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Breaking Down Biosimilar Insulins: A Look at the Regulatory Process and Impacts

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and joining us for a discussion on insulin biosimilars is Dr. Simon Heller. Not only is Dr. Heller a Professor of Clinical Diabetes at the University of Sheffield, but he's also the Director of Research and Development and an Honorary Consultant Physician at Sheffield Teaching Hospitals Foundation Trust in the United Kingdom. Simon, thanks so much for speaking with me today.

Dr. Heller:
It's a pleasure, John. Thanks for inviting me.

Dr. Buse:
You had a paper on biosimilar basal insulins published in *Clinical Diabetes* just recently, and it struck me as particularly instructive. Can you tell our audience why you were drawn to this issue and talk a bit about insulin's role in diabetes management even today and the evolving crisis around the cost of diabetes care worldwide?

Dr. Heller:
Yeah. I've become interested in this area, particularly in relation to work that I've done in working with colleagues in India and some of the other developing countries, because in the UK, we don't even think about insulin in terms of their cost. We're much more concerned with getting the right product to the right person, be they someone with type 2 or type 1 diabetes. Everything in the UK in what I think is called a socialized care system is free at the point of use. And although we are made aware of the cost of insulin, frankly, it doesn't impinge upon the average healthcare professional who's prescribing the insulin, whereas in discussions I've had with colleagues in India, it's clear that the price of insulin is prohibitive for many. And I worked briefly in the U.S. some years ago and have continued to work with colleagues, and there, of course, price is a very big issue, and so the idea that biosimilars could be used at lower cost is one which interested me.

Dr. Buse:
With that in mind, let's talk a bit about the regulatory process for "biosimilar insulin." Can you describe that at a top level? How are these products approved?

Dr. Heller:
Well, I understand that biosimilars and bringing them to market in a regulatory process is pretty common be it the FDA or EMA, which used to be the way in which these insulins were approved in the UK—and we still essentially follow that guideline—and I think you have to prove equivalence, be it at a basic level in terms of how long the drug is present for, pharmacokinetics, and the pharmacodynamics, so there is a requirement to do that. And then, finally, there needs to be relatively brief clinical studies to show that they have the same effects.

Now that is all very well, but there are other areas where there were some concerns certainly early on. For example, when you inject a foreign protein into a human being or mammal, they can make antibodies, and very high antibody levels could affect the drug. So very briefly that's the process. And I think it will be fair to say despite some anxieties, it has become apparent through the way in which these insulins have been tested that the vast majority have demonstrated equivalence, and they can be safely used with confidence by clinicians that they will produce the same effect as the original product.

Dr. Buse:

Your article focuses on basal insulin, which is by far the most commonly used insulin worldwide. Can you take us through the key properties of the available basal insulins?

Dr. Heller:
So we still have available human insulin and, in some countries, animal insulin, which is the product which was developed called NPH, neutral protamine Hagedorn, which was discovered back in 1936, I believe, in Denmark and is an insulin which is still very widely used today, including in the UK. It lasts for about 8 to 10 hours, and the larger the dose, the longer it lasts. Also, it's generally used within the UK, where I have familiarity, twice a day in people with type 1 diabetes, and generally, it's used in people with type 2 diabetes for so-called basal insulin. It's given at bedtime. And then during the day, people with type 2 diabetes use different products, often oral agent in combination.

The problem is that these insulins have a peak, and if they're used in the evening as can happen, then it peaks in the middle of the night so there's a risk of hypoglycemia during the night. And in some countries, they can be mixed with a rapid-acting insulin, so-called premixed insulin, which is commonly used in type 2 diabetes, sometimes with type 1 diabetes twice a day, and there they're given before an early evening meal in UK, 5:00, 6:00 in the evening, and 9:00 a.m., and the problem with that is if you're trying to get a glucose down the next morning or fasting glucose levels, then the more you increase that, the more the likelihood of hypoglycemia at night. So these were always the limitations.

Now, we have newer products which have earned their worth. Insulin glargine, I believe, is the most commonly prescribed. It's often given at bedtime for people with type 2 diabetes. It's often given twice daily for people with type 1 diabetes. And then we have insulin detemir, which is comparable, made by another company, and then we have the ultra long-acting insulin, insulin degludec, which is a true 24-hour insulin, and insulin glargine as well. They're more expensive, but they have shown their worth in reducing hypoglycemia, in particular, during the night. These basal insulins can cause hypoglycemia, but most of the problem is during the night, and so the newer insulins have undoubted benefit in reducing that risk.

Dr. Buse:
For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Simon Heller about insulin biosimilars.

Regarding the basal insulins in the United States, Lantus was the original formulation of insulin glargine. Basaglar was technically a "follow-on" to insulin glargine and wasn't regulated under the same sort of biosimilar laws. Rezvoglar, or insulin glargine-aglr, is a more recent biosimilar formulation of glargine. And now, we have something called Semglee, or insulin glargine-yfgn, and that's the only interchangeable biosimilar formulation of glargine in the U.S.

Simon, for the remainder of our discussion, I'd like to focus on switching among biosimilars. So, first, is there anything that clinicians should be aware of when doing so? And is there a particular significance to interchangeability?

Dr. Heller:
Yeah, a really good question. And, of course, the point of your question is these insulins are cheaper by and large, but the price differential isn't as high as one might expect. But if you can drop the price by 20 or 30 percent, which is a very significant saving, worldwide it really makes a huge difference. So the advantage is clear, but I think that these benefits, if I can call them that, are also important.

And my own view, and it's the recommendation in the UK, is that although in many countries they can be used interchangeably without notification—in other words, pharmacists can just prescribe them unless there's clear specific instructions by the prescriber—an individual might suddenly find themselves on a different insulin, and they might be even unaware of it. Now, the evidence is that they're pretty comparable and no harm will come, but I think for me, and it's certainly in the UK, the relationship between the prescriber, the way in which they're using insulin and the way in which they relate to their patients is pretty fundamental, and so to do that without informing them and discussing it with them would be against advice in the UK. Frankly, I don't know how it would be regarded in the U.S., and if your copayment goes down significantly, maybe that's something that you would take pretty seriously, but in the UK, we have very clear instructions, ones that I agree with, that if we're going to do this, we take the person who's taking the insulin into our confidence.

Dr. Buse:
In the U.S., I think often the pharmacy will let the provider know but will go ahead and dispense the Semglee, not let them know for approval, just let them know. But I think one other topic I'd like to talk about is that in the U.S., an insurance company's pharmacy vendor will often change their formularies, so we have to make decisions about switching patients, let's say, from Tresiba, or insulin degludec, to insulin glargine because now the former isn't covered and the latter is. The switching among biosimilars, these different formulations of glargine fundamentally is different from switching between drugs like from degludec to glargine. Is that your impression

from the work that you've done?

Dr. Heller:
I think that's a very accurate appraisal as I understand it, and it's intriguing to me that once you're on one biosimilar you might be switched to another one, and I can see how that might be regarded with equanimity. They wouldn't be too worried about that. But as you describe that, the idea that we might switch somebody from insulin glargine to degludec or back again would really cause a great deal of concern.

Dr. Buse:
This has been a wonderful discussion. Is there anything else that you'd like to tell us before we wrap up?

Dr. Heller:
Yeah. I think that my view is that these insulins have a real place to play in prescribing in Europe, the U.S., and other countries to an extent, but I think the real savings can be made worldwide. We know that in many developing countries, particularly Sub-Saharan Africa, the price of insulin is prohibitive for many, particularly those in poorly served communities, and countries spend a huge amount of money. And although there have been attempts by the insulin manufacturers to drop that price, for various reasons insulin remains very expensive, and I think judicious use of these products could save many millions of dollars and allow more people with diabetes worldwide to be treated safely and more effectively.

Dr. Buse:
Well, this has been a really interesting conversation. I'd like to thank my guest, Dr. Simon Heller, for being here and for sharing his insights on biosimilar insulins. Simon, thank you so much for joining us today.

Dr. Heller:
It's been a pleasure talking with you, John. Thank you.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit *Diabetes Discourse* on ReachMD.com where you can Be Part of the Knowledge. Thanks for listening.