Open Access
Volume 5 Issue 1
Editorial Article

Journal of Medical and Clinical Studies
ISSN: 2582-0869

PUBTEXTO

Latest Topic for Clinical Effects of Tirzepatide as Dual GIP/GLP-1 Receptor Agonist

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Article Info

Article History:
Received: 02 July, 2022
Accepted: 06 July, 2022
Published: 10 July, 2022

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Abstract

Treatment for Type 2 Diabetes (T2D) includes incretin hormones, such as glucagon-like peptide-1 (GLP-1) and also glucose-dependent insulinotropic polypeptide (GIP). As latest agent for T2D, twincretin of dual GIP and GLP-1 receptor agonist, tirzepatide has been studied for SURPASS clinical trials. Clinical efficacy of tirzepatide (5, 10, 15mg) has been reported, where HbA1c reduction showed 2.01%, 2.24% and 2.30%, respectively and weight reduction of tirzepatide was larger than semaglutide as 1.9kg, 3.6kg and 5.5kg, respectively. For comparative study of four-component major adverse cardiovascular event (MACE-4), tirzepatide showed Hazard Ratios (HRs) of 0.80 for MACE-4 and 0.90 for cardiovascular death.

Keywords: Glucagon-like peptide-1 (GLP-1); Glucose-dependent insulinotropic polypeptide (GIP); Dual GIP and GLP-1 receptor agonist; Tirzepatide; SURPASS clinical trials; Four-component major adverse cardiovascular event (MACE-4)

Editorial

Various agents for diabetes were historically introduced to medical practice. Recently, incretin hormones are in focus, which are released in the intestine and responsive to the nutrients in the lumen. Main incretins include glucagon-like peptide-1 (GLP-1) and also glucose-dependent insulinotropic polypeptide (GIP) [1]. GLP-1 stimulates insulin secretion, inhibits glucagon secretion and brings slowing of gastric emptying. GIP has been main peptide for causative factor of incretin effects in healthy person. However, insulin response is much reduced after GIP secretion in patients with Type 2 Diabetes (T2D). Thus, glucose homeostasis would be critical, which is regulated by GLP-1, GIP, glucagon and others [2].

From embryological and endocrinological animal points of view, proglucagon-derived peptides were present in phylogenetically ancient fish act [3]. They include natural dual agonists for GLP-1 receptor (GLP-1R) and glucagon receptor with lamprey GLP-1 as well as paddlefish glucagon that is most effective factor for stimulating insulin secretion from BRIN-BD11 beta cells. For zebrafish, GIP can act for a dual agonist of GLP-1R and GIP receptor (GIP-R). In the case of insulin-deficient transgenic mice, the peptide brought the increase of beta-cell mass with additional efficacy on trans-differentiation from glucagon-producing cell to insulin-producing cell.

GLP-1R and GIP-R are the class B1 G protein-coupled receptors, which are stimulated by GLP-1 and GIP for gastrointestinal hormones [4]. Consequently, GLP-1 and GIP show the physiological role of strengthening insulin secretion due to nutrient-induced stimulus from the gut. The axis of entero-insular (gut-endocrinological pancreas) seems to be indispensable for keeping normal glucose tolerance situation. GLP-1 and GIP reveal additive efficacy for insulin secretion, and GIP shows larger physiological role [5]. For T2D, incretin efficacy has been decreased despite almost normal secretion of GLP-1 and GIP. Although insulinotropic efficacy of GLP-1 is some impaired in T2D, GIP reveals much decreased insulinotropic activity in T2D. At pharmacological concentrations, GLP-1 may reduce appetite, food intake leading to weight reduction. Similar evolving role has been found in animal investigation, but some differences may exist in human. For GLP-1 and GIP, beneficial effects have been found on neurodegenerative central nervous system (CNS) impairments and cardiovascular disorders.

Incretin pathway shows self-regulating feedback system, which connects the gut with liver, pancreas and brain. Its main role includes post-prandial glucose control, as well as extra-glycemic efficacy on endovascular tissue and fat metabolism [6]. Main two incretin are GLP-1 and GIP, where it would be innovative method to enhance these mutual salubrious functions. For T2D patients, dual agonists may show powerful benefits for glucose variability and weight control. For phase 2b trial of GIP/GLP-1 dual agonists, tirzepatide (1, 5, 10, 15 mg), remarkable reduction of HbA1c and weight was found compared with dulaglutide (1.5 mg) and placebo [7]. Improvement of glucose variability was associated with biomarkers of lipoprotein, triglyceride, insulin resistance and beta-cell function.

As phase 3 clinical trials of tirzepatide, SURPASS trials were conducted [8]. Among them, SURPASS J-mono and J-combo were found in Japan [9]. The former was single study for 636 T2D, in which subjects were divided to 4 groups as 1:1:1:1 for 5, 10, 15 mg of tirzepatide weekly and duraglutide 0.75mg weekly. The results showed A1c reduction for 52 weeks was -2.37 to -2.82% for 3 tirzepatide, and -1.29% for duraglutide. Weight reduction was -5.8-10.7 kg for 3 groups and –0.5kg for duraglutide group. In SURPASS J-combo (combination study), subjects were 443 T2D cases, and HbA1c changes was -2.57% (5mg), -2.98% (10mg) and -3.02% (15mg). Similarly, weight reduction was -3.8kg, -7.5kg and -10.2kg, respectively. The adverse event was gastrointestinal (GI) problems, with no occurrence of severe hypoglycemia. The overall incidence of adverse events was 77.4%, including nausea (16.7%), constipation (12.2%), and diarrhea (11.5%) and vomiting (6.8%). Thus, GI symptoms are common, caused by activation of central GLP-1 receptor [10].

From accumulated data of SURPASS, cardiovascular outcomes were investigated. The protocol included subjects given tirzepatide (n=4887) and control (n=2328) [11]. Among them, 142 cases showed at least one MACE-4 (four-component major adverse cardiovascular event), which included myocardial infarction, cardiovascular death, stroke and hospitalized unstable angina. As a result, Hazard Ratios (HRs) compared as controls were 0.80 for MACE-4, 0.90 for CV death and 0.80 for all-cause death. Tirzepatide did not elevate CV event risks for T2D patients versus controls.

For clinical effect and safety of tirzepatide, a systematic review and meta-analysis for T2D was conducted. The study consisted with 7 studies with 6609 participants [12]. The main results included the comparative data of tirzepatide 5, 10, 15mg and/or other agents at least 12 weeks. Other results of secondary efficacy revealed ratio of target HbA1c, which were <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol) and <5.7% (39 mmol/mol). The results showed the dose-dependent superiority for decreasing HbA1c for three doses of tirzepatide. They were from 1.62% to 2.06% compared with placebo, and 0.29% to 0.92% vs GLP-1Ras, and 0.70% to 1.09% vs basal insulin treatment. For weight reduction, tirzepatide showed more efficacious results compared to GLP-1RAs, where 1.68kg for tirzepatide 5mg, and 7.16 kg for tirzepatide 15mg.

A comparative study was performed for phase 3, 40-week open-label for tirzepatide [13]. The protocol showed 1879 T2D patients, and 4 groups were set for tirzepatide 5mg, 10mg, 15mg and semaglutide 1mg. Average HbA1c at baseline was 8.28%, age 56.6 years and weight 93.7 kg, in average. HbA1c reduction was, -2.01%, -2.24% and -2.30% for 5, 10, 15mg of tirzepatide, and -0.15%, -0.39% and -0.45% between tirzepatide and semaglutide, respectively. Weight reduction of tirzepatide was larger than semaglutide as 1.9kg, 3.6kg and 5.5kg, respectively ($p<0.001$). This comparison would be significant for clinical studies [14].

For actual clinical setting, the effects of GLP-1RA vs tilzepatide have been compared [15]. For GLP-1RA, 51-79% of T2D subjects achieved HbA1c <7.0% and 4-27% subjects showed weight reduction >10%. The achievement rate of <7.0% would be up to 80% vs up to 97%, and weight reduction >10% would be up to 50% and 69% for GLP-1RA vs tirzepatide, respectively.

In summary, treating T2D using incretin analogues has become increasing plausible [16]. From now, tirzepatide may be the most promising analogue. This article is hopefully presenting useful information for clinical practice.

Conflict of Interest

The authors declare no conflict of interest.

Funding

There was no funding received for this paper.

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