Comprehensive Update of **BIOSIMILAR THERAPIES:** Your Questions Answered

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This activity is a collaboration of the AGA Institute and the Crohn's & Colitis Foundation.

This program is supported by independent education grants from Boehringer Ingelheim Pharmaceuticals, Inc. and Pfizer Inc.

Slide 1: Welcome and Introduction

Operator:

Good evening and welcome to ***Comprehensive Update of Biosimilar Therapies: Your Questions Answered***. The activity is a collaboration of the AGA Institute and the Crohn's & Colitis Foundation. This program is supported by independent education grants from Boehringer Ingelheim Pharmaceuticals Incorporated and Pfizer Incorporated.

Throughout the webinar, to participate in the Q&A, simply type your question and then hit "Submit".

I'm pleased to introduce your moderator for this evening's program, Gary Lichtenstein, MD, the Director of Center for IBD at the University of Pennsylvania School of Medicine.

Dr. Lichtenstein:

Thank you, Orna, and welcome, everyone. I'm glad you could join us tonight for what we think will be exciting. And, tonight I'm joined by Dr. David Rubin, Chief of Gastroenterology at University of Chicago, and also, by Dr. Brian Feagan, who's Director of Robarts at University of Western Ontario. We have what we think is going to be something educational and fun as well.

We're going to start with some simple polling questions on the next slide, please, if you would.

Slide 2: Polling Question 1

How comfortable do you feel discussing biosimilars with your IBD patients?

- Very comfortable
- Somewhat comfortable
- Not at all comfortable

Please choose your best selection.

Slide 3: Polling Question 2

Our next question we'll ask is: Biosimilars have the same effectiveness and safety profile as the originator biologic.

- True
- False

Please select what you believe to be the appropriate answer.

Slide 4: Polling Question 3

And, then our final question is: If a new biosimilar therapy demonstrates similar safety and efficacy to the originator biologic in rheumatoid arthritis, what is your opinion regarding its use in inflammatory bowel disease?

- If it works similar to the originator therapy in rheumatoid arthritis, I'm satisfied that it will work similarly in IBD; or
- Just because it works similar to the originator doesn't mean it will work similar to the originator in IBD, more study is needed; or lastly,
- I don't know.

Please choose the appropriate choice for yourself.

Slide 5: Disclosures – Brian Feagan

Okay. Our next slide are disclosures for Dr. Brian Feagan and Dr. Feagan, I'm pleased you could join us tonight.

Slide 6: Disclosures – Gary Lichtenstein

Our next slides are my disclosures that are before you.

Slide 7: Disclosures – David Rubin

And, the subsequent slide are the disclosures for Dr. David Rubin.

Slide 8: Biosimilars in IBD

With that in mind let's begin our program.

Slide 9: Biologic Agents in the U.S.

And, our next slide really opens up the idea that biologic agents in the United States account for about 1% of all written prescriptions, but if we look at the expenditure from drugs themselves, they account for 28% of drug expenditures.

Slide 10: Biosimilar Cost

The next slide highlights that the average daily cost for a biologic in the United States is $45, compared to $2 for a chemical drug. If we look at global sales of biologic agents, they're expecting to reach over $180 billion by this particular year at this point in time, and about 50% of the sales coming from 11 specific agents that face a loss of exclusivity by 2022. If we look at the cumulative savings to healthcare in the EU and USA, as a result of using biosimilars, the overall estimates are over $56 billion in aggregate over the next 5 years and as much as $112 billion might be saved. So, this is data from IMS Health that has estimated that.

Slide 11: What are Biosimilars?

The next slide, please.

You might be asking, so what is a biosimilar? In the EU, there's a definition and in the United States, the Food and Drug Administration has defined this, and I'd like to review that of the US because it's really more applicable for us tonight.

The biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. And, this is important. There's no clinically meaningful differences between the biologic agents and the reference products in terms of safety, purity, and potency.

Slide 12: Biosimilar

Next slide.

So, in other words, you have to have the same strength, the same dosage form, injectable, for example, and route of administration as the reference product.

And, that's the important thing. They really are very similar. They're not exactly the same. And I'll get into that more.

Slide 13: Biologics Differ From Small Molecules

The next slide highlights this is a biologic that is a biosimilar, is not the same as a generic. And, you might say what are the differences? Well, the biologics and small molecules have differences. The competition for – composition for a biologic is proteins, small molecules are organic chemicals, the structure for biologic is variable 3D, and a small molecule is well defined. The administration differs, parenteral versus oral, and the degradation is more catabolism versus metabolism. The mechanism of action is either blocking or depletion when we think of a biologic, as opposed to enzyme inhibition for a small molecule. And, the manufacturing costs are certainly much higher in biologics than small molecules.

Slide 14: Clarifying Terminology

Next slide.

If you create a biologic that is superior to the originator and the originator is the original molecule of terminology, this is termed a bio-better or a bio-superior. And, a biosimilar is not a bio-better. If it's better in ways of its production, then it's something that we would note is not a biosimilar, and we'll talk more about that.

Interchangeability is the medical practice of changing 1 medication for another that's expected to achieve the same clinical result in a given clinical setting, and in any patient on the initiative or with the agreement of the prescriber. There's currently no US biosimilar agents that are deemed interchangeable.

Slide 15: Principle Requirements for the Extrapolation of Indications of Biosimilars

And, there's another thing that we think of when a biosimilar is FDA approved, it's approved for an indication that is not necessarily a disease state that you'll be treating. For example, in IBD, the particular indications that were studied before the initial biosimilar for infliximab was approved was rheumatoid arthritis and psoriatic arthritis. So, what happens is this is then extrapolated to a different indication and it gets approved for all the indications, which are deemed appropriate. And, the FDA has regulations for this. It's basically scientifically justification for extrapolization, should be based on the following issues of the tested and extrapolated conditions of use.

Firstly, the mechanism of action in each condition for which licensure is sought. Secondly, the pharmacokinetics and bio-distribution of the product in different patient populations. Thirdly, the immunogenicity of the product in different patient populations. Also, differences in expected

toxicities for each condition of use in patient populations. And lastly, any factor that could affect the safety or efficacy of the product in each condition of use in patient population for licensure is sought.

Slide 16: Extrapolation of Clinical Data Across Indications

So, our next slide sort of illustrates what happens. If you look here, you have the 2 studies that were done, a Phase III and a Phase I study, one for rheumatoid arthritis, the other frank ankylosing spondylitis, and the majority of the indications were extrapolated based on the biosimilarity exercise to comparing it with what we know as Remicade®, the brand, the originator. Crohn's disease, ulcerative colitis, psoriatic arthritis, plaque psoriasis in pediatric Crohn's, were approved based on that initially.

Slide 17: Totality of the Evidence

And, what is looked at is the totality of the evidence. In the next slide you see this highlighted.

The clinical – the animal studies, the clinical immunogenicity, the clinical knowledge, in other words post-market experience, the pharmacokinetics, the pharmacodynamics, and structure and functional characterization. And, as opposed to an originator, where the clinical studies really drive the totality of the evidence for approval, it's more the structural and functional characterization that lead to the most important findings and it's highly similar, hence termed a biosimilar.

And, the FDA then evaluates the applicant's integration and various types of information to give advice on the scope of extent of the development plan and to determine if this is considered appropriate. The totality of the evidence is what's looked at.

Slide 18: Comparison Across Various Biosimilar Regulations: Extrapolation of Indication

If you look at different countries, there's different regulations for extrapolation of indication, and the next slide highlights this. I won't belabor the point, but just say it's possible with sufficient justification addressing mechanism of action in each proposed indication, pharmacokinetics, bio-distribution in different populations, and differences in expected toxicities in each population. The EU, Japan, Canada, and other places have different potential understandings of this.

Slide 19: Celltrion Conducted Two Large RCTs with CT-P13 (infliximab biosimilar) Based on the EMA Guidelines

So, let's move on to some of the clinical data that led to regulatory approval. The next slide highlights this. Two trials, published in 2013, now 4 years ago, Celltrion conducted 2 large randomized controlled trials, CT-P13 is one of the biosimilars and we'll talk about the different ones we have currently. It's an infliximab biosimilar based on the EMA guidelines. Randomized, double-blind, multicenter, parallel prospective study comparing pharmacokinetics, safety, and efficacy of CT-P13 and the innovator infliximab in patients with ankylosing spondylitis, otherwise known as the PLANETAS study, and then another study, randomized, double-blind parallel study equivalence in efficacy of this agent compared to the innovator infliximab, in co-administration with methotrexate, in patients with active rheumatoid arthritis, otherwise known as the PLANETRA study.

Slide 20: CT-P13 Clinical Trials Supporting the Therapeutic Indications

And, the next slide shows the endpoints that were looked at. The ACR20 at week 30 for the rheumatoid arthritis data and the pharmacokinetic equivalence at steady state, the area under

the curve, the Cmax, and steady state, in patients with ankylosing spondylitis. And, this led to the approval, given the totality of the evidence, was such that it was considered to be equivalent biosimilar, if you would.

Slide 21: Switching vs. Substitution

Now, when we look at different ways patients can be treated, we look at ways in which things may occur in clinical practice. And, the next slide highlights switching versus substitution. And, these are illustrations of different studies. There may be a transition study, a substitution study, or an interchangeability study, and we'll talk about that shortly. But, a transition study is where biosimilar, for example, and originator products are used concurrently in 2 different groups, and then the groups are switched to all 1 product, say, biosimilar.

A substitution study is where they're started on originator, say, for example, and a biosimilar, and then they're switched to other products. In other words, the originator goes to the biosimilar, the biosimilar goes to the originator.

And, then an interchangeability study is similar to a substitution study, but there's multiple switches. And, this is perhaps what's going to be clinically relevant in the future and Dr. Feagan, Dr. Rubin, we'll ask for their opinions shortly when it comes to the questions and answers.

Slide 22: NOR-SWITCH Trial

So, some of the data. One of the most well-quoted studies is the NOR-SWITCH study. Our next slide highlights the design.

Phase IV, multiple indications, prospective non-medical switch study – and when they mean non-medical switch, it means they're switched because there is not a medical reason, but it's just a switch that occurs between the biosimilar originator directly, as is illustrated here, so this is a transition study, if you would, to a degree.

Fifty-two weeks randomized double-blind, non-inferiority study. And, the primary outcome was worsening of disease at 12 months. And, for Crohn's disease, the Harvey-Bradshaw Index was used and for ulcerative colitis the Activity Index was used directly. And, anti-drug antibodies were looked at. And, looking at this study, the Remicade versus the Celltrion product, CT-P13, 23 or 36.5% versus 21% for Crohn's, and in ulcerative colitis 9.1 versus 11.9%. And, we'll ask Brian and David to comment on that in the future, what their thoughts are.

Slide 23: P III randomized, DB, controlled trial to compare biosimilar infliximab (CT-P13) with infliximab in patients with active Crohn's disease

Another study presented recently looked at ECCO, and our next slide highlights this, 220 patients in a Phase III randomized double-blind controlled trial, to compare biosimilar infliximab with infliximab in patients with active Crohn's. And, this was looked at, 58 centers, 16 countries, it was presented at ECCO, and they basically found that the efficacy was similar of the biosimilar to infliximab in terms of the Crohn's Disease Activity Index drop of 70 points, of 100 points in clinical remission up to 6 weeks in patients with Crohn's, and a similar safety profile was that compared to infliximab up to 6 weeks.

Slide 24: The PROSIT cohort of infliximab biosimilar in IBD: a prolonged follow-up on the efficacy and safety of CT-P13 across Italy

Another large study presented at ECCO was the PROSIT Cohort, and this is 680 consecutive

patients from academic centers, 13 in total, and non-academic centers, 12 total, so 25 different centers. Four hundred were naive to anti-TNFs. About half-half with Crohn's and ulcerative colitis, and 171 patients of these had prior exposure to biologics. The patients were switched after a mean of about 18 infusions of infliximab, 109 patients, and a total of 4000 infusions overall. And, it's really one of the largest studies that looked at patients treated with CT-P13. And, they found no signals of difference in safety or efficacy as observed. But, these are not prospective randomized, double-blind large trials and that's something you'll see here that is a point of importance. It's not the, quote, registration studies that we're acclimated to.

Slide 25: Biosimilars for Adalimumab in the Pipeline as of 09/2016

As of September 2016, our next slide highlights the different individual applicants that have come through the Food and Drug Administration in various phases for adalimumab and infliximab, and as of most recently, I understand there's 63 products that have been submitted in various stages.

Slide 26: Current Biosimilar Nomenclature

Now just to go over some of the nomenclature that there is. The next slide highlights this.

In August 2015, the FDA proposed a naming for biosimilars and the name has 4 lower case letters at the end. So, for example, infliximab-dyyb. That's otherwise known as Inflectra®. They have no meaning, they're random choices, and the intention is to avoid inaccurate perception of biosimilar efficacy, and also to be able to trace these. So, we have infliximab-hjmt, which is the originator, infliximab-dyyb is Inflectra, infliximab-abda is Renflexis™, adalimumab-atto is Amjevita®, and adalimumab-adbm is Cyltezo®, which recently just got approved in August 2017.

Slide 27: Possible Clinical Scenarios for Biosimilars Use

When you treat patients directly, you have to think of what are the scenarios that you can have. Well, our next slide highlights this.

It could be a new start, so starting with either an originator or a biosimilar. It could be a primary non-responder. So, a patient gets an original agent and then decides to switch to a biosimilar if they don't respond. And, I would argue that's not appropriate because they're really very similar, so if you don't respond to the originator and you have adequate drug level, then you need to think of another mechanism.

It could be a stabilized responder, where the prescribed – the person prescribing medication either elects to maintain the original product and continue that, the originator, or you could do what's called a non-medical switch and switch to a biosimilar, and that's sort of what we alluded to. Or, you have a loss of response. And, if that's attributed to a high anti-drug antibody, switching to a biosimilar is not something one should do. You need to switch to another therapy.

Slide 28: Who will Benefit from ~20-30% Cost Savings

So, who benefits from the cost savings? Next slide. In a recent Rand analysis that was published about a month and a half ago, said really that if total biologic market continues to expand, there's going to be no overall cost savings on a national basis, but we'll have better access to medication. And, that's one of the endpoints that's desired. In the UK with [IMS Health Report] this was something that was suggested based upon their data, that they had more people able to access medication at a cheaper cost.

Will third party payers benefit? Yes, they will, including the government. And, patients will not benefit up front, but long term they will. So, this is something that in the long term the patients will benefit. Their copays are such that it will be less of a cost, at least the Rand Corporation has hypothesized this.

Slide 29: Biosimilars in IBD Conclusions

So, I'd like to conclude here and we'll go on to some questions very shortly. Biosimilars are not generics and the FDA allows for extrapolation of indications for biosimilars, and the available data suggest that biosimilars to anti-TNFs will behave similarly to the reference products.

I should mention as well, drug assays for the reference products are expected to work similarly for the biosimilars. And, remember anti-drug antibodies to reference products will cross-react with the biosimilar. So, if you have a positive antibody, you don't want to switch to a biosimilar.

And, there's no interchangeable designation yet in the United States. Europe and Asia suggest that this is likely, will be okay, at least in single transition studies.

Slide 30: Outstanding Questions

So, the pathway to biosimilars is still a work in progress. There are several questions I'll pose directly. How comfortable will physicians be prescribing biosimilars? How comfortable will the patients be using biosimilars? How will insurers manage these agents? And, we can touch upon different scenarios there. And, can we switch from native biologic to biosimilar without immunizing the patient? Do we need to use immune modulators, for example? Do we have to use them for 6 months duration, for example, before? Can we do a double or triple switch? So, when we have a biosimilar, can we switch from originator to biosimilar 1, to biosimilar 2? And, we have no data yet for that, but these are things that are important and we'll be discussing.

Moderated Panel:

Dr. Gary Lichtenstein; Dr. Brian Feagan; Dr. David Rubin; Kira (Patient)

So, I'd now like to open this up to questions to Dr. Feagan and also to Dr. Rubin.

And, I'll ask first, how comfortable will physicians be prescribing biosimilar agents?

Dr. Rubin:

Hi, Gary, great job tonight. I think you covered the topic very well. So, in terms of comfort, I think we can first acknowledge that some of our colleagues are nervous about these agents because they are familiar with the originator or reference agents that have been available in the US market, and this is something different. But also, as you nicely mentioned, they may be concerned because of this concept of extrapolation, that we haven't studied them in IBD. So, we recognize some of that anxiety and I think we need to address in the way that you just did by explaining carefully how we've come to appreciate this, but also learning from the European and the Asian experiences with transitions. So, I think continuing to educate and address these concerns is appropriate.

Dr. Lichtenstein:

Brian, any differences in Canada or globally that you perceive with regards to acceptance?

Dr. Feagan:

No, I think really in terms of the extrapolation issue, the federal regulatory authorities and all jurisdictions now have approved biosimilar, so if a payer elects to substitute a new start, I don't think there's a lot that physicians can do about that, so they can be agitated, but it won't really make any difference.

I think as far as acceptance goes, acceptance will come with time and personal experience, and that's what we've seen with the introducing of all originator biologics, is that gastroenterologists are pretty conservative animals and it takes a while for them to get used to something.

Dr. Lichtenstein:

I think one of the main things is going to be education, to really explain the situation, the scenarios, and otherwise. What do you think will be the best venues for doing this, other than, say, a teleconference like we're having tonight?

Dr. Feagan:

David, this is more in your camp, but I'll take a stab at it. Well, I think it's through national professional societies is the most relevant venue and I think you're going to hear more about biosimilars at those venues. And, then there are a variety of – purveyors of medical education that can help with this. Let David to comment.

Dr. Rubin:

I think that part of this will just be that it's a little bit out of our hands, so what we've learned from the European experience is once the therapies were in the market and they were being used, the gastroenterology community became more confident and comfortable in accepting their use. I think that people do need to understand what the potential limitations are and what we don't know yet, which is specifically related to multiple changes over time, or the concept of interchangeability. In theory, that might cause some trouble and it hasn't been studied sufficiently. And, my concern has been, and I think others reflect this as well, that it'll just be a race to see who's cheapest this time when the contracts are renewed and patients may end up getting switched back and forth. I think we do need to be on guard against that.

My only other comment about that is that the Crohn's & Colitis Foundation has worked on a position statement that I think provides some guidance and reassurance to our colleagues and that'll be available on their website or at least part of it is already.

Dr. Feagan:

Yeah, I'd agree with David that I think that really the non-medical switching and the possibility of multiple switches across different agents that are similar but not identical, is really the frontier that we don't have any data on, and this is why a lot of people will feel really uncomfortable in that situation, taking a stable patient on originator, switching them, and then having them subjected to multiple switches, depending upon contracting.

In animals, certainly that's a very provocative maneuver, to break tolerance to a foreign protein. And, I think the human experiment will be done. It's interesting to note that the NOR-SWITCH study was really done because the Norwegian government was going to switch from originator to biosimilar. They made a wholesale switch, including non-medical switching. And, this year I understand the

contract has gone back to the originator. So, this isn't a theoretical consideration, it's something that's going to happen.

Dr. Lichtenstein:

David or Brian, what are your thoughts on the NOR-SWITCH study? Is it a well-done study, is it something we should be relying on, does it comfort physicians, does it comfort you?

Dr. Feagan:

No, it's not a well-done study and I don't really take anything out of NOR-SWITCH. I mean it has huge flaws with it in that it's a composite study, where 6 different diseases were aggregated, and a common definition of treatment failure was hammered out, that is really I don't think valid.

And, then one of the really interesting things – and this is the contentious issue – is that what are considered non-inferiority studies, you know, if this is a new chemical entity, the size of the study would be approximately 3 times. And, so biosimilars are cut a break with regard to the precision around the estimates in non-inferiority or equivalency studies. And, I think that's a contentious point as well.

But, as I said earlier, I don't think it matters in the sense that the extrapolation has occurred, these drugs are going to become – are or going to become regulatory approved, and the payers will substitute them for new starts.

Dr. Lichtenstein:

Physicians are faced with this scenario of that they're going to get a non-medical switch. Do you think that certain things should be done, are there certain durations of time that you could foresee or minimal amounts that they should perhaps stay on an originator before switching to a biosimilar?

Dr. Feagan:

Well, there's been a lot of strategies put forward in that situation because of the discomfort level with non-medical switching. And, those include, well, making sure the patients on an immunosuppressive in case there is immunogenicity issue, considering taking therapeutic drug monitoring, getting drug concentrations before and after switching to assess that the PK isn't different. None of these have been really validated in any scientific study.

Dr. Rubin:

Yeah, I agree with Brian. I would just add that there's also the chance that a patient who's seemingly stable is actually going to relapse either way, but the patient and the provider or the physician won't know when they relapse. They'll attribute it to the biosimilar. So, I agree that in some situations, especially the less stable or the sicker patients, you'd want to know the drug level and have a good sense of where the drug is before the switches are made.

The practical point I've also raised is that if there's a delay in the transition, let's say that the place that's going to infuse notifies the patient or notifies the physician and there's some delay in understanding what that means or some push-back, and then suddenly the patient doesn't get their drug on time, then we're setting them up for problems, and that's sort of a real-world issue that is not reflected in the available transition studies that we've seen so far. And, I think that that may cause a new wrinkle in all of this.

Dr. Lichtenstein:

If you were managing, let's say, in a home, you know, and you had, you know, as some institutions are now going to IBD homes and they're deciding between originator and biosimilar, or let's say you're an insurer, what would you be doing at this point in time? Going for the least costly agent, but then if you were offered another agent, say, 3 months later at a much lower price, is that something that you would consider? I mean these are the things that patients I think are concerned about and physicians alike.

Dr. Rubin:

Well, I can tell you that our specialty pharmacy here surveyed academic and community practices throughout the Midwest, not just in the Chicago-land area, but some other practices throughout the Midwest, and what we found is that the majority have already made the switch to the biosimilar. And, that was the decision that we here have decided to do, primarily for cost reasons, at least this first switch that we've agreed to do. I've made it very clear to them at our institution that any additional changes in the way we do things will have to be carefully reviewed. But, for now I think people are making the same decisions, depending on their available cost and what they can afford and what's available to them on a contract basis. We're seeing it already.

Dr. Lichtenstein:

Kira, are you online?

Kira:

I sure am.

Dr. Lichtenstein:

Oh, okay. So, Kira, can you tell us what your thoughts are? I think this is something that is obviously critical when it comes to patient input and we really learn a lot from our patients. Tell us your perspective and tell us who you represent, of course.

Kira:

Yeah, absolutely. I am a patient with Crohn's disease. I've been diagnosed, gosh, about 6 or 7 years now, and am currently on biologics, and actually have had a lot of discussions with my doctor team about biosimilars. We hadn't switched me to any at this point. I was actually on Remicade for a while and I built immunity to that and that was kind of when we talked about those options, but we decided to go a different route with a different therapy, but that was a huge discussion. And, honestly, the first – the day that that came up, I was like what is a biosimilar? I didn't really get it. And, I think that for patients is probably a huge hurdle, explaining first, you know, biologics I think are becoming more mainstream and probably more patients are getting comfortable with them, but biosimilar, that's just something else to educate the patient and making them comfortable with it as well. So, I think that takes a lot of time and patience from, you know, our medical teams to really make us feel like we're on the same page there.

In terms of when it comes to switching, you know, I – living with chronic illness is expensive, so I'm all for cost-savings, you know, as long as they make sense for me long term, and I think, you know, that's probably something that can be really relatable for a lot of patients across the board, is, you know, as

long as I'm being treated and it's maintained and my doctor feels very confident in it, I'd probably be open to, you know, saving some money long term. But, I think that – I would have to be really, really confident in the biosimilar to switch to that, you know, without a lot of consideration from my doctor. It would be a tough sell for me to save some dollars down the road because I mean I'm already spending a lot of money, so if I'm spending a little bit extra to make sure that I'm getting something good, that we feel good about, then I'm okay with it. But that's my opinion.

Dr. Lichtenstein:

Thank you, great, great answer. Brian, David, can you talk about the nocebo effect per se? In other others, when someone is – we do a trial, there is either, you know, active drug versus placebo, but when you're telling someone that they're getting a drug, they might have side effects, if you would, if it's not the originator.

Dr. Feagan:

It's an expectation bias and, you know, it's psychology. If you're doing perfectly well and you're switched to something else, I mean there's really logically, there's only one way you can go when you're going to attribute any deterioration to the product, so it's a real thing.

Dr. Rubin:

Yeah, I brought this up as well. I think there's an ethical issue to doing interchangeability studies where patients who are doing well are going to be electively switched with the expectation that the only thing that can happen is that they're going to do worse. So, nocebo effect implies that there's some psychological or some other reason that they might feel worse when they get this other therapy. That's another reason why we go back to what Brian suggested, which is understanding the PK and truly knowing your patient's status before changes are made.

Dr. Lichtenstein:

So, when we switch to a biosimilar, are we going to be checking drug levels to see if they've changed? Is that something you foresee as a future, quote, guidance?

Dr. Feagan:

I think it's a reasonable thing to do if you're forced into a non-medical switch. I think it's a prudent thing to do.

Dr. Lichtenstein:

And, if they start going down, then it might be appropriate to change drug because it's really not going to be similar then, if you will.

Dr. Feagan:

Well, Gary, it raises the issue of immunogenicity and how you assess it. And, I think your comment earlier about drug assays being okay, the assays, the existing assays measuring originator will, because it's a TNF binding assay, will be able to detect concentrations of biosimilar. Where things get trickier is the – the antibody assays. To validate an anti-drug antibody assay is a complicated business because you have to walk the different – the antibody, anti-drug antibody concentration back to

clinically meaningful events, loss of effect and deterioration of PK, and that's a complicated thing to do. It takes many patients and we just don't have studies like that.

Dr. Lichtenstein:

I'll remind any of the listeners to please write in questions if you have them.

What happens when we have multiple agents on the market? What do you foresee as the non-medical switches with multiple agents? Is there going to be some, I guess, general guidance that you would have for us? And, from a patient perspective as well, Kira, is there a certain thing that you feel that other patients should be doing when it comes to that? Push back against things, should you be on these a minimal amount of time? And, I know that these are not firm answers that we have, but at least some general guiding principles to the clinicians in the audience.

Dr. Feagan:

Well, it's a completely unknown era. I think Kira should handle that question because we don't have any data to help her with it, but how do you feel about switching back and forth between 2 or 3 drugs?

Kira:

You know, I personally am okay with it. I've actually been on 3 or 4 already. I kind of have – I know a few other patients that feel the same way as – you kind of feel like a walking experiment sometimes. So, I'm game for it, as long as, you know, I'm feeling good in the end. You know, eyes on the prize, right?

Dr. Feagan:

Just to be clear, though, it's a little bit different. You switched to another class because you got sensitized to infliximab and I guess what I was trying to point out earlier is that the potential risk of non-medical switching across multiple biosimilars or originator plus multiple biosimilars is sensitization.

Kira:

Right. I, you know, going in that direction, if I was doing fine, if I was in remission, I wouldn't want to change therapy I was on just because it's cheaper or it's something new or something, you know. I would really want to stay stable with what I had as long as it was working. So, I personally wouldn't be really excited about doing a switch unless it was really, really necessary.

Dr. Feagan:

What if your copay was horrific?

Kira:

You know, that would be definitely a motivating factor for me. However, I have noticed that a lot of the medications have copay assistance programs, so that's something that I would look to the producer of the medication to see if they had something, you know, along those lines. Because right now, I know that that's very – it's pretty simple to find those and apply and get approved for copay assistance programs, so I would say it would be a last-last resort for me.

Dr. Lichtenstein:

Have you found, Kira, copay assistance with respect to biosimilars?

Kira:

You know, I haven't actually looked into any of the biosimilars to see if they have copay assistance programs, but I know Remicade has them, I know Humira® had one, and Entyvio® has one, and Cimzia® had one as well. So, I think those are all originators that I was looking into. So, it would be interesting to see if the biosimilars did as well.

Dr. Lichtenstein:

David or Brian, are you aware of any similar programs for the biosimilars?

Dr. Rubin:

Not yet.

Dr. Feagan:

I'm not.

Dr. Lichtenstein:

I haven't seen that as well.

Dr. Rubin:

You know, all the companies making biosimilars invited us to the dance, saying that they were going to do what they could to help the field of IBD and our patients, blah blah blah, and then they get their approval and I'm not hearing from anyone.

Dr. Lichtenstein:

I haven't seen anything as of yet. From a patient perspective, Kira, what are the things you think that physicians need to do when it comes to biosimilars, other than explain things? Are there other aspects? When should the explanation occur? Ideally, not when you're just ready to get the drug – by the way, we switched the drug – but, you know, how far in advance? In the office, would you say, before the infusion, or what would you foresee as the appropriate course that we can do?

Kira:

That's a really great question. I personally have had some really wonderful doctors that were explaining this to me at the time and they really laid out – and I like that they basically had a roadmap of time, with the information we have right now, of times that they would explore these areas, so it was really, really far in advance. Not like we were going to switch it. It was just if this ever happens, we might want to consider switching to this biosimilar. So, having that foundation really early on in the process when you're talking about the different kinds of therapy, I think is where you really start to establish that comfort level with the patient. And, then later on, you know, it's not just something that's being sprung on them because if I was going in for my infusion and I got a call and be like, hey, your insurance company decided to, you know, switch out to this biosimilar because it's saving them some money, I would be – I'd be furious. You know, that's not when you want to hear about it, so you

want to definitely make sure that that's something that is very planned, thought out, and giving a long lead time on things like that, if possible. Of course, I know that there's some instances where it may not be – you're not able to do that. But I think having that long-term discussion of areas where you think it would make sense with the patient is really, really helpful.

Dr. Lichtenstein:

So, David and Brian, I mean if you had to design an experiment for the multiple switches, how would you do that? And let's say ideal world [sic], money was no object.

Dr. Feagan:

Well, with great trepidation actually. Because, you're taking patients on stable originator and then you're switching back and forth between originator and the control – in the intervention arm – and the biosimilar. You'd probably have to do 12-week, 16-week time periods between switch, well, at switching. And, you'd probably have to do 3 or 4 of them, so it's a 1-year study. And, the control arm just stays on the originator. And, the endpoint in those studies I don't think is a clinical endpoint, it's develop an immunogenicity associated with deterioration of the pharmacokinetic profile, sensitization essentially. And, the study would be pretty ambitious. I mean, probably at least a couple of hundred patients undergoing 4 switches over a year, and to get the PK immunogenicity profile. And, the biggest – why I said with some trepidation is that if you're a patient, why would you go into that study? You know, it's strict altruism and, you know, I'm sure that there are lots of patients with IBD who are altruistic, but it's a lot to ask of a patient.

Dr. Lichtenstein:

So, it sounds like it's something we're not going to see in the near future.

Dr. Feagan:

I think it'll be very difficult.

Dr. Lichtenstein:

Difficult to do and, you know, it's hard to say if it's even appropriate to do such a switch with multiple things.

Dr. Feagan:

So, in the absence of an RCT that's going to clarify the situation, you're left with, I think, long-term cohort studies with sophisticated assessment of failure patients, immunologically and pharmacokinetically.

Dr. Lichtenstein:

So, I think it sounds like everyone feels comfortable with a new patient starting, it's the multiple switches where we just don't have the data yet that's really the primary concern, and it sounds like this is a nice alternative in an effort to cost reduce and perhaps eventually pass on savings to patients.

I believe our time is at the point. Do we have further time? If I could get a signal as to when our time is that we're expected to wrap things up, because I've not seen any questions from participants.

Okay, I have a signal.

So, I'd like to thank everyone tonight for participating. To receive CME credit please complete the evaluation as it comes on your screen.

Dr. Rubin, I appreciate your expertise, Dr. Feagan and Kira, I appreciate your participation. And, thank you all for your participation tonight. Hopefully, this was an educational forum. And, I'd like to thank the sponsors as well.

Have a good evening.

Dr. Rubin:

Thank you, Gary.

Dr. Feagan:

Thank you, Gary.

END