NAFLD activity score (NAS) by saroglitazar (3 mg/kg) was significantly more prominent than pioglitazone (25 mg/kg) and fenofibrate (100 mg/kg) [14]. A phase 2, RDBPCT comparing three doses of saroglitazar (1 mg, 2 mg or 4 mg) with placebo in NAFLD is now ongoing (EVIDENCES II; NCT03061721). This study was initiated in April 2017, and is designed to enroll 104 patients with NAFLD/NASH. The primary endpoint of the study is percentage change from baseline in serum ALT levels at week 16 in the saroglitazar groups as compared to the placebo group.

2.2.2. PPARα/δ agonist

Elafibranor (GFT505) is an unlicensed dual agonist of PPARα/δ receptors, and has been shown to improve steatosis, inflammation, and fibrosis in mouse models of NAFLD [15]. A phase 2b RDBPCT showed patients resolving NASH without worsening hepatic fibrosis with 120 mg elafibranor in those with NAS >4 (GOLDEN-505) [16].Treatment was not effective in those with NAS <4 (19% vs.12%, p=0.045). A multicenter, phase 3 RDBPCT study to evaluate the efficacy and safety of elafibranor in NASH without cirrhosis is ongoing (RESOLVE-IT, NCT02704403). The primary objectives of this study are to evaluate the effect of elafibranor (120 mg/day) treatment in NASH patients (NAS≥4) with stage 2/3 fibrosis compared to placebo on 1) histological improvement and 2) all-cause mortality and liver-related outcomes in NASH patients with fibrosis. This study was initiated in March 2016, and is expected to enroll 2,000 patients at 250 centers worldwide, with initial results slated for 2021.The 30-month pre-planned safety review conducted by the Data Safety Monitoring Board (DSMB) in December 2018, found no safety issues that warranted any modifications in the conduct of the trial. Enrolment for phase 3 trial of elafibranor has experienced delays. Such delays are likely a reflection of the relatively low awareness of NASH, the low diagnosis rates, the asymptomatic nature of the disease, and the reluctance of patients to undergo liver biopsy.

2.3. Pan-PPAR agonists

Lanifibranor (IVA337, Invetiva Pharm) is an anti-fibrotic treatment with a unique mechanism of action going through the activation of all three alpha, gamma and delta PPARs (pan-PPAR agonist). In animal models, lanifibranor is shown to be superior to selective PPARα, PPARγ, and PPARδ [17]. Lanifibranor is effective also in experimental skin fibrosis and lung fibrosis [18,19]. Privately-held Inventiva's once-daily oral drug candidate lanifibranor is under a phase 2b study in patients with NASH. A phase 2b RDBPCT in NASH to assess lanifibranor was completed (NATIVE, Inventiva Pharm). The NATIVE trial (NAsh Trial to Validate IVA337 Efficacy) is a RDBPCT 24 week multicenter phase 2b clinical study. The study includes two active dose arms (800 and 1200 mg/day) and a placebo comparator arm. The study is will enroll up to 225 patients in 12 European countries and more than 40 centers have been selected (NCT03008070). The primary endpoint is a decrease from baseline of the SAF (steatosis, activity, and fibrosis) score. The study was initiated in February 2017, with a target enrollment of 225 patients. Initial results are expected in the first half of 2020.

2.4. Mitochondrial Target of Thiazolidinedione

MSDC-0602K (Cirius Therapeutics) : is a an oral, once-daily next-generation small molecule, PPARγ-sparing thiazolidinedione which is mitochondrial target of thiazolidinedione modulating insulin sensitizer. MSDC-0602K is believed to work by regulating the entry of pyruvate, an important intermediate of carbohydrate metabolism, into the mitochondria. MSDC-0602K has shown activity in PPARγ knockout animal models, supporting that its activity is not primarily through PPARγ, and has been shown to be protective in NASH animal models. A phase 2b study to evaluate the safety, tolerability and efficacy of MSDC 0602K in patients with NASH is ongoing (EMMINENCE trial). This is a RDBPCT of three doses of MSDC-0602K (62.5, 125 and 250 mg) or placebo given orally once daily for 12 months to subjects with biopsy proven NASH with stage 1-3 fibrosis (NCT02784444)[20]. Initiated in July 2016, EMMINENCE trial enrolled 402 participants with an average NAS at baseline of 5.3. The primary outcome is reduction in NAS of 2 points or more. According to the interim results from the EMMINENCE trial, observations included significant improvement at six months in fasting glucose, HbA1c, insulin levels and HOMA-IR at the 125mg and 250mg dose levels, in addition to significant reduction in ALT and AST [21].

2.5. Farnesoid X receptor ligand

2.5.1. Bile acid

Obeticholic acid (OCA, Intercept), a ligand of farnesoid X receptor (FXR), is a synthetic

variant of natural bile acid chenodeoxycholic acid. In animal models, FXR activation has been demonstrated to reduce hepatic glucogenesis, lipogenesis, and steatosis. In the FLINT trial, treatment with OCA achieved a primary end-point of improving the necro-inflammation without worsening of fibrosis in 46% of the treated patients with NASH. Moreover, compared to placebo, NASH resolution was obtained in 22% of treated patients [22]. In contrast, a phase 2, RDBPCT in Japan (FLINT-J trial) showed that high doses of OCA (40 mg/day) significantly resolved NASH compared with placebo (38 % vs 20 %, p= 0.049). Fibrosis improvement in the OCA treated group is similar to that in the placebo group. There are plausible reasons explaining this discrepancy between FLINT and FLINT-J study. In the FLINT-J study, NASH with mild fibrosis at entry is prevalent. Some patients in the OCA group refused post-treatment liver biopsy, and those are classified into non-responders. Unfortunately, OCA was withdrawn from the development in Japan and Korea. An international, phase 3 study (REGENERATE study) is now ongoing with study completion anticipated in October 2022. Initiated in September 2015, the REGENERATE trial is designed to enroll 2,065 NASH patients with stage 2 or 3 liver fibrosis. The interim analysis of the trial showed that OCA 25mg/day for 72wk significantly improved hepatic fibrosis (more than 1 stage fibrosis) compared to placebo (Fig 1). However, OCA has several drawbacks such as elevated LDL levels, itching, and high cost [22]. A study of combination OCA and statins for monitoring of lipids (CONTROL trial, NCT02633956) is on going. This phase 2, multicenter, RDBPCT will evaluate the effect of OCA, and the subsequent addition of statin therapy, on lipoprotein metabolism in subjects with NASH with fibrosis stage 1 to 4, but no evidence of hepatic decompensation. A phase 3 trial of OCA in NASH patients with cirrhosis is now on going (REVERSE trial). The REVERSE trial will be conducted at sites in North America, Europe, Australia and New Zealand. The primary endpoint is the percentage of subjects with histological improvement in fibrosis by at least one stage using the NASH Clinical Research Network (CRN) scoring system after 12 months of treatment. Patients are being randomized in a 1:1:1 ratio to one of the three treatment arms: once-daily dosing of OCA 10 mg, once-daily OCA 10 mg with titration to 25 mg at three months, or placebo. Patients who successfully complete the double-blind phase of REVERSE will be eligible to enroll in an open-label extension phase for up to 12 additional months. The primary objective of this study is to evaluate whether OCA can lead to histological improvement in fibrosis without worsening of NASH in adults with compensated NASH cirrhosis. Although OCA was granted accelerated approval by the FDA for PBC in May 2016, the deaths of 19 patients being treated with the drug for its approved indication of PBC has raised concerns about the safety. Overdosing of patients with liver impairment was determined to be the problem.

2.5.2. Non-bile acid

As mentioned above, OCA has several disadvantages such as itching and elevated LDL.

Selective non-bile acid synthetic FXR agonists have been developed to resolve disadvantage of OCA. Those have the potential to provide metabolic effects without increasing side effects of pruritus and elevated LDL. Phase 2 studies with cilofexor (GS-9674) are ongoing in patients with NASH (NCT02854605), PBC and primary sclerosing cholangitis (PSC). Three other FXR agonists, tropifexor [23] (LJN452, NCT02855164), LMB763 (NCT02913105), and EDP-305 have been developed and are in phase 2 trials. Tropifexor (TXR, LJN452, Novaritis), a once-daily, oral compound, is under a phase 2 trial, dubbed FLIGHT-FXR (NCT02855164). Initiated in August 2016, FLIGHT-FXR is designed to enroll 345 patients. Interim results from the study were presented in Liver Meeting 2018 [24], with the study expected to be completed in July 2019. TXR can increase FGF-19 levels without elevating LDL-C. In the overall population, the absolute decrease of hepatic fat fraction by >5% was observed in 33.3% (21/63) of patients in TXR 90μg arm, 27.8% (10/36) of patients in TXR 60μg arm, and 14.6% (6/41) of patients receiving placebo. LMB763 (Novaritis): Another drug candidate of Novartis being tested for NASH is LMB763, a once-daily, oral compound, which is also under a phase 2 study (NCT02913105). This study was initiated in October 2016, and is designed to enroll 192 patients. The study is expected to be completed in November 2019. Cilofexor (GS-9674) is a FXR agonist which was originally developed by Phenex before its acquisition by Gilead. A phase 2, RDBPCT evaluating the safety, tolerability, and efficacy of cilofexor in noncirrhotic patients with NASH was completed (NCT02854605. Oral administration of cilofexor induces fibroblast growth factor (FGF)-19 via activating intestinal FXR activation. According to results presented in Liver Meting 2018 during the annual meeting of the American Association for the Study of Liver Diseases (AASLD), 140 NASH patients were randomized to cilofexor 100mg (n=56), cilofexor 30mg (n=56), and placebo (n=28) for 24weeks. MRI-PDFF response defined by more than 30% percent relative reduction was obtained in cilofexor 100mg group (38.9%) compared placebo group (12.5%, p=0.01). Cilofexor was safe and well tolerated. This agent for 12 weeks significantly improvements in liver biochemistries and markers of cholestasis also in patients with PSC [25]. EDP-305 (Enata pharmacueticals): EDP-305, a novel FXR agonist, reduces fibrosis progression in animal models of fibrosis [26]. A phase 2 dose ranging, RDBPCT evaluating the safety, tolerability, pharmacokinetics and efficacy of EDP-305 in NASH is on going (NCT03421431).

2.6. Apical Sodium-dependent bile acid Transporter Inhibitors

An apical sodium-dependent bile acid transporter (ASBT) inhibitor inhibits bile acid reuptake via the apical sodium bile acid transporter located on the luminal surface of the ileum. The resulting increase in bile acid synthesis from cholesterol could be beneficial in NASH patients [27].

2.6.1. Volixibat (SHP-626, Shire): Phase 1 study which investigated the safety, tolerability,

pharmacodynamics, and pharmacokinetics of volixibat (more than 20mg/body) was completed (NCT02287779) [28] .Shire plc. stopped evaluating once daily, orally-administered Volixibat (SHP626) in a phase 2 study for the treatment of NASH with liver fibrosis in adults (NCT02787304), because of severe ALT elevation in phase1 study.

2.6.2. Elobixibat (Albireo): Elobixibat is an ASBT inhibitor approved in Japan for the treatment of chronic constipation, the first ASBT inhibitor to be approved anywhere in the world [29]. Also, in other clinical trials in constipated patients, elobixibat given at various doses and for various durations reduced LDL-cholesterol and, in one trial, increased levels of GLP-1 [30]. Elobixibat will become a promising agent also for the treatment of NASH. It is expected that phase 2 studies will be started in 2019.

2.6.3. A4250 (Albireo): A4250, another ASBT inhibitor, showed significant improvement ($p<0.05$) on the NAS in an established model of NASH in mice known as the STAM™ model and improvement in liver inflammation and fibrosis in another preclinical mouse model.

2.7. Fibroblast Growth Factors

2.7.1. Fibroblast growth factor-21 (Pegbelfermin, BMS-986036)

FGF-21, a hepatokine, is a 181- amino- acid- secreted protein that is produced in the liver. FGF-21 regulate glucose in the liver and the white adipose tissue and its circulating levels are elevated in NAFLD patients, considered to play a protective role against NAFLD [31]. An RCT in a small group of obese T2DM patients with FGF-21 found significant improvement in lipid profiles as well as weight loss, reduced insulin levels, and raised adiponectin [32]. A phase 2 study of pegbelfermin, a recombinant pegylated FGF-21 in NASH patients for 16 weeks is completed (NCT02413372). Bristol-Myers exclusively licensed the rights to pegbelfermin from Ambrx Inc. This was a multicenter, RDBPCT (1:1:1) in adults with BMI ≥25 kg/m2, biopsy-proven NASH with stage 1-3, and hepatic fat fraction ≥10%, assessed by MRI-PDFF. Patients received subcutaneous injections of pegbelfermin 10 mg daily (n=25), pegbelfermin 20 mg weekly (n=23), or placebo (n=26) daily for 16 weeks. The primary efficacy endpoint was absolute change in MRI-PDFF at week 16. At week 16, both dosing regimens of pegbelfermin (10 mg daily or 20 mg weekly) significantly reduced liver fat as measured by MRI-PDFF versus placebo (6.8 % and 5.2 %, respectively, vs. 1.3 %, $p= 0.0004$ and $p= 0.008$). Both dosing regimens also improved Pro-C3 (N-terminal type III collagen propeptide, a fibrosis biomarker [33]), liver stiffness evaluated by MRE, as well as adiponectin, ALT and AST. Improvements in lipid profiles were also observed in the treatment groups. Overall, pegbelfermin had a favorable safety profile, with no deaths or serious adverse events related to treatment, and no discontinuations due to adverse events (NCT02413372) [34]. In contrast, twelve-week

pegbelfermin treatment did not impact HbA1c concentrations in another randomized phase 2 study [35]. An international phase 3 study of pegbelfermin for the treatment of NASH with stage 3/4 may be planned.

2.7.2. Fibroblast growth factor-19

NGM-282 (NGM Biopharmaceuticals Inc.) is a recombinant variant of FGF-19 that acts on liver and leads to decreased bile acids synthesis from cholesterol via cytochrome P450 7A1 and decreased lipogenesis and glucogenesis in an insulin independent manner. In a mouse model of NASH, treatment with NGM-282 for 3 weeks significantly reduced ALT and hepatic fat content with resolution of NASH. NGM-282 was completed in a phase 2 study to determine the effects on liver fat content in 82 patients with biopsy-proven stage1-3 NASH (NCT 02443116). NGM-282 3mg or 6mg/day achieved in 79% patients at least a 5% reduction in absolute liver fat content from baseline. AEs of this agent include injection site reactions (n=28 [34%]), diarrhoea (n=27 [33%]), abdominal pain (n=15 [18%]), and nausea (n=14 [17%]) [36]. However, several concerns were raised, including gastrointestinal adverse effects and safety of longer administration [37]. An additional phase 2 expansion cohort is on going to assess the histological effect of NGM-282 1 mg in NASH patients at 24 weeks as compared to placebo. In addition, NGM Bio plans to evaluate NGM-282 0.3 and 3 mg doses in a 24-week RDBPCT phase 2b study of NGM-282 in NASH patients with stage 2/3 fibrosis commencing in the first quarter of 2019. Another phase 2 study of NGM-282 for 4 weeks in T2DM patients has been completed (NCT01943045), although this results have been unpublished. In an open-label study, NGM282 improved the histological features of 43 patients with NASH in 12 weeks with significant reductions in NAS and fibrosis scores, accompanied by improvements in noninvasive imaging and serum markers [38].

2.8. Acetyl-CoA Carboxylase Inhibitors

Acetyl-CoA carboxylase (ACC) is a key enzyme that regulates the conversion of malonyl-CoA to acetyl-CoA [39]. Malonyl-CoA is a key regulator of fatty acid metabolism, controlling the balance between de novo lipogenesis and fatty acid oxidation. An open-label, proof-of-concept study evaluating firsocostat (GS0976 , phase 2, Gilead Sciences), an investigational inhibitor of ACC, in NASH patients. The data, from ten patients treated with firsocostat 20 mg taken orally once daily for 12 weeks, indicated that treatment was associated with statistically significant improvements in liver fat content and noninvasive markers of fibrosis (NCT02856555). At week 12, patients receiving firsocostat experienced a 43 percent median relative decrease in liver fat content, from 15.7 percent to 9.0 percent (p=0.006), as measured by MRI-PDFF. Median liver stiffness, a noninvasive marker of fibrosis, declined from 3.4 to 3.1 kPa at week 12 (p= 0.049), as assessed by MRE. In addition, patients with

reductions in hepatic fat demonstrated improvements in liver biochemistry and serum markers of fibrosis and apoptosis, supporting the biological activity of firsocostat [40,41]. A separate phase 2, RDBPCT evaluating firsocostat in 126 patients with NASH was completed. A 12 weeks administration of firsocostat significantly reduced hepatic steatosis and serum biochemistries compared to placebo. A raised concern of ACC inhibitors is that this agent can promote a compensatory increase in SREBP-1 activity, which stimulates triglyceride (TG) generation from peripheral free fatty acids (FFAs) and promotes hypertriglyceridemia via increasing very low density lipoprotein (VLDL) secretion [42]. In fact, firsocostat was well tolerated in this study, but raised levels of serum TG were found in a part of enrolled patients [43]. A phase 2a, dose-ranging study with PF-05221304 (Pfizer Inc.), another ACC inhibitor, in NAFLD is now on going (NCT03248882) to evaluate safety, tolerability, and pharmacodynamics of PF-05221304 administered daily for 16-weeks in adults subjects with NAFLD. Primary outcome is percent change from baseline in liver fat, as assessed using MRI-PDFF, at week 16. This study was initiated in August 2017, and is designed to enroll 360 patients. Initial results from the study are expected in February 2019. The trial is slated for completion in March 2019. MK-4074 (Merck) is a liver-specific inhibitor of ACC1 and ACC2, enzymes that produce malonyl-CoA for fatty acid synthesis [44]. A phase 1 study of changes in hepatic fat following 12wk administration of MK-4074 and pioglitazone hydrochloride (MK-4074-008) NCT01431521). In that study, percent change from baseline in hepatic fat evaluated by MRI was -35.73 (-44.53 to -26.93)% in the MK-4074 group (n=10), -18.04 (-26.84 to -9.24) % in the pioglitazone hydrochloride grpup (n=10), and 8.63 (-0.17 to 17.43) % in the placebo group (n=10) [45].

2.9. Stearoyl-CoA Desaturase Inhibitor

Aramchol, a cholic-arachidic acid conjugate, has inhibitory effects of stearoyl-CoA desaturase (SCD). Aramchol was initially produced for treatment of gallstone [46]. However, animal experiment showed a strong reduction of hepatic fat accumulation rather than gallstone dissolution. In humans, hepatic fat content was significantly reduced in the aramchol (300 mg/day) group [47]. Higher doses of aramchol, 400 mg and 600 mg, were completed on biopsy-proven NASH patients (n=247) without cirrhosis in a 52-wk phase 2b trial which evaluate their effect on hepatic TG content using MR spectroscopy (ARamchol for the REsoltuion of STeatohpatitis [ARREST] trial, NCT02279524). The ARREST trial was initiated in January 2015, and has enrolled 247 patients. Patients enrolled in this trial have advanced NASH with more than 60% having fibrosis in stages 2 and 3. Aramchol showed liver fat reduction, biochemical improvement, NASH resolution and fibrosis reduction. Results favored the 600mg dose with a dose response pattern. In particular, compared to placebo, the aramchol 600mg arm achieved the following endpoints: i) NASH resolution without worsening of fibrosis, ii) fibrosis stage reduction without worsening of NASH, and iii) decrease in ALT, AST, and better glycemic control (HbA1c). These data were presented in The Liver Meeting® 2018 during the

AASLD 2018 Annual Meeting being held in San Francisco [48]. Aramchol will be planned into a phase 3 registration trial (ARMOR pivotal study) at the end of the second quarter or early in the third quarter of 2019. Aramchol is also being studied in a proof-of-concept phase 2a clinical trial designed in up to 50 patients with HIV-associated NAFLD and lipodystrophy. The study (ARRIVE study) has enrolled 50 patients, and top line data did not meet its primary endpoint which was improvement of liver fat at 12 weeks as measured by MRI-PDFF.

2.10. Ketohexokinase Inhibitor

Ketohexokinase (KHK, PF-06835919) is the principal enzyme responsible for fructose metabolism. This agent may reduce HbA1c and insulin resistance. A phase 2a, RDBPCT is on going to evaluate the safety, tolerability, and pharmacodynamics of PF-06835919 administered once daily for 6 weeks in adults with NAFLD (NCT03256526). In this study, 47 patients were completed without severe AEs. Mean percent changes of hepatic fat evaluated by MRI-PDFF in placebo (n=17), PF-06835919 75 mg (n=17), and PF-06835919 300 mg (n=13) were -7.97±24.521%, 2.84±22.246%,and -25.43± 22.434%, respectively.

2.11. Diacylglycerol Acyltransferase 2 inhibitor

Diacylglycerol acyltransferase (DGAT), of which there are two isoforms (DGAT1 and DGAT2), catalyzes the final step in TG synthesis [49]. A phase 1b, RDBPCT (sponsor-open) to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of multiple oral doses of DGAT2 inhibitor (PF-06865571) for 2 weeks in adults with NAFLD is on going. Primary outcome is reduction in hepatic steatosis evaluated by MRI-PDFF (NCT03513588)

2.12. Direct adenosine monophosphate-activated protein kinase activator

PXL770 (POXEL) directly activates adenosine monophosphate-activated protein kinase (AMPK), an enzyme that controls whole-body energy metabolism. Through its unique mechanism of action that directly activates AMPK, PXL770 acts on a very important biological target. This target has the potential to treat chronic metabolic diseases, including diseases that affect the liver, such as NASH. Poxel will anticipate initiating a phase 2a clinical proof-of-efficacy study in patients with NAFLD/NASH in 2019 (NCT03763877). This study will include 12 weeks of treatment with a primary end point of change in liver fat mass based on MRI-PDFF. PF-06409577 is a activator of liver specific AMPK β1-biased activator, is able to inhibit de novo lipid and cholesterol synthesis pathways, and causes a reduction in hepatic lipids and mRNA expression of markers of hepatic fibrosis [50].

2.13. Gemcabene

Gemphire Therapeutics Inc.'s experimental drug for NASH is known as gemcabene. Gemcabene has a mechanism of action that involves: i) enhancing the clearance of VLDL; and ii) blocking the overall production of hepatic TG and cholesterol synthesis. Based on prior clinical trials, the combined effect for these mechanisms has been observed to result in a reduction of plasma VLDL-C, LDL-C, TG and hsCRP, as well as elevation of HDL-C. Gemcabene showed dose-dependent and significant reduction in LDL-C levels as add-on to stable statin therapy in hypercholesterolemic patients [51]. Gemcabene significantly downregulated hepatic mRNA markers of inflammation, lipogenesis and lipid modulation, and fibrosis [52]. In a phase 2 study, 40 children ages 12-17 years with histologically confirmed NAFLD or MRI based diagnosis and elevated ALT will receive 300 mg of gemcabene per day for 12 weeks (NCT03436420). A phase 2a proof-of-concept clinical trial of gemcabene in adults with familial partial lipodystrophy (FPL) disease, a rare genetic disorder characterized by an abnormal distribution of fatty tissue, which can lead to a variety of metabolic abnormalities including NASH was initiated in December 2017 (NCT03508687). This study is expected to enroll 8 FPL patients with elevated TG and NAFLD, and top line results from the trial are expected in 2020.

2.14. The thyroid hormone receptor β

The thyroid hormone receptor β (THRβ) is the predominant liver thyroxine (T4) receptor, through which increased cholesterol metabolism and excretion through bile is mediated [53]. Resmetirom (MGL-3196, Madrigal Pharmaceuticals Inc.), a highly selective THRβ agonist, has been developed to target dyslipidemia but has also been shown to reduce hepatic steatosis in fat-fed rats [54]. Phase 2 trials were completed in patients with biopsy proven NASH and ≥10% liver steatosis using percent change from baseline hepatic fat fraction (HFF) assessed by MRI-PDFF as a primary outcome (NCT02912260). Initiated in September 2016, this study enrolled 125 patients 18 years of age and older. Top-line results from the study that were reported in December 2017, revealed statistically significant improvement in the relative decrease in liver fat in patients treated with resmetirom compared with placebo at 12-weeks. The study was completed in April 2018. Statistically significant reductions in ALT and AST were observed in resmetirom treated patients; greater reductions in ALT and AST, statistically significant relative to placebo, were observed in the prespecified group of 44/78 patients with relatively higher resmetirom drug levels [55]. A phase 3, multinational, RDBPCT of resmetirom in patients with NASH and fibrosis to resolve NASH and reduce progression to cirrhosis and/or hepatic decompensation is now recruiting (MAESTRO-NASH, NCT03900429). This study is designed to enroll 2000 subjects. VK2809 Viking Therapeutics Inc. was also evaluating oral, once-daily VK2809 in a phase 2 trial in NAFLD patients with elevated LDL-C (NCT02927184). This

study enrolled 45 patients, who were randomized to receive placebo (n=14), 10mg VK2809 dosed every other day (n=15), or 10mg VK2809 dosed daily (n=16) for 12 weeks. This study successfully achieved its primary endpoint, with patients receiving VK2809 demonstrating statistically significant reduction in LDL-C compared with placebo. In addition, the secondary endpoint was achieved, with VK2809-treated patients experiencing statistically significant reduction in hepatic fat content by MRI-PDFF compared with placebo (median , -58.1% vs. -8.9%, $p<0.01$). No serious AEs were reported among receiving VK2809 or placebo.

3. Antidiabetic Drugs

3.1. Dipeptidyl peptidase-4 (DPP-4) inhibitors

Unfortunately, there are conflicting evidences showing efficacy of DPP-4 inhibitors in NASH/NAFLD patients with T2DM, although a number of patients involved into these studies is relatively small [56]. Evogliptin (DA-1229, SuganonTM), a novel DPP-4 inhibitor, was developed by the South Korean pharmaceutical company Dong-A ST [57]. A safety concern is that the use of DPP-4 inhibitors may be associated with an increased risk of inflammatory bowel disease [58]. Treatment with saxagliptin, a DPP-4 inhibitor, was associated with an increased risk or hospitalization for heart failure (HF) [59]. Therefore, we must hesitate to administrate DPP-4 inhibitors for T2DM patients with NAFLD.

3.2. Glucagon-like peptide receptor agonists

3.2.1. Liraglutide: The efficacy of liraglutide, a glucagon-like peptide receptor agonists (GLP-1RA), was reported in NASH patients in the West (phase 2 LEAN study [60]) and Japan (LEAN-J study [61]). According to the AASLD practice guidance 2018 [62], however, it is premature to consider GLP-1RA to specifically treat in NASH/NAFLD patients without T2DM, because of insufficient evidences. Phase 3, open-label study is now ongoing to compare effects of liraglutide and bariatric surgery on weight loss, liver function, body composition, insulin resistance, endothelial function and biomarkers of NASH in obese Asian adults (CGH-LiNASH, NCT02654665).

3.2.2. Dulaglutide: Since most of patients naïve to injection therapy will hesitate daily injection therapy, dulaglutide, a novel weekly GLP-RA, has some advantages such as weekly injection, disposable and prefilled device, and similar safety profiles to other GLP-1RAs [63]. Sub-analyses of AWARD programme (AWARD-1, AWARD-5, AWARD-8, and AWARD-9) proved dulaglutide significantly reduced serum transaminase activities and gamma-glutamyl transpeptidase levels compared to placebo [64].

3.2.3. Semaglutide: Semaglutide, a novel GLP-1 RA, is recently approved for diabetic patients in US, EU, Canada and Japan. To investigate the effect of semaglutide on NASH, a phase 2 RDBPCT comparing the efficacy and safety of three different doses of once-daily subcutaneous semaglutide versus placebo in 288 participants with NASH (stage 1-3 fibrosis) is now ongoing (SEMA-NASH study, NCT02970942). Initial results from the study are expected in May 2020, with the study completion anticipated in July 2020. Semaglutide has three advantages over other GLP-1RAs. First, SUSTAIN-6 trial showed that semaglutide has a potential benefit on prevention of cardiovascular events [65]. In sub-analyses of the SUSTAIN-6 study, semaglutide significantly reduced ALT levels in T2DM subjects with elevated ALT (n=1,365).(Sanyal AJ et al.. The Liver Meeting 2017). Second, semaglutide is proved to be superior to dulaglutide on glucose control and weight loss in T2DM patients (SUSTAIN 7 trial)[66]. SUSTAIN 7 is a phase 3b, 40-week, efficacy and safety trial of 0.5 mg semaglutide vs 0.75 mg dulaglutide and 1.0 mg semaglutide vs 1.5 mg dulaglutide, both once-weekly, as add-on to metformin in 1,201 people with T2DM. Novo Nordisk initiated its phase 3a program (STEP) to study the efficacy of 2.4 mg of semaglutide once per week in obesity indications in 1H18. This study program, which will comprise four trials, is expected to be completed in 2020. As a result, among a variety of GLP-1 RAs, dulaglutide or semaglutide will be the most promising in the treatment of diabetic NASH [56,67].

3.3. Sodium glucose cotransporter (SGLT) inhibitors

3.3.1. SGLT2 inhibitors: Several pilot studies have found significant reduction in transaminase activities, body weight, the fatty liver index and liver histology (steatosis and fibrosis) in NAFLD patients [68-73]. Two open RCTs has been reported from Japan to compare the efficacy of SGLT2 inhibitor to other diabetic medications such as pioglitazone and metformin. The first repot is to compare the effect of luseogliflozin to metformin in T2DM patients with NAFLD. Hepatic steatosis, evaluated by liver to spleen (L/S) ratio on CT, was significantly reduced in the luseogliflozin group compared to in the metformin group [73]. The aim of another report is to compare the efficacy of ipragliflozin versus pioglitazone in NAFLD patients with T2DM. Serum ALT levels, HbA1c, and fasting plasma glucose were similarly reduced in the two treatment groups. Nevertheless, body weight and visceral fat area showed significant reductions only in the ipragliflozin group compared with the pioglitazone group [74]. Not only HbA1c and transaminase activities but also hepatic fat content evaluated by MRI-hepatic fat fraction were significantly decreased after the 24wk therapy with luseogliflozin. Although hepatic fibrosis markers unchanged, serum ferritin levels reduced and serum albumin significantly increased after the treatment (LEAD trial) [75]. The E-LIFT trial were presented at the Endocrine Society's 100th annual meeting in Chicago, Ill. The study, funded by the Endocrine and Diabetes Foundation India in New Delhi, included 50 T2DM patients with NAFLD who were 40 years or older. The patients were randomly assigned to receive empagliflozin (10 mg/

day) plus their standard medical treatment for T2DM, such as metformin and/or insulin, or to receive only their standard treatment without empagliflozin (control group). All patients were aware of their group assignment. At the beginning of the study and 20 weeks later, the patients had blood tests of their liver enzyme levels, which are typically elevated in NAFLD. They also underwent measurement of their liver fat using an MRI-PDFF. After 20 weeks of treatment, the liver fat of patients receiving empagliflozin decreased from an average of 16.2 to 11.3 % ($p<0.0001$), whereas the control group had only a decrease from 16.4 to 15.6 % ($p=0.057$), a statistically significant difference between groups [76]. The effects of empagliflozin treatment on hepatocellular lipid content, liver energy metabolism and body composition is now investigated in a multicenter, RDBPCT, interventional and exploratory pilot study in patients with newly diagnosed T2DM (NCT02637973). The effect of SGLT2 inhibitors versus other diabetic drugs (metformin, sulfonyl urea) is also investigated (NCT02696941, NCT02649465). The effect of empagliflozin on liver aminotransferases (ALT and AST) were analysis in the EMPA-REG OUTCOME trial. In the trial, patients with T2DM and established cardiovascular disease were randomized to receive empagliflozin 10 mg, 25 mg or placebo in addition to standard care. Changes from baseline ALT and AST were assessed in all treated patients (n = 7020). The results were reduction in ALT and AST with empagliflozin vs. placebo, with greater reductions in ALT than AST, in a pattern consistent with reduction in liver fat. This study also demonstrated that reductions in ALT were greatest in the highest tertile of baseline ALT (placebo-adjusted mean difference at week 28: −4.36 U/l [95% CI −5.51, −3.21]; $p<0.0001$)[77]. A phase 3, RDBRCT, study is on going to evaluate histological efficacy and safety of dapagliflozin in NASH (DEAN study, NCT03723252). Remogliflozin-etabonate (KGT-1681), a novel SGLT2 inhibitor, reduced liver fat content and transaminase activities in diet-induced obese male mice [78]. Avolynt is developing remogliflozin-etabonate for NASH and expects to initiate the REIN (Remogliflozin Etabonate in NASH patients) study in 2016. Remogliflozin significantly reduced non-invasive fibrosis markers such as FIB-4 index and NAFLD fibrosis score (NFS). However, remogliflozin has been discontinued because of evaluating circumstances including the development status of SGLT2 inhibitors by competitors. Ertugliflozin (MK-8835/PF-04971729, Steglatro™) is an orally active SGLT2 inhibitor being developed by Merck and Pfizer as a treatment for T2DM (VERTIS MONO extension study) [79].

3.3.2. SGLT1 inhibitors (KGA-3235)

Although most of the drugs in development in this therapeutic class are SGLT2 inhibitors, agents that block SGLT1 activity in the small intestine also show improvement in glucose levels due to decreased intestinal absorption of glucose. The SGLT1 transporter is responsible for glucose and galactose absorption in the gastrointestinal tract and, to a smaller extent, glucose reabsorption in the kidneys. Selective SGLT1 inhibitors are currently being developed, such as KGA-3235. Kissei has discovered the SGLT1 inhibitor, KGA-3235 for diabetes, and licensed

the development and marketing right of the agents in the US and Europe to GlaxoSmithKline. With regard to the development of SGLT inhibitors, GlaxoSmithKline has decided to continue to develop KGA-3235.

3.3.3. Dual SGLT1/2 inhibitors

Dual SGLT1/SGLT-2 inhibitors such as sotagliflozin (LX4211, Lexicon) and LIK066 (Novartis) are now under development. Sotagliflozin has been established to be effective in T1DM patients uncontrolled with insulin [80]. Although phase 3 and 2 trials are now on going for the treatment of patients with T2 DM and heart failure (HF), respectively, NASH studies have never been considered. (http://www.nashbiotechs.com/nash-biotech-analysis/biotechs-targeting-nash/index.html). LIK066 is a once-daily, oral compound, is also under a phase 2 study in obese patients with NASH stage 1-3 (NCT03205150). Initiated in October 2017, this study is designed to enroll 110 patients, with completion slated for October 2019. Primary outcome is change from baseline in ALT at week 12.

3.4. Combination of SGLT2/GLP-1RA

Recent study using network analysis showed that the use of SGLT-2 inhibitors or GLP-1 RA was associated with lower mortality than DPP-4 inhibitors [81]. Therefore, we believe that SGLT2 inhibitors and GLP-1RA will become central players also in the treatment of T2DM with NASH [56]. Though the combinations of SGLT2/GLP-1RA have already been evaluated in patients with T2DM in several studies (AWARD 10, Duration 8, and PIONEER4), there have been no studies evaluating efficacy of combination therapy of these agents in the treatment of NASH.

3.5. Novel Antidiabetic Agents

MEDI0382 [82], a GLP-1/glucagon receptor (GCR) dual agonist, dramatically reduces hepatic collagen in a mouse model of NASH. Hepatic lipid was reduced by 40% with MEDI0382 treatment ($p<0.0001$), which was more effective than liraglutide or switch to LFD. Hepatic collagen, quantified by type 1 collagen immunohistochemistry, was increased more than 2-fold with NASH and was reduced by 40% in MEDI0382-treated mice ($p=0.005$). A phase 2a RDBPCT showed that MEDI0382 has the potential to deliver clinically meaningful reductions in blood glucose and bodyweight in obese or overweight individuals with T2DM [82]. Oxyntomodulin (JNJ-64565111) which binds both the GLP-1 receptor and the glucagon receptor improves steatohepatitis and liver regeneration in mice [83]. Several studies of oxyntomodulin (phase 1, Jansen) is now on going for T2DM or obese patients. SAR425899 [84] is a novel dual GLP-1 and GCR agonist. A 52-week RDBPCT, phase 2 study to assess the

efficacy and safety of SAR425899 for the treatment of NASH was scheduled but withdrawn by sponsor decision unrelated to safety concern (RESTORE, NCT03437720).

Tirzepatide (LY3298176 Lilly), a dual gastrointestinal peptide (GIP) and GLP-1 RA, showed significantly better efficacy with regard to glucose control and weight loss than did dulaglutide, with an acceptable safety and tolerability profile [85].

G-protein-coupled receptor 119 (GPR119, APD778) is a promising target for T2DM. Although the role of GPR119 activation in hepatic steatosis and its precise mechanism has not been investigated [86], the GPR119 ligand alleviates hepatic steatosis by inhibiting SREBP-1-mediated lipogenesis in hepatocytes.

Imeglimin, the first in a new tetrahydrotriazine-containing class of oral antidiabetic agents, improve impaired glucose uptake by muscle tissue, excess hepatic gluconeogenesis, and increased beta-cell apoptosis [87]. Imeglimin reduced serum transaminase levels in Japanese phase 2 trial. A phase 3 trial in Japan will enroll 1100 patients with T2DM.

4. Anti-inflammatory and anti-apoptosis agents

4.1. Emricasan (IDN-6556, Conatus Pharmaceuticals Inc.: Conatus Pharmaceuticals Inc's drug candidate for NASH is known as Emricasan, and is being developed in collaboration with Novartis. Emricasan, an irreversible caspase inhibitor, improves NAS and fibrosis in murine models of NASH [88] . In a recent phase 2 RDBPCT of 38 patients with noncirrhotic NAFLD (NCT02077374), 28 days of Emricasan (25mg twice daily) resulted in a substantial reduction in liver enzymes and cytokeratin-18 (CK-18) [89]. A phase 2b study in 318 patients with NASH (stage 1-3) at 87 EU and US sites evaluated the efficacy of 72wk of emiricasan 10 mg or 100 mg (EmricasaN, a Caspase inhibitOR, for Evaluation [ENCORE] -NF, NCT02686762). According to top line results reported in March 2019, desired effects (fibrosis improvement more than 1 stage without worsening NASH) have not been obtained. Another phase 2b study in patients with NASH with compensated or early decompensated cirrhosis and severe portal hypertension is assessing the efficacy of 3 doses Emricasan (10 mg, 50 mg, 100 mg/day) on portal hypertension (ENCORE-PH, NCT02960204). Primary outcome is mean change in hepatic venous pressure gradient (HVPG). A phase 2b clinical trial of Emricasan in approximately 210 patients with decompensated NASH cirrhosis, dubbed ENCORE-LF (for Liver Function), is advancing toward an event-driven analysis of clinical outcome results expected in mid-2019.

4.2. IMM-124e (Immuron, Australia)

IMM-24e is an IgG-rich extract to bovine colostrum from cows immunized against

lipopolysaccharide (LPS). IMM-24e can reduce exposure of the liver to gut-derived bacterial products and LPS. An open-label, phase 1/2 clinical trial in 10 patients with biopsy-proven NASH improved liver enzymes as well as glycemic control via increase in serum levels of GLP-1, adiponectin and T regulatory cells [91]. A phase 2, RDBPCT of IMM-124E for 24wk was completed for biopsy-proven NASH patients (NCT02316717). Initiated in December 2014, the phase 2 trial enrolled 133 participants. The primary endpoint is the change in liver fat content confirmed by MRI, and change in ALT. A significantly greater proportion of patients with at least 30% reduction in serum ALT compared to placebo was observed. Additional biomarkers including aspartate transaminase (AST) and cytokeratin-18 (CK-18) were also reduced by IMM-124E including. However, IMM-124E did not have a significant effect on hepatic steatosis as measured by the hepatic fat fraction. IMM-124E is also being evaluated in a phase 2 study in children with pediatric NAFLD (NCT03042767).

4.3. Toll-like receptor 4 antagonist

JKB-121 (Taiwan J Pharmaceuticals) is a long-acting small molecule that is efficacious as a weak antagonist at the toll-like receptor 4 (TLR4). It is a non-selective opioid antagonist which has been shown to prevent the LPS induced inflammatory liver injury in a methionine/choline deficient diet fed rat model of NAFLD. In vitro, JKB-121 neutralized or reduced the LPS-induced release of inflammatory cytokines, deactivated hepatic stellate cells, inhibited hepatic stellate cell (HSC) proliferation, and collagen expression. Inhibition of the TLR4 signaling pathway may provide an effective therapy in the prevention of inflammatory hepatic injury and hepatic fibrosis in NASH patients [92]. Taiwan-based Taiwan J Pharmaceuticals is testing twice daily oral dosing of JKB-121 (5mg,10mg) in a phase 2, RDBPCT study for the treatment of NASH (NCT02442687). Finally, 65 patients with NASH stage 1-3 were enrolled, and 52 patients were completed. JKB-121 did not further improve the response rate in NASH patients compared to placebo (http://www.natap.org/).

4.4. Solithromycin (Cempra)

Solithromycin is a highly potent next-generation macrolide antibiotic. In a phase 2 open label study, all six NASH patients had reductions in NAS (mean reduction, -1.3) and ALT level (mean reduction, -17.8 U/L) after 90 days of treatment with solithromycin (NCT02510599). However, Cempra suspended development of solithromycin for NASH due to “unclear” efficacy.

5. Antifibrotic agents

Given that hepatic fibrosis stage is the most important determinant of mortality in

NASH patients [93,94], there is an unmet medical need for an effective anti-fibrotic treatment for those with advanced fibrosis. Several anti-fibrotic agents have been developed for the treatment of NASH. HSCs are the major producers of fibrous matrix in liver. Thus, mediators of HSC activation, such as transforming growth factor β(TGF-β), are important therapeutic targets. Pamrevlumab, a monoclonal antibody against the TGF-β's target gene connective tissue growth factor (CTGF), improved idiopathic pulmonary fibrosis (IPF) and may soon be studied in NASH.

5.1. Cenicriviroc (Allergan)

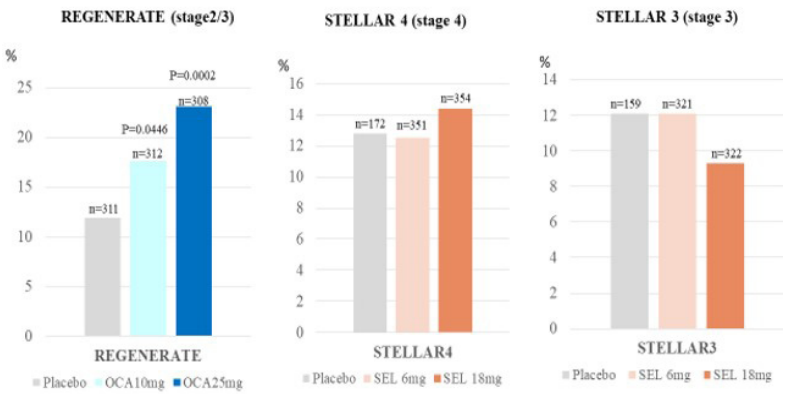
Cenciviroc **(**CVC**)**, a C-C motif chemokine receptor-2/5 (CCR2/5) antagonist, has been developed to primarily target inflammation. This agent has also antifibrotic effects and improves insulin sensitivity. Macrophage recruitment through CCR2 into adipose tissue is believed to play a role in the development of insulin resistance and T2DM. Administration of CCR2 antagonist resulted in modest improvement in glycemic parameters compared with placebo [95]. CCR5 antagonist is expected to impair the migration, activation, and proliferation of collagen-producing HSCs [96]. According to phase 2b trial (CENTAUR study), significant improvement of fibrosis without worsening NASH after 1yr of CVC treatment was found (20%) compared with placebo (10%) [97]. Although asymptomatic amylase elevation (grade 3) was more frequent in the CVC group than in the placebo group, this agent is well tolerated. A significant improvement of fibrosis without worsening NASH after 2yr of CVC treatment was not found (35%) compared with placebo (20%). This results were reported in the 53rd annual meeting of the European Association for the Study of the Liver (EASL) in 2018. Phase 3 evaluation for the treatment of NASH with stage 2/3 fibrosis is now ongoing and recruiting (AURORA study; NCT03028740)[98]. Initiated in April 2017, the AURORA trial is designed to enroll about 2,000 patients, and initial results are expected July 2019. The study is expected to be completed by July 2024.

5.2. Selonsertib

Apoptosis signal-regulating kinase 1 (ASK1) is activated by extracellular TNFα, intracellular oxidative or ER stress and initiates the p38/JNK pathway, resulting in apoptosis and fibrosis [99]. Inhibition of ASK1 has therefore been proposed as a target for the treatment of NASH. An open-label phase 2 trial evaluating the investigational ASK1 inhibitor selonsertib (SEL, GS-4997) alone or in combination with the monoclonal antibody simtuzumab (SIM) in NASH patients with moderate to severe liver fibrosis (stages 2/3). The data demonstrate regression in fibrosis that was, in parallel, associated with reductions in other measures of liver injury in patients treated with SEL for 24 weeks. Patients receiving SEL demonstrated improvements in several measures of liver disease severity, including fibrosis stage, progression

to cirrhosis, liver stiffness (measured by MRE) and liver fat content (measured by MRI-PDFF). As no differences were observed between combination and monotherapy, results are presented for SEL (18 mg and 6 mg) with/without SIM and for SIM alone [100]. SEL also significantly improved patient reported outcome (PRO) [101]. Thus, international phase 3 trials evaluating SEL among NASH patients with stage 3 (STELLAR3; NCT03053050) or cirrhosis (STELLAR4; NCT03053063) (STELLAR program) was initiated. The STELLAR 3 trial was initiated in February 2017, and is designed to enroll 800 patients. Initial results are expected in January 2020, with study completion slated for October 2023. Initiated in January 2017, the STELLAR 4 trial enrolled 877 participants with NASH stage 4 .Unfortunately, the STELLAR 4 trial was discontinued because SEL did not meet the primary endpoint (Fig 1). STELLAR 4 found that 14.4% of patients treated with SEL at 18mg (p=0.56 versus placebo) and 12.5% treated at the lower 6mg dose (p=1.00) achieved at least a ≥ 1-stage improvement in fibrosis according to the NASH CRN classification without worsening of NASH, compared with 12.8% of placebo recipients. In the STELLAR 3 trial of 802 enrolled patients, 9.3% of patients treated with SEL 18 mg (p=0.42 vs. placebo) and 12.1% of patients treated with SEL 6 mg (p=0.93) achieved a ≥ 1-stage improvement in fibrosis without worsening of NASH after 48 weeks of treatment, versus 13.2% with placebo. SEL was generally well tolerated and safety results were consistent with prior studies (**Figure 1**).

Figure 1: Top line results of phase 3 trials



5.3. Simtuzumab

Simtuzumab (SIM) is a monoclonal antibody against the enzyme lysyl oxidase-like 2 (LOXL-2) responsible for the cross-linking of collagen and overexpressed during the fibrosis progression [102]. SIM has been expected to be of use for IPF. Unfortunately, this agent could not bring additional benefit over 96wk treatment of SEL to improve hepatic fibrosis in phase 2b study [103]. Finally, SIM was withdrawn from candidates of IPF and NASH treatments.

5.4. Galectin-3 antagonist (GR-MD-02, Galectin Therapeutics Inc.)

Galectin-3 protein expression, which is essential to the development of hepatic

fibrosis, was increased in NASH with highest expression in macrophages surrounding lipid laden hepatocytes. In mice models, GR-MD-02, a galectin-3 inhibitor, resulted in marked improvement in liver histology with significant reduction in NASH activity and collagen deposition [104]. Although there was no safety concern in phase 2a trial in NASH patients with stage 3 fibrosis [105], there was no apparent improvement in the three non-invasive tests (NITs) for assessment of liver fibrosis. A phase 2b clinical trial to evaluate the safety and efficacy of GR-MD-02 for the treatment of liver fibrosis and resultant portal hypertension in 162 patients with NASH cirrhosis (NASH-CX trial) was completed (NCT02462967). In the phase 2b trial, dubbed NASH-CX, GR-MD-02 was administered as infusion every other week for 52 weeks, for a total of 26 doses. About half of the NASH cirrhosis patients in the trial had esophageal varices and the other half of the subjects were without esophageal varices. The NASH-CX trial missed the primary endpoint of reaching statistical in reducing hepatic venous pressure gradient (HVPG), when the total group of patients was considered. However, a statistically significant and clinically meaningful effect of GR-MD-02 was observed on the primary endpoint measurement of HVPG in the subgroup of NASH cirrhosis patients without esophageal varices. The company plans to advance GR-MD-02 into phase 3 testing.

5.5. ND-LO2-s0201/BMS-9862631

Hsp47 (heat shock protein 47) is a collagen-specific molecular chaperone that is essential for the maturation and secretion of collagen. ND-LO2-s0201/BMS-9862631 is a vitamin A-coupled lipid nanoparticle containing siRNA against HSP47. A phase 1 open study is completed to evaluate in subjects with severe hepatic fibrosis (stage 3/4, NCT02227459).

6. Drug repositioning

6.1. Tipelukast (MN-001, Medicinova)

Tipelukast has anti-anti-inflammatory and anti-fibrotic activity via leukotriene (LT) receptor antagonism, inhibition of phosphodiesterases (PDE) (mainly 3 and 4), and inhibition of 5-lipoxygenase (5-LO).The Phase 2a trial is a multi-center, proof-of-principle, open-label study designed to evaluate the efficacy, safety, and tolerability of MN-001 in subjects with NASH/NAFLD with hypertriglyceridemia (serum TG >150 mg/dL). Tipelukast significantly reduced mean serum TG, a primary endpoint, from 260.1 mg/dL before treatment to 185.2 mg/dL after 8 weeks of treatment (p=0.00006) This data were reported in the 53rd annual meeting of the EASL in 2018.

6.2. Amlexanox

Amlexanox is an inhibitor of noncanonical IκB kinases IKK-ε and TANK-binding kinase 1. Amlexanox is an approved small-molecule therapeutic presently used in the clinic to treat aphthous ulcers and asthma. Treatment of obese mice with amlexanox elevates energy expenditure through increased thermogenesis, producing weight loss, improved insulin sensitivity and decreased steatosis. Because of its record of safety in patients, amlexanox may be an interesting candidate for clinical evaluation in the treatment of NAFLD [106]. An open label study and a phase 2 RDBPCT are currently assessing the effects of 12 weeks of amlexanox in patients with diabetes, obesity and fatty liver on hepatic fat content by MRI, HbA1c and weight (NCT01975935 and NCT01842282).

6.3. Pirfenidone

Pirfenidone (PFD) is an orally bioavailable pyridone derivative that has been clinically used for the treatment of idiopathic pulmonary fibrosis [107]. PFD markedly attenuated liver fibrosis in western diet (WD) -fed melanocortin 4 receptor-deficient (MC4R-KO) mice without affecting metabolic profiles or steatosis. PFD prevented liver injury and fibrosis associated with decreased apoptosis of liver cells in WD-fed MC4R-KO mice [108]. PFD can be repositioned as an antifibrotic drug for human NASH.

7. Other agents

7.1. Canabinoid receptor 1 (CB1) antagonist (Namacizumab)

Namacizumab is the only known negative allosteric modulating antibody (NAMA) to CB1. Namacizumab is a multi-modal therapeutic candidate with fibrotic, inflammatory and metabolic mechanisms of action [109]. Namacizumab is promising agent for NASH [110]. A single ascending dose (SAD) trial in 24 healthy volunteers will assess safety, tolerability, and pharmacokinetics. A multiple ascending dose (MAD) trial will be initiated following the safety review of the last SAD cohort and will include up to 60 NAFLD patients.

7.2. Namodenoson (CF102, Can-Fite BioPharma Ltd.): Namodenoson is a small orally bioavailable drug that binds with high affinity and selectivity to the A3 adenosine receptor (A3AR). Namodenoson is being evaluated in Phase 2 trials for two indications, as a second line treatment for HCC, and as a treatment for NAFLD/NASH. Namodenoson is an oral twice daily under a phase 2 study. Initiated in November 2017, this study is designed to enroll approximately 60 NAFLD patients, with or without NASH. Patients who suffer from NAFLD/NASH with evidence of active inflammation are treated twice daily with 12.5 or 25 mg of oral

Namodenoson vs. placebo. The primary end point of the Phase 2 study is the anti-inflammatory effect of the drug, as determined by ALT blood levels, and the secondary end points include percentage of liver fat, as measured by MRI-PDFF. The company anticipates the completion of patient enrollment toward the end of 2018 and data release in the first half of 2019.

7.3. Angiopoetin-like 3 (ANGPTL3) protein drug (ISIS 703802, IONIS)

Angiopoetin-like 3 (ANGPTL3) is a liver-derived protein that modulates plasma TG clearance [111]. A phase 2 study is a multicenter, dose-ranging RDBPCT to evaluate the safety, including tolerability, of ANGPTL3 protein drug (ISIS 703802) and to assess the efficacy of different doses and dosing regimens of ISIS 703802 on glucose and lipid metabolism, and liver fat in subjects with hypertriglyceridemia, T2DM, and NAFLD (NCT03371355).

7.4. A variety of combination therapies

The possibility of drug combinations as a future therapeutic option is increasingly likely because of concern that attacking a single target will not be sufficiently potent. Most combination therapies are seeking to include metabolic targets with one agent, combined with either antifibrotic and/or anti-inflammatory agent in another.

A phase 2 study (ATLAS study) is on going to evaluate safety and efficacy of SEL, cliofexor, firsocostat, and combinations in participants with stage 3 or compensated cirrhosis (stage 4) due to NASH (NCT03449446). This study enrolled 395 patients. Top line data will be presented in 2019. A phase 2 study (TANDEM study) is now recruiting to evaluated safety, tolerability, and efficacy of a combination treatment of tropifexor and CVC in adult patients with NASH and liver fibrosis (NCT03517540). Allergan announced the initiation of a phase 1 study of CVC in combination with evogliptin, a novel DPP-4 inhibitor. Seladelpar (PPARδagonist) in combination with liraglutide can decrease liver fat content.

The concept of combining leucine, metformin and sildenafil (NS-0200) [112] is novel and aims at augmenting the effect on a particular pathway, the 5′ adenosine monophosphate-activated protein kinase (AMPK)/Sirtuin 1 (Sirt1) pathway. Metformin alone does not improve liver histology in NASH. In animal studies, when combined with leucine, hepatic steatosis improvements were noted, and further addition of sildenafil synergistically enhanced these effects by further stimulating Sirt1 and improving liver histology.On the basis of these preclinical studies, Chalasani and colleagues conducted a 16-week multicentre randomised controlled trial in patients with nonalcoholic fatty liver disease (NAFLD) who were randomised to either low-dose NS-0200 (1.1 g leucine/0.5 g metformin/0.5 mg sildenafil) bid or high-dose NS-0200 (1.1 g leucine/0.5 g metformin/1.0 mg sildenafil) bid or placebo. The trial population included

patients with MRI-PDFF≥15%. Liver histology was not assessed. The primary outcome was reduction in MRI-PDFF. Neither dose of the active treatment arm was better than placebo in reducing liver fat. A post hoc analysis showed that patients with baseline ALT above 50 U/L who received the high dose of NS-0200 had 15.7% relative reduction in MRI-PDFF. Body weight decreased in the high-dose group (−2.4 ± 0.5 kg, p= 0.025). This study has notable strengths. It included patients with MRI-PDFF ≥15% which would have allowed us to see a significant difference relative to placebo thereby reducing the likelihood of type 2 error. Indeed, it was recently shown that patients with higher liver fat (MRI-PDFF ≥15.7%) have higher fibrosis progression. Thus, these trial participants were more likely to have progressive NAFLD and were appropriate candidates for an early phase trial. The therapeutic effect seen with the higher dose also led to an appreciable weight loss. This weight loss is unlikely to be due to metformin alone as both the low-dose and high-dose treatment groups received the same metformin dose but the weight loss in the low-dose group was not significant. Although NS-0200 has a biologically plausible mechanism of action, the lack of appreciable potency at the 2 tested doses in the per-protocol analyses is a notable finding. Utilizing a higher dose or slight modifications in the individual doses of either leucine or metformin or sildenafil within the combination regimen may not be unreasonable to explore before undertaking further trials in patients with NASH. Each study within the landscape of treatment trials for NAFLD provide unique insights regarding treatment trial design and the study population, and this trial adds additional insights that help inform the future of NASH treatment trial design.

8. Conclusion

To prevent liver-related morbidity/mortality in NASH patients, those with fibrosis should be considered for pharmacotherapies in addition with conventional dietary interventions. The 1st line therapy for those without diabetes is vitamin E on the basis of accumulating evidences, because vitamin E prevented progression to decompensation or liver transplantation in NASH patients with advanced fibrosis [110]. Diabetic NASH patients should be preferentially treated with novel drugs licensed for diabetes treatment such as GLP-1RA and SGLT2 inhibitors. SPPARMα (pemafibrate) is promising in NASH patients with dyslipidemia. There are currently several innovative agents in the drug pipeline for NASH worldwide. Six agents (OCA, elafibranor, SEL, CVC, resmetirom and dapagliflozin) have entered phase 3 trials. Cost-effectiveness data and patient-centered benefits are also required to position their medications in the practical guidelines of NASH.

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