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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What is the Rationale for Fixed-Ratio Combinations of Basal Insulin Analogs and GLP-1 Receptor Agonists?

Announcer: Welcome to CME on ReachMD. This segment, *What Is the Rationale for Fixed-Ratio Combinations of Basal Insulin Analogs and GLP-1 Receptor Agonists?*, *is provided by Global Education Group*. Paradigm Medical Communications, LLC is the educational partner. The activity is supported by an educational grant from Novo Nordisk, Inc. Joining host Dr. John Russell is guest expert Dr. Wendy S. Lane, an endocrinologist at the Mountain Diabetes and Endocrine Center in Asheville, North Carolina.

Here is Dr. Russell.

Dr. Russell: Type 2 diabetes affects over 29 million in the United States and approximately 416 million people worldwide. This chronic, progressive disease remains the seventh leading cause of death in the United States and places an enormous burden on patients in terms of disease complications and society in terms of high cost of health care and lost work productivity. Dr. Lane, welcome to the program.

Dr. Lane: Thank you.

Dr. Russell: So, Dr. Lane, what are some of the biggest challenges that patients with type 2 diabetes face?

Dr. Lane: It's important to control blood glucose levels to prevent the complications of diabetes, but controlling the glucose without incurring hypoglycemia or weight gain is one of the biggest challenges in managing the disease, and insulin, which is the most effective agent, also puts people at the highest risk for weight gain and hypoglycemia. This may be why 39% of insulin-using patients in the latest NHANES study were the most poorly controlled, with a hemoglobin A1C above 8%.

Dr. Russell: So, Dr. Lane, as a primary care physician, I have about a dozen different choices of anti-diabetic agents. With so many choices, do my patients still need insulin?

Dr. Lane: What we need to remember is that type 2 diabetes is a progressive disease because of progressive beta cell dysfunction and loss of insulin production, so patients' treatment regimens will have to be intensified over time. Unfortunately, there's a misconception among not just patients but also physicians, that insulin is some form of punishment for a patient who didn't manage his or her diabetes properly. This leads to clinical inertia both with patients and clinicians, where insulin is initiated late in the process. Both the ADA (American Diabetes Association) and AACE (American Association of Clinical Endocrinologists) recommend adding insulin if an individual patient's A1C goal isn't met with other agents, and both groups recommend starting basal insulin any time the patient's A1C is greater than 9%, which is what AACE recommends, or over 10%, which is what the ADA recommends, even at the time of diagnosis. However, finding a way to use insulin in a way that limits the potential for weight gain and reduces the risk of hypoglycemia remains a major unmet need in managing type 2 diabetes.

Dr. Russell: What are the advantages of combining basal insulin in a GLP-1 receptor agonist for the management of hyperglycemia in type 2 diabetes?

Dr. Lane: Using GLP-1 receptor agonists and basal insulin together yields greater A1C reductions than using either injectable agent alone. When these agents were used as separate components in a combination therapy regimen, the A1C reductions were greater than basal insulin or a GLP-1 receptor agonist used alone. This is illustrated in the Get Goal Duo 1 Study, where you see further A1C

reductions when a GLP-1 receptor agonist—lixisenatide—was added to a combination of insulin glargine plus metformin with or without thiazolidinediones (TZDs). The A1C reduction when glargine was added to oral agents was 0.4%, but when you then add lixisenatide on top of the basal insulin plus the oral agents, you have an additional 0.3% reduction for a total A1C reduction of 0.7%. This reduction was highly statistically significant compared to not having the GLP-1 receptor agonist.

In the Liraglutide-Detemir study, insulin detemir was added to liraglutide and metformin in patients whose A1C was over 7% after 12 weeks of treatment, and you can see that there was also a good reduction when insulin detemir was added to the GLP-1 receptor agonist plus metformin. After 12 weeks of treatment, patients were stable, but when you added the detemir, there was an additional reduction in hemoglobin A1C of 0.5%.

Looking at the rates of hypoglycemia, you can see that the rate of having no hypoglycemia was higher when a GLP-1 receptor agonist and basal insulin were used together than with either insulin glargine or with detemir alone, but insulin-associated weight gain was minimized or even cancelled out by the GLP-1 component when the agents were combined.

Dr. Russell: Why is this weight loss effect important?

Dr. Lane: Obesity is the leading cause of insulin resistance and a contributory cause to the disease of diabetes. Because it contributes to the pathophysiology of diabetes, it is driving the disease process, so it's important to regulate weight. Of course, the majority of patients with type 2 diabetes also have obesity, so we need to control it. Patients' obesity as well as their diabetes are risk factors for cardiovascular disease.

Dr. Lane: Liraglutide, which reduces weight as well as glucose, decreased cardiovascular events in the LEADER study. Now, these improved cardiovascular outcomes were likely to be at least partly a result of the weight loss, but there are also likely to be other anti-atherosclerotic effects of liraglutide, which led to these positive cardiovascular effects.

Dr. Lane: However, in the ELIXA trial, which was done with lixisenatide, lixisenatide did not show cardiovascular benefit, although it did show safety and neutrality. It did not cause any cardiovascular adverse outcomes. Now we know that lixisenatide doesn't usually elicit as much weight loss as liraglutide, but we don't know for sure if this is why there were different outcomes between the LEADER trial and the ELIXA trial. We have to be cautious about comparing the results of these two studies because ELIXA and LEADER involved two different patient populations. The ELIXA population had already had a recent cardiovascular event, plus this was a shorter-duration trial, whereas LEADER involved high-risk patients for cardiovascular disease who had not necessarily yet had an event, and it was also a longer duration study. So, the LEADER patients may not have had as advanced cardiovascular disease or maybe they didn't even yet have established cardiovascular disease, whereas the ELIXA subjects were further along in the disease process and they had established cardiovascular disease. If the ELIXA population had been studied earlier and for longer, they may also have experienced cardiovascular risk reduction.

Dr. Russell: Dr. Lane, for our patients, what are the advantages of combining basal insulin in GLP-1 receptor agonists into a single delivery system?

Dr. Lane: The main advantage is convenience and efficacy compared to giving either individual component alone. Let's look at the evidence for this, and let's first look at the DUAL studies, which examine the effects of liraglutide combined with insulin degludec. These studies involved patients with a mean age in their mid-50s; they had had diabetes for 7-11 years. The mean BMI was 31 ^{2} in DUAL I and 34 in DUAL II. In DUAL I, patients were only taking oral agents at baseline, while in DUAL II they were already taking some form of basal insulin plus metformin.

Dr. Lane: Let's focus on DUAL I. In this study, patients with a mean hemoglobin A1C of 8.3% on metformin with or without pioglitazone at baseline were randomized to insulin degludec alone, liraglutide alone, or the combination agent iDegLira. iDegLira reduced the hemoglobin A1C more than the other treatments, demonstrating non-inferiority compared with degludec and superiority to liraglutide. The iDegLira patients experienced a hemoglobin A1C drop of 1.9% from a baseline of 8.3%, whereas those treated with degludec alone experienced a hemoglobin A1C drop of 1.4%, and those treated with liraglutide alone experienced a drop of 1.3%. Another important advantage is the insulin-sparing effect of the combination agent, which reduces the overall risk of hypoglycemia. The insulin dose is 28% lower in the iDegLira group compared to the degludec group, and although the overall incidence of hypoglycemia was similar in the two insulin groups, it was slightly lower in the iDegLira group. Similar effects were seen in the other studies using iDegLira.

Dr. Russell: Dr. Lane, what were the results like in the studies with iGlarLixi?

Dr. Lane: iGlarLixi is a combination agent that combines insulin glargine and the GLP-1 receptor agonist lixisenatide. These studies were called the LixiLan studies. The LixiLan studies involved patients with a mean age of about 60 years who had had diabetes for a little bit longer, between 9 and 12 years. The mean BMI was 32 in LixiLan-O and 31 in LixiLan-L. The LixiLan-O patients were taking

only oral agents at baseline, whereas the LixiLan-L patients were already taking some form of basal insulin with or without an oral agent.

Dr. Lane: In the LixiLan-O study, the fixed-dose combination product iGlarLixi, which is a combination of glargine and lixisenatide, significantly reduced A1C more than either glargine alone or lixisenatide alone. So, from a baseline hemoglobin A1C of 8.1%, iGlarLixi reduced A1C by 1.6%, whereas insulin glargine alone reduced A1C by 1.3%, and lixisenatide alone reduced A1C by 0.9%. Hypoglycemia rates and the insulin dosage in the LixiLan study were similar between the insulin-containing agents.

Dr. Russell: Nausea can be a problem with the GLP-1 receptor agonist. What were the adverse effects like in these studies?

Dr. Lane: Here are the rates of nausea and the other GI side effects in Dual and the LixiLan trials. First of all, nausea with the GLP-1 receptor agonist fortunately tends to diminish over time, and the nausea rates were, as they were higher with the single GLP-1 agents, lower with the combination agents. In DUAL I, the overall withdrawal for iDegLira was 12%; for degludec 12% (the same), and for liraglutide 18%. So it was higher for the single GLP-1 agents, again driven by GI side effects. In LixiLan-O, the overall withdrawal rates were 2.6% for iGlarLixi; 1.9% for glargine, and for lixisenatide, the single agent, 9%—so there was a similar pattern for withdrawal because of nausea. The single GLP-1 receptor agonist tends to have more nausea than the combination agent.

Dr. Russell: In your practice, how do you identify which patients would be candidates for treatment with a fixed-ratio combination of the basal insulin in a GLP-1 receptor agonist?

Dr. Lane: There are three types of patients who would be eligible. First, patients who are already on a GLP-1 receptor agonist with or without oral agents whose A1C is above target would be candidates for these agents. Second, patients who are already on basal insulin but need prandial glucose control would also be candidates for these agents. There's a third category of patients with high hemoglobin A1Cs above 9% who may or may not be taking any other agents, but because of how high their A1C is, they need intensive therapy right away. These patients would also be, in my opinion, candidates for these agents. Now, keep in mind that putting a patient newly diagnosed with a very high A1C on these agents would be an off-label use because the fixed-ratio combinations are currently indicated to be used in patients who are already taking basal insulin or already using either of the GLP-1 receptor agonists. However, this would also be an appropriate use of these agents, in my opinion, for patients who needed intensive therapy with a combination of agents from diagnosis because of the magnitude of their hyperglycemia. Patients who experience something called the dawn phenomenon, where they have high fasting blood glucose levels regularly because of more insulin resistance overnight, would also be good candidates because these would be effective agents to control the fasting glucose better than either agent alone.

Dr. Russell: We talked about the three groups of patients who would be candidates for the medicine. Which patients would not be good candidates for these medicines?

Dr. Lane: The patients for whom GLP-1 receptor agonists are contraindicated or whose history indicates there may be problems with tolerability would not be good candidates for these combination agents. These would include, for example, patients with personal or family history of medullary carcinoma of the thyroid, which is a concern more in rodents than in humans, but nevertheless the GLP-1 receptor agonists have warnings from the FDA that patients with this endocrine disease should not receive these agents, so that's one contraindication. Patients who have other gastrointestinal disorders that make them more susceptible to nausea, vomiting, or diarrhea, they also might not be good candidates for these agents because their underlying disease might worsen if they're given something that could make them nauseated. Patients who have already in the past shown that they cannot tolerate a GLP-1 receptor agonist, who had too many side effects, probably would not be good candidates for these because they may again get the side effects. Now, there are patients who use liraglutide not for diabetes management but for weight loss at a higher dosage. Patients who are taking liraglutide at 3 mg for weight loss should not take this agent because they won't be getting enough liraglutide in the combination agent and you don't want to give them two different treatments with the same compound with liraglutide. Also, patients who are already using insulin but have very high insulin requirements, more than 80 units of insulin per day, probably are not good candidates, at least for these agents, in a single injectable device. They may still be candidates for the agents separately, but you probably won't be able to inject enough insulin for patients who truly have high insulin requirements using the combination injection. So, they probably won't be candidates because the injectable devices won't be able to deliver enough insulin to meet their needs.

Dr. Russell: Dr. Lane, thank you so much for your thoughtful analysis of the clinical evidence from the published trials of iGlarLixi and iDegLira.

Dr. Lane: It's been my pleasure. Thank you.

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