An Introduction to Tirzepatide

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Roughly one in 10 Americans have diabetes, and 90–95% of those have type 2 diabetes (1). Uncontrolled diabetes can lead to serious complications, including heart disease, vision impairment, and kidney damage (1). Tirzepatide, a once-weekly injectable medication in late-stage development, has shown promise in its ability to treat type 2 diabetes (2–5).

Expected Indication

Tirzepatide has not yet been approved by the U.S. Food and Drug Administration (FDA). If approved it is expected to have an indication for the treatment of type 2 diabetes.

Mechanism of Action

Tirzepatide is an injectable dual glucagon-like peptide 1 (GLP-1) receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (6). GIP is considered the dominant insulinotropic hormone when compared with GLP-1 and has demonstrated a stronger role in postprandial insulin secretion (7).

Potential Advantages

Impressive A1C reductions to ≤5.7% (discussed below) are unique and highlight the potential clinical efficacy of tirzepatide (2,3,5). Weight loss was also significant in people using this agent (2–5). Tirzepatide therapy is considered an improvement over GLP-1 receptor agonist therapy because of its robust glucose-lowering and weight loss effects and once-weekly administration (8).

Potential Disadvantages

As with many GLP-1 receptor agonists, side effects of nausea, vomiting, and diarrhea are reported with this dual-hormone receptor agonist. These effects were mild to moderate in severity and more common when initiating tirzepatide or increasing its dosage (4).

Cost

Because tirzepatide is not yet approved by the FDA, its cost is not yet known. However, the Institute for Clinical and Economic Review published an independent report assessing the annual health benefit price benchmark of tirzepatide to be $5,500 (9).

Commentary

Several trials have highlighted the clinical usefulness of tirzepatide, with one suggesting its superiority over the GLP-1 receptor agonist semaglutide as a once-weekly injectable medication for type 2 diabetes. In the SURPASS-2 trial (5), tirzepatide was found to be superior in terms of mean change in A1C from baseline to 40 weeks.

Two other commonly cited tirzepatide trials are SURPASS-1 (2) and SURPASS-4 (4). SURPASS-1 was a double-blind, randomized, placebo-controlled phase 3 trial conducted over 40 weeks in people with an A1C ≥7.5% and ≤9.5% (2). After a 3-week lead-in period, study participants received 5 mg (n = 121), 10 mg (n = 121), or 15 mg (n = 121), of tirzepatide or placebo (n = 115); doses in the 10-mg and 15-mg groups were titrated in 5-mg increments every 4 weeks. Participants in each of the three treatment groups experienced reductions in A1C, fasting glucose, and body weight that were superior to placebo. Nearly 90% of the individuals in the treatment groups reached an A1C <7%, and ∼50% reached an A1C <5.7%. Observed body weight loss was dose-dependent, was progressive, and did not flatline by the end of the 40-week time frame. Statistical analysis via least squares means from baseline found weight changes of −7.0 kg with 5 mg, −7.8 kg with 10 mg, and −9.5 kg with 15 mg tirzepatide compared with −0.7 kg with placebo.

The SURPASS-4 trial was an open-label, randomized, active-controlled, parallel-group phase 3 study conducted in people (n = 1,878) with an A1C ≥7.5% and

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https://doi.org/10.2337/cd22-0038

≤10.5% (4). The trial randomly assigned groups in a ratio of 1:1:1:3 to tirzepatide 5 mg, 10 mg, and 15 mg and insulin glargine 100 units/mL (U100), respectively. The primary end point was change in A1C from baseline to 52 weeks; secondary end points included A1C <6.5% or <5.7% from baseline to 52 weeks and weight loss of 5, 10, or ≥15%. At 52 weeks, the observed changes in A1C for tirzepatide 10 mg (−2.34%) and 15 mg (−2.58%) were greater than for U100 glargine (−1.44%). By 52 weeks, reductions in body weight of ≥10% occurred in 36% of individuals receiving 5 mg tirzepatide, 53% of those receiving 10 mg, and 66% of those receiving 15 mg, compared with 2% of those receiving placebo. Body weight reductions were then sustained over 104 weeks of treatment. Hypoglycemia occurred more frequently with U100 insulin glargine (19%) versus tirzepatide (6–9%). However, adverse effects such as nausea, diarrhea, and vomiting were observed to occur more frequently with tirzepatide than with U100 glargine.

SURPASS-5, the most recently completed randomized, double-blind, parallel, placebo-controlled clinical trial of tirzepatide was published in early 2022 and included individuals (n = 451) with an A1C ≥7.5% and ≤10.5% (3). Participants received U100 glargine once daily for the entire 40-week treatment period. Treatment groups included tirzepatide once-weekly injections of 5, 10, or 15 mg or placebo. Ultimately, 85–90% of participants in the tirzepatide groups reached a target A1C of <7%, compared with 34% of those in the placebo group (P <0.001).

Bottom Line

Tirzepatide, if approved by the FDA, will be a novel treatment option for type 2 diabetes with robust glucose- and weight-lowering effects. Although cardiovascular outcomes data for tirzepatide are not yet available, the SURPASS clinical research program has demonstrated the drug's benefits as both monotherapy and in combination with insulin. Given the agent's robust clinical effects, tirzepatide has the potential to become a widely used agent for the treatment of type 2 diabetes in the near future. Time will tell.

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