Postprint: Advances in Clinical Research on the Novel Antidiabetic Drug Tirzepatide

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Abstract

Currently, numerous pharmacological agents are available for diabetes treatment globally; however, many patients still fail to achieve the recommended target glycemic levels, making the development and application of novel hypoglycemic drugs imperative. In May 2022, the FDA approved tirzepatide, a dual GIP and GLP-1 receptor agonist, for once-weekly administration as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Multiple clinical studies have validated its efficacy and safety for type 2 diabetes, while also demonstrating potential therapeutic value in obesity, cardiovascular risk-related diseases, non-alcoholic steatohepatitis, and other conditions. This article provides a review of tirzepatide' s mechanism of action, efficacy, and safety to serve as a reference for its clinical application following market launch in China.

Full Text

Preamble

Research Progress of Tirzepatide, a Novel Hypoglycemic Drug

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Abstract: Despite the availability of various drugs for the treatment of diabetes worldwide, many patients still fail to achieve the recommended target blood sugar levels. Therefore, it is urgent to develop and apply new hypoglycemic agents. In May 2022, the FDA approved tirzepatide, a dual receptor agonist for

glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), for once-weekly administration as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Multiple clinical studies have verified its effectiveness and safety in type 2 diabetes, and it also shows potential applications in obesity, cardiovascular risk-related diseases, and non-alcoholic steatohepatitis. This article reviews the mechanism of action, efficacy, and safety of tirzepatide to provide a reference for its clinical application after market launch in China.

Keywords: Tirzepatide; Type 2 diabetes mellitus; Glucose-dependent insulinotropic polypeptide/Glucagon-like peptide-1 receptor agonist; Obesity; Effectiveness; Safety

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According to the latest diabetes epidemiology data from 2021, there are 537 million people with diabetes worldwide, including approximately 141 million in China. Diabetes accounts for 9% of global health expenditures, totaling $966 billion. Although numerous therapeutic agents are available for diabetes treatment globally, many patients still fail to achieve recommended glycemic targets, making the development and application of novel hypoglycemic drugs imperative. On May 13, 2022, the U.S. Food and Drug Administration (FDA) approved tirzepatide (TZP), a dual receptor agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), for once-weekly injection as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Chinese scholars commonly translate TZP as "替西帕肽" (Tixipatide). Multiple clinical studies have validated the efficacy and safety of TZP for T2DM, while also demonstrating potential value in obesity, cardiovascular risk-related diseases, and non-alcoholic steatohepatitis (NASH). This review focuses on the mechanism of action, efficacy, and safety of TZP to provide a reference for its clinical application following market launch in China.

1.1 Basic Information

TZP is a single-molecule polypeptide formulation that activates both GIP and GLP-1 receptors, the two natural incretin hormones in humans. With a molecular formula of C_{225}H_{348}N_{48}O_{68} and a molecular weight of 4813.45, it is a linear synthetic peptide composed of 39 amino acids based on the native GIP sequence, sharing 19 amino acids with human GIP(1-42). TZP incorporates a biologically active N-terminal GIP sequence and an exenatide-like C-terminal sequence, while also incorporating a fatty acid side chain similar to semaglutide to enable albumin binding and extend its half-life to 116.7 hours (approximately 5 days), allowing for once-weekly dosing. Its chemical structure is illustrated in Figure 1 [Figure 1: see original paper].

1.2 Pharmacokinetics of TZP

TZP reaches maximum plasma concentration 1–2 days after administration. Coskun et al. demonstrated that with once-weekly dosing, steady-state plasma concentrations are achieved after approximately 4 weeks, with pharmacokinetic parameters in T2DM patients being broadly comparable to those in healthy volunteers. After the fourth dose, peak concentrations in the 10 mg and 15 mg dose groups were 214.6 nmol/L and 260 nmol/L, respectively, with time to peak of 24 hours for both. An 8-week multiple-dose-escalation Phase I clinical study conducted in Japanese patients with T2DM found that only the 15 mg dose group showed higher peak concentrations than those reported above, with no significant differences in other parameters.

2 Mechanism of Action

The mechanisms by which TZP improves glycemic and weight control in T2DM patients have not been fully elucidated. The GIP and GLP-1 receptors are class B1 G protein-coupled receptors that regulate glucose, lipid, and amino acid metabolism, and both are expressed in pancreatic -cells. Activation of these receptors leads to increased cyclic adenosine monophosphate (cAMP) and glucose-dependent insulin secretion, representing therapeutic targets for T2DM and obesity. GLP-1 can modulate insulin secretion, control blood glucose, delay gastric emptying, and suppress appetite. The precise role of GIP remains unclear, but research suggests it can bidirectionally regulate insulin secretion, act directly on subcutaneous white adipose tissue to improve insulin sensitivity and fat buffering capacity, and enhance blood flow and storage capacity. GIP also inhibits gastric acid secretion and delays gastric motility, contributing to pancreatic islet protection and insulin secretion modulation. A Phase II clinical trial confirmed that TZP significantly improves glycemic and weight control without increasing gastrointestinal adverse reactions, indicating benefits beyond simple "super-enhanced" GLP-1 receptor agonism and demonstrating significant contributions from GIP receptor agonism to the dual agonist's effects. Based on preclinical studies, some have proposed that GIP acts as an antiemetic, thereby improving tolerability of GLP-1 receptor agonists.

Thomas et al. found that compared with dulaglutide, TZP improved insulin resistance and pancreatic -cell function to a greater extent, with effects only partially attributable to weight loss, suggesting that the dual receptor agonist confers distinct glycemic control mechanisms. Tim Heise et al., using clamp studies to explore TZP's mechanism of action, proposed that its glucose-lowering effects are achieved through multiple improvements in -cell function, including enhanced insulin sensitivity, first- and second-phase insulin secretion, and -cell glucose sensitivity, thereby significantly reducing fasting and postprandial glucose. While GIP may cause weight gain, TZP exhibits biased cAMP signaling at the GLP-1 receptor, suggesting that pathway bias at the GLP-1 receptor, in addition to GIP receptor signaling, may contribute to TZP's efficacy in glycemic control and weight regulation in T2DM patients.

Additionally, TZP modulates -cell function through different signaling pathways by activating adenylate cyclase, increasing intracellular cAMP concentration, and thereby activating protein kinase A and exchange protein directly activated by cAMP (Epac). Epac has two isoforms: type 1 may have protective effects on -cells, while type 2 promotes glucose-induced insulin secretion, which may partly explain TZP' s superior glucose-lowering effects compared with selective GLP-1 receptor agonists. In summary, TZP is not a simple additive combination of GLP-1 and GIP receptor agonists but achieves a "1+1>2" effect through synergistic and complementary mechanisms.

3.1 Type 2 Diabetes Mellitus

The SURPASS clinical trial program compared the efficacy and safety of TZP with currently available hypoglycemic drugs or placebo. These studies consistently demonstrated significant glycemic and weight reduction efficacy with TZP. SURPASS-1 showed that TZP 5 mg, 10 mg, and 15 mg reduced glycated hemoglobin (HbA1c) by 1.87%, 1.89%, and 2.07%, respectively, compared with only 0.04% in the placebo group. SURPASS-2, a head-to-head comparison with semaglutide (1 mg), revealed that TZP 5 mg, 10 mg, and 15 mg reduced HbA1c by 2.09%, 2.37%, and 2.46%, respectively, versus 1.86% with semaglutide. All TZP doses were superior to semaglutide (1 mg), with 92% and 51% of patients in the TZP 15 mg group achieving HbA1c 6.5% and <5.7%, respectively.

SURPASS-3 compared TZP with titrated insulin degludec as add-on therapy to metformin with or without SGLT2 inhibitors. Results showed HbA1c reductions of 1.93%, 2.20%, and 2.37% in the TZP 5 mg, 10 mg, and 15 mg groups, respectively, compared with 1.34% in the insulin degludec group. A higher proportion of subjects in all three TZP groups achieved HbA1c <7.0% compared with insulin degludec (82–93% vs. lower rates). SURPASS-4 compared TZP with insulin glargine, demonstrating HbA1c reductions of 2.24%, 2.43%, and 2.58% in the TZP 5 mg, 10 mg, and 15 mg groups, respectively, versus 1.44% with insulin glargine. SURPASS-5 evaluated TZP versus placebo added to insulin glargine with or without metformin, showing HbA1c reductions of 2.23%, 2.59%, 2.59%, and 0.93% in the TZP 5 mg, 10 mg, 15 mg, and placebo groups, respectively. The proportion of patients achieving HbA1c <7% was significantly higher in TZP groups (85–90% vs. 34% with placebo).

One study compared TZP with semaglutide 2 mg, finding no significant difference in HbA1c reduction between TZP 5 mg and semaglutide 2 mg at 40 weeks, while TZP 10 mg and 15 mg significantly outperformed semaglutide 2 mg. Another study reported that while 80% of patients receiving high-dose GLP-1 receptor agonists achieved HbA1c targets, 97% of TZP-treated patients reached these goals, with 62% achieving HbA1c <5.7%. SURPASS-AP-Combo assessed TZP versus insulin glargine in T2DM patients on metformin with or without sulfonylureas, showing HbA1c reductions of 2.42%, 2.43%, and 2.49% with TZP 5 mg, 10 mg, and 15 mg, respectively, compared with 0.95% with insulin glargine, and higher rates of achieving HbA1c <7% (75.6–84.9% vs. 23.7%).

Collectively, these studies suggest that TZP 5 mg has comparable glycemic efficacy to semaglutide 2 mg, while higher TZP doses demonstrate superior efficacy compared with current hypoglycemic agents.

3.2 Obesity

Regarding weight reduction, SURPASS-1 showed placebo-subtracted weight losses of 7.0 kg, 7.8 kg, and 9.5 kg with TZP 5 mg, 10 mg, and 15 mg, respectively, compared with 0.7 kg in the placebo group. SURPASS-2 demonstrated weight reductions of 7.8 kg, 10.3 kg, and 12.4 kg with TZP 5 mg, 10 mg, and 15 mg, respectively, versus 6.2 kg with semaglutide, with 40% of patients in the TZP 15 mg group achieving 15% weight loss. SURPASS-3 reported weight reductions of 7.8 kg, 10.3 kg, and 12.4 kg with TZP, while insulin degludec caused a 2.3 kg weight gain. A subgroup analysis based on SURPASS-3 showed that TZP significantly reduced liver fat content, visceral adipose tissue volume, and abdominal subcutaneous adipose tissue compared with insulin degludec. SURPASS-4 revealed weight reductions of 7.1 kg, 9.5 kg, and 11.7 kg with TZP, while insulin glargine increased weight by 1.9 kg. SURPASS-5 showed weight losses of 6.2 kg, 8.2 kg, and 10.9 kg with TZP versus 1.7 kg with placebo. SURPASS-AP-Combo demonstrated weight reductions of 5.0 kg, 7.0 kg, and 7.2 kg with TZP, while insulin glargine increased weight by 1.5 kg. All these subjects had T2DM, and TZP produced dose-dependent weight reduction in this population.

SURMOUNT-1, the first global Phase III study of TZP in non-T2DM patients with obesity or overweight, showed weight reductions of 16 kg, 22 kg, and 24 kg with TZP 5 mg, 10 mg, and 15 mg, respectively, compared with 2 kg with placebo. Furthermore, 89% (5 mg) and 96% (10 mg and 15 mg) of TZP-treated subjects achieved at least 5% weight loss versus 28% with placebo, while 55% (10 mg) and 63% (15 mg) achieved 20% weight loss versus only 1.3% with placebo. Waist circumference reductions from baseline were 14.6 cm, 19.4 cm, and 19.9 cm with TZP 5 mg, 10 mg, and 15 mg, respectively, compared with 3.4 cm with placebo. TZP-treated subjects also showed approximately three times greater reduction in fat mass percentage than lean mass (33.9% fat mass reduction vs. 10.9% lean mass reduction). Additional analysis revealed that TZP reduced systolic/diastolic blood pressure by 7.2 mmHg and 4.8 mmHg, respectively, compared with 6.2 mmHg and 2.83 mmHg reductions with semaglutide. The main glycemic and weight loss clinical trial results for TZP are summarized in Table 1 .

3.3 Cardiovascular Risk-Related Diseases

The SURPASS-CVOT study is a global Phase III cardiovascular outcomes trial for TZP and the first large CVOT to use a proven cardioprotective antidiabetic drug as an active comparator. It aims to evaluate the non-inferiority and superiority of TZP versus dulaglutide regarding cardiovascular outcomes. This multinational study includes over 20 hospitals in China and is expected to com-

plete in 2024. A meta-analysis incorporating seven randomized controlled trials from SURPASS compared the time to first occurrence of four major adverse cardiovascular events (MACE-4: cardiovascular death, myocardial infarction, stroke, and hospitalized unstable angina) between pooled TZP groups and control groups. Results showed a hazard ratio of 0.80 (95% CI, 0.57–1.11) for MACE-4, 0.90 (95% CI, 0.50–1.61) for cardiovascular death, and 0.80 (95% CI, 0.51–1.25) for all-cause mortality, indicating that TZP does not increase the risk of major cardiovascular events in T2DM subjects. Patoulias et al. analyzed the risk of atrial fibrillation with TZP use and found no increased risk in T2DM patients.

GLP-1 receptor agonists have been shown to reduce lipoprotein and chylomicron production, as well as postprandial triglycerides, very-low-density lipoprotein cholesterol, and free fatty acids, though the magnitude of effect is modest. The long-term effects of GIP receptor agonism on lipid profiles remain unclear. Although the mechanism is not fully understood, infusion studies of GIP and GIP receptor antagonists in humans suggest that GIP receptor activation increases adipose tissue blood flow and promotes lipid uptake. One study demonstrated that TZP' s effects on plasma triglycerides were significantly greater than those of GLP-1 receptor agonists. Another study reported that TZP dose-dependently reduced apoC-III and apoB levels and decreased the number of large triglyceride-rich lipoprotein particles and small low-density lipoprotein particles, suggesting net improvement in atherogenic lipoprotein profiles, though this post-hoc analysis had limitations due to incomplete biomarker matching across groups. A post-hoc analysis based on SURPASS-2 found that TZP reduced several cardiovascular risk biomarkers including YKL-40, ICAM-1, and hsCRP at 26 weeks. Based on these multiple benefits, TZP is considered a promising agent for cardiometabolic therapy.

3.4 Non-Alcoholic Steatohepatitis (NASH)

A post-hoc analysis examined the effects of TZP and dulaglutide on NASH and fibrosis biomarkers, showing that high-dose TZP significantly reduced NASH-related biomarkers such as ALT, AST, CK-18, and type III procollagen while increasing adiponectin levels. Synergy-NASH is a randomized, double-blind, placebo-controlled Phase 2 study comparing TZP efficacy and safety in NASH patients, with expected completion in December 2023.

Table 1 Summary of the Main Clinical Research Results of Tirzepatide in Hypoglycemic and Weight Loss

Study	NCT Number	Population	Treatment Duration	HbA1c Reduction (%)		Weight Reduction (kg)	
				15 mg	Control	15 mg	Control

Study	NCT Number	Population	Treatment Duration	HbA1c Reduction (%)	Weight Reduction (kg)	
SURPASS-1	NCT03954834	T2DM, diet/exercise	40 weeks	2.07	0.0	9.5	0.7
SURPASS-2	NCT03987919	T2DM, metformin-treated	40 weeks	2.46 (semaglutide)	1.8	12.4 (semaglutide)	6.2 (semaglutide)
SURPASS-3	NCT03882970	T2DM, metformin ±SGLT2i	52 weeks	2.37 (insulin degludec)	1.3	4 12.4 (insulin degludec)	+2.3 (insulin degludec)
SURPASS-4	NCT03730662	T2DM, 1–3 oral agents	52 weeks	2.58 (insulin glargine)	1.4	4 11.7 (insulin glargine)	+1.9 (insulin glargine)
SURPASS-5	NCT04039503	T2DM, insulin glargine ±metformin	40 weeks	2.59 (placebo)	0.9	3 10.9 (placebo)	1.7 (placebo)
SURPASS-AP-Combo	NCT04093732	T2DM, metformin ±sulfonylureas	40 weeks	2.49 (insulin glargine)	0.9	7 7.2 (insulin glargine)	+1.5 (insulin glargine)
SURMOUNT-1	NCT04184622	Non-T2DM, obese/overweight	72 weeks	—	—	24	2 (placebo)
SURPASS-CVOT	NCT04255433	T2DM with ASCVD	Up to 54 months	—	—	—	—

Note: SURPASS-J-Combo and SURPASS-J-mono were conducted in Japan; SURPASS-6 and SURPASS-CVOT studies have not yet been completed.

4.1 Overall Safety and Tolerability of TZP

TZP' s overall safety and tolerability profile is similar to that of GLP-1 receptor agonists. The most common adverse events are gastrointestinal-related, typically mild to moderate in severity, occurring primarily during dose escalation, including nausea, diarrhea, and constipation, which rarely lead to treatment discontinuation. No significant hypoglycemia has been observed. Studies

in Japanese populations have shown consistent glycemic efficacy, safety, and PK/PD characteristics compared with observations in Western populations, with no apparent racial differences.

In SURPASS studies, the most common adverse events with TZP were mild, moderate, and transient gastrointestinal events, including nausea, diarrhea, and vomiting. Compared with insulin degludec, TZP-treated subjects had higher incidence rates of nausea (12.24%), diarrhea (15.17%), decreased appetite (6.12%), and vomiting (6.10%). Severe hypoglycemic events (blood glucose <3.0 mmol/L) occurred in 0.6%, 0.2%, and 1.7% of subjects in the TZP 5 mg, 10 mg, and 15 mg groups, respectively, compared with 0.4% in the semaglutide group. Treatment discontinuation due to adverse events occurred in 4.3%, 7.1%, and 6.2% of subjects in the TZP 5 mg, 10 mg, and 15 mg groups, respectively, versus 2.6% in the placebo group. Frias et al. compared three different TZP dose-escalation regimens with placebo regarding nausea incidence. At 12 weeks, nausea occurred in 7.7% of the placebo group, compared with 24.1% in the 12 mg group (escalated over 3 weeks), 39.3% in the 15 mg-1 group (escalated over 4 weeks), and 35.7% in the 15 mg-2 group (escalated over 3 weeks), indicating that lower starting doses and smaller incremental increases help reduce adverse effects.

4.2 Effects of TZP on Renal Function

SURPASS-4 demonstrated that TZP exhibits renal protective effects, helping delay the progression of chronic kidney disease in T2DM patients with cardiovascular risk. Compared with insulin-treated subjects, TZP-treated subjects had fewer renal complications, with significantly lower incidence of new-onset macroalbuminuria (HR=0.41). Additionally, TZP reduced markers of CKD progression risk, including rate of renal function loss and urinary protein excretion, in T2DM patients with high cardiovascular risk. Urva et al. investigated the pharmacokinetic effects of TZP in patients with varying degrees of renal impairment, categorizing them by baseline eGFR into mild (60–89 mL/min/1.73m^{2}), moderate (30–59 mL/min/1.73m^{2}), severe (<30 mL/min/1.73m^{2}), end-stage renal disease, and normal (90 mL/min/1.73m^{2}) groups. Analysis of area under the concentration-time curve (AUC) and maximum concentration (Cmax) ratios relative to normal renal function showed similar TZP exposure between renal impairment and healthy subjects. Except for a 25–29% AUC increase in the moderate impairment group, 90% confidence intervals for AUC and Cmax ratios were approximately 1 across all groups, with no clear relationship between TZP exposure and eGFR. The study concluded that TZP pharmacokinetics are not clinically significantly affected by renal impairment, and dose adjustment may not be necessary for patients with renal dysfunction.

4.3 Effects of TZP on Hepatic Function

Urva et al. further evaluated TZP pharmacokinetics and tolerability in subjects with hepatic impairment versus healthy controls. Participants were classified by baseline Child-Pugh scores as normal hepatic function, A (mild impairment), B (moderate impairment), or C (severe impairment), and received a single 5 mg subcutaneous TZP injection. Results showed similar AUC_{0} ∞and Cmax between control and hepatic impairment groups, with no clinically relevant correlations with serum albumin, total bilirubin, or international normalized ratio. No significant safety differences were observed between hepatic impairment and healthy control subjects, suggesting that TZP may not require dose adjustment in patients with hepatic impairment.

5 Summary and Outlook

As a novel hypoglycemic agent, TZP demonstrates excellent glucose-lowering and weight-reduction effects, with preliminary evidence of clinical benefit in T2DM patients with cardiovascular disease or chronic kidney disease. This addresses limitations of existing antidiabetic medications and meets the needs of more T2DM patients, showing broad clinical prospects in glycemic control, weight management, and cardiovascular risk reduction. We anticipate that this promising new drug will soon become available clinically in China, providing more treatment options for Chinese T2DM patients. Mechanistically, TZP alone carries a very low risk of hypoglycemia, contributing to its high HbA1c target achievement rates. However, clinical practitioners should note that when TZP is combined with insulin secretagogues or insulin, doses of these agents should be adjusted promptly to avoid hypoglycemia.

TZP is not yet marketed in China, and international clinical experience remains limited. Future research should strengthen investigations into its safety, efficacy, cost-effectiveness, drug interactions, and use in special populations. Several clinical questions remain unanswered, including long-term efficacy and safety requiring further exploration with longer follow-up data and more information on cardiovascular effects. Whether TZP provides additional clinical benefits beyond those of GLP-1 receptor agonists also warrants investigation. These questions await clarification through evidence from randomized controlled trials and real-world studies to provide robust support for rational clinical application.

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Conflict of Interest: The authors declare no conflict of interest.

Literature Search Strategy: PubMed, Web of Science, CNKI, and Wanfang

Data were systematically searched from inception to June 2022, with manual searches of reference lists from included studies. Chinese search terms included "替西帕肽"(tirzepatide), and English terms included "tirzepatide"and "LY3298176" . Inclusion criteria: clinical, basic, and literature studies on tirzepatide. Exclusion criteria: duplicate publications, unavailable full texts or data, outdated literature, and low-quality studies.

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Note: Figure translations are in progress. See original paper for figures.