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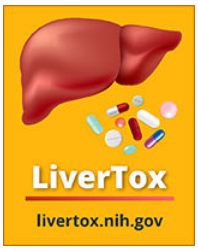

Tirzepatide

Updated: June 20, 2022.

OVERVIEW

Introduction

Tirzepatide is an agonist of the receptors of two insulin sensitizing polypeptides, GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide 1), that is used for type 2 diabetes. Tirzepatide has not been linked to elevations in serum aminotransferase levels during therapy or to episodes of clinically apparent liver injury.

Background

Tirzepatide (tir zep' a tide) is a 39 amino acid modified peptide similar in structure to the glucose-dependent insulinotropic polypeptide (GIP) that acts as an agonist to both the GIP receptor and the glucagon-like peptide 1 (GLP-1) receptor. Tirzepatide therapy increases insulin secretion, decreases glucagon secretion and delays gastric emptying. The result is a decrease in both fasting and postprandial glucose concentrations and an increase in insulin sensitivity. Tirzepatide also results in a decrease in food intake and reduced body weight. In multiple, preregistration clinical trials, tirzepatide therapy improved glycemic control and lowered HgA1c levels in patients with type 2 diabetes. It also resulted in weight loss of 7 to 11 kilograms after 40 to 52 weeks of treatment and to 16 to 24 kilograms after 72 weeks. Tirzepatide was approved for use as an adjunct to diet and exercise in type 2 diabetes in 2022. It is under active evaluation as a weight loss agent for individuals with overweight or obesity but without diabetes and as a potential therapy for nonalcoholic steatohepatitis. Tirzepatide is available as a solution in single use vials of 2.5, 5, 7.5, 10, 12.5 and 15 mg (in 0.5 mL) under the brand name Mounjaro. The recommended starting dosage for type 2 diabetes is 2.5 mg subcutaneously once weekly, with gradual dose escalation in increments of 2.5 mg every 4 weeks to a maximum of 15 mg weekly. Common adverse events include injection site reactions and nonspecific gastrointestinal complaints of nausea, vomiting, diarrhea, constipation, decreased appetite, dyspepsia, and abdominal discomfort. Less common but potentially severe adverse events include hypersensitivity reactions, pancreatitis, gallstones and cholecystitis, hypoglycemia (when used with insulin or insulin secretagogues) and worsening of preexisting severe renal and gastrointestinal diseases.

Hepatotoxicity

In preregistration clinical trials, serum aminotransferase elevations of greater than 3 times the upper limit of normal (ULN) arose in less than 1% of patients during therapy with tirzepatide and similar rates occurred in placebo recipients and in comparator arm groups. In studies of more than 5,000 patients, there were no reports of severe liver test abnormalities or clinically apparent liver injury attributable to tirzepatide. However, tirzepatide has been associated with a slightly higher rate of acute gallbladder disease (cholelithiasis, biliary

cholic and cholecystectomy) reported in 0.6% of treated patients vs none of placebo-treated patients. Gallbladder conditions are mentioned in the warning section of the product label for tirzepatide.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which tirzepatide might cause liver injury is unknown. It is a modified polypeptide and is metabolized to individual amino acids in multiple tissues and cell types including the liver. Because it causes weight loss, it can be accompanied by improvements in serum aminotransferase levels in patients with preexisting nonalcoholic fatty liver. The increased risk of acute gallbladder disease such as cholecystitis is probably related to the rapid weight loss that occurs with treatment.

Outcome and Management

Tirzepatide has not been shown to cause liver injury.

Drug Class: Antidiabetic Agents

Other Related Drugs: Incretin-Based Drugs, Glucagon-Like Peptide-1 (GLP-1) Analogues, Liraglutide, Semaglutide

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tirzepatide – Mounjaro®

DRUG CLASS

Antidiabetic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tirzepatide	2023788-19-2	Protein	Polypeptide

ANNOTATED BIBLIOGRAPHY

References updated: 20 June 2022

Abbreviations used: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c.

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Textbook of hepatotoxicity published in 1999; before the availability of tirzepatide).

De Marzio DH, Navarro VJ. Antidiabetic drugs. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 528-30.

(Review of hepatotoxicity of antidiabetic drugs; mentions that there have been no published reports of hepatotoxicity of the GLP-1 analogues, tirzepatide is not discussed).

Powers AC, D'Alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 863-86.

(Textbook of pharmacology and therapeutics; discusses glucagon-like peptide-1 and the incretin pathway and agents that act on this pathway, but does not discuss tirzepatide).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000MedR.pdf

(FDA website with multidisciplinary review of safety and efficacy of tirzepatide mentions that marked aminotransferase elevations were uncommon and there were no severe hepatic adverse events in preregistration controlled trials, but that gallbladder disease arose in some treated patients [0.6%] but not in controls [none]).

Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, Urva S, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet. 2018;392(10160):2180–2193. PubMed PMID: 30293770.

(Among 316 patients with type 2 diabetes treated with once weekly tirzepatide [1,5,10 and 1 5 mg], dulaglutide [1.5 mg] or placebo for 26 weeks, decreases in HbA1c levels and body weight occurred in a dose-dependent pattern with tirzepatide, and adverse events included gastrointestinal complaints and injection site reactions while cholecystitis occurred in 1 and pancreatitis in 2 of the 211 tirzepatide treated patients).

Hartman ML, Sanyal AJ, Loomba R, Wilson JM, Nikooienejad A, Bray R, Karanikas CA, et al. Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of nonalcoholic steatohepatitis in patients with type 2 diabetes. Diabetes Care. 2020;43:1352–1355. PubMed PMID: 32291277.

(Reanalysis of a controlled trial in 316 patients with type 2 diabetes [Frias 2018], found a decrease in mean ALT levels and increase in adiponectin levels in patients treated with higher doses of tirzepatide [5, 10 and 15 mg], but not with the lowest dose [1 mg] or with dulaglutide or placebo for 26 weeks).

Yanovski SZ, Yanovski JA. Progress in pharmacotherapy for obesity. JAMA. 2021;326:129–130. PubMed PMID: 34160571.

(Brief review of the currently approved drugs for weight loss including the promising two new GLP-1 agonists, liraglutide and semaglutide, and tirzepatide which is in phase III trials in patients with obesity without diabetes).

Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, et al. SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385:503–515. PubMed PMID: 34170647.

(Among 1879 patients with diabetes treated with tirzepatide [5, 10 or 15 mg] or semaglutide [1 mg] once weekly for 40 weeks, tirzepatide resulted in greater improvement in HbA1c levels and greater decrease in body weight [-7.6 to -11.2 kg vs -5.7 kg], while adverse event rates were similar, except for cholecystitis which arose in 12 of 1409 patients on tirzepatide vs no patients on semaglutide [0.9% vs 0%]; no mention of ALT elevations, mean levels decreased by 22% to 30%).

Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, Mao H, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398(10295):143–155. PubMed PMID: 34186022.

(Among 478 diabetic patients with in adequate control treated with tirzepatide [5, 10, or 15 mg] or placebo once weekly for 40 weeks, HbA1c and fasting serum glucose levels improved and weight decreased by 7 to 9.5 kg while adverse events include nausea, diarrhea, constipation, dyspepsia, decreased appetite, and injection site reactions

[2%-3%], while no patient developed pancreatitis and only 1 cholecystitis; no mention of ALT elevation or hepatoxicity).

Ludvik B, Giorgino F, Jódar E, Frias JP, Fernández Landó L, Brown K, et al. 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): a randomised, open-label, parallel-group, phase 3 trial. Lancet. 2021;398(10300):583–598. PubMed PMID: 34370970.

(Among 1444 patients with type 2 diabetes on metformin treated with once weekly tirzepatide [5, 10 or 15 mg] or daily insulin, tirzepatide was associated with greater decreases in HbA1c levels and body weight [-7.5 to -12.9 kg vs +2.3 kg] while gallbladder events were recorded in 4 [0.4%] on tirzepatide, but none on insulin; no mention of ALT elevations or hepatotoxicity).

Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, Aizenberg D, et al. SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet. 2021;398(10313):1811–1824. PubMed PMID: 34672967.

(Among 2002 patients with poorly controlled type 2 diabetes treated with weekly injections of tirzepatide [5, 10 or 15 mg] or daily insulin glargine [titrated doses], HbA1c and fasting glucose levels improved more with tirzepatide as did weight loss [-7.1 to -13.5 kg vs +2 kg] while adverse event rates were similar except for diarrhea, nausea, vomiting, dyspepsia, constipation and decreased appetite, which were more common with tirzepatide but decreased over time; pancreatitis and cholecystitis occurred in less than 1% in all groups; no mention of ALT levels or hepatotoxicity).

Dahl D, Onishi Y, Norwood P, Huh R, Bray R, Patel H, Rodríguez Á. 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. JAMA. 2022;327(6):534–545. PubMed PMID: 35133415.

(Among 475 patients with type 2 diabetes and inadequate glycemic control despite insulin therapy treated with tirzepatide [5, 10 or 15 mg] or placebo weekly for 40 weeks, HbA1c and fasting glucose levels decreased more with tirzepatide as did body weight while adverse events more frequent with tirzepatide included nausea, vomiting, diarrhea, constipation, dyspepsia, decreased appetite; no patient developed pancreatitis and only one cholelithiasis; no mention of ALT elevations or hepatotoxicity).

Sun B, Willard FS, Feng D, Alsina-Fernandez J, Chen Q, Vieth M, Ho JD, et al. Structural determinants of dual incretin receptor agonism by tirzepatide. Proc Natl Acad Sci U S A. 2022;119:e2116506119. PubMed PMID: 35333651.

(Cryogenic electron microscopy determination of structure and binding of tirzepatide to the GIP- and GLP-1 receptors).

Drugs and devices for weight management. Med Lett Drugs Ther. 2022;64:81–88. PubMed PMID: 35650672.

(Concise review of weight loss agents in current use in the US mentions that tirzepatide [an investigational agent] in doses of 5, 10 and 15 mg once weekly for 72 weeks resulted in weight loss of -16 to -24 kg [compared to +2 kg in placebo controls] in overweight and obese adults without diabetes).

Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022 Jun 4. Epub ahead of print. PubMed PMID: 35658024.

(Among 2539 obese or overweight non-diabetic adults treated with tirzepatide [5, 10 or 15 mg] or placebo once weekly for 72 weeks, weight loss was greater with tirzepatide [-16 to -24 kg] than placebo [-3 kg] and adverse events attributed to tirzepatide included nausea, vomiting, diarrhea, constipation and injection site reactions;

pancreatitis occurred in 0.2% vs 0.2%, gallbladder disease in 1.2% vs 0.8%, and mean ALT levels decreased by 26% to 30% vs 13%; no mention of ALT elevations).