Once-Weekly Insulin: Trials, Trends, and Tackling Inertia

Jay H. Shubrook, DO, FAAFP, FACOFP: Hello and welcome. On behalf of MLI and the American College of Osteopathic Family Physicians, thank you for attending *Less is More: The Promise of Weekly Insulin in Type 2 Diabetes*. Today we will be describing the place of novel insulin therapies, including once-weekly basal insulin, in treating type 2 diabetes, along with simplifying data interpretation from CGM. I'm Jay Shubrook, a primary care diabetologist and a professor at Touro University, California. I'm delighted to introduce two experts in the field and my co-presenters.

Carol Wysham: Hi. I'm Dr. Carol Wysham, Clinical Professor of Medicine at the University of Washington and a Clinical Endocrinologist in Spokane, Washington.

Eda Cengiz, MD, MHS: Hi. I'm Dr. Eda Cengiz, Professor of Pediatrics. I'm also director of the Pediatric Diabetes Program at University of California, San Francisco, UCSF.

Dr. Shubrook: Where does basal insulin fit in the overall picture? We know that the American Diabetes Association recommends starting basal insulin when someone has individualized A1C targets that have not been achieved with non-insulin therapies, including things like GLP-1 receptor agonists or SGLT2 inhibitors that have extraglycemic benefits, in individuals who present with significant hyperglycemia, particularly above 300 or an A1C above 10, or those individuals that have catabolic symptoms or symptoms of glucose toxicity. I think we need to talk about the utilization of basal insulin.

We know that this is used for many of our patients with type 2 diabetes, but there's been good evidence, including a review of 22 studies, that showed that basal insulin is not started in a timely manner, it's also not titrated. The mean time to starting basal insulin is five years after where it would be appropriate. We know that those patients have elevated A1Cs, and that period of time where we're delaying insulin actually causes problems for the patient and puts them at risk for severe outcomes. I think we need to identify the use of insulin earlier on. The patient has the opportunity for improvement.

Dr. Wysham: Over the time we have our first-generation insulin analogs, detemir and glargine, which as you know don't always have a full 24-hour duration of action, often requiring twice daily injections. Then our second generation, glargine U300 and Degludec, which do have the ability for our patients to inject them just once daily. Unfortunately, in today's world, we still have about two-thirds of our patients who are either missing some of their basal insulins or mistiming them and obviously resulting in a marked reduction in ability to get good glycemic control.

Finally, we have to remember that patients, 50% of them or so, will stop taking insulin within three months. We really do need to continue the quest to find an insulin that is going to work better for our patients with diabetes. Enter the possibility of a once-weekly insulin. What are our goals for these once-weekly therapies? Clinically, we want to see at least similar glycemic control and hypoglycemia risk but perhaps improved compared to our current insulin therapies. This would result in a reduced treatment burden and hopefully will be easier to overcome therapeutic inertia.

Patients really are interested in this possibility. On the molecular side, we want a long half-life. We want it to have a stable PKPD so that there's less interpatient and intrapatient variability and a slower clearance. Again, our goal is better treatment acceptance and adherence with the providers, as well as the patients. Let's discuss the two once-weekly insulins that are furthest along in development.

Both of these insulins have been based upon the proprietary technology that the companies are using to prolong their GLP-1 agents. You're very familiar with these, when you know about the GLP-1s.

Starting out with insulin efsitora alfa. So, they're using a novel single-chain variant of insulin, which is fused with the human IgG-Fc domain. This results in reduced insulin receptor potency, but with full agonism on the insulin receptor. The time action profile, our half-life is approximately 17 days, so obviously supports once-weekly dosing. It's currently in Phase 3 trials. Insulin icodec, again, is an insulin that has been acylated. There's a 20-carbon fatty diacid side chain, which results in high albumin binding, reduced enzymatic degradation, in addition, has reduced insulin receptor-mediated clearance.

The time action profile results in a half-life of approximately eight days, again, supporting once weekly dosing. The Phase 3 trials are complete. I'd like to start with talking about insulin efsitora alfa. You can see this is a cartoon that highlights the structure of this insulin. When insulin efsitora is injected into the subcutaneous tissue, it enters the bloodstream and then eventually the intracellular space where it interacts with the insulin receptor. Because of the products and the attributes of this insulin, there is a prolonged duration of action in the intracellular space, allowing for a slower degradation.

You can see a graph that compares the time to steady state between efsitora given weekly in blue compared to insulin glargine in the gray levels. As you can see, if you start with a starting dose of efsitora, it takes approximately seven weeks to reach steady state. However, as was done in the clinical trials, if you give a loading dose, you can reach the steady state much more quickly. Now for instance, in the QWINT-2 trials, a loading dose of 300 units or three times the starting dose was given as the first dose. They started with a dose of 100, which was approximately 15 units daily dose equivalent.

Then at week one, they repeated the 100-unit dose and then began titrating at week two, according to the protocol. The Phase 3 trial includes five QWINT trials, four of which were done in patients with type 2 diabetes, both insulin-naive for QWINT-1 and 2, and patients taking insulin. QWINT-3 was basal insulin, QWINT-4 was patients on multiple daily doses of insulin. Then QWINT-5 was done in patients with type 1 diabetes on multiple daily doses of insulin. The trial results are summarized here. I'd like to take a moment just to make sure that it's clear that when an insulin product is being studied, the goal is to prove that it is at least as good as the current products that are available for use. That is, the A1C reduction as well as hypoglycemia reduction.

As you can see, the non-inferiority goal for the efsitora program was met in all of the studies. That is to say, that the A1C reduction was similar to that of the comparator insulins. When they looked for superiority to see if it was better than the current insulins, they did not show superiority. What we can say is that efsitora alfa resulted in similar A1C reductions, and as you can see in the type 2 trials, similar hypoglycemia event rates. There was a statistically higher level of hypoglycemia in the type 1 studies, which I think were related to the way they gave the loading dose in that particular studies. We'll see how the FDA interprets the data.

The safety outcomes, again, as I alluded, there were no significant differences in hypoglycemia rates in the QWINT-1 through 4 trials. The only trial in type 2 that we have detailed information is the QWINT-2 trial, again, that in insulin-naive patients. What they showed is the rate of serious adverse events were similar between efsitora and degludec. The rates of insulin site reactions, all of which were mild, was 2.4% with efsitora, 1.7% with degludec. The average change in body weight was similar at 3.6 kilograms with efsitora and 3.5 kilograms with degludec. I'd like to turn the program over to Dr. Cengiz to review the data related to insulin icodec.

Dr. Cengiz: Insulin icodec is a novel, ultra-long-acting basal insulin analog designed for once-weekly administration. Its half-life is 196 hours, so ballpark 8 days, allowing once-weekly dosing. How does it achieve a long half-life? This figure summarizes how icodec works after its injection into the subcutaneous tissue. Once icodec is injected, it binds to albumin, forming an essentially inactive albumin-bound depot, then slowly absorbed into the bloodstream from the injection site. Once it's in the circulation, approximately 95% of icodec binds reversibly to albumin, and it circulates primarily in an albumin-bound state.

In the intracellular space, icodec binds to the insulin receptor. Icodec has a reduced insulin receptor affinity. Reduced insulin receptor-mediated clearance leads to prolonged half-life. Icodec retains the same biologic properties as natural human insulin with no increase in IGF-1 receptor binding or mitogenicity. Steady-state levels of icodec are achieved after two to three weeks of once-weekly dosing, providing consistent insulin exposure with minimal peak-to-trough variability. One unit of icodec has a comparable glucose-lowering effect to one unit of comparator basal insulin.

Therefore, once-weekly dose of icodec corresponds to seven times the once-daily dose of comparator basal insulin. In inpatients switching from once or twice-daily basal insulin, the dose is generally increased by 50% for the first injection only. This one-time loading dose has been used to shorten the time to reach steady state. These studies investigated icodec in both insulin-naive and insulin-experienced individuals. A1C as the primary outcome was superior for icodec versus comparators in all three trials with insulin-naive patients ONWARDS 1, 3, and 5, as well as in ONWARDS 2, where patients were switched from a daily basal insulin.

The reduction in A1C was superior in 1, 2, 3, and 5. Notably, similar rates of combined level 2 and level 3 hypoglycemia were observed in ONWARDS 1 through 5. Reduction in A1C was achieved without an increase in hypoglycemia. If we look at the rest of the safety outcomes, icodec was not associated with an increased risk of other safety outcomes. In brief, once-weekly insulins offer a safe, effective option with a convenient dosing regimen, potentially reducing the burden of insulin therapy for people with type 2 diabetes.

What is the current approval status? Efsitora insulin is seeking FDA approval. Icodec insulin is already approved under the brand name Awiqli in the EU, Canada, Australia, Japan, and Switzerland for treatment of both type 1 and type 2 diabetes and in China, for treatment of type 2 diabetes.

Dr. Shubrook: There's an opportunity to use technology in these patients who are on new novel therapies. We know that continuous glucose monitoring offers benefits over self-monitoring of blood glucose and could really help patients with novel insulin therapies gain better control. In those patients with type 2 diabetes, combining CGM titrations with once-weekly insulin could reduce the treatment burden by minimizing the number of required basal insulin injections and could reduce the need for finger stick glucose monitoring for those patients. This is really an opportunity to utilize new technologies in insulin and new technologies in sensing to really make the patient experience better.

For those that are less familiar with continuous glucose monitors, it's important to know that the information is not only useful for the patient, but it's also useful for the clinician. You'll see here that there are some key metrics in the uniform ambulatory glucose profile that shows the date range that someone wore it, the percent time that they were wearing it, what was the average glucose, the GMI is the estimated A1C based on the two-week or more wear of that sensor, the glucose variability, and the time and range. We find that when these things are all reported, this reduces the assessment burden for the clinician to really know where we need to focus on our treatment.

It's reimbursable by insurances if reported as such. Then the ambulatory glucose profile also will give you really nice data to look about the lived experience for a patient with diabetes. You can see here

very quickly, rather than having hundreds of points of data, you can see the mean glucose in the dark line in the middle. Then you can start to see the first and second standard deviation. You can very quickly see that this patient has a very big drop in their glucose overnight, resulting in pretty significant hypoglycemia, and then has a climb in the two or three-part modal during the day.

This is someone that probably has too much basal insulin and not enough insulin covering their mealtimes. This would not be the person you'd want to increase the insulin, because it could be very unsafe. This data gives you really fast information that you can help your patient with. Then of course, if you do see a pattern, you can get into the day-to-day glucose pattern to see if this is an isolated event or if this is a recurrent event. Again, you can see very quickly here that if you look from bedtime to morning, many of these days, the person has a significant drop overnight, resulting into an early AM or first AM hypoglycemia.

Again, highlighting the use of this tool to really help us optimize insulin in our patients. This has been an excellent program. Dr. Wysham, can you tell us what people need to know to take away from this?

Dr. Wysham: I think what I'm most excited about is the fact that a once-weekly product is going to make things easier for our patients and particularly given that most of our patients will already be on GLP-1s prior to initiation of basal insulin. They can just take their two injections the same day.

Dr. Shubrook: I love it. Dr. Cengiz, what are your takeaways?

Dr. Cengiz: Treatment. Suboptimal treatment adherence is a major barrier in achieving glycemic targets. Once weekly insulins could address this issue by simplifying diabetes treatment, given that it's reducing daily insulin injections.

Dr. Shubrook: Thank you again for joining us and please stay tuned for the full companion activity, Less is More: The Promise of Weekly Insulin in Type 2 Diabetes. We look forward to seeing you again soon.

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