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EASD: POTENTIAL BENEFITS OF INCRETINS BEYOND GLYCEMIC CONTROL IN T2D

This podcast activity will discuss the practical application of data and frequently asked questions from the independent satellite symposium, Potential Benefits of Incretins Beyond Glycemic Control in T2D, presented at EASD on September 19, 2022.

Moderator:
Hi, Dr. Frias, Dr. Del Prato, we are so grateful to have you both here with us today. Especially in light of all this publicity that we've seen in first in class tool agonist, tirzepatide, it's been getting so much publicity. It was approved by the FDA right before ADA and then the EU right before EASD. So, there's really a lot of buzz around this drug. Dr. Frias, can you help us to understand what's meant by dual agonism and why it seems to be making such a difference in the lives of patients with type two diabetes?

Dr. Juan Pablo Frias, MD:
Yeah, absolutely. So nice to be here. Thank you. And we've had so-called selective GLP-1 receptor agonist from 2005. So, these are medications that bind to and agonise the GLP-1 receptor. And these are very powerful medications. But still, we've learned from data, that there are patients that need additional control, whether it be glycemic or weight loss control. And we've moved now to an era of so called multi-agonism. So, these are single molecules that bind to and agonise multiple receptors. And with respect to tirzepatide, it is a GIP and a GLP-1 receptor agonist, so it binds to and activates both incretin hormone receptors. And it is importantly a single peptide. So it's a single peptide that's actually based on the peptide sequence of GIP. And it's been modified to be able to bind to inactivate both receptors. And by doing so although this isn't an area very active investigation, the mechanism of action by doing so what we've seen in clinical trials, is increased insulin secretion, so first and second phase insulin secretion, reduced glucagon secretion, improved insulin sensitivity, and greater reduction in body weight to perhaps a greater reduction in appetite. And the thought is that this is due to again, the binding and the activation of both of the incretin receptors, both GIP and GLP-1.

Moderator:
That's a great explanation. And so, do you think it's the dual agonism that is making such a difference?

Dr. Frias:
You know, possibly again, as I mentioned, this is an area of a lot of active investigation exactly why there's appetite is more efficacious when it's been compared in head-to-head trials versus selective GLP-1 receptor agonist in the phase two study the main phase two study, we compared to his appetite of various doses to Dulaglutide at 1.5 milligrams and found it to be more efficacious. And in phase three in a study called Surpass-2, it was a head-to-head study looking at tirzepatide, 5, 10 and 15 milligrams versus semaglutide, which is the most potent of the selective GLP-1 receptor agonist at one milligram once weekly and found that the three doses were more efficacious than semaglutide for both lowering glycemic parameters and also lowering body weight. So, we know that it does work more efficaciously we're not exactly sure why, but it is more than likely the fact that it is binding to and activating both of these receptors which coexist in many tissues. And actually, there's some tissues only have GIP such as adipose tissue and some tissues that only have GLP-1 receptors, such as gastric tissue.

Moderator:
That's great. And Dr. Del Prato, how do you see tirzepatide fitting into the treatment regimen in patients with T2D in the EU?

Dr. Stefano Del Prato, MD:
You know, let me remind you that you know, the ADA and EASD has been producing since 2006. A consensus for the management of T2D and the last version has been released at the time of the 58th Annual Meeting of the

European Association for the Study of Diabetes. This has been a recommendation that has been followed the worldwide and what has been recommended in the latest version is that we need to have a more holistic approach of people with type two diabetes a more comprehensive approach for very simple reason. T2D, yes, these are altered by hyperglycemia, but T2D is a syndromic in nature. In other words, together with a permitting glucose control, there is also cardiovascular risk factor. And very often people with T2D are overweight, if not frankly obese. Now, you can look at this and the reason why I'm making this this premise is because you can look at that, you know, I realize to which extent that tirzepatide may satisfy some of the needs that have been highlighted by the consensus, which is control of glucose, reduction or control bodyweight, control on cardiovascular risk factor. And potentially because this is the fourth element of the consensus to identify organ damage in people who already had some problem with your cardiovascular system or kidney system. And it's interesting to see how the tirzepatide can really satisfy each one of these four elements here, in terms of glycemic control. Dr. Frias just mentioned, you know, as even as compared to existing GLP-1 receptor agonist is it tirzepatide but it has been proven to provide as a clinically meaningful impact into glycemic control just to give you an idea. More than close to 90% If I present to the people achieving an A1C over the one or max, there's been so far explored two years of an A1C lower than 7%. But what is even more astonishing, and it was my eye is because it is unprecedented is up to 30-35% of the people reach an A1C level lower than 5.7%, which is the upper limit for the normal range of A1C in other words, for the first time, we have something that has been at least initially suggested and proved that we can normalize glucose control. So, with respect to glycemic control, there is great opportunity here. Now, bodyweight control, tirzepatide is very much effective, you can reduce you know by more than 10 kilos as compared to placebo, but even when you compare the efficacy of tirzepatide versus semaglutide, you can see gained 6-7 kilos of body weight reduction with more than 35% of the people achieving a weight reduction greater than 15% and 90% of the people treated with tirzepatide within the SURPASS program, which is the clinical development program, achieving at least a 5% reduction in the body weight. So here is another you know, point that you know can be met. and then is cardiovascular risk factors are different in nature. It is high blood pressure dyslipidemia, but it's not only that, it's impaired kidney function, low GFR and albuminuria are independent cardio as a cardiovascular risk factors. And nowadays, we have also realized that there is another condition that can really impact into the cardiovascular risk factor that people with T2D, which is the fat in the liver, Nash, NAFLD and Nash. Now, there are data and the data available suggests that tirzepatide is associated with a long term improvement up to two years of the lipid profile with reduction in triglycerides, LDL cholesterol, and non HDL cholesterol, which is even better marker of atherogenic lipoproteins in the circulation, it can reduce by four or five millimeters of mercury systolic and lower extent diastolic blood pressure, it can reduce it at least in a secondary predefined analysis of one of the trials exploring the efficacy and safety of tirzepatide, reducing the progression of impairment in the Negroamaro filtration and reducing albuminuria, which are, as I said before, to independent cardiovascular risk factors. And there are data also suggesting that may reduce the amount of fat in the liver in other words, reducing NAFLD and in a Nash. So, all together, this will bring to the potential for protection of the organ damage. And there are some initial hints although there are specific studies that are going to look at the cardiovascular protection that we can obtain using tirzepatide in people with T2D. And naturally, that is going to be a very important study because this is going to be the first study where one drug is compared to another drug that has been already proven to provide cardiovascular benefit. In the SURPASS CV tirzepatide will be indeed compared to dulaglutide. So, this is really an incredible learning curve. We have a great opportunity. We need to dig into this opportunity. But I think that we need to learn really how to take as much as possible advantage of this opportunity.

Moderator:
I agree. You mentioned obesity, how is it treated in the US maybe differently or the same as it is in the EU? I know that one of our things I wanted to talk with you about was about the label. But if we could just dig into the obesity component for a minute, Dr. Frias, could you compare how obesity is treated in the United States compared to maybe the EU? Or elaborate a little bit on how obesity and diabetes is treated in the US?

Dr. Frias:
Yeah, what I could tell you about obesity is Dr. Del Prato mentioned most of our patients with T2D are overweight or obese. And over the past several years, we've certainly shifted somewhat. And this is based on availability of anti-diabetic agents that actually cause weight loss into more of a treatment philosophy, if you will, that we need to address the root cause of many of the issues that lead to hyperglycemia and other complications of obesity. So, treating obesity, and overweight is critical in the management of patients with type two diabetes. So that's the first thing I would say. And now we have agents that are available that not only improved glucose, but also improved body weight. So, I think we're seeing more and more of these incretin based therapies being used to treat you know, whether it be obesity and overweight without diabetes, perhaps with pre diabetes, or and also in patients with T2D. And as you know, we have selective GLP-1 receptor agonist, both liraglutide three milligrams once daily, semaglutide 2.4 milligrams once weekly for the treatment, specifically of obesity with or without T2D. And that tirzepatide is currently in a clinical development program called a SURMOUNT program, one study which has been completed SURMOUNT-1 which was published in June of this year and presented at the ADA. And then other studies that are currently ongoing, including SURMOUNT-2, which is a study looking at patients who are overweight or obese with T2D. So, I think, in general, I don't know the differences in the US and Europe I imagine they're more similarities than differences with respect to the management. I would say, though, in the US, if you look at the data of all the patients who are eligible for pharmacotherapy for overweight or obesity, only 2% actually receive pharmacotherapy. And that's because up until now, we really have not had the tools to manage patients safely with pharmacotherapy and get the types of results we're getting with GLP-1 receptor agonist and now what we're seeing in clinical trials with the dual GIP and GLP-1 receptor agonist turns up at time.

Dr. Del Prato:
I agree with my friend Dr. Frias. As you know, the main difference I can see in terms of obesity between US and Europe is the prevalence of diabetes, I believe. I mean, we are a little bit lagging your back. But, you know, but is growing up in in Europe. But I think that you are facing an even hotter if I could use has the word problem in in US. But I think that we are on the same ground in terms of the tools we may have in our hands to try to tackle the problem. And the problem is really that we haven't had in the past any significant pharmaceutical intervention that really was able to provide as a long standing and sustained effect in terms of weight reduction. So, we had as we mentioned, in our GIP specific GLP-1 receptor agonist, liraglutide semaglutide high dose, by the way, in our system, you know, Europe is more universal in terms of the coverage and reimbursement but, for instance, in my country, the GLP-1 receptor agonist are fully reimbursed for people with T2D, but not for people with obesity. So, the people with obesity can take advantage of this treatment, but they have to pay out of pocket. So whether you know, having a more effective treatment as leaves tirzepatide seems to promote up to promise. And the result of the SURMOUNT trials has been very, very exciting, is a problem that we're going to discuss and see in the near future. So, I do see a difference in the prevalence of obesity. I do see that we face the same problem in treatment with diabetes. And I think that on both sides of the pond, we are looking at tirzepatide as a new opportunity.

Moderator:
The last couple of minutes that we have… Dr. Frias. Do you want to kind of take us on a journey through the tirzepatide? PI the label, what really stands out to you?

Dr. Frias:
Yes, in the US present baton was approved by the FDA in May of this year of 2022. And shortly thereafter became commercially available. So, it's indicated for adults with T2D for the management as an adjunct to diet and exercise I should say for the management of hyperglycemia. And importantly, it comes in six doses in the US. And each of these doses are in a single use once weekly pen with a with a hidden needle. And the doses are 2.55 milligrams, 7.5, 10, 12.5 and 15 milligrams. And I think what stands out, I guess is a safety and tolerability profile. I think this is very

important, which is quite comparable to that with the GLP-1 receptor agonist with GI side effects being most common but generally manageable in the clinic, but it's something we need to discuss with our patient. Also, for patients who were initiating tirzepatide, who are on either insulin secreted gogs and or insulin, it can augment the risk of hypoglycemia with these agents. So, we should consider proactively reducing the doses of these agents, certainly in my patients, and the recommendation is to patients on Metformin or an SGLT-2 inhibitor, those should generally be continued and stopping DPP-4 inhibitors when tirzepatide is initiated. And again, the initiation dose is 2.5 milligrams. After four weeks, once weekly injections at 2.5, we increase to the five-milligram dose. And then based on the patient's response, and their individualized targets for glycemia, and body weight, it can be increased in 2.5 milligram increments, but no more quickly than every four weeks. So, I have patients who are might be on 7.5. And each of those other doses apart from the 2.5 in the US, anyway, is considered a maintenance dose. So 5, 7.5, 10, 12.5, and the maximal dose is 15 milligrams. And in my personal opinion, I think it's nice to have this wide spectrum of doses, because not everyone needs to lose that much weight, not everyone needs the higher doses to achieve their glycemic targets. So, we need to just be monitoring our patients as we do with any new therapy, making sure that we have their target set. And if they reach the target, we stopped dose escalating on those patients. So those are sort of the keys with respect to the to the US label.

Moderator:
That's fantastic. And thanks for all those practical tips. Dr. Del Prato, what do you think about the EU label? How is it similar? How is it different? And maybe some practical tips that you see?

Dr. Del Prato:
Yeah, the label from EMA is a pretty broad one, because, you know, is a typical indication suggesting the use of monotherapy for tirzepatide if people are not at all and until Metformin. But after that, you know, tirzepatide can be added on top of every existing treatments, of course, I much agree with Dr. Frias that if you have a DPP-4 doesn't make much sense in order to use the components of a GLP-1 stimulation and the concomitant use of the v4, there's never been a study showing that the GLP-1 stimulation, together with inhibition of DPP-4 can provide any further advantage. So, I totally agree with that. And also, I've had the opportunity to coordinate one of the studies with tirzepatide is SURPASS-4 that was very instructive in terms of the management of hypoglycemia, because for the first time, we saw an increase as compared to the previous trial in the rate of hypoglycemia. But that was not because of tirzepatide, was because the trial included people who already were on drugs, that per se can increase the risk of hypoglycemia so often in rural areas in particular, and you want to do really dissect out to those people with sulfonylurea versus those without sulfonylureas. Hypoglycemia happens in those people who are already on on sort of an inroad, which is, I think a very direct practical hints, you know, if you have someone on sulfonylurea, and you do introduce a very powerful lowering glucose lowering agent, you have to be a bit more cautious in terms of the risk of hypoglycemia, maybe you want to cut down the dose if not withdraw at all the sulfonylureas. So, and I have to say that my suggestion is more based on what they've been read because in Europe, you know, tirzepatide is not yet available, and that Dr. Frias really has a much more experience with the use of the drug. But we're looking at with very close eye at what our fellow friends in in the States are elaborating, are experiencing to get ready to start treating patient properly with the tirzepatide in Europe as well.

Moderator:
Well, thank you so much. I have thoroughly enjoyed this conversation. I appreciate all the insights that you shared with us, and I look forward to working with you both in the future. Thank you.