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Investigating SGLT-2 Inhibitors in Diabetes: Considerations & Conversation

Dr. Buse:

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse and joining me to discuss SGLT-2 inhibitors is Dr. Anne Peters, a Professor of Clinical Medicine at the Keck School of Medicine at the University of Southern California and the Director of the USC Clinical Diabetes Programs. Anne, thanks for being here today.

Dr. Peters:

Thanks, John. It's wonderful to be with you.

Dr. Buse:

As you know, SGLT-2 inhibitors have an outstanding record, good glycemic efficacy, weight loss, blood pressure reduction. In studies of type 2 diabetes, they reduce heart attacks, stroke, and cardiovascular death in patients with high risk, in patients with type 2 diabetes, as well as those without diabetes. They've been shown to reduce heart failure hospitalization, progression of kidney disease, and mortality in patients with reduced ejection fraction or advanced albuminuria. In Europe, some SGLT-2 inhibitors are authorized for marketing in the setting of type 1 diabetes as well. But in the U.S., the FDA has not supported use of SGLT-2 inhibitors in type 1 diabetes. You and I were among the first to report DKA as complications of SGLT-2 inhibitors. Anne, where are you now with regards to the general issue of using SGLT-2 inhibitors in patients with type 1 diabetes?

Dr. Peters:

Well, because of the risk of DKA, I'm careful about using SGLT-2 inhibitors in people with type 1 diabetes, but I still use them. I only use them in a setting where patients have access to healthcare and know how to test for ketones. But I use them for two reasons. One is because patients really like what happens when they take an SGLT-2 inhibitor. They feel their diabetes is better controlled. They note a reduction in postprandial glucose levels. They just really want to be on SGLT-2 inhibitors. And I'm a very patient-driven physician and if my patients like it and I feel I can use it safely, then I like it. And then, as I believe we're going to discuss later, there are other indications other than glycemic impact of SGLT-2 inhibitors in terms of renal function and a heart failure that do push me to use these agents in certain patients with those characteristics.

Dr. Buse:

Well, how about more of the details with regards to how you select patients and what do you require of them before prescribing in SGLT-2 inhibitor in the setting of type 1 diabetes?

Dr. Peters:

I think that the most important criteria for my selection of patients is their willingness and ability to understand ketone testing. And I know that sounds odd, but a lot of people were taught about ketone testing when they were first diagnosed with type 1 diabetes, but sort of forgot about it or don't do it. I get so many calls from patients who are on an insulin pump in their pump clogs and their sugars go up and they don't have ketone test strips at home.

So I start patients by having them do ketone testing. And I have them, if I can, do fingerstick ketone testing and do it for a week or two before I'll even start them on an SGLT-2 inhibitor. And not only does that teach them about their ketone levels, it helps me make sure they're ketone levels aren't elevated at baseline. And then I know the person's working with me. And so once that happens, then I'm willing to start them on a low dose and I cut the pills often into quarters to just start the patient on an SGLT-2 inhibitor and then look at their ketones and see what happens. But I'm very careful. But if a patient is willing to work with me and understands about what I'm talking about, that really is a big step in the right direction.

The other things are that if somebody's A1c is really above 9, I know that that person needs to work with me in terms of optimizing their insulin regimen. So I don't want them to be already having one foot on the edge of going into ketoacidosis. So I actually pick patients that I think aren't so vulnerable that I can work with.

And I usually do it in patients whose body mass index is higher, not necessarily based on a certain guideline, but I look at patients, if they're lean, I think that there might be at more risk, maybe even for losing more weight than I want them to. So I tend to use it in patients who have a couple of pounds of weight they want to lose and again, who really want to work with me in terms of the monitoring.

Dr. Buse:

Great. So at our center, we tend to really encourage people to drink plenty of water and avoid low-carb diets just so they end up being on a fair amount of insulin to mitigate the risk of DKA. Are there any other exclusions that you think about?

Dr. Peters:

There's a lot of them in a way. Risk of DKA seems to be higher in women, particularly on insulin pumps. So I want to make sure that my patients know all about pump troubleshooting, that they're willing and able to give an injection of insulin if they need to. Obviously, the low-carb diets, but if a patient is suddenly changing their physical activity, like training for a marathon, then that may change their insulin requirements and physiologic stress, I may have to not take it then. I make sure that patients, if they become ill for another reason, hold the SGLT-2 inhibitor. I have them hold it for a couple of days before surgery. I have them hold it before they're going to fast for a colonoscopy. So I make sure that in real-time, looking at the patients, working with them to hold the SGLT-2 inhibitor if they're running into trouble. Alcoholism, significant drug abuse, those kind of things also make me not want to start it in a patient. And then access to healthcare, because I have patients that I take care of who are underserved, who don't have an easy way to connect with somebody if they get ketones and people need to have access. So that's also a barrier, I think, to using SGLT-2 inhibitors in patients with type 1 diabetes.

Dr. Buse:

Great. So lots of caveats and lots of patient education to make sure people are on board. Does your enthusiasm about using this class of drugs in the setting of type 1 diabetes change in patients who have heart failure or chronic kidney disease or heart disease?

Dr. Peters:

It changes hugely because even though we don't have lots of data of using these agents with patients with those characteristics with Type 1 diabetes, I see no reason to believe that it won't help them because it helps people without diabetes who have CKD and heart failure. Those, however, are more vulnerable patients. So I want to use in an SGLT-2 inhibitor in them.

But again, I start with all of my caveats and testing and do-no-harm focus. And then I start again a very low dose. But I do believe that those patients will get an additional benefit compared to somebody who doesn't have those characteristics. So those are individuals where I might be more likely to use these based on my supposition that they're going to make a difference in terms of renal function and/or cardiac function. But I'm very careful and I'm particularly careful because of issues with fluid balance, if someone has heart failure and they're already on a lot of medication to help them diurese and do all the other things we do with our heart failure patients.

But again, all of this is off label. And remember, when you're doing it, you really have to make sure the patient's aware of it and that you work carefully with the patient's other physicians. Most of my heart failure patients have a cardiologist that I work with. My patients with significant enough CKD will work with a nephrologist. So I use a team to help me work with those patients.

Dr. Buse:

That's outstanding.

For those of you just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse and I'm speaking with Dr. Anne Peters about SGLT-2 inhibitors, particularly in the setting of type 1 diabetes.

Let's continue talking about how you approach different types of patients. How about patients with prior ulceration or amputation? Those as complications have been reported with SGLT-2 inhibitors.

Dr. Peters:

Yes, they've been reported with SGLT-2 inhibitors, but primarily with canagliflozin. And again, it's all about assessing risk and benefit. So if I have a patient with prior foot ulceration who's doing well, they take care of their feet, they have good care, good follow-up, and they really understand the risks, I will use in an SGLT-2 inhibitor -- probably not canagliflozin but one of the others. But it's all about monitoring and it's making sure that the patients are able to assess good care and look at their feet, know what to do if they see any worsening. And I'm, you know, pretty careful with those patients in general because they're our highest risk patients because of the comorbidities they likely have in addition to the lower extremity foot ulceration and problems. So I'm careful. But again, if a patient has a

compelling need, such as heart failure and/or CKD, that would, in my mind, benefit from treatment with an SGLT-2 inhibitor, I will use the agent in those patients, but again, with caution and avoiding canagliflozin.

Dr. Buse:

I agree. So lastly, let's talk about the paper in *Diabetes Spectrum* that got us together for this discussion today. It's entitled "Comparison of Protocols to Reduce Diabetic Ketoacidosis in Patients with Type 1 Diabetes Prescribed Sodium Glucose Transporter-2 Inhibitor." The lead authors were from Close Concerns in San Francisco, but we both participated in it. And basically what they did was they have a compilation of protocols developed, one called STICH and the International Consensus Conference. We both participated in those. There's also STOP-DKA from Canada, your personal protocol, and then guidance from EMA and NICE in Europe. Tell me about what you see as the major learnings from that paper that our listeners could get.

Dr. Peters:

Well, I think that there are multiple key points. But first of all, I think the protocols agree more than they disagree. And the second thing is that none of the protocols have been tested in any kind of systematic way. So most of this is just guesses. Now in the actual clinical trials, looking at the SGLT-2 inhibitors in people with type 1 diabetes, each trial had a different way to look at monitoring of ketones and avoiding DKA. And in fact, in some of the trials like the Phase II trial with canagliflozin, and they were only sort of halfway through and they found out about the risk for DKA and then they changed the protocol. So we don't have any good evidence that these protocols work, but they're our best guesses.

The reason my protocol is there is in part because I've treated so many patients with SGLT-2 inhibitors and because I really wanted a systematic approach to how I did it that made me feel comfortable. I can tell you that even though I'm pretty darn sure of my protocol, it still doesn't work 100 percent. And one of the problems is that I've now had patients on SGLT-2 inhibitors for a number of years. I think that the longest duration of a patient on an SGLT-2 inhibitor with type 1 in my practice is five years. And if I do a whole bunch of teaching and do all the right things at the beginning, what happens is that over time it seems to me that knowledge decays. And so if I get to three years and somebody is sick and I want them to check ketones and oops, they forgot to get ketone test strips or what they have is expired, it's a problem.

So one of the most important things about any of these protocols is that if a patient's long-term on one of these agents, you need to continuously reinforce the rules. And so I think, and I forget to do this, but honestly, we need to reinforce annually. Do you have your glucagon? Do you have your ketone test strips? Do you know what to do if you get sick? Do you know that your glucose levels can be relatively normal? And if you can still go into ketoacidosis, make sure that if you're sick, check your ketones. If your ketones are positive, consume carbohydrates and give insulin. So I actually think one of the most important things about these protocols is the need to reinforce them over time.

But I also think that everybody needs to feel comfortable with the patients they're using these agents in and how they're following them. And I tend to follow my patients more closely, I think, than any of the protocols, because I do the preamble of the two weeks or so of just ketone testing, and I really work with patients to optimize their insulin management. So I'm pretty comfortable, but again, it's the reinforcing of the protocols that I think almost matters more than anything. But I would argue that everybody, if you're going to do this, should have something in writing, something on your website, whatever it is, however it is you communicate with patients, so that they have a protocol so that you have in mind what you're asking patients to do.

And then some of my patients just feel better checking their ketones every single morning. And that's fine with me. I mean, overkill is always fine, but I think that within this, people should find what makes them feel comfortable and then apply it to their patients. And again, I think some patients tend to be at higher risk, at least from the clinical trials of DKA. And so I make sure that I even more reinforce the notion of revert back to injected insulin if there's ever an issue with an infusion set.

So I think the protocols are good. I think that we need to be careful and patient selection and follow-up is key.

Dr. Buse:

I agree. And I do think the publication in *Diabetes Spectrum*, Tang is the first author, is really a great review of the field. I think that's a great way to round out our discussion on SGLT-2 inhibitors and type 1 diabetes in particular, but also type 2 diabetes. I want to thank my guest, Dr. Anne Peters, for joining me. Anne, it was great having you on the program.

Dr. Peters:

It's always good talking with you, John.

Dr. Buse:

I'm Dr John Buse. To access this and other episodes in our series, visit ReachMD.com/DiabetesDiscourse where you can Be Part of the Knowledge. Thanks for listening.

