Bonus: Accessing the New World of Biosimilars—
Implications for Patient Care and Treatment Selection
(Sponsored by The Biosimilars Forum)

Joseph Merola, MD, interviewed by Macartney Welborn, MD

MACARTNEY WELBORN, MD: Hello, everyone, welcome to another episode of *Dialogues in Dermatology*. My name is Macartney Welborn and I am a dermatology resident from the University of Florida College of Medicine. Today's topic centers around Accessing the New World of Biosimilars—Implications for Patient Care and Treatment Selection. In this episode, I am honored to be joined by Dr. Joseph Merola, who will help guide us through this topic.—

--Dr. Merola is an Associate Professor of Dermatology and Rheumatology at Harvard Medical School. He is a board certified dermatologist, also board certified in internal medicine and rheumatology. He completed his dermatology residency at New York University Medical Center and continued residency in internal medicine and fellowship in rheumatology at Brigham and Women's Hospital. Welcome to the podcast, Dr. Merola. We're honored to have you and thank you so much for taking the time out of your busy day to sit down with us.

JOSEPH MEROLA, MD: Thanks so much, Macartney. I'm thrilled to be with you.

MACARTNEY WELBORN, MD: Can you just start by giving our audience a brief overview of what biosimilars are?

JOSEPH MEROLA, MD: This is a really interesting topic and I can tell you, this is really at the forefront of my rheumatology life. And I think it's racing toward dermatology, so it very much is a hot topic. A biologic drug is a drug that's highly similar to a reference or originator product and would be considered to have no clinically meaningful differences with regard to safety, purity, potency, etc. We can think in some respects, folks might want to think about this as a generic drug, I think there's some important sort of differences than what we might consider a "generic," which I'm sure we will talk about.—

--One thing I like to mention to folks when we first enter this topic is it's important to know that there are variations, even among batches of product, of our biologics at baseline of originator product. That may change over time, that may change by batch. That's sort of inherent to the biologic process of making these molecules, which I think sometimes helps us a little bit with getting our head around how a biosimilar may be okay and probably likely is okay for our patients with a variety of the conditions that we might talk about.—

--Also, that there are very strict definitions and processes that are put out by regulatory agencies to think about what makes a biosimilar a biosimilar, including a variety of analytical and structural and functional tests that make us think about what makes a biosimilar a biosimilar of its originator. And then again, I'm sure we'll get into much more detail beyond that.

MACARTNEY WELBORN, MD: We can segue from something you mentioned into what makes a biosimilar different from a generic form of medication.

JOSEPH MEROLA, MD: There's several differences here. And again, one of the reasons there were questions around this early on is that in making a biologic, there are a variety of different chemical processes at play. And these are being made by different, for example, cell types, among other things that can impact, you can imagine, some of the secondary structure and modifications that might happen on the molecule, beyond just producing an antibody in that structure. There's glycosylation that might be different and other elements that may impact immunogenicity. And so a lot of the question that we get into is about the question of immunogenicity.—

--So beyond just safety and efficacy, we have to think about what this means for driving, for example, antidrug antibodies. Will a drug over time fail a patient, if we switch back and forth between originator product and a biosimilar over time? And it also lends itself to another discussion topic which is distinct from the label of a biosimilar, which is interchangeability, or this

idea of can I switch between products in a given patient. Again, I think we'll probably come to that as we talk a little bit more in depth about these molecules.

MACARTNEY WELBORN, MD: Can you give us a few examples of a few drugs that we use in dermatology that have biosimilars that have been approved here in the U.S.?

JOSEPH MEROLA, MD: Probably at the forefront for us are drugs like rituximab, anti-CD20 therapy, which might be used for a variety of conditions in dermatology, including bullous disease, as well as a variety of anti-TNF agents, most proximately is infliximab, where we have several biosimilar infliximab molecules. Many of you likely have either used or been asked to use by a payer, a biosimilar form of infliximab.—

--And there is sort of a tsunami wave of other molecules, in particular other anti-TNF biosimilar drugs, namely adalimumab, etanercept, and others, that will be emerging in the next few years and I think really is why again this is such a hot topic. Hopefully, we'll get to both the positives and negatives of what that might look like for our patients and for us in the office.

MACARTNEY WELBORN, MD: I know you sort of touched on this earlier, but have there been any studies specifically in the dermatology population showing that these biosimilars have similar results and efficacy and safety profiles>?

JOSEPH MEROLA, MD: That's a wonderful question. We have several examples. One in particular is a study that was done for etanercept in psoriasis specifically. It opens up a broader question. So the way that the bioequivalent studies work is that you can do a bioequivalent study in one indication, so for example in rheumatoid arthritis. You can imagine an anti-TNF might do a study or an IBD. And then once bioequivalence is shown, it often can be extrapolated to other disease states.—

--So essentially, the way this is often done is you'll have a given mechanism or a drug, do a study in one area, and then it's extrapolated to other areas, potentially in our disease states. So we may not necessarily see the data for our skin disease state, but instead for another disease state, and then by extension we assume that it will work equally well for our disease state. And that's been sort of the regulatory take on this to date.—

--In terms of other studies that have been done, again it might be worth bringing this up now while we're on it, but there have been a number of studies looking at this other concept of interchangeability, if I can bring that up now, which is the question of can I switch back and forth, to do multiple switches between a reference product and a biosimilar that would result in any difference in the way it works, or in its immunogenicity in driving antidrug antibodies in particular.—

--And we've had several different studies now that have been I think very much reassuring to us. That includes studies like the NOR-SWITCH study, among others, that seemingly show that multiple switches back and forth between a reference product or originator product and the biosimilar seems to demonstrate a low likelihood of antidrug antibodies. In particular what we would be concerned about are what are called anti-idiotype neutralizing antibodies that would interfere with how the drug works over time and may even interfere with going back to the originator drug, which would not be a good outcome for our patients.—

--So we do have a good number of studies at this point that are reassuring I think to us around efficacy and around overall this concern of immunogenicity, although I think it's not a closed case. I think we still certainly need to see how these behave over the long haul of switching in patients over many years and even decades for some of our chronic conditions in dermatology.

MACARTNEY WELBORN, MD: It will be interesting to watch this over time and see how it impacts our clinical practice and prescribing habits. Have you been able to use biosimilars in

your own clinical practice? And if so, is there a particular patient group in which you're prescribing them?

JOSEPH MEROLA, MD: Certainly, we have been not only able to use them, but in some cases, I say this tongue in cheek but, forced to use them, based on a variety of payer preferences. So to date, it has mostly been again around rituximab, as well as infliximab biosimilar use in patients. The challenge, of course, and we'll come to challenges a little bit later, is that this is very much becoming a payer-driven concept and discussion.—

--So when we get to some of the challenges, I think that will be the question. But yes, we have had a deep knowledge now, and particularly in my rheumatology life, somewhat in my dermatology life as well, with these biosimilars. And they have overall been good clinical experiences. I'll save my commentary for administrative experiences for a little bit.

MACARTNEY WELBORN, MD: Are you able to prescribe a biosimilar for an off-label use, as we often do in dermatology?

JOSEPH MEROLA, MD: With all the same caveats and challenges that might come with an originator product, we certainly can consider these biosimilar products for off-label use, with the usual barriers that may come with them, but yes.

MACARTNEY WELBORN, MD: Yes, we are all very aware of those barriers unfortunately. What are the positives and challenges you perceive with the use of biosimilars?

JOSEPH MEROLA, MD: I think this is where we kind of get in the weeds. The positives, of course, this is also a complicated question because, at least in theory, a positive here would be increased access for patients, in patients who may have had challenging access in the past. Again, in theory this should help with cost. Should be a savings to the system and to the patient.

Of course, we know at least in the U.S., there is a complex, behind the scenes network that involves PBMs and others that can sometimes really make this challenging.--

--And challenging to understand, where originator products may be placed or packaged in a way that they may even be cheaper than a biosimilar. And so I think the landscape will evolve, we'll get to understand this better. At least globally, this has helped with access, with cost in many countries, and I hope that it also helps here in the U.S. So increased access would be a wonderful positive to come from this over time.—

--This is sort of a very nuanced topic, but as we get more sophisticated over time with ideas about combination approaches, even combination biologics and other things, it would be really wonderful to have less expensive options that would permit us to do more sophisticated treatments in the future. And we have some paradigms now where that may make sense, where induction regimens, followed by maintenance regimens with different mechanisms would be really brilliant, but it can be really challenging right now because of cost and payer limitations.—

--So those are a few of the positives. On the negative side, I will say there are a reasonable number of negatives. So despite all the reassuring words I have had about efficacy and safety to date, I do think there's a lot of potential for burden on the physician and on the patient around this. So for one thing, when a patient is doing well on a given medication, it can be really challenging for a patient to accept a change.—

--They may be afraid of changing. It may generate a lot of anxiety. It may generate a lot of calls and interactions with the office. I think that's not a minor point for a patient in terms of their disease journey and their treatment journey. There is a documented potential for nocebo effect here, so that's new or worsening symptoms that are brought on around negative expectations regarding a therapeutic intervention.—

--A patient again switching to the new drug and noticing a side effect or noticing something that may or may not be real to the mechanism but has real impact on their experience. One of the major things I wanted to raise is the potential for confusion with devices. So one of the things that would be really interesting here is you may have a patient who understands their adalimumab device for the past how many years. And what comes with this new product is a totally new device, totally new way to use it, it looks different. And so it may impact adherence, it may lead to some safety issues, a patient misfiring devices, etc., calls to the office.—

--So it's going to carry its own burden. And a lot of the support programs that we've had for years with some of the originator products and the support for those may not exist with the biosimilar product. So I think those are all some intangibles that we're going to have to think about in terms of generating calls and burden and education. It will just raise the question of who is going to be able to handle the burden in the office when there are potentially less support services and other services facing potentially some of these biosimilar products.

MACARTNEY WELBORN, MD: I think you raise a lot of really great points and things to think about. Humans struggle with change, whether that's a very small change to their medicine change. And sometimes I think the nocebo point is also a great thing to point out with these, so it will definitely be probably a learning curve for us in educating our patients and also for them as we go through. Do you foresee that like if a patient has been on Humira for many years and then their insurance company may decide to stop covering that, and so you would have to prescribe the biosimilar, is that kind of how you see part of them fitting into a patient's pathway?

JOSEPH MEROLA, MD: It's really fascinating. So yes, and I think the one thing that folks do need to know about, and this is another hot topic, is there was a law enacted, something called the Biologics Price Competition and Innovation Act, or BPCIA, in the U.S. And essentially, this has to do with that interchangeability piece. It means that if a biosimilar is deemed

interchangeable, and this may be regulated by a state where allowed, but it means that a biosimilar may be substituted for a reference product without a provider intervening.—

--So it's one thing if we're at least allowed the point to make a decision or to discuss this with the patient, with the payer, but it may depending on where one lives and how these laws fall over time, may be the case that similar to going to the pharmacy to pick up your statin, you get just a generic version on Tuesday and the next week, you get a different generic depending on how it goes. I'm not sure yet that that's the way things should be, but it certainly may become the case in many states that there is a substitution allowed in that way.—

--And I want to be clear that that would be around not just any biosimilar, but those deemed interchangeable. And I think we still very much are opposed to what would be considered nonmedical switching, which is a separate issue, but between drugs or between mechanism, that would be a very different idea here. But I think that also is something we need to be on the lookout for and also something we as a group need to be thinking about from an advocacy standpoint in terms of what that means for our patients in the longer term.

MACARTNEY WELBORN, MD: That's another great point. I know that also that's often seen in our isotretinoin prescriptions, where sometimes our patients will say that they've picked up one form and then it is another brand the next time they go, and it changes things. And sometimes they feel like they experience different things, just like we're kind of talking about, so that's a great point.

JOSEPH MEROLA, MD: For me, I think if you can imagine that scenario, but instead of just it went from a small brown pill to a small pink pill, and instead it's now an entirely new device with a different mechanism, etc. I do think it will generate more angst for patients and I think it will generate more calls to the office. It also may be the case that some subtle piece, like a needle size or an excipient might mean one hurts more than another, or something along those lines.

So I think tolerability may also come up over time as a point of distinction among these different agents.

MACARTNEY WELBORN, MD: That will be very interesting to see how this all goes over time. Thanks for all this wonderful discussion. Based on our conversation, do you have a few key clinical pearls or take home points for our listeners regarding clinical practice and biosimilars and what's on the horizon?

JOSEPH MEROLA, MD: Yes, I'll try to quickly summarize a couple of the points. I think, number one, we should not fear the biosimilar. I think there's a lot of evidence that they are as good as the originator products. I think that we will be using these in the future, so they are coming and I think it's something we need to embrace. We do have to distinguish this concept of interchangeability as we discussed, an understanding what can be switched back and forth with an originator product or between biosimilar products over time.—

--Again, there is evidence to support that but we do have to keep an eye on that over time with our patients. And I do think that there are both positives and negatives, as we discussed. Whether we like it or not, my gut is that this will generate more burden on the office and will generate some amount of anxiety and angst among patients who are asked to switch. And so I think that it's a conversation that we will continue to have to have. And pun intended, a dialogue that we will have to have among us as colleagues and with our patients. So thank you for the time to chat about this.

MACARTNEY WELBORN, MD: Thank you, everybody, for joining us today and listening to *Dialogues in Dermatology*. And a huge thank you to Dr. Joseph Merola for all this wonderful information.

JOSEPH MEROLA, MD: Thank you.