Tirzepatide in Type 2 Diabetes

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Tirzepatide (TZP) is a once-weekly glucagon-like peptide 1 (GLP-1) and glucose-dependent-insulinotropic-polypeptide (GIP) receptor co-agonist approved for T2D. TZP provides promising evidence in improving glucose control and weight loss in T2D and obesity across preclinical and human studies, including data from the SURPASS program. TZP dramatically changes the clinical course of T2D in different clinical scenarios.

tirzepatide type 2 diabetes glycemic control weight loss cardiovascular outcomes renal outcomes liver steatosis

1. Background

Tirzepatide (TZP) is a once-weekly glucagon-like peptide 1 (GLP-1) and glucose-dependent-insulinotropic-polypeptide (GIP) receptor dual agonist approved for T2D in several countries. TZP binds to both GIP and GLP-1 receptors with different degrees of affinity but efficiently replaces the incretin signaling dampened in T2D [1]. TZP has been included in a novel class of antihyperglycemic agents, also known as “twincretins”, with excellent results in terms of improvement of glucose control and weight loss, as indicated by preclinical studies and clinical trials [2][3][4], attributable to the synergistic effects of the concomitant dual agonism on GIP and GLP-1 receptors.

2. Tirzepatide and Glucose Control

The SURPASS program of randomized clinical trials (RCTs) provided evidence of TZP efficacy and safety in several clinical settings [5], from naïve patients to uncontrolled T2D with basal-insulin regimen.

In SURPASS-1 [6], TZP amounts of 5, 10, and 15 mg/week significantly reduced the levels of glycated hemoglobin (HbA1c) compared to placebo in a cohort of naïve patients recently diagnosed with T2D. More precisely, up to 92% of them achieved HbA1c levels less than 7%, considered the optimal glucose target for most, and up to 52% of participants normalized their glucose levels (HbA1c < 5.7%).

In SURPASS-2 [7], TZP has demonstrated superiority over 1 mg of semaglutide in terms of HbA1c reduction, with 92% of patients obtaining the optimal glucose target (i.e., HbA1c < 7%), and 51% normalized their glucose control, as indicated by HbA1c levels less than 5.7%.

In SURPASS-3 [8], TZP was demonstrated to be superior to insulin degludec U100, as up to 93% of individuals randomized to TZP had HbA1c < 7% and up to 48% had HbA1c levels less than 5.7% at the trial end.

In SURPASS-5 [9], TZP significantly improved glucose control in add-on to insulin glargine U100 over glargine U100 alone titrated with a rigorous treat-to-target approach. Up to 97% of patients had HbA1c < 7% and up to 62% normalized their glucose levels (HbA1c < 5.7%).

The cardiovascular safety trial SURPASS-4 [10] showed that TPZ, compared to a rigorously titrated regimen of insulin glargine U100, significantly improved glucose control in T2D patients with high CV risk. Also, TZP provided considerable weight loss and lower frequency and severity of hypoglycemic episodes with CV effects comparable to that of insulin glargine U100.

Most importantly, TZP was demonstrated to be superior to comparators at all doses (5, 10, and 15 mg/week). The mean change in HbA1c ranged from −1.6% to −2.06% over placebo, from −0.29% to −0.92% over each GLP-1 receptor agonist (GLP-1RA), and from −0.7% to −1.09% over basal insulins [11].

In SURPASS-6, TZP was compared to insulin lispro U100 as an add-on to basal insulin (glargine U100) in patients with uncontrolled T2D [12]. After 52 weeks of treatment, HbA1c levels were lower in patients intensified with TZP than insulin lispro U100 (−2.1% vs. −1.1%, respectively), with TZP as an add-on to glargine U100 performing better than basal-bolus insulin regimen (HbA1c at the study end: 6.7% vs. 7.7%, respectively).

Overall, TZP provides additional evidence supporting the choice of incretin-based antihyperglycemic agents as the first injectable treatment for most with T2D over basal insulin and more composite insulin regimens, such as basal-plus and basal-bolus [13].

3. Tirzepatide and Body Weight

The results of two meta-analyses showed that TZP induces a significant weight loss, compared to placebo by around 7.5 (5 mg/week), 11 (10 mg/week), and 12 kg (15 mg/week) [14][15]. Compared to GLP-1RAs, TZP reduces body weight from −1.68 kg to −7.16 kg depending on the dose (5 to 15 mg, respectively) [11]. Compared to basal insulin alone rigorously titrated using a treat-to-target approach, TZP added onto basal-insulin results in the best strategy to improve the study outcome with a composite endpoint of improved glucose control and weight loss [16]. The SURPASS-6 found similar results, in which TZP in add-on to insulin glargine U100 reduced body weight by 9 kg in mean (versus weight gain in basal-bolus users: +3.2 kg) [12]. So far, no direct comparisons have been analyzed between TZP and sodium-glucose (co)transporter type 2 inhibitors (SGLT2is). SGLT2is were proven to induce mild-to-moderate weight loss. According to the results of one systematic review and network metanalysis, SGLT2is cause a body weight reduction of 1.3 to 3.1 kg, depending on patients' characteristics and background antihyperglycemic treatment, without a statistically significant difference between the molecules [17].

According to the results of indirect comparisons among all anti-hyperglycemic classes, including TZP, on body weight in T2D, TZP resulted in the most significant reduction in body weight with an estimated mean difference of −8.6 kg [18].

Impressive findings on weight loss have also been confirmed in obese individuals who were treated with TZP, irrespective of background diabetes. In the SURMOUNT-1 trial, the mean change in weight from baseline after 72 weeks of treatment was −15% (5 mg), −19.5% (10 mg), and −20.9% (15 mg). Body weight reduction was significantly more than placebo (−3.1%). Patients lost more than 20% of baseline body weight more frequently on TZP with 10 mg (50%) and 15 mg (57%) than on placebo (3%) [19]. The results of the SURMOUNT-2 trial confirmed important findings in patients with obesity and T2D [20]. TZP amounts of 10 and 15 mg induce more weight loss with a comparable safety profile also compared to high-dose single GLP-1RAs, such as daily semaglutide 0.4 mg, weekly semaglutide 2.4 mg, and daily liraglutide 3 mg, as a network meta-analysis of randomized clinical trials has recently found [21].

TPZ is expected to readdress the role of medical compared to surgical (bariatric) treatment in the management of comorbid obesity [22].

4. Tirzepatide and Cardiovascular Outcomes

Cardiovascular (CV) diseases (CVD), especially coronary disease and stroke, affect approximately 30% of patients with T2D and represent the most common cause of mobility and mortality in T2D [23].

While megatrials indicated that intensive treatment of hyperglycemia resulting in more stringent glucose control is associated with a considerable reduction of microvascular complication, less clear is the relation between optimal glucose control and improvement of CV outcomes in T2D [24][25][26][27]. Evidence indicates that intensive multifactorial intervention targeting glucose, arterial pressure, lipid control, and behavior modification has sustained beneficial effects in terms of CV prevention, CV and all-cause mortality, thus resulting in the best management of CV prevention and CVD in T2D [28].

More recently, the results of CV outcome trials have indicated that specific GLP-1RAs and SGLT2is have proven CV benefits beyond the glycemic effect. Liraglutide, compared to placebo, reduced the risk of occurrence of the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), CV mortality, and all-cause mortality by 13%, 22%, and 15%, respectively [29]. Once-weekly semaglutide, compared to placebo, reduced the risk of nonfatal myocardial infarction by 26% (statistically significant for non-inferiority) and nonfatal stroke by 39% [30]. In PIONEER-6, oral semaglutide compared to placebo reduced the CV and all-cause mortality by 51% and 49%, respectively [31].

Empagliflozin was demonstrated to reduce the primary composite outcome of CV mortality, nonfatal myocardial infarction, or nonfatal stroke by 14% compared to placebo. The result was mostly driven by a considerable reduction in the rate of deaths for CV events by 38%; moreover, the use of empagliflozin was associated with a

substantial reduction in the relative risk of hospital admission for decompensated heart failure (−35%) and all-cause mortality (−32%) [32]. In the CANVAS trial, canagliflozin reduced the primary outcome by 14%, resulting in statistically significant superiority over placebo [33]. Dapagliflozin, compared to placebo, reduced the composite endpoint of CV death and hospital admission for heart failure by 17%, which reflected a significantly lower rate of hospitalization due to decompensated heart failure (−37%) [34].

The cardiovascular outcome trial SURPASS-CVOT is ongoing to address the CV safety of TZP compared to dulaglutide in T2D individuals at high CV risk [35]. As is known, dulaglutide has been demonstrated to reduce the primary composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes by 12% in a population of T2D on primary and secondary CV prevention, as the REWIND trial demonstrated [36]. Post hoc analyses have been carried out to address the CV safety of TZP. Sattar meta-analyzed CV data from the SURPASS program, finding that TZP, compared to placebo, had a neutral effect on cardiovascular and all-cause death and composite CV outcome [37].

Nonetheless, TZP has important pleiotropic effects, anticipating CV benefits based on the impact of TZP on surrogate outcomes. For example, arterial pressure control is associated with a significant reduction of new onset and progression of microvascular complication and ischemic stroke in T2D, with most of the benefit achieved with systolic and diastolic arterial pressure < 130/80 mmHg [38]. It has been found that TZP, over background antihypertensive treatment and statins, reduces systolic arterial pressure by 4 to 6 mmHg (5 mg to 15 mg/week) and total cholesterol by 4–6% compared to baseline [39], also improving specific signs of insulin sensitivity, such as liver steatosis and waist circumference [40].

Although there are no direct comparisons between TZP and antihyperglycemic agents with proven CV benefits in terms of improvement of arterial pressure and cholesterol levels, it should be taken in mind that SGLT2is with proven CV protection in add-on to background antihypertensive treatment are associated with a mild reduction of systolic and diastolic arterial pressure by 2.5 and 1.4 mmHg, respectively [41]. Moreover, SGLT2is induce a mild improvement or neutral effect on lipid profile when added to hypocholesterolemic agents [42][43][44]. Nevertheless, better results have been found in patients with fatty liver disease, in which SGLT2is reduce both total cholesterol by 2.7 mg/dL and triglycerides by 16.8 mg/dL [45]. GLP-1RAs with proven CV benefits, compared to SGLT2is, induce a similar decrease in both systolic and diastolic arterial pressure, which are clinically insignificant [46], with a modest improvement or neutral effect on lipid profile [47][48].

Overall, data on surrogate endpoints indicate that TZP could have a relevant therapeutical potential in the prevention of CV diseases in T2D, even if specific and event-driven trials are needed to confirm this hypothesis.

5. Tirzepatide and Renal Outcomes

Chronic kidney disease (CKD) is one of the most common chronic complications in T2D. Up to 40% of individuals with diabetes have chronic renal impairment [49], with a wide range of renal damage, as defined by the Kidney

Disease Improving Global Outcomes classification [50]. CKD represents the leading cause of end-stage renal disease and death for renal causes in T2D [51][52].

As above mentioned for CVD, antihyperglycemic drugs with proven renal benefits are desirable to affect the natural history of renal impairment associated with T2D. Compared to placebo, liraglutide has been demonstrated to reduce the composite endpoint of persisting macroalbuminuria, doubling serum creatinine level, end-stage renal disease, or death for renal disease by 26%. This finding was mostly driven by a significant reduction in the relative risk of new onset macroalbuminuria (−26%) compared to placebo [53]. Dulaglutide, compared to placebo, reduced the primary composite endpoint of first occurrence of new macroalbuminuria, sustained decline in eGFR ≥ 30% from baseline, or chronic renal replacement therapy by 15%. As observed for liraglutide, dulaglutide reduced the relative risk of new onset of macroalbuminuria by 23% in T2D [54]. Secondary analyses from the SUSTAIN-6 trial found that semaglutide reduced the risk of new onset or deterioration of chronic renal disease, as the composite outcome of persisting macroalbuminuria, doubling of serum creatinine, or end-stage renal disease was reduced by 36% [30]. The result of a systematic review and meta-analysis indicates that GLP-1RAs, compared to placebo, provide a statistically relevant improvement in albuminuria by around 16% [55].

SGLT2is provided consistent evidence to improve significantly renal outcomes regardless of glucose control and the presence of T2D. The CREDENCE trial was the first renal outcome trial to be designed and published for estimating the role of canagliflozin in the prevention of renal outcomes in T2D. Canagliflozin, compared to placebo, reduced the relative risk of the primary outcome (composite of end-stage renal disease, a doubling of the serum creatinine level, or death from renal or cardiovascular causes) by 30% and the relative risks of mortality for renal causes or end-stage renal diseases by 34% and 32%, respectively [56]. Dapagliflozin was found to reduce the primary composite outcome of sustained decline in the GFR ≥ 50%, end-stage kidney disease, or death from renal or cardiovascular causes by 44%. Interestingly, the protective effect of dapagliflozin was seen in both T2D and non-diabetic individuals [57]. In the EMPA kidney trial, empagliflozin was found to improve the primary study outcome, a composite of end-stage kidney disease, a sustained decrease in eGFR to <10 mL/min/1.73 m^2, a sustained reduction in the eGFR of ≥40% from baseline, or death from renal or CV causes, by 28% compared to placebo [58]. The result was in line with another pooled analysis in which SGLT2is were found to reduce albuminuria by 26.2% [59]. SGLT2is have demonstrated to reduce the composite kidney outcome (development of new-onset macroalbuminuria, decline in glomerular filtration rate, progression to end-stage kidney disease, or death attributable to kidney causes) by 14% to 21% [60][61][62].

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, was found to improve renal outcomes in patients with T2D and chronic renal disease on top of renin–angiotensin system blockers. In the FIDELIO trial, finerenone reduced the relative risk of the primary outcome (composite of kidney failure, a sustained decrease in the eGFR ≥ 40% from baseline, or death from renal causes) by 18% in T2D individuals with established diagnosis of CKD [63]. Similar results were found by Pitt et al. in the FIGARO trial. In this trial, the cardiovascular and renal benefits of finerenone were assessed in T2D patients with a broader range of renal function (eGFR 25–90 mL/min/1.73 m^2). Finerenone improved the renal composite outcome by 13% compared to placebo, but the result was not statistically significant [64].

No specific trials have been conducted so far to assess the renal effect of TZP. A post hoc analysis of SURPASS-4 revealed that TZP compared to glargine U100 delayed the mean rate of glomerular filtration decline (−1.4 mL/min vs. −3.6 mL/min, respectively), reduced the mean rate of urinary albumin excretion (−6.8% vs. +36.9%, respectively), and was associated with a lower occurrence of the composite renal endpoint by 42% (HR 0.58 [0.43; 0.80]) [65]. Despite benefits being more evident in patients with baseline renal impairment, the protective effects of TZP were also observed in normoalbuminuric and those with glomerular filtration higher than 60 mL/min [66]. To confirm positive results on renal outcomes, the meta-analysis by Mima et al. found that TZP remarkably reduced the risk of composite renal outcome by 45% and worsening albuminuria by 62% [67].

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