Opinion

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Semaglutide in Obesity and Non-Alcoholic Fatty Liver Disease

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ABSTRACT

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Introduction

Semaglutide injection was introduced in the US as an anti-diabetic medication for type 2 diabetes in December 2017 by Novo Nordisk. It is available in subcutaneous pen injector and oral tablets.

Solution pen injector, subcutaneous: Ozempic 0.25mg, 0.5 mg, 1 mg

Tablet, oral: Rybelsus 3 mg, 7 mg, 14 mg

Solution pen injector, subcutaneous: Wegovy 2.4 mg (approved 2021)

Semaglutide is a selective glucagon-like peptide -1 (GLP-1) receptor agonist that activates the receptor for incretin, increasing glucose dependent insulin secretion, decreases inappropriate glucagon situation and slows gastric emptying. As we know, the first GLP-1R agonist approved for clinical use was exenatide (synthetic exendin-4), a peptide originally isolated from Heloderma suspectum lizard (Gila monster) venom by John Eng in 1992. It was approved in the US by the FDA in 2005.

Semaglutide and Obesity

Recent research results from the STEP1 study group showed significant improvements with once weekly semaglutide at 2.4 mg subcutaneous in overweight or obese adults who did not have type 2 diabetes. The study was a double-blind trial which enrolled 1961 adults with a BMI of 30 or greater who did not have diabetes and randomly assigned them in 2:1 ratio for 68-weeks trail of once-a-week treatment with subcutaneous semaglutide at a dose of 2.4 mg or placebo plus lifestyle intervention. Results were very encouraging at the end of 68 weeks. It was noted that in the semaglutide group mean body weight from baseline to weeks 68 was -14.9% compared to -2.4% with placebo, a change in weight of -15.3 kg in the semaglutide group as compared to -2.6 kg in the placebo group [1].

Participants who received semaglutide were more likely to lose 5% or more, 10% or more, 15% or more and 20% or more of baseline body weight at 68 weeks. 1047 participants in the semaglutide group achieved a coprimary endpoint of weight reduction of 5% or more compared to 182 adults in the placebo group. 838 adults had a weight reduction of 10% or more in the semaglutide group compared to 69 in the placebo group and 612 adults had 15% or more compared to 28 adults in the placebo group at week 68. Other supportive secondary endpoints that were achieved during the study were greater reduction from baseline than placebo with semaglutide in waist circumference, BMI, systolic and diastolic blood pressures, glycated hemoglobin, fasting plasma glucose, C-reactive protein and fasting lipid levels. SF–36 physical functioning score also improved significantly more with the semaglutide than the placebo at week 68. In the DEXA subpopulation, total fat mass and regional visceral fat mass are reduced from baseline with semaglutide.

Main adverse events noted during the study were gastrointestinal disorders typically nausea diarrhea vomiting and constipation which were reported and 74.2% of the semaglutide group versus 49.9% in the placebo group. Serious adverse events were noted to be serious gastrointestinal disorders in 1.4% of the semaglutide participants compared to 0% in the placebo group and hepatobiliary disorder in 1.3% with semaglutide compared to 0.2% with placebo. More participants in the semaglutide group than the placebo group discontinue treatment owing to gastrointestinal events 4.5% versus 0.8%. Overall 94.3% of the participants completed the trial, 91.2% had a body weight assessment at week 38 and 81.1% adherent to treatment. With obesity being a global health challenge and limited pharmacotherapeutic options, once weekly semaglutide injection in addition to lifestyle modifications might be a great option for people looking for nonsurgical treatment.

Semaglutanide and NAFLD/ NASH

Nonalcoholic fatty liver disease (NAFLD) is admitted because of liver disease worldwide and among the top indications for liver transplant in developed countries. NAFLD encompasses a spectrum of liver disease ranging from simple nonalcoholic steatosis/nonalcoholic fatty liver to Nonalcoholic Steatohepatitis (NASH) which is progressive and can lead to cirrhosis as well as hepatocellular carcinoma. Prevalence of NASH among NAFLD patients is estimated to be close to 60%. Based on the original article published in New England Journal of Medicine on March 25, 2021 [2]. It is encouraging to see that subcutaneous semaglutide has significant morbidity and mortality benefits for patients with hepatic fibrosis/advanced NASH. This was a double-blind phase 2 trial involving biopsy confirmed NASH and liver fibrosis F1–F3 patient's who received once daily subcutaneous semaglutide at a dose of 0.1, 0.2 or 0.4 mg or corresponding placebo. The primary endpoint was resolution of NASH. Secondary endpoint was improvement of at least 1 fibrosis stage. He exclusion criteria were hemoglobin A 1C of greater than 9.5 at 6 screening, causes of chronic liver disease other than NASH, excessive alcohol consumption and confounding concomitant drug use.

After 72 weeks of following these patients, the percentage of patients and home Nash resolution was achieved with no worsening of fibrosis was significantly higher in the semaglutide group than in the placebo group (59% in the 0.4 mg group versus 17% in the placebo group; odds ratio 6.87; 95% confidence interval 2.60-17.63; P<0.001). The difference between the semaglutide 0.4 mg group in the placebo group and the percentage of patients who had an improvement of at least 1 fibrosis stage without worsening of NASH after 72 weeks was not significant. An improvement of at least 2 fibrosis stages is according to 25% of the patients in the semaglutide 0.1 mg who, 19% in the 0.2 mg group, 20% in the 0.4 mg group and 17% in the placebo group. Among all the patient's underwent randomization, worsening of fibrosis according to 10%, 8% and 5% of the patients in the semaglutide 0.1 mg, 0.2 mg and 0.4 mg groups respectively and 19% of the patients in the placebo group. Gastrointestinal disorders were the most common adverse events reported which included nausea, constipation, decreased appetite, vomiting and abdominal pain. These seem to be dose dependent. The percentage of patients will discontinue treatment because of adverse events per 7% and semaglutide and 5% in placebo.

Semaglutide was associated with an increase from baseline to weeks 72 and amylase and lipase levels that were greater than those in the placebo group. Based on the discussion provided by the researchers, we still do not understand the mechanism of action of GLP-1 receptor agonists–. They are speculating if this could be an indirect benefit from weight loss and improvement in insulin resistance which would reduce metabolic dysfunction, likely toxic effect and inflammation and Nash patients. The safety profile of subcutaneous hemoglobin eyes was consistent with that observed in patients with type 2 diabetes and other trials.

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