Oral Semaglutide: Balancing Promising Therapeutics with Adverse Effects and Access Barriers

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COMMENTARY

The days of 3 drug choices (metformin, sulfonylureas, and insulin) are in the past. Rapid medication advancements for patients with type 2 diabetes mellitus (T2DM) have caused therapeutic confusion for primary care providers, in addition to changing guidelines and the metrics they are held accountable for under value-based payment systems. Evidence reports that provide concise tools to be used as guides for prescribing are needed.

Glucagon-like peptide-1 receptor (GLP-1) agonists, sodium glucose co-transporter 2 (SGLT2) inhibitors and dipeptidyl peptidase 4 inhibitors have demonstrated ability to improve diabetes control among the 30+ million people in the United States with diabetes.^{1,2} In patients with diabetes, 27.7% had hemoglobin A1c (A1c) of 8% or above in 2016, with a higher rate of poor diabetes control in patients aged 19-44 years.¹ Complications are also rising, such as 19% with stage 3-4 chronic kidney disease and nearly 70% with systolic blood pressure greater than 140 mm Hg, diastolic pressure greater than 90 mm Hg, or on prescription blood pressure medications.¹ T2DM disproportionately affects American Indian, Alaska Natives, people of Hispanic origin and non-Hispanic Blacks, and there is a higher rate in adults with less than a high school education.¹

Increased numbers of patients and resulting complications come with a high burden of direct and indirect costs, estimated at \$327 billion in 2017, an increase of \$49 billion in direct costs alone from 2012-2017.¹ The cost of diabetes medication is the subject of state and federal legislative scrutiny, particularly the rising cost of insulin. Diabetes medication costs have severely affected Medicare patients because they are unable to use manufacturer-based copay reduction programs and may have high deductible plans.^{3,4}

As new drugs with promising outcome data are realized, the goal of improving diabetes outcomes seems in sight. Yet, an evaluation of the “cascade of diabetes care” from 2005-2016 found no significant improvement in target achievement for A1c, blood pressure, smoking cessation, or lower cholesterol. Women, younger patients, and non-Hispanic blacks had lower odds of reaching treatment goals, as did a lack of insurance coverage.⁵ The bottom line: Advances in therapeutics cannot

and will not make an impact if they are not clearly understood by providers, used by providers and patients, and accessible to those in need.

In December 2019, the Institute for Clinical and Economic Review (ICER) published its evidence report “Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value.”⁶ Oral semaglutide (Rybelsus) is a novel oral GLP-1 receptor agonist. Unlike subcutaneous semaglutide, which has been on the market since 2017, the U.S. Food and Drug Administration has not approved oral semaglutide to reduce the risk of major cardiovascular events in patients with T2DM and cardiovascular disease.⁷

The 8 PIONEER trials were evaluated as a part of the ICER review. Blood glucose outcomes data were evaluated with oral semaglutide alone compared with placebo, semaglutide, and metformin versus empagliflozin and metformin, semaglutide, and metformin±sulfonylurea versus sitagliptan and metformin ±sulfonylurea. In these studies (PIONEER-PIONEER 3), a greater number of semaglutide patients achieved A1c goal <7% with more weight loss than comparator oral agents, particularly for oral semaglutide 14 mg daily, with dose-dependent effects on blood glucose lowering and weight loss.⁸ Oral semaglutide 14 mg daily was also compared (PIONEER 4) with liraglutide 1.8 mg once daily with statistically significant benefit of oral semaglutide at 52 weeks in achievement of goal A1c and weight loss.⁸

The value of a novel antidiabetic agent also lies in its morbidity and mortality effect, including effects on cardiovascular adverse events (AEs) and heart failure hospitalizations, as well as slowing progression of renal disease. Several studies have addressed the cardiovascular outcomes of oral semaglutide, but none are in comparison with other GLP-1 and SGLT 2 medications with known benefit in these areas. The rate of major adverse cardiovascular events (MACE) with oral semaglutide was not statistically different than placebo, while liraglutide and empagliflozin reduced MACE.

The ICER report used a network meta-analysis (NMA) to attempt to define benefit in cardiovascular risk reduction due to a lack of active comparator studies with the oral dosage form.⁶ The NMA, which combined oral and injectable semaglutide, found a significant reduction in MACE compared with sitagliptan.⁶ As with other studies, only empagliflozin reduced the risk of heart failure hospitalization. While these results show differences in MACE between oral and injectable semaglutide combined versus sitagliptan, information on the effects of oral semaglutide will not be available until 2024, with the results of the Heart Disease Study of Semaglutide in Patients

with T2DM (SOUL) study, which will evaluate patients with at least 1 of the following: existing cardiovascular disease, cerebrovascular disease, peripheral vascular disease, or chronic kidney disease with estimated glomerular filtration rate <60 ml/min.⁹ Thus, the current evidence does not clearly support a role for oral semaglutide in the prevention or treatment of cardiovascular disease, reducing its advantages over existing GLP-1 or SGLT2 therapies.

It is also important to note the AEs seen in oral semaglutide trials. As expected from GLP-1 agonists, the most common AEs were gastrointestinal, with nausea (up to 20%), vomiting (up to 10%), and diarrhea (up to 15%) and with the 14 mg dose resulting in the highest percentage of adverse gastrointestinal effects.^{6,8} While these are significant, the key point to consider is if they result in medication discontinuation. Discontinuation was very high, with 10%-13% of patients on the 14 mg dose discontinuing because of AEs.⁶ While AE rates are decreased with the 7 mg dose, so are the clinical results for lowering blood glucose and weight loss.

In an attempt to reduce discontinuation because of AEs, the manufacturer suggests a starting dose of 3 mg daily for the first 30 days and a slow titration with dose changes only every 30 days to a maximum dose of 14 mg daily.⁷ In addition to the slow titration, oral semaglutide has very low bioavailability, and its absorption is significantly affected by the presence of food, requiring it to be taken on an empty stomach with no more than 4 ounces of plain water only and with no other food or drink for at least 30 minutes. It is unclear how real-world outcomes will be affected by slow titration and specific instructions regarding food and drink, which may invite provider inertia in titration and introduce patient confusion with complex dosing instructions.

An additional concerning AE was seen in semaglutide trials: retinopathy in up to 5% of patients. Consistent with increases in retinopathy seen with injectable semaglutide, it is unclear whether this is an AE from the rapid lowering of blood glucose or if it has another etiology. The FOCUS trial (How semaglutide compared to placebo affects diabetic eye disease in people with T2DM) will be completed in 2025 and will provide further information.¹⁰

Given the lack of data regarding cardiovascular benefits with oral semaglutide, increased administration complexity, and a slower 3-step (vs. 2-step) titration versus some subcutaneous GLP-1 agonists, one is left wondering if there is a clear reason for use of the oral dosage form over injectable GLP-1 agonists in those situations when a GLP-1 agonist is the best choice for the patient. While there are studies looking at preference for oral versus injectable therapies in other therapeutic areas, the unique issues with these 2 agents are deserving of a real-world study of patient preference, particularly comparing prolonged titration daily oral dosing with once weekly subcutaneous dosing.

Regarding the cost-effectiveness evaluation in the ICER report, the clinical choice is often between an SGLT2 inhibitor and a GLP-1 agonist in most T2DM patients who are not glucose toxic and who are not achieving goal A1c levels on metformin. Given the improved cost-effectiveness and known cardiovascular (including heart failure) and chronic renal disease benefits of the SGLT2 inhibitors, the cost-effectiveness data point to the use of empagliflozin over oral semaglutide at this time.

American Diabetes Association Standards of Medical Care for Diabetes 2020 encourage the selection of medications based on cardiovascular comorbidities, renal function, and nephropathy, hypoglycemia risk, effect on weight, risk of side effects, patient preferences, and cost.² Patients make the ultimate decision for primary and continued adherence by how much the cash price, copay, or coupon discount will affect their bottom line.¹¹ With high deductible plans for commercially insured and Medicare patients, true medication accessibility is not ensured with formulary inclusion or cost-effectiveness—those are just the beginning. And, as in the investigation of the “cascade of diabetes care” and its lack of improvement with new therapeutic agents, the value of a medication is only present when it can be consistently used by the individual patient over the long term. Improving under- and uninsured patients access to new medications, as well as to safe environments for physical activity and education about and access to healthy food, are all needed to change health outcomes for all patients with T2DM.

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