Will Tirzepatide Become a Game-Changer Anti-Obesity Drug?

Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387:205–216. https://doi.org/10.1056/NEJMoa2206038.

SUMMARY OF THE STUDY

Tirzepatide is a novel, first-in-class, dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist approved by the Food and Drug Administration in 2022 for type 2 diabetes mellitus (T2DM).[1] To study the efficacy and safety of tirzepatide for weight reduction in non-diabetic obese individuals, the SURMOUNT-1 trial was conceived, whose findings were reported in the recent issue of the New England Journal of Medicine by Jastreboff *et al.* This was a 72-week phase III, multicenter, double-blind, placebo-controlled, randomized clinical trial in overweight or obese persons, conducted at 119 sites in nine countries, comparing three different doses of tirzepatide with placebo.[2] After a 2-week screening period, 2539 participants were randomized in a 1:1:1:1 ratio to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or placebo, administered subcutaneously once weekly for 72 weeks as an adjunct to lifestyle intervention. The lifestyle intervention included regular counseling sessions, delivered by a qualified healthcare professional or a dietitian, to help the subjects adhere to healthful, balanced meals, with a deficit of 500 calories per day and at least 150 min of physical activity per week. The average weight reduction at 72 weeks was 15% with the 5 mg dose, 19.5% with the 10 mg dose, and 20.9% with the 15 mg dose; while there was only 3.1% weight reduction in the placebo group. Tirzepatide treatment also reduced waist circumference and lowered systolic and diastolic blood pressures, lipids, fasting insulin, and glycated hemoglobin. Serious and non-serious adverse events were limited to gastrointestinal symptoms, such as nausea, diarrhea, and constipation, like those associated with other GLP-1 agonist drugs for weight loss.

COMMENTS

Obesity is a chronic, multifactorial, and inflammatory disease of maladaptive adipose tissue mass involving complex links among genetics, hormonal signaling, and the environment.[3] It is the most prevalent chronic disease globally, affecting millions of adults and adolescents. For each 5 kg/m^2 higher body mass index, the overall mortality increases by 30%, explained by the increases of 40% for vascular diseases, 60–120% for diabetic, renal, and hepatic diseases, 20% for respiratory disease, and 10% for cancers. At 30–35 kg/m^2 body mass index, median survival was reduced by 2–4 years, and at 40–45 kg/m^2 it was reduced by 8–10 years.[4]

Treatments that result in substantial weight reduction may improve outcomes for people living with obesity. Lifestyle intervention alone is generally associated with moderate weight loss of around 5–7%, which is gradually regained in most people. The American Gastroenterological Association recommends adding pharmacological agents to adults with obesity, who have an inadequate response to lifestyle interventions alone. The panel suggested the use of semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER and naltrexone-bupropion ER, and phentermine and diethylpropion for long-term management of overweight and obesity.[5] However, these pharmacological agents have been able to achieve only a modest weight reduction of up to 10%. Till now, bariatric surgery remains the most effective anti-obesity management strategy characterized by an average of 30–40% weight loss, but it comes at the cost of irreversibility, surgery-related morbidity, and a considerable percentage of early and late complications.[6]

Incretins are gut hormones that are secreted from enteroendocrine cells into the blood within minutes after eating. One of their many physiological roles is to regulate the amount of insulin that is secreted after eating. There are two incretins, known as GIP and GLP-1, that share many common actions in the pancreas and also have distinct actions outside of the pancreas. Both incretins are rapidly deactivated by an enzyme called dipeptidyl peptidase 4 .[7] The receptors of GLP-1 and GIP are widely expressed in the body, particularly in the brain. GLP-1 increases satiety and decreases gastric emptying. It also has direct effects on adipocytes, as well as the cardiovascular tissue and bone. GIP has fewer organ-specific actions than GLP-1, but it may positively influence the adipose tissue regulation of lipid storage and has a direct activity in the central nervous system.[8] For almost two decades, two classes of drugs based on the incretin action have been approved for lowering blood glucose levels in T2DM: incretin mimetics (GLP-1 agonists such as liraglutide and semaglutide) and incretin enhancers (dipeptidyl peptidase 4 inhibitors such as sitagliptin and linagliptin). Both liraglutide and semaglutide were also found useful for weight reduction in both diabetics and non-diabetics with obesity.[9]

Combining the properties of both incretins, GIP and GLP-1, as a single co-agonist is an exciting possibility, and

Abbreviations: AGA: American Gastroenterological Association; FDA: Food and Drug Administration; GIP: Glucose-dependent insulinotropic peptide; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium-glucose transport protein 2; T2DM: Type 2 diabetes mellitus

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Tirzepatide is a novel, first-in-class, dual GIP and GLP-1 receptor agonist. It was recently approved by the Food and Drug Administration for T2DM.[1] In a randomized, open-label, parallel-group, phase 3 trial in people with T2DM, inadequately controlled by metformin with or without sodium-glucose transport protein 2 inhibitors, tirzepatide was not only found superior to titrated insulin degludec, with greater reductions in HbA_{1c}, it was also found to significantly reduce weight. In a 15 mg tirzepatide group, 88% of the patients were able to reduce ≥5%, 69% achieved ≥10%, and 43% achieved ≥15% of their total weight.[10] In another large randomized controlled trial in patients with T2DM, tirzepatide was found to be superior to semaglutide with respect to the mean change in glycated hemoglobin, and also induced greater weight loss than semaglutide with a relative difference of 5.5 kg from baseline in 40 weeks. At 40 weeks, the mean reductions in body weight with tirzepatide at a dose of 5 mg, 10 mg, and 15 mg were −7.6 kg, −9.3 kg, and −11.2 kg, respectively, as compared with −5.7 kg with semaglutide.[11]

In the current SURMOUNT-1 trial, it is remarkable that the magnitude of weight loss with tirzepatide was similar to that with bariatric surgery, which raises the potential for alternative medical approaches to the treatment of obesity. The strengths of the trial are the inclusion of a large number of participants, the racial and ethnic balance, and the lack of major off-target side effects. However, long-term studies are needed to study whether the remarkable weight loss achieved by tirzepatide can be sustained even after stopping the drug or will the drug need to be continued for life.

CONFLICTS OF INTEREST

None.

FUNDING

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A Review on "IL-1 Receptor Antagonist Plus Pentoxifylline and Zinc for Severe Alcohol-Associated Hepatitis"

Abbreviations: AH: Alcoholic hepatitis; ALD: Alcoholic liver disease; COMB: Anakinra, pentoxifylline and zinc; MDF: Maddrey's discriminant function; MELD: Model for End-Stage Liver Disease; PRED: Methylprednisolone

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