

# Rounding@IOWA: The Wild West of Biosimilars

[Upbeat theme music plays]

## Transcript

### **Dr. Clancy**

Welcome to Rounding@IOWA, a continuing medical education podcast developed by and for healthcare teams. I'm your host, Dr. Gerry Clancy, Professor of Psychiatry and Emergency Medicine and Senior Associate Dean for External Affairs here at the University of Iowa's Carver College of Medicine.

If you watch the evening news, ESPN or late night TV, You may experience what I experience, and that is being bombarded with advertisements for Remicade, Humira, Stelara, and many more medications. And it seems like new ads for new medications like these are out each week. I must admit, I'm a little bit confused by these numerous ads and the numerous treatment options that are now available. So fear not. We've got experts today to help us through this. Some of these new medications fall into the FDA categories of biologics and biosimilars. Today we will discuss guidance for clinicians and their patients regarding this rapidly evolving and highly competitive world of biologics and how they relate to biosimilars.

For this podcast edition, our objectives include, first, we hope our participants can define and explain to their patients some important terms in this area, including biologics or biologic products, reference products, and biosimilars. Second, we hope our participants are able to compare and contrast biologics and biosimilars. We will focus on the treatment of immunologic disorders, primarily in the areas of inflammatory bowel disease such as ulcerative colitis and Crohn's disease, and the immune-related arthritic and skin disorders, as these are the areas our clinical experts work the most. And third, our participants will be able to discern the cost advantages of biosimilars and the treatment of these disorders.

Our expert guests today are Dr. Ashlyn Johnson, who serves as a clinical pharmacist on the inflammatory bowel disease treatment team. She received her PharmB from North Dakota State University in 2019. and completed her acute care residency at Sanford USD Medical Center in South Dakota. She joined the University of Iowa in September of 2023 and specializes in medication management for patients with Crohn's disease, ulcerative colitis, and eosinophilic esophagitis.

Dr. Brittany Bettendorf is a clinical associate professor at the University of Iowa where she is a practicing rheumatologist. Her clinical interests are in reproductive rheumatology and transitioning pediatric patients to adult rheumatology. She received her MD from the Medical College of Wisconsin, where she also completed her residency in internal medicine and pediatrics, as well as her fellowship in adult rheumatology. She holds a Master's of Fine Arts degree in nonfiction writing from the University of Iowa. Dr. Bettendorf served as a member of the Literature Review Committee and co-author of the 2020 American College of Rheumatology Reproductive Health Guideline. Dr. Bettendorf teaches a class to first-year medical students and physician assistant students on social justice, and she also teaches an advanced elective to medical students on opinion editorial writing to help students improve the public's understanding of health and health care. She's a faculty member in the program in bioethics and humanities at Carver College of Medicine. During her small amount of free time, she has been a competitive figure skater, speed skater, and a synchronized skating team member.

Dr. Johnson and Dr. Bettendorf, welcome to Rounding@IOWA.

**Dr. Bettendorf**

Thanks for having us. Pleasure to be here.

**Dr. Johnson**

Yeah, excited to be here.

**Dr. Clancy**

Well, I'm very glad you're here as well to help me with an area that I am not very good at all. So I just provided our listeners your official titles and a summary of some of your training. Could you give us a better idea of your daily efforts and what a work week might look like for you? And let's start with Dr. Johnson.

**Dr. Johnson**

Yeah, absolutely. So currently I work in the digestive health clinic here at the university. My primary role is treating and helping with managing patients who have IBD or irritable bowel disease, which often includes Crohn's disease and ulcerative colitis. We also have a handful of patients who suffer from eosinophilic esophagitis, and we do often treat patients with recurrent *C. difficile* infections as well. So my role in the clinic is really to collaborate with all of our different providers, help them with product selection, make sure that we kind of work through all those different clinical scenarios. Once we've decided which product we're going to use, I will educate the patients on the medication that we have chosen, make sure they know how it will work, what side effects they can anticipate. And then we also

help triage any insurance questions, side effects after the fact, and then help coordinate patient assistance too if needed.

**Dr. Clancy**

Really good. Dr. Bettendorf, how about you? What's a work week look like for you?

**Dr. Bettendorf**

Sure. My day-to-day work involves quite a bit of variety with classroom and clinical teaching as well as scholarly efforts. I see a wide variety of patients in my clinical practice at the university, including patients with general rheumatology conditions, as well as patients who have rheumatologic conditions who are pregnant or seeking preconception counseling, and also young adults with rheumatologic conditions who are transferring care from pediatric rheumatology and they're learning how to manage their own healthcare and navigate the healthcare system as adults.

I work closely with our clinical pharmacists in clinic, and I'm so grateful for their expertise. I ask them a lot of questions, and I appreciate that they are there to help counsel our patients as we prescribe new medications.

I teach students, residents, and fellows in clinic, and when I'm not in clinic, I teach in the classroom, prepare lectures, work on course syllabi, grade things, create new course materials, and I also have the opportunity to teach ethics and work on some research projects. I get a lot of variety.

**Dr. Clancy**

Yep, you both do. A lot of variety and a lot of direct patient care and we're glad you're here. Anything special that drew you to focusing on these immune related disorders? And again, let's start with Dr. Johnson.

**Dr. Johnson**

Yeah, I actually have close family and friends who have suffered from a variety of autoimmune diseases, even specifically Crohn's disease. So I guess that's what initially drew me into the position. But personally, I do like to experience new and different clinical areas. So this is actually a new experience for me to be in the IBD clinic and just really the opportunity to learn more.

**Dr. Bettendorf**

I had no idea I was going to become a rheumatologist until I was placed on a rheumatology elective during my residency because the elective I had actually requested was full. And so

I had no idea what rheumatology was and quickly kind of learned that I loved the complexity of the patients that we were getting consulted on to see inpatient. Most of the conditions that we were seeing could affect nearly any organ system. And so I quickly realized like how important it was to be a good internist in order to be a good rheumatologist. And anytime there was a mystery, like a patient that had fever of unknown origin or somebody who had some kind of diagnosis that they couldn't figure out, rheumatology seemed to get called. And so it kind of felt like being a medical detective. And I loved the idea of putting together the different puzzle pieces and trying to form a larger picture that would encompass everything we were seeing happening to the patient.

I also really like living in the realm of uncertainty. And I think a lot of times in rheumatology, we think, well, it could be this, could be this, could be none of this. And maybe I don't have the right idea at all. And so I think rheumatology really challenges possibilities from bread and butter diagnoses all the way to the kind of the zebra diagnoses.

The other thing that's really cool in rheumatology is that most patients don't graduate from rheumatology because a lot of our conditions are lifelong. And so we get to know our patients really well and have lifelong relationships. And so I love that. And then what we're talking about today, I love that in rheumatology we have this giant toolbox with really effective medications that can put people into disease remission. and really help them maintain functionality from conditions that might otherwise be really devastating.

### **Dr. Clancy**

So before we get to our main topic of clinical use of biosimilars, we need to work through some important terminology that our listeners may not be well versed in. Can we start with defining biologic or a biologic product?

### **Dr. Johnson**

Yeah, absolutely. Yeah, biologic products include a large variety of products, including vaccines, blood and blood components, somatic cells, gene therapy, insulin, all good things. But essentially, biologics are composed of sugars, proteins, and nucleic acid and are often from living entities such as cells or human tissue. And this is different than the traditional medications that we take because those are often made-up of different chemicals instead of true living entities.

### **Dr. Clancy**

So they're complicated. That sounds expensive to develop and then test for FDA approval and then get approved for insurance, then it sounds expensive to produce for the general

public. How much can a new biologic cost for a year of treatment? Because both of you talked about these being oftentimes chronic diseases.

**Dr. Bettendorf**

Yeah, I can talk about this a little bit. And Ashlyn, I'm sure you've got great information to add. Biologics are highly effective, but the downside is that they're very expensive and they represent a significant portion of the pharmaceutical product cost and up to \$210 billion, or 17.5% of total US medical expenditures in a year. So if we look at Humira, and I'm choosing that one intentionally since it's been the highest grossing drug in the world for years, and its exclusivity patent expired in 2023, and so many biosimilars have actually just hit the market. So if we look at Humira, a box of two pens, which is a one month supply, can cost upwards of \$8,000, depending on the particular insurance the patient has and how that's working the drug company. But thus, if we look at that cost of 8,000 a month, a year of medication could cost \$96,000. So now if the patient has insurance, most of that's going to be covered by insurance with some of it may be part of the patient's responsibility. And in some cases, the pharmaceutical company will have like patient assistant programs that will help cover the cost of the drug, or they'll have something called a copay card that can help make a patient's copay more affordable for the patient. But nevertheless, these drugs are a huge cost to our healthcare system.

**Dr. Clancy**

Ashlyn, anything you want to add to that?

**Dr. Johnson**

I would just say, Humira has been around for almost 20 years and we think of the price of it being, that \$8,000 a month. When we get into these newer biologic agents that I work with, specifically Stelara and Skyrizi, these are upwards of \$130,000 a year for patients. So cost really becomes an issue for us and for our patients, understandably, because most people are not able to afford something like this.

**Dr. Clancy**

Wow. Wow. Well, you both are young, but in the treatment of immune-related disorders, what were some of the first biologics and what was the original source of those biologics?

**Dr. Bettendorf**

So I had to do a little digging on this because this predated my time in medicine. So one of the earliest biologics approved for our rheumatologic conditions was infliximab, which was approved by the FDA in 1998. And this is a recombinant DNA derived chimeric IgG

monoclonal antibody. And so that's a big mouthful, but basically it contains both mouse and human components that together inhibit tumor necrosis factor alpha, which is a signaling protein that is involved in systemic inflammation. So if we can block that, we can sort of block that pathway of systemic inflammation. This was a game changer for rheumatoid arthritis. And we also use it in many of our other conditions like psoriatic arthritis, ankylosing spondylitis, sarcoidosis. In Ashlyn's world, in the GI world, it's an important therapy for inflammatory bowel disease. Along came rituximab in 1997, and that was initially approved for oncologic conditions, I think non-Hodgkin's lymphoma at the time. And it didn't get FDA approved for rheumatoid arthritis until 2006. But that's another big one for us in the rheumatologic world. We use it for many different indications, not as rheumatoid arthritis, very important medication for vasculitis as well. Enbrel got approved in 1998. Humira came along in 2002. And so unlike infliximab, which was that first one in our rheum world to really hit the market, infliximab was derived from both mouse and human components, but Humira was the first fully humanized monoclonal antibody that the FDA approved. And then a TNF receptor, on the other hand, is made from the combination of two naturally occurring soluble TNF receptors that are linked to a particular part of the IgG1 called the FC portion. And the effect was that this was an artificially engineered fusion protein. So as time has gone on and biologics have evolved, the ways in which they're made and designed has looked different as well. And I'm sure Ashlyn can give a lot more insight into that as well.

### **Dr. Johnson**

It's really interesting because, a lot of the medications that Dr. Bettendorf mentions that are approved for her disease states, we subsequently followed and got approval for Crohn's and ulcerative colitis. So infliximab was our first biologic agent in 1998 for Crohn's disease, and we actually didn't get the designation for ulcerative colitis until 2005. And again, similar with Humira or adalimumab, we received approval in 2007 for Crohn's disease and then again, in 2012 for ulcerative colitis. Majority of the new medications that have come along for us in recent years have all been the humanized monoclonal antibodies compared to the chimeric antibodies that were initially produced. So I'm just curious to kind of see where science continues to push us forward as far as new drug development from here.

### **Dr. Clancy**

Great, great answers. I am a biochemistry nerd and so I'm just soaking this all up. This is really good. Again, both of you are relatively young and some of these medications were being used as you were being trained. But do you have a sense of how biologics change the game as far as treating both sets of immune related disorders? What was it like before the biologics were around and how have things gotten better or how are things different now?

**Dr. Johnson**

I know for the IBD world, and since we've had the approval of infliximab and adalimumab and things like that, patients are not only seeing an improvement of symptoms, which is ultimately giving them increased quality of life, we're also seeing better responses of remission for our patients. And these new therapies often don't have to be something that's taken every single day as compared to treatments prior. We're seeing better side effect profiles for our patients and ultimately just better control of their disease.

**Dr. Bettendorf**

I'll add to that. So how biologics changed the game in the world of rheumatology was really before my time. So I trained in the era after biologics were already a mainstay of therapy for many of our rheumatologic conditions. But I can add to this in that I think one important study that rheumatologists often reference when we think about the effectiveness of biologics for our conditions is called the RACCAT trial. The RACCAT trial was published in New England Journal of Medicine back in 2013, and it was a 48-week, double-blind, non-inferiority trial where patients that had active rheumatoid arthritis, despite being on full doses of methotrexate, were randomly assigned to triple therapy, and that is in methotrexate, sulfasalazine, and hydroxychloroquine, or the other arm was randomly assigned to etanercept plus their methotrexate. And what they looked at was, so how the study proceeds that patients who did not improve after 24 weeks were then switched in a blinded way to the other therapy. And what the investigators found was that triple therapy was non-inferior to etanercept plus methotrexate, and there were no significant differences in radiographic progression. So that has to do with like the joint damage seen on X-rays, for example. No significant differences in pain and health-related quality of life, nor in major adverse events. So it is important to note, I bring this up because it's important to note that we had good effective therapy for rheumatoid arthritis even before we had biologics. But where I really see the difference in my clinical practice is in patients who have had their condition for decades before the existence of conventional DMARDs. And conventional DMARDs being like methotrexate, sulfasalazine, with leflunomide, hydroxychloroquine, that sort of type of medication, And thinking about, methotrexate wasn't FDA approved for rheumatoid arthritis until the late 1980s. So, some of my patients have had this condition for many, many years and they've had their rheumatoid arthritis, for example, for so long that they were treated with aspirin until their ears rang or infusions of gold, which is what they had, you know, before my time, long before my time. And so I've inherited some of these patients that had their condition during that era and they have unfortunately, irreversible severe joint damage. And with the advent of conventional DMARDs and now the advent of biologics, we see so much less of that severe joint damage. It's really incredible. But knowing that triple therapy when it's taken correctly is as effective as a biologic plus

methotrexate is important to keep in mind. But that being said, a lot of patients have reasons they can't take triple therapy because of contraindications, renal dysfunction, intolerances, allergies, or other issues. And so having access to other therapy like biologics really opens up a whole new realm of treatment possibilities for that group of patients.

**Dr. Clancy**

Yeah, great, great. Well, I do remember gold therapy [chuckle] and I do remember a lot of methotrexate back then as well. So, yep.

**Dr. Bettendorf**

You also remember when the Field House hosted the basketball games ..

**Dr. Clancy**

Yes, yes, I do. I was a ball boy for the Iowa Hawkeyes in the Field House [laughter] So yes. So in understanding this subject, we still have a little bit more terminology to go. Let's continue with defining what a reference product is, because I see that used in some of the literature. What is a reference product?

**Dr. Johnson**

The reference product is what we would call the originator product. So essentially it's the drug that did the bulk of the work to become FDA approved. They had to complete significant clinical trials in order to prove safety and efficacy and then ultimately obtain approval for their subsequent disease states. And they kind of received those initial patents and approvals.

**Dr. Clancy**

Got it. What is a biosimilar?

**Dr. Johnson**

So a biosimilar is designed to be almost a near identical copy of that reference or originator product. Given the complexity of the drug design, the biosimilars cannot be exact copies of that reference product, but they still contain the same active ingredient, the same mechanism of action, and the same dosing.

They are not all interchangeable with their originator product. The FDA required specific distinction for biosimilars to become interchangeable. So not all biosimilars are interchangeable. In order for a biosimilar to be interchangeable with the parent product, it has to meet certain benchmarks by the FDA. So they have to have the biosimilar designation. They have to produce the same clinical outcome as the reference product, but

they also have to complete additional studies proving efficacy, the ability to change back and forth between themselves and the reference product. truly, a lot of the biologic products do not have to undergo the same lengthy and expensive clinical trials that these initial parent products had to go through. They essentially just had to prove that they were clinically efficacious and did not need those direct comparator studies. And actually most biosimilars were not studied in Crohn's disease and ulcerative colitis, and a majority of them were just studied in rheumatoid arthritis and psoriatic arthritis as well.

**Dr. Clancy**

Just to see as far as safety as well, I see.

**Dr. Johnson**

Correct.

**Dr. Clancy**

So this is kind of new territory, newer territory for the FDA. With the original biologics being highly effective and easier for the patients, but also so expensive, did the FDA facilitate the development of alternatives through biosimilars? Was the FDA kind of encouraging this?

**Dr. Bettendorf**

Yeah, I did a little. kind of diving into the history of this. And yes, it looks like the answer is yes. And when I look back historically, in the 1980s, drug costs that were associated with branded synthetic products, so not talking about biologics here, but they reached record highs. And then that led to the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendment. And that created this approval pathway for generic drugs to become what would become one of the most impactful cost savings interventions in the US healthcare system at that time. And so now we're seeing the sort of same history sort of repeating itself where we've had record highs in drug costs related to biologics, much, much more so than what we saw back in the 80s with the branded synthetic products. And so the Public Health Service Act got amended in 2009 to include the Biologic Price Competition and Innovation Act, or BPCI Act, also referred to as the 351K Approval Pathway. And so that pathway created an abbreviated licensure pathway for biosimilars, since the goal was not to reestablish, like Ashlyn mentioned, you know, not to reestablish primary safety and efficacy of a biologic compound. That's already been done back when the reference product got approved. But instead, this pathway is really to demonstrate that the biosimilar product is highly similar to the reference product. And so that's how developers are actually able to bring biosimilars to the market at the lowest viable cost.

**Dr. Clancy**

Ashlyn, this is complicated territory. Anything else you want to add to that?

**Dr. Johnson**

I do think it's interesting that the European Union is actually years ahead of us on the biosimilar front. Their first biosimilars were approved in 2006. And when we think, we just got recently had the Affordable Care Act to allow us to start into the biosimilar realm, I think that's very interesting. I just think an interesting part of it all is that infliximab and adalimumab have actually had FDA approved biosimilars since 2016. But because of that exclusivity on their patent, like Dr. Bettendorf mentioned earlier, we have been unable to use these biosimilars. So we have been approving them left and right, and now we're truly just seeing them start to come to market because of the legality of it all.

**Dr. Clancy**

Wow. And that explains what happens in late night TV and all the commercials we're getting now.

[laughter]

**Dr. Bettendorf**

You raise such an interesting point though, because we're literally like almost a decade behind Europe in terms of bringing these products to market here in the US. And so when people are like, oh, these are new experimental drugs, like, oh, a lot of these drugs have been around for a long time. It's just taken the US a while to bring them to market for legislative reasons. And the US didn't bring the first biosimilar to market until 2015. So think about in Europe, back in 2006. One of the other kind of interesting things I found was that pharmaceutical companies that make reference products, like the big name, large companies that are making these reference products are actually kind of also hopping on the bandwagon and manufacturing some of the biosimilars, understanding that that's the competition for their product when their exclusivity patent expires. So I think important for patients to keep in mind that a lot of these things are even actually produced by the same large companies. Not all of them, but some of them are.

**Dr. Clancy**

Wow. So Brittany, you touched on a word and maybe both of you can help us with this. How is this different than generics then? And do biosimilars themselves have their own patent protections?

**Dr. Johnson**

So biosimilars and generic drugs are like in some ways, as they are both versions of a brand name drug, but there are also many differences between the two. So generic drugs are often generally smaller, simple chemical compounds and more straightforward to copy. And then the biosimilar cannot be copied exactly because the products need to contain a slight variation of that parent product. So the mix will never be the same as that reference product. With as far as patents are concerned, in order for a biosimilar to get a new patent, they would have to have a new invention. So if they have a new device that they're using or they're a new formulation, a new dosage regimen, all of those would then be considered for a new patent.

**Dr. Bettendorf**

I don't have much to add to that. I think it's just like you said, because the legislative requirements allow for the approval of a biosimilar to have certain differences between the biosimilar and the reference product, that does give a certain leeway that differences can occur. And so if there is something novel about that biosimilar with regards to like a longer shelf life, for example, or ease of manufacture, then there might be something patentable about that biosimilar.

**Dr. Clancy**

Well, you guys are doing a great job educating the psychiatrist here. The naming of the biologics and biosimilars also baffles me with the name and then four or five letters afterwards. Can you shine any light on that as well as how this naming goes with the biosimilars and the biologics and how they're related?

**Dr. Johnson**

This was actually really interesting for me when I was looking into it. The FDA finalized the guidance on this in 2017. And essentially they proposed that the suffix following the drug name had to be 4 lowercase letters, be unique and be devoid of any meaning. And it should not be promotional. It could not include abbreviations used in common practice that could be misinterpreted. It could not contain or suggest any drug substance name or core name and could not be mistaken for the name of a currently marketed product or be too similar to any other suffix designation. So in essence, there's no rhyme or reason for most of them. It's just the combination of letters they have chosen.

[chuckle]

**Dr. Clancy**

So after all of this, has this resulted in the biosimilars being less expensive?

**Dr. Bettendorf**

From what I'm discovering, they are significantly less expensive. And it looks like biosimilars are going to help save billions of healthcare dollars with projections really varying from 2 to \$2.8 billion between 2010 and 2029. Biosimilars offer efficacy that's really similar to the reference product, but at significantly lower prices. And so that's bringing competition into the healthcare marketplace. They vary from between 10 and 50% cheaper than the reference drug and sometimes even much cheaper than that. I found a one-month supply of adalimumab AQVH, branded as Yusimry, on cost plus drugs for \$584 a month compared to the \$7,000 to \$8,000 cost of Humira per month. So you can see a significant cost savings there that may change the future of the healthcare marketplace.

**Dr. Clancy**

I want to come back to something that Dr. Bettendorf was touching on, and Ashlyn, I want to bring you into the conversation with inflammatory bowel disease. When you're talking to patients as far as traditional treatments versus the biologics and biosimilars, how do they hold up as far as maintaining function, lessening risk for loss of joint function? And Ashlyn, how do they hold up as far as risk for colon cancer? So Dr. Bettendorf, let's start with you.

**Dr. Bettendorf**

Sure. So I think biologics and biosimilars are highly effective for treating many of our rheumatologic conditions, and they're the standard of care for many of our conditions if that condition does not respond to conventional disease-modifying anti-rheumatic drugs or if the patient has a contraindication where they can't use those. And that's really in my mind the biggest advantage of biologics. When we think about comparing triple therapy, which methotrexate, sulfasalazine, and hydroxychloroquine, if that's taken at full dose and with folic acid supplementation, that is actually upwards of 72 pills per week just for the triple therapy alone, not counting any of the other pills the patient might be taking for other conditions. And so that regimen, you know, if it's taken incorrectly, there's a very real risk of harm. And that's a huge responsibility for a patient to be able to manage 72 pills a week. And the reality of it is like not all patients can manage a regimen like this due to their busy lives, the complexity of that regimen and other factors. And so with the advent of biologics, some patients are maintained solely on an injection that they might take once a week or even once every 8 or 12 weeks, depending on the condition and the treatment that they're on. And so that's a huge sort of change in terms of the convenience, the lifestyle and the safety of management of that drug for our patients.

**Dr. Clancy**

Ashlyn, how about you? What do you see as far as the ulcerative colitis in the Crohn's patients? Are they healthier? Do they do better than some of the traditional treatments?

**Dr. Johnson**

Yeah, so reduction in colon cancer is not traditionally a part of the traditional study criteria. There have been some retrospective cohort studies done. There is one that was completed between 1999 and 2020 that evaluated over 62 million patients with Crohn's disease and ulcerative colitis. And they were able to see that these patients have a reduction in colon cancer than the average patient. But again, nothing that's been completed. That's been kind of a prospective study, but we have good retrospective data to show that.

**Dr. Clancy**

Good. So both of you in the clinics working with a lot of patients, start a patient on a biologic, a biosimilar becomes available. Have you seen much difference between the biologics and the biosimilars for treating conditions? So within rheumatoid arthritis, within ulcerative colitis, within Crohn's, Is there a go-to first one that you would like to go to, whether it's a biologic or a biosimilar, without cost being an issue?

**Dr. Bettendorf**

I think it's rare that I'll have a patient who absolutely needs a reference drug or a name brand drug. Biosimilars, because they need to prove that they're not inferior to the biologic reference product in order to be approved, I don't typically observe issues with effectiveness. If the patient was previously controlled on the reference drug, they're typically going to be controlled on the biosimilar. That being said, sometimes different intolerances can occur, like injection site reactions, maybe related to other non-active components of that drug, or even in the device itself, like a device containing latex or something like that. In rare cases, I've had patients develop worsened disease activity on a biosimilar, and that's rare. But in those situations, if they were previously stable on the name brand product or the reference drug, then we would appeal to insurance for that name brand product.

**Dr. Clancy**

Got it. Ashlyn, any, you know, on the ground in the trenches, any differences between the biosimilars and biologics that you see?

**Dr. Johnson**

I think we'll definitely need more real world experience to kind of confirm what, the clinical trials have shown us that there is no difference in efficacy, but I'm curious to see what our real world experience is. One thing too that we kind of have been talking about is kind of the nocebo effect for our patients. So this is essentially like the psychological, physical, and neurobiological phenomenon associated with the potential perceived harm from switching from this parent or reference product to a different biosimilar product. So just kind of the patient's negative expectations or connotations that they could have from switching to this incredible drug that has done so well to treat their disease, just their fear with that is definitely something that we overcome and educate on. So it's just kind of an interesting phenomenon that we've been dealing with as well.

**Dr. Clancy**

Finally, I'm relevant in this conversation with psychiatry and psychology, so all right.

[laughter]

**Dr. Bettendorf**

I would add to Ashlyn's answer that like Humira, with just having the biosimilars come out on the market this year, I agree, we need more time to understand really what are those going to look like in clinical practice and how effective are they. So far, I'm not seeing much different and I've had many, many patients have mandated switching. My answer, I think I'm largely basing on infliximab, which has had biosimilars around for many years and I typically don't see any issue with the reference product compared to the biosimilar for those.

**Dr. Clancy**

So let's bring in the influence of the payer, Medicare, Medicaid, and commercial insurance and pharmacy benefit managers for the biologics and biosimilars. How do they influence your prescribing specific biologics and biosimilars? And I know, Ashlyn, in our intro, you talked a little bit about that's part of your role. So how does that kind of, in a way, almost the negotiation happen of this is the drug that we're going to be able to match for you the most?

**Dr. Johnson**

Truly they play the largest role in product selection for our team. Oftentimes insurances will require patients to step through certain therapies or try and fail certain therapies before they will decide to approve a biologic product themselves or even a biosimilar. A lot of the Humira biosimilars that we have encountered have been insurance mandated, just as the

formularies change and, you know, insurance companies see that they can get this drug for cheaper and see what that benefit will be to them as well. And obviously they're kind of passing that on to their patients optimally, which is causing those switches.

**Dr. Bettendorf**

I agree. I would add like insurance companies often have like a preferred product list for different disease states and they typically won't cover non-preferred products unless that patient has tried and failed a number of their preferred products first or has some very significant contraindication or reason they can't be on a preferred product. And because these products are so expensive, if the insurance isn't going to pay for a non-preferred product, paying out of pocket for the drug is often not an option for patients. And so we're sort of at the mercy of insurance companies' algorithms for what they require before they'll approve certain products, which can be really a source of frustration, I think, as a clinician. And certainly, patients have reasons they can't take the insurance company's preferred drug or drugs, or we have a good reason to believe that drug or drugs aren't going to be effective. And then in those cases, we would go through the appeals process. When it comes to Medicare, things get really tricky because if a patient has Medicare without a supplement, injectable biologics are typically going to be covered, and Ashlyn, correct me if I'm wrong, but typically going to be covered at 80%. which leaves the remaining 20% to be covered by the patient. And often that is just not doable because these are such expensive medications. In patients that have a supplement, we often find ourselves utilizing the infusible biologics over the injectables because then those are covered 80% by the patient's Medicare plan and the remaining 20% is then picked up by the supplement, which helps to make those medications more affordable for patients.

Unfortunately, there's still problems even with this system, because if a patient has a rare diagnosis that has no FDA approved treatment for it, we might have good evidence in our literature that supports the use of a certain drug for that rare diagnosis. But because it hasn't been FDA approved for that indication, it can be almost impossible to get Medicare to approve it. And in those cases, we rely on our social work team, which is incredible. And that helps connect patients with patient assistant programs that get offered directly through pharmaceutical companies or grant programs to try to help them get this medication. But the sad reality is that some patients fall through the cracks because they're over income, so they don't qualify for the patient assistant program, for example, and the Medicare is not going to cover their medicine for a non-approved FDA indication. So this is where getting the cost down through bringing biosimilars to the market and increasing market competition will really help patients who get stuck in these situations, having to pay out of pocket. And you could imagine that \$90,000 plus that it would cost to be on Humira for a year is not doable for most people. But if there's a biosimilar available

that costs 7,000 per year, then it becomes maybe more manageable, although still quite expensive.

**Dr. Johnson**

What is actually interesting from our perspective is we have seen Medicare and Medicaid be some of the slowest adapters to the biosimilar product. So oftentimes, even with this Humira biosimilar change that we've been going through with a lot of our insurance companies, a majority of our Medicare and Medicaid patients have not been pushed to switch to alternative agents and are able to stay on that reference product.

**Dr. Clancy**

Wow. Well, let's talk through a term you both introduced to me as we prepared for this. What is the term non-medical switching then mean?

**Dr. Bettendorf**

So I think about this term as when an insurance company requires a patient who's doing well on their current therapy to switch to a different product. And that's typically one of their preferred products for no medical reason. So usually insurance companies determine their preferred products based on which drugs they're able to get at a cheaper cost than others. And so sometimes their preferred product list will change and they may say, oh, now we're expecting the patient to switch to one of these drugs. And so that's something that depending on the nature of what kind of switch they're requesting, we would look at and see, does this make clinical sense for the patient or is it something that I need to appeal and advocate for my patient to continue getting the current treatment?

**Dr. Clancy**

Sure, sure. So by the nature of this topic, we are working in the immune system and we're hopefully calming the immune system for some of these immune related disorders. But do you have issues with immunogenicity with some of these biologics and then switching over to biosimilars? Do you worry about that? Do you see it from time to time that someone has some type of immune related reaction to a medication that we're trying to calm the immune system itself?

**Dr. Johnson**

I have seen kind of a handful of allergic reactions come through as we switch from the reference product to a biosimilar product. And whether this be from different additives that are in these new biosimilars that were not initially in the reference product. Some of these new devices can also contain latex, which patient may have not known they were allergic to

prior to. And they're also often thankfully produced without preservatives. So kind of preventing that aspect. But I think We'll need continued research on if there is going to be any immunogenicity with these biosimilars. Like I mentioned earlier, for them to be interchangeable, they had to prove interchangeability, but I think prolonged interchangeability will be quite interesting, especially going back to that non-medical switching. If you are changing insurance companies throughout the year, you could be changing from one product to another product to another in the course of three to six months. So I think that's a good point to bring up going forward is what this will look like for patients.

**Dr. Bettendorf**

Yeah, I agree. I think we really need more research, especially on the possibility of immunogenicity happening with non-medical switching to biosimilars. Most of the studies that I found didn't show any difference in safety profiles or immunogenicity rates in patients that were switched to a biosimilar, which makes sense if the product is similar enough, it really shouldn't generate immunogenicity. But I think we need more information But non-medical switching between drug classes, which I think you were talking about at the end, Ashlyn, and so not talking about switching to a biosimilar, but actually a patient who is asked or recommended, sort of forced, I guess, by insurance to make a non-medical switch to a different drug class because of a change in preferred products or a change in insurance, that could cause immunogenicity. And patients may develop anti-drug antibodies to their original drug that they were previously doing well on if they end up having to go back on that drug and it may be if it's utilized again, unfortunately. Does that sound fair, Ashlyn? Is that what you have found?

**Dr. Johnson**

Yes, I would agree with that.

**Dr. Clancy**

So Dr. Johnson, when you're sitting down with a patient and you know you've got to do a non-medical switch, what kind of tips do you have as far as counseling a patient through that?

**Dr. Johnson**

We like to first let the patients see the device they'll be switching over to. While these devices are quite similar in the sense that most of them are auto injector pens or syringe options for patients, they are still different. Some will have multiple caps, some will require a push motion or pushing buttons. And that education piece is really important, especially

for patients. And thinking back to adalimumab, if you have been on a drug like Humira for 10 years, you kind of know that rhythm and know how that feels to inject that every couple of weeks. But if you're switching to a new product and you're anticipating the same rhythm, that would be incorrect. So educating them on that this device may feel different, work different, but we also talk about the sense that they may see some uptick in their side effects again. Now, although these medications are highly similar, like we mentioned, there are different additives that are in there that could induce a side effect that you maybe forgot about when you first got started on Humira. So that's something we like to educate them on. And really we tell them and we anticipate that we should see no difference between the drug that they were on to the drug that they are switching over to and that they should continue to have the same disease control. So just really putting everything into perspective from them. We also like to tell them what biosimilars are. It's a new topic for you, but not only every patient that we encounter with on a daily basis. So kind of bringing that to their level and helping them to understand what we're doing and how it's not going to change their therapy.

**Dr. Bettendorf**

I would agree with that. I don't tend to have much reservation about switching a patient to a biosimilar. as most of the patients are going to do just as well on that biosimilar as the reference product. But I do think it's important to talk to patients about the efficacy and safety processes that biosimilars must undergo in order to get approved and try to help combat that nocebo effect that Ashlyn was talking about earlier. If the insurance is requiring a non-medical switch to a biosimilar product, that's typically going to be a hard battle to fight. And the reality of it is that most of the time the biosimilar is more cost effective and is a beneficial alternative. But if the patient were to have a reaction, like Ashlyn was talking about, to that biosimilar, one of the additives to it, for example, or their condition became more active after switching to the biosimilar, then we have a way that we can sort of appeal for the name brand, sort of a case for appealing for the name brand. But again most patients don't need that.

**Dr. Clancy**

Let's circle back to one topic that Brittany, you talked a little bit about, but the financial support kind of whole market that's out there, what is available to that patient that is. got maybe a very basic insurance that's not going to get a whole lot of coverage that has a high deductible or one of those Medicare patients that isn't able to themselves afford a supplement. How does it all work as far as getting these patients these medications in a way that they can at least afford it?

**Dr. Johnson**

Thankfully, almost all of these biosimilar companies are offering a sort of patient assistance typically, and it's for commercially insured patients versus a Medicare or a Medicaid patient. But they do offer coupon cards that oftentimes we can get the cost down to around \$5 or so. And if they are completely unable to afford it based on what their insurance coverage provides, they are coming out with patient assistance programs. And like Dr. Bettendorf mentioned earlier, we have a wonderful team here of social workers at the university that help walk patients through these kind of very complex patient assistance programs that these drug manufacturers provide. And thankfully they are able to get the cost of the medication to, you know, from \$5 to free for patients. And then thankfully we have other options like Dr. Bettendorf mentioned earlier with the Mark Cuban's cost plus pharmacy that can provide a cheaper option for patients. But again, that's still a \$500 cost per month of medication. So still expensive. We do use the grants and things like that too if they are available. Unfortunately, those are things that often run out quite quickly. I know I don't think there are currently any active grants open for patients with Crohn's disease or ulcerative colitis, which is unfortunate. But we do everything in our power to try and get something that is going to be either partially or fully covered for our patients because we want them to be treated. So this is kind of a big role that we play within the clinic to make sure that our patients can get the appropriate medication at an acceptable cost for everyone.

**Dr. Clancy**

Really encouraging. Gonna put out the crystal ball a little bit. What does the future hold for biologics and biosimilars as you both kind of look to the future? Do you see new treatments out there, new biologics themselves, new ways to calm the immune system for some of these immune-related conditions.

**Dr. Bettendorf**

I think it's an exciting time. It's an exciting time to be in rheumatology, to be in immunology, I imagine to be in pharmacy. There's a lot of change happening. As of December 2023, the FDA has approved 45 biosimilars. And by comparison, Europe has approved twice as many. The US is slower to approve biosimilars due to misinformation, lack of education, patent lawsuits, drug companies offering rebates on brand name biologics, lots of different things kind of coming into play with why we're sort of lagging behind. But that being said, I think the future holds many more biologics and biosimilars and opportunities to treat complex conditions that were previously untreatable. And so I think it's a whole new world and excited to see where things lead in my lifetime of being a rheumatologist.

**Dr. Clancy**

Great. Dr. Johnson, what do you see out in the future?

**Dr. Johnson**

Yeah, I would just echo what Dr. Bettendorf said. Lots of new drugs on the horizon. They're doing a lot of interleukin receptor specific trials to kind of see if we can find any more targeted treatments. I will say on my forefront, as far as biosimilars are concerned, Stelara will actually have biosimilars entering the market in January of 2025. So that is definitely one of the bigger ones on my radar right now to kind of see what options will be like for patients next year.

**Dr. Clancy**

As we close, what take home points do you want to leave with our listeners on how they can help their patients with biologics and biosimilars? And Dr. Johnson, let's start with you.

**Dr. Johnson**

For myself, I feel like education and communication with patients is the biggest component. Helping them to understand that the biosimilar that they will be receiving is approved. We have the clinical evidence to show that it is safe and efficacious for your disease state. And then for my piece is just educating them on the device, making sure that they understand and can anticipate any changes that they might pop up. I just want my patients to feel comfortable and understood in the sense that we are continuing to do the best that we can to treat their disease.

**Dr. Clancy**

Dr. Bettendorf, how about you? What are some take home points?

**Dr. Bettendorf**

Yeah, take home points that I hope patients and providers alike will have from our conversation is that biologics and biosimilars are highly effective for treating many different conditions and they can have life-changing benefits. But biologics are expensive and they drive up the cost of healthcare. And I'm hoping that collectively as a society, we will embrace biosimilars as a safe and effective way of reducing healthcare costs by introducing competition into the marketplace. And these products are well studied and I think will have a really important role in treating different disease states. So hoping that patients and providers can partner together to feel more comfortable using these medications.

**Dr. Clancy**

Well, great conversation, both of you, Dr. Johnson and Dr. Bettendorf. We really thank you for joining us on Rounding@IOWA and for the work you've done in helping us understand this complicated and rapidly changing landscape of biologics and biosimilars. For our listeners, you can access instructions for continuing education within our show notes. And as always, we hope you'll join us again for another session of Rounding@IOWA.

[Upbeat theme music plays]