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VOLUME 2 — ISSUE 3: TRANSCRIPT

Beyond Basal Insulin: Combination Therapy with GLP-1 RAs

Our guest author is Kathleen Dungan, MD, MPH, Associate Professor and Associate Division Director for Clinical Services, in the Division of Endocrinology, Diabetes and Metabolism at The Ohio State University.

After participating in this activity, the participant will demonstrate the ability to:

- Describe the glucose lowering effects of GLP-1 receptor agonists (GLP-1 RA) added on basal insulin.
- Compare the safety and efficacy of GLP-1 RA and prandial insulin in combination with basal insulin.
- Identify the physiologic differences between continuous and intermittent GLP-1 RA, alone and in combination with basal insulin.

This discussion offered as a download about audio file and companion transcript, covers the important topic of GLP-1 Receptor Agonists in Combination in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 2, Issue 2 eDiabetes Review newsletter – Beyond Basal Insulin: Combination Therapy with GLP-1 RAs.

Unlabeled/Unapproved Uses
Kathleen Dungan, MD, MPH has indicated that there will be references to the unlabeled/unapproved uses of IDegLira, degludec, and lixisenatide.

MEET THE AUTHOR

Kathleen Dungan, MD, MPH
Associate Professor, Associate Division Director of Clinical Services
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University
Columbus, Ohio

Faculty Disclosure
Kathleen Dungan, MD, MPH has indicated that she has received grant/research funding from AstraZeneca, GlaxoSmithKline, Merck & Co., Inc., and Sanofi-Aventis; has served as a paid member of committees, panels, or boards for Eli Lilly and Company; has served as a consultant for GlaxoSmithKline; and has received honorarium from UpToDate®.

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MR. BOB BUSKER: Welcome to this *e*Diabetes Review Podcast.

Today's program is a follow-up to our newsletter topic: Beyond Basal Insulin: GLP-1 Receptor Agonists in Combination. With us today is that issue's author: Dr. Kathleen Dungan, Associate Professor in the Division of Endocrinology, Diabetes and Metabolism at The Ohio State University in Columbus.

*e*Diabetes Review is jointly presented by the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from AstraZeneca and Merck.

Learning objectives for this audio program include:

- Describe the glucose lowering effects of GLP-1 receptor agonists when added to basal insulin.
- Summarize safety concerns with the use of insulin/GLP-1 receptor agonist combinations.
- Identify the physiologic differences in lowering post-prandial glucose between continuous and intermittent GLP-1 receptor agonists.

Dr. Dungan has indicated that she has received grant and/or research funding from AstraZeneca, GlaxoSmithKline, Merck & Co., Inc., and Sanofi-Aventis. She has served as a consultant for GlaxoSmithKline and has been a paid member of committees, panels, or boards for Eli Lilly and Company. In addition, she has received honorarium from UpToDate®. Her discussion today will reference the unlabeled or unapproved use of lixisenatide.

I'm Bob Busker, managing editor of *e*Diabetes Review. Dr. Dungan, thank you for joining us today.

DR. DUNGAN: It's a pleasure to be here.

MR. BOB BUSKER: In your newsletter issue, doctor, you reviewed some of the recent research into the problem of what to do when basal insulin in combination with oral agents fails to achieve adequate glycemic control. Now until fairly recently, the solution to that problem has usually been to add a prandial insulin. But as the investigations you reviewed pointed out, in many cases adding a GLP-1 receptor agonist to basal insulin instead can provide similar control and add some important additional benefits as well.

Today I'd like to look at how that information can translate into use in clinical practice. So start things out, if you would please doctor, with a patient scenario.

DR. DUNGAN: This is a 45 year old female with a 14 year history of type 2 diabetes who presents for a routine follow-up visit. She currently takes glargine 45 units daily, glipizide 10 mg twice daily, and linagliptin daily. She tries to limit her calories and follow a carb-controlled diet, but often works an irregular schedule and often 12 hours days, so she finds herself eating out and overeating.

Her HbA1c is 8.2%. At her last visit six months ago the HbA1c was 8.4%. Her weight is 74 kg with a body mass index of 34, and she is trying to avoid additional agents because she feels she just needs to be more disciplined with her diet and exercise.

MR. BOB BUSKER: So she's on insulin, a sulfonylurea, and a DPP-4 — and her A1c is still too high. But she's opposed to adding another medication. First question: Do you think diet and exercise will be enough to get her sugars under control?

DR. DUNGAN: Diet and exercise remain important cornerstones of therapy; however, particularly without a substantial commitment to changes in lifestyle, it's unlikely she will get her HbA1c to goal. Clinicians should recognize both patient and provider causes of clinical inertia. In this case she may have additional reasons for not wanting to intensify her therapy. Additionally, treatment adherence should be addressed: is she actually taking the medications she is prescribed? And finally, if we wanted to avoid additional therapies, we could explore whether it might be reasonable to increase her dose of glargine to get her fasting glucose to target, if that has not been done already.

MR. BOB BUSKER: So what would you consider the most appropriate next step?

DR. DUNGAN: Treatment guidelines often recommend adding a GLP1 receptor agonist or prandial insulin as next possible options. Prandial insulin may be considered. The easiest way might be to start with her largest meal of the day and titrate that dose up to meet her postmeal glucose target.

Alternatively, a GLP1 receptor agonist may also be used in combination with one or more oral agents before adding insulin. In this case, the GLP1 receptor agonist would be added after the basal insulin. GLP1 receptor agonists have shown improvement in HbA1c that is similar to or better than that of basal insulin, while at the same time minimizing the weight gain and hypoglycemia that are often observed with insulin.

MR. BOB BUSKER: What issues should clinicians be aware of when considering adding a GLP-1 receptor agonist in a patient on insulin?

DR. DUNGAN: First, we would want to be mindful of the increased risk of hypoglycemia whenever any GLP1 receptor agonist is added to other agents that cause hypoglycemia. For example, the sulfonylurea should be discontinued, or at least the dose should be reduced by half. Any concomitant DPP4 inhibitor, such as the linagliptin in this case, should be discontinued because the two drugs don't add any incremental benefit when used together. Then, if the A1c is less than 8.0%, we should generally reduce the dose of glargine by about 10% to 20%. This was done in most clinical trials and worked fairly well in preventing additional hypoglycemia. Unfortunately, most patients will not be able to discontinue their insulin therapy entirely, but if they can implement the necessary dietary and lifestyle changes, they could minimize additional need for titration.

MR. BOB BUSKER: And how should the GLP-1 receptor agonist therapy be initiated?

DR. DUNGAN: In general, when starting a GLP1 receptor agonist, it's best to start at the lowest dose and titrate up slowly, based on how the tolerability profile turns out. Since the patient is already on insulin, a self-titration schedule should be provided for her so that she can adjust the dose of insulin to achieve her fasting glucose targets.

MR. BUSKER: A GLP-1 receptor agonist – should that be combined only with basal insulin? Can it be combined with prandial insulin, or even as an add-on to a full basal/bolus regimen? What does the evidence say?

DR. DUNGAN: The available clinical trials data support the use of a GLP1 receptor agonist with basal insulin. One clinical trial demonstrates the effectiveness of using a continuous-acting GLP1 receptor agonist with prandial insulin without basal insulin. However, using GLP1 receptor agonists with both basal and prandial insulin has not been adequately studied, at least in prospective clinical trials.

If one were to combine prandial insulin with a GLP1 receptor agonist, one should reduce the dose of prandial insulin substantially. In the clinical trial that was published, the dose was reduced in half.

MR. BUSKER: Now the terms continuous acting and intermittent acting GLP1 receptor agonists: define those briefly for us, if you would, please.

DR. DUNGAN: A continuous-acting GLP1 receptor agonist continuously activates the GLP1 receptor, whereas an intermittent-acting agent only intermittently activates the receptor. Examples of a continuously activating agent are liraglutide, dulaglutide, exenatide once weekly, and albiglutide once weekly; whereas the intermittent acting agents currently available are exenatide twice daily in the US and Europe, and lixisenatide which is available in Europe.

MR. BUSKER: So in this patient, maintaining her insulin, discontinuing both her sulfonylurea and her DPP-4, and adding a GLP1 receptor agonist — what kind of A1c reduction might she expect to see?

DR. DUNGAN: In this patient who is on basal insulin and also has a baseline A1c of 8.2%, the addition of a GLP1 receptor agonist is expected to result in a small, approximately 0.5% reduction in HbA1c. A larger reduction in A1c has been observed with patients who have a higher A1c and also as second line therapy, for example, after failure of a single oral agent. In these cases, one can observe up to a 2% A1c reduction, or even more.

MR. BUSKER: Thank you for that case and discussion, doctor. And we'll return, with Dr. Kathleen Dungan from The Ohio State University, in just a moment.

SUSAN PORTER: Hello. I'm Susan Porter, clinical nurse practitioner and certified diabetes educator at the Johns Hopkins University School of Medicine. I'm one of the program directors of *e*Diabetes Review.

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For more information or to subscribe to receive our newsletters and podcasts without charge, please visit www.ediabetesreview.org. Thank you.

MR. BUSKER: Welcome back to this eDiabetes Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Kathleen Dungan, associate professor in the Division of Endocrinology, Diabetes and Metabolism at the Ohio State University. And our topic is: Combining Insulin with GLP-1 Receptor Agonists.

We've been discussing how some of the new information Dr. Dungan reviewed in her newsletter issue can be applied in clinical practice. So let's continue, if you would, please, doctor, with another patient scenario.

DR. DUNGAN: This is a 62 year old female with a 20 year history of type 2 diabetes who presents for a follow-up visit. She currently takes detemir 55 units each night and metformin 1 gm twice daily. The A1c is 8.6%. The patient had a trial of a GLP1 receptor agonist eight years ago, but she believes she stopped it because of nausea. She is also concerned about long-term safety.

MR. BUSKER: She's on insulin and metformin, with an A1c of 8.6%, and she's concerned about the safety of trying a GLP-1 receptor agonist again. What do clinicians need to know to realistically set patient expectations? Let's start with GI side effects.

DR. DUNGAN: The GI side effects are common in the first eight weeks of therapy. These might include nausea, vomiting, and diarrhea; however, these GI side effects go away in most patients within one to two months. Therefore, we should advise her to avoid skipping meals, and use a lower dose of the GLP1 agonist, if available, and we should also note that some preparations may cause less nausea than others. For example, exenatide once weekly causes less nausea than twice daily dosing; and albiglutide, for example, has also shown less nausea than some other agents.

MR. BUSKER: What about the potential for hypoglycemia when combining a GLP-1 receptor agonist with insulin?

DR. DUNGAN: GLP1 receptor agonists stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner. Therefore, the inherent potential for hypoglycemia is fairly low. GLP1 receptor agonists, however, may cause hypoglycemia when combined with agents that otherwise cause hypoglycemia such as insulin. GLP1 receptor agonists also allow for better A1c reduction without increasing the risk of hypoglycemia. Hypoglycemia risk in general is less than that of adding a prandial insulin, however.

MR. BUSKER: She's also concerned, as you said, about long-term safety. Again, what do clinicians need to know to effectively address this issue with their patients?

DR. DUNGAN: Long-term safety is always a hot issue, and it is currently under investigation with almost all of the GLP1 receptor agonists in long-term follow-up studies. Of particular interest is pancreatitis, which appears to be very low in incidence, but nonetheless is probably associated with all of these agents. Medullary thyroid cancer is a concern in the preclinical studies, in which rats developed medullary thyroid tumors; however, in humans no clinical signal has yet arisen. It does remain a contraindication for patients with a history of medullary thyroid cancer.

In addition, there is a 2 to 4 beat per minute increase in heart rate with all of these agents. This is more prolonged with a continuous-acting agent compared to the intermittent-acting agents. Finally, injection site reactions may be observed with some of the once weekly formulations.

MR. BUSKER: Besides that slight increase in heart rate you mentioned, what else should clinicians tell their patients about cardiovascular safety?

DR. DUNGAN: There are small reductions in blood pressure and cholesterol, which can be beneficial for many patients. Long-term cardiovascular outcomes studies are underway. The first of these, ELIXA, using lixisenatide, was recently announced and showed no increase in risk of cardiovascular events. Unlike some of the DPP4 inhibitors, there is no signal for heart failure in the ELIXA study or in other shorter-term studies of GLP-1 receptor agonists thus far.

MR. BUSKER: Thank you for that case and discussion, doctor. Now if you would, please – bring us one more patient scenario.

DR. DUNGAN: A 56 year old male with a six-year history of type 2 diabetes is seen in follow-up. He currently takes NPH 10 units in the morning and 5 units at supper, and metformin 1 gm twice daily. The patient is checking his glucose four times daily. A glucose log shows morning readings in the 70s to 110s, and postprandial glucoses frequently between 180 and 200 mg/dL. The A1c is 7%. He reports hypoglycemia in the 50s to 60s three days per week, both overnight and daytime. The patient has gained six pounds over the last six months, despite brisk walking for 30 minutes five times per week. He has also been to a dietitian and is following a reduced calorie diet. He is interested in GLP1 receptor agonists that he saw on television.

MR. BUSKER: His current regimen has got him under control, he's around 7%, so the focus here is really how to maintain that control while reducing his hypoglycemic episodes, minimizing his weight gain, and reducing his postprandial glucose spikes. Let's start with weight: what effects might the addition of a GLP1 receptor agonist provide?

DR. DUNGAN: The weight loss is variable, but on the order of 2 to 3 kg in combination with metformin therapy. Less weight loss can be expected with concomitant insulin, sulfonylurea, or a thiazolidinedione. Weight gain may be observed with greater insulin titration, though this is considerably lower than that which would be observed without a GLP1 receptor agonist.

Slight differences are observed in clinical trials among some of the GLP1 receptor agonists for reasons that are unclear; however, weight loss does occur even in the absence of nausea with all of the drugs when used with therapies that allow for weight reduction.

MR. BUSKER: Those "slight differences" between the GLP-1 receptor agonist agents you just mentioned — how might they impact determining which agent should be added?

DR. DUNGAN: Certainly formulary limitations guide which therapy is used for any individual patient. There are considerations for using intermittent agents such as exenatide twice daily and lixisenatide which is available in Europe. These agents intermittently activate the GLP1 receptor, while continuous agents, all other available agents, activate the receptor continuously. It is theorized that continuous receptor activation attenuates gastric emptying over time. This may explain why intermittent agents have greater effect on postprandial glucose. However, this effect is only observed at meals immediately following the dose, and it does not translate into greater A1c reduction due to the less pronounced effects that these agents will in turn have on fasting glucose.

MR. BUSKER: So specific considerations for agent selection?

DR. DUNGAN: Consider exenatide twice daily if isolated postprandial hyperglycemia exists; otherwise, consider using continuous-acting agents, which will have more pronounced effects on fasting glucose. Consider once-weekly agents for patients who have lifestyle considerations that prohibit the use of injections every day. You can consider the need for reconstitution, however, with some of these once-weekly agents, including exenatide once weekly, and albiglutide. Most patients, however, can learn to effectively administer these drugs with minimal instructions.

Finally, tolerability profiles differ slightly between these agents, as mentioned previously, with the differential effects of these agents on nausea.

MR. BUSKER: One of the key challenges in the patient you presented was reducing his postprandial glucose spikes. What are the effects of GLP1 receptor agonists on postprandial glucose?

DR. DUNGAN: All GLP1 receptor agonists substantially reduce postprandial glucose. The intermittent-acting GLP1 receptor agonists actually produce somewhat more postprandial glucose lowering than the continuous-acting agents, again because of their effect on gastric emptying. But the postprandial glucose advantage occurs only with meals immediately following the dose. Continuous-acting GLP1 receptor agonists cause greater reduction in fasting glucose; therefore, the relevance of the effect of postprandial glucose may be limited in this setting. In addition, the relevance may be limited in the setting of concomitant basal insulin or prandial insulin.

MR. BUSKER: So with the patient you described for us — he's currently controlled with NPH 10 units in the morning and 5 units at supper, plus metformin 1 gm twice daily. If you add a GLP-1 receptor agonist, how would you change his regimen?

DR. DUNGAN: In this patient, since he has pretty tightly controlled fasting glucose, I would reduce the NPH dose by about 50% before starting a GLP1 receptor agonist. I would provide a reverse dose titration schedule for possible eventual discontinuation, since these are fairly low doses. If that's unsuccessful, I would consider switching this patient to a once daily, long acting basal insulin analog just to simplify his regimen. A sulfonylurea, if present, could be reduced.

MR. BUSKER: Thank you for today's cases and discussion, doctor. Let me ask you to look to the future for us now, if you would please: What do you see happening with combining GLP-1 receptor agonists with insulin?

DR. DUNGAN: I think the future holds a lot of interest in reducing the complexity of medication regimens; for example, fixed dose combination regimens of GLP1 receptor agonists and basal insulin are currently under development. In addition, studies are underway comparing these agents with SGLT2 inhibitors, which is another emerging class of diabetes therapy. So both head to head comparisons as well as combination regimens are underway. And finally, investigations into other routes of administration of GLP1 receptor agonists, including the oral route, are currently underway.

MR. BUSKER: Thank you for sharing your thoughts, Dr. Dungan. I'd like to wrap things up now by reviewing what we discussed today in light of our learning objectives. So to begin: the glucose lowering effects of GLP-1 receptor agonists when added to basal insulin.

DR. DUNGAN: GLP1 receptor agonists may be useful for reducing clinical inertia because they allow reduction of HbA1c without the added baggage of hypoglycemia or weight gain that's often associated with insulin therapy alone. GLP1 receptor agonists reduce A1c even when used in combination with insulin while at the same time reducing the risk of hypoglycemia and weight gain.

MR. BUSKER: And our second learning objective: safety concerns with the use of insulin/GLP-1 receptor agonist combinations.

DR. DUNGAN: GI side effects are common early after treatment initiation, but generally they subside over time. It's important to keep patients on these agents if these side effects are tolerable. These agents have little inherent hypoglycemia risk; however, when combined with insulin, insulin dose reduction may be needed. Finally, long-term cardiovascular and other safety outcomes are ongoing, but initial results are reassuring.

MR. BUSKER: And finally: the physiologic differences in lowering postprandial glucose between the continuous- and the intermittent-acting GLP1 receptor agonists.

DR. DUNGAN: Intermittent agents are those that are only intermittently activating the GLP1 receptor. These include exenatide twice daily and lixisenatide once daily. Continuous-acting agents include liraglutide, albiglutide, and dulaglutide and continuously activate the GLP1 receptor. Continuous agents may cause less nausea and result in better fasting glucose, in addition to possible HbA1c reduction; however, they provide slightly less postprandial glucose lowering because the continuous activation of the GLP1 receptor may slow any effect on gastric emptying.

Intermittent agents may provide targeted postprandial glucose control in those who need it. Finally, agents differ by frequency of administration and administration complexity.

MR. BUSKER: Dr. Kathleen Dungan from the Ohio State University, thank you for participating in this *e*Diabetes Review Podcast.

DR. DUNGAN: Thank you for inviting me to review this important topic.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ediabetesreview.org/test.

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