

Review article

Antidiabetic therapy in the treatment of NASH

Running title; antidiabetic drugs in NAFLD

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Abstract: Liver related diseases are the 3rd leading causes (9.3%) of mortality in type 2 diabetes mellitus (T2DM) in Japan. T2DM is closely associated with nonalcoholic fatty liver disease (NAFLD) which is the most prevalent chronic liver disease worldwide. Nonalcoholic steatohepatitis (NASH), a severe form of NAFLD, can lead to hepatocellular carcinoma (HCC) and hepatic failure. There are no established pharmacotherapies for NASH patients with T2DM. Though vitamin E is established as a 1st line agent in NASH without T2DM, its efficacy was recently denied in NASH with T2DM. The effects of pioglitazone on NASH histology with T2DM have extensively been established, but several concerns exist such as body weight gain, fluid retention, cancer incidence, and bone fracture. Glucagon-like peptide 1 (GLP-1) receptor agonists and sodium/glucose cotransporter 2 (SGLT2) inhibitors are expected to ameliorate NASH (LEAN study, LEAD trial, and E-LIFT study). Among a variety of SGLT2 inhibitors, dapagliflozin have already entered phase 3 trials (DEAN study). A key clinical question is what kinds of anti-diabetic drugs are the most appropriate for the treatment of NASH to prevent progression of hepatic fibrosis resulting in HCC/liver-related mortality without increasing risk at cardiovascular or renal events. The combination therapies such as glucagon receptor agonist/GLP-1 or gastrointestinal peptide /GLP-1 will be under development. This review focuses on antidiabetic agents and future perspectives on the view of the treatment of NAFLD with T2DM.

Key Words: Dipeptidyl peptidase-4; Fibroblast growth factor; Gastrointestinal peptide; Glucagon-like peptide 1; Glucagon receptor; Peroxisome proliferator-activated receptor ; Sodium glucose cotransporter

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 deposition 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 killer", 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 (9.3%) in T2DM according a nationwide survey (2001-2010) [4]. T2DM patients are at higher risk for the development or mortality of HCC [5,6]. NASH can be called "diabetic liver disease (DLD)". It is estimated that the prevalence of diagnosed NASH will reach 45 billion US dollars by 2027 in US, Japan, and EU 5 (England, 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. 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 [7]. In T2DM patients with NASH, however, vitamin E alone did not significantly change the primary histological outcome (a two-point reduction in NAFLD activity score [NAS] from two different parameters, without worsening of fibrosis). The combination therapy of vitamin E and pioglitazone was better than placebo in improving liver histology in NASH patients with T2DM [8]. Metformin is now the 1st line pharmacotherapy for T2DM [9], but it has no effect on NAFLD. In this way, there are no established pharmacotherapies for NASH with T2DM. The leading cause of mortality in NAFLD is cardiovascular events. NASH drugs require cardioprotective effects as well as hepatoprotective effects. This review provides an overview of the role of current and novel antidiabetic agents in the treatment of NASH (Table 1).

2. Pioglitazone

First of all, pioglitazone (peroxisome proliferator-activated receptor [PPAR] γ agonist) show a statistically significant improvement in NASH compared to placebo [10-12]. 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 PPAR γ modulator (SPPARM γ), 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 [13]. Although no study with INT131 for the NASH treatment has been initiated, its agent will be expected in the future.

3. 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 [14]. Evogliptin (DA-1229, SuganonTM), a novel DPP-4 inhibitor, was developed by the South Korean pharmaceutical company Dong-A ST [15]. However, treatment with saxagliptin, a DPP-4 inhibitor, was associated with an increased risk or hospitalization for heart failure (HF) [16]. Another safety concern is that the use of DPP-4 inhibitor might be associated with an increased risk of cholangiocarcinoma (hazard ratio [HR] 1.77, 95% confidence interval 1.04 to 3.01)[17] or inflammatory bowel disease (HR 1.75, 95% confidence interval 1.22 to 2.49) [18] in adults with T2DM. Therefore, we had better refrain from administrating DPP-4 inhibitors for T2DM patients with NAFLD.

4. Glucagon-like peptide receptor agonists

4.1. Liraglutide (VictozaTM)

The efficacy of liraglutide, a glucagon-like peptide receptor agonists (GLP-1RA), was reported in NASH patients in the West (phase 2 LEAN study [19]) and Japan (LEAN-J study [20]). According to the American Association for the Study of Liver Diseases (AASLD) practice guidance 2018 [21], 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).

4.2. Dulaglutide (*TrulicityTM*)

Since most of patients naïve to injection therapy will hesitate daily injection therapy, dulaglutide has some advantages such as weekly injection, disposable and prefilled device, and similar safety profiles to other GLP-1RAs [22]. 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 [23]. REWIND trial proved that dulaglutide has cardioprotective effects in 9901 T2DM patients who had either a previous cardiovascular event or cardiovascular risk factors. In this study, primary composite outcome (the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes) occurred in 594 (12.0%) participants at an incidence rate of 2.4 per 100 person-years in the dulaglutide group and in 663 (13.4%) participants at an incidence rate of 2.7 per 100 person-years in the placebo group (HR 0.88, 95% CI 0.79-0.99; $p=0.026$). All-cause mortality did not differ between groups (536 [10.8%] in the dulaglutide group vs 592 [12.0%] in the placebo group; HR 0.90, 95% CI 0.80-1.01; $p=0.067$) [24].

4.3. Semaglutide (*OzempicTM*)

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 randomized double blind placebo-controlled trial (RDBPCT) comparing the efficacy and safety of three different doses of semaglutide (once-daily subcutaneous injection) 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 [25]. In sub-analyses of the SUSTAIN-6 study, semaglutide reduced ALT and hypersensitive C-reactive protein (CRP) [26]. Semaglutide was proved to be superior to dulaglutide on glucose control and weight loss in T2DM patients (SUSTAIN 7 trial) [27]. SUSTAIN 7 trial 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. SEMA-MR trial is also on going. Lastly, oral semaglutide under development showed significant CV risk reduction. Novo Nordisk initiated its phase 3a program (STEP) to study the efficacy of 2.4 mg of semaglutide once per week in obesity indications. This study program, which will comprise four trials, is expected to be completed in 2020. According to a recent meta-analysis of 7 trials consisting of ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), Harmony outcomes (albiglutide), REWIND (dulaglutide), and PIONEER 6 (oral semaglutide), Treatment with GLP-1 RA has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with T2DM [28]. As a result, GLP-1 RA will be the most promising in the treatment of NASH with T2DM [14,29].

5. Sodium glucose cotransporter (SGLT) inhibitors

5.1. 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 [30-35]. Two open randomized controlled trials (RCTs) has been reported from Japan to compare the efficacy of SGLT2 inhibitor to other diabetic medications such as

pioglitazone and metformin. The first report 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 [36]. 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 [37]. 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) [38]. 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 magnetic resonance imaging - proton density fat fraction (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 [39]. 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 $-5.51, -3.21$]; $p < 0.0001$)[40]. A phase 3, RDBRCT, study is ongoing to evaluate histological efficacy and safety of dapagliflozin in NASH (NCT03723252). The study of dapagliflozin efficacy and action in NASH (DEAN study) is now recruiting and will enroll 100 participants. This is a phase 3, multicentre, RDBPCT to assess the efficacy and safety of dapagliflozin on improving NASH as determined by liver biopsies and metabolic risk factors. DAPA-HF trial was conducted in patients with HF with reduced ejection fraction (HFrEF) on standard of care treatment, including those with and without T2DM. Dapagliflozin met the primary composite endpoint with a statistically-significant and clinically-meaningful reduction of cardiovascular death or the worsening of heart failure (defined as hospitalisation or an urgent heart failure visit), compared to

placebo. Remogliflozin-etabonate (KGT-1681), a novel SGLT2 inhibitor, reduced liver fat content and transaminase activities in diet-induced obese male mice [41]. 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 fibrosis-4 (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) [42].

5.2. 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.

5.3. Dual SGLT1/2 inhibitors

Dual SGLT1/2 inhibitors such as sotagliflozin (LX4211, Lexicon) and licogliflozin

(LIK066, Novartis) are now under development. Sotagliflozin has been established to be effective in T1DM patients uncontrolled with insulin [43]. Although phase 3 and 2 trials are now ongoing for the treatment of patients with T2DM and heart failure (HF), respectively, NASH studies have never been considered. Licogliflozin is a once-daily, oral compound, SGLT1/2 dual inhibitor. The phase 2a study in 110 obese patients with NASH stage 1-3 was completed (NCT03205150). Primary outcome is change from baseline in ALT at week 12. Enrolled patients were randomly divided into three groups including licogliflozin 30mg/d (n=44), licogliflozin 150mg/d (n=44), and placebo (n=22). In the Liver Meeting 2019®, Harrison S and colleagues demonstrated dose-dependent improvement in liver enzymes and PDFF associated with weight loss. However, 76.5% of patients in the higher dose group experienced diarrhea vs ~40% for placebo and low dose group.

6. 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 [44]. Therefore, we believe that SGLT2 inhibitors and GLP-1RA will become central players also in the treatment of T2DM with NASH [14]. 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.

7. Mitochondrial target of thiazolidinedione

MSDC-0602K (Cirius Therapeutics) is a an oral, once-daily next-generation small

molecule, PPAR γ -sparing thiazolidinedione which is mitochondrial target of thiazolidinedione modulating (mTOT) 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 PPAR γ knockout animal models, supporting that its activity is not primarily through PPAR γ , 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 was completed (EMMINENCE trial). This is a randomized double blind placebo controlled trial (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 2/3 fibrosis (NCT02784444) [45]. 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 with a ≥ 1 point reduction in either ballooning or inflammation without worsening fibrosis stage. According to the interim results from the EMMINENCE trial, histological improvement in the MSDC-0602K group was not different from the placebo group (Table 2). However, 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 [45]. Unfortunately, Overall adverse event (AE) rate was similar across placebo and all doses of MSDC-0602. In 2020, phase 3 study (MMONARCh) will be initiated.

8. 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. 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 [46]. A phase 2 study of pegbelfermin, a recombinant pegylated FGF-21 in NASH patients for 16 weeks is completed (NCT02413372). This was a multicenter, RDBPCT (1:1:1) in adults with body mass index (BMI) ≥ 25 kg/m², biopsy-proven NASH with stage 1-3, and hepatic fat fraction $\geq 10\%$, 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 [47]), liver stiffness evaluated by magnetic resonance elastography (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 AEs related to treatment, and no discontinuations due to AEs (NCT02413372) [48]. Unfortunately, twelve-week pegbelfermin treatment did not impact HbA1c concentrations in another randomized phase 2 study [49]. International phase 2b studies (FALCON 1 and 2) of pegbelfermin for the treatment of NASH stage 3 (NCT03486899) and 4 (NCT03486912) are ongoing.

9. 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 ongoing 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 $-7.97 \pm 24.521\%$, $2.84 \pm 22.246\%$, and $-25.43 \pm 22.434\%$, respectively [50].

10. Novel antidiabetic agents

Glucagon receptor (GCR) agonist is being investigated for the treatment of NAFLD due to its appetite and food intake-reducing effects, as well as its ability to increase lipid oxidation and thermogenesis. MEDI0382 [51], a GLP-1/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 [51]. Oxyntomodulin (JNJ-64565111) which binds both the GLP-1 receptor and the GCR improves steatohepatitis and liver regeneration in mice [52]. Several studies of oxyntomodulin (phase 1, Jansen) is now ongoing for T2DM or obese patients. SAR425899 [53] 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 (TZP, 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 [54]. Results from a sub-analysis also showed that treatment with TZP led to larger ALT reduction in the TZP group (10 or 15 mg/d) compared to dulaglutide (1.5mg/wk). TZP group (10 or 15 mg/d) showed adiponectin elevation compared to placebo (Figure 1). Phase 2b study of TZP for NASH will be planned in 2020.

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 [55]. Imeglimin reduced serum transaminase levels in sub-analysis of Japanese phase 2 trial. A phase 3 trial in Japan will enroll 1100 patients with T2DM (Trials of IMeglimin for Efficacy and Safety [TIMES]). Interim analysis reported significant reduction in HbA1c. Imeglimin will be planned for the treatment of NASH.

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 [56], the GPR119 ligand alleviates hepatic steatosis by inhibiting SREBP-1-mediated lipogenesis in hepatocytes. Co-administration of GPR119 with linagliptin prevents progression of NASH in mice models [57, 58].

11. Combination therapies (Table 3)

Cenicriviroc (CVC) is an oral inhibitor of the C-C motif chemokine receptor-2/5 (CCR2/5), which plays an important role in the hepatic recruitment of the macrophages

[59]. AURORA, a phase 3 study [60], will evaluate the effects of CVC on hepatic fibrosis in 2000 patients with NASH and is expected to be completed in 2019. A Phase 2a, multi-center RDBPCT of CVC to be conducted in approximately 50 adult obese subjects ($\text{BMI} \geq 30 \text{ kg/m}^2$) with prediabetes or T2DM and suspected NAFLD (ORION study, NCT02330549). Other combination therapies are planned, including antidiabetic drug plus metabolic modifiers (PPAR δ agonist or farnesoid X receptor agonist) or anti-inflammatory agents such as CVC.

12. Conclusions

To prevent liver-related morbidity/mortality in NASH patients, those with fibrosis should be considered for pharmacotherapies in addition with conventional dietary interventions. Diabetic NASH patients should be preferentially treated with novel drugs licensed for diabetes treatment such as GLP-1RA and SGLT2 inhibitors, because these agents have also cardioprotective and renoprotective efficacy. There are currently several innovative diabetic agents in the drug pipeline for NASH worldwide, including GLP-1/GCR agonist, and GIP/GLP-1 agonist, and imeglimin. Among a variety of SGLT2 inhibitors, dapagliflozin have entered phase 3 trials (DEAN study). SGLT1/2 dual inhibitors are also expected. Cost-effectiveness data and patient-centered benefits are also required to position their medications in the practical guidelines of NASH.

Figure legends:

Figure 1 Sub-analyses of efficacy and safety of tirzepatide (TZP) in patients with type 2 diabetes: a randomised, placebo-controlled and dulaglutide-controlled phase 2 trial [56]

* $p < 0.05$ change from baseline vs. Dulaglutide

$p < 0.05$ change from baseline vs. placebo

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Abbreviations

AASLD American Association for the Study of Liver Diseases

AE adverse event

ALT alanine aminotransferase

AST aspartate aminotransferase

BMI body mass index

CCR2/5 C-C motif chemokine receptor-2/5

CVC cenicriviroc

CRP C-reactive protein

DLD diabetic liver disease

DPP-4 dipeptidyl peptidase-4

FGF fibroblast growth factor

FIB-4 fibrosis-4

GCR glucagon receptor

GIP gastrointestinal peptide

GLP-1RA glucagon-like peptide 1 receptor agonist

GPR119 G-protein-coupled receptor 119

HCC hepatocellular carcinoma

HF heart failure

HFrEF heart failure reduced ejection fraction

HR: hazard ratio

KHK ketohexokinase

MRE magnetic resonance elastography

MRI - PDFF magnetic resonance imaging - proton density fat fraction

mTOT mitochondrial target of thiazolidinedione

NAFLD nonalcoholic fatty liver disease

NASH nonalcoholic steatohepatitis

NAS NAFLD activity score

NFS NAFLD fibrosis score

PPAR peroxisome proliferator-activated receptor

RCT randomized controlled trials

RDBPCT randomized double blind placebo-controlled trials

SGLT sodium/glucose cotransporter

T2DM type 2 diabetes mellitus

TZP tirzepatide

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