

Comparing the Efficacy and Safety of Obeticholic Acid and Semaglutide in Patients With Non-Alcoholic Fatty Liver Disease: A Systematic Review

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Abstract

Patients with non-alcoholic fatty liver disease (NAFLD) have an increased risk of developing progressive fibrosis, cirrhosis, and hepatocellular carcinoma. As of now, there are no FDA-approved treatments for NAFLD/non-alcoholic steatohepatitis (NASH) or its associated fibrosis. Although many drugs are under clinical trial, both obeticholic acid (OCA) and semaglutide are among the few that have reached phase III clinical trials, but they were never compared.

We decided to conduct a systematic review of randomized controlled trials and meta-analyses. A total of 6,589 articles were found after searching PubMed, OVID Embase, OVID Medline, PubMed Central, and clinicaltrials.gov. Only full-text peer-reviewed articles published in the past six years were put through the Cochrane bias assessment tool or the Assessment of Multiple Systematic Reviews (AMSTAR) tool to screen for bias. After strict quality assessment, data from five randomized controlled trials (n=2,694) and three systematic reviews/meta-analysis (n=8,898) was extracted and included.

The data extraction from these studies showed that semaglutide and OCA cause histological improvement, but NASH resolution is exclusive to semaglutide. Although high doses of OCA can cause dyslipidemia and severe pruritus, it is the only therapeutic that causes improvement in NASH-associated hepatic fibrosis. Semaglutide is the safest option among the two and leads to significant weight loss compared to OCA; thus, a better outcome on hepatic steatosis follows. The indications of each of these drugs should be based on the NAFLD activity score and NASH fibrosis stage. OCA should be used with caution among patients with hyperlipidemia and ischemic heart disease as it may make these conditions worst.

Categories: Internal Medicine, Gastroenterology, Other

Keywords: non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, obeticholic acid, semaglutide, liver fibrosis, chenodeoxycholic acid, glucagon-like peptides

Introduction And Background

According to a Markov model, in the USA, predictions show that non-alcoholic fatty liver disease (NAFLD) will have a 21% increase from the years 2015 to 2030, leading to a 33.5% presence by 2030 [1]. By the year 2030, this 63% surge in non-alcoholic steatohepatitis (NASH) cases will lead to a 168% surge in patients with decompensated cirrhosis and a 137% surge in patients developing hepatocellular carcinoma [1].

Steatohepatitis and fatty liver disease can have various etiologies, but to be classified as NAFLD, other causes of steatosis must be excluded, such as alcohol consumption [2]. NAFLD is characterized by hepatic steatosis or buildup of fat in the liver [2]. NASH is an advanced stage of NAFLD characterized by steatosis and findings of liver cell injury with inflammation leading to fibrosis [2]. The early stage of NAFLD is non-alcoholic fatty liver, which is generally a benign, non-progressive disease [2]. The hepatocellular injury in NASH is caused by an increase in metabolic substrates (glucose, fructose, and fatty acids), leading the fatty acids to participate in pathways that cause cellular injury and a poor response to that injury [3]. The pathogenesis of this disease is largely associated with obesity, type 2 diabetes, and increasing age [3]. NAFLD has been projected to become the most common cause of liver transplantation within a decade [3]. We created Figure 1 in order to summarize the progression of NAFLD and its related features.

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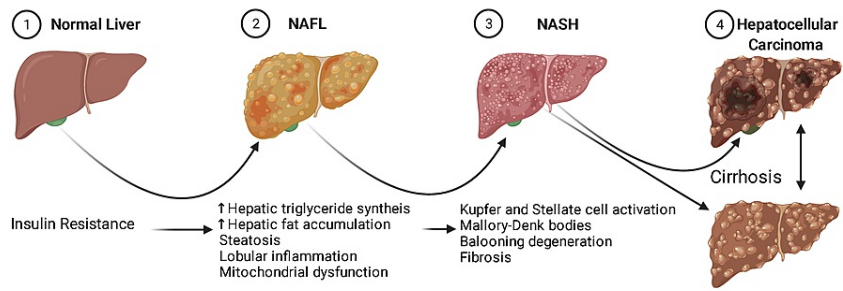


FIGURE 1: NAFLD progression sequence

NAFL, non-alcoholic fatty liver; NASH: non-alcoholic steatohepatitis

The figure is authors' original illustration

Multiple clinical trials are in progress and have been conducted to find an approved medical treatment of NAFLD/NASH [4]. Currently, no FDA-approved medications are listed for NAFLD or NASH and its associated fibrosis [5]. Lifestyle changes are recommended, with studies showing that losing around 10% of body weight may lead to resolution and regression of NASH [6]. Among all the drugs being assessed for the treatment of NAFLD, no single one has shown the right combination of effects and safety required to be considered for FDA approval [7].

Semaglutide, a GLP-1 (glucagon-like peptide 1) agonist, is a well-researched FDA-approved drug for type 2 diabetes in 2019 and chronic weight management in 2021. Semaglutide has become a drug of interest for NASH since many studies show a decrease in alanine transaminase (ALT) and high-sensitivity C-reactive protein (hs-CRP) in patients diagnosed with type 2 diabetes and obesity [8]. Obeticholic acid (OCA) is a semi-synthetic analog derived from chenodeoxycholic acid, a natural ligand for the Farnesoid X receptor (FXR) [9]. OCA causes a decrease in inflammatory cell infiltration and fibrosis due to the reduction in hepatic monocyte chemoattractant protein-1 (MCP-1) mRNA [10]. OCA is approved by the FDA for the treatment of primary biliary cholangitis. Due to its anti-fibrotic, anti-cholestatic, and anti-inflammatory properties, OCA is currently under a six-year-long phase III clinical trial regarding its therapeutic effects in NASH [10]. Both of these drugs have gone through extensive trials and analyses in regard to NAFLD. Although lifestyle changes are critical, it is not always possible, making additional therapeutic agents necessary to combat this upcoming pandemic of NAFLD. Due to the lack of any FDA-approved treatment, we decided to perform a systematic review to assess the safety and efficacy of semaglutide and OCA in patients with NAFLD to reduce liver fibrosis and resolution.

Review

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and principles were used to design this systematic review and report its results, with a full breakdown shown in Figure 2 [11].

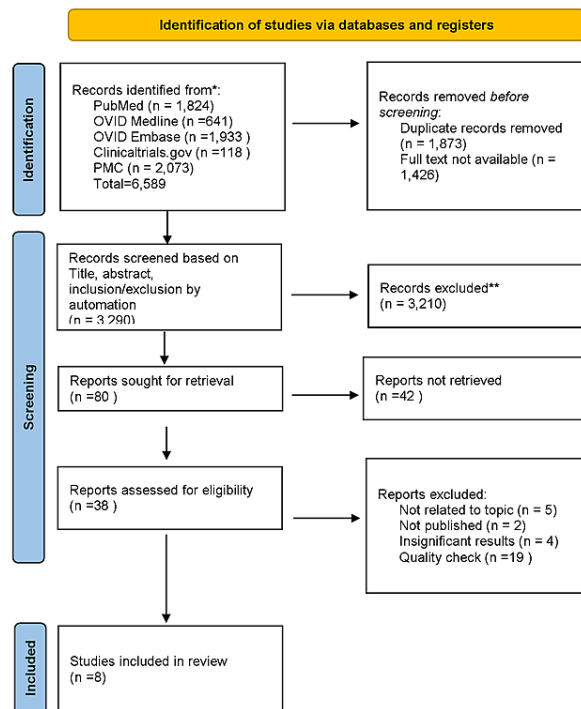


FIGURE 2: PRISMA 2020 flow chart

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Search strategy

We used major literature databases, including PubMed, OVID Embase, OVID Medline, PubMed Central, and clinicaltrials.gov. When searching, we used appropriate keywords and the Medical Subject Headings (MeSH) thesaurus to find relevant articles mentioning OCA or semaglutide's efficacy and safety in treating NASH.

For our literature search, the keywords used were "Obeticholic acid," "Semaglutide," "Non-alcoholic fatty liver disease," "Liver Fibrosis," "GLP-1 agonist". Using PubMed Central, we searched for their corresponding MeSH terms. The combined MeSH terms for all of the aforementioned keywords are as follows: Non-alcoholic fatty liver disease OR NAFL OR NAFLD OR metabolic associated fatty liver disease OR MAFLD OR non-alcoholic steatohepatitis OR NASH OR ("Non-alcoholic Fatty Liver Disease/drug therapy"[Majr] OR "Non-alcoholic Fatty Liver Disease/prevention and control"[Majr]) AND Obeticholic acid OR Ocaliva OR ("Chenodeoxycholic Acid/administration and dosage"[Majr] OR "Chenodeoxycholic Acid/adverse effects"[Majr] OR "Chenodeoxycholic Acid/therapeutic use"[Majr] OR "Chenodeoxycholic Acid/toxicity"[Majr]) AND GLP-1 agonist OR Ozempic OR Semaglutide OR ("Glucagon-Like Peptides/administration and dosage"[Majr] OR "Glucagon-Like Peptides/adverse effects"[Majr] OR "Glucagon-Like Peptides/therapeutic use"[Majr] OR "Glucagon-Like Peptides/toxicity"[Majr]).

For OVID Medline and OVID Embase, we used the following keywords combined with Booleans: Non-alcoholic fatty liver disease OR NAFL OR NAFLD OR metabolic associated fatty liver disease OR MAFLD OR non-alcoholic steatohepatitis OR NASH AND Obeticholic acid OR Ocaliva OR Farnesoid X Receptor Agonists AND GLP-1 agonist OR Ozempic OR Semaglutide. For clinicaltrials.gov, we used "NAFLD."

After compiling the papers using the search strategy, we screened each paper. We removed duplicates, went through the title and abstracts, and only selected full-text papers after applying the detailed eligibility criteria. If the full-text article was not extracted, the paper was removed.

Inclusion and exclusion criteria

We selected articles published within the past six years (2015-2021) in English. We filtered to include only peer-reviewed randomized controlled trials (RCTs) and meta-analysis to have the most accurate and up-to-date information. Grey literature was not used, and only full-text articles were considered.

Analysis of quality of each study and data extraction

Each paper was screened using a quality appraisal tool. The systematic reviews/meta-analyses were screened using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Table 1).

| AMSTAR Criteria (Yes, No, Uncertain) | Kulkarni et al., 2021 [10] | Majzoub et al., 2021 [7] | Mantovani et al., 2021 [12] |
|---|----------------------------|--------------------------|-----------------------------|
| A priori design | Uncertain | Uncertain | Uncertain |
| Duplicate study selection and data extraction | Uncertain | Yes | Uncertain |
| Literature search | Yes | Yes | Yes |
| Status of publication | Yes | Yes | Yes |
| List of studies | Yes | Yes | Yes |
| Characteristics of included studies | Yes | Yes | Yes |
| Scientific quality | Yes | Yes | Yes |
| Formulation of conclusion | Yes | Yes | Yes |
| Method used to combine findings | Yes | Yes | Yes |
| Likelihood of publication bias | Yes | Yes | Yes |
| Conflict of interest | Yes | Yes | Yes |
| Our evaluation | 9/11 (medium quality) | 10/11 (high quality) | 9/11 (medium quality) |

TABLE 1: AMSTAR tool

AMSTAR, Assessment of Multiple Systematic Reviews

The RCTs were screened using the Cochrane bias assessment tool (Table 2).

| Cochrane Criteria (Yes, No, Uncertain) | Baekdal et al., 2018 [13] | Flint et al., 2021 [14] | Neuschwander-Tetri et al., 2015 [15] | Newsome et al., 2021 [16] | Younossi et al., 2019 [17] |
|---|---------------------------|-------------------------|--------------------------------------|---------------------------|----------------------------|
| Adequate sequence generation? | Yes | Yes | Yes | Yes | Yes |
| Allocation concealment used? | Uncertain | Uncertain | Uncertain | Yes | Uncertain |
| Blinding? | Yes | Yes | Yes | Yes | Yes |
| Are concurrent therapies similar? | No | Yes | Yes | Yes | Yes |
| Incomplete outcome data addressed? | Yes | Yes | Yes | Yes | Yes |
| Uniform and explicit outcome definitions? | Yes | Yes | Uncertain | Yes | Yes |
| Free of selective outcome reporting? | Yes | Yes | Yes | Yes | Yes |
| Free of other bias? | Yes | Yes | Yes | Yes | Yes |
| Overall risk of bias? | Yes | Yes | Yes | Yes | Yes |
| Our Evaluation | 7/9 (medium quality) | 8/9 (high quality) | 8/9 (high quality) | 9/9 (high quality) | 8/9 (high quality) |

TABLE 2: Cochrane bias assessment tool

The papers were then rated from a range of high, medium, or low quality. Only the papers that were rated as medium or high quality were used. The other medium-quality papers that did not meet our quality appraisal were used in basic concept explanations of our paper. We then extracted information related to both drugs' safety and efficacy, comparing and contrasting information from each selected study.

Results

Our initial search yielded 6,589 articles. Out of these, we removed duplicates (n=1,873) and those without the full text available (n=1,426). We were left with 3,290 articles. Next, we screened the articles based on title, abstract, inclusion/exclusion criteria manually and by automation (n=3,290). This screened out 3,210 articles, leaving 80 articles that we sought for full-text retrieval. The full text of 42 of these articles was not retrieved, leaving us with 38 articles. Finally, after a thorough review using strict quality checks and inclusion criteria, we included eight articles in our systematic review.

Our systematic review contains four RCTs, one interim analysis of an ongoing phase III RCT, and three systematic reviews with meta-analysis that include either semaglutide or OCA's efficacy or safety in treating patients with NAFLD or hepatic impairment. All the analyzed articles have a population of confirmed NASH/NAFLD patients except one of the RCTs examining the safety of semaglutide in patients with hepatic impairment. Refer to Table 3 for the individual study breakdown.

| Study/Year | Location | Study Type | Drugs Used/Patient Group | Result | Conclusion | Total Patient Population/Comorbidities |
|----------------------------|----------|----------------------------------|---------------------------------|---|---|--|
| Kulkarni et al., 2021 [10] | India | Systematic review, meta-analysis | OCA in patients w/ NASH | 25 mg and 10 mg of OCA showed histological improvement. Increased the risk of pruritus mainly from 25-mg dose. No steatosis improvement was shown. Improved ELF score, thus improving fibrosis. | 25 mg of OCA may be more potent and effective for NASH resolution, but 10 mg of OCA is the adequate alternative due to AEs. | 2,834 |
| Majzoub et al., | | Systematic review, | OCA, pioglitazone, semaglutide, | RCTs show that OCA was superior to placebo in ≥ one stage improvement in | Therapies that improve NASH resolution be | |

| | | | | | | |
|--------------------------------------|---------|--|--|---|---|--|
| 2021 [7] | USA | meta-analysis | liraglutide in patients w/ NASH | fibrosis. Network meta-analysis showed that semaglutide was ranked the most effective for NASH resolution | combined with therapies that have an anti-fibrotic effect should be assessed. | 5,129 |
| Mantovani et al., 2021 [12] | Italy | Systematic review, a meta-analysis | GLP-1 receptor agonists in patients w/ NAFLD or NASH | No significant AE. Increased frequency of GI symptoms. Decreased liver fat content assessed using MRI or MRS was up to 32%. Significant improvement of hepatic steatosis. Semaglutide showed histological resolution of NASH with no worsening fibrosis. | MRI and liver histology proves that GLP-1 receptor agonist improves NAFLD. If confirmed through larger phase III RCTs with liver biopsy, therapy should be considered. | 935 |
| Baekdal et al., 2018 [13] | Denmark | RCT | Oral semaglutide in patients w/ hepatic impairment and w/o hepatic impairment | Headache was the most frequently reported AE (14.3%) along with GI symptoms: hypoglycemic episodes also occurred w/ glucose level of 70 mg/dL reported in a few patients. | Patients tolerated oral semaglutide well. AEs are not significant. | 56 patients total. 6 patients w/ type 2 diabetes, 12 in CTP class A, 12 in CTP class B, and 8 in CTP class C |
| Flint et al., 2021 [14] | Denmark | Phase I RCT | Subcutaneous semaglutide 0.4 mg in patients w/ NAFLD | Reductions in liver steatosis were significantly greater with semaglutide at weeks 24, 48, and 72. Decreased liver enzymes, body weight, and HbA1c. Decreased appetite and nausea were reported. | Didn't have a significant impact on liver stiffness. Decreased steatosis, along with w/ decreased liver enzymes and metabolic parameters, shows a good impact on disease activity. | 67 total. 48 patients w/ type 2 diabetes and 62 patients classified obese |
| Neuschwander-Tetri et al., 2015 [15] | USA | Phase IIb RCT | OCA in patients ≥ 18 years old. Liver biopsy proven NASH or borderline NASH, NAFLD activity score ≥ 4. | 45% of patients improved liver histology. The resolution was the same with a placebo. Increased serum cholesterol and LDL w/ decrease in HDL and decrease in serum ALT and AST. Weight loss and decreased systolic BP. AE: pruritus, hyperglycemia, dysarthria, dizziness, and insulin resistance | OCA improves histological features of NASH, but long-term safety requires further investigation. May increase risk of atherogenesis. More trials are needed on the resolution of NASH from OCA. | 283 total. 149 patients w/ type 2 diabetes and 173 patients w/ hyperlipidemia |
| Newsome et al., 2021 [16] | UK | Phase II RCT | Subcutaneous semaglutide patients with biopsy-confirmed NASH and liver fibrosis of stage F1, F2, or F3 | 40% of patients achieved NASH resolution without worsening of fibrosis. Improvement in fibrosis stage occurred in 43%, 13% mean weight loss occurred in those receiving 0.4 mg. GI disturbances were higher in 0.4 mg. Malignant neoplasms were reported in three patients. | Semaglutide causes NASH resolution. Improvement in fibrosis is not substantial since the placebo group also improved. | 320 total. 199 patients w/ type 2 diabetes. Mean BMI: 35.8. |
| Younossi et al., 2019 [17] | USA | Ongoing RCT phase III interim analysis | OCA 10 mg or OCA 25 mg in patients w/ definite NASH. NAFLD activity score of ≥4 and liver fibrosis of stage F2/F3. | OCA 25 mg significantly improved fibrosis. Clinically significant histological improvement was noted. | Likely to predict clinical benefit. Indicated for patients with advanced fibrosis. | 931 total. 517 patients w/ type 2 diabetes. 633 patients w/ dyslipidemia. |

TABLE 3: Breakdown of individual studies included in the review

AE, adverse effects; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CTP, Child-Turcotte-Pugh classification; ELF, enhanced liver fibrosis; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; RCT, randomized controlled trial

Obese: BMI ≥ 30 kg/m²

Both OCA and semaglutide effectively improve histology of the liver as assessed by the NAFLD activity score

(NAS) [10,12]. Semaglutide achieved NASH resolution without worsening fibrosis, while OCA failed to do so [15,16]. OCA is highly effective in improving liver fibrosis caused by NASH, whereas semaglutide is only effective in halting fibrosis progression [10,17]. Semaglutide achieved greater weight loss than OCA without a significant rebound weight gain after drug cessation [12,15-17]. The adverse effects (AEs) of semaglutide are non-significant at any dose, with headache and loss of appetite being the most frequently reported AE followed by gastrointestinal (GI) symptoms: dyspepsia, vomiting, decreased appetite, and diarrhea [13]. OCA comes with its own set of AE, making its use rather controversial. These can include severe pruritus, hyperglycemia, dysarthria, dizziness, and insulin resistance [15]. One of the most significant AE is decreased hepatic lipogenesis, leading to increased total cholesterol and low-density lipoprotein (LDL) [15].

Discussion

Both semaglutide and OCA are among the few promising drugs that have the potential of becoming FDA-approved for NAFLD therapy. This is the first systematic review to compare the efficacy and safety of semaglutide and OCA regarding NAFLD to the best of our knowledge. NAFLD/NASH has become the most common etiology of chronic liver disease (CLD) worldwide [18]. The development of cirrhosis (due to fibrosis) is predictive of a poor prognosis of liver-related morbidity and mortality [18,19]. The prevention or decrease in fibrosis may keep the patient from developing cirrhosis and CLD [19]. Some risk factors of NASH are controllable, including obesity and type 2 diabetes, making lifestyle changes a viable option. The same cannot be said about patients with uncontrollable risk factors and those who are unable to make the lifestyle changes required.

Mechanism of Action of Semaglutide and Obeticholic Acid

NAFLD is caused by an increased accumulation of lipids, leading to hepatic lipotoxicity. In patients with insulin resistance, most of the free fatty acid (FFA) pool comes from adipose tissue lipolysis along with minor amounts from the diet or lipogenesis. These FFAs will be oxidized and become triglycerides, and this increased accumulation may lead to steatosis or get secreted as very LDL [19]. Hepatic stellate cells help mediate the fibrosis associated with NASH, causing type I collagen and connective tissue growth factor expression [20]. In patients with excessive abdominal adipose tissue, there is an increased production and release of inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6, resulting in a cycle of inflammation and toxicity, leading to further fibrosis [20].

Semaglutide is a GLP-1 receptor agonist, primarily used for type 2 diabetes and weight loss [21]. It activates the peroxisome proliferator-activated receptor (PPAR- α) of the liver, which decreases the production of apolipoprotein-C and breaks down fat in plasma and triglycerides [20,21]. The activation of this receptor may also cause delayed gastric emptying. Overall, this improves lipid metabolism and prolongs the feeling of satiety, decreasing waist circumference. The waist circumference is directly proportional to insulin resistance. The pancreatic islet β and Δ cells express GLP-1 receptors to control insulin [21]. Therefore, semaglutide causes an increase in insulin production and secretion with a decrease in glucagon secretion.

Semaglutide is administered subcutaneously at doses of 0.1 mg, 0.2 mg, or 0.4 mg for NAFLD/NASH. It can also be taken orally but is not as effective. According to a study, the oral form of semaglutide was not as effective as 0.5 mg and 1.0 mg of subcutaneous semaglutide in reducing weight [22].

OCA is a semi-synthetic, modified bile acid derived from chenodeoxycholic acid [23]. OCA is primarily used for the treatment of primary biliary cholangitis. It is a highly selective agonist of the FXR found in the liver, kidney, adrenal glands, and intestines [24]. Lipophilic bile acids have been known to regulate metabolism and insulin sensitivity. When lipophilic bile acids are attached to the FXR, insulin sensitivity is increased along with a decrease in hepatic gluconeogenesis and serum triglycerides [15]. FXR activation causes expression of the hepatic scavenger receptors (SRB1), which increases HDL clearance [15]. The mechanism of OCA decreasing hepatic fibrosis in humans is unclear. FXR's agonists regulate the production of bile acids by causing the release of fibroblast growth factor-19, which suppresses cholesterol 7-alpha-hydroxylase (CYP7A1), preventing cholesterol conversion to bile acid [25]. This can cause unwanted AEs such as hyperlipidemia and an increase in LDL.

Comparing Both Semaglutide and Obeticholic acids Efficacy on NAFLD/NASH Patients

Many therapeutic categories are sought out in regard to NASH. These can include NASH resolution without worsening fibrosis, decrease in METAVIR fibrosis stage (liver stiffness), decrease in NAS (histological improvement), and weight loss. We created Figure 3 to outline the mechanism of action and effects of both drugs. We broke down each of these categories and compared each drug based on the selected studies.

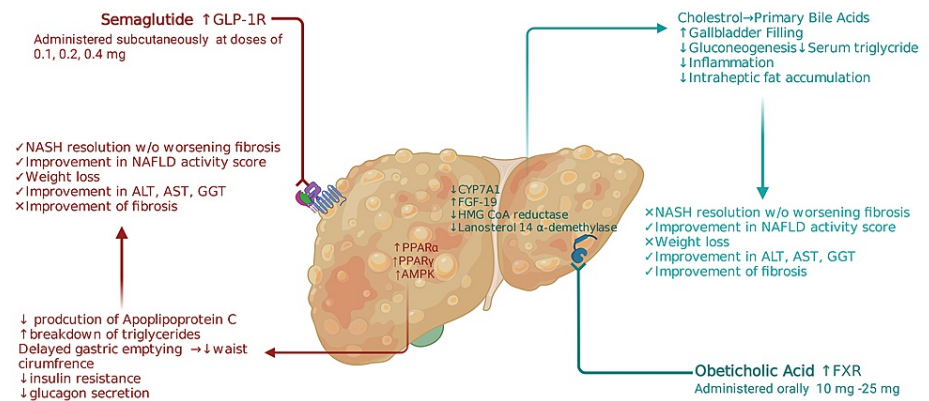


FIGURE 3: Mechanism of action and effects on NAFLD/NASH

ALT, alanine aminotransferase; AMPK, activated protein kinase; AST, aspartate aminotransferase; CYP7A1, cholesterol 7 alpha-hydroxylase; FXR, Farnesoid X receptor; FGF-19, fibroblast growth factor 19; GGT, gamma-glutamyl transpeptidase; GLP-1R, glucagon-like peptide 1 receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor

Authors' original illustration

NASH resolution without worsening of fibrosis

Resolution of NASH entails histological absence of hepatocyte ballooning with decreased or absence of inflammation [26]. OCA was assessed in a multicenter phase IIb RCT of 283 patients compared to a placebo group [15]. There was a lack of resolution of NASH with similar rates as the placebo group. But according to Younossi et al.'s interim analysis at 18 months, OCA 25 mg achieved NASH resolution twice as much as the placebo group [17]. Although still ongoing, we believe that the phase III RCT interim analysis findings should be taken into consideration since it was a longer study and more recent. The difference in results may be due to bias in a pathologist post hoc analysis conducted in the ongoing phase III RCT.

In 2021, Newsome et al. conducted a phase II double-blind RCT in biopsy-confirmed NASH patients comparing the efficacy of subcutaneous semaglutide 0.1, 0.2, and 0.4 mg with a placebo group. Among patients with F2/F3 fibrosis, NASH resolution without worsening fibrosis was highest in the 0.4 mg group [16]. According to a recent meta-analysis, both liraglutide and semaglutide showed evidence of NASH resolution [12]. In Majzoub et al.'s network meta-analysis forest plot, both OCA and semaglutide were given a SUCRA (surface under the cumulative ranking curve) score in regard to their efficacy in resolution of NASH. Among 20 other possible therapeutics, subcutaneous semaglutide 0.4 mg was given the highest SUCRA score of 89%, whereas OCA was only about half of that [7]. Semaglutide is the most effective for NASH resolution, but there is a lack of concrete evidence that OCA leads to NASH resolution.

Fibrosis stage and liver stiffness

Fibrosis improvement is a crucial part of NASH therapy. Magnetic resonance imaging proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE) are two imaging techniques that assessed liver stiffness and steatosis in Flint et al.'s study on the effects of semaglutide [14]. The stages can vary from stage 0-4, no fibrosis to cirrhosis, respectively [27]. According to the study, there was no significant improvement in liver stiffness compared to placebo [14]. In another RCT involving 320 patients taking subcutaneous semaglutide, groups did not significantly reduce fibrosis either [16]. Although semaglutide may not improve fibrosis, the studies consistently indicated protection against worsening fibrosis [14,16]. In both studies, majority of patients had either type 2 diabetes or obesity, with semaglutide improving both of these conditions.

OCA has been found to be the only drug to significantly impact fibrosis in multiple studies [7,10,15,17]. The phase III RCT interim analysis at 18 months that included 1,968 patients was long enough to assess this relatively slow process. In Kulkarni et al.'s meta-analysis funnel plot, 25 mg of OCA showed significantly better fibrosis improvement than the placebo group with an odds ratio of 1.95 and a small confidence interval [10]. These results are consistent with other RCTs and systematic reviews, making OCA a highly effective candidate for NASH fibrosis stage improvement. OCA 10 mg is also sufficient enough to improve fibrosis and should be the recommended dose for NASH since OCA 25 mg does substantially increase the risk of AEs.

NAFLD activity score (NAS)

The NAS helps distinguish NASH from NAFL along with any significant changes in histology [28]. Both drugs

showed a significant improvement in NAS.

Studies assessing semaglutide's efficacy indicated an improvement of the NAS (≥ 1), with similar effects found in all doses [12,14,16]. We believe that this was due to the combined effect that GLP-1 receptor agonists have on weight loss and insulin resistance. Newsome et al.'s RCT showed that almost all patients receiving subcutaneous semaglutide had ≥ 1 improvement in the NAS [16].

According to two RCTs, OCA is also effective in improving histology and NAS [15,17]. These studies broke down each category of the NAS and the histological improvement associated. It is rather odd that OCA has shown an improvement in NAS but failed to reach NASH resolution. We believe that NAS is not a good indicator for NASH resolution and rather a scale of severity of the disease.

Weight loss

The only FDA-approved therapy for NAFLD/NASH is lifestyle changes leading to weight loss. Studies have shown that 7-10% of weight reduction may lead to regression of fibrosis and a significant decrease in liver enzymes, liver steatosis, and fibrosis [14,29,30]. One would expect medication-induced weight loss to have a similar effect. This weight loss is not ideal because weight gain after cessation of medication is probable.

On average, GLP-1 RAs can cause 4-5 kg of weight loss and continue up to week 44 of the regimen [12,16]. These findings were unexpected since regression of fibrosis did not occur even though weight loss was significant.

OCA caused weight loss of approximately 2% and significantly rebounded after treatment discontinuation [15,17]. With obesity being one of the most common associations, OCA failed to show promising results in this essential therapy category. This amount is lower than expected when considering the decrease in liver enzymes and significant liver histology (NAS) improvement.

Adverse Effects of Obeticholic Acid and Semaglutide in Patients With NASH or Hepatic Impairment

Many clinical trials have been conducted assessing the safety of these drugs, but very few contain the long-term clinical effects of OCA on cardiovascular health. The safety and AEs of semaglutide change slightly based upon the mode of administration. OCA's AEs substantially change based on increasing dosages.

Among 56 patients with or without hepatic impairment taking oral semaglutide in a multicenter RCT, almost all AEs reported were mild or moderate [12]. According to this study, the most common AE was a headache, but in another RCT assessing subcutaneous semaglutide's safety, headache was not mentioned as a significant AE [13,16]. We believe that this difference in AE is due to the mode of administration. In all other studies regarding the safety of semaglutide, GI effects were reported as the most common AE [16]. The use of semaglutide should be monitored in patients with pre-existing GI conditions. All four of the studies on semaglutide have indicated that semaglutide is a safe well studied therapeutic for NAFLD/NASH patients [12-14,16].

The AEs of OCA are important to consider when assessing a patient for treatment. Higher doses of OCA (25-50 mg) lead to more significant AE; according to Younossi et al.'s interim analysis, OCA 25 mg led to the highest rates of pruritus and hyperlipidemia compared to OCA 10 mg [17]. We believe that both of these are class effects due to the activation of the FXR. Cilofexor is another FXR agonist with pruritus as a common AE [31]. Pruritus may be avoided to a great degree with OCA 10 mg and should be the recommended daily dosage.

It is unknown if OCA-induced hyperlipidemia is associated with cardiovascular mortality. In a phase II RCT, the addition of atorvastatin decreased the LDL and the mean LDL particle concentration levels below baseline in all dosages of OCA [32]. The use of statins along with OCA may help regulate dyslipidemia caused by OCA, making this a safer option for at-risk patients. Other AEs are not significant, and OCA is generally well-tolerated [17]. More research should be done to determine the long-term safety of OCA and its impact on at-risk cardiovascular patients.

According to multiple studies, among patients with NAFLD, approximately 51% are obese and up to 80% have dyslipidemia [33,34]. Therefore, high doses of OCA (25-50 mg) can cause dangerous AEs among the vast majority of NAFLD patients.

Limitations

This systematic review has some potential limitations. There are currently no clinical trials directly comparing the effects and safety of semaglutide with OCA. All the RCTs we selected were assessing each drug individually. Our exclusion criteria did not allow us to use articles that did not contain an abstract, further limiting article selection. Lastly, most studies on NAFLD/NASH do not mention a definitive

diagnostic method used to determine patient selection limiting quality studies.

Conclusions

By comparing the efficacy and safety of semaglutide and OCA, it is evident that each drug is meant for its own specific patient population based on therapy goals and comorbidities. Both therapies improve liver histology and liver enzymes, but other therapeutic effects differed. Semaglutide is most effective for NASH resolution. OCA is unique because of its effects on hepatic fibrosis, which is the biggest predictor of liver mortality in NASH. We would like to see trials of both of these drugs used for their combined therapeutic effects. At high doses, OCA may induce hyperlipidemia and severe pruritus, making its use contradictory toward the risk factors of NASH. If fibrosis improvement is not the mainstay of treatment, then the use of OCA is not advised, especially among patients with risk factors of heart disease. However, our study results show that to minimize these AEs, an OCA regimen should be started at lower doses, and, if required, combining it with a statin or antipruritic. Semaglutide largely differed in this aspect, being unremarkably safe and well-studied both in the long-term and short-term safety. Lifestyle modifications will remain critical, but additional therapeutics will be necessary to combat the projected surge of NAFLD especially among patients with type 2 diabetes or obesity.

Our study consists of data from recent high-quality RCTs and meta-analyses, giving an updated evaluation of the possible future management of NAFLD. We hope this will provide clinicians and the respective regulators with the evidence necessary to move one step closer toward an approved therapeutic.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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