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# Tirzepatide Produces NASH Resolution and Decreases Fibrosis: Results from the SYNERGY-NASH Trial

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LIVER

This article reviews Loomba R, Hartman ML, Lawitz EJ. et al. Tirzepatide for metabolic-dysfunction associated steatohepatitis with liver fibrosis. NEJM 2024 Jun 8. Online ahead of print.

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## STRUCTURED ABSTRACT

**Question:** Does tirzepatide, a once weekly glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) agonist, decrease fibrosis in and resolve metabolic-dysfunction associated steatohepatitis (MASH)?

**Design:** Phase 2 multicenter, dose-finding, double-blind, placebo-controlled, randomized controlled trial (RCT).

**Setting:** One hundred and thirty sites across 10 countries (Belgium, France, Israel, Italy, Japan, Mexico, Poland, Spain, United Kingdom, United States) between January 2020 and January 2023.

**Patients:** Adults aged 18 to 80 years, with or without type 2 diabetes, body

mass index (BMI) between 27 and 50 kg/m$^2$ and biopsy-confirmed MASH. All participants had biopsies at time of screening or no more than 6 months prior to screening and were required to have nonalcoholic fatty liver disease activity score (NAS) $\geq$ 4 and fibrosis stage of F2 or F3. Exclusion criteria included: 1) alcohol consumption $\geq$14 standard drinks weekly for women and $\geq$21 standard drinks weekly for men; 2) HgbA1c > 9.5%; 3) concomitant use of GLP-1 receptor agonists or other medications to promote weight loss; and 4) fibrosis stage F0 (no fibrosis), F1 and F4 (cirrhosis).

**Interventions:** Participants randomized 1:1:1:1 to 1 of 4 study arms: 1) tirzepatide 5 mg once weekly; 2) tirzepatide 10 mg once weekly; 3) tirzepatide 15 mg once weekly; or 4) placebo once weekly, all administered subcutaneously for 52 weeks. Tirzepatide starting dose was 2.5 mg once weekly and increased by 2.5 mg every 4 weeks until target dose attained (based on assigned study arm).

**Outcomes:** Primary endpoint was resolution of MASH without worsening of fibrosis (defined as no increase in fibrosis stage) at week 52. MASH resolution was defined as no steatosis (steatosis score of 0) or simple steatosis (steatosis score of 1, 2, or 3) without steatohepatitis and lobular inflammation score of 0 or 1 and ballooning score of 0. Outcomes were assessed by central, independent review by 2 pathologists. Key secondary endpoints included: 1) decrease of at least 1 fibrosis stage without worsening of MASH (i.e., no increase in NAFLD activity score); 2) decrease in NAFLD activity score by at least 2 points with reduction of at least 1 point in each of 2 NAFLD activity score components (steatosis, lobular inflammation, hepatocyte ballooning); 3) changes in liver fat content assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF); and 4) changes in body weight.

**Data Analysis:** Intention-to-treat analysis, with missing values imputed assuming they would follow the pattern of results in the placebo group.

**Funding:** Eli Lilly, manufacturer of tirzepatide.

**Results:** Among 190 participants randomized (mean age 54.4 years, 86% White, 12% Asian, 36% Hispanic ethnicity), 165 completed the trial and 157 had end-of-treatment biopsies that could be evaluated at week 52. Mean body mass index was 36.1, 52% had type 2 diabetes, mean NAFLD activity score was 5.3, and fibrosis stage was F2 in 43% and F3 in 57% at enrollment.

Target tirzepatide dose was achieved with dose escalation among 96%, 96% and 85% in the 5-mg, 10-mg, and 15-mg groups, respectively. Dose reduction was later required in 0%, 20%, and 3% in the 5 mg, 10 mg, and 15 mg groups, respectively.

At week 52, MASH resolution without worsening fibrosis was achieved in 44% of participants in the tirzepatide 5 mg arm, 56% in the tirzepatide 10 mg arm and 62% in the tirzepatide 15 mg arm compared to 10% in the placebo arm ($P < 0.001$ for all comparisons).

Regarding the secondary endpoint of improvement by at least 1 fibrosis stage without worsening of MASH, this occurred in 55%, 51% and 51% of participants in the tirzepatide 5 mg, 10 mg, and 15 mg arms, respectively, compared to 30% in the placebo arm.

At week 52, mean percentage change in body weight compared to baseline was -10.7%, -13.3%, and -15.6% in the 5 mg, 10 mg, and 15 mg tirzepatide arms compared to -0.8% in the placebo arm. Larger decreases in aminotransferases (AST, ALT) and noninvasive assessments of liver fat, inflammation, and fibrosis were also observed in the tirzepatide arms at week 52 compared to placebo.

Adverse events (AEs) were common in both the tirzepatide (92%) and placebo (83%) arms. In the tirzepatide arms, the most common AEs were gastrointestinal events (nausea, diarrhea, decreased appetite, with 96% being mild to moderate in severity). Serious AEs occurred in 6% of participants in the tirzepatide arms and 6% in the placebo arm. Ultimately, AEs led to trial discontinuation in 4% of participants in the tirzepatide arms and 4% in the placebo arm.

## COMMENTARY

### *Why Is This Important?*

GLP-1 receptor agonists (GLP-1 RAs) have revolutionized the management of patients with obesity and type 2 diabetes, with beneficial effects beyond weight reduction and improved glycemic control, including better control of hypertension, improvements in metabolic profile, improved outcomes in patients with obstructive sleep apnea, and overall reduction in cardiovascular risk.[1-4] Weight loss (by lifestyle changes, diet modification, and bariatric surgery) has well-documented benefits in MASH, and until recently,[5] no drugs had been proven effective in phase 3 trials to improve MASH. Early placebo-controlled randomized controlled trials (RCTs) of GLP-1RAs conducted in patients with obesity and type 2 diabetes

suggested beneficial effects on the liver, including improvements in liver biochemistries suggesting reduction in inflammation. Further, the addition of GIP receptor agonism to GLP-1 receptor agonism, as in tirzepatide, has direct effects on white adipose tissue (beyond weight loss alone) also believed to be beneficial in MASH. The SYNERGY-NASH trial included additional histologic assessments to demonstrate the efficacy of tirzepatide for MASH improvement without worsening of fibrosis compared to placebo, an endpoint endorsed by the Food and Drug Administration.

### *Key Study Findings*

Among patients with biopsy-proven MASH and liver fibrosis (F2 or F3), all three doses of tirzepatide (5 mg, 10 mg, and 15 mg doses administered once weekly) were superior to placebo with regard to MASH resolution without worsening of fibrosis.

Tirzepatide use was also associated with improvements in body weight, liver biochemistries, and noninvasive assessments of liver fat, inflammation and fibrosis. Overall, tirzepatide appears to be safe and well-tolerated, with the most common adverse events being gastrointestinal; serious events and adverse events leading to trial discontinuation were similar across the 4 study arms, including the placebo arm.

### *Caution*

It is hypothesized that MASH resolution may result in regression of fibrosis, which is the most important predictor of major adverse liver outcomes (MALO),[6] defined as the development of hepatic decompensation (ascites, overt hepatic encephalopathy, variceal bleeding), liver transplantation or liver-related death.[7] One limitation of the SYNERGY-NASH trial (as well as other recently published phase 2-3 RCTs in MASH[5, 8]), is the trial duration was not long enough to assess the effect of tirzepatide on MALO. Further, given the study's relatively small sample size (N=190), there was insufficient power to detect differences in fibrosis improvement with tirzepatide compared to placebo. The authors of the trial acknowledge that fibrosis improvement will likely require more than 52 weeks of therapy. Further, it is unknown whether there is a "celling" of fibrosis regression that can be achieved with GLP-1RAs (or weight loss alone). Lastly, the study excluded patients that have progressed to cirrhosis (F4) and those that have yet to develop fibrosis (F0) or have earlier stages of fibrosis (F1). Thus, it remains unclear whether tirzepatide will benefit this broader population.

### *My Practice*

Since I'm not an obesity specialist, I'm relying on commentary from one of *Evidence-Based GI's* former Associate Editors, Sonali Paul, MD, who is certified in obesity medicine as well as being a hepatologist who specializes in treating MASH and uses tirzepatide in her practice.[9] Dr. Paul has noted that the results of these studies are helpful to quote when educating her patients about the potential benefits of tirzepatide for

MASH/MAFLD, although she primarily uses tirzepatide in patients with concurrent obesity or Type II DM. Dr. Paul previously noted that insurance coverage for GLP-1 RAs can be an issue, but this has been improving.

Again, per prior commentaries in Evidence-Based GI,[9] gastroenterologists should be prepared to get referrals for patients experiencing GI side effects on GLP-1 receptor agonists. Per Dr. Paul, a common problem is increasing the dose of GLP-1 RAs too quickly. When she prescribes agents like tirzepatide, she usually increases the dose gradually in 2.5 mg increments every 4 weeks based on tolerability. Therefore, if clinically important nausea develops, then 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.

### *For Future Research*

Studies with longer duration and larger sample sizes are needed to further clarify the efficacy of tirzepatide (and other agents under investigation for MASLD) on fibrosis regression and risk reduction of major adverse liver outcomes (MALO). Additionally, future studies will be needed to assess efficacy and safety of tirzepatide in patients that have already developed cirrhosis. Given high prevalence of MASLD in the US, ongoing efforts to screen and define the at-risk population for MALO and identify those most likely to benefit from long-term MASH therapy remains of critical importance.

### *Conflict of Interest*

Dr. Rich has served as consultant or on advisory boards for AstraZeneca, Eisai, Exelixis and Genentech, unrelated to the present work.

The authors of this work are active on social media. Tag them to discuss their work and this EBGI summary:

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