DRUG UPDATE

Tirzepatide

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INTRODUCTION

Tirzepatide (also called as 'twincretin') is the first-in-class and only dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist, which can significantly reduce glycemic levels and improve insulin sensitivity, and decrease body weight by more than 20%.[1] Tirzepatide (Proprietary Name- Mounjaro of Eli Lilly and Company) has been recently approved by the Food and Drug Administration (FDA) for use in the United States of America (USA). The approved indication of Tirzepatide being to normalize blood glucose levels in adult patients with Type II Diabetes Mellitus (DM) in addition to diet and exercise. Several clinical trials are underway that have also shown initial prospects for the use of Tirzepatidein Obesity control in Type II DM patients.

Type II DM is the most common form of diabetes, a chronic and progressive condition in which the body does not make or use insulin normally, leading to high levels of glucose in the blood. Despite the availability of a number of medications to treat diabetes, many patients do not achieve the recommended blood glucose goals. Three different doses of tirzepatide (5 milligrams, 10 milligrams and 15 milligrams) were evaluated in a total of five clinical trials as either a stand-alone therapy or as an add-on to other diabetic medicines. Patients that were randomized to receive the maximum recommended dose of tirzepatide (15 milligrams) had lowering of their hemoglobin A1c (HbA1c) level by 1.6% more than placebo when used as stand-alone therapy and 1.5% more than placebo when used in combination with a long-acting insulin. In trials comparing tirzepatide to other diabetes medications, patients who received the maximum recommended dose of tirzepatide had lowering of their HbA1c by 0.5% more than semaglutide, 0.9% more than insulin degludec and 1.0% more than insulin glargine. Obesity was common among study participants, with an average body mass index of 32 to 34 kg/sqm reported. Among patients randomized to the maximum recommended dose, the average weight loss with tirzepatide was 15 pounds more than placebo when neither were used with insulin and 23 pounds more than placebo when both were used with insulin. The average weight loss with the maximum dose of tirzepatide was 12 pounds more than semaglutide, 29 pounds more than insulin degludec and 27 pounds more than insulin glargine. It was also seen that those patients receiving insulin without tirzepatide tended to gain weight.

Chemical Structure

Tirzepatideis a linear peptide,$C_{225}H_{348}N_{48}O_{68}$ which contains 39 amino acid, size is same as GIP and GLP-1. It is trade name is Mounjaro and other brand names are LY3298176, GIP/GLP-1 RA.It belongs to the secretin family related hormones of gut peptides. The starting amino acid sequence is the same as human GIP and it retains 9 homologous AAs from this peptide 10 AAs shared by GIP and GLP-1 as well. 4 AAs correspond of GLP-1 molecule at same position, and 10 amino-terminal are identical to the sequence of exendin-4 (a lizard salivary peptide known as Helodermasuspectum),also called exenatide.

Mechanism of Action

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist for the treatment of Type II DM and also lowering blood glucose levels. It is also used for long standing Type II DM to achieve normal glucose levels. Tirzepatide stimulates cAMP generation in combination of GIP and GLP-1 in pancreatic ß-cells.Tirzepatide is an acylated

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peptide engineered to activate the GIP and GLP-1 receptors[1]. insulin secretion which expressed in regions of the brain it regulate food intake.Tirzepatide at 5–15 mg per week reduces both HbA1c (1.24 to 2.58%) and weight (5.4–11.7 kg) which is not done by any other single drug.

Dosing, Efficacy and Safety

Start with a 2.5 mg dose, which is not intended for glycemic control. After 4 weeks,we can increase 5 mg injected subcutaneously once weekly. If more glycemic control is needed, add 2.5 mg increments after a minimum 4 weeks. In continuous glucose monitoring (CGM) to compare the 24 hr glucose profile for participants given tirzepatide compared with those given insulin degludec,[2,3] if was found that, the treatment with tirzepatide is superior glycemic control measured as Once-weekly using CGM compared with insulin degludec in participants with Type II DM on metformin, with or without a SGLT2 inhibitor. These data provide additional evidence to the effect of tirzepatide and potential for achieving glycemic targets without increase of hypoglycaemic risk compared with a basal insulin[4]. A dose-dependent superiority on glycemic efficacy and decrease weight is evident with tirzepatide vs placebo, GLP-1 RAs and basal insulin. Tirzepatide did not increase the odds of hypoglycaemia but was associated with increased gastrointestinal adverse events.

In efficacy and safety of tirzepatide versus titrated insulin degludec in Type II DM controlled by metformin with or without SGLT2 inhibitors,in patients with Type II DM, tirzepatide (5, 10, and 15 mg) is superior to titrated insulin degludec, with markedly decrease in HbA1c and bodyweight at week 52 and a less risk of hypoglycaemia. Both Tirzepatide and GLP-1 receptor agonists shows similar safety profile.Theglycaemic efficacy of GIP/GLP-1 receptor agonist tirzepatide in Type II DM results from concurrent improvements in diabetes pathophysiology, namely β-cell function, insulin sensitivity, and glucagon secretion. These effects were large and help to explain glucose-lowering ability. It is glucose dependent insulinotropic polypeptide.

Other GLP-1 receptor agonist drugs include: Dulaglutide (Trulicity) (weekly), Exenatide extended release (Bydureonbcise) (weekly),Exenatide (Byetta) (twice daily),Semaglutide (Ozempic) (weekly), Liraglutide (Victoza, Saxenda) (daily).

Adverse Effects

Nausea, vomiting, diarrhoea, constipation, decreased appetite, upper abdominal discomfort and abdominal pain are the common adverse effects to the use of tirzepatide. It can result in a substantial weight loss as well. Pharmacologically, signaling studies demonstrate that tirzepatide mimics the actions of native GIP at the GIP receptor but shows bias at the GLP-1 receptor to favor cAMP generation over β-arrestin recruitment, weaker ability to drive GLP-1 receptor compared to GLP-1.

Clinical Development

Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether Tirzepatide causes such tumors, including medullary thyroid cancer, in humans. Tirzepatide should not be used in patients with a personal or family history of medullary thyroid cancer or in patients with type MEN syndrome. Tirzepatide has not been studied in patients with a history of pancreas inflammation (pancreatitis), and it is not indicated for use in patients with type 1 diabetes.Tirzepatide received priority review designation for this indication.

Tirzepatide works like two hormones that help people feel full after eating[5]. At those doses, tirzepatide achieved a reduction of A1C of f 2.09% and a weight loss of 7.8 kg (17 lbs). In contrast, semaglutide(Ozempic) posted a drop of 1.86% in A1C and 6.2 kg (14 lbs) in body weight[6]. It's not yet approved for weight loss, but doctors can prescribe. One of the most popular existing weight loss drugs, called semaglutide, originated as a diabetes medication,was FDA-approved to treat obesity in 2021[7]. In the SURPASS-2 study, all doses of tirzepatide were superior to semaglutide 1 mg, a selective GLP-1 RA, in both HbA1c and body weight change from baseline at week 40 in patients with Type II DM, taking metformin with HbA1c more than target value. The overall safety profile of tirzepatide is equal to semaglutide[8]. Both tirzepatide and dulaglutide are GLP-1-type drugs indicated for the treatment ofType II DM,, but they work in slightly different ways.The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown. Semaglutide and tirzepatide, the two molecules do not act in precisely the same way. Semaglutide is a GLP-1 analogue whereas tirzepatide is a GIP/GLP-1 agonist. Both are prone to gastrointestinal side-effects. Injection of tirzepatide at 15 mg for the same duration lowered the body weight by 13.1% in surpass-2 with an ETD of 6.4% compared to semaglutide 1 mg treatment. Use of tirzepatide other than diabetes-Eli Lilly's (NYSE:LLY)

tirzepatide has demonstrated a significant weight loss benefit in individuals without diabetes in a late-stage trial. Insulinotropic effect is glucose-dependent insulinotropic peptide that stimulates the release of insulin from the beta cells in the pancreas in order to maintain low blood sugar levels after eating. It also increases the production of these cells and reduces the rate at which they break down.

CONCLUSION

Type II DM and Obesity are illnesses that have no particular cure so far, although, can be kept under control by proper treatment and integrating lifestyle adjustments. The disturbing increase in the number of Type II DM patients with obesity in recent years, requires new medical advancements in order to improve administration, reduce dosing, and simultaneously address multiple comorbidities with a single medication. Tirzepatide offers a novel and better alternative in this regard. However, additional clinical trials on a larger subset of population are required to ascertain its efficacy and safety.

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