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How Fixed-Ratio Combinations Are Individualizing Type 2 Diabetes Treatment

Announcer: Welcome to CME on ReachMD. This segment, *How Fixed-Ratio Combinations Are Individualizing Type 2 Diabetes Treatment, 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. Jennifer Caudle is guest expert Dr. Javier Morales, of Hofstra Northwell School of Medicine in Hempstead, New York.

Here is Dr. Jennifer Caudle.

Dr. Caudle: Type 2 diabetes is notoriously difficult to treat, with only about half of patients meeting target A1C levels. It is a disease that truly requires clinicians to apply the art of medicine to help their patients achieve their goals. Dr. Morales, welcome to the program.

Dr. Morales: Thanks very much. The management of type 2 diabetes is quite intricate, and over the years, we have made some strides in terms of allowing our patients to achieve appropriately ascribed hemoglobin A1C targets, but we are not really getting to the 100% mark, and we have a little bit of room to go.

Dr. Caudle: So, let us get started with our first case. Dr. Morales, our first patient is Miriam, a middle-aged woman who was diagnosed with type 2 diabetes 7 years ago.

Dr. Caudle: What are your initial thoughts about this patient?

Dr. Morales: Miriam is very interesting. She is a 55-year-old, Asian female who suffered gestational diabetes at age 34. Her hemoglobin A1C currently is 7.9%. Her fasting plasma glucose is 160 mg/dL.

Dr. Morales: Unfortunately, Miriam has had some trouble tolerating liraglutide, with recurrent bouts of diarrhea, even at a low dosage of 1.2 mg per day. Miriam is not alone. Certainly, we have had some challenges with GI-related issues with GLP-1 receptor agonists. Aside from the nausea that patients may experience because of its effect on delayed gastric emptying—and this nausea tends to be somewhat self-limited and eventually tolerable—diarrhea can sometimes be seen.

Dr. Morales: Now, metformin is at the crux of recommended medical therapy for management of type 2 diabetes, and oftentimes metformin can produce a little bit of diarrhea; however, to circumvent the diarrhea that one can see with metformin, we have extended-release preparations such as the one that Miriam is taking.

Dr. Morales: Miriam is doing well in terms of her lifestyle and weight management. We need to take into consideration the fact that Miriam is Asian. One thing about the Asian population is that a little bit of adiposity translates into a whole lot of insulin resistance. She also has a family history of type 2 diabetes, chronic renal insufficiency, and cardiovascular death. Now, she does have a moderately elevated albumin-creatinine ratio, and there tends to be some diminution in her glomerular filtration, which may be iatrogenic with the presence of the angiotensin-converting enzyme inhibitor for blood pressure control. We do know that her hemoglobin A1C and fasting plasma glucose target are certainly above the ascribed target that we would like to achieve and, of course, there is the diarrhea she is currently experiencing.

Dr. Caudle: What diabetes management goals would you recommend for this patient?

Dr. Morales: The American Diabetes Association guidelines recommend a hemoglobin A1C of less than 7%; the American Association of Clinical Endocrinologists recommend an A1C target of less than or equal to 6.5%. The reason we want to keep those hemoglobin A1Cs lower, particularly in the younger population, is to circumvent the evolution of microvascular complications that sometimes can develop with type 2 diabetes, that being the nephropathy, the neuropathy, and the retinopathy. What we've learned from the American Diabetes Association's guidelines is that we need to take a patient-centered approach and have a collaborative scheme with the patient to allow the patient to participate in appropriate management decisions and medication selection. Subsequently, hemoglobin A1C targets will need to vary on the basis of the patient's age of presentation, longevity, and comorbidities. So, a target hemoglobin A1C of less than 7% for Miriam seems to be an appropriate target; however, if we are able to get to a lower hemoglobin A1C safely without hypoglycemia, then it would certainly be welcome. She is young; she has no history reported of hypoglycemia; and she does have some mild diabetic nephropathy, as depicted in the case presentation. She does have elevated cardiovascular risks, but she really does not have any evidence of active coronary artery disease. That being the case, her fasting glucose goal probably should be less than 100 mg/dL, and I would certainly encourage her active participation in lifestyle management.

Dr. Caudle: What changes in her anti-diabetic regimen would you recommend?

Dr. Morales: The addition of basal insulin or maybe the consideration of a fixed-ratio product is an interesting concept in the management of Miriam. While the high fasting plasma glucose suggests that the patient needs greater fasting glucose control, we can easily achieve that with the use of a basal insulin because, after all, basal insulins are designed to suppress nocturnal hepatic glucose output and offer inter-meal control. However, we need to take into consideration the postprandial rises in her meal, and oftentimes that's actually achieved with the use of a GLP-1 receptor agonist, which induces insulin secretion out of that beta cell in a glucose-dependent fashion to try to circumvent that postprandial rise. Let's take a look at some data with iGlarLixi, which is a novel combination product containing insulin glargine, which is a basal insulin, in combination with a short-acting GLP-1 receptor agonist, lixisenatide. In looking at these data, we can see that the glucose, or the glycemic excursions, are significantly reduced with the combination product of iGlarLixi relative to either insulin glargine or the short-acting GLP-1 receptor agonist, lixisenatide, alone.

Dr. Caudle: Would you add the basal insulin separately to Miriam's regimen or use a fixed-ratio combination of a GLP-1 receptor agonist and insulin?

Dr. Morales: We have two different combination products that are in the marketplace currently: iGlarLixi, which I had just mentioned, and also iDegLira. Both are indicated for use in patients who are already taking a basal insulin or lixisenatide in the case of iGlarLixi or liraglutide in the case of iDegLira. So, let's take a look at some data, looking at composite endpoints of achieving a hemoglobin A1C target of less than 7% in the absence of weight gain without hypoglycemia. One trial is called the DUAL I study, in which iDegLira was compared to insulin degludec and compared with liraglutide. We can see that the relative percentage of patients achieving a hemoglobin A1C target of less than 7% was achieved in 60% of patients who were treated with liraglutide and in 65% of patients who were treated with insulin degludec, but, interestingly, 81% of patients in the combination of iDegLira were able to achieve that hemoglobin A1C target. Now, if you are looking at composite endpoints of achieving A1C of less than 7% without weight gain or hypoglycemia, we saw 52% of patients achieve that value with liraglutide; 14% of those who were on degludec; and 36% of those who were on the combination of iDegLira. So, iDegLira winds up being a really interesting combination that actually achieves the best of both worlds, which is a little bit of insulin and little bit of GLP-1 receptor agonist, which translates into a whole lot of A1C reduction.

Dr Morales: So, let's take a look at the LixiLan-O study, which looked at insulin glargine in combination with lixisenatide, a short-acting GLP-1 receptor agonist, versus insulin glargine alone and versus lixisenatide alone. As we saw the DUAL I study, of those patients who were in the LixiLan-O study, 33% of patients on lixisenatide, which is a short-acting GLP-1 receptor agonist, were able to achieve a hemoglobin A1C of less than 7%; 59.4% of patients who were treated with insulin glargine achieved that hemoglobin A1C target of less than 7%; and when we look at the combination of iGlarLixi, 73.7% of patients were able to achieve that hemoglobin A1C target of less than 7%. Finally, looking at achievement of an A1C of less 7% in the absence of weight gain or hypoglycemia, that composite endpoint, 26.2% of patients with lixisenatide did it; 18.9% of those who were on insulin glargine did it; and looking at the combination of iGlarLixi, 31.8% of those patients were enabled to do so.

Dr. Caudle: Suppose you prescribed iGlarLixi for Miriam. How would you start it and titrate it?

Dr. Morales: iGlarLixi really consists of 1 microgram of lixisenatide, a short-acting GLP-1 receptor agonist that is exendin-4 based, per 3 units of insulin glargine. The starting dose for a patient like Miriam, who has never been on insulin before, is 15 units of glargine and 5 micrograms of lixisenatide once daily, but it needs to be administered within the hour prior to the first meal of the day. So, it is labeled as 15 units on the pen, and this is the lowest available dose for that pen. The titration really should occur by 2-4 units every week until Miriam's fasting glucose goal of less than 100 mg/dL is achieved. The maximum dose of iGlarLixi is 60 units. The product label says to stop iGlarLixi and switch to another treatment if more than 60 units is required in order to achieve that hemoglobin A1C target. The label

also says to stop iGlarLixi and switch to something else if less than 15 units a day is needed in order to meet that fasting glucose goal.

Dr. Caudle: Let's move on to the next case. Julius is a 61-year-old African-American man.

Dr. Morales: Julius is an African-American male, 61 years of age, diagnosed with type 2 diabetes at age 55. He unfortunately suffered a myocardial infarction at age 58.

Dr. Morales: Julius does recognize that his hemoglobin A1C is too high, and he is reluctant to increase his insulin dosage for several reasons that are shared by many different patients who suffer with type 2 diabetes and may be on insulin, and that's the fear of hypoglycemia and how hypoglycemia can potentially impair his ability to do his job.

Dr. Caudle: What would you recommend as this patient's A1C target?

Dr. Morales: Currently his hemoglobin A1C is greater than 8%. It's too high. It puts him at risk for microvascular as well as macrovascular diabetes complications. Obviously, he has already suffered a macrovascular complication, that being a myocardial infarction. So, this gentleman should be having a hemoglobin A1C target anywhere between 7% and 8%, but obviously closer to 7%. This would also enable us to limit the potential for hypoglycemia because of the intensification therapy, which may have an effect on his job as well as his cardiovascular history.

Dr. Caudle: Would a fixed-ratio combination of basal insulin and a GLP-1 receptor agonist be appropriate for this patient?

Dr. Morales: I think so and, in general, either agent, whether it be iGlarLixi or iDegLira, would be good options, depending on the patient's preference. iGlarLixi certainly would not increase his cardiovascular risk. iDegLira may be a more appropriate option for Julius, given his history of cardiovascular disease and the added benefit of liraglutide's cardiovascular risk reduction, as was demonstrated in the LEADER study.

Dr. Morales: iDegLira may be better than simply increasing his insulin dosage. One clinical trial, the DUAL II study, involved patients who were already on a basal insulin at baseline, and if this basal insulin was substituted with iDegLira, it yielded significantly better hemoglobin A1C reductions and weight loss with a similar rate of hypoglycemia compared with just titration of insulin degludec alone.

Dr. Caudle: Let's say you prescribe iDegLira for Julius. How do you start and titrate this agent?

Dr. Morales: iDegLira consists of 100 units per milliliter of insulin degludec and 3.6 mg per milliliter of liraglutide. The recommended starting dosage for a patient like Julius, who has been taking less than 50 units of basal insulin, is 16 units, which includes 16 units of degludec and 0.58 mg of liraglutide. The titration would either be up or down by 2 units every 3 to 4 days until that fasting plasma glucose target that's appropriate for Julius is achieved. So, the recommended fasting blood glucose is about 100 mg/dL. We can down-titrate iDegLira to a minimum of 10 units of insulin plus 0.36 mg of liraglutide in that 10-unit dosage. The prescribing information says that if the patient's glucose is persistently controlled on less than 16 units of iDegLira, you should switch to a different antihyperglycemic agent. Clinicians have to use their clinical judgment to decide what *persistent* actually means. I would give it about 4 or 5 days. Now, the interesting thing is, in someone like Julius, who has been using less than 50 units of basal insulin, initiation with 16 units of the iDegLira will certainly lead to worsened control in the short term. However, we need to be cognizant of practicing safety first, so even though we have lost control temporarily with the reduced dose of the iDegLira, this certainly allows us to titrate to the appropriate level in order to achieve the hemoglobin A1C target. The maximum dose of iDegLira is 50 units. The label says to stop iDegLira and switch to another treatment if more than 50 units are needed. The label also says to stop the iDegLira if fasting glucose goal is met consistently on less than 16 units, then try a different treatment.

Dr. Caudle: Thank you Dr. Morales for your insights into meeting the treatment challenges faced by patients with type 2 diabetes.

Dr. Morales: Thank you for having me as a presenter for this program, and hopefully our audience learned some good takeaway points about how to use these new tools available for the management of type 2 diabetes.

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