EDITORIAL

The Future of the GLP-1 Receptor Agonists

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The discovery of the enteric hormone glucagon-like peptide 1 (GLP-1), and subsequent demonstration that its physiologic actions to lower blood glucose levels can be extended to the treatment of type 2 diabetes, have been important therapeutic advances.[1,2] The approval of exenatide for clinical use in the United States and Europe in 2005 was the first of several GLP-1 receptor agonists (GLP-1RAs) to advance the clinical use of the dual effects of these drugs to lower glycated hemoglobin (HbA_{1c}) and reduce body weight. This introduced a new and needed option to treat patients with diabetes. The actions of the currently available GLP-1RAs are specific for the endogenous GLP-1 receptor signaling system and thus share many pharmacodynamic characteristics. However, these agents differ in properties that alter pharmacokinetics, with dosing schedules that vary from daily to weekly injections among the various agents.

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Despite reliable potency for glycemic lowering and expected weight loss of 3 to 4 kg over several months of treatment adoption of the GLP-1RAs into clinical practice has been relatively slow, and these drugs account for a limited proportion of prescriptions for diabetes medications.[3] Gastrointestinal adverse effects are common, and some patients cannot tolerate the drugs. These agents also are quite expensive, further limiting use. In addition, all GLP-1RAs are peptides that require subcutaneous injection, a route that is less preferable compared with oral administration.[4]

Several recent cardiovascular outcome trials have generated increased interest in the GLP-1RA class of diabetes drugs. The LEADER trial to determine the effect of liraglutide and the SUSTAIN-6 trial to test semaglutide compared these drugs with standard care among patients with type 2 diabetes, with study cohorts that were enriched with individuals at risk of cardiovascular disease.[4] In both studies, the GLP-1RA reduced the risk of cardiovascular events, a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. In the LEADER trial, which included 9340 patients, there was a 1.9% absolute difference in the primary outcome. In the SUSTAIN-6 trial, which included 3297 individuals, there was a 2.3% absolute reduction in the primary outcome. These results are consistent with some but not all cardiovascular outcome trials that have evaluated drugs in the GLP-1RA class.[5] It is not clear whether the differences in the outcomes of these studies is related to specific features of the different drugs, distinct characteristics of the populations studied, or other facets of trial conduct. However, the results of LEADER and SUSTAIN-6 identify another major therapeutic advantage conferred by at least some of the GLP-1RAs, and because cardiovascular disease remains the leading cause of mortality in patients with diabetes, this may be the ultimate treatment benefit of these agents.

The cardiovascular benefit of several GLP-1RAs has led to changes in treatment recommendations for type 2 diabetes. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes now suggest adding a GLP-1RA with proven cardiovascular benefit to metformin for individuals with proven atherosclerotic cardiovascular disease who need further glycemic lowering.[6] Given the beneficial effect of these agents on obesity, they are also suggested therapy after metformin because of their potential to promote weight loss. In fact, the properties of these agents are so desirable that the GLP-1RAs are now recommended by the ADA as the first injectable agent, prior to use of insulin.[6]

Against this background, Rosenstock and colleagues report the results of the PIONEER 3 trial in this issue of *JAMA*.[7] In this 78-week clinical trial, 1864 adults with type 2 diabetes who were taking metformin with or without sulfonylurea were randomly assigned oral semaglutide, 3 mg/d, 7 mg/d, or 14 mg/d, or sitagliptin, 100 mg/d, in a double-blind design. Study outcomes were compared between the different dosages of semaglutide and sitagliptin for both noninferiority and superiority, and the analysis used both intention-to-treat ("treatment policy" estimand [with estimand referring to the objective of the analysis]) and per-protocol ("trial product" estimand) approaches. Based on HbA_{1c} and weight reduction at 26 weeks, the prespecified primary and secondary end points, oral semaglutide at dosages of 7 mg/d and 14 mg/d was more effective than sitagliptin using both analytic approaches. The estimated treatment differences from baseline to 26 weeks for oral semaglutide at 7 mg/d and 14 mg/d vs sitagliptin for HbA_{1c} reduction were −0.3% and −0.5%, respectively, and for body weight reduction were −1.6 kg and −2.5 kg, respectively. Greater effectiveness for HbA_{1c} reduction with 14 mg/d of semaglutide and weight loss with 7 mg/d and 14 mg/d of semaglutide was maintained at 78 weeks, whereas glucose lowering remained significant for the 7-mg/d dosage only with the trial product estimand.

Gastrointestinal effects were the most common adverse event with semaglutide, as they are with all GLP-1RAs, and occurred more frequently with the highest drug dosage. Premature discontinuation of study medication for any reason was 16.7%, 15.0%, and 19.1% for the 3-mg/d, 7-mg/d, and 14-mg/d semaglutide dosages and 13.1% for sitagliptin. Discontinuation rates due to adverse events were 5.6%, 5.8%, and 11.6% for the 3 doses of semaglutide and 5.2% for sitagliptin. Overall, this study demonstrated substantially greater effectiveness for HbA_{1c} and weight reductions for 14 mg/d of oral semaglutide compared with sitagliptin, but with higher rates of

adverse effects. The 7-mg/d semaglutide dosage had modestly better glucose lowering than sitagliptin, as well as greater weight loss, with comparable safety and tolerability.

The PIONEER 3 trial represents another advance for the GLP-1RA class of diabetes medications. Subcutaneously administered semaglutide is potent, with reductions in HbA_{1c} (1.5%-2%) and body weight (5-7 kg) that are greater than other diabetes medications, including other GLP-1RAs.[8] Previous studies have demonstrated dose-dependent amounts of glucose lowering with oral semaglutide, and effects of high doses (40 mg) of ingested drug that are comparable with the standard subcutaneous dose of 1 mg.[9] The results of PIONEER 3 extend these findings by demonstrating greater effectiveness relative to sitagliptin, a commonly used oral agent to treat type 2 diabetes. In reality, greater glucose lowering and weight loss compared with sitagliptin is not surprising given that this effect has been reported for other GLP-1RAs, including subcutaneous semaglutide.[8] However, the comparable rates of adverse events and overall safety, at least with the 7-mg/d dosage, are notable because sitagliptin is one of the better-tolerated drugs available to treat diabetes.

The highest dosage of semaglutide tested in PIONEER 3 (14 mg/d) was associated with higher rates of gastrointestinal adverse effects and illustrates the difficult balance between clinical effectiveness and tolerability that has been a challenge in the development of GLP-1RAs. There is evidence that adverse events with drugs like semaglutide wane over time while taking the treatment and can be mitigated with a slower escalation of dosage,[9] although adverse gastrointestinal symptoms remain an important limiting factor with GLP-1RAs. Another likely limitation to widespread use of oral semaglutide is cost. Other oral diabetes medications, such as metformin, sulfonylureas, and pioglitazone, are available as inexpensive generic preparations; sitagliptin will soon join this list. With greater amounts of medication expense in the United States being borne by patients, cost is increasingly a major factor in treatment decisions.[6]

What should not be overlooked is the successful development of technology to permit oral availability of peptide-based drugs. The oral formulation of semaglutide requires an absorption enhancer that should be a model for other drugs.[10] The most compelling example would be insulin, for which development of an oral formulation has been attempted for decades with a variety of approaches: enzyme inhibitors, absorption enhancers, chemical modification for endogenous receptor-mediated absorption, and mucoadhesive polymers.[11] To date there has been minimum success, but the hope is that this field, as seen with semaglutide, will progress to allow oral formulations in the future.[12]

Overall, the findings of the PIONEER 3 trial, along with other recent studies, indicate that the introduction of semaglutide, the first oral preparation of a GLP-1RA for which the subcutaneous agent has shown positive cardiovascular benefit, should be an important addition to the growing list of pharmacologic options for type 2 diabetes. However, if history can predict the future, many patients who could benefit from this new agent may not have access to this drug unless the cost is substantially reduced.

ARTICLE INFORMATION

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