The role of basal insulin and GLP-1 receptor agonist combination products in the management of type 2 diabetes

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Abstract: The prevalence of type 2 diabetes necessitates the development of new treatment options to individualize therapy. Basal insulin has been a standard treatment option for years, while glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have grown in use over the past decade due to glucose-lowering efficacy and weight loss potential. There are two new combination injectable products that have recently been approved combining basal insulins with GLP-1 RAs in single pen-injector devices. United States guidelines recently emphasize the option to use combination injectable therapy with GLP-1 RAs and basal insulin once the basal insulin has been optimally titrated as a second- or third-line agent in addition to metformin without reaching the goal A1c. Insulin glargine/lixisenatide 100/33 (IGlarLixi) can be dosed between 15 and 60 units once daily from a single pen-injector device. Insulin degludec/liraglutide 100/3.6 (IDegLira) can be dosed between 10 and 50 units once daily, also from a single pen-injector device. Maximum doses, while measured in units, correspond to limits defined by each individual GLP-1 RA. The dual use of basal insulin plus GLP-1 RA is non-inferior compared with basal insulin plus a single injection of prandial insulin at the largest meal and compared with twice daily-dosed premixed insulins; and this combination is associated with weight loss and less hypoglycemia. These new combination products could help providers effectively and efficiently follow clinical practice guidelines while enhancing patient adherence with injectable medications.

Keywords: basal insulin, GLP-1 receptor agonist, combination injectable therapy, glargine/lixisenatide, IGlarLixi, degludec/liraglutide, IDegLira, type 2 diabetes

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Introduction

In 2015, diabetes was the seventh leading cause of death in the United States (US).¹ With over 30 million Americans now afflicted with diabetes, over 84 million with prediabetes, and 1.5 million annual hospital admissions for major cardiovascular diseases associated with diabetes,¹ health care providers need more treatment options to fit the individual needs of these patients, with the ultimate goal to reduce the incidence of long-term complications. Approximately 95% of people with diabetes have type 2 diabetes (T2DM)¹ which is often accompanied by overweight/obesity, insulin resistance, and the need for multiple medications to control blood glucose levels, often including insulin.

In recent years, several new drugs and even new drug classes have become available for use in this population and some even have evidence supporting use for weight loss and cardiovascular risk reduction. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become highly recommended agents due to their A1c-lowering efficacy, potential for weight loss, and more recently, the evidence of cardiovascular risk benefits seen with liraglutide.² There are two new dual-agent products that are now available combining basal insulins with GLP-1 RAs. These new combination products could help providers effectively and efficiently follow clinical practice guidelines while enhancing patient adherence with injectable medications.

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US guidelines

The American Diabetes Association (ADA) has long recommended metformin for initial therapy of T2DM; unless the baseline A1c is elevated to a level more appropriately treated by insulin. After metformin, several options exist for second-line use including basal insulin. Basal insulin is often added alone as a second-line agent with metformin or as a third-line agent after the addition of a second drug to metformin has not successfully achieved the A1c goal. Since the 2015 Standards of Care in Diabetes, the ADA has recommended an option for combination injectable therapy which may include a GLP-1 RA. However, the 2017³ and 2018⁴ editions emphasize this option more than in past installments of the guideline. Direction has been included to guide early therapy based on the degree of A1c elevation as well. If the A1c is $\geq 9\%$, initiating dual therapy is an option; which could include basal insulin. In the presence of marked symptoms, an A1c $\geq 10\%$, or blood glucose levels ≥ 300 mg/dl, combination injectable therapy is recommended.^{3,4} Combination injectable therapy is also suggested for patients with an elevated A1c under 9 if single or dual therapy was initiated and basal insulin eventually added and titrated without successful achievement of the goal A1c or if the dose is >0.5 units/kg/day. A total of three options are listed for addition to basal insulin for combination injectable therapy: add a GLP-1 RA; add one rapid-acting insulin injection before the largest meal with titrations and additional meal-time doses when necessary; or change basal to a premixed insulin twice daily before breakfast and supper with titrations.^{3,4} The American Association of Clinical Endocrinologists (AACE) 2017 guidelines have very similar recommendations. Once basal insulin has been titrated to >0.5 units/kg/day and the A1c remains elevated, then either a GLP-1 RA or prandial insulin may be added.⁵

These recommendations are supported by evidence of non-inferiority of basal insulin plus GLP-1 RAs compared with basal insulin plus a single injection of prandial insulin at the largest meal and compared with twice daily-dosed premixed insulins^{3,4,6,7} in regard to glucose control. Traditionally, once basal insulin has been initiated and titrated, many providers have viewed the next logical step in pharmacologic management to be the addition of rapid-acting prandial insulin. However, even though basal insulin improves fasting plasma glucose levels, it can also cause increased hypoglycemia and weight gain,^{8,9} as can prandial insulin as well. The option to add a GLP-1 RA to basal insulin instead

of prandial insulin allows for less use of insulin in general. GLP-1 RAs work to lower blood glucose by increasing glucose-dependent insulin secretion, decreasing glucagon secretion, and slowing gastric emptying. They may contribute to weight loss without increasing hypoglycemia risk.^{10–14} This is desirable as the components of the new combinations seem to combat the shortcomings of the individual agents. Indeed, recent studies and meta-analyses have associated these combination products with weight loss and less hypoglycemia.^{6–8,15} A 2017 meta-analysis by Maiorino and colleagues found that combination therapies of basal insulins with GLP-1 RAs led to the same glycemic control compared with intensified insulin regimens (without GLP-1 RAs), but with less hypoglycemia and reduced weight.¹⁵ This duo was first recommended when the products were only available as individual agents. Now, the combination of these products in one pen-injector device could have convenience benefits to improve regimen adherence.

Novel basal insulin/GLP-1 RA combination products

The two new basal insulin/GLP-1 RA titratable fixed-ratio combination products, insulin glargine/lixisenatide (Soliqua 100/33) (IGlarLixi) and insulin degludec/liraglutide (Xultophy 100/3.6) (IDegLira), were approved by the US Food and Drug Administration in November 2016. IGlarLixi is also a new addition in the European Union, having been granted marketing authorization by the European Commission in January 2017. However, diabetologists in the European Union have had access to IDegLira since September 2014. Both are indicated for treatment of T2DM in adjunct to lifestyle changes including diet and exercise, and are administered subcutaneously once daily. Neither product is recommended to be injected cold, so storage after initial use should be at room temperature.^{16,17} Contraindications, adverse effects, and monitoring should all be applied for each of the individual agents within each product. So, monitoring for hypoglycemia is necessary, as with any insulin agent, especially while in use with other glucose-lowering agents. GLP-1 RAs may cause gastrointestinal adverse effects such as nausea and vomiting, carry a warning for pancreatitis, and should not be used in patients with a personal or family history of medullary thyroid carcinoma or with multiple endocrine neoplasia syndrome type 2.^{16,17}

Insulin glargine/lixisenatide

IGlarLixi is available in a pen-injector device in a ratio of insulin glargine 100 units/ml to lixisenatide 33 µg/ml.¹⁶ Patients who are already taking either of the individual agents alone should discontinue use prior to starting the combination product. Ultimate dosing is limited by the maximum dose of lixisenatide at 20 µg daily.¹⁸ However, dosing of the product is based on the units of insulin being administered. Patients with insufficient diabetes control taking either lixisenatide alone or on less than 30 units of basal insulin should be started at 15 units of the combination product (15 units insulin glargine/5 µg lixisenatide). Patients already taking 30–60 units of basal insulin should be started at 30 units of the combination product (30 units insulin glargine/10 µg lixisenatide). The dose may be titrated by 2–4 units every week until the desired fasting plasma glucose is achieved up to a maximum of 60 units (60 units insulin glargine/20 µg lixisenatide) daily. The pen will only deliver doses between 15 units and 60 units, so necessary dosing outside of this range will require alternative agents. The daily dose should be administered within 1 h before the first meal of the day. Once the product is initially used, it may be kept at room temperature for use up to 14 days.¹⁶

Insulin degludec/liraglutide

IDegLira is available in a pen-injector device in a ratio of insulin degludec 100 units/ml to liraglutide 3.6 mg/ml.¹⁷ Patients who are already taking either of the individual agents alone should discontinue use prior to starting the combination product. This is intended for patients with inadequate diabetes control taking either liraglutide alone or on less than 50 units of daily basal insulin. Ultimate dosing is limited by the maximum dose of liraglutide at 1.8 mg daily.¹⁹ However, dosing of this product is also based on the units of insulin being administered. IDegLira should be initiated at 16 units daily (16 units insulin degludec/0.58 mg liraglutide).¹⁷ This allows for a starting dose of liraglutide that is very similar to the starting dose of the individual agent, which is 0.6 mg daily to help reduce the incidence of nausea. The dose may be titrated by 2 units every 3–4 days as needed for blood glucose control up to a maximum of 50 units (50 units insulin degludec/1.8 mg liraglutide) daily. The pen will deliver between 10 units and 50 units, which allows for dosing below the recommended starting dose; however, dosing outside of this range will require

alternative agents. The daily dose may be administered with or without food, but should be at the same time each day. After initial use, the pen may be kept at room temperature for up to 21 days.¹⁷

Product differentiation

While these two new combination products appear to be very similar, they do have their differences. Basal insulin gives both products an agent with a focus on controlling fasting plasma glucose levels. The DEVOTE trial demonstrated that insulin glargine U-100's glucose-lowering capability is comparable to that of insulin degludec U-100 when used in conjunction with oral agents. However, glargine U-100 was also associated with more severe hypoglycemia and nocturnal hypoglycemia than degludec U-100.²⁰ Whereas postprandial glucose levels are affected by liraglutide, its longer half-life gives it more of an impact on fasting plasma glucose levels. The shorter half-life and duration of lixisenatide allows for a more significant impact on postprandial glucose levels compared with liraglutide.^{21–25} These differing effects of liraglutide and lixisenatide on fasting plasma glucose and postprandial glucose levels has caused some to hypothesize that patients requiring more assistance with postprandial glucose levels may have more success with IGlarLixi, whereas patients still in need of more fasting glucose assistance may benefit more from IDegLira. However, a 2017 meta-analysis by Cai and colleagues, comparing IDegLira with IGlarLixi, found that both treatments significantly lowered A1c and fasting plasma glucose levels from baseline, and there were no significant differences found in absolute A1c reduction or fasting plasma glucose change between the two treatment groups.⁸ Neither had an advantage over the other in these regards.

While both liraglutide and lixisenatide have evidence of cardiovascular safety, lixisenatide has not yet shown evidence of cardiovascular risk reduction in patients with high cardiovascular risk. The ELIXA trial found lixisenatide to be non-inferior to placebo regarding the primary outcome (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization from unstable angina), but failed to find superiority.^{2,25,26} However, in the 2016 LEADER trial, liraglutide was able to demonstrate statistically significant cardiovascular risk reduction.² This finding is significant in the grand scheme of diabetes management. Although, in

theory, all glucose-lowering agents contribute to reduction of risk of microvascular complications, very few have shown a reduction in macrovascular complications, which significantly impacts the long-term prognosis of patients with diabetes. Since this does not seem to be a class effect, distinctions may need to be made when choosing a GLP-1 RA product for patients at higher cardiovascular risk.

Conclusion

Both IGlarLixi and IDegLira provide promising new options in the arsenal of drugs used to manage T2DM. In developed countries, medication adherence among patients with chronic diseases is only about 50%.²⁷ Some factors associated with decreased adherence include the complexity of the medication regimen and associated adverse events. These new basal insulin/GLP-1 RA combination products may eliminate some of these factors. They reduce the regimen complexity by combining fixed-dosed combinations into one pen-injector device, thus minimizing the quantity of injections per day; especially considering alternative regimens that include prandial insulin products. GLP-1 RAs help with weight reduction and may further reduce the need for larger or more frequent insulin doses which could, conversely, lead to more weight gain. With a lower incidence of hypoglycemia compared with alternative regimens, these combination products seem to carry safety advantages as well. These products could become preferred agents, used earlier in therapy, over basal-bolus insulin regimens.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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