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How Effective are Obesity Medications for Reducing Hepatic Decompensation in MASH?

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LIVER

This summary reviews EngströmA, Wintzell V, Melbye M, et al. Association of glucagon-like peptide-1 receptor agonists with serious liver events among patients with type 2 diabetes mellitus: A Scandinavian cohort study. Hepatology 2024; In Press doi: 10.1097/HEP.0000000000000712

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STRUCTURED ABSTRACT

Question: Do glucagon-like peptide-1 (GLP-1) receptor agonists decrease serious liver events in patients with type 2 diabetes mellitus (DM)?

Design: Retrospective cohort study using active-comparator and nationwide health and administrative databases.

Setting: Sweden, Denmark, and Norway.

Patients: Individuals aged 35-54 years who were started on GLP-1 receptor agonists or dipeptidyl peptidase-4 (DPP4) inhibitors, a common treatment for type 2 DM that does not appear to have any impact on hepatic function, between 2007-2020. Although presence of type 2 DM was not an explicit inclusion criterion due to limitations in patient registries, individuals receiving GLP-1 receptor agonists for obesity indication were excluded. Additional exclusion criteria included history of any chronic liver disease except non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD)*.

Interventions/Exposure: Patients were followed from treatment initiation until the first occurrence of one of the following: emigration, death, end of the study period, initiation of a DPP4 inhibitor among patients who entered the study on a GLP-1 receptor agonist or vice versa, or the occurrence of a study outcome.

Outcome: Primary outcome was serious liver events, defined as incident diagnoses of compensated or decompensated cirrhosis or hepatocellular carcinomas that was captured by patient registries. Compensated and decompensated cirrhosis were defined as presence of esophageal varices, portal hypertension, liver failure, liver transplantation, hepatorenal syndrome, liver cirrhosis, but not ascites or hepatic encephalopathy. Secondary outcomes were: (a) compensated and decompensated cirrhosis; and (b) hepatocellular carcinoma (HCC).

Data Analysis: Standardized mortality ratio weighting based on propensity score was used to adjust for confounding. Adjusted hazard ratios (aHR) calculated using Cox proportional hazards model.

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Results: The study cohort included 91,479 new users of GLP-1 receptor agonists (81% oral liraglutide, 4% subcutaneous semaglutide) and 244,004 new users of DPP4 inhibitors (73% sitagliptin). Demographic data demonstrated a mean age of62 years old; 415 females; median follow-up time of 3 to 3.6 years (interquartile range 1.2-6.1), and 0.6% diagnosed with NASH/NAFLD at study inception. Among new users of GLP-1 receptor agonists, 21% also carried a diagnosis of obesity while only 8.4% of new users of DPP4 inhibitors had this diagnosis at study inception.

New users of GLP-1 receptor agonists had 16.9 serious liver events per 10,000 person years compared with 19.1 serious liver events per 10,000 person years among new users of DPP4 inhibitors (aHR 0.85; 95% confidence intervals [CIs] 0.75-0.97). In sub-group analysis, new users of GLP-1 receptor agonists had less compensated or decompensated cirrhosis compared to new users of DPP4 inhibitors (aHR 0.85; 95% CIs 0.75-0.97), but no difference in HCC was demonstrated.

***Note:** As per recent nomenclature change, NASH is now labelled as metabolic-dysfunction associated steatohepatitis (MASH) and NAFLD is labelled metabolic-dysfunction associated steatotic liver disease (MASLD).

COMMENTARY

Why Is This Important?

Per the National Institute of Health, approximately 24% of the US population has MASLD and up to 6% have MASH. Estimates about the progression from MASLD to decompensated cirrhosis vary widely, with some experts estimating that up to 20% of patients with MASLD may progress to serious liver events.[1] However, data from the largest prospective natural history study of MASH patients demonstrated hepatic decompensation rates are very small among patients with stage F0-F2 fibrosis (0.05 per 100 person-years), but increase significantly with stage F3 fibrosis (0.99 per 100 person-years, crude HR 18.6; 95% CI 5.4-62.6).[2] Despite this low rate of progression, the high prevalence of MASLD means that this will lead to decompensated cirrhosis in many individuals and effective treatments are sorely needed.

The 2023 American Association for the Study of Liver Disease (AASLD) guideline on NAFLD[1] recommends the following treatments: cessation of alcohol if MASH with ≥F2 fibrosis score, weight loss, increased exercise, Mediterranean diet, consideration of bariatric surgery for obese patients, and consideration of pioglitazone if a patient also has Type 2 DM or consideration of semaglutide (a subcutaneous GLP-1 receptor agonist) if patient also has obesity or Type 2 DM. As summarized in this issue of EBGI, the US Food and Drug Administration (FDA) just approved the first treatment for MASH, resmetirom, an oral thyroid hormone beta-selective agonist that is liver-directed and demonstrated to be more effective than placebo at MASH resolution and reduction in fibrosis. However, could GLP-1 receptor agonists be a better option for most patients with MASH?

Phase 2 randomized controlled trial (RCT) data of 320 MASH patients with F1-F3 fibrosis scores demonstrated that daily semaglutide produced MASH resolution versus placebo, but did not achieve statistical significance for decrease in hepatic fibrosis.[3] The value of the study by Engström et al is that it demonstrates a reduction in serious liver events associated with GLP-1 receptor agonist use in patients with Type 2 DM. However, as discussed below, the study has many limitations. Another retrospective cohort study from South Korea is currently in press in the *Journal of the American Medical Association Internal Medicine*[4] produces similar results, albeit with similar study limitations. Ultimately, the most common cause of death among patients with MASLD are cardiovascular disease and non-hepatic malignancy. Thus, for these conditions, effective treatment of obesity with substantial weight loss may be more effective than specific liver-directed treatments for MASH, like resmetirom.

Key Study Findings

In this observational study, patients with Type 2 DM who were treated with GLP-1 receptor agonists were less likely to develop serious liver events compared to patients receiving DPP4 inhibitors (aHR 0.85; 95% CIs 0.75-0.97).

Caution

Given substantial study design limitations, this should be considered a hypothesis-generating study as opposed to a study which guides management. Specifically, the study design was limited because the vast majority of patients treated with GLP-1 receptor agonists received oral liraglutide, which has not demonstrated similar impact on weight loss as semaglutide. Also, assessment of presence/absence of MASH or MASLD at baseline and change in weight over time were not assessed. Fewer than 1% of study patients had confirmed MASH/MASLD during study inception. The study was limited to patients with Type 2 DM, although the ideal population would be patients with MASH.

My Practice

Since I'm not an obesity specialist, I again consulted with an EBGI former Associate Editor, Sonali Paul, MD, who is certified in obesity medicine and has expertise in using these medications for management of MASH and MASLD patients with obesity and/or Type 2 DM. She noted that the results of this study will not change her practice, but it's helpful to quote this and other studies when educating her patients about the potential benefits of GLP-1 receptor agonists for MASH/MASLD. Dr. Paul noted one issue is insurance coverage for GLP-1 receptor agonists. Based on her anecdotal experience, this has improved over time, especially for patients with Type 2 DM. However, shortages of GLP-1 receptor agonists as well as tirzepatide, a GLP-1 receptor agonist and glucose-dependent insulinotropic polypeptide, has made it difficult to start new patients on these agents.

For gastroenterologists who see patients experiencing gastroinstestinal side effects from GLP-1 receptor agonists, Dr. Paul emphasized the following pearls, which we have discussed in prior EBGI summaries.[5-6] First, when she prescribes GLP-1 receptor agonists, like semaglutide, she usually increases the dose gradually in 2.5 mg increments every 4 weeks based on tolerability. Therefore, if clinically important nausea develops, the next step should be to revert to a lower dose as opposed to starting an anti-nausea agent or simply discontinuing the medication totally. Remember, continued treatment will be required to maintain weight loss in most patients since obesity is a chronic disease. If patients develop mild constipation, then treatment with an osmotic laxative without lowering the dose is acceptable.

Finally, she also follows other recommendations in the AASLD guideline. She encourages MASH/MASLD patients to limit alcohol consumption or

stop drinking alcohol completely, to modify their diets to lose weight and frequently recommends the Mediterranean diet and advises patients to exercise regularly.

For Future Research

Ongoing research will clarify if GLP-1 receptor agonists do decrease hepatic decompensation in in MASH/MASLD patients with obesity and define the magnitude of any benefit. The ongoing MAESTRO-NASH RCT will also determine if resmetirom, which produces histologic improvement in MASH and is the only FDA-approved treatment for MASH, decreases hepatic decompensation, although those results will not be available for several years.

Conflict of Interest

Dr. Schoenfeld reports no relevant conflicts of interest.

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