Bonus: Physician Preferences With Biosimilars
(Sponsored by The Biosimilars Forum)

Robert E. Kalb, MD, FAAD, interviewed by Brad Glick, DO, MPH, FAAD

BRAD GLICK, DO, MPH, FAAD: Welcome to *Dialogues in Dermatology*, summer session. Our topic today is "Physician's Preferences with Biosimilars." I am Dr. Brad Glick and I am Assistant Clinical Professor of Dermatology at the FIU Herbert Wertheim College of Medicine, in Miami, Florida. I will be your host. Joining me today is Dr. Robert Kalb, who is Clinical Professor of Dermatology, State University of New York (SUNY), Buffalo School of Medicine and Biomedical Sciences, Buffalo Medical Group, in Buffalo, New York.—

--He is also Adjunct Professor of Dermatology at the University of Pennsylvania School of Medicine, Department of Dermatology, Philadelphia, Pennsylvania. Dr. Kalb is a member of the AAD Coding and Reimbursement Committee, as well as the International Psoriasis Council Biosimilar Committee. He has extensive teaching responsibilities with fourth year medical students and residents rotating in his office on a daily basis. He has a comprehensive experience in research and treatment of psoriasis and he has presented numerous lectures at local, national, and international meetings.—

--Additionally, he is the author of over 60 peer reviewed publications. Dr. Kalb received his dermatology training from 1983 to 1986 at the College of Physicians and Surgeons at Columbia University in New York, and his MD degree, cum laude, from Downstate Health Sciences Center in Brooklyn, New York, in 1982. Dr. Kalb, thank you so much for being here today.

ROBERT E. KALB, MD, FAAD: Dr. Glick, it's my pleasure, thank you.

BRAD GLICK, DO, MPH, FAAD: By the way, I'm from Brooklyn, as well, too, so I know Downstate very, very well. So let's jump right in. It's an exciting time. Biosimilars, price reduction through competition, increased access, possible less prior authorizations and step edits, and

adalimumab, one of our best selling drugs, the market leader so to speak in the U.S., will have nine biosimilars by 2023. That this might be particularly important in dermatology, are there going to be some benefits from biosimilars? We're soon to find out, with your expertise.—

--So I want to jump in right away. And let's for our audience discuss biosimilars. What are they? What's the difference between a generic and a biosimilar? Or simply, what is a biosimilar, tell us.

ROBERT E. KALB, MD, FAAD: So the term "biosimilar" was coined by the European Medicines Agency, the EMA, when they discovered that these drugs, with the same safety and efficacy, were slightly different. And what was the difference if you compare generic drugs made in a chemistry laboratory, short amino acid sequence, each drug is identical. What a biosimilar is a recombinant therapeutic protein, it's made in a living cell.—

--So when this cell manufactures this drug, there may be some slight differences in terms of its configuration, in terms of some sugar moieties at the end. But I think the best way to look at it is the lock and key. So when you manufacture a biosimilar, in this case we're going to primarily be talking about TNF drugs, anti-TNF drugs, it unlocks the key, it blocks TNF.—

--But the other end of the key may be slightly different. It may be circle-shaped, it may be square-shaped. But there's no difference in the active key part, it will still block TNF. There may be a slight difference in clinically inactive compounds.

BRAD GLICK, DO, MPH, FAAD: It seems to me like biosimilar is the perfect term. So it's kind of a replacement but it's not an exact replica, but it's pretty darn close. Is that accurate?

ROBERT E. KALB, MD, FAAD: Yes, in terms of the safety and efficacy and the many studies that have been done, there has not been shown to be a significant clinical difference. So an example that I like to use is I first prescribed adalimumab, Humira, in 2004. The adalimumab,

the Humira that I prescribed yesterday is slightly different in terms of its configuration, in terms of the other end of the key.—

--But the active part of the molecule that blocks TNF is the same. So in some way, the adalimumab I prescribed yesterday is a biosimilar to the original one from 2004.

BRAD GLICK, DO, MPH, FAAD: Let's jump into the approval process. The biosimilars are here, we have some already. Not really using them just exactly yet in dermatology, although one could, and I know you'll talk about that where infusions are concerned, let's say with infliximab. But what is the approval process for biosimilars? And is it different from other agents and the other biologic therapies of the originator products?

ROBERT E. KALB, MD, FAAD: The approval of biosimilars was part of the 2010 Affordable Care Act. And what the FDA stipulated is that each biosimilar, in addition to the name, adalimumab will have a four digit suffix, so that these products can be followed in terms of their pharmaco-vigilant studies. So after the biosimilar is determined to unlock the key, to block the TNF, they have to go through significant studies to show safety, purity, potency.—

--And these are conducted to measure the immunogenicity, the pharmacokinetics, the pharmacodynamics. And then the safety and efficacy are done through clinical studies. Now, what's interesting is that the FDA now, because of the biosimilars coming on the market, realizes that there can be subtle differences. So if a company manufactures it at a different site or uses a different cell culture media, they may be slightly different.—

--So the FDA has instituted some vigilance programs for not only the biosimilars but for the originator drugs, to make sure that they still maintain their safety and efficacy.

BRAD GLICK, DO, MPH, FAAD: Fantastic, great information there and appreciate that. What have been some of the initial concerns about biosimilars? And should we be concerned in the now?

ROBERT E. KALB, MD, FAAD: Justifiably, people did have concerns that the products would be of lower quality, that the safety base was not as sufficient, that they would understand that these drugs are as safe as the originating molecule. There's some increased immunogenicity that maybe more autoantibodies with the biosimilars. That the efficacy may be slightly different. And then there was a concern about switching.—

--But the bottom line is that based on a significant number of studies, there have been over 90 studies that switching between an originator and biosimilars, and all of the safety data and efficacy data primarily where there's much more experience in Europe has not shown these concerns to be realized. So far, they have been safe and have been effective and there has not been significant clinical issues identified.

BRAD GLICK, DO, MPH, FAAD: Now we have some experience with biosimilars in other specialties here in the States. But as you alluded to, the greatest amount of experience that we know from studies and different disease states, and perhaps even those that cross over into our world of dermatology, like psoriasis, psoriatic arthritis, what have been the experience in other countries?

ROBERT E. KALB, MD, FAAD: The primary biosimilar experience has been in Europe. The actual first monoclonal antibody biosimilar approval was with infliximab and it was in Europe in 2013 and in the United States in 2016. But in Europe overall, there has been nearly a 14 year experience, there's 70 biosimilars approved, and there's been an over 2 billion patient day exposure to biosimilars there.—

--But it's interesting that the uptake between countries varies. So as an example, in the Scandinavian countries the uptake of the biosimilar adalimumab and infliximab have been upwards of 90 percent. Whereas in some of the southern European countries, it's 40, 50, 60 percent. So there are some slight differences and much has to do with the physician comfort.—

--Interestingly enough that in Europe, etanercept was approved later, the biosimilars etanercept. But that upkeep was higher because I think physicians had more comfort with this whole biosimilar issue and some of the original concerns that we had.

BRAD GLICK, DO, MPH, FAAD: Very helpful information once again. What about transitioning to our experience here in the States? And I believe that you have some experience as well with biosimilars. I believe most of our colleagues, whether it's even in academic practice but even in the trenches in clinical dermatology, have really not experienced biosimilars. Nevertheless, I think we're getting closer and closer to that experience in our clinical practices. So what has been your experience thus far and in general? And what ages?

ROBERT E. KALB, MD, FAAD: So Brad, as you mentioned, one of the issues is that the two biosimilar drugs that there is experience in dermatology are infliximab and rituximab. Unfortunately, probably 95 percent of the dermatologists in practice don't have a significant amount of experience with these drugs. Now, interestingly enough, when the first anti-TNF drugs were approved, etanercept and infliximab, back in the early 2000s I started using them for psoriatic arthritis and patient with bad psoriasis.—

--But at that time, an etanercept shortage occurred, so I started using infliximab. And it was extremely effective, based on some preliminary data. So I have literally now patients on infliximab for 20 years. Now, I knew it was approved as a biosimilar in 2016. And at one point, I'm fortunate because in our group we have an oncology infusion area, that's where it's done. So infliximab was approved in 2016. I specifically remember in 2019, 2020 calling our infusion

center head nurse and say, “I’m wondering how come there’s been no biosimilar infliximab used?”—

--Her answer was that, “Well, the price has come down a little bit. They have significant rebates. There’s no cost differential.” And so basically, everyone was still on brand name Remicade. Now, what happened in the last year and year and a half, there’s been some pressure and I think it’s coming primarily from the insurance companies. So any new starts for infliximab or rituximab, obviously which is used for pemphigus vulgaris and bullous diseases, any new start they’re demanding the biosimilar product, the insurance company.—

--And the only way you can get the originator product in some cases is that the patient has a much higher copayment, so they’re putting the burden on the patient. But as a general rule, they’re demanding new starts go to the biosimilar. And there’s been some pressure about switching. But I have noticed though that rituximab biosimilar was approved in 2018, a couple of years after infliximab and now there’s been more pressure recently again because I think there’s been more comfort with physicians and then with the insurance companies to use these drugs.

BRAD GLICK, DO, MPH, FAAD: I’m going to throw out a question to you in a couple of moments about cost savings. But on this subject before we move on, I’m presuming that one of the reasons why there has been a switch to biosimilar infliximab and biosimilar rituximab is because of cost savings. So have you noticed any specific cost savings in your institution? I know we’ll talk a little bit about cost savings in a couple of moments, but specific to your facility and these two products, I’m presuming that’s one of the reasons why they wanted to do that?

ROBERT E. KALB, MD, FAAD: So the cost savings so far has been primarily for the insurance companies and the pharmacy benefit managers who supply the medication. Our group per se, the cost savings have been minimal. But there definitely are savings. The question becomes, at one point the cost was essentially the same, is it just a 5 percent, a 10 percent?—

--But hopefully with increased competition, it will definitely drive the share of biosimilars higher, so that there can be more cost savings and hopefully increased access. To give you an example again, the Scandinavian countries have a 90 percent biosimilar share with these TNF drugs. A lot of the European countries, it's in the 50, 60 percent range. But in the United States, infliximab only about 35 percent is biosimilar, it's still 65 percent originator drug.—

--So there's been less pressure but I think it's going to be driven by the insurance companies mandating these changes.

BRAD GLICK, DO, MPH, FAAD: We'll get back to cost in a couple of minutes and I'm actually going to ask a couple of other questions as it relates to cost. But I wanted to ask this. What biosimilars are of interest to the U.S. dermatologist? Now, we mentioned one of them already, so maybe talk about that and maybe what else might be coming.

ROBERT E. KALB, MD, FAAD: So the primary biosimilar drug that's going to be of interest to dermatology is adalimumab. And as you mentioned in the introduction, it should be available in 2023. There's actually nine biosimilars that have already been approved of adalimumab. Etanercept has some patent protections until the late 2020s, so that won't be available. The other drug that likely would become available in the next few years is ustekinumab.—

--But dermatologists are familiar with adalimumab and we'll see what happens next year when it's approved, in terms of where the pressures are coming from, if any, for the approval or the use of the biosimilar over the brand name product. One of the potential advantages of biosimilars, in my opinion, is the bane of our existence is the prior auths, the step edits, going through methotrexate, cyclosporin, phototherapy before you can get a drug that in most cases will be felt to be the best option.—

--So maybe it will get to a point where we don't have to go through methotrexate or cyclosporin and we can move right to a drug, but in this case a biosimilar. The question now becomes has psoriasis therapy moved even further that people would argue that an IL-17 blocking agent or a p19 blocking agent would likely be safer and more efficacious than a TNF agent. But we'll see what happens, as unfortunately a lot of our lives are dictated by what we can have authorized by the insurance company, rather than what we think may be the best for our patient. But in one way, again if there's easier prior access to biologic drugs, that may be an advantage.

BRAD GLICK, DO, MPH, FAAD: In my experience here in Florida in this last five years, I've seen some change where I don't have to navigate through methotrexate or cyclosporin so much. But there has been somewhat of a stepwise approach with maybe going to the TNF blocker first, that was more preferred from the insurance company. But there has been a reasonable amount of choice. My concern, even when you and I had some preliminary conversation, is are we going to have to go retro and select a tumor necrosis factor inhibitor first? Which isn't the end of the world, these are pretty effective therapies.—

--But to your point, interleukin-17 blockers, p19/interleukin-23 blockers are so highly effective right now, there is somewhat of an impediment there, but at least we'd be getting our patients these more highly effective therapies. My experience has not been that methotrexate was such a highly effective therapy for psoriasis in this modern era. Cyclosporin is great but, of course, it's so limited by side effects.

ROBERT E. KALB, MD, FAAD: So I definitely agree in terms of these step edits. If you can get by the systemic conventional agents you mentioned, I have found also that a patient needs to fail a TNF agent or the IL-12/23 ustekinumab agent before they can move onto the other, again what people would consider more efficacious and likely safer drugs. And we'll just have to wait

to see what happens. Unfortunately, much of this is out of our control with the plans' prior authorization and step edit requirements.

BRAD GLICK, DO, MPH, FAAD: As we like to say these days, unfortunately our prescription pads are now more like suggestion pads. Nevertheless, let's move on and talk a little bit about a couple of educational points that I think are very important, and that is extrapolation and interchangeability. Tell us about extrapolation and interchangeability and what do they signify with respect to biosimilars?

ROBERT E. KALB, MD, FAAD: Well, we'll use the example of adalimumab, which actually I believe it now has 11 FDA indications. So the common ones are psoriasis, psoriatic arthritis, inflammatory bowel disease, rheumatoid arthritis. So as I mentioned before, there's a lot of in vitro and then clinical studies required for the FDA to approve the biosimilar. So as an example, adalimumab biosimilar, we did clinical studies in our office in psoriasis.—

--So if the studies are done appropriately and the FDA approves the biosimilar in psoriasis, the indication is extrapolated to the others. So in other words, if it's approved by the FDA, you can extrapolate that it's also going to be approved for rheumatoid arthritis and inflammatory bowel disease. So one of the original arguments was that, well, if it works in IBD, maybe it won't work as well in psoriasis. And again, that's not been borne out with clinical studies.—

--But the interchangeability is different because with that, they needed to do additional studies to have this indication. So in that case, the pharmacist can switch to the biosimilar without the physician's approval. Whereas the extrapolation, if a person is on a brand name originator drug and you want to switch them to the biosimilar, then to switch again, the physician needs to know.—

--But interchangeability, the physician does not necessarily know that the drug has been switched. But that varies by state, some states don't allow that and some states do. But the argument is that in terms of following patients, which drug did they get? Are they getting different biosimilar versions of adalimumab in terms of the long term safety and efficacy?

BRAD GLICK, DO, MPH, FAAD: In your experience, has there been an allowance for extrapolation by the FDA?

ROBERT E. KALB, MD, FAAD: So as a general rule, if the drug is indicated for multiple indications, if they do the clinical studies and the FDA approves the drug, they have allowed the extrapolation into the other indications. Now, to give you a specific example with adalimumab, there are 11 FDA indications. But there are two, hidradenitis and uveitis, where they have not allowed the extrapolation, so other studies would need to be done to have that performed or that indicated.

BRAD GLICK, DO, MPH, FAAD: So it's interesting, it's really an FDA judgment. So those biosimilar companies are going to have to spend a fair amount of money to be able to do those trials, like were done previously for the branded adalimumab. Super interesting.

ROBERT E. KALB, MD, FAAD: Many people would argue that the interchangeability, because additional studies have been done, that maybe that would be a better choice. So as I mentioned, as of now there will be nine adalimumab biosimilars. One of them already has an interchangeable designation from the FDA. It's likely that one or two more will have that designation. Would that be a better choice to start with this drug, because additional studies have been done? Some people would argue it that way.

BRAD GLICK, DO, MPH, FAAD: This is phenomenal information and really appreciate that. I want to get back to just general comments from your perspective and knowledge of biosimilars

on cost savings. Can we really expect significant cost savings? And just from my experience, I've heard variable cost savings. In the beginning, we have been told the cost savings is going to be as much as 40 percent, which I think is a really large number. But what are your thoughts and what is your experience thus far?

ROBERT E. KALB, MD, FAAD: I think that's the $64,000 question is the ultimate cost savings. I know that they have realized in the 30 percent range in Europe. But these drugs, recombinant therapeutic proteins, made in living cells, they are expensive to manufacture. And the issue becomes will competition drive down the cost and to what point.—

--A five to ten percent savings, although it's significant, is still not going to I think drive the use of these drugs, where certainly, a 30, 40 percent would. And so time will tell as to how many companies are interested, and what the insurance company pressure is, and how physicians feel comfortable with it. Adalimumab is the number one selling drug in the United States, that's why there's nine biosimilars there hoping that they can get part of that market share. And so time will tell.

BRAD GLICK, DO, MPH, FAAD: And to your point, hopefully where that is competition, typically drug prices will come down, fingers crossed. Segueing to really the next question, and again your perspective and knowledge thus far, and you've had some experience with biosimilars in the clinic, is will these agents lessen our step edits and prior authorizations? We're dating ourselves, both of us, but it is a $64,000 question. What are your thoughts?

ROBERT E. KALB, MD, FAAD: Unfortunately, in many cases it's a cost decision. And I think that's where the methotrexate came from, when there's clear evidence that these drugs are safer and more efficacious over time. And so hopefully, with the increased cost savings and with competition, we will find decreased amount of office work, step edits, the coordinators, the

nursing staff which again, such a significant amount of time is spent in physicians' offices who use a lot of biologic therapy.—

--So again, I'm cautiously optimistic. The biosimilar use in terms of the drugs I've used has not been an issue. Patients in general have done very well. There's always that individual exception. And I'm hoping that with time, it will make it easier.

BRAD GLICK, DO, MPH, FAAD: I want to finish up with one very important question. What is the potential impact of biosimilars as it relates to healthcare disparities that we've seen unmasked since the pandemic?

ROBERT E. KALB, MD, FAAD: So the issue has always been access, access to these very effective medications. And again, my cautious optimism is that when biosimilars come on the market and when they become more mainstream, it will increase access to patients in underserved areas, to patients who haven't been able to go to a physician because of the cost issues. Unfortunately, these drugs are extremely expensive and that hopefully, with time, the price will come down to increase access to these groups.

BRAD GLICK, DO, MPH, FAAD: Well, this has been a tremendous session. I've enjoyed it immensely. I appreciate your knowledge base on all of this information on biosimilars, Dr. Kalb. I want to remind our audience, as well, that the American Academy of Dermatology does have a position statement on biosimilars. And you can review that at AAD.org. Go into the search bar and actually place the topic "biosimilars" for various disease states like psoriasis, and you should be able to find that.—

--I thank you once again, Dr. Kalb. It's been a great opportunity to spend this time with you. And I very much look forward to the opportunity to following up with you and learning more about biosimilars, once they are put into use in our space of dermatology. So thank you once again.

ROBERT E. KALB, MD, FAAD: And thank you, Brad, it's been my pleasure. And again, I'm cautiously optimistic that this will be the similar situation that we experience with generic drugs. The initial hesitancy, but not just mainstream, but with its infancy right now, biosimilars. But so far, the studies have shown that these are safe and effective drugs and we should be able to use them without a problem.

BRAD GLICK, DO, MPH, FAAD: Fantastic, thank you so much.

ROBERT E. KALB, MD, FAAD: Thank you.