



Semaglutide for nonalcoholic steatohepatitis: closer to a solution?

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In the issue of March 25, 2021 of the *New England Journal of Medicine*, Newsome *et al.* published the results of a phase II clinical trial of semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), given once-daily, subcutaneously for 72 weeks for the treatment of non-alcoholic steatohepatitis (NASH) (1). The authors found that among 230 NASH patients with fibrosis stage of F2 or F3 the primary endpoint of the study (NASH resolution with no worsening of fibrosis) was achieved in 59% of patients with semaglutide at a dose of 0.4 mg compared to 17% in the placebo group (OR 6.87; 95% CI: 2.60–17.63; $P < 0.001$). Up to now, this is the highest response rate that an active drug has ever achieved in a trial including patients with NASH.

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in the developed world with a global prevalence of approximately 25% (2). It has also risen in the top of the indication list for liver transplantation in the United States and is rapidly growing in the rest of the world (3). NAFLD encompasses a wide spectrum of liver damage, ranging from simple steatosis (or non-alcoholic fatty liver, NAFL) to NASH, which is the progressive form of the disease that can lead to advanced fibrosis and cirrhosis, as well as hepatocellular carcinoma (4). The prevalence of NASH among NAFLD patients is estimated to be close to 60% (2).

The pathogenesis of NAFLD is multifactorial, and several pathogenetic pathways have been proposed. The cornerstone of the pathogenesis is based on the concept that fat accumulation (steatosis) can result under certain circumstances in lipotoxicity and subsequent immune system activation. Two mechanisms contribute to elevated synthesis

of lipids: (I) increased hepatic fatty acid delivery due to an increase in adipose triglyceride lipolysis, mainly driven by insulin signaling and (II) de novo lipogenesis (DNL), a process where glucose and fructose are enzymatically converted into lipids (5). Insulin resistance (IR), another key pathogenic driver of NASH, that on the same time is a shared characteristic of type 2 diabetes mellitus (T2DM) and obesity, may also contribute to the increased levels of free fatty acids and carbohydrates that are seen in patients with NASH (6). Finally, genetic susceptibility, alcohol consumption and dysbiosis may also play a role in NAFLD progression and NASH development (5).

According to the guidelines from the American Association for the Study of Liver Diseases, the management of NAFLD should consist of treating the liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia, T2DM and IR (7). Based on these suggestions, the management is currently based on a comprehensive lifestyle modification approach that combines energy restriction diet with macronutrient composition, exclusion of fructose intake, strict daily limit for alcohol consumption, increased coffee intake, daily physical activity and bariatric surgery in selected patients. Regarding body weight in patients with increased body mass index (>25) the optimal target is a sustained weight loss of $>10\%$ of the initial body weight (8). Pharmacological treatments are primarily aimed at improving liver disease to those with biopsy-proven NASH and fibrosis. Thiazolidinediones and vitamin E have been used for the treatment of NASH as they have shown modest improvement in NAFLD histology (9). Nonetheless, possible adverse effects of these compounds

and the recommended short-term use of vitamin E have made the need for the development of alternative agents urgent. Numerous compounds are currently studied for the treatment of NASH, some of them already in phase III trials (10).

GLP-1 RA is a class of drugs with multifactorial effects on several human organs including the brain, the pancreas and the adipose tissue (11). They can improve body weight, glucose and lipid metabolism and may induce NASH resolution with potential benefits on inflammation. Semaglutide is a human GLP-1RA with increased homology (94%) to human GLP-1 (12). Recent studies showed that semaglutide induced weight loss, improved glycemic control in patients with obesity and T2DM and was associated with reduced levels of alanine aminotransferase and markers of inflammation (13-15). Furthermore, semaglutide was associated with reduced cardiovascular risk among patients with T2DM at high cardiovascular risk (16).

In order to evaluate the safety and efficacy of semaglutide in patients with biopsy confirmed NASH and liver fibrosis of stage F1, F2, or F3, the authors of the recently published trial in the NEJM conducted a 72-week randomized double-blind multicenter phase II trial (1). Patients were randomly assigned, in a 3:3:3:1:1:1 ratio, to receive once-daily subcutaneous semaglutide at a dose of 0.1 (80 patients), 0.2 (78 patients), or 0.4 mg (82 patients) or placebo (80 patients). Once-daily semaglutide was initiated at a dose of 0.05 mg, subsequently increased to 0.1 mg after 4 weeks and then increased by 0.1 mg every 4 weeks until the randomly assigned dose was reached. Liver biopsy was performed at screening visit to determine the baseline characteristics (mainly the activity score for NAFLD and the fibrosis stage) and also at the end of the trial to assess potential changes. Each biopsy was evaluated centrally by two independent expert hepatopathologists. The primary end point was resolution of NASH with no worsening of liver fibrosis. Secondary endpoint was an improvement of at least one fibrosis stage and no worsening of NASH.

The authors found that the percentage of patients that achieved the primary endpoint was significantly higher in the semaglutide groups than in the placebo groups with the highest percentage observed in the 0.4 mg group (59% *vs.* 17%; OR 6.87; 95% CI: 2.60–17.63; $P < 0.001$). However, semaglutide did not show any improvement of at least one fibrosis stage without worsening of NASH in patients who received semaglutide 0.4 mg compared to the placebo group (OR 1.42; 95% CI: 0.62–3.28; $P = 0.48$). The main

analysis included only patients with fibrosis stage of F2 or F3 ($n = 230$). Nonetheless, the results of the analyses that included all the patients who underwent randomization (any fibrosis stage) were consistent with those of the main analysis and were also unaffected by the diabetes status of the patients. Moreover, semaglutide was associated with significant weight loss, which may have played an additional role in NASH resolution. In the 0.4 mg semaglutide group, the mean percent change in body weight was -13% . Notably, the authors noticed that weight loss was continued until 28 to 44 weeks of therapy with semaglutide and was sustained thereafter. Glycated hemoglobin reduction was observed in patients with or without T2DM treated with semaglutide, more prominently in the 0.4 mg group (-1.15%).

Gastroenterological disorders (nausea, constipation, decreased appetite, vomiting and abdominal pain) were the most common reported adverse events. The study showed a dose-dependent association of the gastroenterological disorders between the semaglutide groups with greater percentage in the 0.4 mg group (68%). These events occurred mainly in the first 20 weeks of therapy with semaglutide, during the period of dose escalation. The percentage of patients who discontinued treatment because of adverse events was 7% with semaglutide (all doses) and 5% with placebo. Furthermore, the authors observed that patients in the semaglutide group had more frequently gallbladder related disorders than placebo (7% in the 0.4 mg group and 2% in the placebo group), as well as benign, malignant and unspecified neoplasms (15% *vs.* 8% in the placebo group).

GLP-1 RA is one of the various classes of drugs that are currently evaluated for the treatment of NASH. This large, multicentre, randomised clinical trial has provided undoubted confirmation of the effect of a potent GLP-1 agonist, semaglutide, on NASH resolution. Although the secondary endpoint (improvement in fibrosis stage) was not reached by semaglutide in this study, it is conceivable that longer duration of treatment is needed to observe a possible impact of semaglutide in liver fibrosis. Currently, semaglutide is being evaluated at a dose of 2.4 mg once-weekly in a phase III clinical trial that will last for 5 years and is scheduled to assess the time to first liver-related clinical event (NCT04822181). In addition, it is evaluated in combination with the FXR agonist, cilofexor and with the ACC inhibitor, firsocostat, in a phase 2 proof-of-concept trial (NCT03987074). Given its definite impact on

metabolic dysfunction, lipotoxic effects, and inflammation, semaglutide at present seems a very promising drug for the treatment of NASH (6).

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References

1. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med* 2021;384:1113-24.
2. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73-84.
3. Younossi ZM, Marchesini G, Pinto-Cortez H, et al. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: Implications for Liver Transplantation. *Transplantation* 2019;103:22-7.
4. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011;34:274-85.
5. Parthasarathy G, Revelo X, Malhi H. Pathogenesis of Nonalcoholic Steatohepatitis: An Overview. *Hepatol Commun* 2020;4:478-92.
6. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. *JHEP Rep* 2019;1:312-28.
7. Chalasani N, Younossi Z, Lavine JE, et al. The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328-57.
8. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology* 2015;149:367-78.e5.
9. Larion S, Khurana S. Clinical studies investigating the effect of vitamin E therapy in patients with NASH. *Clin Liver Dis (Hoboken)* 2018;11:16-21.
10. Vuppalanchi R, Noureddin M, Alkhouri N, et al. Therapeutic pipeline in nonalcoholic steatohepatitis. *Nat Rev Gastroenterol Hepatol* 2021;18:373-92.
11. Wang XC, Gusdon AM, Liu H, et al. Effects of glucagon-like peptide-1 receptor agonists on non-alcoholic fatty liver disease and inflammation. *World J Gastroenterol* 2014;20:14821-30.
12. Lau J, Bloch P, Schäffer L, et al. Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. *J Med Chem* 2015;58:7370-80.
13. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2020;46:100-9.
14. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomized, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018;392:637-49.
15. Newsome P, Francque S, Harrison S, et al. Effect of semaglutide on liver enzymes and markers of inflammation

- in subjects with type 2 diabetes and/or obesity. *Aliment Pharmacol Ther* 2019;50:193-203.
16. Marso SP, Bain SC, Consoli A, et al. Semaglutide and

cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834-44.

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