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Glucagon-Like Peptide-1 (GLP-1) Analogues

Updated: April 10, 2019.

OVERVIEW

Glucagon-like peptide-1 (GLP-1) is an incretin, a gastrointestinal polypeptide hormone that binds to specific receptors on pancreatic beta cells and increases insulin release. The incretins – GLP-1 and gastric inhibitory peptide (GIP) – are secreted from the upper gastrointestinal tract in response to feeding and act on the pancreas, increasing insulin release even before blood glucose levels are elevated. The incretins also delay gastric emptying and suppress glucagon secretion, features that may increase their beneficial effects in type 2 diabetes. Both hormones are polypeptides that are rapidly cleared from the serum by the peptide cleaving enzyme, dipeptidyl peptidase-4 (DPP-4). The incretin pathway provides several potential targets for therapy of type 2 diabetes, the main ones being DPP-4 (inhibition) and GLP-1 receptors (agonist activity). Several GLP-1 analogues (also called GLP-1 receptor agonists) have been developed and approved for use in the United States for type 2 diabetes: exenatide (also known as exendin-4, Byetta) in 2005, liraglutide (Victoza) in 2010, albiglutide (Tanzeum) and dulaglutide (Trulicity) in 2014, lixisenatide (Adlyxin) in 2016 and semaglutide (Ozempic) in 2018. All are given parenterally and are approved for use in type 2 diabetes only. The GLP-1 analogues are recombinant polypeptides, have little or no hepatic metabolism and have not been convincingly implicated in causing clinically apparent liver injury.

Selected references to the safety and potential hepatic injury associated with these agents are given after this introductory section.

Drug Class: Antidiabetic Agents

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

ANNOTATED BIBLIOGRAPHY

References updated: 10 April 2019

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).

Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2005; 143: 559-69. PubMed PMID: 16230722.

(Controlled trial of 26 weeks of exenatide vs insulin in 551 patients with poorly controlled diabetes; overall efficacy was similar, but nausea, vomiting and diarrhea were more common with exenatide; no mention of ALT elevations or hepatotoxicity).

Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007; 298: 194-206. PubMed PMID: 17622601.

(Systematic review of 29 controlled trials of incretin-based therapies of diabetes [exenatide, liraglutide, sitagliptin and vildagliptin], concluding that they have "modest efficacy", but were well tolerated with few side effects that occur more frequently than in controls; no mention of ALT levels or hepatotoxicity).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver injury in the US collected from 2004 to 2008, none were attributed to incretin based agents).

Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368 (9548): 1696-705. PubMed PMID: 17098089.

(Review of the basis for use of GLP-1 agonists and DPP-4 inibitors in treating diabetes; no discussion of ALT elevations or hepatotoxicity).

Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, Porter L; DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008; 372 (9645): 1240-50. PubMed PMID: 18782641.

(Controlled trial of standard exenatide given twice daily vs long acting exenatide given once weekly for 30 weeks in 295 patients with type 2 diabetes; long acting preparation gave bettern control of HgA1c levels and have equivalent safety; "No clinically significant abnormalities in...chemistry...values were reported during the study").

Scheen AJ. Exenatide once weekly in type 2 diabetes. Lancet 2008; 372: 1197-8. PubMed PMID: 18782642.

(Editorial regarding study by Drucker [2008] of long acting exenatide, which is given once weekly and may have better efficacy and safety compared to standard formulation that is given twice daily).

Norris SL, Lee N, Thakurta S, Chan BK. Exenatide efficacy and safety: a systematic review. Diabet Med 2009; 26: 837-46. PubMed PMID: 19719703.

(Systematic review of 17 studies of exenatide; "there was no evidence of" hepatic effects across studies; postmarketing experience identified more than 30 cases of acute pancreatitis).

Norris SL, Lee N, Thakurta S, Chan BK. Exenatide efficacy and safety: a systematic review. Diabet Med 2009; 26: 837-46. PubMed PMID: 19719703.

(Systematic review of 17 studies of exenatide; "there was no evidence of" hepatic effects across studies; postmarketing experience identified more than 30 cases of acute pancreatitis).

Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1-5 studies. Diabetes Obes Metab 2009; 11 Suppl 3: 26-34. PubMed PMID: 19878259.

(Summary of 6 controlled trials of liraglutide, alone or with other antidiabetic agents in more than 4000 patients; most common side effects were gastrointestinal, particularly nausea; serious adverse events were no more common than with comparator arms; no mention of ALT elevations or hepatotoxicity).

Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. Nat Rev Endocrinol 2009; 5: 262-9. PubMed PMID: 19444259.

(Review of mechanism of action, pharmacology, clinical efficacy and safety of incretin-based therapies of diabetes; both exenatide and liraglutide are associated with weight loss and side effects of nausea and diarrhea; no mention of hepatotoxicity or ALT elevations).

Rosenstock J, Reusch J, Bush M, Yang F, Stewart M; Albiglutide Study Group. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. Diabetes Care 2009; 32: 1880-6. PubMed PMID: 19592625.

(Among 356 patients with diabetes treated with albiglutide given weekly, biweekly or monthly or with placebo or twice daily exenatide for 16 weeks, side effects were dose related and included nausea, diarrhea, headache and injection site reactions; no mention of ALT elevations or hepatotoxicity).

Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, et al.; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; 374: 39-47. PubMed PMID: 19515413.

(Controlled trial of 16 weeks of liraglutide vs exenatide in 464 patients with type 2 diabetes; no mention of ALT levels or hepatotoxicity).

Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology 2010; 86: 44-57. PubMed PMID: 20616619.

(Review of safety and efficacy of exenatide in 8 and liraglutide in 7 controlled trials; no mention of ALT levels or hepatotoxicity).

Russell-Jones D. The safety and tolerability of GLP-1 receptor agonists in the treatment of type-2 diabetes. Int J Clin Pract 2010; 64: 1402-14. PubMed PMID: 20716148.

(Discussion of the safety of exenatide and liraglutide in diabetes; no mention or discussion of ALT elevations or hepatotoxicity).

Kenny PR, Brady DE, Torres DM, Ragozzino L, Chalasani N, Harrison SA. Exenatide in the treatment of diabetic patients with non-alcoholic steatohepatitis: a case series. Am J Gastroenterol 2010; 105: 2707-9. PubMed PMID: 21131943.

(8 patients with diabetes and nonalcoholic steatohepatitis were treated with exenatide for 28 weeks; average weight decreased by 5%, ALT levels decreased from 69 to 45 U/L, and liver histology improved in 3 patients, but overall showed no change; no patient developed hepatotoxicity).

Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, et al.; 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010; 375: 1447-56. PubMed PMID: 20417856.

(Open label study of 26 weeks of liraglutide vs sitagliptin in 665 patients with diabetes; nausea and diarrhea were more common with liraglutide as was weight loss; no mention of ALT elevations or hepatotoxicity).

Ayoub WA, Kumar AA, Naguib HS, Taylor HC. Exenatide-induced acute pancreatitis. Endocr Pract 2010; 16: 80-3. PubMed PMID: 19703814.

(64 year old woman developed abdominal pain soon after starting exenatide leading to its discontinuation after 3 weeks, followed by hospitalization with pancreatitis at 4 weeks [amylase 131 U/L, lipase 2700 U/L, normal liver tests, CT showing a swollen pancreas, but no gallstones], resolving within 2 weeks).

Thong KY, Jose B, Sukumar N, Cull ML, Mills AP, Sathyapalan T, Shafiq W, et al.; on behalf of the ABCD nationwide exenatide audit contributors. Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit(*). Diabetes Obes Metab 2011; 13: 703-10. PubMed PMID: 21410858.

(Survey of exenatide use in the UK comparing patients with and without concurrent insulin treatment; insulin treated patients had more side effects, hypoglycemia and discontinuations; no mention of ALT elevations or clinically apparent liver injury).

Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B; LEAD-3 (Mono) Study Group. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab 2011; 13: 348-56. PubMed PMID: 21205128.

(One year open label extension of controlled trial of liraglutide vs glimepiride in 927 patients with diabetes; diarrhea and nausea were more common with liraglutide; no mention of ALT elevations or liver injury).

Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012; 8: 728-42. PubMed PMID: 22945360.

(Review of the structure, mechanism of action, efficacy and safety of the GLP-1 analogues with focus on development of long acting formulations including exenatide-LAR, liraglutide, albiglutide and dulaglutide; no mention of ALT elevations or hepatotoxicity).

Fonseca VA, Alvarado-Ruiz R, Raccah D, Boka G, Miossec P, Gerich JE; EFC6018 GetGoal-Mono Study Investigators. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). Diabetes Care 2012; 35: 1225-31. PubMed PMID: 22432104.

(Among 361 patients with previously untreated diabetes, HbA1c responses were more frequent with a 12 week course of lixisenatide vs placebo and adverse events more frequent with lixisenatide were nausea and vomiting; no mention of ALT elevations or hepatotoxicity).

Ahrén B, Leguizamo Dimas A, Miossec P, Saubadu S, Aronson R. Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M). Diabetes Care 2013; 36: 2543-50. PubMed PMID: 23536584.

(Among 680 patients with inadequately controlled diabetes treated with lixisenatide or placebo injections once daily, morning or evening, for 24 weeks, glycemic control was improved with lixisenatide and more frequent adverse events included hypoglycemia [2.4% and 5.1% vs 0.6%], nausea [23% and 22% vs 8%] and vomiting [9% and 13% vs e%]; no mention of ALT elevations or hepatotoxicity).

Elkinson S, Keating GM. Lixisenatide: first global approval. Drugs 2013; 73: 383-91. PubMed PMID: 23558600.

(Review of the history of development, pharmacology, clinical efficacy, and adverse events of lixisenatide focusing upon hypoglycemia and lixisenatide antibodies; no mention of ALT elevations or hepatotoxicity).

Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes Obes Metab 2013; 15: 1000-7. PubMed PMID: 23627775.

(Among 484 patients with diabetes inadequately controlled by pioglitazone who were treated with lixisenatide or placebo injections for 24 weeks, glycemic control was improved by addition of lixisenatide and adverse events including nausea, vomiting, allergic reactions; no mention of ALT elevations or hepatotoxicity).

Rosenstock J, Raccah D, Korányi L, Maffei L, Boka G, Miossec P, Gerich JE. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care 2013; 36: 2945-51. PubMed PMID: 23698396.

(Among 336 patients with diabetes inadequately controlled on metformin who were treated with lixisenatide or exenatide for 24 weeks, HbA1c improved similarly in both groups and overall and serious adverse event rates were similar, and "no clinically relevant changes" in ALT or AST occurred in either group).

Armstrong MJ, Houlihan DD, Rowe IA, Clausen WH, Elbrønd B, Gough SC, Tomlinson JW, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther 2013; 37: 234-42. PubMed PMID: 23163663.

(Among 442 patients with diabetes treated in 6 trials of 24-weeks of liraglutide vs placebo, 2241 [51%] had abnormal ALT levels at baseline, among whom ALT levels decreased more with liraglutide [-8 U/L] than placebo [-5 U/L], but the effect was not seen after adjusting for differences in weight loss).

Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, et al.; HARMONY 7 study group. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014; 2: 289-97. PubMed PMID: 24703047.

(Among 841 adults with inadequately controlled diabetes treated with injections of albiglutide [weekly] or liraglutide [daily] for 32 weeks, HbA1c levels decreased in both groups and adverse event rates were similar; no mention of ALT elevations or hepatotoxicity).

Bolli GB, Munteanu M, Dotsenko S, Niemoeller E, Boka G, Wu Y, Hanefeld M. Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabet Med 2014; 31: 176-84. PubMed PMID: 24117597.

(Among 484 patients with diabetes inadequately controlled on metformin who were treated with lixisenatide or placebo once daily for at least 52 weeks, glycemic control was greater with lixisenatide therapy and side effects associated with it included nausea and vomiting, hypoglycemia and allergic reactions, while "analysis of safety laboratory… data did not reveal and specific safety signals").

Gluud LL, Knop FK, Vilsbøll T. Effects of lixisenatide on elevated liver transaminases: systematic review with individual patient data meta-analysis of randomised controlled trials on patients with type 2 diabetes. BMJ Open 2014; 4: e005325. PubMed PMID: 25526792.

(Among 15 controlled trials of lixisenatide for which individual results were available, 1070 patients had elevated ALT levels at baseline lixisenatide had a beneficial effect in normalizing ALT levels in overweight and obese subjects, but not in those with normal weight, and no effect was found on AST, alkaline phosphatase or bilirubin levels).

Two new GLP-1 receptor agonists for diabetes. Med Lett Drugs Ther 2014; 56 (1455): 109-11. PubMed PMID: 25372847.

(Concise review of the mechanism of action, efficacy, side effects and costs of albiglutide and dulaglutide shortly after their approval in the US mentions that gastrointestinal effects are the most common side effects of GLP-1 analogues and that they have been rarely associated with pancreatitis; no mention of ALT elevations or hepatotoxicity).

Dungan KM, Povedano ST, Forst T, González JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet 2014; 384 (9951): 1349-57. PubMed PMID: 25018121.

(Among 599 patients with diabetes poorly controlled on metformin who were treated with either dulaglutide or liraglutide for 24 weeks, efficacy and side effects were similar, common adverse events being nausea [20%], diarrhea [12%], dyspepsia [8%] ane weight loss [~3 kg]; no case of pancreatitis and no mention of ALT elevations or hepatotoxicity).

Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, Kuhstoss D, Lakshmanan M. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 2014; 37: 2159-67. PubMed PMID: 24879836.

(Among 976 patients with diabetes poorly controlled on metformin and pioglitazone who were treated with 1 of 2 doses of dulaglutide, exenatide or placebo for 52 weeks, common side effects of dulaglutide were nausea, vomiting, diarrhea, dyspepsia, decreased appetite and hypoglycemia; 1 patient developed pancreatitis, but no mention of ALT elevations or hepatotoxicity).

Umpierrez G, Tofé Povedano S, Pérez Manghi F, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care 2014; 37: 2168-76. PubMed PMID: 24842985.

(Among 807 patients with diabetes treated with dulaglutide or metformin for 52 weeks, common adverse events included nausea, vomiting, diarrhea, decreased appetite and hypoglycemia; no mention of ALT elevations or hepatotoxicity).

Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care 2014; 37: 2149-58. PubMed PMID: 24742660.

(Among 1098 patients with diabetes treated with 2 doses of dulaglutide, sitagliptin or placebo for 1 year, common adverse events were nausea, vomiting and diarrhea; no mention of ALT elevations or hepatotoxicity).

Ahrén B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C, Feinglos MN; HARMONY 3 Study Group. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care 2014; 37: 2141-8. PubMed PMID: 24898304.

(Among 999 patients with diabetes poorly controlled on metformin who were treated with the addition of albiglutide, glimepiride, sitagliptin or placebo for 2 years, common side effects included injection site reactions, diarrhea, nausea and 2 of 302 albiglutide treated patients developed pancreatitis; no mention of ALT elevations or hepatotoxicity).

Reusch J, Stewart MW, Perkins CM, Cirkel DT, Ye J, Perry CR, Reinhardt RR, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. Diabetes Obes Metab 2014; 16: 1257-64. PubMed PMID: 25155146.

(Among 310 patients with diabetes on pioglitazone with or without metformin who were treated albiglutide or placebo injected weekly for up to 3 years, overall rates of side effects were similar in both groups [diarrhea in 9% vs 11%] and no patient developed pancreatitis; no mention of ALT elevations or hepatotoxicity).

Kern E, VanWagner LB, Yang GY, Rinella ME. Liraglutide-induced autoimmune hepatitis. JAMA Intern Med 2014; 174: 984-7. PubMed PMID: 24733687.

(A woman of unstated age developed jaundice 4 months after starting liraglutide for type 2 diabetes [bilirubin 9.5 mg/dL, ALT 1123 U/L, Alk P not given, INR 1.3, ANA negative] and subsequently worsened despite stopping liraglutide, biopsy showing submassive necrosis and responding to corticosteroid therapy which was required long term).

Weissman PN, Carr MC, Ye J, Cirkel DT, Stewart M, Perry C, Pratley R. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia 2014; 57: 2475-84. PubMed PMID: 25208756.

(Among 779 patients with diabetes inadequately controlled on metformin who were treated with injections of albiglutide weekly or insulin daily for one year, gastrointestinal side effects were more common with albiglutide, but hypoglycemia and weight gain were less common while no patient developed pancreatitis; no mention of ALT elevations or hepatotoxicity).

Thompson AM, Trujillo JM. Dulaglutide: the newest GLP-1 receptor agonist for the management of type 2 diabetes. Ann Pharmacother 2015; 49: 351-359. PubMed PMID: 25565404.

(Review of the pharmacology, mechanism of action, efficacy and safety of dulaglutide, the most common side effects are gastointestinal symptoms; pancreatitis occurs, but is rare; no mention of ALT elevations or hepatotoxicity).

Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015; 373: 2247-57. 26630143. PubMed PMID: 26630143.

(Among 6068 patients with diabetes and a history of a recent acute coronary syndrome who were treated with lixisenatide vs placebo added to standard diabetes care, subsequent cardiovascular endpoints occurred in a similar proportion of both groups [13.4% vs 13.2%] and adverse event rates were similar for hyperglycemia, pancreatitis and hepatobiliary events, but lixisenatide treated subjects had higher rates of nausea and vomiting resulting in drug discontinuation [3% vs 0.4%]).

Wysham CH, MacConell LA, Maggs DG, Zhou M, Griffin PS, Trautmann ME. Five-year efficacy and safety data of exenatide once weekly: long-term results from the DURATION-1 randomized clinical trial. Mayo Clin Proc 2015; 90: 356-65. PubMed PMID: 25744115.

(Among 258 diabetic patients enrolled in a 5 year extension study of weekly exenatide therapy, beneficial effects on HbA1c and glucose levels were maintained and "liver function changes from baseline … were minimal", ALT levels decreasing by 4.4 U/L; no mention of episodes of clinically apparent liver injury).

Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivanek Z, Milicevic Z. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes Obes Metab 2015; 17: 849-58. PubMed PMID: 25912221.

(Among 1098 patients with diabetes treated with dulaglutide or sitagliptin for up to 2 years, decreases in HgA1c levels were greater with dulaglutide as were gastrointestinal adverse events such as nausea, vomiting and diarrhea, but no mention of ALT elevations or hepatotoxicity).

Dungan KM, Weitgasser R, Perez Manghi F, Pintilei E, Fahrbach JL, Jiang HH, Shell J, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes Obes Metab 2016; 18: 475-82. PubMed PMID: 26799540.

(Among 300 patients with diabetes being treated with glimepiride to which was added once weekly injections of dulaglutide vs placebo for 24 weeks, decreases in HgA1c levels were greater with dulaglutide and adverse events included nausea [10% vs 0] and diarrhea [8% vs 0]; no mention of ALT elevations or hepatotoxicity).

Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016; 387 (10019): 679-90. PubMed PMID: 26608256.

(Among 52 patients with nonalcoholic steatohepatitis [NASH] treated with daily injections of liraglutide [1.8 mg] or placebo for 48 weeks, ALT levels and histological features of injury improved more with liraglutide as did weight loss [5.3 vs 0.6 kg], and there were no cases of pancreatitis or worsening of liver disease).

Seko Y, Sumida Y, Tanaka S, Mori K, Taketani H, Ishiba H, Hara T, et al. Effect of 12-week dulaglutide therapy in Japanese patients with biopsy-proven non-alcoholic fatty liver disease and type 2 diabetes mellitus. Hepatol Res 2016 Nov 2. [Epub ahead of print]. PubMed PMID: 27917557.

(Among 15 Japanese patients with NASH treated with dulaglutide [0.75 mg weekly] for 12 weeks, ALT levels decreased, histological features of injury improved, and there were no serious adverse events).

Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. Diabetes Care 2016; 39: 1501-9. PubMed PMID: 27311491.

(Among 404 patients with diabetes inadequately controlled on metformin enrolled in a controlled trial for 26 weeks, glycemic control was better, but adverse event rates were higher with once-daily liraglutide than lixisenatide; no mention of ALT elevations or hepatotoxicity).

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, et al.; LEADER Steering Committee.; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375: 311-22. PubMed PMID: 27295427.

(Among 9340 patients with diabetes at high risk of cardiovascular complications treated with liraglutide [1.8 mg] or placebo injections daily for a median of 3.8 years, cardiovascular deaths were lower with liraglutide than placebo [4.7% vs 6%], but rates of nonfatal endpoints were no different and adverse events associated with liraglutide included weight loss, acute gallstone disease [3.1% vs 1.9%], injection site reactions, nausea [1.6% vs 0.4%], vomiting, diarrhea, and abdominal pain; no mention of ALT elevations or hepatotoxicity).

Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obes Sci Pract 2017; 3: 3-14. PubMed PMID: 28392927.

(Review of 5 placebo controlled trials of liraglutide for weight loss mentions a 4 to 6 kg greater loss with liraglutide vs placebo with common adverse events of nausea, diarrhea, vomiting, headache, fatigue, dizziness, abdominal pain and increased lipase; no discussion of ALT elevations or hepatotoxicity, but mentions that liraglutide should be used cautiously in patients with impaired liver function).

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).

Lixisenatide for type 2 diabetes. Med Lett Drugs Ther 2017; 59 (1513): 19-21. PubMed PMID: 28118649.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of lixisenatide shortly after its approval in the US; mentions the uncommon side effects of anaphylaxis [0.1%], renal insufficiency and pancreatitis, but no mention of ALT elevations or hepatotoxicity).