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Glucagon-Like Peptide 1 Drugs as Second-Line Therapy for Type 2 Diabetes

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Two relatively new classes of therapeutics, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists (Table 1 and Table 2), have been widely adopted in practice for diabetes management based on

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clinical trial evidence demonstrating effective glycosylated hemoglobin control, benefits for weight management, and low risk of hypoglycemia. It has been suggested that these agents may also reduce risk for cardiovascular outcomes among patients with diabetes. This benefit has recently been reported in a placebo control randomized clinical trial (RCT) for the GLP-1 agonist Liraglutide (Victoza) (A). GLP-1 agonists amplify glucose-mediated insulin secretion, whereas DPP-4 inhibitors enhance and prolong the action of endogenously secreted GLP-1.

While the first drug of choice in type 2 diabetes is metformin, many patients require additional therapy to adequately manage blood glucose levels, and the choice of second-line therapies is best tailored to individual patients. For example, relatively lean individuals with diabetes not controlled by metformin are good candidates for a sulfonylurea or, if necessary, insulin. In contrast, there is clearly a need an alternative to simply escalating the dose of insulin in obese patients with diabetes who are unable to sustainably alter their lifestyle to achieve weight reduction. Escalating insulin doses in such individuals is often ineffective, may exacerbate weight gain, and has been postulated to contribute to the increased risks of car-

diovascular disease and cancer in obese patients with type 2 diabetes.¹ Gastric bypass surgery is increasingly advocated for these patients, but is available only to a minority and may be associated with significant complications.²

Recently, Vanderheiden and colleagues³ reported a small 6-month trial among patients with morbid obesity (body mass index [calculated as weight in kilograms divided by height in meters squared], 41) and poorly controlled type 2 diabetes prescribed high-dose insulin who were randomized to the addition of the GLP-1 mimetic liraglutide or placebo. The addition of liraglutide improved glycemic control without weight gain and reduced insulin dosage, breaking the cycle of escalating insulin doses and progressive weight gain. Approximately a third of patients receiving liraglutide had gastrointestinal tract adverse effects, such as nausea, in the first weeks of therapy, but in most these resolved. There was also an increase in pancreatic lipase levels, reproducing findings observed in larger RCTs, and raising the issue of potential adverse effects of GLP-1 drugs on the exocrine pancreas, addressed by Azoulay and colleagues⁴ in this issue of *JAMA Internal Medicine*.

This impressively large study combined retrospective observational data from 7 consortiums and found no increased risk of pancreatitis in users of GLP-1-based drugs (DPP-4 inhibitors or GLP-1 mimetics) compared with users of 2 or more other oral antidiabetic drugs. The same group also recently found no increased risk of pancreatic cancer with GLP-1-based therapy in the same study population.⁵ The possibility of GLP-1-induced pancreatitis first came up as a signal in the

Table 1. GLP-1 Receptor Agonists

Characteristic	Albiglutide	Dulaglutide	Exenatide	Exenatide ER	Liraglutide
Trade name	Tanzeum	Trulicity	Byetta	Bydureon	Victoza, Saxenda
Initial adult dose	30 mg subcutaneously once weekly	0.75 mg subcutaneously once weekly	5 µg subcutaneously twice daily	2 mg subcutaneously once weekly	0.6 mg subcutaneously once daily
Maintenance adult dose	30 to 50 mg subcutaneously once weekly	0.75 to 1.5 mg subcutaneously once weekly	10 µg subcutaneously twice daily	2 mg subcutaneously once weekly	1.2 to 1.8 mg (Victoza); 3 mg (Saxenda) subcutaneously once daily

Abbreviation: GLP, glucagon-like peptide.

Table 2. DPP-4 Inhibitors

Characteristic	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Trade name	Nesina	Tradjenta	Onglyza	Januvia
Usual dosage	25 mg once daily	5 mg once daily	2.5 or 5 mg once daily	100 mg once daily

Abbreviation: DPP-4, dipeptidyl peptidase-4.

FDA adverse event reporting system with the first marketed GLP-1 mimetic, Exenatide (Byetta). The US Food and Drug Administration (FDA) adverse event reporting system consistently shows a signal for acute pancreatitis with other DPP-4 inhibitors and GLP-1 mimetics.⁶ A cause of more concern is that the FDA system also shows a signal for pancreatic cancer with both classes of GLP-1 drugs.⁶ Not surprisingly, the publication of that association set off controversy.⁷ A legitimate argument in defense of the GLP-1 class of drugs was that clinical trials are the gold standard and that the FDA adverse event reporting system is prone to bias and confounding. Results of clinical trials with the GLP-1 class of drugs required by the FDA to document cardiovascular safety have shown mostly, but not all,⁸ shown a modest increase of pancreatitis.⁹ The absence of pancreatitis associated with GLP-1-based therapy in retrospective analyses, even in a large cohort,⁴ falls short of the gold standard, the RCT.

The same critique can be made of the retrospective cohort study by the same group, which found no association between pancreatic cancer and GLP-1-based therapy.⁵ Also, since the concern that GLP-1 therapies might cause neoplasia relates to growth promoting properties, the median duration of follow-up in this cohort of 1.3 to 2.8 years is insufficient to assure that there is no increased risk of pancreatic cancer. However, given the shortcomings of the FDA adverse event reporting system, and since it is not feasible to perform a RCT of sufficient size to address the potential for increased risks for relatively infrequent events such as pancreatic cancer, analyses of large patient cohorts after more prolonged drug exposure are required. The study power issue is highlighted by the 13 vs 5 events of pancreatic cancer reported for Liraglutide vs placebo (odds ratio, 2.6; $P = .06$) in the recently published RCT for cardiovascular safety with Liraglutide (Victoza).⁸ The study, while powered for the intended cardiovascular end points was not powered for pancreatic cancer but cannot be viewed as reassuring.

A second report in the current issue addresses another unanticipated adverse outcome of GLP-1 mimetic therapy, bile duct, and gall bladder disease. Faillie and colleagues¹⁰ examined a primary care database from the United Kingdom and report increased gall bladder and biliary disease with GLP-1 mimetics but not DPP-4 inhibitors, reproducing the findings in RCTs of the GLP-1 mimetic liraglutide.¹¹

Two potential explanations might account for the difference between GLP-1 mimetics and DPP-4 inhibitors. The weight

loss induced by the GLP-1 mimetics may promote gall stone formation. Alternatively, GLP-1 mimetics may act pharmacologically on the gall bladder and biliary tree by decreasing gall bladder emptying¹² and increasing cholangiocyte proliferation induced by GLP-1.¹³ Another possible discrepancy between DPP-4 inhibitors and GLP-1 mimetics is increased reports of thyroid cancer with GLP-1 mimetics but not DPP-4 inhibitors in the FDA adverse event reporting system.⁶ Since there is a source of GLP-1 (α -cells) in the pancreas, but not the thyroid or biliary tree, these discrepancies would be consistent with the pharmacological actions of GLP-1 mimetics at all sites but comparably high concentrations of GLP-1 only achieved by DPP-4 inhibitors at sites of secretion.

In conclusion, 3 complementary reports offer useful insights for internists considering second-line (after metformin) therapy for patients with type 2 diabetes. In the first,³ a small RCT suggests that GLP-1 mimetics can break the cycle of escalating insulin doses and progressive obesity in type 2 diabetes. A second report,⁴ based on a large retrospective cohort addressed the more controversial issue of adverse effects of GLP-1 based drugs on the pancreas, and in contrast to the higher level of evidence provided by RCTs, found no increased risk of pancreatitis associated with either GLP-1 mimetics or DPP-4 inhibitors. In a third report,¹⁰ increased gall stone and biliary tract disease was noted with GLP-1 mimetics but not DPP-4 inhibitors. As with all new drug classes, especially when the intended use is over a long term, vigilance as to the actual long-term benefits (not yet established with either of the GLP-1 class of drugs) vs potential adverse events is important. In patients with uncontrolled type 2 diabetes and obesity, the addition of GLP-1 mimetics to metformin and, if necessary, to insulin, is a logical choice given current evidence if there is no history of pancreatic or biliary disease or thyroid cancer. The possible increased risk of pancreatitis with the GLP-1 class of drugs, based on consistent findings in sufficiently powered RCTs, seems reassuringly low. However, the unresolved concern is whether the relatively low risk of pancreatitis and the more frequently observed increase in lipase levels herald a subclinical proinflammatory effect that in the longer term could increase the risk for pancreatic cancer. With the increasing adoption of electronic health records, postmarketing surveillance for unexpected adverse outcomes might reasonably be established for all new drug classes, and will hopefully be more robust than diagnoses now largely dependent on insurance claims.

ARTICLE INFORMATION

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REFERENCES

- Currie CJ, Johnson JA. The safety profile of exogenous insulin in people with type 2 diabetes: justification for concern. *Diabetes Obes Metab*. 2012;14(1):1-4.
- Garg T, Rosas U, Rivas H, Azagury D, Morton JM. National prevalence, causes, and risk factors for bariatric surgery readmissions. *Am J Surg*. 2016; 212(1):76-80.

3. Vanderheiden A, Harrison L, Warshauer J, Li X, Adams-Huet B, Lingvay I. Adding liraglutide to a high-dose insulin regimen: a randomized, double-blind, placebo-control study [published online June 6, 2016]. *JAMA Intern Med.* doi:10.1001/jamainternmed.2016.1540.
4. Azoulay L, Filion KB, Platt RW, et al. Association between incretin-based drugs and the risk of acute pancreatitis [published online August 1, 2016]. *JAMA Intern Med.* doi:10.1001/jamainternmed.2016.1522.
5. Azoulay L, Filion KB, Platt RW, et al; Canadian Network for Observational Drug Effect Studies Investigators. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. *BMJ.* 2016;352:i581.
6. Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? *Diabetes Care.* 2013;36(7):2118-2125.
7. Drucker DJ, Sherman SI, Bergenstal RM, Buse JB. The safety of incretin-based therapies: review of the scientific evidence. *J Clin Endocrinol Metab.* 2011;96(7):2027-2031.
8. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee on Behalf of the LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes [published online June 13, 2016]. *N Engl J Med.* doi:10.1056/NEJMoa1603827.
9. Abbas AS, Dehbi HM, Ray KK. Cardiovascular and non-cardiovascular safety of dipeptidyl peptidase-4 inhibition: a meta-analysis of randomized controlled cardiovascular outcome trials. *Diabetes Obes Metab.* 2016;18(3):295-299.
10. Faillie J-L, Yu OH, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of bile duct and gallbladder diseases with the use of incretin-based drugs in patients with type 2 diabetes mellitus [published online August 1, 2016]. *JAMA Intern Med.* doi:10.1001/jamainternmed.2016.1531.
11. US Food and Drug Administration. SAXENDA: Highlights of prescribing information. 2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf. Accessed June 3, 2016.
12. Keller J, Trautmann ME, Haber H, et al. Effect of exenatide on cholecystokinin-induced gallbladder emptying in fasting healthy subjects. *Regul Pept.* 2012;179(1-3):77-83.
13. Marzioni M, Agostinelli L, Candelaresi C, et al. Activation of the developmental pathway neurogenin-3/microRNA-7a regulates cholangiocyte proliferation in response to injury. *Hepatology.* 2014;60(4):1324-1335.