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Review Article

Twincretin (Dual GIP/GLP-1 Receptor Agonists): The New Kid on The Block

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Abstract

The incretin axis has been the interest of study and development for newer drugs towards the treatment of Type 2 diabetes. From oral therapies focusing on dipeptidyl peptidase-4 (DPP-4) inhibitors to injectable GLP1 analogs and most recently the dual GIP/GLP-1 receptor agonists; have all been contributing towards better glycemic control for adult type 2 diabetic patients. This article focuses on the latter dual acting GIP/GLP-1 receptor agonist (Tirzepatide) and its benefits in both monotherapy and combination therapy along with its pleiotropic actions in improvements in lipid profile and reduction of cardiometabolic risk for type 2 diabetic adults. Phase 3 clinical trials have compared Tirzepatide with placebo, GLP1 agonists like semaglutide and dulaglutide, basal insulin like glargine insulin, rapid acting insulins like insulin lispro; with patients who have treatment naïve and those who have been uncontrolled with monotherapy or combination therapy with or without the use of injectable antidiabetic agents. All of them have shown either a non-inferiority or a superiority of the use of titrated dosing of tirzepatide in achieving near normoglycemia, HbA1c reduction, weight loss and fewer adverse effects; while being used with or without concomitant oral antidiabetic therapy or insulins. The most common seen adverse effects have been gastrointestinal effects such as nausea and vomiting which have been more in the patients receiving higher doses of the drug.

Keywords: Dual GIP/GLP-1 Receptor Agonists; Tirzepatide; Incretins; HbA1c Reduction; Weightloss

Twincretin (Dual GIP/GLP-1 receptor agonists): The new kid on the block

Insulin had remained the only injectable anti-diabetic treatment offered to both Type 1 and Type 2 Diabetic patients for their hyperglycemia which remained uncontrolled despite optimized Oral Hypoglycemic Agent (OHA) therapy. However; the risk of hypoglycemia, cost of pen devices over the available vial preparations, the lack of variety of fixed dose combinations, fluctuations in insulin regimen (single dose to multiple dose regimen) and the general misconceptions surrounding insulin use for diabetes; had all contributed to a suboptimal use of this very apt drug.

The "incretin effect" is the stimulation of insulin secretion after an oral glucose load via the incretin hormones, namely Glucagon-Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP). GLP-1 is released from the intestinal L cells in the distal ileum and colon while GIP is released by the intestinal K cells in the duodenum and jejunum. Both these hormones are inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme. In diabetic individuals, this incretin response is blunted and this further contributes to the hyperglycemic response in addition to the decreasing beta cell activity/mass [1,2].

Both of these, GLP-1 and GIP, when used as therapeutic modalities contribute towards normoglycemia by reviving insulin excretion, delaying gastric emptying, inhibiting glucagon production from pancreatic α-cells and decreasing pancreatic β-cell apoptosis in addition to promoting their proliferation [3]. Cardiovascular benefits from this class includes reduction in body weight, blood pressure lowering effects, decreasing cholesterol; improving left ventricular Ejection Fraction (EF), myocardial contractility, coronary blood flow, cardiac output, and endothelial function while reducing infarction size and overall risks for a cardiovascular event [4,5]. Other pleiotropic effects include an increased muscular glucose

uptake, decreased hepatic glucose production, neuroprotection, increased satiety due to hypothalamic actions [6].

Currently available injectable GLP1 agonists include Exenatide and Tirzepatide (Exedin based) and Liraglutide, Semaglutide (similar to liraglutide, but with a larger linker molecule to, and an increased length of, the fatty acid derivate) and Dulaglutide (GLP-1 analogue covalently linked to a constant Fragment (Fc) of a human immunoglobulin class 4 (IgG4)) which are human GLP1 based. Lixisenatide (GLP-1R agonist) and Albiglutide (generated by genetic fusion of a GLP-1 dimer to human albumin) have been further discontinued [7]. Presently, Tirzepatide is the only dual acting GIP analog that activates both the GLP-1 and GIP receptors, hence the nickname "twincretin".

Mechanism of Action:

Both GIP and GLP-1 exert their effects by binding to their specific receptors, the GIP receptor (GIPR) and the GLP-1 receptor (GLP-1R), belong to the G-protein coupled receptor family, activating adenylate cyclase and increasing levels of intracellular cyclic Adenosine Monophosphate (cAMP) in pancreatic beta cells, thereby stimulating insulin section glucose dependently. Both GIP and GLP-1 exert their insulinotropic effects by binding to GIP and GLP-1 receptors that are expressed on pancreatic beta cells. Incretin-bound receptors increase intracellular cAMP levels, thereby activating protein kinase A (PKA) and exchange protein activated by cAMP2 (EPAC2)/cAMP-guanine nucleotide exchange factor (GEF) II. PKA and EPAC2 are involved in a wide variety of intracellular events including altered ion channel activity, elevated cytosolic calcium levels and enhanced exocytosis of insulin-containing granules, all of which contribute to stimulation of insulin section in a glucose-dependent manner [8].

Animal model studies showed that compounds having receptor activation to both GIP and GLP-1 were more effective in reducing body weight and achieving better glucose control than a selective GLP-1R agonist (GLP-1RA). Additionally, the stimulation of the satiety centres and decrease in appetite may be due to the expression of GIPR on arcuate nucleus neurons and other hypothalamic regions [9,10].

Clinical Studies

The Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in adult patients (> 18 years) with type 2 diabetes (SURPASS-1) trial was a 40-week, double-blind, randomized, placebo-controlled, phase 3 trial performed at 52 medical research centres and hospitals in India, Japan, Mexico, and the USA. Enrolled subjects were Type 2 diabetic adult who were not exposed to injectable hypoglycemic agents and were inadequately controlled by diet and exercise alone. The subjects were assigned to either a placebo or once weekly dose of tirzepatide (5, 10, or 15 mg) using a computer-generated random sequence. After 40 weeks, it was seen that tirzepatide when compared to the placebo group, showed superiority with respect to changes from baseline in HbA1c, fasting serum glucose, bodyweight reduction, and HbA1c targets of less than 7·0% (<53 mmol/mol) and less than 5·7% (<39 mmol/mol). A weight loss of 7 – 9.5 kilograms was observed in the tirzepatide group [11].

A 40-week, open label, phase 3 trial comparing the efficacy and safety of once-weekly tirzepatide as compared with semaglutide (SURPASS-2) was performed in 128 centres in USA, Argentina, Australia, Brazil, Canada, Israel, Mexico, and the United Kingdom. 1879 adult patients (> 18 years) with type 2 diabetes who had inadequately controlled sugars with metformin at a dose of at least 1500 mg/day were enrolled in the study. Subjects were randomly assigned to receive a once-weekly subcutaneous injection of either tirzepatide (5 mg, 10 mg, or 15 mg; the doses were double-blinded) or semaglutide (1 mg) for a 40-week treatment period, followed by a 4-week safety follow-up period. After 40 weeks, it was seen that tirzepatide when compared to the semaglutide group, showed superiority with respect to changes from baseline in HbA1c, fasting and post prandial blood glucose, body weight reduction and improvement in lipid parameters (lower triglyceride, very-low-density lipoprotein levels, high-density lipoprotein). 69 - 80% of tirzepatide group and 64% in the semaglutide group had a glycated hemoglobin reduction to <6.5%. Additionally, 27- 46% of tirzepatide group and 19% in the semaglutide group, had a glycated hemoglobin reduction to <5.7%. A weight loss of 7.6 – 11.2 kilograms was observed in the tirzepatide group as compared to 5.7 kilograms reduction in the semaglutide group [12].

The Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3) trial was a 52 week, randomized, parallel group, phase 3 trial done at 122 centres. 1444 adult patients (> 18 years) with type 2 diabetes, insulin-naive and treated with metformin alone + SGLT2 inhibitor for > 3 months prior screening were randomly assigned to once-weekly subcutaneous tirzepatide (5, 10, or 15 mg) dose or once-daily subcutaneous titrated insulin degludec dose, and were stratified by country, HbA1c, and concomitant use of oral antidiabetic medications. After 52 weeks, it was seen that tirzepatide when compared to the insulin degludec group, showed superiority with respect to changes from baseline in HbA1c and body weight reduction. In the latter, a weight gain by 2.3 kilograms was observed. A HbA1c <7·0% (<53 mmol/mol) reduction at week 52 was greater ($p<0·0001$) in all three tirzepatide groups (82%–93%) versus just 61% in the insulin degludec group. Severe hypoglycemia of < 54 mg/dl was noticed in 7% of subject on the insulin degludec group as compared to fewer numbers in the tirzepatide treated group. Hence, it proved the non-inferiority and superiority of tirzepatide to insulin degludec in adults with type 2 diabetes [13].

The Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomized, open-label, parallel-group, multicentre, phase 3 trial done is 187 centres over 52 weeks. 2002 adult patients (> 18 years) with type 2 diabetes randomly assigned to receive either once weekly tirzepatide (5 mg, 10 mg, or 15 mg) or titrated doses of insulin glargine (100 U/mL) in order to achieve a fasting blood glucose of < 100 mg/dL. After 52 weeks, it was seen that tirzepatide when compared to the insulin glargine group, showed superiority with respect to changes from baseline in HbA1c and hypoglycemic episodes. 109 subjects had adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina) however, these were not increased in tirzepatide group when compared with glargine group (hazard ratio 0·74, 95% CI 0·51-1·08). Hence, it proved the non-inferiority of tirzepatide to insulin glargine in adults with type 2 diabetes [14].

The Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial was an open labeled, randomized, phase 3 trial performed in 45 centres over 8 countries. 475 adult patients (> 18 years) with type 2 diabetes and inadequate glycemic control while on treatment with once-daily insulin glargine + metformin were studied over 40 weeks. After 40 weeks, it was seen that tirzepatide when compared to the placebo group, showed better results with respect to changes from baseline in HbA1c and body weight reduction. 85-90% of subjects in the tirzepatide group when compared to the placebo group (34%) were able to achieve a HbA1c of <7%. Therefore, the addition of tirzepatide once weekly subcutaneously for a type 2 diabetic patient who is not adequately controlled with insulin glargine, showed a better improvement in glycemic control after 40 weeks [15].

The Tirzepatide vs Insulin Lispro Added to Basal Insulin in Type 2 Diabetes: The SURPASS-6 Randomized Clinical Trial was an open-label, phase 3b clinical trial carried out over 135 centres in 15 countries. 1428 adult patients (> 18 years) with type 2 diabetes, while on basal insulin (glargine) were randomized to receive titrated doses of tirzepatide (5 mg, 10 mg, or 15 mg) or prandial thrice-daily insulin lispro and studied over 52 weeks. At the end of 52 weeks, it was seen that tirzepatide when compared to the insulin lispro group, showed better results with respect to changes from baseline in HbA1c (-2.1% vs -1.1%) and body weight reduction (-9 kilograms vs 3.2 kilograms, respectively). 68% of subjects in the tirzepatide group when compared to the lispro group (36%) were able to achieve a HbA1c of <7%. Therefore, the addition of once weekly tirzepatide to inadequately controlled type 2 diabetics on basal insulin (glargine), contributed to better reductions in HbA1c and body weight with less hypoglycemia when compared to insulin lispro [16].

The Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomized, phase 3 trial was performed in 46 centres in Japan. 636 type 2 diabetic adults (>20 years), who were treatment naïve or had discontinued oral antihyperglycaemic monotherapy were randomized to receive either titrated doses of tirzepatide (5 mg, 10 mg, or 15 mg) or dulaglutide (0·75 mg) once per week for 52 weeks. At the end of the study, the tirzepatide group had a greater dose-dependent decrease in bodyweight as compared to that of the dulaglutide group. Similarly, HbA1c reductions were also significantly greater in the tirzepatide group than the dulaglutide group, thereby showing the superiority of tirzepatide over dulaglutide in adult type 1 diabetic patients in Japan [17].

The Safety and efficacy of tirzepatide as an add-on to single oral antihyperglycaemic medication in patients with type 2 diabetes in Japan (SURPASS J-combo): a multicentre, randomized, open-label, parallel-group, phase 3 trial was performed at 34 centres in Japan. 443 type 2 diabetic adults (>20 years), who were on oral monotherapy (sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinedione, glinides, or SGLT2 inhibitors) for at least 3 months were randomized to receive titrated doses of tirzepatide (5 mg, 10 mg, or 15 mg) in addition to their oral medications to control their hyperglycemia. At the end of the 52 weeks study, the tirzepatide group had a greater dose-dependent decrease in bodyweight and glycemic improvement irrespective of background oral antihyperglycaemic medication [18].

The Tirzepatide versus insulin glargine as second-line or third-line therapy in type 2 diabetes in the Asia-Pacific region: the SURPASS-AP-Combo trial was a phase 3, randomized, open-label trial, insulin-naive type 2 diabetic adults (≥18 years of age) who were uncontrolled on metformin (with or without a sulphonylurea), performed in 66 hospitals in China, South Korea, Australia and India. 917 patients were randomized to receive either once weekly tirzepatide (5 mg, 10 mg, or 15 mg) or titrated doses of insulin glargine. At the end of the 40-week study, it was seen that tirzepatide was not only non inferior but also superior to insulin glargine when added as a second-line or third-line therapy w.r.t changes from baseline in HbA1c and body weight reduction in the well tolerated in an Asia-Pacific, predominately Chinese, population [19].

The Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics are an ongoing randomized, double-blind, active-controlled CV outcomes trial performed at 640 sites in 30 countries. 13,299 type 2 diabetic adults (> 40 years) with an established atherosclerotic cardiovascular disease (including coronary artery disease, cerebrovascular disease or peripheral

arterial disease) are included in this study over a 2 year period (54 weeks). The patients are to receive either once weekly tirzepatide (5 mg, 10 mg, or 15 mg) or once weekly dulaglutide 1.5 mg subcutaneously. Primary outcome measures are time to first occurrence of death from Cardiovascular (CV) causes, Myocardial Infarction (MI), or stroke (MACE-3). Secondary outcome measures include time to death from any other cause, time to occurrence of first MI, stroke, revascularization, hospitalization due to unstable angina, nephropathy (new or worsening); percentage of subject with > 10% weight loss and change from baseline body weight, HbA1c, lipids [20].

Conclusion

Promising results of this novel dual agonist of both GLP1 and GIP, gives hope for newer molecules working on the same principle of activation and action. Better endpoint reductions; in comparison to single GLP-1 receptor agonists; in reduction of HbA1c, body weight, ectopic fat reduction, lesser gastrointestinal adverse events and MACE make it a potential candidate for obese type 2 diabetic adult subjects.

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