OBSERVATIONS

Pancreatitis Associated With Incretin-Based Therapies

In recent years, incretin-based therapies such as glucagon-like peptide-1 agonists (GLP-1) and dipeptidyl peptidase-IV inhibitors (DPP-IV) have become important therapeutic options for treatment of type 2 diabetes. Although these agents are considered safe, long-term safety outcome studies are lacking. Theoretically, the combination of these two classes of agents could increase efficacy, but there is no strong supporting clinical evidence. While both GLP-1 and DPP-IV agents are approved for use as monotherapy and with other diabetes drugs, the combined use of these drugs classes has not been approved by the U.S. Food and Drug Administration (FDA).

In a recent case report, Patel et al. (1) noted an improvement in glycemic control in a patient with type 2 diabetes on a combination of sitagliptin and exenatide in addition to glipizide. In a separate randomized noninferiority study, Violante et al. (2) reported that in patients with type 2 diabetes inadequately controlled with metformin and sitagliptin, the addition of twice-daily exenatide (ADD group) improved glycemic control in comparison with the group switched to exenatide and metformin (SWITCH group). The primary efficacy outcome in their study was a change in HbA_{1c} over a period of 20 weeks. The study demonstrated a 0.3% reduction in HbA_{1c} for the ADD group in comparison with the SWITCH group. Although these studies highlight the potential benefit of the combination on glycemic control, the adverse effects of the combination remain worrisome.

With the influx of reports on GLP-1 and DPP-IV drug-related pancreatitis, there is a need for close surveillance of these agents. Acute pancreatitis has been reported with both exenatide and sitagliptin (3,4). Our group recently reported a case of fatal necrotizing pancreatitis in a 76-year-old woman prescribed drugs from both of these classes (5). The patient had been taking exenatide for years without problems. However, 2 weeks after her primary care physician added sitagliptin, she developed necrotizing pancreatitis. Based on her history, laboratory studies, and autopsy report, all other causes of pancreatitis were ruled out.

Over the last several years postmarketing reporting of adverse events to the FDA has resulted in manufacturer strengthening of its labeling with regard to acute pancreatitis. In fact, incretin-based therapies are now contraindicated by the FDA for use in patients with a history of pancreatitis. These data should be taken into serious account prior to considering their use in patients with diabetes mellitus. Given the lack of randomized studies addressing the long-term adverse effects of these incretin-based therapies, we strongly discourage the use of GLP-1 agonists and DPP-IV inhibitors in combination. The rapidly evolving concerns of pancreatitis with incretin-based agents when used as monotherapy or in combination implicate the need for additional rigorous evaluation before widespread use. We strongly recommend that when prescribers desire using combination therapies with the aim of optimizing glycemic control, they follow guidelines as previously reported by the American Diabetes Association and the European Association for the Study of Diabetes. Strict adherence to prescribing guidelines and a vigilant eye on medication safety literature should guide management of individual patients receiving newly approved medications with potential life-threatening side effects.

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DOI: 10.2337/dc12-1987

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Acknowledgments—No potential conflicts of interest relevant to this article were reported.

S.N.I. wrote the manuscript. C.E.M. reviewed the manuscript. R.L.W. contributed to the discussion. A.J.D. edited the manuscript. R.J.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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