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EDITORIAL

Glucagon-like peptide 1 agonists are potentially useful drugs for treating metabolic dysfunction-associated steatotic liver disease

Maurizio Soresi, Lydia Giannitrapani

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Maurizio Soresi, Lydia Giannitrapani, Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo 90127, Italy

Corresponding author: Maurizio Soresi, MD, Associate Professor, Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Via del Vespro 141, Palermo 90127, Italy.
maurizio.soresi@unipa.it

Abstract

In this editorial, we comment on Yin *et al*'s recently published Letter to the editor. In particular, we focus on the potential use of glucagon-like peptide 1 receptor agonists (GLP-1RAs) alone, but even more so in combination therapy, as one of the most promising therapies in metabolic dysfunction-associated steatotic liver disease (MASLD), the new definition of an old condition, non-alcoholic fatty liver disease, which aims to better define the spectrum of steatotic pathology. It is well known that GLP-1RAs, having shown outstanding performance in fat loss, weight loss, and improvement of insulin resistance, could play a role in protecting the liver from progressive damage. Several clinical trials have shown that, among GLP-1RAs, semaglutide is a safe, well-studied therapeutic choice for MASLD patients; however, most studies demonstrate that, while semaglutide can reduce steatosis, including steatohepatitis histological signs (in terms of inflammatory cell infiltration and hepatocyte ballooning), it does not improve fibrosis. Combinations of therapies with different but complementary mechanisms of action are considered the best way to improve efficiency and slow disease progression due to the complex pathophysiology of the disease. In particular, GLP-1RAs associated with antifibrotic drug therapy, dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA or GLP-1 and glucagon RAs have promoted greater improvement in hepatic steatosis, liver biochemistry, and non-invasive fibrosis tests than monotherapy. Therefore, although to date there are no definitive indications from international drug agencies, there is the hope that soon the therapeutic lines in the most advanced phase of study will be able to provide a therapy for MASLD, one that will certainly include the use of GLP-1RAs as combination therapy.

Key Words: Non-alcoholic fatty liver disease; Glucagon-like peptide 1; Semaglutide; Liver fibrosis; Therapy

Core Tip: In this editorial, we comment on Yin *et al*'s recently published Letter to the editor. Despite the widespread diffusion, up to now there have been no drugs capable of reliably blocking the evolution of non-alcoholic steato-hepatitis towards advanced stages of fibrosis. We agree with Yin *et al* that glucagon-like peptide receptor agonists monotherapy does not perform well as an antifibrotic therapy. The use of combination therapy according to disease stage and co-morbidities, will also be a challenge in the near future.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease[1], characterized by an accumulation of fat in the liver greater than 5%.

The highest NAFLD prevalence has been described in Latin America (44.37%), followed by the Middle East and North Africa (36.53%), South Asia (33.83%), South-East Asia (33.07%), North America (31.20%), East Asia (29.71%), Asia Pacific (28.02%) and Western Europe (25.10%)[1].

It can be considered as an "umbrella" term under which various histological and clinical liver conditions are grouped: From simple liver steatosis (NAFL) to non-alcoholic steato-hepatitis (NASH), which in addition to steatosis shows lobular inflammation and hepatocyte ballooning, with or without fibrosis; the latter, if present, can be perisinusoidal or extended and become pan lobular[2].

NASH, in turn, can regress towards steatosis alone or evolve towards liver cirrhosis, which can be complicated with hepatocellular carcinoma and portal hypertension of varying degrees[3].

Recently, a multi society Delphi consensus published a statement on the new fatty liver disease nomenclature, changing the definition of NAFLD into steatotic liver disease (SLD), an overarching term to encompass the various etiologies of steatosis[4], which in turn includes metabolic dysfunction-associated SLD (MASLD), a condition in which steatosis is associated with metabolic dysfunctions typical of metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), arterial hypertension, visceral obesity, hypertriglyceridemia, low high-density lipoprotein levels, all of which are conditions related to insulin resistance.

MASLD associated with alcohol intake (MetALD) of varying degrees, is between 20 g and 50 g/day in women and 30-60 g/day in men.

Alcohol related liver disease (ALD) is associated with > 50 g/day in women and > 60 g/day in men.

SPECIFIC ETIOLOGY OF SLD

Drug-induced liver injury includes Monogenic diseases: Lysosomal acid lipase deficiency, Wilson disease, hypobetalipoproteinemia, and inborn errors of metabolism; Miscellaneous: Celiac disease, human immunodeficiency virus, malnutrition, and hepatitis C virus (HCV).

Those with no identifiable cause (cryptogenic SLD), may be re-categorized in the future pending developments in our understanding of disease pathophysiology. There are also particular situations, such as MASLD associated with autoimmune hepatitis or HCV or HBV infections, defined as MASLD + (Tables 1 and 2).

This new classification better defines the spectrum of steatotic pathology, also allowing a better prognostic evaluation; indeed, a MASLD patient has a lower risk of mortality from all causes [hazard ratio (HR) = 1.234, 95%CI: 1.12-1.39] compared to MetALD (HR 1.69, 95%CI: 1.21-2.39) and ALD patients with MASLD (HR = 1.99, 95%CI: 1.27-3.12)[5,6]. The natural history of SLD is variable and depends on non-modifiable (age, sex, race/ethnicity, family history, genetics) and modifiable (lifestyle/diet/exercise, comorbidities, drugs, alcohol) risk factors[7,8].

Despite the widespread diffusion of SLD, up to now there have been no drugs capable of reliably blocking the evolution of NASH towards advanced stages of fibrosis and its consequent complications. The complex pathophysiological mechanisms that often interact with each other probably make it difficult to find an effective therapy, and even lifestyle and diet modifications, although important, are not effective on their own.

THERAPY

The severity of the clinical pictures that the evolution of NASH can produce, along with the complexity of its patho-

Table 1 Steatotic liver disease, new classification

Subcategories	Etiologies
MASLD	Presence of hepatic steatosis and 1 cardiometabolic risk factor out of 5 (see Table 2) and no other discernible cause for hepatic steatosis. If additional drivers of steatosis are identified, then this is consistent with a combination etiology
MetALD	MASLD and increased alcohol intake: 20-50 g/day (females); 30-60 g/day (males)
Alcohol Associated (Alcohol related liver disease-ALD)	Alcohol intake > 50 g/day (females) and > 60 g/day (males)
Specific etiology SLD	(1) Drug-induced liver injury; (2) Monogenic diseases: Lysosomal acid lipase deficiency, Wilson disease, hypo-betalipoproteinemia, inborn errors of metabolism; and (3) Miscellaneous: Celiac disease, HIV, malnutrition, HCV
Cryptogenic SLD	Those with no identifiable cause (cryptogenic SLD) may be re-categorized in the future pending developments in our understanding of disease pathophysiology

MASLD: Metabolic dysfunction-associated steatotic liver disease; MetALD: Metabolic and alcohol related/associated liver disease; ALD: Alcohol related liver disease; SLD: Steatotic liver disease; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus.

Table 2 Cardio-metabolic risk factors

Risk factors	Cut-off values
BMI	BMI > 25 kg/m^2 (23 in Asia) or waist circumference > 94 cm (males)/ > 80 cm (females) or ethnicity-adjusted
Fasting serum glucose	Fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) or 2-h post-load glucose levels ≥ 7.8 mmol/L (≥ 140 mg/dL) or HbA1c ≥ 5.7% (39 mmol/L) or T2DM or treatment for T2DM
Blood pressure	Blood pressure 130/85 mmHg or specific antihypertensive drug treatment
Plasma triglycerides	Plasma triglycerides ≥ 1.70 mmol/L (≥ 150 mg/dL) or lipid lowering treatment
Plasma HDL cholesterol	Plasma HDL cholesterol ≤ 1.0 mmol/L (≤ 40 mg/dL) (males) and ≤ 1.3 mmol/L (≤ 50 mg/dL) (females) or lipid lowering treatment

BMI: Body mass index; T2DM: Type 2 diabetes mellitus; HDL: High-density lipoproteins.

genesis, have led to the identification of a series of therapeutic targets, from those used to treat diseases that contribute to its development and progression (*i.e.*, antidiabetic agents) to drugs targeting liver inflammation and fibrosis.

The first to be studied were metabolic targets: Insulin resistance, adipose tissue dysfunction, lipid flux in the liver, and de novo lipogenesis.

Historical studies were conducted on the effects of the PPAR γ agonist pioglitazone on the NAFLD activity score (NAS) or other histological components of NASH improvements[9,10]. Then, other PPAR agonists (PPAR α agonist, pemafibrate, dual PPAR γ and PPAR α, saroglitazar, dual PPAR α and PPAR δ, elafibranor and pan-PPAR agonist, lanifibranor) were tested, with wide-ranging results from no improvement at all to improvements in NASH histology[11].

Certain other drugs lead to improvements in NASH as they improve insulin resistance and cause weight loss[12,13], while others have a direct effect on the liver[14,15].

Categories of drugs that aim to control the mechanisms of cell death and inflammation resulting from lipotoxicity, such as chemokine antagonists, anti-apoptotics or VAP1 inhibitors (NCT04897594), are currently under study or have been discontinued, such as c-Jun N-terminal kinase inhibitors (NCT04048876)[16].

Another class of drugs are antifibrotics which act directly on the fibrogenic process. Unfortunately, these drugs (*i.e.*, simtuzumab, belapectin, emricasan) have not produced good results in clinical trials. This may be due to two reasons: Firstly, because they have been used on patients with very advanced stage fibrosis and cirrhosis, and, secondly, because antifibrotic action alone, without blocking the inflammatory condition present in NASH, may be insufficient[16].

FXR agonists, and in particular obeticholic acid (OCA), a semi-synthetic chenodeoxycholic acid analogue, have been tested in several clinical trials, with the most important being a multicenter, randomized, placebo-controlled phase 3 trial whose interim analysis showed that 25 mg OCA significantly improved fibrosis and key components of NASH disease activity among patients with NASH[17]. However, in a very recent 48-week trial of a highly potent non-bile acid FXR agonist, Tropifexor, no improvement in fibrosis or resolution of NASH relative to placebo was observed[18].

The involvement of thyroid hormone receptor beta in the regulation of lipid metabolism and insulin sensitivity has led to the use of thyroid hormone receptor beta agonists in trials in NAFLD patients. Resmetirom is the most frequently used, with promising results, and a double-blind placebo controlled randomized phase 3 study to evaluate whether Resmetirom resolves NASH and/or reduces fibrosis on liver biopsy and prevents progression to cirrhosis and/or advanced liver disease in patients with NASH and fibrosis (MAESTRO-NASH) is still ongoing.

Finally, among the newer antidiabetic drugs that work on the pathophysiological mechanisms shared by T2DM and MASLD, sodium-glucose cotransporter (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1RAs) have long been studied. In particular, SGLT2 inhibitors, developed for the management of T2DM due to their beneficial

Table 3 Clinical trials with glucagon-like peptide 1 receptor agonists dual therapy

Molecule and trial	Primary aim	Type of study	Duration of therapy	State of recruitment	Main results
Cotadutide (GLP-1/glucagon receptor agonist)[28]	To evaluate the effects of cotadutide on hepatic and metabolic parameters in participants with overweight/obesity and type 2 diabetes	Randomized, phase 2b study	54 weeks	Completed	Improved glycemic control and weight loss, improvements in hepatic parameters
Cotadutide (GLP-1/glucagon receptor agonist), NCT04019561	To evaluate the safety (including hepatic safety), tolerability and pharmacodynamic effects of two dosage levels of cotadutide in obese subjects with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis	Randomized, double-blind, placebo-controlled, phase 2 study		Completed	
Tirzepatide (GIP/GLP-1 receptor agonist)[30]	To determine the effect of tirzepatide on biomarkers of non-alcoholic steatohepatitis and fibrosis in patients with type 2 diabetes	Post hoc analysis in a phase 2 trial	26 weeks	Completed	Higher tirzepatide doses significantly decreased non-alcoholic steatohepatitis-related biomarkers and increased adiponectin in patients with type 2 diabetes
Tirzepatide (GIP/GLP-1 receptor agonist)[31]	To characterize the changes in liver fat content, volume of visceral adipose tissue, and abdominal subcutaneous adipose tissue in response to tirzepatide or insulin degludec in a subpopulation of the SURPASS-3 study	Randomized, open-label, parallel-group, phase 3 study	52 weeks	Completed	Significant reduction in liver fat content and visceral adipose tissue and abdominal subcutaneous adipose tissue volumes compared with insulin degludec in this subpopulation of patients with type 2 diabetes in the SURPASS-3 study
Tirzepatide, (GIP/GLP-1 receptor agonist), NCT04166773 (SYNERGY-NASH)	To determine whether tirzepatide, administered once weekly, is safe and effective as a treatment for non-alcoholic steatohepatitis	Randomized, double-blind, placebo-controlled phase 2 study	52 weeks	Completed	
Efinopegdutide (GLP-1/glucagon receptor co-agonist)[32]	To assess the effects of the GLP-1/glucagon receptor co-agonist efinopegdutide relative to the selective GLP-1 receptor agonist semaglutide on liver fat content in patients with non-alcoholic fatty liver disease	Randomized, phase 2a, active-comparator-controlled, parallel-group, open-label study	24 weeks	Completed	In patients with non-alcoholic fatty liver disease, treatment with efinopegdutide 10 mg weekly led to a significantly greater reduction in liver fat content than semaglutide 1 mg weekly

GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide.

effects on glycemic control, have now entered the guidelines for the treatment of heart failure thanks to their action on sodium homeostasis and water retention[19]. As a consequence of their role in the treatment of MetS, to date several studies have been conducted to evaluate the efficacy of SGLT2 inhibitors in the treatment of NAFLD, with significant heterogeneity of end points and results, but most of them have been proven to be efficient in reducing liver fat content (LFC), aspartate aminotransferase/alanine aminotransferase levels, and even liver stiffness[20].

GLP-1 is an incretin synthesised by the intestine that induces the release of insulin from pancreatic beta cells in response to blood glucose levels, suppresses glucagon production, delays gastric emptying and decreases appetite, thus contributing to glycemic homeostasis[21]. GLP-1RAs have recently become one of the cornerstones of T2DM and obesity treatment.

As a consequence, considering the hypothetical role of antidiabetic drugs with weight loss against steatosis, several studies have been conducted on the use of GLP-1RAs in NASH patients. In particular, a randomized controlled trial (the LEAN trial) in 52 patients with NASH found that liraglutide reduced steatosis and hepatocyte ballooning[22].

Moreover, in a phase 2 study, semaglutide at a dosage of 0.4 mg was shown to reduce NASH when compared to placebo (59% *vs* 17%, $P < 0.001$), but had no effect on fibrosis[23]. A randomized, placebo-controlled trial that included 71 patients with compensated cirrhosis related to NASH, showed that high-dose (2.4 mg) semaglutide is safe; however, it did not improve fibrosis or increase NASH resolution rates compared to placebo[23,24]. A meta-analysis of randomized controlled trials found that liraglutide and semaglutide improved MRI-assessed steatosis, the histological signs of NASH, but confirmed no improvement in fibrosis[25].

Furthermore, recent studies have revealed that the use of GLP-1 agonists in cirrhotic diabetic subjects reduces mortality from all causes, from cardiovascular diseases and the probability of decompensated cirrhosis, both when comparing the population taking GLP-1RAs with non-using patients[26] and when compared with patients taking dipeptidylpeptidase-4 inhibitors or sulfonylureas[27].

Starting from these premises, it has been hypothesized that combination therapy with drugs having complementary mechanisms could be more beneficial (Table 3), and clinical trials have been launched to prove this. For example, Cotadutide, a dual GLP-1 and glucagon receptor agonist, has been studied in overweight or obese and T2DM subjects [15], and is now under development for NASH (NCT04019561).

Tirzepatide, a novel dual incretin receptor agonist (twincretin) acting on both GLP-1 and GIP receptors, has demonstrated superior efficacy on HbA1c and body weight improvements in T2DM than incretins alone[28]. Tirzepatide has also been studied in a post hoc analysis in a phase 2 trial, proving its positive effect on biomarkers of NASH and liver fibrosis in T2DM individuals[29]. In a sub-study of the SURPASS-3 trial (SURPASS-3 magnetic resonance imaging study), tirzepatide promoted a significant reduction in LFC when compared with insulin degludec[30], and it is being used in the ongoing trial, "A study of Tirzepatide (LY3298176) in participants with non-alcoholic steatohepatitis (NASH) (SYNERGY-NASH)", NCT04166773, which has been recently completed.

Finally, a very recent paper evaluated the efficacy and safety of efinopegdutide (a GLP-1/glucagon receptor co-agonist) in patients with NAFLD, demonstrating in a phase IIa randomized active-comparator-controlled parallel-group open-label study, the superiority of treatment with efinopegdutide in terms of reducing magnetic resonance imaging-estimated LFC than semaglutide in patients with NAFLD[31].

CONCLUSION

We agree with Yin *et al*[32] that GLP-RA monotherapy does not perform well as an antifibrotic therapy, but we also have to consider its proven efficacy in reducing LFC and controlling the risk factors of MetS. It is undeniable that combination therapy looks like the most promising strategy, with ongoing clinical trials that will give us answers regarding the possible indications in MASLD, at least in its early phases. In any case, tailoring the use of combination therapy to the individual patient, according to disease stage and co-morbidities, will also be a challenge in the near future and further exploration of the mechanisms of action of these drugs will be crucial to track future research directions.

FOOTNOTES

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Country of origin: Italy

ORCID number: Maurizio Soresi 0000-0001-7850-555X; Lydia Giannitrapani 0000-0003-2845-5296.

Corresponding Author's Membership in Professional Societies: Società Italiana di Ultrasonologia in Medicina e Biologia; Società Italiana di Medicina Interna; Associazione Italiana per lo Studio del Fegato; Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti.

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