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### ReachMD

[www.reachmd.com](http://www.reachmd.com)

[info@reachmd.com](mailto:info@reachmd.com)

(866) 423-7849

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## Playing the Long Game: Improving Durable Control in IBD

### Announcer:

Welcome to CME on ReachMD. This activity, titled "Playing the Long Game: Improving Durable Control in IBD" is provided by Clinical Care Options, LLC dba Decera Clinical Education.

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### Dr. Afzali:

So first of all, what we recognize is that inflammatory bowel disease, as we are all well aware, it is a relapsing-remitting disease condition. Whether you suffer from ulcerative colitis or Crohn's disease, despite being on standard therapy or even optimized or escalated therapy, you can see here, as per a report of patients with their reported ongoing symptoms, that there is, in fact, an ongoing report of having symptoms. Bowel-related symptoms, or what we call extraintestinal manifestations related to that as well. We want that light purple to be 100%, but indeed what we see is, despite therapy, our patients continue to have ongoing reported symptoms.

### Symptom Impact in IBD as Reported by US Patients

What are those symptoms? We see a variety. Based off of ulcerative colitis or Crohn's disease: abdominal pain, sleep disturbance, fatigue, anxiety, depression. Here you can see that indeed regardless of whether their bowel disease is active or inactive, these are those patient-reported outcomes or symptoms that are very frequently reported whether a patient suffers from ulcerative colitis or Crohn's disease.

### Impact of Disease Flares and Progression in IBD

In fact, we absolutely know that factors consistently associated with the quality of life are not only the symptoms I just described, but that also relates to increased utilization of healthcare, whether that is increased emergency department visits, whether that is hospitalization rates, work disability, number of relapses, and even increased disease activity. Having these ongoing symptoms and not addressing them can relate to having an increased risk for a disease flare.

When we evaluate a patient's quality of life, we have to recognize that their overall quality of life and how they score that - that is the EQ5D summary score - we certainly know that if their quality of life is scored in a sense of being poor, then the association and the risk for a disease flare or ongoing utilization of healthcare needs and resources increases just by simply having a poor quality of life associated with those patient reported symptoms.

### Cardiovascular Comorbidities in IBD

What we also know is, and we are learning much more, that inflammatory bowel disease, ulcerative colitis, or Crohn's disease also is very frequently related to having an increased risk of cardiovascular comorbidities. That includes the metabolic syndrome, if you will, hypertension, hyperlipidemia, obesity, and diabetes. Then also some other disease states that are related to cardiovascular comorbidities and even related to major adverse cardiovascular events. That includes a higher risk for peripheral vascular disease as well as ischemic stroke, fatty liver, ischemic heart disease. All of these are intertwined. The recommendation, more and more as we are

learning, as far as inflammatory bowel disease, is that our patients who suffer with inflammatory bowel disease are at a higher risk of having cardiovascular comorbidities.

Here is a risk assessment and how we would recommend to evaluate this based off of the right patient. If they fit the profile of increased risk factors, indeed, a closer monitoring and assessment for risk for cardiovascular complications is also recommended.

### Anemia in IBD

Another component that is recommended is anemia. An evaluation for anemia. We know that fatigue oftentimes is multifactorial. This patient that reported that the case example I started with, that patient was having increased fatigue. Certainly, that could be related to ongoing bleeding because of their symptoms. However, if they do not have bleeding and bloody stools or blood in stools that they are actively seeing or even occult bleeding, then certainly fatigue could be related to other conditions. That is included in here in the bottom right corner. Whether that is medication-related, whether that is vitamin B12 deficiency, folate deficiency, or other causes.

I will add here, about 70% of patients who suffer with inflammatory bowel disease are at risk of having some form of anemia, either anemia of chronic disease, iron deficiency anemia, or other forms of anemia. This is a good little cheat sheet or guidelines in the sense of how we would recommend evaluating the patient's anemia, also specifically including not just hemoglobin but ferritin and the transferrin saturation to evaluate for causes and sources.

### Factors Influencing Quality of Life

Other factors influencing the quality of life for our patients - this is a callout of the importance of mental health - we have absolutely found an association between depression and anxiety, increasing the risk of flares and also increasing the risk of hospitalizations, emergency department utilization, and increased resources throughout our clinics.

Absolutely, addressing this and being able to provide, if you are unable to personally provide that level of care, a referral to psychology or psychiatry or behavioral therapy or any of the rest is absolutely recommended. Physical activity, diet, chronic pain, we know that that is a component as well.

When we talk about overall quality of life, it is important to be able to incorporate a quality-of-life questionnaire. The one I incorporate into my clinic is the IBDQ. That is an extensive questionnaire, if you will. It gives me a better understanding of where is my patient at when it comes to their report of their quality of life, of their symptoms, and the impact that that could potentially have as me and the patient are collectively managing their disease.

### Discussing Treatment Risks with Patients

Oftentimes, our patients' quality of life is one aspect, but of course, how we discuss treatment and management of a chronic disease such as inflammatory bowel disease becomes quite apparent and important. This is the value of shared decision-making: making sure we understand what are our patient's goals of therapy as well as what do we need to make sure that the goals of therapy are incorporated, knowing that we need to manage the disease, but holistically. That is that comprehensive disease management.

This is a little cheat sheet again of how we typically communicate, and some of the strategies we use when we are discussing our therapies, when we are discussing our management and treatment options. We try to avoid the use of vague descriptions such as, "That is very rare," or "This is really common," but instead of those words, we use more of the common denominators to be able to think of it a little bit more clearly. For example, I say, "If you imagine a room full of 100 people, of those 100, three or two people are at risk of a non-melanomatous skin cancer," or whatever it might be. Being able to appropriately frame it is very important.

### Defining Optimal Control

Then being able to define what are the goals of therapy collectively with our patients. At the top, you see that those functional outcomes, if you will, that normalization of quality of life, restoring mental health, no sleep disturbances. I will add with mental health, I am including mental health, sexual health, physical health, all of that as far as quality of life. Then we move on to the symptoms with managing the symptoms. What is both the patient-reported symptoms as well as the additional symptoms related to ongoing inflammation? That would be, of course, still included in patient-reported as well: fecal urgency, abdominal pain, bleeding, the extraintestinal manifestations, and then the markers of inflammation. Are there biomarkers or inflammatory markers normal, or is it still elevated? Have we achieved mucosal healing? Then, of course, a big goal continues to remain: can we keep our patients off of steroids, off of prednisone?

### The SHARE Approach: Shared Decision-making in IBD Care

This approach takes that SHARE approach, or shared decision-making approach. This is an approach I very often and always take with my patients. Seek the patient's participation. Help them understand, provide that level of information, help the patient compare what the

treatment options are, and being able to give the potential risks and benefits of each of the options and treatments we give. Assess patient's values and preferences. Reach a decision with the patient. Then evaluate the patient's decision.

This shared decision-making approach through SHARE is a good way to ensure that you are listening to your patients, you are being able to incorporate their goals, but then also being able to understand what the recommendations are from your perspective as well to ensure the best of care for each individual patient.

### Posttest 1

Having said that, and we already got the majority right, when we go back to this posttest question of being able to recognize that our patient here, she reported stopping exercise due to fatigue. As I noted to you, also having some of these cardiovascular risk factors as well. She has obesity, she has hypertension. She stopped exercising because of her fatigue. Knowing that this requires a further workup is what I hope I was able to convince you of. Go ahead and see if you are able to now, again, confirm the right choice.

### Kelly:

Go ahead and submit your answer. Looks like we are 100% B.

### Dr. Afzali:

Excellent. That is what I like to hear. Thank you. Again, this is a reminder. I will start from the bottom. We will not just escalate therapy because of reported symptoms. There is no need. Biomarkers were already normal, so that does not make sense.

Reordering the biomarkers when they are already normal. That is not cost-effective, not appropriate. Then, of course, continuing current therapy and come back and see me in two weeks, that also is not appropriate.

### Rationale

Here, evaluating the symptoms is most appropriate.

### Patient Case Discussion

Let us do a patient case discussion here.

### Patient Case: 38-Yr-Old Woman with Ulcerative Colitis

We have a 38-year-old woman with ulcerative colitis. She presents to your office and reports a six-year history of left-sided ulcerative colitis. Says, "I am exhausted most afternoons. I stopped yoga because I am worried I will suddenly need to go to the restroom." She has that urgency. She has about two to three bowel movements a day. They are formed with no bleeding, no nocturnal symptoms. Past medical history and medications here as listed. Her current is vedolizumab, no steroids. Her relevant labs are as described here, with her last colonoscopy being unremarkable with no inflammation biomarkers. CRP, fecal calprotectin normal. The blood counts here, her hemoglobin, MCV, and ferritin. I want to make note of those. Her saturation.

What opportunities, in general, when you are looking at this as a comprehensive collective, would we say? What opportunities exist to improve this visit? What challenges may impact your treatment decisions? You are seeing everything here. We have talked about some of the approaches we would take.

### Poll 3

My ask now is - you could either type it in the chat or scan the QR code and just give me some opportunities. What would you do here? Just give some additional opportunities for improvement in her care approach. Go ahead.

Kelly: If you guys want to just put those in the chat.

### Chart 2: Treat-to-Target Guidance in IBD Care

Dr. Afzali: While you are putting those in, I am just going to keep going because this is more of a conversation and a discussion. Let us switch gears a little bit. We have started talking about that comprehensive approach, listening to our patients, shared decision-making. Now, let us switch to the second objective, which is taking that treat-to-target approach for each individual patient.

### Pretest 2

We have a 36-year-old female with moderate to severe ileal Crohn's disease. She is on adalimumab. She is on that every two weeks. Now 16 weeks pregnant, she reports worsening abdominal pain increased stool frequency. She has adequate drug levels, no antibodies. Reassessment shows elevated CRP and fecal calprotectin. Stool studies are negative for an infection. You perform, or someone performs an intestinal ultrasound, and indeed we see ileal active inflammation.

What would you do next in this situation?

- A. Would you initiate an IL-12/23 or an IL-23 inhibitor as monotherapy? In essence, changing the class of treatment.
- B. Would you continue the current therapy and start low-dose prednisone and keep her on that throughout pregnancy?
- C. Would you initiate a JAK inhibitor, or
- D. Would you increase adalimumab to weekly?

Go ahead and vote for this one.

**Kelly:**

Please go ahead and vote. Waiting for more responses.

**Dr. Afzali:**

This might be a little bit tougher, just with the choices and some caveats, if you will, that we will talk about respectively. Do not worry. Just give your best-case votes.

**Kelly:**

We have three votes. Two have said A; one has said D.

**Dr. Afzali:**

Okay. We will talk about why it will be A. The few votes that said A is the most appropriate. We will discuss this here next.

Why Is Treat-to-Target Important in IBD?

Before we talk about that, let us take that treat-to-target approach. What does that mean? Why do we emphasize this? I am at every podium emphasizing these words: treat-to-target. What we recognize is, and the reason it is important is we absolutely know that taking a more targeted approach with our endpoints and our goals of therapy reduces the natural risks and the natural progression of the disease. It reduces complications of the disease. The long-term, even sometimes the short-term complications related to the disease.

It prevents disease-associated disability, improves quality of life, lowers risk for hospitalization, and even lowers the risk of surgery. We indeed know that it increases the efficacy or rates that we see when we take a more treat-to-target approach, rather than the conventional therapy and standard approach. This is what we are going to talk about.

STRIDE-II: Dynamic Treat to Target in IBD

This is what that treat-to-target approach is. It is called the STRIDE-II recommendations. I will say in this fall, we are coming in with our STRIDE-III recommendation. The STRIDE-II recommendations is immediate or short-term, intermediate, and long-term targets. Short-term targets is symptomatic response. Is your patient at least improving in symptoms? You and I both know none of us wants to be on any form of therapy unless it starts making us feel better.

Of course, naturally, when we start initiating any therapy, our short-term target or immediate target is that, on that therapy, regardless of which therapy, our patients are at least feeling better. They are having a symptomatic response.

Our intermediate target - that intermediate becomes about three to six months after initiating therapy - we want not only them to feel better, but we want symptomatic remission, meaning their symptoms have completely resolved. We also want a normalization or at least a very good trend in normalized CRP as well as fecal calprotectin. That is the intermediate target.

The long-term target - by long term, we say about 6 to 12 months, regardless of therapy. The long-term target is indeed endoscopic healing or mucosal healing. That also includes normalization in the quality of life, absence of disability. For our pediatric population, normalization and growth.

These are the targets that we, when we say treat-to-target we go with the short-term or immediate, intermediate, and long-term targets, recognizing that we need to proactively monitor the disease throughout to ensure that these targets are being achieved.

Treat-to-Target Strategies in IBD

The way we take that approach again is, the targets of treat-to-target includes certainly subjective clinical response as far as reported symptoms, the patient-reported symptoms, rectal bleeding, stool frequency, whether it is for ulcerative colitis or Crohn's disease. For Crohn's disease, the patient-reported outcome of abdominal pain is also included.

Then we include the objective. That is the subjective, and then we include the objectives throughout with these targets: the biomarkers,

the endoscopic assessment.

Histology is not yet a formal target, but we do look at histology more and more. In fact, in our STRIDE-III recommendations and guidelines, we will incorporate histology for ulcerative colitis. Radiologic, certainly, IUS, or the intestinal ultrasound, or an MR, or CT. These are ways that we evaluate for transmural healing. Quality of life, as I discussed. Then the molecular, we really have not gone into the genetics as targets, and I do not think our STRIDE-III recommendations will also include that.

### PROFILE: Infliximab vs Standard of Care for Patients with Newly Diagnosed and Active CD

The reason that those targets are important and that treat-to-target is important is a recent study that was actually published in Lancet in 2024. The PROFILE study took home and reemphasized exactly what we knew, which is early appropriate therapy for aggressive disease. It is not aggressive therapy; it is early appropriate therapy for aggressive disease. That aggressive disease, the PROFILE study said, "Among a few hundreds of patients who were recently or newly diagnosed with Crohn's disease, let us take the standard of care approach, which is we first see them and then we start them on some steroids, and then we wait and then see what is next and delay that approach of symptoms and monitoring and steroids."

Then the other cohort within this study was the approach of saying, "We diagnose you with Crohn's disease. We know you have active disease. Now we are going to immediately start you on infliximab with a concomitant immunomodulator." Standard of care as compared to appropriate therapy.

What was found was that if you start early appropriate treatment among patients with newly diagnosed Crohn's disease that are newly diagnosed and have active disease, the outcomes for the patients who started appropriate therapy within two weeks were much better. Achieving endoscopic remission, not requiring steroids, remaining surgery-free. Even remaining in endoscopic remission, not just by endoscopy but also by biomarkers, you can see that early appropriate therapy and timing matters.

### CALM: Tight Control vs Clinically Driven Management for Patients with Moderate to Severe CD

The CALM study was another study that said, "Should we take this treat-to-target approach and really be stringent and tight on it? We monitor CRP, we monitor fecal calprotectin. If those are elevated, we optimize the therapy, or should we take the conventional approach?" Which, once again, is we start therapy, and then we do not as strictly or as tightly monitor the biomarkers or perform our colonoscopy. We base it more on symptoms alone. Then, about 6 to 12 months later, we determine if we optimize. The conventional management was more of, "Come see me in six months; we will see how things are," as compared to that tight control of that treat-to-target approach, which is, "Let us monitor your biomarkers. Let us have a colonoscopy whether you are improving or not, and then determine the opportunity to optimize your therapy."

The CALM study showed us that tight control versus clinically-driven management or conventional management achieves better outcomes again, so deep remission, biologic remission, remaining on the biologics and being in remission with the biomarkers, mucosal healing, complete endoscopic remission. All these endpoints were achieved if we were able to tightly monitor and appropriately optimize the treatment our patients are on.

PROFILE told us that early, appropriate therapy for aggressive Crohn's disease was good. CALM told us that we should monitor those treat-to-targets effectively and accordingly optimize therapy when needed to give us the best outcomes.

### Posttest 2

Here, knowing that our patient is pregnant, now 36 years old, again on adalimumab every two weeks. Adalimumab can be given weekly. However, here you see that she has adequate drug levels. She is also pregnant, and she is reporting symptoms. Now we are placing her at risk with her symptoms, but also the baby. Remember, she is pregnant. She has elevated biomarkers. These are those targets I discussed. You have an intestinal ultrasound confirming that there is inflammation. Think back and just look at this and see if, with a little bit of discussion, you would know why we would choose what we would. Go ahead and revote, please.

**Kelly:**

We need more votes. Okay. We have 100% A.

**Dr. Afzali:**

Perfect. Why is that perfect? Let us again skip A - A is the right answer - and go straight to B. Why is that not right? She is pregnant. We do not want to just keep her on prednisone until delivery. She is 16 weeks, and that is a long exposure for the patient to be on prednisone, and she is also pregnant. This is not something as far as a maintenance that we give throughout pregnancy. Certainly, if she needed it for an acute induction of something, sure, I am not concerned. However, keeping it that until pregnancy is not good. JAK inhibitors are contraindicated for pregnancy. That is why we say no JAK. Then increase adalimumab to weekly; we would not do that

because we already know she has adequate drug levels.

Rationale

The class of medications that I am going to specifically focus on are the class of IL-23 inhibitors, as well as IL-12/23 as monotherapy. This is a newer class, if you will, not so new anymore. We have had IL-12/23 for over a decade, and the IL-23 inhibitors which is the newest kid on the block. That is also been a few years old now as well, so we have good familiarity and comfort with it. We have incorporated it. I have written the ACG Crohn's disease guidelines with my co-authors. We are incorporating it throughout our guidelines.

Chart 3: Evidence in Action for the Long Haul

Let us talk about the long haul, reviewing some of those options as far as the durability. We are talking about efficacy of do our treatments work? I also want to ensure that we are talking about durability as far as will they continue to work.

Pretest 3

We have a 29-year-old female with ileocolonic Crohn's that initially responded to anti-TNF therapy, but then lost response within six months. She was subsequently switched to mirikizumab and achieved clinical remission, which has lasted for the last six months. She asks if she can stop therapy now. She is feeling great. She got on mirikizumab, feels great, and says, "Maybe I could stop treatment now." What are the options;

- A. Continue therapy given sustained remission and safety profile.
- B. Continue therapy with consideration to de-escalate if remission remains durable, whatever that means.
- C. Gradually increase the dose interval. Just kind of phase it out slowly, or
- D. Discontinue therapy with close monitoring of fecal calprotectin and CRP.

What would you recommend?

**Kelly:**

Let us go ahead and vote even if you are not sure of the answer. It looks like we have about 75% A, 25% B.

**Dr. Afzali:**

We will talk about this. I will say, I am sure you get asked this often by your patients, as do I, which is, "I feel great. Now I want to stop treatment because I feel great." We unfortunately recognize and know that this disease is a relapse-remission type of disease, so that risk of disease reoccurring or progressing is certainly there regardless of which therapy our patients are on.

Long-term Outcomes in Crohn's Disease

Let us talk about some long-term outcomes in Crohn's disease specifically with our therapies.

IM-UNITI LTE: SC Ustekinumab Long-term Outcomes in CD

I mentioned that I am going to talk about IL-12/23, which is ustekinumab. Then we will talk about IL-23 inhibitors as next. As far as for Crohn's disease, the ustekinumab long-term outcomes - this is a treatment we give... Oftentimes, what we have learned with our anti-TNF, such as infliximab or adalimumab, is that after one year of being on therapy, our patients are at least a 50 to up to 70% higher risk of developing a secondary loss of response. Oftentimes, a loss of response is because the patient has developed antibodies to the anti-TNF. What we have learned is that the risk of immunogenicity, or that risk of developing antibodies with non-anti-TNF, such as an IL-12/23, such as ustekinumab, is actually very low. By very low, I mean less than 5%.

About 50% to 70% risk of losing a response by year two with an anti-TNF as compared to less than 5%. That already tells us the durability of our interleukin 12/23, or interleukin 23 inhibitors are not only effective but also durable in the sense of that risk of losing a response is not seen.

Here, based off of ustekinumab data for Crohn's disease at five years, with or without previously being exposed to an anti-TNF - you indeed can see that over time, and even throughout up to five years of data, we have, and we actually have longer data than this now - that the patients who remain on ustekinumab continue to remain on ustekinumab. Overall, the kind of difference that you are seeing as far as losing a response, that delta is much, much smaller risk of losing a response as compared to what we have seen with anti-TNFs and certainly here with placebo.

VIVID-2 OLE: Mirikizumab Long-term Outcomes in CD

Mirikizumab for Crohn's disease. Again, based off of the open-label extension trials and data... Mirikizumab is your IL-23 inhibitor. Here you can see that with mirikizumab for moderate to severe Crohn's disease, among the patients who achieve that endoscopic response at that week 52, among them following these patients up to week 152, which is about two to three years, you are seeing that these patients continue to remain on endoscopic remission, endoscopic response, clinical response, clinical remission. All those endpoints are maintained at that, following year one and then year two and year three. Here, consistently, that durability continues on, and safety profile is consistent. No new safety signals.

### SEQUENCE OLE: Risankizumab Long-term Outcomes in CD

SEQUENCE was our second head-to-head study that evaluated an IL-23 compared to an IL-12/23. Compared risankizumab to ustekinumab. Here, based off of those patients and on SEQUENCE, what was found was that risankizumab was superior to the IL-12/23, which is ustekinumab. The SEQUENCE open-label long-term outcomes found that among the patients who continue to remain on risankizumab, and following them for an additional year onwards or two years, here you can see that ongoing, the patients continue to remain in remission - clinical remission, steroid-free remission. Again, emphasizing the durability of this class of medications, whether it is an IL-12/23 or an IL-23, you can indeed see that efficacy was sustained beyond the one-year endpoint, emphasizing again that with our anti-TNFs, we are seeing that higher risk of losing a response after that one year and requiring dose optimization or combination therapy or whatnot. Here we are seeing on monotherapy with an IL-23 inhibitor or an IL-12/23 inhibitor, you are seeing sustained efficacy beyond that one-year endpoint.

### GALAXI 2/3 and GRAVITI LTEs: Guselkumab Long-term Outcomes in CD

GALAXI and GRAVITI were studying guselkumab. With here similarly - and I was heavily involved from designing GALAXI, all the clinical trials and studies - to now having this type of endpoints and output, if you will. This was really exciting to see that with guselkumab, similar to mirikizumab as an IL-23 inhibitor and similar to risankizumab, that sustained endoscopic response and remission were observed at 96 weeks.

### U-ENDURE OLE: Upadacitinib Long-term Outcomes in CD

Let us switch gears to a JAK inhibitor, upadacitinib, for long-term outcomes. Again, sustained results achieved beyond the initial 48 weeks. All of this is re-emphasizing that our newer therapies beyond our anti-TNFs continue to be effective beyond that one year that we had a little bit of. That therapeutic ceiling, that limitation with our anti-TNFs previously.

### Long-term Outcomes in Ulcerative Colitis

What about long-term outcomes in ulcerative colitis?

### UNIFI LTE: Ustekinumab Long-term Outcomes in UC

Once again, with ustekinumab, again, you are seeing our patients continue to remain steroid-free. This is beyond that one-year mark into that week 200, and no new safety signals. Again, ustekinumab is your interleukin 12/23.

### LUCENT-3 OLE: Mirikizumab Long-term Outcomes in UC

Mirikizumab very similar to Crohn's disease mirikizumab data. Here again, mirikizumab is your IL-23 inhibitor. Beyond that initial induction and maintenance, and up to now, we are at week 212. Here, you are seeing that ongoing endpoints were continued to be achieved and remain for our patients.

### COMMAND OLE: Risankizumab Long-term Outcomes in UC

Risankizumab, again, re-emphasizing that beyond the initial endpoint of that one-year data and onwards, similar rates and efficacy remain stable throughout. Once again, no new safety signals.

### QUASAR LTE: Guselkumab Long-term Outcomes in UC

Guselkumab, same take-home message. No new safety signals. Efficacy was achieved and maintained beyond that one-year trial of the maintenance data, with no new safety signals.

### U-ACTIVATE LTE: Upadacitinib Long-term Outcomes in UC

The JAK inhibitor, once again emphasizing beyond the initial clinical trials and that open-label and evaluating, patients continue to remain on upadacitinib. No new safety signals.

### OCTAVE Open LTE: Tofacitinib Long-term Outcomes in UC

Overall, you are seeing that. What about tofacitinib? You can see that tofacitinib is also a JAK inhibitor. Here again, beyond the initial maintenance trials, the clinical and endoscopic response at that 36 months and then following thereafter is tolerated. There were some common adverse events that were reported, specifically herpes zoster. Overall, no new safety signals.

### True North OLE: Ozanimod Long-term Outcomes in UC

Ozanimod is an S1P modulator for ulcerative colitis. Oftentimes I give it for mild to maybe a little bit of moderate disease, but usually for mild ulcerative colitis. It is an oral tablet. Here again, durable and effective into that five-year follow-up with no new safety signals. In fact, safety signals were exactly identical to what the patients were initially exposed to, had, and reported throughout the initial induction and maintenance.

### ELEVATE UC OLE: Etrasimod Long-term Outcomes in UC

Etrasimod, which is another S1P modulator, here again, seeing that overall durable efficacy was found beyond the initial week 52 endpoint. Now we have longer data even beyond week 104 that we actually are publishing and presenting in Barcelona in a few months as well. We have long-term data, up to three years, and more to be shared about this in the future.

### Discontinuing Advanced Therapy in IBD

Let us take it back to our case, which basically says: should we stop treatment? We know that there is risk in stopping, discontinuing, or de-escalating therapy. Because of that, all of us within our guidelines, whether it is the ACG ones that I have been involved in, ECCO, European, or British BSG, overall, you can see, is withdrawal overall supported? We say we should be very cautious and probably only in a select patients and probably not. Overall, we say that if a patient really wants to, there has to be some prerequisites. Part of that is sustained deep remission, which includes clinical, meaning complete normalization of clinical symptoms. It includes biomarkers, which is that biochemical remission. It absolutely includes mucosal healing, which is that endoscopic complete normalization. Maybe incorporating some prerequisites. Then, if you do discontinue or de-escalate, it will be a really stringent approach with that treat-to-target approach, evaluating and monitoring the biomarkers. However, overall, we would say this needs to be mostly discouraged, recognizing that the safety profile of our newer therapies are quite safe. We know that there is still a risk of relapse with the disease, and so discontinuing treatment or just lowering the dose of therapy, we do not want to lose efficacy and then place our patients at risk of ongoing disease recurrence, which could be quite severe. Overall, most of the organizations says, "We do not want to really de-escalate treatment knowing this is a disease that is relapse-remission, high risk for disease progression. In the right patient with some prerequisites, maybe we can say we would do, but it would require careful monitoring.

### Posttest 3

Having said that, hopefully I primed you up a little bit for this; we have a 29-year-old again. This is that patient who responded initially to anti-TNF but then lost her response. Already, you have a patient who had a response, loss of response. Now she is on mirikizumab, and she has a response, and she has achieved clinical remission, but she says that she wants to stop treatment. What would you do based off of the discussion we had and the risks that we talked about? Go ahead and try to vote for this again.

### Kelly:

Okay. Wait for a few more responses. It looks like 100% for A.

### Rationale

### Dr. Afzali:

You are absolutely correct. Hopefully, as we are talking about this - continuing therapy with consideration to de-escalate if remission remains durable - again, we do not really want to emphasize that or discuss that because we do not want to de-escalate. We do not have that concern for the safety profile. We want to maintain efficacy. De-escalating places our patients at risk. Certainly, gradually increasing the dose interval for a medicine that is effective. That is how it is been studied. The trials have shown that those are the effective doses and the frequency. Why do we want to mess around with that? When you change the dosing interval, you change the pharmacokinetics and place your patients at risk of not having an effective treatment given at the time it should.

Then discontinue therapy with close monitoring of fecal and CRP. Yes, if you absolutely decide to, but overall, we just do not think that we are there yet with discontinuation or de-escalation of treatment. Just discontinuing it and then monitoring it, not recommended. You are right. We want to continue therapy. Again, using that SHARE approach, that shared decision-making approach, you want to help understand why do they want to stop treatment. What are their concerns? What are their goals? What are we not achieving with their current therapy, or what have we achieved with their current therapy that they want to either maintain or they are concerned about? Being able to discuss that is more important and most important than simply de-escalating, stopping, or discontinuing.

### Key Takeaways

I hope that in the past 45 minutes, I have been able to talk about the importance of patient-centric care, that comprehensive care. Hopefully, I have been able to emphasize to you the importance of the STRIDE recommendations, which is that treat-to-target, the immediate or short-term, the intermediate, and the long-term, and that we need to proactively monitor our patients based off of symptoms, biomarkers, endoscopic imaging, ultrasound, what have you.

I hope I was able to demonstrate to you that unlike our prior therapies - I will say here, I did not say before - there is still a role for anti-TNFs. I am not saying there is no role for anti-TNFs, but I hope I was able to show you that with our newer therapies, not so new anymore, we are finding that beyond the anti-TNFs, we have treatment options that are effective, that are durable, and that are actually sustainable for our patients, and it does not have higher, in fact, it has almost compared to placebo, the safety profile is quite safe. Overall, we are not having to exchange safety with efficacy with the newer therapies.

I hope these innovative therapies or newer therapies beyond the anti-TNF was demonstrated to you, so you two can converse that and discuss that with your patients as well.

### Patient Case Discussion

#### Patient Case: 29-Yr-Old Woman with Ileocolonic CD

A 29-year-old with ileocolonic Crohn's disease comes to your office with newly diagnosed disease. She says, "I cramp after meals. I am starting to avoid eating when I leave the house." She reports weight loss because she is skipping meals. She explains that her symptoms briefly improved after steroids and then followed by anti-TNF therapy, and then her symptoms recurred six months later. Again, relapse-remission.

Her symptoms, she is having increased bowel movements, some postprandial abdominal pain. She has fecal urgency, no bleeding. She is currently on adalimumab, an anti.

Relevant labs here as described. Definitely, you can see that the colonoscopy about six months ago still showed deep ulcerations in the TI in the right side of the colon. Fecal calprotectin was not ordered then, nor now.

The CRP previously at that six months was elevated, and now it is 22, which is still elevated. CBC and the iron panel here. The next steps that this person went through - not my patient - was switched to vedolizumab and reassessed at four weeks. The question to you is what opportunities overall, just seeing all of this, knowing our endpoints, knowing the immediate, intermediate, and long-term, what additional aspects of evaluation management would you do? That is part one of the question. You could just put that in the chat. Then also, do you agree with vedolizumab? If not vedolizumab, would you have considered anything else?

### Poll 4

This is more a conversation that maybe, at this point, I believe this is my last slide. In that situation, if you could scan this or put it in the chat, go ahead and do so. Kelly, maybe you could read off some of those stuff for me, and then we could talk about some additional approaches and considerations.

### Kelly:

All right. If you guys could just put your answers in the chat. I have a really quiet group today. I think this is an area that they just do not -

### Dr. Afzali:

We do not hear about enough. I am really happy to be able to do this with the group here. Really appreciate each of you. Let me go back to the case.

#### Patient Case: 29-Yr-Old Woman with Ileocolonic CD

This is a management conversation. What additional opportunities would you want to do? The last colonoscopy was six months ago. Now we are hitting that STRIDE recommendation. We are at that part where we need to monitor and reassess potentially. There are some deep ulcerations in the terminal ileum, but we do not really have any additional studies to tell us what is happening upstream from the terminal ileum. Would you want something to evaluate that?

The labs do not look so great. Do we need to do some more evaluation for that? That is how I want you to approach this in the sense of treat-to-target. What are my targets? We want clinical? She is not doing well. We want biochemical? It looks like we are still elevated there. We do not have endoscopic. We do not have cross-sectional. Those are some opportunities. For the sake of time, I will say that she was switched to vedolizumab.

I personally do not switch from an anti-TNF to vedolizumab very much so. Why is that? I believe our studies have definitely found that vedolizumab is certainly appropriate in Crohn's disease, just like in ulcerative colitis. However, for those deep ulcerations in the TI that did not respond to an anti-TNF, I personally, and these are per our recommendations, ACG and AGA, we would actually recommend an IL-23 inhibitor or an IL-12/23 inhibitor or even a JAK inhibitor. Definitely, I personally would not have done vedolizumab.

Reassessing at four weeks, that also just becomes a little bit of a concern because the clock is ticking. She has lost weight. She has a high inflammatory burden. She has deep ulcerations. She is anemic. She is symptomatic. She is young. A JAK inhibitor in a woman of childbearing age, do you want to start something where you know you are going to have to stop it? That becomes a consideration as well because it is contraindicated.

That is how I would approach this.

Poll 5

With all that said, do you plan to make any changes - I hope the answer is yes - from what we have discussed today?

**Kelly:**

If you guys could just vote. We have 100% yes.

**Dr. Afzali:**

Thank you all. Go ahead. If you could just make sure that we keep this type of programs actively going.

Poll 6

Please take a moment to enter one key change that you would want to start incorporating into your clinical practice from today's program.

You could scan it or put it in the comments section. I think scanning is the best way for this one, if you can.

Q&A

In the meantime, Kelly, if there are any questions, I am happy to take them. I do want to again share my gratitude for the invitation to be a part of your program and your day.

**Kelly:**

We do have a question. Paula, do you want to unmute and go ahead and ask it?

**Paula:**

My question is, I am hearing a lot of research, mainly not in the US and stuff, about GLP-1, like either microdosing or not, for inflammatory properties and IBD. I know there is not any clinical guidelines yet, but there is just a lot of talk and research going on. What are your thoughts? I have had quite a few of my IBDs ask me about this. I do not really know what to tell them.

**Dr. Afzali:**

That is a great question. We actually have some great studies on this now, as well as, I will say that we are... A few things. First of all, we initially collectively as a community asked the question of are GLP safe during or having inflammatory bowel disease? The answer is yes. If our patients needed and they fit the reasons and the factors to be on a GLP, we say, "Yes, please. That is absolutely fine." Knowing that the cardiovascular risks are higher, the metabolic risks are higher, all of this is inflammatory. In fact, with being on a GLP and managing that, we could actually better control maybe their inflammation and get them to respond to therapy. The answer is yes.

We have a clinical trial now that is evaluating the use of a GLP in combination with their IBD treatment in order to determine if, as a combination, would that be effective. Thus far, that also has been found to be effective and recommended. All in all, I would say safety. No concerns, yes, if necessary, and in fact, it is even being studied for a potential.

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