EDITORIAL

Tirzepatide for Patients With Type 2 Diabetes

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Clinicians providing care for patients with type 2 diabetes have an increasing number of options in their armamentarium. Within the brief period allotted for a visit, clinicians will likely advocate for healthier lifestyle choices and then consider medication. They will evaluate patterns of glycemia and aim to reduce the risk of complications, while minimizing drug-drug interactions and adverse effects. Clinical research studies are needed that apply to the patient population for whom physicians and other clinicians provide care and that reflect the practical aspects of their daily professional activities.

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Patients do not always have the same priorities as their clinicians. In addition to better health outcomes and few adverse effects, patients may have preferences for minimizing multiple insulin injections, avoiding hypoglycemia, maximizing their ability to lose weight or reducing risk of weight gain, and avoiding high medication costs.

In this issue of *JAMA*, Dahl et al present the findings of the SURPASS-5 clinical trial that compared 3 doses of the dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide vs placebo in the treatment of patients with type 2 diabetes within an insulin glargine titration protocol.[1] The study included 475 patients receiving insulin glargine (with or without metformin) who were not at the target hemoglobin A_{1c} (HbA_{1c}) level of 7.5% to 10%. The mean (SD) age of study participants was 61 (10) years, suggesting that the study population included few people with type 2 diabetes younger than 40 years, which is an important and growing demographic group. Despite 45 participating sites in 8 countries, only 1.3% of study participants self-identified as Black or African American individuals.

Participants were excluded if they had retinopathy requiring acute treatment, estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 (or <45 mL/min/1.73 m^2 for patients receiving metformin), severe diabetic gastroparesis, history of pancreatitis, signs and symptoms of liver disease (except for nonalcoholic fatty liver disease with alanine aminotransferase <3.0 times the upper limit of normal), hospitalization for major cardiovascular event including heart failure in the past 2 months, or hypoglycemia unawareness. Other exclusion criteria included alcohol use disorders, psychiatric disorders, active autoimmune disease that was likely to require corticosteroid use over the next 12 months, transplanted organ, or active/untreated malignancy. Similar to other clinical trials of novel therapeutics, the resulting study cohort may not have been representative of patients with diabetes treated in many clinical practice settings.

The protocol compared subcutaneous injection of 5-mg (n = 116), 10-mg (n = 119), and 15-mg (n = 120) tirzepatide and volume-matched placebo (n = 120) over 40 weeks in the setting of titrating a once-daily dose of insulin glargine. The study protocol did not allow for dividing glargine doses or adding short-acting insulin or other prandial therapies, and thus may represent a departure from usual clinical care. In particular, the baseline 7-point self-monitored blood glucose profiles (eFigure 2 in Supplement 2 of the article by Dahl et al[1]) show a pattern of steadily increasing glucose values. Clinicians who encounter patients with such a profile may target postprandial control rather than continuing to "double down" on once-daily glargine. Conversely, because the inclusion criteria allowed study participants with HbA_{1c} values of 7.5%, many clinicians might look to other treatment options besides insulin glargine to achieve the small improvement needed to reach target levels.

The results showed that tirzepatide was effective compared with placebo for the primary outcome of change in HbA_{1c} from baseline to week 40. The mean HbA_{1c} change from baseline to week 40 was −0.86% with placebo, −2.11% with 5-mg tirzepatide (difference vs placebo, −1.24% [95% CI, −1.48% to −1.01%]), −2.40% with 10-mg tirzepatide (difference vs placebo, −1.53% [97.5% CI, −1.80% to −1.27%]), and −2.34% with 15-mg tirzepatide (difference vs placebo, −1.47% [97.5% CI, −1.75% to −1.20%]). Tirzepatide was also associated with weight reduction, whereas titration of insulin glargine was associated with weight gain. Mean body weight change from baseline was −5.4 kg with 5-mg tirzepatide (difference, −7.1 kg [95% CI, −8.7 to −5.4]), −7.5 kg with 10-mg tirzepatide (difference, −9.1 kg [95% CI, −10.7 to −7.5]), −8.8 kg with 15-mg tirzepatide (difference, −10.5 kg [95% CI, −12.1 to −8.8]), and 1.6 kg with placebo (P < .001 for all). In addition, greater percentages of participants reached target HBA_{1c} of less than or equal to 7%, 6.5%, and 5.7% in the tirzepatide groups than in the placebo group.[1] The first 2 targets were established by the American Diabetes Association[2] and the American Association of Clinical Endocrinologists[3] to reduce risks for complications. An HbA_{1c} value of 5.7% is used as the threshold for prediabetes[4] and has not been a goal of therapy for patients with existing type 2 diabetes.

It initially seems surprising that patients who received tirzepatide and who lost 5.4 kg and 7.5 kg (in the 5-mg and 10-mg tirzepatide groups, respectively) had little, if any, reduction in insulin glargine doses. The higher dose of 15 mg resulted in reductions in insulin glargine of −6.7% (baseline HbA_{1c} ≤8%) and −13.1% (baseline HbA_{1c} >8%). However, a review of previous studies of GLP-1 receptor agonist agents noted that protocols allowing insulin dose adjustments reported reductions in

bolus insulin doses more often than basal.[5] It may be that medications targeting incretin pathways may need adequate basal insulin to achieve their glycemic end points.

There were no differences in the incidence or aggregated rates (events/patient-year) of hypoglycemia, and the rates were generally low (<1 event per patient-year). These findings were based on fingerstick glucose measurements and not on continuous glucose monitoring data. However, because participants were testing 7 times daily (before/after meals and at bedtime), this study should reassure clinicians about the risk for hypoglycemia with tirzepatide and once-daily glargine.

Intermediate clinical outcomes for nephropathy, retinopathy, and neuropathy were not included in the current report by Dahl et al,[1] but should be reported in future publications. Other indices of interest will be evaluating the effect of tirzepatide on hepatic steatosis. The higher doses (10 mg and 15 mg) demonstrated some improvement in alanine aminotransferase (eTable 6 in Supplement 2 in the study by Dahl et al[1]). The cardiovascular outcome trial involving tirzepatide is currently ongoing and involves an active comparator group.[6]

At the end of the 40-week study period, tirzepatide improved HbA_{1c} and weight, as well as total cholesterol, triglycerides, and low-density lipoprotein cholesterol. If this drug is approved, clinicians will clearly want to know about dosing. Statistical analysis compared each dose with placebo; doses were not compared statistically to each other. All doses of tirzepatide had significant beneficial effects on HbA_{1c} and weight. Similar percentages of study participants achieved HbA_{1c} values less than or equal to 7% with all 3 doses. However, there appears to be little difference in change from baseline HbA_{1c} between the 10-mg and 15-mg doses. Regarding weight loss, the percentage of participants who lost at least 5% of weight increased with each of the 3 doses. Yet, differences between 10-mg and 15-mg doses appear to be similar for weight loss of at least 10%. Perhaps future analyses will clarify whether a dose-response effect was present for the drug's effects. Practitioners and patients need further comparative information about doses to properly assess benefits and risks.

Adverse effects are a major concern to patients, clinicians, and pharmaceutical companies. In the trial by Dahl et al, 10.7% of participants discontinued the treatment prematurely.[1] Not surprisingly, gastrointestinal adverse effects, including nausea, diarrhea, vomiting, and dyspepsia, were more common in participants treated with tirzepatide. Although the number of individuals with increased lipase levels was small (Table 3 in the report by Dahl et al), small but significant changes in lipase and amylase levels were observed for all doses of tirzepatide (eTable 6 in Supplement 2).[1] Of some reassurance, there were no cases of pancreatitis among the 475 study participants.

Overall, the study by Dahl et al[1] in this issue of *JAMA* demonstrated that use of tirzepatide was associated with significant reductions in HbA_{1c} and weight in a fairly homogeneous cohort of patients with type 2 diabetes who were receiving insulin glargine with or without metformin. The protocol answered questions about efficacy but left open questions about generalizability and effectiveness in different populations, especially patients with certain complications or comorbid chronic diseases. Importantly, the study did not compare tirzepatide with other treatments that could have been used to target the postprandial glycemic pattern of the study population. Although patients are likely to embrace a medication with weight loss outcomes, the protocol also leaves unanswered questions about reducing insulin and evaluating the comparative risk of adverse effects. Thus, even though the results of this investigation are important for demonstrating the potential clinical benefit of this dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist, and may help to advance the goal of achieving US Food and Drug Administration approval, the study may leave clinicians uncertain about when and how to best use tirzepatide to improve clinical outcomes for patients with type 2 diabetes.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: None reported.

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