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REVIEW

Tirzepatide for type 2 diabetes

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Abstract

One in ten adults worldwide is living with diabetes, with 95% having type 2 diabetes (T2D). Sustained glycaemic control in people with T2D is difficult to achieve despite recent advances in T2D management with the advent of glucagon-like peptide 1 receptor agonists (GLP1RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i). Tirzepatide represents a first-in-class agent as a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP1RA to be approved in the USA and Europe for the treatment of T2D. This narrative review intends to list and discuss the glycaemic efficacy, key safety and weight loss outcomes related to the treatment of T2D with tirzepatide. Tirzepatide has been evaluated in five published clinical trials (n=6278) within the SURPASS clinical trial programme, with a focus on glycaemic control and weight loss. These trials have demonstrated significant improvements in glycosylated haemoglobin (−1.24% to −2.11% *versus* placebo and −0.6% to −1.14% *versus* active comparator) and weight (up to 15.5 kg *versus* placebo or active comparator) in patients with T2D. Notably, tirzepatide exhibited superior glycaemic control and weight loss when compared directly with a GLP1RA. Adverse events with the use of tirzepatide are similar to other approved GLP1RA and are predominantly gastrointestinal (nausea, vomiting). The tirzepatide cardiovascular outcomes trial (SURPASS-CVOT) is in progress and is expected to be completed in the fall of 2024. Tirzepatide represents an attractive new option and first-in-class agent for the treatment of T2D in people unable to achieve their glycaemic or weight management goals.

Keywords: diabetes mellitus, glucagon-like peptide 1 receptor agonist, glucose-dependent insulinotropic polypeptide, tirzepatide, type 2 diabetes.

Citation

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Introduction

Current estimates suggest that one in ten adults worldwide is living with diabetes, with 95% having type 2 diabetes (T2D).[1] The advent of glucagon-like peptide 1 receptor agonists (GLP1RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) has revolutionized glycaemic management of T2D as well as key comorbidities, including atherosclerotic cardiovascular disease (ASCVD), diabetic kidney disease and heart failure (HF). Diabetes management guidelines have been updated to reflect the preference for these agents early in the course of T2D treatment for all patients based on their high efficacy and high likelihood of achieving glycaemic goals. Additionally, these agents are recommended as first-line treatment in people with T2D and certain comorbidities based on their beneficial effects in ASCVD, chronic kidney disease and HF.[2,3]

Tirzepatide represents a first-in-class agent for the treatment of T2D. Tirzepatide is a once-weekly injectable dual glucose-dependent insulinotropic polypeptide (GIP)/GLP1RA.[4] It is approved for use in Australia, Canada, the European Union, the United Kingdom and the United States. The exact place in therapy of tirzepatide is still being finalized because its effects on major adverse cardiovascular events (MACE), diabetic kidney disease and HF are still being investigated. However, its very high glycaemic efficacy and substantial effects on weight loss make it an attractive option for the treatment of T2D.[2–4]

This narrative review intends to list and discuss the glycaemic efficacy, key safety, and weight loss data related to the use of tirzepatide for T2D. To perform this review, we conducted an English-language Medline search from 1995 through May 2023 using the terms “LY3298176”, “tirzepatide”, “dual GIP and GLP1RA”, “GIP”, and “GLP1RA” alone and in various combinations. All human studies

comparing the primary efficacy and safety of tirzepatide for the treatment of T2D were eligible for inclusion. A manual search of the references identified within these articles was performed to identify additional relevant articles for inclusion.

Review

Pharmacology

Mechanism of action

Tirzepatide is a 39-amino-acid modified peptide with a C20 fatty diacid moiety that enables binding to albumin and prolongs the half-life to achieve once-weekly dosing. It selectively binds to and activates both the GIP and GLP1 receptors — the targets for native GIP and GLP1 — making it a first-in-class dual GIP/GLP1RA.[4]

Pharmacodynamics

In a glucose-dependent manner, tirzepatide enhances both first-phase and second-phase insulin release to reduce both fasting and postprandial glucose levels and glucagon levels.[5] Tirzepatide 15 mg subcutaneous injection reduces fasting glucagon levels by 28% and the glucagon area under the curve (AUC) by 43% after a meal, compared with no change observed with placebo. Similar to other GLP1RA, tirzepatide increases feelings of satiety, delays gastric emptying and reduces weight.[4]

Pharmacokinetics

Tirzepatide has been studied in people with and without T2D, with a similar pharmacokinetic (PK) profile observed in both populations. Tirzepatide is administered via subcutaneous injection and exhibits 80% bioavailability via this route of administration, whether administered via the abdomen, upper arm or upper thigh. It reaches maximum plasma concentrations within a timeframe of up to 72 hours and thus takes approximately 4 weeks to reach steady-state concentrations. Tirzepatide is highly protein bound, with 99% bound to plasma albumin, and has a half-life of approximately 5 days, which enables once-weekly dosing. Tirzepatide is metabolized via proteolytic cleavage of its peptide backbone, beta-oxidation of its C20 fatty diacid moiety, and amide hydrolysis. Importantly, tirzepatide is not metabolized via the cytochrome P450 (CYP450) system, which reduces opportunities for drug–drug interactions. It is eliminated via urine and faeces. Tirzepatide pharmacokinetic parameters are unaffected by renal and hepatic impairment, age, sex, race, ethnicity or body weight.[4]

SURPASS clinical trial programme

Six clinical trials have evaluated tirzepatide for the treatment of T2D, of which five have been published (Table 1).[6–11] Tirzepatide has been studied as monotherapy, as an additive to metformin ± SGLT2i therapy, as an additive to metformin ± insulin therapy and as an additive to insulin therapy. A tirzepatide cardiovascular outcomes trial (CVOT) is in progress and is expected to be completed in October 2024.[12]

Monotherapy

In the SURPASS-1 trial, tirzepatide was evaluated in treatment-naive people with T2D who were unable to achieve glycosylated haemoglobin (HbA1C) goals using lifestyle modifications alone.[6] This was a phase III, double-blind, placebo-controlled trial that randomized 478 people with T2D to a tirzepatide maintenance dose of 5 mg, 10 mg, 15 mg or placebo once-weekly for 40 weeks. Mean age was 54.1 years, 48% were women, mean weight was 85.9 kg and mean baseline HbA1C was 7.94%. The primary efficacy endpoint was mean change in HbA1C from baseline to week 40. Tirzepatide treatment at all doses led to a significant change in HbA1C compared with placebo (−1.87% with 5 mg, −1.89% with 10 mg and −2.07% with 15 mg *versus* +0.04% with placebo) at week 40, resulting in estimated HbA1C treatment differences *versus* placebo of −1.91%, −1.93% and −2.11%, respectively (all $p<0.0001$).[6] Treatment with tirzepatide significantly reduced fasting serum glucose levels and more patients treated with tirzepatide achieved target HbA1C levels by week 40. Weight reduction was significant for the tirzepatide groups *versus* placebo (−7.9%, −9.3% and −11.0% *versus* −0.9%). The most frequent adverse events experienced with tirzepatide use were nausea (12–18% *versus* 6% with placebo), diarrhoea (12–14% *versus* 8% with placebo) and vomiting (2–6% *versus* 2% with placebo). All gastrointestinal (GI) adverse events were noted to be mild to moderate in nature and decreased over time. No clinically significant or severe hypoglycaemia occurred with the use of tirzepatide. This trial demonstrated the viability of tirzepatide as a monotherapy agent for people with T2D, with robust glucose and weight reduction with no increased risk of hypoglycaemia.

Compared with injectable semaglutide added to metformin

The SURPASS-2 trial investigators randomized 1879 adults with T2D who were inadequately controlled on a metformin dose of ≥1500 mg daily in a 1:1:1:1 ratio to tirzepatide 5 mg, 10 mg or 15 mg, or semaglutide 1 mg once-weekly for 40 weeks in open-label fashion.[7] Mean age was 56.6 years, 53% were women, mean HbA1C was 8.28% and mean weight was 93.7 kg. The primary efficacy endpoint was the assessment of whether tirzepatide 10 mg or 15 mg was non-inferior to injectable semaglutide 1 mg at 40 weeks. At 40 weeks, the mean HbA1C changes were −2.01 percentage points, −2.24 percentage points and −2.30 percentage points with tirzepatide 5 mg, 10 mg and 15 mg compared with −1.86 percentage points for injectable semaglutide 1 mg; the

Table 1. SURPASS clinical trial programme.

Trial	n	Patient population	Follow-up mean (wk)	Primary outcome	Body weight outcome
SURPASS-1 (ref.[6])	478	T2D uncontrolled with diet and exercise alone	40	A1C change from baseline *versus* placebo: -1.91% (T5), -1.93% (T10), -2.11% (T15); all $p<0.0001$	Weight change from baseline *versus* placebo: -6.3% (T5), -7.1% (T10), -8.8% (T15) [all $p<0.0001$]
SURPASS-2 (ref.[7])	1879	T2D uncontrolled with use of ≥1500 mg/day metformin	40	A1C change from baseline *versus* injectable semaglutide: -0.15 percentage points (T5), $p=0.02$; -0.39 percentage points (T10), $p<0.001$; -0.45 percentage points (T15), $p<0.001$	Weight change from baseline *versus* injectable semaglutide: -1.9 kg (T5), -3.6 kg (T10), -5.5 kg (T15) [all $p<0.001$]
SURPASS-3 (ref.[8])	1444	T2D uncontrolled with use of metformin ± SGLT2i	52	A1C change from baseline *versus* insulin degludec: -0.59% (T5), -0.86% (T10), -1.04% (T15); all $p<0.0001$	Weight change from baseline *versus* insulin degludec: -9.8 kg (T5), -13.0 kg (T10), -15.5 kg (T15); all $p<0.0001$
SURPASS-4 (ref.[9])	2002	T2D uncontrolled with use of oral antihyperglycemic agents	52	A1C change from baseline *versus* insulin glargine: -0.80% (T5), -0.99% (T10), -1.14% (T15); all $p<0.0001$	Weight change from baseline *versus* insulin glargine: -9.0 kg (T5), -11.4 kg (T10), -13.5 kg (T15); all $p<0.0001$
SURPASS-5 (ref.[10])	475	T2D uncontrolled with use of once-daily insulin glargine ± metformin	40	A1C change from baseline *versus* placebo: -1.24% (T5), -1.53% (T10), -1.47% (T15); all $p<0.001$	Weight change from baseline *versus* placebo: -7.1 kg (T5), -9.1 kg (T10), -10.5 kg (T15); all $p<0.001$
SURPASS-6 (ref.[11])	1428	T2D uncontrolled with use of once-daily insulin glargine ± metformin		A1C change from baseline *versus* insulin lispro (U-100); results not yet published	Weight change from baseline *versus* insulin lispro (U-100); results not yet published
SURPASS-CVOT (ref.[12])	13,299	T2D uncontrolled on current oral or injectable regimen		Composite 3-point MACE outcome *versus* dulaglutide; results not yet published	

A1C, glycosylated hemoglobin; 3-point MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction, or stroke); T5, tirzepatide 5 mg once weekly; T10, tirzepatide 10 mg once weekly; T15, tirzepatide 15 mg once weekly; T2D, type 2 diabetes.

HbA1C-lowering achieved with all three doses of tirzepatide were superior compared with injectable semaglutide 1 mg ($p=0.02$, $p<0.001$ and $p<0.001$ for the three doses of tirzepatide *versus* placebo). Greater reductions in fasting serum glucose levels were seen with all doses of tirzepatide *versus* injectable semaglutide 1 mg. Weight reductions with tirzepatide were dose-dependent and superior to semaglutide 1 mg at all doses (−7.6 kg, −9.3 kg, −11.2 kg *versus* −5.7 kg; $p<0.001$ for all comparisons). The most frequent adverse effects were GI effects and were similar between groups. Nausea (17–22% *versus* 18%), diarrhoea (13–16% *versus* 8%), vomiting (6–10% *versus* 8%) and decreased appetite (7–9% *versus* 5%) were reported most commonly, were mild to moderate, and improved over time. This study demonstrated that HbA1C reduction at 40 weeks with tirzepatide was superior to injectable semaglutide 1 mg in patients with T2D on a background of metformin.

Compared with daily insulin degludec added to metformin ± SGLT2i

In the open-label, parallel-group, phase III study SURPASS-3, 1444 adults with T2D who were insulin-naive and unable to achieve glycaemic goals despite treatment with metformin ± an SGLT2i were randomized 1:1:1:1 to tirzepatide 5 mg, 10 mg or 15 mg weekly or once-daily titrated insulin degludec (titrated to a self-monitored fasting blood glucose of <5.0 mmol/L [<90 mg/dL]).[8] Mean age was 57.4 years, 44% were women, mean HbA1C was 8.17% and mean weight was 94.3 kg. The primary efficacy endpoint was the assessment of whether tirzepatide 10 mg or 15 mg, or both were non-inferior to titrated insulin degludec at 52 weeks. At 52 weeks, the mean HbA1C changes were −1.93%, −2.20% and −2.37% for tirzepatide 5 mg, 10 mg and 15 mg, respectively, *versus* −1.34% for insulin degludec; all doses of tirzepatide were superior to insulin degludec with respect to HbA1C reduction ($p<0.0001$ for all comparisons). More patients in the three tirzepatide groups achieved an HbA1C <7% compared with insulin degludec. One-third of patients in each group were receiving an SGLT2i in addition to metformin, but no differences in HbA1C were noted in these patients *versus* those receiving metformin alone. All three doses of tirzepatide significantly reduced bodyweight *versus* insulin degludec, which increased weight; the estimated treatment difference of tirzepatide *versus* insulin degludec was −9.8 to −15.2 kg ($p<0.0001$ for all comparisons). Incidence of nausea (12–24% *versus* 2%), diarrhoea (15–17% *versus* 4%), vomiting (6–10% *versus* 1%) and decreased appetite (6–12% *versus* 1%) were all greater with tirzepatide at any dose compared with insulin degludec. Clinically significant or severe hypoglycaemia was reported in 1–2% of tirzepatide-treated patients compared with 7% of insulin degludec-treated patients. This study demonstrated that HbA1C and weight reductions with tirzepatide were superior to insulin degludec, with an increased risk of GI side-effects and less risk of hypoglycaemia.

Compared with daily insulin glargine added to oral background regimen in people with T2D and increased cardiovascular risk

SURPASS-4 investigators randomized 2002 adults with T2D with cardiovascular (CV) disease or at increased risk of CV events in a 1:1:1:3 ratio to treatment with tirzepatide 5 mg, 10 mg, 15 mg or once-daily insulin glargine titrated to a fasting blood glucose of <100 mg/dL.[9] Patients could be receiving any combination of metformin, sulfonylureas or SGLT2i at baseline. Mean age was 63.6 years, 38% were women, mean HbA1C was 8.52% and mean weight was 90.3 kg. The primary efficacy endpoint was the assessment of whether tirzepatide 10 mg or 15 mg were non-inferior to titrated insulin glargine at 52 weeks. Because these patients were at high risk for CV events, the incidence of the first MACE-4 endpoint (transient ischaemic attacks, coronary revascularization, HF hospitalization and mortality) was evaluated. At 52 weeks, the mean HbA1C changes were −2.24%, −2.43% and −2.58% for tirzepatide 5 mg, 10 mg and 15 mg, respectively, *versus* −1.44% for insulin degludec; all doses of tirzepatide were superior to insulin glargine with respect to HbA1C reduction ($p<0.0001$ for all comparisons). More tirzepatide-treated patients achieved an HbA1C of <7% and a more robust reduction in fasting serum glucose. Tirzepatide-related weight reductions were dose-dependent and superior to insulin glargine (estimated treatment difference of −9.0 kg, −11.4 kg and −13.5 kg compared with placebo; $p<0.0001$ for all comparisons). Over the study duration, there were 109 MACE-4 events and there was no increased risk of MACE-4 events for pooled tirzepatide use compared with insulin glargine use (hazard ratio 0.74; 95% CI 0.51–1.08). Incidence of nausea (12–23% *versus* 2%), diarrhoea (13–22% *versus* 4%), vomiting (5–9% *versus* 2%) and decreased appetite (9–11% *versus* <1%) were all greater with tirzepatide at any dose compared with insulin glargine. Clinically significant or severe hypoglycaemia was reported in 8% of pooled tirzepatide-treated patients compared with 19% of insulin degludec-treated patients. This study demonstrated that in people with T2D and increased CV risk, HbA1C and weight reductions with tirzepatide were superior to insulin glargine, with a side-effect profile similar to GLP1RA and with no CV safety concerns.

Added to titrated insulin glargine

SURPASS-5 investigators evaluated the addition of tirzepatide to titrated insulin glargine compared with volume-matched placebo. Adults with T2D ($n=475$) were randomized 1:1:1:1 to receive tirzepatide 5 mg, 10 mg, 15 mg or placebo in addition to titrated insulin glargine.[10] Mean age was 61 years, 44% were women, mean HbA1C was 8.31% and mean weight was 95.2 kg. The primary efficacy endpoint was mean change in HbA1C from baseline to week 40 for the tirzepatide 10 mg and 15 mg groups and placebo. Tirzepatide 10 mg and 15 mg doses led to a significant change in HbA1C compared with placebo (−2.40% and −2.34% *versus* −0.86%) at week 40, resulting in estimated HbA1C treatment differences *versus* placebo of −1.53% and −1.47%, respectively ($p<0.001$ for both tirzepatide doses).[10] Treatment with all three tirzepatide doses significantly reduced fasting serum glucose levels and more patients treated with tirzepatide achieved target HbA1C levels by week 40 compared with placebo. Weight reduction was significant for the three tirzepatide groups *versus* placebo (−5.4%, −7.5% and −8.8% *versus* +1.6%). The most frequent adverse events experienced with tirzepatide use were nausea (12.9–18.3% *versus* 2.5 with placebo), diarrhoea (12.1–20.8% *versus* 10.0% with placebo), vomiting (6.9–12.5% *versus* 2.5% with placebo), decreased appetite (6.9–14.2% *versus* 1.7% with placebo) and nasopharyngitis (6.7–15.5% *versus* 19.2% with placebo). All GI adverse events were noted to be similar to those of other GLP1RA and decreased over

time. Clinically significant or severe hypoglycaemia occurred in 14.2–19.3% of tirzepatide-treated patients compared with 12.5% of patients receiving placebo (*p* values not reported). This trial demonstrated the efficacy and safety of tirzepatide as an add-on to insulin glargine in patients with T2D and inadequate glycaemic control.

Compared with insulin lispro (U100) added to insulin glargine (U100) with or without metformin

The SURPASS-6 trial compared treatment with tirzepatide 5 mg, 10 mg or 15 mg to insulin lispro (U100) dosed three times daily in 1428 people with T2D not optimally controlled on insulin glargine (U100) with or without metformin. The primary outcome studied was a change in HbA1C from baseline, and the secondary outcomes included the percentage of participants who achieved an A1C <7% and change in body weight from baseline. The trial was completed in November 2022 but has not yet published trial results.[11]

SURPASS clinical trials: special populations

The SURPASS-CVOT aims to compare treatment with tirzepatide with dulaglutide on three-point MACE outcomes (CV death, myocardial infarction or stroke) in people with T2D. The trial has enrolled 13,299 participants and is expected to complete in October 2024.[12]

Tirzepatide has been studied specifically in Japanese adults aged ≥20 years with T2D as monotherapy and combination therapy.[13,14] In the monotherapy trial (SURPASS J-mono), patients were either treatment-naive or had discontinued oral therapy. In the combination trial (SURPASS J-combo), patients had uncontrolled glycaemia despite receiving oral antihyperglycaemic monotherapy. Participant baseline HbA1C had to be ≥7% to <11% to be eligible for enrolment. In the monotherapy trial, tirzepatide was superior to dulaglutide with respect to reduction in both A1C and weight, and, in the combination trial, tirzepatide was effective in lowering HbA1C and weight, regardless of background oral antihyperglycaemic therapy. In both studies, the types and frequencies of adverse events were similar to those of other GLP1RA and to the adverse event profiles in the SURPASS 1–5 clinical trials. The authors of each study concluded that tirzepatide is a safe and effective treatment option in Japanese adults with inadequately controlled T2D.[13,14]

FDA-approved indication and dosing

As previously stated, tirzepatide (Mounjaro) was approved by the FDA and EMA in 2022 as an adjunct to diet and exercise to improve glycaemic control in adults with T2D.[15,16] The FDA and EMA recommended a starting dose of 2.5 mg subcutaneously once-weekly for 4 weeks, followed by a titration to 5 mg subcutaneously once-weekly, with subsequent dose titrations of 2.5 mg occurring at least 4 weeks after each dose titration if additional glycaemic control is needed, with a maximum dose of 15 mg once-weekly.[4] Tirzepatide is contraindicated in people with a personal or familial history of medullary thyroid carcinoma or in people with multiple endocrine neoplasia syndrome type 2 (MEN-2) or any known hypersensitivity to tirzepatide, similar to other GLP1RA products.

ADA, AACE/ACE and EASD recommendations

The American Diabetes Association (ADA) recommends the use of tirzepatide as an adjunct to metformin for additional glycaemic control and is one of the favoured agents secondary to its higher efficacy to achieve glycaemic goals.[2] Additionally, it is considered an agent with very high dual glucose and weight efficacy in patients with T2D who are working on achieving weight management goals. The American Association of Clinical Endocrinology/American College of Endocrinology (AACE/ACE) guidelines for the management of T2D recommend tirzepatide as one of the preferred agents to add to metformin in people who are not achieving their glycaemic targets and have overweight or obesity, an increased hypoglycaemia risk, and/or have experienced severe hyperglycaemia.[3] These guidelines were both recently updated in 2023 and include tirzepatide in their updated algorithm as a preferred agent in multiple scenarios based on data supporting the very high dual glucose and weight efficacy in patients with T2D. A 2022 consensus report by the ADA and the European Association for the Study of Diabetes (EASD) echoes these same recommendations.[17] At the time of this review, tirzepatide has not been approved by the FDA or EMA for weight loss specifically.

Adverse events

Tirzepatide safety has been evaluated in T2D monotherapy and combination therapy phase III trials over the past few years. These clinical trials have reported on the incidence of adverse effects compared with placebo. As it relates to GI adverse events, the rates of nausea, decreased appetite, diarrhoea, constipation, vomiting, dyspepsia and abdominal pain occurred more frequently with tirzepatide than with placebo at all doses studied. The percentage of patients experiencing adverse events in clinical trials has been dose-dependent but increased compared with placebo. When looking at these rates compared with the minimum therapeutically effective dose (5 mg) *versus* the maximum dose (15 mg), the rates are as follows: nausea (12% *versus* 18%), diarrhoea (12% *versus* 17%), decreased appetite (12% *versus* 11%), vomiting (5% *versus* 9%), constipation (6% *versus* 7%), dyspepsia (8% *versus* 5%) and abdominal pain (6% *versus* 5%).[4]

Tirzepatide has not been studied in people with a history of pancreatitis; pancreatitis has occurred infrequently in clinical studies and tirzepatide should be discontinued if pancreatitis occurs.[4] Tirzepatide has also not been studied in people with a history of diabetic retinopathy; people receiving tirzepatide who have a history of diabetic retinopathy should be closely monitored with ophthalmic exams to monitor for signs of disease progression.[4] Like other commercially available GLP1RA, tirzepatide is known to cause thyroid C cell tumours in rats and should not be prescribed to anyone with a personal or family history of thyroid cancer.[4] Whilst gastroparesis is not specifically mentioned in clinical studies of tirzepatide, the prescribing information notes that it should not be used in people with 'severe gastrointestinal illness', which gastroparesis could be considered as being; thus, people with gastroparesis should preferably not be treated with tirzepatide.[4]

Drug interactions

Drug–drug interactions with tirzepatide are not a common concern. However, monitoring for hypoglycaemia when coadministering tirzepatide with other agents that are insulin secretagogues or insulin should be conducted. This typically does not require pre-emptive dose reductions of either tirzepatide or the interacting drug, but monitoring blood glucose values is important with coadministration and often reduction in dose of the insulin secretagogue or insulin is required to avoid hypoglycaemia. Tirzepatide is known to delay gastric emptying and, based on this effect, it has the potential to impact the absorption of other medications given concomitantly. Therefore, especially with medications with a narrow therapeutic index (e.g. warfarin) administered at the same time as tirzepatide, there should be caution when coadministered and the affected drug may require more frequent monitoring. Additionally, tirzepatide may decrease the efficacy of oral hormonal contraceptives, which has the potential to result in an unintended pregnancy. The package insert advises patients taking oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method for contraception for the first month after initiation of tirzepatide and after any tirzepatide dose escalation.[4]

Implications for practice

Tirzepatide is the only dual GIP/GLP1RA approved by the FDA and EMA as of the writing of this review. There is extensive clinical trial experience demonstrating the positive impact of tirzepatide on glycaemic control in T2D, with improvements in HbA1C and fasting plasma glucose, both as monotherapy and as combination therapy with metformin, SGLT2i, or basal insulin. Tirzepatide has proven superior efficacy over once-weekly GLP1RA like injectable semaglutide with respect to both glucose lowering and weight loss. Clinical trials support the role of initiating treatment with a dose of 2.5 mg weekly and titrating up to 5 mg (the minimum therapeutically effective dose) after 4 weeks. Beyond that, tirzepatide may be titrated up to the maximum dose of 15 mg weekly to optimize glycaemic improvement. As noted by the ADA, AACE/ACE and EASD, tirzepatide is a highly effective medication that can be used after metformin to improve glycaemic control and potentially help with reducing weight in patients with overweight or obesity. The weight loss achieved by patients with T2D during clinical trials is promising, but, at the time of this review, it has yet to be approved as a weight loss agent by the FDA or EMA.

The ongoing CVOT will provide further guidance for how to best position tirzepatide in the T2D treatment armamentarium. If there is demonstrated CV benefit in patients with T2D and ASCVD, tirzepatide has the potential to surpass GLP1RA and SGLT2i as preferred agents in patients with or at very high risk of CVD because it would have CV benefit with robust weight loss potential. There may also be a role for tirzepatide in people with dyslipidaemia due to its effects on lipid homeostatis.[5] Additional outcomes of importance to understanding the role in therapy of tirzepatide are its effects on renal function and HF.

In addition to tirzepatide, there are other dual GIP/GLP1RA in development (e.g. VK2735 from Viking Therapeutics) and triple agonists of GIP/GLP1RA/glucagon (e.g. LY3437943 from Eli Lilly and Company). Clinical trial outcomes with the use of dual and eventually triple agonists will further evolve our approach to the management of people with T2D.

Conclusions

Tirzepatide has been recently approved by the FDA and EMA as a dual GIP and GLP1RA for improving glycaemic control in patients with T2D. Clinical trials have demonstrated improvement in A1C, fasting plasma glucose and decreased weight in patients with T2D when tirzepatide is used as monotherapy or in addition to metformin, SGLT2i and/or basal insulin. The most common adverse events reported with the use of tirzepatide are nausea and diarrhoea, which are known adverse events consistent with GLP1RAs. The ongoing trial SURPASS-CVOT will evaluate whether there is CV benefit with the use of tirzepatide in patients with T2D and ASCVD.

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