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REVIEW
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Dual Glucose-Dependent Insulinotropic Polypeptide and Glucagon-Like Peptide-1 Receptor Agonists

ABSTRACT

Glucagon-like peptide-1 is the most potent incretin secreted from the intestinal tract. It is synthesized by L-cells in the jejunum and distal ileum of the gastrointestinal system. Glucose-dependent insulinotropic polypeptide is a polypeptide released by specialized endocrine cells called K cells, most commonly in the duodenum and jejunum, in response to oral food, especially carbohydrates and lipids. Glucose-dependent insulinotropic polypeptide receptors are found in various tissues such as adipose tissue, gastric mucosa, adrenal cortex, pancreas, bone, heart, and brain. The long-term effect of GIP and Glucagon-like peptide-1 receptor agonism was first demonstrated by Finan et al. They have developed a single-molecule dual Glucose-dependent insulinotropic polypeptide and Glucagon-like peptide-1 receptor agonist called "Twincretin." Twincretin has been shown to have negligible glucagon receptor activity and a high affinity for Glucagon-like peptide-1 and Glucose-dependent insulinotropic polypeptide receptors. Tirzepatide is a once-weekly dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist currently under trial to evaluate glycemic efficacy and safety in people with type 2 diabetes, non-alcoholic steatohepatitis, and obesity. Tirzepatide significantly improved glycemic control and body weight and had an acceptable safety profile, this indicates that it is an effective therapeutic option for glucose lowering in patients with type 2 diabetes.

Keywords: Diabetes mellitus, obesity, tirzepatide, twincretin

Introduction

The term incretin, which was first defined in 1932, emerged when it was seen that enteral nutrition causes more insulin release than intravenous nutrition. The greater insulinotropic effect of glucose absorbed from the gastrointestinal tract (GIS) was attributed to the hormones released from the intestines. These hormones are called incretins. The increase in insulin secretion with oral glucose compared to intravenous glucose is called the incretin effect.[1] Glucagon-like peptide-1 (GLP-1) is the most potent incretin secreted from the intestinal tract. It is synthesized by L-cells in the jejunum and distal ileum of the GIS.[2-4] Glucose-dependent insulinotropic polypeptide (GIP) is a 42 amino acid polypeptide, released in response to oral lipids and carbohydrates, by special endocrine cells, most abundant in the duodenum and jejunum called K cells. The first isolated incretin was named gastric inhibitory polypeptide because it inhibited gastric acid. Later, it was understood that the insulinotropic and blood sugar-regulating effect of the GIP molecule was more potent and the gastric inhibitory effect was weaker, and the name of the molecule was changed to glucose-dependent insulinotropic polypeptide.[5] Glucose-dependent insulinotropic polypeptide and GLP-1 are destroyed within minutes by the DPP4 enzyme released from the capillary endothelium in the villi. Glucose-dependent insulinotropic polypeptide breaks down in 7 minutes, GLP-1 in 1-4 minutes. Glucose-dependent insulinotropic polypeptide and GLP-1 show their glucose-dependent acute insulinotropic effects by binding to pancreatic β-cell surface receptors and increasing cAMP. With their chronic effects, they increase the gene expressions of β-cells and provide longer β-cell life with an increase in insulin synthesis and an increase in cell mass.[6] Glucose-dependent insulinotropic polypeptide is more responsible for incretin action than GLP-1. Glucose-dependent insulinotropic polypeptide has a glucagonotropic property in the normoglycemic and hypoglycemic and a glucagonostatic effect in the hyperglycemic state. Glucose-dependent insulinotropic polypeptide and GLP-1 show their glucose-dependent acute insulinotropic effects by binding to pancreatic β-cell surface receptors and increasing cAMP. The effect of GIP on the regulation of body weight and adipose tissue has not yet been determined. Some studies show that chronic elevation of GIP concentrations in a transgenic mouse reduces diet-induced obesity and improves insulin sensitivity, beta-cell function,

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and glucose tolerance while other studies show that GIP receptor knockout mice are resistant to diet-induced obesity.[5,7,8] Glucose-dependent insulinotropic polypeptide receptors are found in various tissues such as adipose tissue, pancreas, adrenal cortex, gastric mucosa, heart, bone, and brain.[5,6] The long-term effect of GIP and GLP-1 receptor (GLP-1R) agonism was first demonstrated by Finan et al. They have developed a single-molecule dual agonist of GIP and GLP-1 receptors called "Twincretin." Twincretin has been shown to have negligible glucagon receptor activity and a high affinity for GLP-1 and GIP receptors.[9]

Glucagon-like peptide-1 and Glucose-Dependent Insulinotropic Polypeptide Dual Agonism

Unimolecular dual incretins, twincretins, derived from GLP-1and GIP, resulted in greater potentiation of glucose or GLP-1-induced insulin secretion than stimulation with either peptide alone in animal models.[10] Acute exposure to GIP has been reported to be superior to exposure to GLP-1 in terms of insulin release in human islets from non-diabetic and type 2 diabetic donors. After prolonged exposure, the combination of both incretins has synergistic effects on insulin synthesis and insulin secretion.[11]

RG7697/NNC0090-2746

RG7697/NNC0090-2746, a fatty-acylated dual agonist achieved steady-state concentration within 1 week by daily dosing in phase 1 trials. Glycated hemoglobin A1C (HbA1c), postprandial and fasting plasma glucose decreased after 2 weeks of treatment at doses >0.75 mg.[12] Doses up to 2 mg once daily, glycemic control and reduced body weight, and leptin and total cholesterol were significantly reduced compared to placebo. Treatment with NNC0090-2746 was well tolerated and safe.[13] In another study, a dose of 0.25 mg, 0.75 mg, 1.1 mg, 1.5 mg, 2.0 mg, or 2.5 mg once daily was given for 2 weeks. Dose-related decreases in fasting and postprandial glucose levels and increased insulin sensitivity were observed. At the highest 2.5 mg dose, significant reductions in HbA1c levels and body weight were observed. The most common side effects were mild nausea, diarrhea, and decreased appetite.[12] In another double-blind study, RG7697/NNC0090-2746 was given at doses ranging from 0.03 mg to 5 mg. At 1.8 mg doses, it reduced glucose and insulin levels during the meal tolerance test. The drug has been well tolerated at doses of up to 3.6 mg and mild adverse gastrointestinal events have been reported. An increase in heart rate was observed. Anti-RG7697/NNC0090-2746 antibodies were not detected.[14] In another trial, 1.8 mg of NNC 0090-2746 was compared with 1.8 mg of liraglutide. Reduction in glycated hemoglobin was observed in patients with type 2 diabetes mellitus (T2DM) similarly to the group treated with liraglutide, while the body weight reduction was significantly greater than that of liraglutide.[13]

Tirzepatide (LY3298176)

Tirzepatide is a novel dual GIP/GLP-1 receptor agonist, containing 39 amino acids based on the native GIP sequence and provides weekly dosing by binding to a 20-carbon fatty diacid albumin, extending its half-life to 5 days.[15] Tirzepatide has 5 times lower GLP-1 receptor affinity than native GLP-1 and similar GIP receptor binding affinity to native GIP.[15] In phase 1 and phase 2 studies, T2DM patients, tirzepatide was dose-dependent; it reduced HbA1c up to 2.4% and body weight up to 11.3 kg.[16]

In the phase 2 study of tirzepatide; 258 participants with an average of 9 years of T2DM completed 26 weeks of treatment. 1 mg, 5 mg, 10 mg, or 15 mg of tirzepatide compared to 1.5 mg of dulaglutide or placebo. About 1.94% reduction in HbA1c with 15 mg tirzepatide and 1.21% with dulaglutide was observed. Body weight reduction ranged from −0.9 kg to −11.3 kg for tirzepatide, −0.4 kg for placebo, and −2.7 kg for dulaglutide. The most common side effects of dose-dependent gastrointestinal were vomiting, nausea, and diarrhea.[17]

In another study, doses of LY3298176, dulaglutide, or placebo were compared. A total of 4.52 kg decrease in body weight with 4.5 mg tirzepatide, 4.05 kg reduction with 10 mg tirzepatide, and 1.3 kg decrease with 1.5 mg dulaglutide were observed. Significant reductions in HbA1c, fasting glucose, and insulin levels were observed in the groups taking tirzepatide compared to placebo. Statistically significant reductions in body weight were seen at doses of 10 mg and 15 mg of tirzepatide compared to placebo (2.39 kg for 10 mg and 2.95 kg for 15 mg and 0.32 kg for placebo). The most observed mild to moderate side effects were gastrointestinal events that included diarrhea, nausea, vomiting, decreased appetite, and abdominal distention.[15]

In another study, tirzepatide (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1.5 mg), or placebo was given per week. Serum lipoprotein profile, apolipoprotein (apo)AI, B, and C-III, and preheparin lipoprotein lipase (LPL) were measured. Lipoprotein particle profile was evaluated at baseline and at week 26 by nuclear magnetic resonance. The lipoprotein insulin resistance (LPIR) score was calculated. At week 26, tirzepatide dose-dependently decreased apoB and apoC-III levels and increased serum preheparin LPL compared to placebo. Tirzepatide 10 mg and 15 mg reduced large triglyceride-rich lipoprotein particles (TRLP), small low-density lipoprotein particles (LDLP), and LPIR scores compared to both placebo and dulaglutide. Treatment with dulaglutide also reduced apoB and apoC-III levels but had no effect on serum LPL or large TRLP, small LDLP, and LPIR score. The total LDLP count was also reduced with tirzepatide 10 mg and 15 mg compared to placebo. A greater reduction in apo C-III was observed with tirzepatide in patients with elevated baseline triglycerides compared with normal baseline triglycerides.[18]

In another study, 316 patients with T2DM were given LY3298176 (1 mg, 5 mg, 10 mg, 15 mg), dulaglutide (1.5 mg), or placebo. The study was performed in 47 regions in 4 countries. The proinsulin/insulin and proinsulin/C-peptide ratios were significantly reduced with tirzepatide 10 mg and 15 mg compared to placebo and dulaglutide. Tirzepatide 10 mg and 15 mg significantly reduced fasting insulin.[19]

In a 40-week trial comparing tirzepatide with semaglutide, each was administered once weekly by subcutaneous injection in 1879 patients with T2DM taking metformin monotherapy. The reduction in A1C was −2% to −2.3% with tirzepatid compared to semaglutide with a −1.86% reduction. The mean reduction in body weight was also greater with tirzepatide compared to semaglutide. Gastrointestinal adverse effects such as nausea and diarrhea were similar in the tirzepatide and semaglutide treatment groups.[20]

SURPASS clinical studies are investigating the safety and efficacy of tirzepatide in randomized controlled trials in patients with T2DM (Table 1). SURPASS1 was investigating tirzepatide as monotherapy, SURPASS2 tirzepatide versus semaglutide, SURPASS3 tirzepatide versus degludec, SURPASS4 tirzepatide versus glargine, SURPASS 5 tirzepatide add-on basal insulin, SURPASS AP- Combo tirzepatide versus glargine, SURPASS-CVOT tirzepatide is up against dulaglutide, SURPASSJ-mono, and SURPASS J-combo are ongoing clinical trials, comparing weekly tirzepatide against weekly dulaglutide.[21]

Table 1. Overview of the SURPASS Phase 3 Clinical Trials of Tirzepatide for the Treatment of T2DM

Trial	Sample Size	Concomitant Therapy	TZP Dose	Comparator Group	Primary Outcome	Treatment Duration (weeks)	Mean HbA1c Decrease with TZP	Mean HbA1c Decrease with CG
SURPASS-1	472	None	5 mg 10 mg 15 mg	Placebo	Change from baseline in HbA1c	40	1.87% 1.89% 2.07%	0.04%
SURPASS-2	1881	Metformin	5 mg 10 mg 15 mg	Semaglutide	Change from baseline in HbA1c	40	2.01% 2.24% 2.30%	1.86 %
SURPASS-3	1420	Metformin or metformin plus SGLT2i	5 mg 10 mg 15 mg	Insulin degludec	Change from baseline in HbA1c	52	1.93% 2.20% 2.37%	1.34%
SURPASS-4	1878	Metformin, SGLT2i or SU	5 mg 10 mg 15 mg	Insulin glargine	Change from baseline in HbA1c	52	 2.43% 2.58%	1.44%
SURPASS-5	472	Insulin glargine once daily with or without metformin	5 mg 10 mg 15 mg	Placebo	Change from baseline in HbA1c	40	2.11% 2.40% 2.34%	0.86%
SURPASS-AP combo	956	Metformin with or without SU	5 mg 10 mg	Insulin glargine	Change from baseline in HbA1c	40	-	-
SURPASS-J mono	636	OAD-naive or OAD monotherapy	5 mg 10 mg 15 mg	Dulaglutide 0.75 mg	Change from baseline in HbA1c	52	-	-
SURPASS-J combo	441	OAD monotherapy	5 mg 10 mg 15 mg	N/A	Number of participants with ≥1 SAE	52	-	-
SURPASS-CVOT	12500	Oral or injectable anti-hyperglycemic medication	Maximum tolerated dose up to 15 mg	Dulaglutide 1.5 mg	Time to first occurrence of a component of event of MACE	Event driven	-	-

HbA1c, glycated hemoglobin; TZP, tirzepatide; MACE, major adverse cardiac event; OAD, oral anti-hyperglycemic drug; SAE, serious adverse event; SGLT2, sodium–glucose co-transporter 2; SU, sulfonylurea; CR, comparator group.

SURPASS-1 is a randomized double-blind, phase 3 trial. Seven hundred five patients from 52 medical research centers and hospitals (with 54.1 years mean age) with T2DM inadequately controlled by diet were given once a week placebo ortirzepatide (5 mg, 10 mg, or 15 mg), for 40 weeks. The mean diabetes duration was 4.7 years, HbA1c was 7.9%, and body mass index was 31.9 kg/m^2. After 40 weeks, a dose-dependent decrease was seen in HbA1c and body weight by tirzepatide. Tirzepatide induced a dose-dependent body weight loss ranging from 7.0 kg to 9.5 kg. Mean HbA1c decrease from baseline was 1.87% with tirzepatide 5 mg, 1.89% with tirzepatide 10 mg, and 2.07% with tirzepatide 15 mg versus 0.04% with placebo. The most frequent adverse effects were gastrointestinal events such as nausea, diarrhea, and vomiting. No clinically significant or severe hypoglycemia was reported with tirzepatide.[22]

SURPASS-2 was an open-label, phase 3 clinical trial. A total of 1879 patients with mean age 56.6 years received tirzepatide (5 mg, 10 mg, or 15 mg) or semaglutide (1 mg) for 40 weeks. At baseline, HbA1c was 8.28%, while the mean weight was 93.7 kg. Reductions in body weight were greater with tirzepatide than with semaglutide but mean change in the HbA1c was similar between all doses of tirzepatide and semaglutide. Tirzepatide induced a dose-dependent body weight loss ranging from 1.9 kg to 5.5 kg. Mean HbA1c decrease from baseline was 2.01%, 2.24%, and 2.30% with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 1.86% with semaglutide. The most frequent adverse events were gastrointestinal events primarily mild to moderate in severity in the tirzepatide and semaglutide groups (nausea, 17% to 22% and 18%; diarrhea, 13% to 16% and 12%; and vomiting, 6% to 10% and 8%, respectively.[23]

SURPASS-3 was an open-label, phase 3, multicenter (122 sites), multinational (13 countries) study, 1947 patients with T2DM inadequately controlled by metformin, with or without SGLT2 inhibitors received tirzepatide or insulin degludec for 52 weeks. Glycemic control and losing weight were better with tirzepatide than with insulin degludec. Reductions in HbA1c at week 52 were 1.93% for tirzepatide 5 mg, 2.20% for 10 mg, 2.37% for 15 mg, and 1.34% for insulin degludec. A higher incidence of diarrhea (15%-17%), nausea (12%-24%), decreased appetite (6%-2%), and vomiting (6%-10%) was reported in patients treated with tirzepatide than in those treated with insulin degludec (2%, 4%, 1%, and 1%, respectively). Hypoglycemia (<54 mg/dL or severe) was reported in 5 (1%), 4 (1%), and 8 (2%) participants on tirzepatide 5 mg, 10 mg, and 15 mg, respectively, versus 26 (7%) on insulindegludec.[24]

SURPASS-4 was an open-label 52-week trial, done in 187 sites in 14 countries on 5 continents with 2002 T2DM patients treated with tirzepatide or with insulin glargine who were taking baseline a sulfonyl urea, metformin or an SGLT-2 inhibitor with a mean duration of diabetes of 11.8 years, a baseline HbA1c of 8.52%, a baseline weight of 90.3 kg, and body mass index ≥25 kg/m^2. At 52 weeks, mean HbA1c reduction with tirzepatide was 2.43% with 10 mg and 2.58% with 15 mg, versus 1.44% with glargine. The mean reduction in HbA1c with tirzepatide 10 mg and 15 mg was greater than with glargine. The percentage of participants with hypoglycemia (glucose <54 mg/dL or severe) was lower with tirzepatide (6%-9%) versus glargine (19%). Cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina occurred in 109 participants and were not increased on tirzepatide compared with glargine. The most seen side effects of tirzepatide were nausea, diarrhea, decreased appetite, and vomiting.[25]

SURPASS-5 was a randomized, phase 3, double-blind trial, and 475 patients were treated with tirzepatide versus placebo inpatients with T2DM inadequately controlled on insulin glargine with or without metformin. A total of 451 (94.9%) patients completed the trial with mean age of 60.6 years and mean HbA1c of 8.31%. After 40 weeks, mean HbA1c reduction with tirzepatide was 2.11% with 5 mg, 2.40% with 10 mg tirzepatide, and 2.34% with 15 mg tirzepatide versus 0.86% with placebo. Mean body weight reduction from baseline was −5.4 kg with 5 mg tirzepatide, −7.5 kg with 10 mg tirzepatide, −8.8 kg with 15 mg tirzepatide, and 1.6 kg with placebo. The most common side effects of tirzepatide were diarrhea and nausea.[26]

SURPASS AP-Combo is a randomized, phase 3, open-label study, comparing the effect of tirzepatide once weekly versus titrated insulin glargine on glycemic control in 917 patients with T2DM on metformin with or without a sulfonyl urea over a 40-week period. The study was completed on November 24, 2021.[27]

SURPASS-CVOT is a randomized, double-blind, large phase 3 trial with the purpose to assess the efficacy and safety of tirzepatide to dulaglutide in 12 500 patients with T2DM and increased cardiovascular risk for 54 months. Tirzepatide was administered subcutaneously (sc) once a week while dulaglutide was administered sc once a week. Primary outcome measures are the time taken for the first occurrence of death from cardiovascular reasons, myocardial infarction, or stroke. Estimated study completion time is October 2024.[28]

SURPASS J-mono is a phase 3 ongoing clinical trial of tirzepatide monotherapy (5 mg, 10 mg, or 15 mg) against weekly dulaglutide 0.75 mg in patients with T2DM. Primary outcome measure is change from baseline in HbA1c. Secondary outcome measures are change from baseline in average 7-point self-monitored blood glucose values, percentage of participants who achieve weight loss ≥5% from baseline, change from baseline in homeostasis model assessment, number of participants with anti-tirzepatide antibodies, and side effects over 52 weeks of treatment. Estimated study completion time is October 2024.[29]

SURPASS J-combo is ongoing a phase 3, long-term safety study of tirzepatide (5 mg, 10 mg, or 15 mg) in combination with monotherapy of oral antihyperglycemic medications (sulfonylurea, biguanide, alpha-glucosidase inhibitor, thiazolidinedione, glinide, or sodium-glucose cotransporter type 2 inhibitor in 443 patients with T2DM for 52 weeks. Primary outcome measure is the number of participants with 1 or more serious adverse events baseline through 52 weeks. Secondary outcome measures are change from baseline in HbA1c, mean change from baseline in daily average 7-point self-monitored blood glucose values, percentage of participants who achieve a weight loss of ≥5% from baseline, number of participants with hypoglycemia incidence, and rate with blood glucose <54 mg/dL, or severe hypoglycemia.[30]

SYNERGY-NASH is a randomized, double-blind, placebo-controlled phase 2 study comparing the efficacy and safety of tirzepatide in 196 patients with nonalcoholic steatohepatitis (NASH) for 52 weeks in 120 study locations. Primary outcome measure is the percentage of participants with absence of NASH with no worsening of fibrosis on liver histology. Secondary outcome measures are percentage of participants with ≥1-point decrease in the fibrosis stage with no worsening of NASH on liver histology, the percentage of participants that achieve a ≥2-point decrease in NASH on liver histology, with ≥1-point reduction in at least 2 NASH components, mean absolute change from baseline in liver fat content by magnetic resonance imaging proton density fat fraction (MRI-PDFF), mean absolute change from baseline in liver fat content by MRI-PDFF, and mean change from baseline in body weight after 52 weeks.[31]

SURMOUNT-1 is a randomized, double-blind, placebo-controlled trial planned to investigate the efficacy and safety of tirzepatide once a week in participants without T2DM who have obesity or are overweight with weight-related comorbidities. It is planned for 2400 participants who do not have T2DM, have a body mass index of ≥30 kg/m^2 or ≥27 kg/m^2, and have at least 1 comorbidity (hypertension dyslipidemia, obstructive sleep apnea, or cardiovascular disease) from the comorbidities. Primary outcome measure is the percent change from baseline in body weight after 72 weeks. Secondary outcome measures are the percentage of participants who achieve ≥5%-10%-15%-20% body weight reduction, change from baseline in short form survey-36 version 2 acute form physical functioning domain score, change from baseline in the impact of weight on quality of life-lite-clinical trials version (IWQOL-Lite-CT) physical function composite score after 72 weeks.[32]

Conclusion

Twinretins have been gaining much attention recently as novel anti-diabetic agents that can potentially control glycemia and body weight. GLP-1R/GIPR dual agonists can add additional therapeutic efficacy to tailored diabetes care, especially among obese individuals with T2DM. The most frequent adverse effects were gastrointestinal events such as nausea, diarrhea, and vomiting. Studies are still ongoing to reveal the place of twincretins in the treatment of many diseases.

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