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Research Article

Who are the Best Candidate Patients with Diabetes for Tirzepatide?

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Abstract

Background: Tirzepatide is a dual receptor agonist of the 2 incretin hormones: Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) which is was recently approved for treatment of type 2 diabetes.

Objective: To define the most appropriate patients that may benefit from tirzepatide.

Methods: Pubmed search until August 10, 2022. Search terms were GLP-1, GIP, tirzepatide, efficacy, safety, obesity. Clinical trials and pertinent animal studies and reviews were included.

Results: Tirzepatide was more effective in lowering hemoglobin A1c (HbA1c) levels and body weight than submaximal doses of semaglutide (1.0 mg once-weekly), dulaglutide (1.5 mg once-weekly), insulin degludec (mean daily dose 48.8 U) and insulin glargine (mean daily dose 43.5 U). In patients with type 2 diabetes and Non-Alcoholic Fatty Liver Disease (NAFLD), tirzepatide significantly decreased Liver Fat Content (LVC). Safety profile of tirzepatide was generally similar to that of GLP-1 agonists, but frequency of Gastrointestinal (GI) adverse effects are slightly higher with tirzepatide. Incidence of severe hypoglycemia (blood glucose < 54 mg/dl) is also slightly higher with tirzepatide than semaglutide and dulaglutide, but much lower than insulin degludec and glargine. Drug discontinuation rates due to adverse effects were higher with tirzepatide compared with semaglutide, dulaglutide, and insulin.

Conclusions: Tirzepatide may be most appropriate for patients with type 2 diabetes who are obese, as alternative to GLP-1 agonists or basal insulin, and in patients with NAFLD.

Keywords: Tirzepatide; Semaglutide; Dulaglutide; GLP-1; GIP; Efficacy; Safety; Weight loss

Introduction

Tirzepatide (LY3298176) is a dual GIP/GLP-1 receptor agonist [1]. Its 39 amino acid sequence is mainly based on that of native GIP which consists of 42 amino acids [1]. Tirzepatide is attached to a 20-carbon fatty diacid moiety which binds to albumin. Albumin binding prolongs its half-life to approximately 5 days allowing once a week subcutaneous administration [2]. Tirzepatide has similar GIP receptor binding affinity to native GIP. Yet, it has 5 times lower affinity to GLP-1 receptor compared to native GLP-1 [2]. Tirzepatide is given in 3 weekly doses: 5,10,15 mg. To alleviate GI adverse effects, the drug is started with weekly dose of 2.5 mg that can be increased by 2.5 mg every 4 weeks until the desired dose is attained [3]. Tirzepatide (Mounjaro) was approved in May 2022 by the Federal Drug Administration (FDA) for treatment of type 2 diabetes [3]. The main purpose of this article is to define the most appropriate patients with type 2 diabetes for tirzepatide based on available data and drug profile.

The SURPASS Trials

Tirzepatide FDA approval was based on a series of phase 3 clinical trials (called SURPASS-1 through 5) [4-8]. Primary endpoint of SURPASS 1-5 trials was the change in HbA1c levels with tirzepatide compared to baseline versus comparator. SURPASS 1 and 5 studies were double-blind and placebo-controlled trials. The other 3 trials were open-label comparing tirzepatide with semaglutide (SURPASS-1), insulin degludec (SURPASS-3) and insulin glargine (SURPASS-3). Most patients in the SURPASS trials were obese with mean baseline HbA1c levels ranging from 7.9% to 8.5% [4-8]. Overview and main results of SURPASS trials are summarized in table 1 and discussed further below.

Mechanisms of Action of Tirzepatide

In SURPASS-1 trial, Rosenstock et al [4] have shown that tirzepatide decreased insulin resistance in comparison with placebo as assessed by the homeostatic model assessment. Using the gold standard method of evaluating insulin resistance, the glucose clamp disposition index, Heise et al [9] found that tirzepatide significantly increased both insulin secretion and sensitivity versus placebo and semaglutide 1 mg/week in patients with type 2 diabetes. In addition, tirzepatide decreased glucose excursions and inhibited plasma glucagon more than semaglutide during the mixed meal testing [9]. Greater weight loss with tirzepatide 15 mg (-11.2 kg) versus semaglutide 1 mg (-6.9

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kg) may be a major factor behind these differences [9]. Meanwhile, experiments in mice have shown that tirzepatide improved insulin sensitivity in a weight-dependent and independent manners [10]. The mechanisms of weight-loss promoting action of tirzepatide are not fully understood. Animal studies suggest that GIP receptors in the hypothalamus mediate satiety [11]. Another factor that may contribute to weight loss induced by tirzepatide is the relatively common occurrence of nausea and vomiting associated with its use (see below). Comparison of the extent of weight loss between patients who reported nausea and vomiting with tirzepatide versus those who did not might clarify this issue. Unfortunately, investigators in the SURPASS-trials did not report such important information.

Candidate Patients for Tirzepatide

As Alternative to GLP-1 Agonists

Tirzepatide versus semaglutide: Current data suggest that the GLP-1 receptor agonist semaglutide is the most effective GLP-1 agonist both in terms of anti-hyperglycemic and weight loss effects [12-14]. Meanwhile, emerging evidence suggests that tirzepatide may be more effective than semaglutide. In SURPASS-2 trial, patients with type 2 diabetes on metformin were randomized to receive once weekly tirzepatide 5 mg, 10 mg, 15 mg or semaglutide 1 mg once weekly [5]. At 40 weeks, mean HbA1c reductions from baseline with tirzepatide 5 mg, 10 mg, and 15 mg were -2.01, -2.24 and -2.30%, respectively, as compared with -1.86% with semaglutide [6]. Moreover, reductions in weight were greater with tirzepatide than with semaglutide (see below). Therefore, results of SURPASS-2 trial suggest that tirzepatide may be a viable alternative to semaglutide in patients requiring additional reductions in HbA1c and weight. However, tirzepatide was less tolerated than semaglutide. Thus, withdrawal due to adverse effects were 6-8.5% and 4.1% in the tirzepatide and semaglutide groups, respectively [5]. In addition, tirzepatide was not compared with the maximal effective dose of semaglutide 2.4 mg/week. An indirect comparison by Vadher et al [15] showed that HbA1c and weight reductions were significantly greater with tirzepatide 10 and 15 mg/week versus semaglutide dose of 2.0 mg/week. Clearly, direct head to head trials are needed to confirm the superiority of tirzepatide over semaglutide 2.4 mg/week.

Tirzepatide versus dulaglutide: Similar results as above were reported when tirzepatide was compared with dulaglutide. In a phase 2 trial of 26-week duration (n=316), tirzepatide in weekly doses of 10 mg and 15 mg (but not 5 mg) was more effective than dulaglutide 1.5 mg once weekly with differences in HbA1c values of 0.67% and 0.73% in favor of semaglutide 10 mg and 15 mg, respectively [16]. Weight loss was also greater with tirzepatide 15 mg (11.3 kg) versus dulaglutide (2.7 kg). Meanwhile, the highest dose of tirzepatide 15 mg/week was less tolerated than dulaglutide, with discontinuation rates as result of adverse effects being 24.5% and 11.1%, respectively [16]. In addition, the highest effective dose of dulaglutide 4.5 mg once weekly was not evaluated in this study [17].

Patients with Overweight or Obesity

Tirzepatide exerts a potent dose-related effect on weight loss that was more pronounced compared with that caused by semaglutide 1 mg. The differences being -1.9 kg, -3.6 kg, -5.5 kg with the 5, 10, and 15 mg tirzepatide doses, respectively [5]. Contrary to their effects on HbA1c levels that plateaued after 24 weeks, weight reduction associated with tirzepatide and semaglutide use continued until the end of intervention at 40 weeks [5]. In fact, due to its high efficacy in promoting weight loss, tirzepatide was recently evaluated as anti-obesity agent in subjects without diabetes in the SURMOUNT trial [18]. The latter was a large (n=2,539), double-blind, placebo-controlled, randomized multi-center trial including. At baseline, the mean body weight was 104.8 kg and mean body mass index (BMI) was 38.0 kg/m^2 [18]. At week 72, the placebo-adjusted mean percentage change in weight was -11.9% (95% CI -13.4 to -10.4), -16.4% (95% CI, -17.9 to -14.8), and -17.8% (95% CI, -19.3 to -16.3) for the 5 mg-dose, 10mg-dose and 15 mg-dose, respectively (P<0.001 vs placebo) [18].

Patients who are Reluctant to Take Insulin

Many patients with type 2 diabetes refuse to take insulin because of fear of frequent injections, weight gain and/or hypoglycemia. There is good evidence that tirzepatide is superior to titrated once daily basal insulin in terms of glycemic control and weight reduction. In SURPASS-3, from a mean baseline HbA1c of 8.17%, the reductions in HbA1c levels at week 52 were 1.93%, 2.20%, and 2.37% in the tirzepatide 5, 10, 15 mg groups, respectively, compared with a decrease of 1.34% in the insulin degludec group (mean daily dose at week 52 was 48.8 U) [6]. The estimated treatment difference between tirzepatide and degludec ranged from 0.59 to 1.04% [6]. In a substudy of 243 patients enrolled in SURPASS-3 trial, Battelino et al [19] compared diurnal glucose profile of tirzepatide 10 mg and 15 mg pooled groups with insulin degludec by continuous glucose monitoring. After 52 weeks, tirzepatide-treated patients had 25% (95% CI, 16-33) greater proportion of time spent in target range (71-140 mg/dl) than degludec-treated patients [19]. Moreover, the use of tirzepatide (10-15 mg) was associated with significant decrease in within-day glucose variability of -8.2%. Conversely, insulin degludec was associated with an increase in variability of 4.8% [19]. With respect to weight changes, form a baseline weight of 94.3 kg, all tirzepatide doses decreased weight by 7.5 to 12.9 kg, whereas degludec was associated with mean weight increase of 2.3 kg [6]. Similar findings were reported in SURPASS-4 trial comparing tirzepatide with insulin glargine (mean daily dose 43.5 U) [7]. Thus, after 52 weeks, HbA1c levels were 0.80%-1.14% and weight was 9-13.5 kg lower in the 3 tirzepatide groups versus glargine group [7]. A third advantage of using tirzepatide in place of insulin is the lower risk of hypoglycemia (see "Hypoglycemia" below). Yet, despite these advantages, discontinuation rates due to adverse effects were much higher with tirzepatide 7-11% versus either degludec (1%) or glargine (5%) (Table 1) [6,7].

As Add-On Therapy in Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin

In SURPASS-5 trial, tirzepatide was added to ongoing glargine and metformin therapy in the setting of uncontrolled type diabetes (mean baseline HbA1c 8.3%) [8]. Glargine doses were titrated in all treatment groups with a target of fasting blood glucose of < 100 mg/dl [8]. After 40 weeks, tirzepatide use was associated with greater reduction in HbA1c values (2.1 to 2.4% vs 0.86% with placebo), and in weight: 5.4 to 8.8 kg vs a weight gain of 1.6 kg with placebo [8]. Glargine daily doses increased by an average 25.1 units, whereas

Table 1: Main results of the SURPASS trials of tirzepatide 5, 10, 15 mg once weekly.

Trial name, patient number (n), percentage of females (F), mean age, mean *BMI, and duration	Comparator	Change in mean HbA1c	Change in mean weight (kg)	Proportions of patients who discontinued drug due to adverse effects
SURPASS-1, n=478, 48% F, 54 years, 31.9 kg/m^2, 40 weeks [4]	Placebo (P)	-1.87% to -2.07% with tirzepatide (T) and + 0.04% with P	-7.0 to -9.5 with T vs P - 0.7	3 to 7% with T vs 3% with P
SURPASS-2, n=1,879, 53% F, 56 years, 34.2 kg/m^2, 40 weeks [5]	Semaglutide (S) 1 mg/week	-2.01% to -2.30% with T vs -1.86% with S (p<0.001 vs S)	-7.6 to -11.2 with T vs -5.7 with S (p<0.001 vs S).	6 to 8.5% with T vs 4.1% with S
SURPASS-3, n=1,437, 56% F, 57 years, 33.5 kg/m^2, 52 weeks [6]	Once daily titrated insulin degludec. Mean (SD) dose at 52 weeks 48.8 (30.4) U/d	-1.93% to -2.37% with T vs degludec -1.34% (p<0.001)	-7.5 to -12.9 with T vs degludec +2.3 (p<0.0001)	7 to 11% with T vs degludec 1%
SURPASS-4, n=1,995, 38% F, 63 years, 32.6 kg/m^2, 52 weeks [7]	Once daily titrated insulin glargine. Mean (SD) dose at 52 weeks 43.5 (24.9) U/d	-2.43% to -2.58% with T vs -1.44% with glargine (P<0.0001 for T 10-15 mg vs glargine)	-9.0 to -13.5 with T vs glargine (P<0.0001). Weight changes compared to baseline were not reported.	9 to 11% with T vs glargine 5%
SURPASS-5, n=475, 44% F, 60 years, 33.4 kg/m^2, 40 weeks [8]	Placebo (P). All patients were on insulin glargine	-2.11% to -2.40% with T vs -0.86% with P (p<0.001 vs P)	-5.4 to -8.8 with T vs +1.6 with P (p<0.001)	6.0 to 10.8% with T vs 2.5% with P

*BMI: Body Mass Index

they decreased by 3.8 units with the highest dose of tirzepatide 15 mg. Hence, addition of tirzepatide to ongoing basal insulin may decrease HbA1c levels and weight without increasing insulin doses. However, these advantages occurred at the expense of increased risk of hypoglycemia (see below).

Patients with Non-Alcoholic Fatty Liver Disease

Preliminary data suggest that tirzepatide may be beneficial in treatment on NAFLD in patients with type 2 diabetes. In a substudy of SURPASS-3 (n=296), absolute reduction in Liver Fat Content (LFC) assessed by magnetic resonant imaging-proton density fat fraction (MRI-PDFF) was significantly greater for the pooled tirzepatide 10 mg and 15 mg groups versus the insulin degludec -8.09%, and -3.38%, respectively at 52 weeks (p<0.0001) [20]. In addition, all tirzepatide doses significantly reduced visceral adipose tissue volume by 1.10-1.65 L. On the contrary, insulin degludec significantly increased both visceral adipose tissue (by 0.38 L) and abdominal subcutaneous adipose tissues (by 0.63 L) [20]. In addition, liver enzymes were significantly decreased with tirzepatide versus degludec [20].

Effects of Tirzepatide on Cardiovascular Risk Factors

Tirzepatide treatment was associated with greater amelioration of blood pressure, lipid profile, and hyperinsulinemia [4-8]. These changes are largely attributed to weight loss.

Safety of Tirzepatide

Rates of drug discontinuation due to adverse effects reflect the overall tolerance and safety of a given drug. These rates were approximately double among patients randomized to tirzepatide (10-15 mg) compared with placebo (5-7% vs 3%) and semaglutide (8.5% vs 4.1%) (Table 1) [4-8].

Gastrointestinal Adverse Effects

The most common adverse effects of tirzepatide are related to the GI system, namely nausea, diarrhea and vomiting. They are dose-related, generally described as mild to moderate, and occur in the first few weeks or months after initiation of tirzepatide during dose escalation [4-8]. When compared with semaglutide 1 mg, GI adverse effects were slightly more common with the highest dose of tirzepatide (15 mg): nausea (22.1% vs 17.9%), diarrhea (13.8% vs 11.5%), and vomiting (9.8% vs 8.3%).

Hypoglycemia

The frequency of clinically significant hypoglycemia (defined as blood glucose <54 mg/dl) was approximately 4 times greater with tirzepatide 15 mg when compared with semaglutide (1.7% and 0.4%, respectively) [5]. Similarly, frequency of hypoglycemia (blood glucose < 70 mg/dl) was greater with tirzepatide (7.5-9.8%) vs dulaglutide (3.7%), but no severe hypoglycemia was reported in any treatment group [16]. Meanwhile, the highest rates of tirzepatide-associated hypoglycemia were observed when used in conjunction with insulin. Thus, when tirzepatide was added to ongoing insulin glargine, proportions of patients who reported blood glucose <54 mg/dl were higher in tirzepatide-treated patients (14.2-19.3%) than placebo-treated patients (12.5%) [8]. The increase in tirzepatide-associated hypoglycemia occurred despite lowering insulin doses by 20% in patients with HbA1c < 8.0% upon starting tirzepatide. Therefore, caution should be exercised when adding tirzepatide to insulin. It may be wise to reduce insulin doses by approximately 30% rather than 20% to prevent potential hypoglycemia. On the other hand, when compared head to head with basal insulin, incidence of hypoglycemia was less frequent with tirzepatide. Thus, frequency of blood glucose <54 mg/dl was 1-2% with tirzepatide versus 7 % with insulin degludec, and 6-9% versus 19% with insulin glargine [6,7].

Increase Heart Rate

Increase heart was reported with all GLP-1 agonists [21]. Both tirzepatide and semaglutide 1 mg were associated with a similar increase in heart rate of approximately 2.5 Beats Per Minute (bpm) [4]. The greatest increase in mean pulse rate was observed in SURPASS-5 trial: 1.3 to 5.6 bpm in the tirzepatide groups versus a decrease of 0.8 bpm with placebo. [8]. A meta-analysis of SURPASS trials reported no significant increase in risk ratio (RR) of atrial fibrillation with tirzepatide; RR 1.59 (95% CI, 0.46-5.47) [22]. However, the number of events was small (8 cases and 2 cases in tirzepatide and comparator group, respectively) [22].

Effect of Tirzepatide on Cardiovascular Events and Mortality

Data related to the impact of tirzepatide on Cardiovascular (CV) events and mortality is limited. The best available information may be derived from the SURPASS-4 trial, in which comparison

of adjudicated CV events between tirzepatide and glargine were a prespecified safety objective [7]. Importantly, the SURPASS-4 trial recruited patients with type 2 diabetes with high CV risk at baseline. Thus, patients were older than in other SURPASS trials (mean age 63.6 years) and 87% of them had history of CV disease [7]. Compared with glargine, tirzepatide was associated with a non-significant trend for reduction of the 4 major adverse CV outcomes (MACE-4), namely CV death, myocardial infarction, stroke and hospitalization for unstable angina [7]. Thus, after a median duration of follow-up of 85 weeks, hazard ratio for MACE-4 compared with glargine was 0.74 (95% CI, 0.51-1.08) [7].

Limitations of Tirzepatide

Despite the encouraging preliminary results reported with tirzepatide use, this drug has several important limitations. First, the incidence of GI adverse effects was higher than all comparators. Second, data is limited to 5 phase 3 trials lasting only 40-52 weeks in most patients. Thus, it is not known whether its effects on glycemic control and weight are durable. Second, patients with Chronic Kidney Disease (CKD) with Estimated Glomerular Filtration Rate (eGFR) below 45 ml/min/1.73 m^2 were excluded from SURPASS trials [4-8]. One study by Urva et al [23] has shown that renal impairment including need for hemodialysis has no clinically relevant effects on pharmacokinetics of tirzepatide. However, the latter investigation was a single-dose study that used tirzepatide in a small dose of 5 mg [23]. Third, patients with diabetic maculopathy and proliferative retinopathy and HbA1c levels > 10.5% were also excluded. Fourth, long-term safety of tirzepatide, including its effects on CV and renal events, are not known.

Conclusions and Current Directions

Introduction of tirzepatide represents a welcome introduction of a new class for treatment of type 2 diabetes. Available data suggest that this dual GLP-1 and GIP receptor agonist may be superior to selective GLP-1 agonists and basal insulin in terms of anti-hyperglycemic efficacy and weight loss. Therefore, based on available data, tirzepatide may be an ideal medication for the following groups of patients with type 2 diabetes. First, in obese patients as add-on therapy to metformin. Second, as alternative to GLP-1 agonists when additional reductions in HbA1c levels and weight are needed. Third, as alternative to basal insulins in patients who are reluctant to take insulin. It would be interesting to compare tirzepatide directly with the highest doses of semaglutide (2.4 g/week) and dulaglutide (4.5 mg/week). The impact of tirzepatide on incidence of CV and renal events and mortality is certainly of crucial importance. This issue is currently under investigation in SURPASS-CVOT trial. The latter study is a large (n=12,500) double-blind trial comparing tirzepatide with dulaglutide 1.5 mg/week and is expected to terminate in October 2024 [24].

Conflicts of Interest

The author has no conflict of interest to declare.

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