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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Semaglutide. [Updated 2019 Apr 10].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Semaglutide

Updated: April 10, 2019.

OVERVIEW

Introduction

Semaglutide is a recombinant DNA produced polypeptide analogue of human glucagon-like peptide-1 (GLP-1) which is used in combination with diet and exercise in the therapy of type 2 diabetes, either alone or in combination with other antidiabetic agents. There have been no published reports of hepatotoxicity attributed to semaglutide therapy.

Background

Semaglutide (sem" a gloo' tide) is a glucagon-like peptide-1 (GLP-1) analogue (also called a GLP-1 receptor agonist) that acts like the native gastrointestinal hormone (incretin) to increase insulin secretion. Semaglutide reproduces the activity of GLP-1, binding to specific receptors on pancreatic beta cells and increasing insulin secretion, which can lead to improvement of glycemic control in patients with type 2 diabetes. Semaglutide is a recombinant DNA-produced polypeptide that is 94% homologous to endogenous human GLP-1(7-37) and differs only by minor amino acid substitutions and other structural modifications, which prolong its half-life and make it resistant to degradation by dipeptidyl peptidase 4 (DPP4). Semaglutide, like other GLP-1 analogues, is given parenterally, but its long half-life allows weekly dosing. Semaglutide was approved for use in the United States in 2017, the sixth GLP-1 receptor agonist to be approved. Current indications are for management of glycemic control in adults with type 2 diabetes in combination with diet and exercise, with or without other oral hypoglycemic agents. Semaglutide is available under the brand name Ozempic in prefilled multidose pens that contain 2 mg in 1.5 mL, one formulation that delivers 0.25 or 0.5 mg per injection and one that delivers 1.0 mg. The usual starting dose is 0.25 mg by subcutaneous injection once weekly, which can be increased to 0.5 mg and to 1 mg once weekly. Recent studies indicate that semaglutide is absorbed orally to some degree and high doses (10 to 40 mg) are as effective as parenteral doses (0.25 to 1.0 mg) in improving glycemic control and inducing weight loss. Semaglutide is moderately well tolerated, but side effects can be dose limiting and include injection site reactions, diarrhea, nausea, vomiting, abdominal pain, dizziness, headache, fatigue and hypoglycemia. Rare potential adverse events include pancreatitis, thyroid C-cell tumors and hypersensitivity reactions.

Hepatotoxicity

In large clinical trials, serum enzyme elevations were no more common with semaglutide therapy than with placebo or comparator agents, and no instances of clinically apparent liver injury were reported. Indeed, treatment with semaglutide and other GLP-1 analogues is often associated with improvements in serum aminotransferase levels (and hepatic steatosis) making them possible treatments for nonalcoholic fatty liver. Since licensure, there have been no published case reports of hepatotoxicity due to semaglutide and the product

label does not list liver injury as an adverse event. Thus, liver injury due to semaglutide must be rare, if it occurs at all.

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

Mechanism of Injury

Semaglutide is a polypeptide and is metabolized to amino acids by serum and tissue proteases and is unlikely to have any direct hepatotoxic potential. Semaglutide acts through the incretin pathway to affect glucose metabolism and, thus, is often grouped with other incretin-based antidiabetic mediations such as the DPP-4 inhibitors such as sitagliptin and other GLP-1 analogues such as exenatide.

The annotated bibliography on the hepatotoxicity of other incretin-based drugs are given in the Overview section of the GLP-1 Analogues.

Drug Class: Antidiabetic Agents

Other Drugs in the Subclass, Incretin-Based Drugs, Glucagon-Like Peptide-1 (GLP-1) Analogues: Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Semaglutide – Ozempic®

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
Semaglutide	910463-68-2	Protein	Complex Polypeptide

ANNOTATED BIBLIOGRAPHY

References updated: 10 April 2019

Abbreviations used: sc, subcutaneously.

Zimmerman HJ. Oral hypoglycemic agents and other diabetes therapy. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 575-9.

(Textbook of hepatotoxicity published in 1999 and before the availability of exenatide or GLP-1 analogues).

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).

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).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that mean levels of ALT and AST usually decrease on semaglutide therapy probably as a result of weight loss and that ALT elevations during therapy are no more frequent than with placebo or comparator arms, rising to above 5 times ULN in 0.5% or less).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that mean levels of ALT and AST usually decrease on semaglutide therapy probably as a result of weight loss and that ALT elevations during therapy are no more frequent than with placebo or comparator arms, rising to above 5 times ULN in 0.5% or less).

Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375: 1834-44. PubMed PMID: 27633186.

(Among 3297 adults with type 2 diabetes on standard regimens treated with addition of semaglutide [0.5 or 1.0 mg] or placebo injections weekly for two years, nonfatal myocardial infarction and stroke were less in semaglutide treated subjects, while cardiovascular death rates were similar and gastrointestinal adverse events [51-52% vs 35-36%] and discontinuations [11.5-14.5% vs 5.7-7.6%] were more frequent; no mention of ALT elevations or hepatotoxicity).

Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. JAMA 2017; 318: 1460-70. PubMed PMID: 29049653.

(Among 632 patients with type 2 diabetes and inadequate glycemic control on metformin treated with oral semaglutide [2.5, 5, 10, 20 or 40 mg] or placebo vs once weekly sc semaglutide for 26 weeks, glycemic control and weight loss were more frequent with oral semaglutide than placebo and, at higher doses, similar to that of semaglutide given sc; no mention of ALT elevations or hepatotoxicity).

Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, Chow F. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes(SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol 2017; 5: 341-54. PubMed PMID: 28385659.

(Among 1231 patients with type 2 diabetes with inadequate glycemic control on oral agents with addition of semaglutide [0.5 mg or 1.0 mg weekly] improved HbA1c levels more than sitagliptin [100 mg daily], but was associated with higher rates of gastrointestinal adverse events and discontinuations [8%-10% vs 3%]; no mention of ALT elevations or hepatotoxicity).

Aroda VR, Bain SC, Cariou B, Piletič M, Rose L, Axelsen M, Rowe E, DeVries JH. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017; 5: 355-66. PubMed PMID: 28344112.

(Among 1089 patients with type 2 diabetes with inadequate control on metformin treated with semaglutide sc once weekly or insulin daily for 30 weeks, HbA1c levels improved more with semaglutide while hypoglycemic episodes were less, although gastrointestinal adverse events were greater; no mention of ALT elevations or hepatotoxicity).

Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, Hjerpsted JB. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017; 19: 1242-51. PubMed PMID: 28266779.

(Among 30 obese subjects treated with once weekly semaglutide or placebo given sc, weight loss was greater with semaglutide [-5 kg vs + 1 kg]; no mention of ALT elevations or hepatotoxicity).

Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, Bain SC. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 2017; 5: 251-60. PubMed PMID: 28110911.

(Among 381 patients with type 2 diabetes not controlled with diet and exercise, sc semaglutide led to better glycemic control and more weight loss than placebo, although gastrointestinal side effects were greater [38% vs 15%]; no mention of ALT elevations or hepatotoxicity).

Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care 2018; 41: 258-66. PubMed PMID: 29246950.

(Among 813 adults with type 2 diabetes with inadequate glycemic control on oral agents treated with addition of semaglutide [1.0 mg] or exenatide ER [2.0 mg] weekly, HbA1c levels and body weight decreased more with semaglutide while adverse event rates were similar, nausea being more frequent with semaglutide [22% vs 12%], but injection site reactions with exenatide [0% vs 12%]; no mention of ALT elevations or hepatotoxicity).

O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, Carson CG, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet 2018; 392(10148): 637-49. PubMed PMID: 30122305.

(Among 957 patients with obesity treated with semaglutide in 4 doses or liraglutide in 1 dose or placebo given daily for 52 weeks, weight loss was 2.4-6.2 kg with semaglutide, 8.5 kg for liraglutide and 2.5 kg for placebo, while gastrointestinal adverse events were more common with the GLP-1 analogues [62-82% vs 38%] and "hepatic events" were less [0-3% vs 7%] and none were considered serious).

Kluger AY, McCullough PA. Semaglutide and GLP-1 analogues as weight-loss agents. Lancet 2018; 392 (10148): 615-6. PubMed PMID: 30122306.

(Editorial in response to O'Neil [2018] on use of GLP-1 analogues and other antidiabetic medications as weight loss agents, the major reservation being gastrointestinal side effects and poor tolerance).

Lingvay I, Desouza CV, Lalic KS, Rose L, Hansen T, Zacho J, Pieber TR. A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without metformin. Diabetes Care 2018; 41: 1926-37. PubMed PMID: 30026333.

(Among 705 patients with type 2 diabetes not controlled with metformin treated with semaglutide or liraglutide or placebo given subcutaneously [sc] daily for 26 weeks, glycemic control was better with the GLP-1 analogues than placebo, while gastrointestinal adverse events were more common; no mention of ALT elevations or hepatotoxicity).

Tuchscherer RM, Thompson AM, Trujillo JM. Semaglutide: the newest once-weekly GLP-1 RA for type 2 diabetes. Ann Pharmacother 2018; 52: 1224-32. PubMed PMID: 29932006.

(Review of the mechanism of action, pharmacokinetics, clinical efficacy, safety and ongoing research on semaglutide as therapy of diabetes, obesity and nonalcoholic fatty liver; no mention of ALT elevations or hepatotoxicity).

Baekdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, safety, and tolerability of oral semaglutide in subjects with hepatic impairment. J Clin Pharmacol 2018; 58: 1314-23. PubMed PMID: 29693715.

(In a pharmacokinetic study of 10 days of oral semaglutide in 32 patients with mild-to-severe hepatic dysfunction and 24 healthy controls, peak and area under-the-curve plasma concentrations were similar in all groups as was plasma half-life, and adverse event rates were similar).

Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, Araki E, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab 2018; 103: 2291-301. PubMed PMID: 29688502.

(Among 397 patients with type 2 diabetes not controlled with insulin and metformin treated with semaglutide or placebo sc once weekly for 30 weeks, HbA1c levels improved with semaglutide [-1.4% and -1.8%] but not with placebo [-0.1%], while gastrointestinal adverse events were more with semaglutide; no mention of ALT elevations or hepatotoxicity).

Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol 2018; 6: 275-86. PubMed PMID: 29397376.

(Among 1201 patients with type 2 diabetes and inadequate glycemic control on metformin treated with semaglutide or dulaglutide sc once weekly for 40 weeks, semaglutide led to greater improvements in glycemic control while adverse even rates were similar; no mention of ALT elevations or hepatotoxicity).

Semaglutide (Ozempic)--another injectable GLP-1 receptor agonist for type 2 diabetes. Med Lett Drugs Ther 2018; 60 (1539): 19-21. PubMed PMID: 29364197.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of semaglutide shortly after its approval in the US; mentions common adverse events of nausea, vomiting, diarrhea, constipation and abdominal pain as well as skin hypersensitivity reactions, but does not mention ALT elevations or hepatotoxicity).