A CaseWise™ Initiative – Mission Possible: Matching Treatment Goals of Patients and Providers in IBD in Clinical Practice

CMEO Podcast Transcript

Miguel Regueiro, MD:

Well, welcome everybody. It's wonderful to see so many people here today. I'm Miguel Regueiro. The activity may include discussions of products and devices that are not currently labeled by the U.S. Food and Drug Administration (FDA). We will try to avoid that as much as possible, and, if we do deviate from that, we will also disclose that as well. I'm Miguel Regueiro. I'm Chief of the Digestive Disease Institute at Cleveland Clinic, and I'm going to go down the line and let my panelists introduce themselves. Anita, let's start with you.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Absolutely. Well, welcome and thank you. Good afternoon. It's a pleasure being here with my colleagues. I'm Anita Afzali. I'm a professor of medicine at the University of Cincinnati and currently serve as interim Chair of the Department of Medicine. On to you, Dr. Barnes.

Edward L. Barnes, MD, MPH:

Yes. Hi. Thanks, Anita. I am Ed Barnes. I am at the University of North Carolina (UNC) at Chapel Hill. I'm an associate professor of medicine, and I'm Co-Director of the Inflammatory Bowel Disease (IBD) Center as well. Now, I'll pass it over to Angelina to introduce herself.

Angelina Collins, MSN, ANP-BC:

Hi, I am Angelina Collins. I'm a nurse practitioner at the Inflammatory Bowel Disease Center at the University of California San Diego.

Miguel Regueiro, MD:

And also part of the program, not in the room, some of these folks are actually at this conference, but they're not actually in the room. This will be a unique program and I'll come back to this in a minute, but Jessica Allegretti will be highlighted and Ed Loftus will be highlighted, as well as Millie Long. I think more and more in the world of inflammatory bowel disease we're trying to include patients and patient voices and stakeholders, so you'll hear from a couple of our patients. They've been active in many of the programs like this, at the congress, and others, and it's really a treat to have both Natalie and Kaylaa' today as well.

These are our faculty disclosures. They'll also be in your program. Each of us has listed our potential conflicts of interest in our disclosures here, including Jessica, Ed, Millie, Natalie, and Kaylaa' as well. This is also a peer-reviewed program and this goes through the traditional CME vetting. The learning objectives will be to integrate the latest data and recommendations on interleukin (IL)-23s into your clinical practice and to come up with treatment plans and a shared-decision approach with patients. In a minute, I'll get to this, but this is a very case-based presentation. We'll also look at the latest clinical trial efficacy and safety data and utilize the latest in clinical evidence.

In this program, just to break it into how this will look, the first part will be a very brief didactic program. I'll go through the efficacy and safety data with the IL-23 class. I'll engage my panelists after both the ulcerative colitis

and Crohn's portion. But then, really, the meat of this, which I think is unique and we'd love your feedback at the end, is we have three wonderful cases that are very real world. We show the couple of the patients who are involved in this. Now, we have adjusted, at their permission, some of the case to also stimulate some of the discussion. For me, these are cases that I would see in my own practice in Cleveland. I imagine for all of you, you would see them. I know our panelists have vetted these as well, and this will stimulate a conversation on the cases that I think will be informational as well.

I'll go through some of the didactics here. For treat-to-target precision care, we've really evolved in the way we've looked at treating both ulcerative colitis, on the left-hand side, and Crohn's disease, on the right-hand side. A theme that I'll mention up front is the early treatment with advanced therapy for both ulcerative colitis and Crohn's disease. This will be a concept you'll hear repeatedly. I know you've heard this in the last few years, you're hearing at the congress there, but your first therapy early, it's probably the early use, is going to be most important, but we'll go through some of the patient characteristics. Access is obviously something that we all live with, and especially the United States, in terms of we can't access something. That's a barrier, so that's something that we recognize, and then obviously efficacy and safety.

Why is the IL-23 class important? I remember some of the early Genome-Wide Association (GWA) genetic studies where we identified IL-23 as a putative factor in inflammatory bowel disease. It leads to a pathogenic Th17 response. It promotes inflammation. Interestingly, increased IL-23 also may predict resistance to tumor necrosis factor (TNF) inhibitors. This needs to be borne out in clinical studies, but that may be why some of our patients don't respond to a TNF inhibitor but do respond to an IL-23 inhibitor. We will get into the selective IL-23p19 class and go through some of the efficacy and safety.

I like this slide because this puts all of the pivotal trials that have been done in IL-23s on one slide. In the blue lettering are the ulcerative colitis pivotal trials, and these are the regulatory trials that led to approval of the IL-23s in ulcerative colitis, and kind of in the dark black is the Crohn's disease. You can see we'll discuss risankizumab, guselkumab, mirikizumab. We'll show the data. I think one of the nice things, and we'll get to this in a minute, is that you can take this information with you afterwards. As mentioned before, there are a lot of data in the first set, but this is something that we really want for you as well. These are busy slides. I'm not going to present all of these, but this puts into context, and people often say to put the data together, guselkumab and mirikizumab on this slide, you can see the FDA indications are for all of them, ulcerative colitis and Crohn's. But you can see the route of administration, and we'll get into some of the differences of that when we have our panel discussion here in a minute.

And then also the efficacy. On the right-hand side, you can see the different efficacy. Again, it's not meant to compare across each of them but to give you a sense of efficacy. I'll say up front that the efficacy of these look similar, but we can't say that in a comparative effect of approach. This is risankizumab, ustekinumab. We'll focus primarily on guselkumab, mirikizumab, and risankizumab. We'll talk about ustekinumab and some of the pivotal head-to-head comparisons, but we're not going to focus on ustekinumab. But if you have questions about ustekinumab, we can certainly do that.

Safety, I think you've realized this and many of you have prescribed these medicines already to realize the safety with the IL-23 class has been quite good. But you can see the serious infection rates are quite low, similar to placebo. The most common adverse events are listed, monitoring, which is usually tuberculosis (TB) screening, and we do baseline testing for liver function tests (LFTs), then after induction. That's very similar really for all of them. And then finally, for Crohn's disease, again, same thing, looking at guselkumab, mirikizumab,

risankizumab, far right ustekinumab. Also, safety in Crohn's disease looks quite good. There's nothing new today in terms of safety we're going to present to you that you have not already seen in the publications and in some of the pivotal presentations.

Let me briefly go through some of the ulcerative colitis data. I'll ask all of you in terms of what your thoughts are at a high level. We'll go through each of the IL-23s. We'll present the data and, as I mentioned, we'll do ulcerative colitis first, then we'll do Crohn's disease, and then we'll get to the cases. Let's look at clinical remission and endoscopic improvement. This was the QUASAR study, and this is the guselkumab induction for ulcerative colitis study. You can see in red here is guselkumab, the 200 milligram intravenous (IV) dose at 0, 4, and 8 weeks. Then looking at the 12-week endpoint from left to right, clinical remission, symptomatic remission, response, endoscopic improvement, and histologic endoscopic mucosal improvement (HEMI). And you can see, for each of the endpoints, statistically higher efficacy of guselkumab compared to placebo in that induction course.

And then we look at the maintenance, the week 44 endpoints. The reason there are two shaded red is that's guselkumab is subcutaneous (sub-Q) every 4 weeks, which is one of the FDA-labeled maintenance doses, or the lighter red, the 100 milligrams every 8 weeks sub-Q. And then, again, you can see placebo. You can see the primary and secondary major secondary endpoints were all met. I'm not going to read through all of them on the bottom, but you can see these were all met for ulcerative colitis. One thing that comes up, and I'm sure it comes up in your own practice, is what if a patient's naive to therapy or what if a patient has already been on an advanced therapy? How do these medicines perform? This is the guselkumab study for previously treated patients with ulcerative colitis. On the left-hand side is naive, so that's a patient where guselkumab in the QUASAR study was the first therapy the patient received in advanced therapy. And as we've seen with our other studies, you can see a nice delta between the red bar, guselkumab, and the darker bar, placebo.

And then what about patients who have been on maybe a Janus kinase (JAK) inhibitor or another biologic? Still statistically significant, although barely met with one and a lower response, but still we see a difference between guselkumab and placebo. I think one area of guselkumab that you've probably all realized now is that there is a sub-Q induction, so use sub-Q induction followed by sub-Q maintenance. This is the ASTRO study. This is looking at sub-Q guselkumab induction for ulcerative colitis. Again, on the top are bio-naïve and on the bottom are bio-experienced. Interestingly, when you look visually at the bottom, sub-Q, there's no drop-off, meaning using sub-Q induction. I'll ask my panelists whether they're using IV or sub-Q for both ulcerative colitis and Crohn's induction, but you're seeing good efficacy with sub-Q induction. Now, sub-Q induction is 400 milligrams, which is two times the 200 milligrams IV. Just pharmacokinetically, it's double, but it's still given at 0, 4, and 8 weeks.

Mirikizumab, also the data in ulcerative colitis, this is LUCENT-1. Mirikizumab, you can see in blue, the dose is 300 milligrams, placebo in gray, and again you see a nice statistical efficacy, mirikizumab compared to placebo. On the right side, a primary endpoint was bowel urgency. You can see kind of the separation of bowel urgency, meaning the improvement of bowel urgency as an endpoint with mirikizumab over the first 12 weeks. Maintenance with mirikizumab for ulcerative colitis, the LUCENT-2 study. You can see, again from left to right, the blue compared to placebo. Again, we're seeing statistical efficacy of mirikizumab for the treatment of ulcerative colitis.

And then finally risankizumab and ulcerative colitis. It's called the INSPIRE study. In this, the purple is risankizumab, the gray is placebo. The left-hand side is looking at the clinical response and remission rates at week 12, which are the primary endpoints. And then you can see on the right-hand side the ranked secondary

endpoints, again statistically significantly met with risankizumab compared to placebo. And then looking at the maintenance for ulcerative colitis with risankizumab, similar theme. For risankizumab, as you know, there are two different maintenance dose options. On this slide, the light purple is 180 milligrams every 8 week sub-Q, now given as an on-body injector in clinical practice, and the dark purple is risankizumab 360 milligrams. You can see both of those were statistically significantly higher than placebo for most of these endpoints.

Before we pivot to Crohn's, and maybe, Anita, I'll call on you first, it's a lot of data, but your overall impression of ulcerative colitis, IL-23s, maybe just give your thoughts on that.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Yes. I would say, overall, the data are really great to see. We're finally seeing numbers. We've been talking for the longest time about hitting that therapeutic ceiling and, now, with these kinds of endpoints, really stringent endpoints both clinically as well as endoscopic and we have histologic data for ulcerative colitis, it's really great to see this level of efficacy and durability as well, especially for ulcerative colitis. I also want to highlight, Miguel, for example, with the guselkumab, we had the cohort, sub-cohort analysis, and these were also patients who were previously exposed to JAK inhibitors. With the timing of when guselkumab was approved, we had more patients previously on a JAK inhibitor as well. So this is very telling that we're seeing these types of efficacy results even among patients who were previously exposed to a JAK.

Miguel Regueiro, MD:

Right, so not just the naive patient.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

That's right.

Miguel Regueiro, MD:

Not just the previous biologic, but the JAK inhibitors.

Ed, let me ask you a question about the sub-Q. Going back to, and I'll date myself, I came out and I trained in 1997, infliximab came out shortly after that, and we always thought you had to use IV therapy for induction and that IV was better than any other modality. Yet for ulcerative colitis, we're seeing pretty good data in the ASTRO's data with sub-Q induction, with guselkumab. I guess, Ed, that has surprised you, and what are you doing in your own practice?

Edward L. Barnes, MD, MPH:

I would say it is a little bit surprising because it's counterintuitive to what we think about ulcerative colitis, where we think about the mucosa being leaky in really sick patients, think about acute severe ulcerative colitis, coming in with a low albumin, and we're making a decision about, "Are we even going to use an anti-TNF because they're losing protein across that barrier?" I think it's a really good question. The data would suggest, in terms of those clinical remission rates and the endoscopic endpoints that Anita mentioned, that we're not supposed to compare study group to study group. But if you just think bar graph to bar graph, you're getting those same rates of remission at the same endpoint. I would say, to answer your first question, yes, I think it is

believable that we can achieve the same types of remission and the same type of outcomes that are sort of matched using a sub-Q induction regimen.

To answer your question, the second part of it, we have transitioned to patients using sub-Q in ulcerative colitis as well for two reasons. One, I think, logistically, at least for us at UNC, it's hard to get patients into an infusion and to get them into an infusion in a rapid chair. You have to go through the process of getting them a chair, getting the insurance approval. I think that's a really important point. And then, second, you can know that your patient's leaving and when they're going to get on a drug. That timely induction, as was mentioned on one of the first slides, is really important.

Miguel Regueiro, MD:

And then, Angelina, I guess you see a lot of patients as an advanced practice provider (APP), they often come to you first and ask about safety and education around safety. Although I showed it in the table, I didn't present it necessarily in the additional information. Talk to us about...ustekinumab, obviously, everybody knew that was very, very safe. What about the IL-23 class? Anything additional? What are you actually telling your patients in the clinic?

Angelina Collins, MSN, ANP-BC:

Yes, it's a great question because you're right. I like to pair the conversation of efficacy with safety at the same time. You can't talk about one without the other. Your patient is probably thinking more about safety upfront to be honest, in many ways, unless they're really sick, and that's the easiest of the conversations we could ever have is with the super sick patient. They're like, "Just make me feel better, and I'm good." I think the safety conversation is quite easy, relatively speaking for the IL-23 entire class. For those people who have been exposed to an IL-12/23, I think it's particularly easy because you can say, "There's not really a difference in safety with the exception that we're just going to be monitoring for the medications. We need to be monitoring liver enzymes for hepatotoxicity." That may look a little bit different, but in reality, in my practice, actually I'm practicing the same way they would have anyway.

I'm getting baseline labs at the beginning. I am monitoring at a certain point to see that the patients are responding anyway and I was doing this already, honestly. They may not have understood exactly the rationale that I was doing to check both – are the labs looking better than they did initially and also you're looking for the safety as well. That all really looks the same. To me, I feel equally reassured that the real things that matter, that there's not an increased risk for cancer, for example. I think that's really helpful. There's non-increased risk for lymphoma. It's very helpful to be able to state that to your patient because they're worried about cancer. And then the serious infection risk being very low, that reassures me and, hopefully, as well as the patient also.

Miguel Regueiro, MD:

Yes, I think you and I practice very similarly, and I think the safety with these is excellent. I think probably you, as an audience who are using these, see that. I do the same thing pretty much with all of our therapies, where I usually get a comprehensive metabolic panel (CMP) and complete blood count (CBC), a baseline LFTs and then after induction. I have, in the IL-23 class, as Angelina mentioned, seeing some of these patients have a transient elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). And if I see that after

induction, it does prompt me to not say, "Let's wait 6 months to a year to get another set." Probably within the next couple months, we get another, just to make sure that's not going up.

Before I go on, there are a couple questions from our virtual audience. I'm going to ask you first, Anita, kind of the best candidate or positioning of the therapies. The question was best candidate for guselkumab, but how do you position these three in ulcerative colitis? And then, Ed, there was a question about bowel urgency, which I mentioned with mirikizumab. Is mirikizumab the only one that has that or are there others? Anita, you first in terms of positioning of the three. Obviously they all look good. How do you decide?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Overall, the best candidate is the patient in front of you, and you have to look at the factors that are associated with that. It comes down to several factors. I think we're seeing efficacy here as outlined but certainly recognizing that there becomes the patient preference. We talked about the IV induction and as well as the sub-Q formulation. With guselkumab, it's the only IL-23 that has the formulation of the sub-Q. For many of us, I'm very fortunate to have an entire team work through that whole process for me, so I don't deal with that stress. But for the convenience factor of going through the authorizations for getting the IV and then the sub-Q and all of this, it's probably that “easy button,” Miguel, that I think that is also not only the patient preference but potentially also the prescriber preference. To have that “easy button,” you want to start an IL-23 and you want the convenience factor as well.

Miguel Regueiro, MD:

Yes. The take-home from Dr. Afzali is the “easy button” and, quote, "I don't deal with that stress."

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Yes, I can't have wrinkles. Come on.

Miguel Regueiro, MD:

That's a take-home for me.

All right. Ed, let me ask you a quick question, then we'll go on. In bowel urgency, mirikizumab has shown the data. Do the others have that? Maybe speak to that.

Edward L. Barnes, MD, MPH:

Yes. I think it's a great question because bowel urgency is, if not the most, critical symptom that your patients will have. I think the reason that the mirikizumab data are really important is because, if you're like me in clinic, you can talk to your patients about, "Do you have bowel urgency?" And they don't say, "Yes, my urgency numeric rating score," which I'll tell you in a second, "is a 7." They say, "I can't make it through a meeting" or, "I can't make it through my commute." We now have a way to quantify that through the mirikizumab trial program.

Miguel showed you that curve that fell off compared to placebo, and so that was the urgency numeric rating scale (NRS). That's why I think you saw that rapid drop in urgency. That's something that's really important to know about mirikizumab, but that's not the only...even IL-23, that has data for urgency. Hidden in one of the

other bar graphs on the mirikizumab, you saw a large improvement in patient-reported urgency scores as well in the mirikizumab data. I think probably a lot of our therapies will help urgency because they're helping the patient's symptoms of ulcerative colitis. But I think the mirikizumab program did a really nice way of quantifying this so that we can track it over time and not have to ask some of these questions that are really important to patients, but then we can quantify it in a clinical trial program.

Miguel Regueiro, MD:

I think the mirikizumab had a numeric score that was developed, and they implemented it a priori as an endpoint. Just to be clear, as Ed said, the other IL-23s have either post-hoc data or data that do show improvement in bowel urgency. It's not maybe specific to the IL-23 mirikizumab improving urgency. It was measured a priori, which I think was really well done, but probably all of them do that.

All right. Let's finish out the didactic presentation. Anita, when we get to the end of this, I'll talk to you because I know you were one of the primary authors on GALAXI. Now, we're switching to Crohn's disease, and this is guselkumab induction in Crohn's. I'm going to point out two things here. You'll see different induction doses with the different colors of red. I will say that the light pink is the 200 milligrams, which is FDA-approved, but you can see the higher doses didn't have any additional improvement. This is why the FDA chose the 200 milligrams, which is what we use for IV induction in Crohn's. The other thing you'll notice that's built into the study, which I think is unique, is a head-to-head guselkumab, and the green bar on the right-hand side is with ustekinumab. Built into the study is not just placebo but really looking at a head-to-head with ustekinumab.

This is GALAXI-2 and -3 now looking at the maintenance in Crohn's disease. And again, the reason there's the light pink and the dark is that's the two different doses for maintenance of 100 milligrams every 8 weeks or 200 milligrams every 4 weeks. There's no placebo on this. The green bar is ustekinumab, and at the end I'll ask you to comment, Anita, but we are seeing statistical benefit and efficacy of guselkumab not just over placebo but IL-12/23 ustekinumab. Now, like ASTRO, sub-Q for ulcerative colitis, GRAVITI, sub-Q induction for Crohn's disease. In a very similar theme to what we just talked about in ulcerative colitis, the sub-Q induction, we did see statistical efficacy for clinical remission and endoscopic response independent of bio-naive, which are the middle sets of bars, or bio-IR, so patients who had been on a biologic therapy. I'm seeing these nice deltas.

Similarly, if you use sub-Q induction in the GRAVITI and then you carry it out to week 48, you are seeing fairly large separation. If you look at the placebo responses here, very low, but quite a delta compared to guselkumab. The sub-Q for Crohn's disease induction, as we talked about for ulcerative colitis, we're seeing benefit in efficacy with that.

In VIVID-1 we're looking at the mirikizumab induction in Crohn's disease. You can see the blue is mirikizumab and the gray is placebo. This is the week 12 data, and you can see clinical response. By patient-reported outcomes, endoscopic remission and clinical remission against statistical endpoints were met. These are the maintenance data with mirikizumab in Crohn's disease. Also, at week 52, the endpoints were met. Now, in one of the studies, VIVID-1, one of the secondary endpoints was comparing mirikizumab to ustekinumab. Ustekinumab here is in green. I think you can see something different than what we saw with guselkumab in that we're not seeing a statistically higher benefit or efficacy of mirikizumab versus ustekinumab. The bars look very similar. Some of that has to do with the methodology, the way the study was designed, but we did see a separation with guselkumab and ustekinumab. We are not seeing that with mirikizumab and ustekinumab.

Risankizumab induction in Crohn's, ADVANCE and MOTIVATE. The patient population in ADVANCE was a mixed population, meaning somewhere bio-naive, somewhere bio-failure. MOTIVATE on the right-hand side is all bio-failure. Again, you're seeing statistically higher rates with risankizumab compared to placebo. This is looking at side-by-side clinical remission and endoscopic response with the theme and the message that we're seeing good, not only clinical remission but also endoscopic response with risankizumab in Crohn's disease. And then finally risankizumab did have a comparator trial sequence with ustekinumab and, as I mentioned, with guselkumab, although this trial was designed a bit differently and GALAXI did build in an arm of ustekinumab. But nonetheless, with risankizumab compared to ustekinumab, you do see a separation and an efficacy benefit with risankizumab compared to ustekinumab.

So, before we get to the cases, and this will be the remainder of our next hour to hour and a half, I want to ask you, Anita, in terms of the GALAXI study, and I know you were involved in that, to maybe give high-level comments. We talked about the built-in arm with ustekinumab. Any observations you want to share?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Yes. With the GALAXI study, we were able to have a treat-through design, which, in other words, says that no matter what the medication the patient was started on at the start of the study, they continued on with that, and so that really allows more of that real world, if we could use that, this is the real world, actual clinical practice of what happens when a patient gets started on guselkumab or ustekinumab or is on placebo. So, that was very telling for us. As you highlighted, Miguel, overall, you could see that for both doses, 100 milligrams or the 200 milligrams, we were able to see efficacy at, again, high percentages that typically we have not seen previously. Having that active comparator with ustekinumab was very informative. SEQUENCE, as you alluded to, was designed differently.

But incorporating ustekinumab into GALAXI allowed us to do several post-hoc analyses, of which we've presented at many of the major congresses, and it's manuscript is in the process, so that's coming here at a theater near you. It allowed us to perform an analysis, Miguel, where we asked, "What about the patient who initially received ustekinumab and then lost a response or didn't have a response? Now, can we perform our analyses? When we switched them to guselkumab, what happens?" What we actually found was that once we switched them to guselkumab, and this was without an IV induction, we went straight to the sub-Q, we switched them to 200 milligrams sub-Q of guselkumab, previously have been exposed to ustekinumab, and we found that the efficacy, durability…all of those endpoints were comparable to as if a patient was in that cohort of bio-exposed and then received guselkumab. That's very telling for us, an answer that SEQUENCE was unable to give us.

Miguel Regueiro, MD:

Yes, and I think really important data that I didn't present, that I think you presented at one of the European meetings, is that the question comes up, "If a patient's been on ustekinumab and failed or lost response, can you use an IL-23?" We do have efficacy data with guselkumab that it didn't present. Angelina, let me ask you a question about the sub-Q induction with Crohn's, kind of similar to ulcerative colitis. Maybe the answer is going to be identical. Are you using IV guselkumab in Crohn's induction or you've really switched over to sub-Q? What is that looking like in your practice?

Angelina Collins, MSN, ANP-BC:

Honestly, this has to do a bit with patient preference and what is going to be easiest for the patient to do. I've been surprised. I thought everyone's going to want sub-Q. Why would you want to go into an infusion center for IV? But, in fact, I've had some patients who have really said, "I want, I'm used to that." They're used to being monitored and having an IV, but I will say the majority of my patients are now going, "I'm going with sub-Q induction." It really is shortening the time to medication when you can use the sub-Q induction compared to IV. You're not just waiting for an insurance authorization. And then, to Ed's point, finding a chair and getting your patient scheduled, the sub-Q does really get the drug to the patient faster.

Miguel Regueiro, MD:

Yes, I agree. You're right, there might be a rare exception. Most of my patients were using sub-Q induction with guselkumab for both Crohn's and ulcerative colitis. There might be a rare, rare, rare exception. Ed, there was a question that came in. And then we will start with the cases. The higher doses of IL-23, are they related to side effects? The question was specifically...I showed the doses of guselkumab that were done, and the 200 milligrams had the higher efficacy, but there were even higher doses that didn't show any benefit. But for risankizumab and guselkumab in maintenance, we do have two doses, a lower and a higher. Higher, maybe we get some efficacy benefit. But then is that a trade-off where we've seen safety problems with the higher doses?

Edward L. Barnes, MD, MPH:

That's a great question. I would say, contrary to what we see in some other mechanisms of action, we don't see that. Just to be very clear about what I'm talking about, when we see induction doses with JAK inhibitors, for instance, I think we tend to see more shingles risk, more infections risk when we have the high dose compared to when we go down to the lower dose for maintenance. We don't see that with the higher dose of IL-23 that I'm aware of. If any of the panelists know that data better than me, definitely correct me, but I don't think we've seen that with IL-23.

Miguel Regueiro, MD:

I think one of the nice things, and just a take-home point, is that sometimes people say, "Well, I don't want to use the higher dose of risankizumab or guselkumab in maintenance because I'm worried." We talked about the liver or some other potential side effects. We are not seeing a safety trade-off. So, the nice thing with this is we're not seeing a safety ceiling, meaning higher doses don't equate to worse safety. So, generally in my practice, and I realize I have a referral bias at Cleveland Clinic where I might have a sicker patient, I am using the higher doses in maintenance for both guselkumab 200 every 4 weeks and for risankizumab the 360 every 8 weeks. The data on the lower doses and maintenance for both of those look quite good, so I don't want the take-home to be you have to use the higher dose but we are not seeing a safety trade-off with that.

All right, so let's dive into our patients. First of all, get ready because, as an audience, I'm going to present the case and then we're going to ask you all first what you would do in terms of the multiple choice options for therapy. So, this is a real patient. Some of you may have seen Natalie at some of our meetings. She's also a patient advocate. She's 42 with longstanding Crohn's ileitis, and she's had this since 21. She now has worsening symptoms that you can see there. She's actually been in a long-term remission with adalimumab and there was

a payor-mandated switch to adalimumab biosimilar and she felt, not only that she was frustrated but that she also started to get more symptoms.

One very quick editorial comment is that we have not seen a difference in terms of efficacy in biosimilars compared to the innovator product, and I want to make it very clear I am personally comfortable with the biosimilars; however, we do have patients like Natalie who tell us and it might be more than even the nocebo and then we can get into whether we check levels. Nonetheless, she started to have more symptoms and now she's saying, "Okay, I've been on adalimumab every 2 weeks and don't want to be on an IV therapy." And, by the way, in the very bottom right of this is something that you may see in your patients on TNF, she's noticing that she's starting, it's not terrible but she's starting to get the psoriasiform reaction in the umbilicus, around the ears, and on the scalp.

I tell my fellows, if you examine patients on TNF inhibitors, patients will say “I have a little dryness in my belly button,” and that's probably actually a psoriasiform reaction on TNF. Usually, it's very mild and you don't have to do anything about it but she's starting to get it on her scalp and ears. You can see that, based on objective data, C-reactive protein (CRP), fecal calprotectin, she has elevation. Importantly is the third bullet point, an adalimumab trough level was measured and it was 19, which would represent what I would consider an optimal trough level, and she has no antibodies and you can see her hemoglobin, platelets. Her albumin is 3.5. It's on the low end of normal but it's not abnormal.

All right, so here is where all of you come in. What would you do next? We have a small percentage who said increase weekly adalimumab and some said switch to another TNF. The large majority, 87.1%, said switch to an IL-23. Some said go ahead and switch to vedolizumab, and some said switch to upadacitinib. Some said give her a little bit of budesonide and see how she does. Before I get to the community gastroenterologists and how they answered, Ed, is anything surprising here? Any comments you would want to make?

Edward L. Barnes, MD, MPH:

So, I think it's a little bit interesting that we have at least one answer to each one and I think that really shows you what you said, that there's maybe not one right answer. So, people can think about this in a little bit different way. When I think through this case and how this case is progressing, I think the psoriasiform rash is the thing that stands out to me the most. The disease activity we could probably tackle in a couple of different ways but, in my experience, when you have a psoriasiform rash, especially to the anti-TNF, that is not likely to respond to another anti-TNF. In fact, the anti-TNF will probably drive that same reaction again. And knowing now that we have so many different mechanisms of action that we could use, as seen by this screen, an IL-23 works really, really well in this situation. An IL-12/23 also works really well in this situation, but we talked about some of that head-to-head data so I think an IL-23 would probably be my go-to initial decision in this particular situation.

Miguel Regueiro, MD:

Angelina, let me ask it a little bit differently. Are any of these choices one that you would not do where you would look at it and say, "You know, that's not a great idea?"

Angelina Collins, MSN, ANP-BC:

Yes. That's a good way of looking at it too because I call that “the back door.” Instead of, sometimes when you're like, "There are multiple good answers," but what is not an awesome answer, I think, of a 19 trough level of adalimumab, 19 as being within the therapeutic range, so that's not, I don't think, going too weekly is going to benefit the patient in the sense of symptom control and also because of the psoriasiform rash. I agree completely on that ,that once you start seeing that, it is likely to worsen over time. Maybe starting off mild but, really, if you've seen this before, to Miguel's point, it's one thing if it's in a belly button, which is hideable, you don't have to show that, but once you start getting it in the ears and around the scalp, if you've ever seen severe cases of this, it is debilitating. I have had people, when you start getting it on the scalp, who will start losing their hair, and it can be really awful, almost to the point where people are really not wanting to even leave the house.

So, I do take the psoriasiform rashes pretty seriously. The topicals are okay if you're dabbling in it but it can become really messy really fast. So, long story short, I really would think about that between...The anti-TNF would not be the selection I would do because the trough is good, and switching to another anti-TNF agent, as Ed already mentioned, is likely to continue this issue as we go on, so those were the easy throw-outs for me.

Miguel Regueiro, MD:

Yes. So, I think the take-home is, if you dabble in it and it helps the mild psoriasis, that's okay. I like the dabbling comment but we do worry about the scalp. Anita, now I'm going to ask you which of the three IL-23s you would lean toward. She's a newscaster, and you heard some of her preferences up front, maybe this is self-evident, but which of the three would you lean toward?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Again, the convenience factor and so, with that, being able to have these sub-Q formulations seems to be the most palatable probably for her as well as with that “easy button” we talked about, right?

Miguel Regueiro, MD:

Yes. And I think also, obviously, she is cognizant that she is a public figure so she doesn't want to go in an IV infusion, so there's that as well. All right, so let's go forward. This is going to be cool because now you're going to hear, if you can play the audio, you can read the screen but let's hear what a community gastroenterologist said about Natalie.

Audio Recording:

The patient has been on adalimumab or its biosimilar for some time but she has had flare requiring steroid rescue. Her disease level is at least moderate including constitutional symptoms of anemia. She also has elevated biomarkers. I feel it is time to change to a different class of advanced therapy, and an IL-23 has unsurpassed efficacy, a better safety profile than upadacitinib, and should be efficacious in psoriasis should she prove to have that. Vedolizumab would likely be less efficacious but an acceptable choice if she has any relevant conditions that would make a more gut-specific agent preferable. Also, a subcutaneous route of administration would be preferable given her social circumstances.

Miguel Regueiro, MD:

So, how about a rural gastroenterologist?

Audio Recording:

I would increase dosing frequency of her current adalimumab therapy. She was in long-term remission on adalimumab and has only been symptomatic for 6 to 8 weeks. The only major change was a payor-mandated biosimilar switch 3 months ago. Before I start chasing newer agents, I want to try the most practical, familiar, and insurance-friendly step first. If this is pharmacokinetic loss of response after the switch, dose escalation is a reasonable move and often easier to get approved than a full therapy change. I'm also not ready to assume she needs a whole new mechanism yet. I would check trough and antibody levels, rule out *C. diff*, and recheck CRP and fecal calprotectin. I wouldn't switch to another anti-TNF agent unless she has antibodies or true secondary loss of response. Switching within class is a big step and often difficult with insurance.

I wouldn't switch to an IL 23 inhibitor. I know the data looked good but I'm still cautious with newer therapies. I want more real-world durability and long-term safety experience before making that my go-to, especially when she did well for years on anti-TNF. It may be fine but I don't want to be the first one in my zip code to find out it's not. I wouldn't switch to vedolizumab. It's safe but it's an infusion and she specifically wants to avoid IV therapy. Also, it may take longer to kick in and she's already flaring. I wouldn't switch to upadacitinib. It is effective but it's a systemic JAK inhibitor. I'm not reaching for that unless I really have to – more monitoring, more safety baggage, and it's not my first move in someone who was stable for years. And I wouldn't use budesonide. She has already needed steroids and is still symptomatic. That's how patients slowly drift into chronic steroid dependence while the disease keeps simmering.

Miguel Regueiro, MD:

So, it's interesting, some of you in the audience did say you would go to adalimumab, so this is where you are hearing variations. Let's hear from the community and then I'll show you some other responses.

Audio Recording:

I would switch to an IL-23 inhibitor. She had long-term remission on adalimumab and then had a payor-mandated biosimilar switch, and within 3 months she's flaring again and already needs budesonide rescue. That's a signal this isn't just a bad week. This is loss of control. What really pushes me towards switching mechanisms is the new and worsening psoriasiform rash affecting the umbilicus, ears, and scalp, consistent with paradoxical psoriasis from anti-TNF exposure and I'm not going to fix that by doubling down on the same class. I would pick guselkumab because it offers subQ dosing and she wants to avoid IVs and time away from work, and it supports durable steroid-free control. Increasing the dosing frequency of her current adalimumab therapy could work if this were purely low drug exposure, but the rash makes me think she's developing a class-related problem. I'm not optimizing a drug that's also causing a new inflammatory skin issue.

If she had antibodies or injection issues, maybe I would switch to another anti-TNF agent, but paradoxical psoriasis often follows the class. I'd rather pivot mechanisms than keep rolling the anti-TNF dice. Switching to vedolizumab is effective and safe but it's IV-based and she's trying to avoid infusions. Also, it won't help the rash. Switching to upadacitinib offers strong efficacy and oral convenience, but I would typically use this after

biologic failure or when I need speed. Here, IL-23 gives me durability and skin benefit with a cleaner long-term comfort level. I wouldn't manage symptoms with budesonide and then re-evaluate in 3 months. That's how steroid dependence starts. She's already showing she needs escalation.

Miguel Regueiro, MD:

All right. So, you're hearing some themes. I'm not going to play these but a few other people said they would switch to IL-23. There was somebody, because she had been on a TNF, upadacitinib. And I think we're hearing themes of, as what we're saying, would probably be things we wouldn't do, so certainly budesonide, I think everybody agrees. Let's hear from Millie Long and what she said.

Millie D. Long MD, MPH:

Hi, my name is Millie Long, I'm Professor of Medicine and Chief of the Division of Gastroenterology at University of North Carolina at Chapel Hill and here I specialize in the management of inflammatory bowel disease. So, to start things off, I'd like to discuss case number one, Natalie. My answer for what to do in Natalie's care is actually option C, switch to an IL-23 inhibitor, and let me tell you why. So, Natalie has Crohn's disease, she's 42 years old, she has been on adalimumab and, importantly, she has had a recent level checked which was therapeutic and it's at 19. Also, in her clinical history she actually has started to report a mild psoriasiform rash around her umbilicus and behind her ears. So, what this is most likely an anti-TNF–induced psoriasiform eruption.

Interestingly, you can see some of these paradoxical reactions on anti-TNF and, recently in the literature, it's actually been shown that an IL-23 receptor abnormality, a genetic abnormality is actually associated with this, and so the IL23s are the best agent to manage this psoriasiform eruption. Importantly, it also is an agent that has shown great efficacy in Crohn's disease and individuals who have previously been exposed to an anti-TNF. And she not only has been exposed but she has had a mechanistic failure of that anti-TNF. A couple of other pearls are to remember that we never go on symptoms alone, and she did have objective workup of her symptoms where she had an elevated fecal calprotectin and, importantly, a colonoscopy with a Simple Endoscopic Score for Crohn’s Disease (SES-CD) of 11, really markedly involving the ileum and that's a very high SES-CD if someone has isolated ileal disease. So, she actually has quite severe disease. We need to get our best foot forward.

Miguel Regueiro, MD:

One thing we wanted to show you is this and, actually, this came out and wasn't something we, when we were planning this program, necessarily brought up. But each of us, Angelina, you mentioned it, Ed, Anita, and you're hearing from Millie about this paradoxical reaction. I'm not going to go through this in detail except to say it is something we see in TNF and it is something that will worsen if you continue, increase, or switch within class, so this is really something. And Millie mentioned the very last bullet point on this slide, which I think is interesting. This may actually be one of our predictive markers, the IL-23 receptor gene. It's not something we can necessarily measure in clinical practice yet but usually these patients do quite well with IL-23. We're going to hear now from Jessica Allegretti and then Ed Loftus and then we'll move forward.

Jessica R. Allegretti, MD, MPH, FACG, AGAF:

Hi, everyone, my name is Jessica Allegretti and I'm the Medical Director of the Crohn's & Colitis Center at the Brigham and Women's Hospital in Boston. For case number one, I would choose C, switch to an IL-23 inhibitor, and that's for several reasons. Here we have a young woman who has experienced secondary loss of response to an anti-TNF. We know she has a good drug level. She has not developed antibodies to the drug, so, really, we want to move out of class to a new mechanism of action. We also note that she has a preference toward subQ injections over IV infusions, and we know that there are agents within the IL-23 class, which are entirely subQ or even mainly subQ with an IV load, so I think there's a lot of flexibility there. We also note that this patient has a psoriasiform rash, and we know that IL-23 inhibitors also concurrently treat psoriasis and are approved for that indication as well. So, I think, overall, that's going to be a great choice for this patient.

Miguel Regueiro, MD:

Great. So, Anita, you mentioned the subQ “easy button” which Jessica's mentioning as well. And then, finally, Ed Loftus.

Edward V. Loftus, Jr., MD:

Hello, I'm Ed Loftus, I'm a professor of medicine at Mayo Clinic in Rochester, Minnesota, and I am not a Pittsburgh Steelers fan. Regarding the first case, this is a case of somebody who switched to an adalimumab biosimilar. Their symptoms have been worsening. They're getting a little bit of a psoriasiform reaction. They have a therapeutic trough level, no antibodies. We have objective evidence of inflammation as manifested by the fecal calprotectin and the colonoscopy. So, this patient does need to switch therapies. I probably would not go with an anti-TNF because the psoriasiform reaction will happen with the next one. I do like the option of an IL-23 inhibitor here. I think IL-23 inhibitors work particularly well in this anti-TNF failure setting.

And for this particular patient, because she has expressed a desire for sub-Q therapy, I'd probably be leaning towards guselkumab. I suppose you could also consider the other two anti–interleukin-23 inhibitors, although the initial doses would be IV, though that would be a limited period of time. So, for all those reasons, I'd be probably pick an anti-interleukin here.

Miguel Regueiro, MD:

Great. We did put this through ChatGPT and, just in the effort of time, since you heard already the digital voices, it chose IL-23. I will tell you that the next case has much more variability. I think this one was an easy starter case, but let's hear from Natalie directly and hear her thoughts.

Natalie Hayden:

My name is Natalie Hayden. I'm 42 years old. I was diagnosed with Crohn's disease at age 21. I have three kids, ages 8, 6 and 4. I'm a former TV news anchor and reporter, and I blog at lightscameracrohn's.com. My senior year of college, I went on spring break to the Bahamas and I'll never forget the abdominal pain that I felt and, in the moment, it was the first time I ever dealt with something like this. Fast forward to May, when I graduated from Arquette, my symptoms really started to persist. I'm talking about fevers of up to 104 on multiple occasions and then horrible chills. So, I went into this not even knowing what was wrong with me. They did a

rectal exam and they did a CT of my abdomen and I blacked out in the moment, honestly, because I don't know how I reacted when the doctor walked in the room and he said, "You have Crohn's disease, you are malnourished, you're dehydrated, you are getting hospitalized immediately, and you're doing a colonoscopy in the morning to confirm this," and my world came crashing down. I went from being a perfectly healthy, self-sufficient, driven, ambitious 21-year-old who had the world by the tail, who planned to work in TV news and take it by storm, to somebody who was hospitalized for a week, having to do a colonoscopy.

Miguel Regueiro, MD:

And then in terms of her quality of life.

Natalie Hayden:

So, when you have IBD, you don't know what the next hour brings, you don't know what the next day brings. Yes, you might be in remission today but what about tomorrow? And I think that's something so many patients and caregivers struggle with is the unpredictability and it is such a challenge with this disease. We can think we have it under control, we can think the treatment and therapy is working, we can say the scope looks clean, we can say the labs look like they're on target, but then all of a sudden something could happen the next day. So, that's been a struggle even 20 years in.

Miguel Regueiro, MD:

I think it's important to hear the patient voice in this and we really appreciate Natalie being vulnerable to share her story, and I think this also puts in perspective some of how we need to interact with patients. Now, just coming to the end of this case 1, before we get to case 2, this is the table scorecard of what was discussed, and I think the majority of people and then AI also picked IL-23 but a couple said increase the adalimumab. Somebody said upadacitinib, which, by the way, I don't know was necessarily wrong. It is just the IL-23, in terms of some of the safety, the efficacy, would probably been what I would've gone with as well.

And I think there are some pearls from this case and then we're going to ask all of you again if you've changed your mind or changed your decision one way or the other. We talked about the psoriasiform reaction and we talked about some of the...America College of Gastroenterology (ACG) actually put this in their guidelines in terms of prior intolerance to therapies, safety profile, life stage considerations, and then this idea of a loss of control after a biosimilar, to switch into a biosimilar, which, in Natalie's case, did come up. All right. So, we're going to ask you the same question. You may have the same answers as before or you may have changed your minds. What would you do in Natalie's case? So, it looks like, actually 100%, it looks like everybody switched to IL-23. Any final comments?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

If I could make a comment, I really appreciated everyone's reasoning behind why they would or would not make a treatment selection of one or the other. The one that impressed me the most was, I believe it was one of our community gastroenterologists, rural gastroenterologist community individuals who said that they didn't want to be the first in the zip code to prescribe something. I'm really concerned about that, particularly practicing in a tertiary IBD center, and we're always emphasizing the importance of finding the right patient with the right treatment at the right time, and time is of an essence. So, oftentimes, these patients are in different parts of the

country, rural America, wherever it might be, the suburbs, whatever it might be, and then to see or hear that kind of reasoning makes me a little concerned. So, that was the one comment from all of the reasoning that I just really wanted us to pause on a little bit and ask, “Is that really, as health care professionals, how we should be practicing?”

Miguel Regueiro, MD:

Well, one thing that will come out in the second case, not to give it away too much, is we see that stark contrast as well where newer therapy, IL-23 in this case, raises a pause and concern over safety. I think, Anita, to your point, now with ACG guidelines, American Gastroenterological Association (AGA) guidelines, now long-term extension data with safety, I think the message that I want to make sure we get across, and I think, Anita, you're echoing that, is that this is really one of the safest classes of medicines we have in an IL-23 and we shouldn't limit its use even though it's newer. And I understand that concept but we do have enough data, especially also with psoriasis and some of the rheumatologic indications over time. All right. So, let's move to the next case.

This is our next patient advocate, a 34-year-old with ulcerative colitis. She has had symptoms for the last 3 to 4 months and you can read through those there. This is impacting her quality of life. She has been on multiple courses of prednisone and is worried about long-term effects. And I'm glad to hear that, at least in the first case, the concern about budesonide as a bridge to chronic steroids. Certainly she's worried about this as well. She's been on a 5-ASA, both oral and rectal, and she's been on infliximab in the past. She is feeling discouraged that she's not getting better. A very key important point, bottom right of the slide, is that she is really wanting to start family planning and start trying to get pregnant within the next year. This is a very strong interest that she has and she did bring that out in her visit.

The endoscopy shows that she does have ulcerative colitis, the Mayo Endoscopic Score is 2, so she has moderate colitis. She's not toxic. She doesn't need to be admitted. CRP is high, fecal calprotectin is high. You can see she's a bit anemic, with albumin of 3.5. So, for all of you, she's been on infliximab and multiple steroids. What would you do next? Again, I want to state we don't want to sit up here and say there's one absolutely 100% correct answer. I think there are some that are probably more correct than others. Most would use an IL-23 but some said upadacitinib. Some said vedolizumab. Maybe, Angelina, as she said she's interested in getting pregnant in the near term, is upadacitinib contraindicated in any woman who's interested in getting pregnant or what are the implications of upadacitinib in pregnancy?

Angelina Collins, MSN, ANP-BC:

I'm glad you asked it in that way because I don't think every woman, just because they're within an age that they could get pregnant, means that you have to throw out the entire JAK class. I just think that when the situation's warranted, even though it's the right, to Anita's point, actually, you said it really well, right patient at the right time and the right scenario, you pick the medication that's going to be most effective for the patient. In this situation, however, or in general, I usually don't necessarily want someone who is actively going...who's thinking about pregnancy imminently or actively trying to be pregnant, it's not my preference to have someone on upadacitinib, that's in my practice. There are certain scenarios, I know there's been a lot of talk about this in certain scenarios, patients are really... that have no other options and what you're going to do, that's not what we're talking about here because she really has only previously been on infliximab and she stopped that because of intolerance. I'm curious about those infusion reactions, but that's another topic for another day.

So, she has a lot of good options that are safe in pregnancy. All the biologic agents have really been found to be safe in pregnancy. There are a lot of data surrounding safety in pregnancy and with breastfeeding as well. And remember, we really want our patients to breastfeed. We know that there may be a reduced risk of heritability of IBD in a baby born to a mom who has ulcerative colitis or Crohn's disease if you breastfeed, so there's another rationale for just carrying the medication through not just pregnancy but also in the postpartum period as well. So, for me, I would prefer to use an agent other than upadacitinib in someone who is thinking about pregnancy in the short long-term.

But the only caveat too, I know this is a long answer, but making sure she's in remission before she tries to conceive is also a super important aspect. So, it is really important to understand our patient's goals. I think it is critically important for us as their provider to understand what their goals are and getting to a healthy pregnancy is good but we want them to conceive when they're in remission. And I would usually love for people to be in remission for 6 months if we could, 3 months if you are negotiating or if time is of essence, but that's usually what I would want to do.

Miguel Regueiro, MD:

Yes. I think the message is that upadacitinib is not contraindicated in a woman who wants to get pregnant in the future. But, as Angelina said, if she says, "Look, I want to try to get pregnant in the next 6 months to a year," if you did start upadacitinib you would have to then stop it for a month prior to conception, how long it takes her to conceive a pregnancy then, and then switch to something else. So, I think that's an impact. Ed, just briefly on vedolizumab, what's your thought about vedolizumab after infliximab in ulcerative colitis?

Edward L. Barnes, MD, MPH:

Well, I think that the downside of using vedolizumab after a patient's been on an anti-TNF in ulcerative colitis compared to vedolizumab first line is you do see that drop off in the efficacy. I think, in somebody that's presenting her, she's not, as you said, she's not about to be hospitalized but she certainly is ill, and I think, given the scenario where we have other therapy choices, just like Angelina said, I think it probably wouldn't be my first choice. And I think, just to echo one other point about pregnancy, because her goal is to get pregnant within the next year, you want something that's going to give her the best chance of getting into remission. So, even if my choice was upadacitinib versus vedolizumab or upadacitinib versus any of these other things, I would choose upadacitinib to get her into remission and then give her another therapy rather than choose one that I thought might be less effective, at least based on the evidence that we have.

Miguel Regueiro, MD:

Yes. Even with that though, let's hear the audio for community gastroenterologists who said switch to vedolizumab.

Audio Recording:

The patient has at least moderate ulcerative colitis with several flares that have required repeated steroid rescues. She's had intolerance to an anti-TNF agent, so it’s best to avoid others. Using further steroid therapy is ultimately ineffective and dangerous long term. An IL-23 will be acceptable. Upadacitinib is very effective but

her prospect of pregnancy makes me inclined to use a relatively gut-specific therapy. I would choose vedolizumab in this case.

Miguel Regueiro, MD:

I want to point out this is another community gastroenterologist, 9 years of experience, who also said switch to vedolizumab.

Audio Recording:

I would switch to vedolizumab. She has failed optimized 5-ASA both orally and rectally so she needs escalation, but she has had prior infliximab intolerance and she's considering pregnancy within the next year. Admittedly, I'm not familiar with evidence for IL-23s in pregnancy. I would not continue the 5-ASA and reassess later because she has already had an inadequate response to optimized therapy and waiting prolongs symptoms and increases steroid exposure risk. I would not restart the infliximab, not happening. She had infusion reactions and systemic intolerance. Switching to another anti-TNF agent is the main alternative I would consider, especially since anti-TNFs have strong pregnancy data. But given her prior infusion reaction, experience, and discouragement, I'm less confident she'll tolerate or stick with another anti-TNF. I like IL-23s a lot, but with pregnancy planning within a year I'm going to choose the option I feel most comfortable with in that scenario. I need to know the data with IL-23s in pregnancy. I would not switch to upadacitinib when pregnancy is on the table. I am not choosing that risk profile here.

Miguel Regueiro, MD:

Look at the final bullet points in the left-hand column. This is something I think Anita kind of brought out before, this limited familiarity with IL-23 data in pregnancy. That was really, I think, the driving reason this person said they wouldn't use IL-23 and they would favor vedolizumab. There's a rural gastroenterologist who picked vedolizumab and also had the question about safety of other therapies. I think this is something that is interesting to me. You're seeing it in a fair, balanced way in the real world. And I think about a third of you had said vedolizumab was an option.

Audio Recording:

I would start her on vedolizumab and get her off steroids ASAP. This is moderate-to-severe ulcerative colitis at this point. Three to four months of symptoms, blood, urgency and incontinence, and fatigue, and it's affecting her ability to work. The big red flag is that she's steroid dependent with three plus prednisone tapers in the last year. Prednisone is doing the job short-term, but it's also quietly wrecking her long-term health. I need a durable maintenance therapy that's effective and safe, and I need something I can realistically manage in a rural practice. Vedolizumab is a strong option because it has a solid long-term safety profile. It's effective in ulcerative colitis. It helps me stop the steroid cycle and it's a therapy I'm comfortable using and can follow without excessive monitoring complexities.

Continuing current therapy and attempting another prednisone taper is the definition of steroid dependence. Another taper just kicks the can down the road and raises the risk of long-term steroid toxicity. Switching to another anti-TNF agent is possible but not my first move unless she has a clear reason to stay in class. Anti-TNFs can work, but if she's already on advanced therapy and still steroid dependent, I'm thinking we need a different

mechanism. Switching to an IL-23 inhibitor is a good option, but I'm cautious about jumping to newer therapies first line in my practice unless I need to.

I want more real-world experience, long-term safety data, and payor predictability. Switching to upadacitinib is effective and fast but it comes with more safety concerns in monitoring. In my high-volume practice, I reserve JAK inhibitors for patients who really need that level of firepower or who fail safer options. I don't want to start with the drug that makes me sweat a little. Beginning thiopurine monotherapy and reassessing in 3 to 6 months would be too slow, not reliably effective enough for this severity, and it doesn't match the urgency here. She's already losing function and relying on steroids.

Miguel Regueiro, MD:

And then some additional commentary that we got from others are to switch IL-23 to vedolizumab. But let's get to what Millie said.

Millie D. Long MD, MPH:

For case 2, Kaylaa', she has underlying ulcerative colitis. My option for what I would do in terms of her management would actually be option C, although with a caveat that we also need to consider option D. When you think about Kaylaa', she's quite symptomatic with stools that are frequent with blood and urgency, and she has actually required a good number of prednisone tapers over the last year. And one teaching point, someone should never have recurrent prednisone tapers without a change in therapy. When you're initiating steroids, you need to think about what your exit strategy is going to be in terms of maintenance, whether that is a biologic, a small molecule, some form of an advanced therapy.

Importantly for Kaylaa', she had previously received infliximab but had intolerance to that. Not very specific intolerance, but more headache infusion possible reaction. But I always would want to dig in deeper to that because it's a little bit different if the patient just didn't feel quite well, as compared to actually having an anaphylactic episode where they had shortness of breath, severe rash, blood pressure drop, et cetera. So, you want to dig into that and learn more information. And, importantly, she also had an objective evaluation of her symptoms, meaning she had a fecal calprotectin that was elevated and she had an endoscopy, a flexible sigmoidoscopy that showed Mayo Endoscopic Subscore 2 disease, moderate disease.

So, in this setting we really need to initiate her on an advanced therapy. She had previously had that infliximab exposure, which is why it opens up options in another class. And IL-23 is reasonable here, particularly if she's 34 and is potentially interested in planning a family. When we think about planning a family, all of our biologic agents are safe, but we do want to try to avoid an advanced therapy like a JAK inhibitor if possible.

Miguel Regueiro, MD:

And then how about Jessica?

Jessica R. Allegretti, MD, MPH, FACG, AGAF:

For case 2 we have a young woman who has moderate disease, clearly failing 5-ASA therapy, has had a previous experience with an anti-TNF that did not go well, and very clearly needs to be on an advanced therapy. I think when I'm thinking about this patient, the things I'm taking into consideration are speed and the safety profile.

And additionally this patient wants to start a family soon, so certainly that's going to play a role when we're considering what therapy to start. We know that the JAK inhibitors are currently contraindicated in pregnancy. And if this is a patient who's wanting to start trying to conceive soon, I would not use upadacitinib, and we know that from the PIANO registry with Uma Mahadevan. So, for me, I would choose C, switch to an IL-23 inhibitor in this patient. We know that's going to be safe. Once we get her into remission, she can safely start trying to conceive, and she's going to have some real durability with this agent.

Miguel Regueiro, MD:

All right. We also show we have some data from the PIANO study and I'll show the next slide's gray table. I'm going to call an audible and just ask for a raise of hands. I promise I will not pick on anybody if you raise your hand. How many out there do have questions or concerns about IL-23 in pregnancy? I'm curious, and don't be shy. I do see a few hands out there. This is something that helps us from an educational standpoint because I think we get used to seeing patients in a tertiary center. And you heard from Anita initially, we don't have concerns about IL-23 in pregnancy, but that clearly was a theme that came up with a couple of the other comments in the community and rural gastroenterologists. The PIANO registry, I think we've kind of outlined this already.

This is the table that I'll leave up for a second. This is hot off the press, very recent, the IBD medications from preconception through pregnancy and lactation. You can see preconception on the left all the way to lactation with the different trimesters. I think the bottom-line take-home is I think everybody, if I asked, "Is methotrexate contraindicating pregnancy?" would say yes and raise their hand. I think we all know that. At the very bottom of this slide, the oral small molecules, JAK inhibitors, we haven't talked about the S1Ps, but the S1Ps, ozanimod, etrasimod, are also not used in pregnancy.

But all of the other therapies, the monoclonal antibodies, even thiopurine, amino salicylates, and all the monoclonal antibodies are safe. We don't stop them in preconception. We don't stop them in any trimester pregnancy. We don't try to hold the last dose at the end of pregnancy. So, I think for Kaylaa', and this was educational for me, the concern or question about IL-23 is because it's relatively new and the feeling is we have data; this is actually published. And I think this table is a guide and is very, very helpful. Let's finally hear from Ed Loftus.

Edward V. Loftus, Jr., MD:

For case 2, this is somebody with active ulcerative colitis and they're requiring frequent steroid tapers. They have already failed infliximab; they didn't tolerate it very well. Importantly, they're interested in starting a family in the near future. They have objective evidence of inflammation. The CRP is up, the Mayo Endoscopic Score is 2, so there's moderate disease. So, I think you definitely want to get them on an advanced therapy. You have a lot of different options. Because they failed on the anti-TNF, maybe they didn't tolerate it, I wouldn't be too interested in that.

I would probably be thinking of an IL-23 inhibitor, upadacitinib, although the fact that she's starting a family soon, I probably would not do upadacitinib. If she was saying, "Yeah, that's something theoretically years away," that would be different. So, overall, I'd be leaning towards an anti-interleukin. I guess vedolizumab is an option, although in a patient who has failed an anti-TNF, I'm a little less excited about that as an option. But it would still

be a potential option. So, those would be the two that I would be talking to the patients about, with a slight lean towards the anti-interleukin.

Angelina Collins, MSN, ANP-BC:

It might be worthwhile to talk about a failure versus an intolerance because I think this is something that I keep hearing.

Miguel Regueiro, MD:

Yes, I think you can look at it two ways. What Angelina is referring to is we've had patients who've had an intolerance to infliximab, adalimumab, with kind of vague symptoms, headache, maybe a little bit of fatigue after the injection or the infusion. It's not a reaction because of an antibody development to the therapy. So, I think that's a point well taken and we need to keep that in mind. And I think about a third of you said vedolizumab, almost as if that would've been the first-line therapy. Even though we're saying that, to be fair, a patient who's been on infliximab says they have an intolerance. And in the third case, we'll get to bio-naive vedolizumab as there are some data that are relatively new. And maybe still using in that bio-naive category. But I think again, Angelina, and actually even ChatGPT agrees with you here, they're saying vedolizumab is reasonable. But maybe go ahead and comment. What did you want to say?

Angelina Collins, MSN, ANP-BC:

I just think it's important here, always, we talked about this in the APP track yesterday, thinking about documentation of medications. It's really important to understand when you start a medication, what were the symptoms when you started? And when you stop a medication, why? The difference between a primary non-responder, they never got better, versus a secondary loss of response, they initially got better but then couldn't sustain it. Flared, versus an intolerance, which is, "I didn't feel well, something happened." It wasn't anaphylaxis or an allergy, it's just an intolerance.

Intolerance doesn't mean it was a mechanistic class-act failure, it just means that it was an intolerance and we don't quite understand why typically, right? We don't understand if it was really, was it an active part of the drug, was it an inactive part of the drug? Is it something else that actually was going on that just was a confounder? So, to me, that is very, very, very important. And it's the difference between thinking, a lot of us would inherently think that after an anti-TNF failure we can't really go to vedolizumab. It might not work as well. That's what the data tell us. However, that's not necessarily how this got sorted out, and I really just wanted to take a moment about this as a talking point to think through it.

Miguel Regueiro, MD:

Would you be okay with vedolizumab, ChatGPT?

Angelina Collins, MSN, ANP-BC:

Would I? Yes, I would be okay with vedolizumab.

Miguel Regueiro, MD:

Ed, or sorry, Anita and Ed, I want to ask you this specific question. ChatGPT agrees with you, so I don't know if that's good or bad in a way.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Well, if ChatGPT agrees.

Miguel Regueiro, MD:

I want to focus again on the bottom left and the very bottom right. ChatGPT, when we put this through, was focused on the safety and the experience with vedolizumab, and even to what we heard from some of the others in the community, raised this question about IL-23 and are there enough data in pregnancy? And when asked for show of hands, there were some of you out there, we're still wondering that. Anita, can we put this to rest? Are you comfortable with IL-23 in pregnancy?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Yes.

Miguel Regueiro, MD:

Very good. A woman of few words. Ed?

Edward L. Barnes, MD, MPH:

Yes, maybe I'll use a few more words and I would say yes. And the table that you showed, just so everybody knows where that came from, that's from the Global Consensus Guidelines on the Management of Pregnancy. I was lucky enough to be involved in that. What we did is, I was one of the grade methodologists. We looked at all the available evidence for all of these questions that were asking about how to manage pregnant patients with IBD. And so I'm biased because I was involved in it, but the point of telling you this is it really is a helpful document because it goes through every single question you could potentially have, in my opinion, about how to manage a pregnant patient with IBD or a patient who's contemplating pregnancy with IBD.

And what is the evidence that would support how you would manage that patient during the course of that pregnancy? And if we don't have evidence for that, I think one of the really novel things that we did in this global consensus guidelines is because all of the experts that were involved in the room were from all over the world, and we had these key concept statements that Uma and Millie and people came up with to say, "How should we manage it in the absence of evidence?" And so it's very clinically focused. So, if you haven't seen that document, I would definitely encourage you to see that. That is a little bit longer answer than yes, but I do feel comfortable with it.

Miguel Regueiro, MD:

But yes is your answer.

Edward L. Barnes, MD, MPH:

Yes is the answer.

Miguel Regueiro, MD:

Comfortable with IL-23. Again, the data from this and the table, which is in the publication, will be shared with you after this conference. So, all of this is something that you'll have. Let's listen to Kaylaa'.

Kaylaa' White:

My name is Kaylaa' White. I am an inflammatory bowel disease patient, student, and IBD advocate. I was initially diagnosed in May of 2020. The pandemic definitely made my diagnosis a little bit harder, due to hospitals being chaos, specialists refusing to take new patients, and overall being in that transition period between being a pediatric patient and an adult patient; I was 17 years old. I want to say at first I started noticing blood in my stool and frequency when I had to use the bathroom immediately after eating. From that, things kind of progressed just to more pain, joint swelling, skin irritations, fatigue. And I was a pretty textbook IBD patient, which definitely made my diagnosis a lot easier. I was diagnosed via colonoscopy and biopsies.

Miguel Regueiro, MD:

And then I think we have a little bit more.

Kaylaa' White:

I went to New York and then immediately things just started getting worse from there. I was always so stubborn and really academically driven, so my mom was like, "Kaylaa', you should come home." And I was just like, "Give it another week; the medicine should start working." Or I'd have a virtual appointment with my doctor so they can kind of see what's going on. I came home because I was missing class and it just wasn't sustainable anymore for me to be away from my family. And once I got off the plane, got home, slept, because I got in that night and then went to the hospital the next morning, they checked my levels and my inflammation was off the charts. My doctors told me that if I would've stayed in my dorm another day longer, I probably would've passed out. And due to me having a single dorm for academic accommodations, I don't think my friends would've noticed until a day or two that I wasn't coming to class anymore. So, that kind of is what got me to a stopping point in 2021 where I was faced with, "Do I want to continue with medications or do I want to try to get surgery?"

Miguel Regueiro, MD:

Again, I want to thank Kaylaa', as I did Natalie, for really participating in this program. There's a lot of vulnerability, but you also hear the resilience in our patients, which to me is incredibly inspiring. And I see this in my clinics and hear what these patients are going through, so thank you for patient advocates. In terms of case 2, this is just a summary and you do see a bit of a split. Five said IL-23. I think on the panel I would be in the IL-23, so three of us said IL-23. But Angelina, I think vedolizumab because it wasn't necessarily a failure of infliximab. And I think we're hearing that as well. I think some of the take-homes for this is all of us agree that steroids are not a long-term option and that does mean that we should move to another therapy.

And then this question about treatment and tolerance versus failure and then therapy selection. Let's ask all of you, then we will end with the third case. And then I am definitely going to leave time because there are a lot of questions that are great, so I'm going to make sure we have time at the end. But what would you do? Any changes in how you would treat Kaylaa'? It sounds like most of you actually now are favoring an IL-23, vedolizumab. We didn't talk about thiopurine. I'll tell you that thiopurines, exclusively for me, are used in combination with infliximab. I think that probably now would be considered a wrong action, wrong answer. Upadacitinib is okay, but if she's really trying to get pregnant or getting pregnant soon, I think that's something we consider. And then you heard the rest.

All right, so let's end with the final case. And this also gives some interesting discussion points that you may see in your practices. A 28-year-old, and this is a brand new diagnosis of Crohn's disease having symptoms. It's affecting his quality of life. He has lost some weight. He has been on budesonide, that's really been the primary treatment. And he's also worried about long-term steroids. He has never been on any other therapy, so this is a brand new diagnosis of Crohn's disease. He has inflammation in the ilium and then the cecum. And as you heard Millie Long say, an SES-CD of 12 means that this is certainly moderately to severely active. He doesn't have any complications, but you can see from his inflammatory markers that they're elevated.

Also, his fecal calprotectin is pretty high and didn't get that much better with budesonide. He is anemic and his albumin is right at the end of normal. So what would you do for him? Not to make a generalization, we may see this case less than you, meaning that sometimes when a patient's referred to a tertiary center they've already been seen and treated and now they're coming in. So, this is great. Actually, this is really good because nobody's putting one. I mean, even though TNF, probably if by percentage, was a little bit higher than an IL-23, even upadacitinib, vedolizumab. 5-ASA, by the way, maybe you actually had somebody vote because you said that, 5-ASA is a wrong answer. This is one time I can say that it is a wrong answer. The data with mesalamine in Crohn's disease, especially ileocolonic Crohn's, there's no efficacy at all. So I would not use a 5-ASA in this class.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

And I will add, we…

Miguel Regueiro, MD:

I was going to ask your thoughts, so let's go down the panel. Go ahead.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Even in our updated Crohn's disease guidelines, we were very intentional with bringing home and taking home that message for us, not just for us as prescribers but even for our payors to recognize because certainly there are still some insurance companies that are still mandating a 5-ASA in Crohn's disease. So, we've incorporated that in our Crohn's disease guidelines, the living guidelines through the ACG.

Miguel Regueiro, MD:

All right, so I'm going to go down to each of you, and, Anita, I'll start with you. We'll come back to the audience response and we can just do this. Anita, which therapy? Just say the name of the therapy.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

I would do guselkumab.

Miguel Regueiro, MD:

Okay, guselkumab. Angelina?

Angelina Collins, MSN, ANP-BC:

I would do guselkumab sub-Q induction.

Miguel Regueiro, MD:

Ed?

Edward L. Barnes, MD, MPH:

I would do infliximab-azathioprine combo.

Miguel Regueiro, MD:

Okay, so you're hearing kind of some differences. And I think for the audience it was a little bit higher TNF inhibitor than on IL-23. And, again, actually, let me ask Anita. Upadacitinib, what about that for first-line therapy? The label change, does that help you say that's okay to use?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

It does help me say it's okay to use in the right patient, but this patient is not knocking fully on the hospital door. I mean, as far as how rapidity…and all the rest that I would want or need in this situation, I would still feel very comfortable with having an IL-23, specifically as a class, knowing both rapidity and efficacy is comparable and the safety. It's superior.

Miguel Regueiro, MD:

Yes. The one comment I'll make, and you probably all saw this, is I think it was in October the FDA did change the label for upadacitinib, so, patients who have been on not just the TNF but systemic therapy, now it gets a little bit vague. What's systemic therapy and who are inappropriate to a TNF? What's inappropriate to a TNF? So there is a bit of vagueness in the language. Some people would say systemic therapy would include a steroid, so a steroid could be considered systemic. I'll just say that that's a little bit vague, but I agree with what you said, Anita. So let's go to a community gastroenterologist.

Audio Recording:

He should be tried on an advanced therapy at this point, having failed conventional therapy and having at least moderately severe Crohn's. I would use an IL-23, avoid further steroid use. And I believe that an IL-23 is most likely to affect clinical and deep remission as opposed to conventional therapy, mesalamine or vedolizumab.

Upadacitinib would be a reasonable therapy in this situation, but guidelines suggest not using it as first-line therapy before an advanced systemic therapy is tried. I would use it second line if IL-23s do not deliver results. I would initiate an anti-TNF agent. This guy has moderate Crohn's. SES-CD 12, ileocecal involvement, persistent symptoms for 3 months, weight loss, and he failed budesonide.

He's biologic-naive, so I want the therapy with the deepest track record, the most predictable insurance path, and the highest chance of working fast enough to stop the slow decline. I'm going with an anti-TNF because it's a known quantity and I've used it forever. Also, it is effective for moderate-to-severe Crohn's, including ileal disease. It's a practical first biologic with real-world data and clear troubleshooting. If he doesn't respond, I can still pivot to another mechanism later. I'm not starting with the newest “big guns” before I even know how he behaves on therapy. I'm trying to avoid the pattern of switch to flare to steroid rescue and more switching. I'd rather start strong and optimize.

I like the safety of initiating vedolizumab, but in Crohn's, especially Ileal, it can be slower and less reliable for what I'm seeing here. He's losing weight and still symptomatic after budesonide. I don't have time for a maybe. I haven't used IL-23s in my practice yet. They look great but I want more hands-on experience and real-world comfort first. Also, if I start there and it fails, I've burned a premium option early. I don't want my first IL-23 patient to be the one who doesn't read the brochure.

Initiating upadacitinib could be effective, but it's not where I start in a biologic-naive Crohn's patient when I have other proven options. More safety monitoring, more staff work, and more anxiety for me and the patient. Initiating 5-ASA therapy would not be an effective strategy for ileocecal Crohn's with this severity. This isn't a “let's try something” gentle situation. Initiating thiopurine monotherapy and reassessing in 3 to 6 months is too slow and not dependable enough, and I'm not letting him decline while he loses more weight and stays inflamed.

Miguel Regueiro, MD:

And then another community gastroenterologist said on IL-23…

Audio Recording:

I would initiate an IL-23 inhibitor. This is a biologic and small-molecule–naive, 28-year-old man with moderate ileocecal Crohn's disease, SES-CD 12 persistent symptoms for 3 months, weight loss, and failure of budesonide. He's clearly beyond watch and weight. For him, I want durable control, strong mucosal healing potential, and a plan he can actually live with long term. The IL-23 data are impressive and the subcutaneous dosing is a huge quality-of-life win, especially for a young, active patient trying to maintain work, gym, and social life. So, I'm starting an IL-23 inhibitor because of its high efficacy for Crohn's disease. It offers durability, not just quick symptom suppression. Sub-Q maintenance fits his lifestyle and reduces treatment friction. It avoids the “anti-TNF baggage” some patients run into like immunogenicity, secondary loss of response, et cetera. And it aligns with modern treat-to-target thinking. Control inflammation early, prevent progression. I'm not saving the best tool for later while he is actively inflamed now.

Initiating an anti-TNF agent is totally reasonable and still a great option. But if I'm choosing based on current evidence and patient lifestyle, an IL-23 is where I'm going first for long-term durability and convenience. I like the safety profile of vedolizumab, but for Ileal Crohn's and a patient already losing weight after budesonide I want something with stronger and more predictable efficacy. Initiating upadacitinib could be effective, but I

usually reserve JAKs for later lines or specific scenarios. For a young biologic-naive patient, I'd rather start with a therapy with an excellent efficacy profile and a cleaner, long-term risk-monitoring vibe. I would not initiate 5-ASA therapy. 5-ASA isn't appropriate for moderate ileocecal Crohn's. Initiating thiopurine monotherapy and reassessing in 3 to 6 months is too slow, not reliable enough, and risks delaying control while disease progresses.

Miguel Regueiro, MD:

And then the other respondents, kind of split. What did Millie say?

Millie D. Long MD, MPH:

For case 3, Brandon, he is quite symptomatic and has right-sided inflammation. My choice for Brandon's management would be D, initiate an anti-TNF therapy, with a little bit of an asterisk in that I use combination therapy with a thiopurine with an anti-TNF in the first 6 months to help to prevent immunogenicity. So, I would check thiopurine methyltransferase and potentially initiate a thiopurine with the TNF. In fact, I would actually use, specifically, infliximab. I do think infliximab, in terms of the anti-TNF agents, is my go-to in terms of the highest efficacy. That said, he is naive to other agents so I think this is someone you could consider for an IL-23 inhibitor. You certainly could consider vedolizumab.

I don't choose vedolizumab as readily in someone with predominantly ileal disease. I just don't think it has as great efficacy. And a JAK inhibitor is something we could consider. Now, remember that for JAK inhibitors the initial label said that they should only be used after a TNF agent, but the updated label says that it can be used after other systemic therapy if it's inadvisable to use a TNF. At this point, I don't think it's quite inadvisable to use a TNF, so I might still reserve that. But remember that label change for future use of upadacitinib. There is one answer here that is clearly wrong. All of our guidelines recommend against initiating mesalamine, so that should just not be done in ileocecal Crohn's disease. So that is truly the wrong answer.

In reality, our data truly show that early initiation of advanced therapy improves outcomes. And I think that any of these agents could be utilized. I think you could have a shared decision-making discussion with the patient himself over what he could potentially be most effective with and adherent to. I do emphasize that he really has been using budesonide and other things. Remember that no one should have recurrent courses of steroids, whether that's budesonide or prednisone. We really need to be thinking about an exit strategy.

Miguel Regueiro, MD:

Great. And so, Ed, by the way, is at University of North Carolina. Millie Long is the Chief of the University of Carolina, and their answer was identical.

Angelina Collins, MSN, ANP-BC:

Exactly.

Miguel Regueiro, MD:

So, infliximab and azathioprine, I'm just making that point.

Angelina Collins, MSN, ANP-BC:

I made it under my breath.

Edward L. Barnes, MD, MPH:

I want to have a job on Monday.

Miguel Regueiro, MD:

Let's go to Jessica Allegretti. None of us are with Jessica, so let's see what she said.

Jessica R. Allegretti, MD, MPH, FACG, AGAF:

For case 3 we have a young man who's newly diagnosed or recently diagnosed with ileocecal Crohn's disease and clearly needs to be advanced to an advanced therapy. And so, this will be the first advanced therapy that this patient is starting. We know that he has got fairly significant disease calprotectin in the thousands, getting worse after a steroid course. And so, I think, again, there are a few potential paths that we could take with this patient.

That being said, he doesn't have any big red flags for me that would require an anti-TNF initiation out the gate, so I probably would withhold that until later in his disease course should he need it. And, again, this is a patient where I think an IL-23 inhibitor actually would be most appropriate. It's a great first-line agent, with an excellent safety profile. We know it's going to be effective, durable, and work fast for him. This is likely not a patient where I would want to initiate vedolizumab, given how sick he appears to be and also has primarily ileal disease. And, typically, even though we have label changes with upadacitinib giving us a little bit more broad usage, I still am not typically using that first line.

Miguel Regueiro, MD:

All right. And then let's go to Ed, but listen to Ed on vedolizumab in first line even though he doesn't choose it, and then we'll show you one study that looks at vedolizumab first line for Crohn's disease.

Edward V. Loftus, Jr., MD:

So case 3 is a guy with Crohn's who has had recent increased symptoms. He is worried about the effects of steroids. He has been on budesonide, has definite evidence of inflammation, his fecal calprotectin and CRP are high. He's got an SES-CD score of 12, which indicates at least moderate activity. And previously, I mean here things are wide open because they're advanced therapy–naive. Of the choices listed, I would be considering either vedolizumab, an anti-IL-23, or an anti-TNF agent. I wouldn't probably pull the trigger on upadacitinib this early, and I wouldn't be doing thiopurine monotherapy anymore. I also wouldn't be doing 5-ASA since this is Crohn's disease.

So, of those options, the two that I would be most in favor of would be either the anti-Interleukin or the anti-TNF. Again, probably if vedolizumab is going to be used in Crohn's disease, probably the best time to use it is in a patient like this who's advanced therapy–naive. We know that from the LOVE-CD trial that that's when vedolizumab works the best in Crohn's, as in a patient like this. So, those are three options. I'd be leaning mostly

towards the anti-Interleukin or the anti-TNF. Out of habit I've probably been doing more anti-TNF, but now we have so many options available, anti-interleukin would be a great option too.

Miguel Regueiro, MD:

And another thing, if you did use an anti-interleukin first as a systemic therapy, you are open to use upadacitinib after that. We wanted to show you this. This was just published, so many of you may not have seen this study. This gets to, how does vedolizumab work for first-line Crohn's disease? Brandon's case is perfect for this. One, it's a bio-naive. Second, it is early after diagnosis. That is the key. Important factors. And you can see early Crohn's is the dark, the blue is late Crohn's. You can see a separation that if you were to use vedolizumab as the first-line therapy early, there are efficacy data in Crohn's. So, to be completely fair-balanced, if you were to use vedolizumab for Crohn's, use it as first-line very early. That would be my take-home. You heard before when we talked about infliximab, again, whether it was intolerance or failure, but vedolizumab after an advanced therapy, certainly in Crohn's disease, would not be appropriate. And I think you can even see in the late group that some of those patients had been on other therapies.

What did ChatGPT say? It also picked a TNF inhibitor. So, I think, again, the majority still pick that. And then the case perspective is really a split here. I guess one question I want to ask the group before we have you all vote again, and then we'll get to some of the questions, and Ed kind of mentioned this, I think as we all become more familiar with an IL-23, is there a reason in this kind of patient that we would not just say we're using IL-23 first? The data look very good. There is not a head-to-head yet in the designed way we want with IL-23 compared to a TNF inhibitor like infliximab. Again, if you really were to be fair-balanced, that's the trial you want. We don't have that. The safety is so good with an IL-23. The efficacy is so good. Is there any reason we shouldn't be using IL-23 first line? I'm going to ask each of you the same question. Maybe go down the line, Anita first and then Angelina.

Angelina Collins, MSN, ANP-BC:

I wanted to go first this time, but go ahead.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

Go ahead.

Miguel Regueiro, MD:

All right, go ahead. You look like the newscaster, with the headset and the jacket.

Angelina Collins, MSN, ANP-BC:

I know. The sportscaster, newscaster. I still think in a situation of more severe disease, closer to hospital admission, deep ulcerations, I would probably favor infliximab-azathioprine combination therapy. Like the UNC folks, I do use combination therapy of anti-TNF and immunomodulator in that situation. So, if these were deep ulcerations, significant, I know there are some data on stricturing disease and ability for IL-23 in stricturing disease, but even still, I think that I would favor in a sicker-looking patient and even more severe disease and

ileal disease as well, because ileal disease, we didn't talk about this, but that's another phenotypic beast, I think in treatment I would favor infliximab-azathioprine in a sicker patient.

Miguel Regueiro, MD:

So, the sicker patient. And then maybe, Anita, in a patient who maybe doesn't have the ulcers, we didn't talk about perianal disease, doesn't have perianal disease, why would you not pick IL-23 first? Or is that your go-to now for a patient with Crohn's ileal colitis?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

So, it still remains an IL-23 as a go-to for the naive patient. One thing I want to highlight, and maybe sicker, and that's what I was emphasizing, as far as that burden of disease that the patient is suffering from. We will here soon have results from FUZION, which is guselkumab in perianal fistulizing disease. That's going to be really great to see because at present we only have that kind of level of studies with infliximab. That's why we always think perianal disease, infliximab. So, I didn't fully answer your question, but I would still consider that in this patient, given the factors that Angelina pointed out.

Miguel Regueiro, MD:

And then Ed, would you still use infliximab, azathioprine? Again, no deep ulcers, no perianal disease, moderately active Crohn's ileal colitis. Is that still your first go-to, or are you starting to use IL-23 more?

Edward L. Barnes, MD, MPH:

I don't think IL-23 is wrong. Earlier we were just giving a one-word answer, but it's hard to sort of elaborate, but I think in this particular case I'm using IL-23 more. That's the answer to your question. The rationale in this particular case is, if I think about this guy who has really only had disease for a short period of time, this is not PROFILE where it's 12 days, but it's probably as close as we're going to see in practice in the United States, and he has already been on budesonide and his fecal calprotectin went up, so maybe he's the other arm of PROFILE. And those patients still had some of the highest remission rates that we saw in any clinical trial in the step-up arm. So, he's sort of the steroid step-up arm. They got to 60% at 6 months and the other arm was 80% at 12 months. That's sort of how I rationalized this particular case.

Miguel Regueiro, MD:

Just to be clear, we didn't outline the PROFILE study. For anybody who has journal clubs, you should do the PROFILE study. It's a European-based study within 2 weeks of diagnosis, not a few months or a couple of years, 2 weeks within diagnosis, top-down with primarily infliximab, azathioprine versus step-up. To Ed's point, we saw some of the highest remission rates we've seen in any study.

And what I want to bring up on this slide is, and I'll say this with absolute fair balance and objectivity, I think in newly diagnosed Crohn's, until we have head-to-head data, it may not matter what therapy we use as long as we use it very early and know that we need to monitor and switch. The reason I asked the question about IL-23, with the safety profile being so good and now seeing endoscopic improvement and efficacy, and now the fact that I can go to upadacitinib as the second line, I am tending to use IL-23 first.

And to answer a question I asked the panel before, I am using guselkumab primarily because the sub-Q induction is so easy for me to start and they can stay on it without getting a second payor approval at the maintenance dose. So, just to be clear, it's not a head-to-head efficacy amongst IL-23s. If you used another one, that would be perfectly acceptable based on efficacy, but because of the sub-Q induction. Anita, you want to make a point? And then as you're making the point, if the audience can respond again in terms of what you would do for brand in this new-onset Crohn's ileal colitis patient.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

My point was mostly with the anti-TNFs. A young patient, and certainly for any patient, first of all, when I start an anti-TNF I always, at least for the majority, do combination therapy. So, for that first 6 to 12 months, I'm doing combination therapy unless there are contraindications, older patient, et cetera. With that said, in a young patient, new diagnosis, burden of disease, quality of life, everything else, again, going back to that "easy button," how do I get him back to feeling normal? That's the word that our patients say, "When do I get to go back to feeling normal?" So that's another reason why I would not consider an anti-TNF, because I do combination therapy.

Miguel Regueiro, MD:

So, that kind of speed of onset. The point is very well taken. We do have a few more people saying they would use IL-23 first line, and then I still think in kind of second place is TNF. Upadacitinib kind of dropped off. I'm happy to say this again with fairness that mesalamine dropped off. I'm happy to see that. And then vedolizumab, again, there are still some who would say that's okay, but really it's coming down between the IL-23 and the TNF. I'm going to finish out the slide part, but now I have a lot of questions that I'm going to get to. Somebody asked me what I would do in Brandon's case and I think I answered it already, but I'll say it again. I would use an IL-23, because if it were not to work, TNF is still an option. Upadacitinib is still an option. Because of the ease of sub-Q induction, I am using guselkumab, not because it's better than risankizumab or mirikizumab. There are no data head-to-head, so just to be fair, but because of the sub-Q. I think we covered some of the uncontrolled disease demands and not delaying. Mechanism matters. We are seeing IL-23 as a class. Efficacy alone is not enough. We have to consider the patient, root of administration, safety, and kind of the right therapy for the right patient.

These are the SMART goals that we covered already: improving your confidence in using these different therapies, shared decision-making, which I think obviously you heard from our patients in our cases, the IL-23 class, which I think we are seeing starting to rise as an earlier in first-line therapy. And then obviously avoiding steroids and getting that clinical remission. I am going to show you the additional resources, because I want to make sure that you get this and then I will end with the questions. So, first of all, please visit www.cmeoutfitters.com for clinical information. There are other programs like this. This is an important resource and, similarly, free resources are available. Then we'll ask some questions that have been coming in. These are really, really good. Anita, I'll start with you. Pregnancy, there was a question that, and I don't know that we have the answer specifically. Can you cite the number of patients based on trials treated with vedolizumab or IL-23? I don't know that I can tell the absolute number of patients who have been treated across the trials, but maybe contextualize. I think the question gets at vedolizumab was an answer that people were using, because people are comfortable as it has been out longer, and maybe the question is getting at, what are

the patient-years follow-up? I actually don't know the answer to that, but I don't know if you have any insight on that.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

I don't know the exact number, but certainly the quick way to look at it is monoclonal antibodies. The science molecularly is the same, call it vedolizumab, call it guselkumab, call it infliximab. They're monoclonal antibodies. So, from a pathophysiologic standpoint, the impact to the placenta, to the fetus, to the baby, and to the mother are equivalent, so we could be able to interpret as such.

Miguel Regueiro, MD:

Good. I agree with that. Angelina, you mentioned LFTs and IL-23. I completely agree. One of the questions that came up, which is interesting, is do you switch patients from one IL-23 to another if there is persistent elevation in LFTs in the first IL-23?

Angelina Collins, MSN, ANP-BC:

I haven't personally done that. I would want to make sure, in the scope of this, that what you're really doing is when you are witnessing an LFT elevation, I mean it's really important to kind of classify this, is asking, Is this mild? Is it less than three times the upper limit of normal? Is it greater than five times the upper limit of normal? I mean, it's really important to understand the severity in which this is occurring. The second thing you usually want to do is make sure you really understand, Is it really drug-induced? Is this a really drug-induced situation? Is it getting a little bit more hazy where there may be multiple factors: alcohol, metabolic dysfunction-associated steatohepatitis (MASH), something else that's going on as well? Those things probably matter first before I do anything differently. The bottom line is, make sure you're attributing the LFT abnormality truly to the drug if you're thinking about switching to another. I think that's the best way I would answer it.

I haven't done that personally. I mean, it's possible that when you withdraw the first drug that you might see the liver enzyme normalized. In my experience, what I have seen, and you had mentioned this earlier, it's a transient liver enzyme elevation of what I have seen and it usually doesn't last beyond the induction period. That's typically when I've seen it and it's very mild. I don't even think I've seen one greater than two times the upper limit of normal in my experience, and they do normalize.

Miguel Regueiro, MD:

And I think the bottom line is we don't have data switching IL-23, one to another. Just to be clear, I agree with you. The other is the LFT abnormality that I look out for with any medicine, but I'll say with IL-23, as long as it's not three times the upper limit of normal, above that I still monitor the patient, and, as Angelina said, look for other reasons. Their LFTs might be elevated. If it's persistently three times or it has gone above that, I do stop that therapy. IL-23 would be one. And if that did happen, I wouldn't switch to another. Ed, there were some questions on perianal disease, specifically hidradenitis, which is out of the context of what we talked about. But let me maybe ask it this way, for the question that was asking about hidradenitis, are there any data on IL-23 versus TNF, which obviously there are data, but a patient maybe who failed at TNF? And then perianal disease in general, you kind of answered this already, but what's your first-line, second-line therapy?

Edward L. Barnes, MD, MPH:

I think I'll go to the second question first, because I think Anita alluded to the fact that we need these data to be published, and I think that's going to be very helpful to have that because most of the perianal disease data that we have is in the form of post-hoc data from large trial programs. And so, having dedicated studies is going to be very helpful. Putting it in order right now, I think we have infliximab as a go-to if they haven't been on infliximab. Then it does come down to a JAK inhibitor, IL-23 in my mind. Even though there are vedolizumab data that has been published for perianal disease, I just haven't found that to be as efficacious or as effective in real-world practice.

To the point about hidradenitis, I think this is a really interesting question. In a patient who has been on an anti-TNF that then is not responding to that anti-TNF therapy and they have bad hidradenitis in the setting of IBD, this is where I think going back to the difference between being in an IBD center and having a challenging patient like this in practice, I'm really lucky, because our dermatologist who manages hidradenitis happens to be one of the go-to people in the country. He has trials for this. He will put people on combination therapy, if not tertiary advanced therapies, and he's injecting with methotrexate and he's doing laser therapy weekly. I think this is where I can't tell you there's an algorithm for this and I think it would be to try everything because these are among the most refractory patients we have. So, that's the most un-reassuring answer that we'll probably give you on the panel.

Miguel Regueiro, MD:

I was going to say, Ed, you're not making me feel better and I'm not sure.

Angelina Collins, MSN, ANP-BC:

I think we have to go to UNC then.

Miguel Regueiro, MD:

Except go to UNC to get the most advanced…

Edward L. Barnes, MD, MPH:

But my point is I think once you get beyond standard of care for hidradenitis you try anything because this is so debilitating for the patient. So you just try everything that you can. And that's what I've seen Dr. Syed do.

Miguel Regueiro, MD:

I think one thing with hidradenitis, and then, Angelina, I'll call on you, sometimes perianal hidradenitis is difficult to distinguish from perianal Crohn's disease. Obviously if a patient has axillary changes of hidradenitis in certain other areas of the body, there might be some features that look like hidradenitis. Sometimes we can't tell. Like Ed said, I think a TNF inhibitor is first line, but then when you get beyond that, probably get specialists involved. Angelina, your thoughts?

Angelina Collins, MSN, ANP-BC:

Well, I was just thinking the same, but I also wouldn't have any concerns with putting someone on an IL-23 if they did have hidradenitis, either to see if it would improve things, given that it has favorable skin effects as well. So, I think, again, I agree tremendously. This can be extremely challenging in the management and improvement.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

And then there are a few case series and studies with IL-23 as well as with JAKs to study and evaluate its role and efficacy in hidradenitis.

Miguel Regueiro, MD:

Yes, and I think we've all used probably all of the agents. Generally, our dermatologists love IL-23s. So, if I'm going to send a patient to the dermatologist, I'll start an IL-23 first because if we didn't they're definitely going to do that. If we've done that already, to Ed's point, then you get into additional therapy. Anita, people picked up on a comment you made and there are a number of questions related to speed and rapidity of onset. I didn't show any graphs or data and I know you were involved in some of the IL-23 study, especially guselkumab. Talk a little bit about not only in the data but in your practice what you're seeing as far as rapidity and speed of onset with IL-23.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

We're actually impressed with the level of rapidity that we're seeing with the IL-23s and with my familiarity and involvement with our GALAXY trials. But then we're also looking at GRAVITI, which is the sub-Q formulation, and QUASAR, and looking at rapidity in totality, whether it's ulcerative colitis or Crohn's disease, finding that our data, even though our initial endpoints for Crohn's, be it 8 or 10 weeks or whatever it might be, we were still already seeing the separation even as soon as within week 1. That kind of rapidity is what we had not previously seen with some of our other therapies and that's where the reassuring component came in.

Miguel Regueiro, MD:

Perfect. Ed, this is an interesting question. I'm going to ask you a question about high body mass index (BMI) sub-Q guselkumab and then, Angelina, I'm going to ask you a question that keeps coming up, How do you determine which IL-23 you use first? High BMI, does that make a difference for you in terms of using sub-Q versus IV? And Anita has data. She'll present it, but I'll ask you first.

Edward L. Barnes, MD, MPH:

I think that it's a consideration. I think that this has been a consideration even if we think about anti-TNF therapy and the idea that some of the trials were done with double dosing of adalimumab, for instance, in trying to do higher dosing. So, I think it definitely is a consideration. Whether or not I think every single patient has to be on an IV approach if they have a high BMI is, I think, not necessarily something that I would do in practice because of some of the accessibility issues that we talked about before. So, I'll sort of give it a short answer because I know we're short on time.

Miguel Regueiro, MD:

And then Anita?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

We looked at pharmacokinetic data of IV formulation and sub-Q formulation and utilized and studied different factors and variables and actually BMI did not influence the bioavailability, meaning you could give sub-Q despite their BMI.

Miguel Regueiro, MD:

If you look at the interquartile BMI high and then down the three quartiles, sub-Q and IV were indistinguishable in terms of efficacy, so, kind of that thought of we have to use IV for high BMI, we didn't necessarily see that. Which IL-23 first and why? Again, I know we've answered it, but answer it maybe one more time, Angelina.

Angelina Collins, MSN, ANP-BC:

I think this is where you want to use, if there are head-to-head data, I think it helps a little bit just thinking...well, let me say it differently. I use the data from SEQUENCE. I use the data from the guselkumab study looking at ustekinumab, seeing that both of those studies showed superiority to ustekinumab, and then looking at mirikizumab having non-inferiority. So, to me, that's showing something's a little bit different here. Whether this makes any sense or not, I don't know, but in my mind those are some things that I'm thinking about.

I like for a lot of the patients, and except for the few who are needing IV, the sub-Q induction dosing has been really helpful in a lot of ways. Lately, that has been a go-to for me. In the end, we don't have head-to-head between, say, risankizumab and guselkumab, so I can't necessarily say this is the one to use. So, I think you're good in thinking about what can you get for your patient. We don't want to have delays in therapy because of some small thing. Getting a patient on drug quickly with patient assistance is fantastic, so for me it's often been that I've been writing quite a bit of goals, I guess, lately.

Miguel Regueiro, MD:

And then, Anita, same question. I know you've said it before, but any differences in what you said before?

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

No.

Miguel Regueiro, MD:

All right. And then I'll end with one question. Anita, I'll come back to you, and Ed, I'll end. We can't get through any program without talking about GLP-1, so thank you. There were a bunch of GLP-1 questions. Just for the record, we don't have enough data. Ed, you might talk a little bit about the pouchitis data with GLP-1s. One, Anita, is there any problem using any of our therapies in a patient on a GLP-1? And two, are you using GLP-1s to treat IBD specifically? Completely off-label, not part of this actual program, but just to ask those two questions.

Anita Afzali, MD, MPH, MHCM, FACG, AGAF:

So, no harm in continuing or starting or initiating appropriate therapy for your patient, even if they're on a GLP. In fact, you're probably going to have better outcomes because we know obesity and some of those other medical comorbidities related to that, if we could improve that, because obesity, fat, adipose is inflammatory. We're also seeing better benefits in disease control. In fact, I believe mirikizumab actually has a trial and study with GLP and mirikizumab, or they're evaluating. I don't know if that's taken off. Your second question as far as to use it as a solo? No.

Miguel Regueiro, MD:

Okay, Ed?

Edward L. Barnes, MD, MPH:

I totally agree. And I think that the specific way that we have used the GLP-1s, and this comes up in our pouch clinic, is that aside from the inflammatory component, patients who have an ileoanal anastomosis, a J-pouch, often have high bowel frequency. That's separate from actually the inflammatory component of having parotitis or Crohn's-like disease of the pouch. And what GLP-1 is mediated in is the ileocolonic break. So, if you don't have a colon anymore, then obviously you lose that, and maybe one of the drivers of high bowel frequency, and GLP-1 receptor agonist therapy can actually help in slowing down bowel frequency. We did a small pilot trial at UNC, led by Dr. Hans Herfarth, where patients were on active therapy and randomized to placebo, or placebo and randomized and they were self-controlled and randomized to the active therapy. It showed over a 30% decrease in bowel frequency during a very short trial. So, we've now used that to then get approval for these therapies in a large proportion of our patients in our pouch clinic.

Miguel Regueiro, MD:

But, again, for fair balance, we're not recommending GLP-1 as a sole treatment for IBD but we're completely comfortable if a patient is on a GLP-1. And, as Anita said, there are studies that are now being designed to use GLP-1 as part of the therapy for IBD.

Ed, Angelina, Anita, thank you. I thought that was very interactive and excellent. To the audience in the room and the audience online, thank you for so many questions. Sorry we couldn't get to them all. For those here, enjoy the rest of congress. And I know with the snow storm out there, I wish everybody safe travels back. See you around.