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A Fight Against Obesity: Evaluating Clinical Data from the SURMOUNT-1 Trial

Dr. Buse:
A new trial was the hit of the American Diabetes Association scientific sessions this summer and a lead article in the New England Journal of Medicine and is changing the treatment space for obesity. What do we need to know about the results of this trial?

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And with us today to share highlights from the SURMOUNT-1 trial is Dr. Ania Jastreboff, who is an Associate Professor of Medicine and, among other things, the codirector of Weight Management & Obesity Prevention Program at Yale School of Medicine.

Ania, thanks for being here today.

Dr. Jastreboff:
Thanks so much for having me, John. It's really my pleasure.

Dr. Buse:
Well, to start us off, can you tell us a bit about the molecule tirzepatide? What do we know about it's relevance to the trial that you reported?

Dr. Jastreboff:
Tirzepatide is a novel once-weekly GIP/GLP-1 receptor agonist. It's actually one molecule, and that molecule has affinity for both the GIP as well as the GLP-1 receptor.

Dr. Buse:
Very good. So it has potentially dual actions. I understand we don't know exactly how it works, but it seems to work really well. Can you review the key design elements of the SURMOUNT-1 trial, you know, inclusion/exclusion criteria, what the randomized arms were, the endpoints, what's important about the design?

Dr. Jastreboff:
Sure. Absolutely. So the SURMOUNT-1 study, is a phase III clinical trial. It was designed to assess the efficacy and safety of tirzepatide. In terms of the, the details of the trial design, there were 4 arms, so there were 2,539 participants randomized to four arms. There was a placebo arm and then three doses of tirzepatide, tirzepatide 5 mg, 10 mg and 15 mg, and the trial duration was 72 weeks. In terms of the coprimary endpoints, they were to assess the percent change in body weight from baseline and the percent of participants achieving body weight reductions of at least 5 percent as compared to placebo.

So, main inclusion was adults, who had a BMI of greater than or equal to 30 or greater than or equal to 27 with at least one weight-related disease but not diabetes. And in the trial, as I mentioned, there were 2,539 participants. Their average age was about 45 years old. 67 percent were female, and the average BMI was about 38.

Dr. Buse:
Great. And can you tell us the main results?

Dr. Jastreboff:
Absolutely. So, to summarize the efficacy results, all three doses of tirzepatide demonstrated substantial, clinically meaningful and sustained body weight reduction compared to placebo. In terms of looking at the weight reduction with tirzepatide specifically in trial—so this is the more conservative treatment regimen estimate—with the 5 mg dose, the weight reduction with tirzepatide was 15 percent;

with 10 mg it was 19.5 percent; and with 15 mg, it was 20.9 percent. Additionally, in terms of the endpoint of weight reduction of at least greater than or equal to 5 percent, on the 15 mg dose, 91 percent of participants achieved this target, so 9 out of 10 people in the trial successfully lost weight. And this weight reduction was sustained over the 72 weeks. Additionally, the higher weight reduction targets that were examined—so, for example, we look at 5 percent, but we also want to look at higher weight reduction targets, such as 20 percent percent, which is a lofty weight reduction target, and over half of the participants achieved greater than or equal to 20 percent weight reduction target, and over a third achieved greater than or equal to 25 percent weight reduction target, so that means that more than a third of individuals in this trial lost a quarter of their body weight.

Dr. Buse:
Yeah. That's really amazing. You know, I remember trials in the past where, you know, we struggled to see substantial numbers of people losing 5 percent weight. This is really extraordinary.

Dr. Jastreboff:
Yeah. I mean, so I absolutely agree with you, John. This is results that we have not seen before. And, you know, I'll mention that target of greater than or equal to 25 percent, that was a prespecified but exploratory target, so the idea that, you know, we did not know that this medication or these types of medications would be able to achieve such weight reduction. Additionally, I'll point out that the 5 mg dose, the weight reduction, you know, again on average was 15 percent, and that was also not expected, so, so really remarkable results.

Dr. Buse:
Yeah. Those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Ania Jastreboff about the SURMOUNT-1 trial, which looked at tirzepatide for the treatment of obesity.

Ania, another question. Let's talk about side effects. What was observed in the patients receiving tirzepatide?

Dr. Jastreboff:
So, in general, tirzepatide was tolerated very well. The main side effects, or adverse events that were noted were gastrointestinal, the most common one being nausea, followed by diarrhea and constipation. It's important to know that most of these gastrointestinal side effects were experienced during dose escalation, so the medication is titrated up slowly, in order to mitigate those side effects. So the majority of side effects was, transient during the dose escalation phase, and mild to moderate in nature, so overall very well tolerated.

Dr. Buse:
Great. So, taking a step back, what's the status of tirzepatide in the United States? I know it's approved for diabetes management, but is it available yet for obesity management?

Dr. Jastreboff:
So you're absolutely right, John. Right now, tirzepatide was FDA-approved in May 2022 specifically for the indication for type 2 diabetes, and it became commercially available in June 2022. It is not yet FDA-approved for, specifically for obesity or for chronic weight management alone, So, providers are prescribing it for patients who have type 2 diabetes, and if they were to prescribe tirzepatide for individuals who don't have type 2 diabetes, but do have obesity, that would be off label.

Dr. Buse:
Ania, I believe it's really important how we counsel patients as we're starting these drugs to achieve optimal effects. Can you go through how you talk to patients about this opportunity?

Dr. Jastreboff:
Absolutely. And that is such a great question. I do think that as we start these medications, it's really important to speak to our patients about the potential side effects and how to mitigate those side effects up front. So there are several things. One is that if—Say that a patient is experiencing nausea or some sort of GI side effect, maybe diarrhea. There's no requirement to dose-escalate, meaning that we can up titrate that medication more slowly, and so it's important to communicate with your patients and say, you know, "Let me know how you're doing with this medication and we'll figure out how quickly or how slowly to go up on the dose."

The next thing is to advise your patients that if they're responding to this medication or any medication in this specific class of nutrient-stimulated hormone medications is to say, "If you're responding to this medication, you will likely feel full earlier, and so, if you eat a regular amount of food or the amount of food that you're used to eating, you may actually feel more nauseated or have diarrhea or have some of these negative GI side effects, so, from the get-go, try and put less on your plate and see how you feel. Give your body a little bit of time and think to yourself, 'Am I full right now, or do I want seconds?'" And a lot of the times what happens is that patients will not go back for seconds.

And so, what we basically advise is, try not to eat past the point of fullness because that's when you're going to feel the most sick if you do have nausea, um, and also, pay attention to what foods may exacerbate those GI side effects. So, for example, if you notice that fatty foods induce some diarrhea, especially on day 1 to 3 of that medication—so, again, the medication is dosed weekly—so, on days 1 to 3 the patient may experience more side effects, so pay attention to see are those fatty foods exacerbating any of those GI side effects and potentially eat less of those foods on those particular days, so not eating past the point of fullness, eating smaller amounts but potentially more frequently, and then paying attention to what types of foods may exacerbate side effects if you do have them.

Dr. Buse:
Wonderful. So we're almost out of time, Ania, but before we close, do you have any key takeaways you'd like to leave with our audience?

Dr. Jastreboff:
Sure. So a couple of things. I think one of the most important things about this study is it really gives us a platform to talk about obesity as a chronic, treatable disease because that is what it is, and we should treat obesity as we treat any chronic disease with these types of effective and safe approaches which target underlying disease mechanisms. And these results really underscore this, and tirzepatide may be doing just that. It may be targeting these underlying disease mechanisms. I think these results are impressive and a very important step forward in potentially expanding effective therapeutic options for people with obesity.

Dr. Buse:
Wonderful. That's really a great note to end on as we come to a close of today's program. I'd like to thank my guest, Dr. Ania Jastreboff, for sharing insights on tirzepatide for the treatment of obesity. Ania, thanks for the great discussion today.

Dr. Jastreboff:
Thank you so much for having me, John.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this ep—To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse where you can be Part of the Knowledge. Thanks for listening.