HHS Public Access

Author manuscript

Hepatology. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Hepatology. 2021 October ; 74(4): 2290–2292. doi:10.1002/hep.31886.

The GLP-1 Receptor Agonist Semaglutide for the Treatment of Nonalcoholic Steatohepatitis

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"**A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis (**1**),"** recently published in the *New England Journal of Medicine* (online November 2020) by Newsome et al., is an important investigation of the impact of 72 weeks of the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide compared to placebo in patients with biopsy proven nonalcoholic steatohepatitis (NASH) and liver fibrosis (F1–3). GLP-1 receptor agonists are slightly modified peptides that are resistant to degradation by the dipeptidyl peptidase-4 enzyme but that mimic the effects of endogenous GLP-1, including increasing insulin secretion, decreasing glucagon production and hepatic glucose production, slowing gastric emptying and decreasing appetite (2). Drugs in this class are currently FDA approved for the treatment of type 2 diabetes (T2DM) and for weight loss in individuals both with and without T2DM (3) but are not specifically approved for the treatment of NASH. GLP-1 receptor agonists are a particularly attractive potential therapeutic option in NASH given their beneficial glycemic and weight loss effects.

GLP-1 receptor agonists have previously shown promise for the treatment of NASH, most notably in the "Liraglutide Safety and Efficacy in Patients with Nonalcoholic Steatohepatitis (LEAN) Trial," a randomized, double-blind, phase 2 trial of subcutaneous liraglutide (1.8 mg daily) versus placebo in 52 patients with biopsy-proven NASH (4). This study demonstrated higher resolution of NASH (39% versus 9%, p=0.02) and less fibrosis progression (9% versus 36%, p=0.04) in the context of greater weight loss (−5.5% versus −0.7%, p=0.003) with liraglutide versus placebo without any additional side effects in this patient population. Semaglutide, as administered in the current study, is structurally similar to liraglutide with one additional modification that makes it particularly resistant to degradation and allows once-weekly subcutaneous dosing in contrast to the daily dosing required with liraglutide (2). Studies have demonstrated greater glycemic and weight loss benefits with semaglutide versus liraglutide (1, 2), and it is currently FDA approved to treat T2DM and is dosed via subcutaneous (SC) injection once weekly (starting dose 0.25 mg SC weekly, therapeutic dose 0.5–1 mg SC weekly) or as a once daily oral dose (starting dose 3 mg, therapeutic dosing 7–14 mg daily) (3). However, semaglutide had not previously been studied for the treatment of NASH specifically prior to the current trial.

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Disclosures and conflicts of interest: Dr. Dichtel has received drug donation from Pfizer and scan analysis donation from Perspectum Diagnostics, both by investigator-initiated request.

In the present study, a total of 320 adults ages 18–75 years old with histologic NASH and NAFLD activity score ≥4 both with and without T2DM (HbA1C <10%) were randomized 3:1 to daily subcutaneous semaglutide at 0.1 mg, 0.2 mg or 0.4 mg versus the corresponding placebo dose. The primary endpoint was resolution of NASH without worsening of fibrosis. The secondary endpoint was improvement by one fibrosis stage without worsening of NASH. Biopsies were reviewed by two independent, blinded histopathologists, with relatively low agreement in the composite of all histologic variables (24%) but higher agreement reported across individual components (62–75%). The prespecified analysis, which was established between recruitment and unblinding, limited the primary analysis to the 230 subjects with NASH F2–3 only. The cohort was predominantly Caucasian (78%) and female (61%) with type 2 diabetes (62%) with a mean age and BMI of 55 years and 36 kg/m^2, respectively, and baseline characteristics did not differ between the randomized groups.

The primary endpoint of NASH resolution with no worsening of fibrosis occurred more often in the semaglutide 0.4 mg versus placebo group (59% versus 17%, respectively, $p<0.001$). Notably, while the odds ratios of improvement in NASH appear significant for the 0.1 mg and 0.2 mg semaglutide dose groups versus placebo (OR 3.36, 95% CI 1.29–8.86 and OR 2.71, 95% CI 1.06–7.56, respectively), the authors note that confidence intervals were not adjusted for multiple comparisons and may not be reproducible. Despite the significant improvement in NASH in the 0.4 mg semaglutide group, there was no difference compared with placebo in the confirmatory secondary endpoint of improvement in at least one fibrosis stage with no worsening of NASH, seen in 49% on 0.1 mg, 32% on 0.2 mg, 43% on 0.4 mg semaglutide and 33% on placebo. However, authors did note that fewer participants experienced worsening of fibrosis stage in the semaglutide 0.4 mg dose group versus placebo (5% versus 19%, respectively). This placebo response for fibrosis improvement is higher than that of the LEAN trial (14%) (4) and higher than the mean reported overall in placebo groups of NASH studies by meta-analysis (21±3% with moderate heterogeneity) (5). The particularly high placebo response rate in the improvement in fibrosis (33% placebo response) as compared to the resolution of NASH (17% placebo response) may contribute to the discrepancy in significance between these outcomes in the trial. The authors additionally noted that results for the primary endpoints did not differ when analyzing the full recruited cohort of NASH F1–3 (n=320) or the subset of individuals with type 2 diabetes (n=199). Finally, liver function tests, serum enhanced liver fibrosis (ELF) test and liver stiffness by Fibroscan did improve in the semaglutide groups, again with the caveat that only unadjusted confidence intervals were provided for interpretation of these secondary endpoints.

Side effects in the current study were consistent with those previously reported for the GLP-1 receptor agonists, with no new specific safety signals identified in this population selected for the presence of NASH. As expected, gastrointestinal side effects were reported more commonly in the semaglutide 0.4 mg versus placebo group, with the most frequent being nausea (42% versus 11%, respectively). However, these gastrointestinal side effects did improve over time, and percent of subjects discontinuing the study because of adverse events was only 7% across all doses of semaglutide versus 5% in placebo. The authors also note a higher incidence of gallbladder-related events as well as elevations in amylase and

lipase in the semaglutide versus placebo groups, however, there were no reported cases of acute pancreatitis.

The question remains whether GLP-1 receptor agonists have direct, independent effects to ameliorate NASH or simply affect the pathophysiology secondarily via resulting improvements in weight, insulin resistance and glycemic control. GLP-1 receptors have been identified on human hepatocytes (6), and preclinical studies suggest potential direct effects of GLP-1 receptor agonists on *de novo* lipogenesis, lipotoxicity , fatty acid oxidation, cytokines implicated in hepatic inflammation and fibrosis and the gut microbiome (1, 4). However, definitive human clinical data regarding the mechanisms of the effects of GLP-1 receptor agonists, including semaglutide, in NASH are lacking.

In this context, it is important to note that the improvement in NASH with semaglutide in the current trial was seen in the context of a dose-dependent decrease in body weight of 5% with 0.1 mg, 9% with 0.2 mg, 13% with 0.4 mg semaglutide and 1% in the placebo group. However, one limitation of the study is that there is no additional analysis controlling for changes in weight and HbA1c, which were both substantial, particularly in the 0.4 mg semaglutide group at −13% and −1.2%, respectively. This is an important area of future investigation, as studies of weight loss from lifestyle changes alone have demonstrated resolution of NASH in 58% of individuals with ≥5% weight loss and 90% of individuals with ≥10% weight loss (7). However, such additional analyses are not available at this time for the current study.

In summary, this is an important study that implicates the GLP-1 receptor agonist semaglutide as a potential effective treatment for NASH. Additional studies in larger NASH populations are needed to further define the impact of semaglutide on liver-related endpoints and cardiovascular disease and to determine whether such effects are independent of weight loss. Ideal dosing and frequency of administration (daily versus weekly) of semaglutide needs to be determined in this population as well. Importantly, patients with NASH are at particularly high risk of cardiovascular disease , and certain GLP-1 receptor agonists, including semaglutide, have been shown to have a cardiovascular benefit in patients with T2DM (8). Thus, semaglutide is certainly an exciting potential therapeutic option for patients with NASH in a space where none currently exist.

Acknowledgments

Grant Support: Dr. Dichtel is supported by NIH K23 DK113220.

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