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Semaglutide for the Treatment of Metabolic Dysfunction-Associated Steatohepatitis

HEPATOLOGY

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This summary reviews Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, Cali AMG, Bugianesi E, Rinella ME, Roden M, Ratziu V; ESSENCE Study Group. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025 Jun 5;392(21):2089-2099.

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STRUCTURED ABSTRACT

Question: The goal of this phase 3 trial was to evaluate the efficacy and safety of once-weekly subcutaneous semaglutide for the treatment of metabolic dysfunction–associated steatohepatitis (MASH).

Design: This was an ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial. The reported results are from a planned interim analysis (Part 1) conducted at week 72.

Setting: The trial was conducted at 253 clinical sites across 37 countries.

Patients: The interim analysis included 800 patients with biopsy-defined MASH and liver fibrosis stage 2 or 3. Patients were aged ≥ 18 years.

Exposure: Patients were assigned in a 2:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or a placebo for 240 weeks.

Outcomes: The primary endpoints for Part 1 of the trial were: 1) resolution of steatohepatitis without worsening of liver fibrosis defined as an NAS of 0 for ballooning and 0 to 1 for inflammation, and 2) reduction in liver fibrosis without worsening of steatohepatitis defined as at least a 1-stage reduction on the NASH CRN fibrosis scale.

Data Analysis: Efficacy analyses were based on the intention-to-treat principle. Statistical significance was determined using a graphical testing strategy with a two-sided level of $P < 0.0045$. Missing data were handled using reference-based multiple imputation.

Funding: The study was funded by Novo Nordisk.

Results: The first primary endpoint (resolution of steatohepatitis without worsening of fibrosis) was met, occurring in 62.9% of the semaglutide group vs 34.3% of the placebo group ($P < 0.001$). The second primary endpoint (reduction in liver fibrosis without worsening of steatohepatitis) was also met, occurring in 36.8% of the semaglutide group versus 22.4% of the placebo group ($P < 0.001$). Additionally, patients in the semaglutide group showed significant weight loss (mean change of -10.5%) compared to the placebo group (mean change of -2.0%). Gastrointestinal adverse events (e.g., nausea, diarrhea) were more common in the semaglutide group, but no new safety signals were identified.

COMMENTARY

Why Is This Important?

The glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide is a known treatment for type 2 diabetes and obesity. Multiple studies have also demonstrated the benefit of semaglutide in reducing the risk of major adverse cardiovascular events (MACE), a composite outcome that includes cardiovascular death, nonfatal myocardial infarction, and stroke, and these benefits have been demonstrated regardless of diabetes.[1,2] In addition, improved heart failure outcomes and reduction of major renal outcomes have also been demonstrated.[3,4] The Essence trial provides strong evidence that semaglutide can also effectively treat MASH with fibrosis, a severe form of liver disease that is closely linked to metabolic dysfunction.[5] The findings are significant because they demonstrate both histologic improvements in the liver (resolution of steatohepatitis and a reduction in fibrosis) and broader cardiometabolic benefits like weight loss and improved glycemic control. This dual action addresses a major unmet need for a treatment that can target both the liver disease and its underlying causes.

Compared to placebo, semaglutide significantly improved liver histologic results with resolution of steatohepatitis without worsening of liver fibrosis occurring in 62.9% of the semaglutide group, compared to 34.3% in the placebo group.

Key Study Findings

In addition, a reduction in liver fibrosis without worsening of steatohepatitis was seen in 36.8% of the semaglutide group versus 22.4% in the placebo group, and a combined resolution of steatohepatitis and a reduction in liver fibrosis was reported in 32.7% of patients in the semaglutide group, compared to 16.1% in the placebo group.

Other beneficial effects included a mean change in body weight of -10.5% for the semaglutide group versus -2.0% for the placebo group and semaglutide also appeared to be associated with improvements in glucometabolic factors and noninvasive markers of liver health. The percentage of patients who had an adverse event was 86.3% in the semaglutide group and 79.7% in the placebo group. Adverse events leading to discontinuation were 2.6% for semaglutide and 3.3% for placebo.

Caution

While the results are promising, the study is ongoing. The full long-term clinical outcomes are not yet available. A small number of patients dropped out, which could impact the final analysis. The trial had a small representation of Black patients and a small number of lean patients, so the findings may not be generalizable to these populations.

My Practice

The findings of this trial suggest that semaglutide could become a key therapeutic option for patients with MASH, particularly those with stage 2 or 3 fibrosis. Indeed, many patients with MASH and MASLD are already taking semaglutide or other GLP-1 RAs given the high prevalence of MASLD and MASH in those with type 2 diabetes. On August 15, 2025, the FDA granted approval for semaglutide as a treatment for adults with moderate to advanced fibrosis. Unlike the Phase 2 trial with semaglutide, in this study, semaglutide demonstrated significant improvements in both MASH activity and fibrosis, rather than MASH resolution alone.[6] This is the second approved therapy after resmetirom, a beta thyroid hormone agonist, which was approved in March 2024 for the same population of MASH patients. In my practice, the vast majority of my patients with MASH have features of metabolic syndrome, including type 2 diabetes, and I routinely work with referring physicians to incorporate GLP-1 RA therapies for diabetes and obesity, given previous findings demonstrating improvement in MASH activity as well as the other metabolic benefits and weight loss. The Essence Trial demonstrated, for the first time, improvement in fibrosis with semaglutide, a key endpoint in the treatment of individuals with MASH and moderate to severe

fibrosis. Practicing gastroenterologists now have 2 approved options for pharmacological treatment of MASH in addition to lifestyle interventions.

For Future Research

Future research should focus on the long-term clinical outcomes of semaglutide treatment, including its effects on cirrhosis-free survival, which will be reported in part 2 of this trial. Longer-term prospective studies are also required to explore the role of semaglutide and other GLP-1 RAs in the treatment of those with cirrhosis, which will be important given retrospective administrative database studies suggesting GLP-1 RAs can reduce rates of hepatic decompensation.[7]

Combination therapies with GLP-1 RAs and other MASH therapies and other mechanisms of action, including beta thyroid agonists such as remetirom, will also be important given the pleiotropic mechanisms involved in the pathogenesis of MASH.[8]

Disclosures

Dr Kwo reports the following: Consultant for AbbVie, Durect, Genentech, HepQuant, Inventiva, Mirum, PB Gene, Tune Therapeutics; Advisory Board: Aligos, Amgen, Arbutus, Ausper Bio, Galapagos, Gilead, Novo Nordisk, Ocelot, Salix, Surrozen; Research Grant: Altimmune, Gilead, Inventiva, Novo Nordisk; Target Registries, Ultragenyx, Akero, 89Bio Vir Bio; Grant Support: Ausper Bio, Madrigal, Salix, Takeda; Stockholder: Durect.

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