MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Review of Effect of Tirzepatide on Glycemic Control and Weight Loss

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Abstract

Tirzepatide (Mounjaro) is a new to market glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonist. It has shown to substantially decrease hemoglobin A1c as demonstrated in the SURPASS trials. Additionally, the SURMOUNT-1 trial showed the impact tirzepatide can have on weight reduction independent of diabetes. Tirzepatide has just been implemented into the American Diabetes Association guideline recommendations for type 2 diabetes management with emphasis on weight reduction as of 2023. The current clinical data and upcoming trials have promising evidence to make a significant impact for patients with type 2 diabetes and/or obesity. In this article, we review the clinical trial data for tirzepatide and the applications for pharmacy practice.

Type 2 diabetes mellitus (T2DM) is a chronic health condition characterized by hyperglycemia, insulin resistance, and an impairment in insulin secretion.[1] The CDC estimates that over 37 million people in the United States live with diabetes and that 41.9% of the population is obese, with this being a risk factor of developing T2DM.[2] Roughly 90% of patients with T2DM are classified as overweight or obese and continue to trend up.[3] In 2019, it was estimated that 1.5 million deaths worldwide were directly related to diabetes, making it the ninth leading cause of death in the world.[4] Given the scope of T2DM and the link with obesity, improvements in management of these two concurrent disease states, including pharmaceutical options, is of high value to the health care community.

Currently, GLP-1 receptor agonists are approved for T2DM and two have indications for weight loss (liraglutide, semaglutide). Tirzepatide is a first-in-class glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonist approved by the U.S. Food and Drug Administration (FDA) on May 13, 2022.[5] The GLP-1 agonist component acts as an incretin hormone and has a role in the central nervous system, pancreatic islet cells, and stomach by decreasing food intake, increasing insulin secretion in hyperglycemic states, inhibiting glucagon secretion, and delaying gastric emptying thus increasing satiety.[6] Unlike other GLP-1 receptor agonists on the market, the addition of GIP receptor agonism action makes this a dual mechanism medication. It is thought that GIP receptor agonism will further decrease appetite and food intake, increase insulin sensitivity in adipose tissues, alter nutrient metabolism, increase insulin secretion, and alter glucagon secretion.[7] The dual mechanism action of this medication may lead to clinical significance when determining an antidiabetic regimen.

Patients with diabetes often require multiple anti-diabetic agents to reach and maintain their hemoglobin A1c (HbA1c) goal.[8] Even with multiple agents, meeting a HbA1c goal can be difficult. The dual mechanistic nature of tirzepatide has demonstrated evidence for use in both lowering HbA1c and overall body weight in the SURPASS trials and SURMOUNT-1.[9-14] This literature review analyzes current clinical data by outlining the safety profile, adverse effects, and evidence for use of the novel drug tirzepatide in the management of both T2DM and obesity.

Clinical Data/Literature Review

Tirzepatide has been studied for use in T2DM in a series of phase III randomized-controlled trials known as the SURPASS trials.[9-13] Within these trials, three different tirzepatide doses were evaluated in five clinical trials investigating the use as a stand-alone or add-on therapy with other diabetes medications. The SURPASS-1 and SURPASS-5 trials were conducted versus placebo in which HbA1c changes from baseline were analyzed following a 40-week period of weekly tirzepatide administration at doses of 5, 10, or 15 mg.[9,13] Patients in SURPASS-1 were on diet and exercise alone at baseline whereas in SURPASS-5 patients at baseline were on basal insulin with or without metformin. Additionally, three SURPASS studies compared tirzepatide to standard anti-hyperglycemic medications in effort to prove non-inferiority via ability to reduce HbA1c from baseline over 40- or 52-week periods.[10-12] These studies compared tirzepatide to semaglutide, insulin degludec, and insulin glargine for SURPASS-2, SURPASS-3, and SURPASS-4, respectively. Each of the studies showed statistically significant mean change in HbA1c versus the comparator as shown in Table 1.

A crucial secondary endpoint to each SURPASS trial was reduction of body weight in which tirzepatide was able to significantly outperform each comparator group as well. Tirzepatide demonstrated dose-dependent weight loss ranging from 7 kg on the lower dose to 13 kg on the highest dose (Table 1).[9-13] Safety analyses were conducted on tirzepatide in each of the trials in which diarrhea and nausea were

TABLE 1. Summary of SURPASS Trials Examining Tirzepatide in Patients with Type 2 Diabetes

	SURPASS-1[9]	*SURPASS-2*[10]	*SURPASS-3*[11]	*SURPASS-4*[12]	*SURPASS-5*[13]
Objective	Safety, efficacy, and tolerability in patients with poor glycemic control in addition to diet and exercise	Safety and efficacy in patients with poor glycemic control with metformin	Safety and efficacy in patients with poor glycemic control with metformin ± a sodium glucose-like transporter-2 inhibitor	Safety and efficacy in patients with high cardiovascular risk and poor glycemic control+	Safety and efficacy in patients with poor glycemic control with baseline insulin glargine ± metformin
Comparator	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo
Primary Endpoint	Mean change in HbA1c from baseline at 40 weeks	Mean change in HbA1c from baseline at 40 weeks	Mean change in HbA1c from baseline at 52 weeks	Mean change in HbA1c from baseline at 52 weeks	Mean change in HbA1c from baseline at 40 weeks
Primary Results (%)	Tirzepatide 5 mg (- 1.87)	Tirzepatide 5 mg (- 2.01)	N/A	N/A	Tirzepatide 5 mg (- 2.11)
	Tirzepatide 10 mg (- 1.89)	Tirzepatide 10 mg (- 2.2)	Tirzepatide 10 mg (- 2.20)	Tirzepatide 10 mg (-2.43)	Tirzepatide 10 mg (- 2.40)
	Tirzepatide 15 mg (- 2.07)	Tirzepatide 15 mg (- 2.30)	Tirzepatide 15 mg (- 2.37)	Tirzepatide 15 mg (-2.58)	Tirzepatide 15 mg (- 2.34)
	Placebo (+ 0.04)	Semaglutide 1 mg (- 1.86)	Insulin degludec (-1.34)	Insulin glargine (-1.44)	Placebo (- 0.86)
Mean body weight change from baseline (kg)	Tirzepatide 5 mg (- 7.0)	Tirzepatide 5 mg (-7.6)	N/A	N/A	N/A
	Tirzepatide 10 mg (- 7.8)	Tirzepatide 10 mg (- 9.3)	Tirzepatide 10 mg (- 10.7)	Tirzepatide 10 mg (- 9.5)	Tirzepatide 10 mg (- 7.5)
	Tirzepatide 15 mg (- 9.5)	Tirzepatide 15 mg (- 11.2)	Tirzepatide 15 mg (- 12.9)	Tirzepatide 15 mg (- 11.7)	Tirzepatide 15 mg (- 8.8)
	Placebo (- 0.7)	Semaglutide 1 mg (- 5.7)	Insulin degludec (+ 2.3)	Insulin glargine (-1.9)	Placebo (- 1.6)
Safety Profile, Intervention vs. control (%)	Nausea 12-18 vs. 6	Nausea 17-22 vs. 18	Nausea 23-24 vs. 2	Nausea 12-23 vs. 2	Nausea 13-18 vs. 3
	Diarrhea 12-14 vs. 8	Diarrhea 13-16 vs. 12	Diarrhea 16-17 vs. 4	Diarrhea 13-22 vs. 4	Diarrhea 12-21 vs. 10
	Pancreatitis 0 vs. 0	Pancreatitis 0.4 vs. 0.6	Pancreatitis 0 vs. 0	Pancreatitis 0.3-0.9 vs. 0.3	Pancreatitis 0 vs. 0
	Cholelithiasis 1 vs. 0	Cholelithiasis 0.9 vs. 0.4	Cholelithiasis 1.1 vs. 0	Cholelithiasis 0.3 vs. 0.3	Cholelithiasis 0.9 vs. 0
	Retinopathy 0 vs. 0	Retinopathy 0.4 vs. 0	Retinopathy 0.8 vs. 0	Retinopathy 2 vs. 2	
Hypoglycemia (blood glucose < 54 mg/dL) N, (%)	Tirzepatide 5 mg 0 (0)	Tirzepatide 5 mg 3 (0.6)	Tirzepatide 5 mg 5 (1.4)	Tirzepatide 5 mg 29 (8.8)	Tirzepatide 5 mg 18 (15.5)
	Tirzepatide 10 mg 0 (0)	Tirzepatide 10 mg 1 (0.2)	Tirzepatide 10 mg 4 (1.1)	Tirzepatide 10 mg 20 (6.1)	Tirzepatide 10 mg 23 (19.3)
	Tirzepatide 15 mg 0 (0)	Tirzepatide 15 mg 8 (1.7)	Tirzepatide 15 mg 7 (1.9)	Tirzepatide 15 mg 27 (7.9)	Tirzepatide 15 mg 17 (14.2)
	Placebo 1 (1)	Semaglutide 2 (0.4)	Insulin degludec 26 (7.3)	Insulin glargine 191 (19.1)	Placebo 15 (12.5)

HbA1c= hemoglobin A1c
+Allowed for combination with metformin, sulfonylurea, or sodium-glucose co-transporter 2 inhibitor

the most common, albeit transient, adverse effects. Notably, each of the SURPASS trials distinguished incidence and rate of hypoglycemia as well as the more rare but serious adverse effects such as cholelithiasis, pancreatitis, and retinopathy (Table 1). Incidence of hypoglycemia below 54 mg/dL was rare in tirzepatide monotherapy. However in SUPRASS-4 and SURPASS-5 which allowed concurrent use with sulfonylureas or basal insulin, incidence of significant hypoglycemia increased. The overall incidence of adverse effects within the SURPASS trials for tirzepatide show a dose-dependent relationship and are generally consistent with other GLP1 agents on market.

Another study, the SURMOUNT-1 trial, addressed the potential for tirzepatide as a treatment option for weight loss in overweight or obese patients without a history of diabetes.[14] The phase III trial provided intervention in patients with a BMI greater than 30 kg/m^2 or 27 kg/m^2 with weight-associated complications by administering once weekly tirzepatide (5, 10, or 15 mg) for a 72-week period. Co-primary endpoints of the study assessed patient's percent weight change from baseline and proportion of participants reaching an overall weight reduction of at least 5% of baseline body weight. Results showed significant, dose-dependent, weight reduction in each of the three dosage cohorts -15.0% in tirzepatide 5 mg [P<0.001, 95% confidence interval (CI) -15.9 to -14.2], -19.5% for tirzepatide 10 mg [P<0.001, 95% CI -20.4 to -18.5], and -20.9% for tirzepatide 15 mg [P<0.001, 95% CI -21.8 to -19.9] compared to -3.1% in the placebo group [P<0.001, 95% CI -4.3 to -1.9]. The co-primary endpoint, weight reduction of 5% or more, found 85% [P<0.001, 95% CI 82 to 89], 89% [P<0.001, 95% CI 86 to 92], and 91% [P<0.001, 95% CI 88 to 94] of patients achieving this measurement for 5,10, and 15 mg of weekly tirzepatide, respectively, compared to 35% for placebo.

Application to Practice

The recent FDA approval of tirzepatide, the first GLP-1/GIP dual-agonist on market, provides exciting opportunity and advancement in the realm of diabetes and weight loss as early results from randomized clinical trials are promising. Tirzepatide has been shown to decrease HbA1c on average between -1.87% and -2.58%.[9-13] The 2023 American Diabetes Association (ADA) guidelines have recently modified their treatment algorithm for the management of T2DM.[1] Treatment options are now chosen based on what types of personalized goals the patient has when it comes to their disease state. Tirzepatide is included in the guidelines for patients that wish to achieve and maintain glycemic and weight management goals, with the highest efficacy rating.

Furthermore, even at its lowest therapeutic dose, tirzepatide has demonstrated greater weight loss from baseline compared to semaglutide, a GLP-1 with an FDA indication for weight loss, reducing weight by 7.6 kg and 5.7 kg, respectively.[10] However, it should be noted that in SURPASS-2, the maximum semaglutide dose was 1 mg which is less than what is maximally available (up to 2.4 mg weekly). Additional SURMOUNT trials examining tirzepatide's weight loss potential are expected to be published in 2023. As of October 2022, Eli Lilly received US FDA fast track designation for the investigation of tirzepatide for the treatment of adults with obesity, or overweight with weight-related comorbidities.[15]

The GLP-1 receptor agonists with proven cardiovascular benefit are considered first line in patients with T2DM and a history of cardiovascular disease.[1] A cardiovascular outcomes trial (CVOT) for tirzepatide is currently being conducted with estimated completion in October 2024.[16] Results from CVOT are measuring the time it takes for the composite of death from cardiovascular causes, a myocardial infarction, or stroke in patients who are taking tirzepatide versus dulaglutide. Results of this trial may alter tirzepatide's place in therapy within the ADA guidelines to assist those with cardiovascular disease.

While initial results from SURPASS and SURMOUNT-1 seem promising, there are several barriers to acknowledge when it comes to medication access and tolerability. Tirzepatide is sold as brand name only, Mounjaro®, which raises cost concerns. Additionally, due to the dual mechanistic nature of tirzepatide, the medication may result in a varying degree of tolerability and will require close post-marketing observation. Tirzepatide should only be increased by 2.5 mg increments every 4 weeks to improve tolerability.[17] Tirzepatide pens are single use ranging from 2.5 to 15 mg with a self-contained needle. This can be helpful for patients performing injections with poor eyesight or limited dexterity. Due to the high demand of tirzepatide for weight and HbA1c management, keeping tirzepatide in stock has been difficult for many pharmacies since the fall of 2022. For now, tirzepatide usage may be limited by the above factors.

Conclusion

The addition of tirzepatide to the 2023 ADA treatment guidelines for patients desiring glycemic control and weight management fits the initial data from the SURPASS trials. Forthcoming CVOT and additional SURMOUNT trials should provide additional information on the impact of tirzepatide for patients with T2DM, obesity, and cardiovascular disease. The initial demonstrations of the weight loss potential and HbA1c lowering ability of tirzepatide may lead to a paradigm shift for treatment of T2DM and obesity.

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