Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/weighing-the-evidence-a-case-based-review-in-ulcerative-colitis/13439/

Released: 03/25/2022
Valid until: 03/25/2023
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Weighing the Evidence: A Case-Based Review in Ulcerative Colitis

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Weighing the Evidence: A Case-Based Review in Ulcerative Colitis” is provided by Prova Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Nandi:
This is CME on ReachMD, and I’m Dr. Neil Nandi. I’m here with Dr. David Rubin, and we’re going to explore various approaches in a patient case to help you make the right decisions.

Welcome, Dave.

Dr. Rubin:
Thanks for having me.

Dr. Nandi:
Absolutely. So let’s dive right in. Let’s meet Tabitha. Tabitha is a 37-year-old young lady who was diagnosed with moderate to severe UC about 2 months ago. She was begun on a steroid bridge and began adalimumab. Unfortunately, we did not observe her to have a good clinical response.

Let’s review what we know. She is a nonsmoker. She initially presented with abdominal cramping before each bowel movement, and of course reports significant diarrhea and urgency. During the daytime, she has 7-9 bowel movements, and at night – overnight, she has 1-2 bowel movements. She has blood in most of her stools. Her physical exam reveals some generalized abdominal tenderness. She has a CRP [C-reactive protein] of 13, a fecal calprotectin of 530, and her C. diff PCR [polymerase chain reaction] is negative. Upon flex sig [sigmoidoscopy], she is demonstrated to have ulcerative colitis with a Mayo score of 2, some granular mucosa, superficial ulcerations with some friability.

So that leads to my first question, David. How long do you wait before you declare a person’s response to a medication as a primary non-response, and what parameters specifically determine that?

Dr. Rubin:
The question about how long you wait before you do something else is a really important one, and it varies by patient, by disease, and by the treatment. And, if you look at clinical trial data, it gives you a clue as to how rapidly the therapy works when it is working and how long you might need to wait to make sure that you’re not cutting the cord too soon. We don’t want to stop too early and not give the therapy the best likelihood of responding, and you don’t want to keep it going too late and leave the patient sick too long and potentially have complications. With adalimumab, and with our other anti-TNF therapies, we know that when people respond, we can usually tell within the first 2 weeks. Now that doesn’t mean they’re in remission, but it means they respond fast. But on the other hand, there are some people who take longer to respond, so you wouldn’t want to give up on the therapy until you’ve gone at least 8 weeks, which

means the loading phase, which is the first 4 weeks, and then 1 or 2 maintenance doses. Now obviously, she shouldn't be getting worse during that period of time, but by the time 8 weeks comes around, if she's not significantly improved, you're going to want to know what's going on and you're going to want to consider switching therapies.

Dr. Nandi:
What we've come to appreciate over the last decade or 2, especially in 2022, is that we are now blessed to have more therapies for ulcerative colitis than ever before, and that treatment algorithm continues to evolve. So not only is this great for patient care, but it also, I feel, empowers our frontline GIs who take care of so many of our IBD [inflammatory bowel disease] patients. How can our GI [gastrointestinal] brethren take advantage of these treatment options to approach a patient like Tabitha?

Dr. Rubin:
We've adopted a strategy called "treat to target" in inflammatory bowel disease, which essentially is focused on making sure that we achieve a quality of life for our patients – that's the ultimate goal – and to do so by serially evaluating the disease process and making adjustments in the therapy until we reach a predefined target. So what I routinely do when I start a new therapy in ulcerative colitis, regardless of which treatment it is, is I benchmark the biomarker, just like you did here with the sig, or colonoscopy compared to either CRP or calpro – and we have both in this situation – and then I recheck that 6 weeks after I start therapy, not only in people who aren't obviously responding, but also in the people who are, recognizing that up to 50% of people who are feeling better may still have inflammation. And if we want their quality of life to persist, we want to document that, objectively, we also have the inflammation under control.

Dr. Nandi:
I think those are some really great points. It can be intimidating with these new agents for some to approach these new therapies. What are some general suggestions you might have to someone who has a patient who needs some assistance in picking the next step or the next best therapy?

Dr. Rubin:
Right. Well, if you look at available evidence and available therapies, there is a variety of things to keep in mind. Let me start with the first point, which is that somebody with extensive colitis and who's moderately to severely ill may have a challenge with the pharmacodynamics of the therapy. So the amount of medicine you give is the dose. The amount that the bowel is able to see and the body can respond to is called exposure. So you have a dose-to-exposure challenge in people with extensive and severe colitis, and that may be part of what's happening to Tabitha. So that gets us to this other point, which is that we now have 2 different, synthetic, targeted small molecules. Small molecules means that they're small enough to be absorbed through the lining of the small intestine.

And the 2 different classes of small molecules now approved for ulcerative colitis are different mechanisms, but they essentially have a very predictable, rapid onset and predictable PK [pharmacokinetics] because they're absorbed into the bloodstream from the small bowel, which is not the inflamed colon, and they're not proteins so you don't worry about the same protein loss challenge. The first class of therapies that we should mention is the JAK inhibitors. We have one that's currently available for moderately to severely active ulcerative colitis. That's tofacitinib, and it's meant to be positioned and it's labeled to be positioned after anti-TNF therapies. And the more recent approval is a different class of therapy, which is our first S1P receptor modulator for ulcerative colitis, again. In this case, the S1P receptor modulator that's approved is called ozanimod. That one does not require that the patient fail anti-TNF before they get to it.

So in Tabitha's case, if we were considering the possibility that there may be a dose-to-exposure challenge or a pharmacodynamic challenge of a monoclonal antibody, then either of these 2 small molecules would be available to her. The tofacitinib because she's already been on an anti-TNF or the ozanimod because that can be used anywhere along the line of therapy options. I would consider either of these as a viable option for her in this situation and certainly be talking to her about those as our next step.

Dr. Nandi:
I think that's great that you brought up that the small molecules are now part of our armamentarium and that in this young lady who is a primary TNF non-responder – or as you were saying before, medically refractory to that mechanism of action – that we have that as a new option, these S1P and JAK inhibitors. And I want to come back to that.

I also want to visit some of our other options that we still have in the biologic realm, such as vedolizumab or ustekinumab. How do you choose, in addition to the small molecules, when to use vedo or ustekinumab for a patient like Tabitha?

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Neil Nandi, and here with me today is Dr. David Rubin. We're here discussing a case study involving a 37-year-old woman with severe ulcerative colitis, and the many new options available for our patients after initial treatment nonresponse.

Dr. Rubin:
Let's say, for the sake of argument, that the patient is moderately to severely ill, but they're not having obvious evidence of leakage of protein. Well, then you do have 3 classes of biological therapies to consider, and you have the 2 small molecule classes to consider. One way to approach this is to say, "What other extraintestinal manifestations might the patient have?" And understanding what these therapies can also treat, or may even have different labels to treat, can guide you in that.

And I hope that the audience also knows a bit about vedolizumab, the third class of biologics. Vedo actually works by targeting α4β7 integrins, which are only expressed on lymphocytes that are migrating to the bowel, so it's gut-selective and won't work on extraintestinal problems unless they're directly related to the bowel inflammation. In the updated ulcerative colitis guidelines from the ACG we published in 2019, we suggested that you'd want to choose a gut-selective therapy for its safety and for the organ selectivity before going to systemic therapies, unless there are other reasons to consider those. We then had a head-to-head trial of vedolizumab compared with adalimumab in moderate to severe UC, and at 1 year, vedolizumab was superior in clinical efficacy and in mucosal healing than adalimumab. The safety was actually similar between the 2, despite what I just said about it being organ-selective. So it's nice to know that. So you can think about a variety of reasons and different ways to select our therapies.

Dr. Nandi:
You know, in this young lady, Tabitha, who was adalimumab refractory, let's say she went on vedolizumab and she did well for some time. But as we follow her along for several years of longitudinal care, we find that some patients, you know, may lose response, for whatever reason, and that is an unclear etiology. What can we advise to these patients if they have failed adalimumab, they failed or they have lost response to vedolizumab? What are the next steps that you would say in a patient who may have lost response to 2 agents in that scenario?

Dr. Rubin:
It's a very important question, and I'll start by saying that the approach to a patient who's losing response involves 3 questions. The first one is, are they infected? Remember what we started by saying is that you always want to look for C. diff, and if they've been on an immunosuppressive therapy, you're going to want to do biopsies to look for CMV [cytomegalovirus]. And frankly, any other GI pathogen might be complicating interpretations, so don't forget to start with your GI panel and rule out infections. The second question is, are they inflamed? Remembering that many things can give patients symptoms, including infection, but other sources of causes of symptoms can occur, so confirm that they're inflamed, and if you've benchmarked a biomarker, that might just be as simple as getting a repeat calpro or CRP. And then the third question is, where is the drug? So that is the question where you want to know, first of all, is the patient taking the therapy you prescribed? Sometimes when people are feeling well, we know they skip doses. And the second part is, of course, is the body neutralizing the therapy? The anti-TNFs, of course, can induce immunogenicity, where there's anti-drug antibodies, and then the therapy doesn't work. And they can also end up having plenty of drug present, in which case we would then say that the mechanism may not be working and it's time to get to a different mechanism. After failing 2 biological therapies, you have either a third class of biologics – in this case it would be ustekinumab – or you have your 2 synthetic, targeted small molecules, ozanimod or tofacitinib. Depends on the individual patient which one I might choose.

Dr. Nandi:
You know, I think that gastroenterologists have really become safe and feel accustomed to using the biologics. The small molecules are still a newer class, yet the safety data is very good for the small molecules. Can you briefly review any of the safety concerns or what the clinicians should look out for when they approach the small molecules?

Dr. Rubin:
The safety issues are important to understand, and I'll start with tofacitinib. I mentioned already that it got label-changed to be positioned after TNF inhibitors in patients with ulcerative colitis. And then there was a second label update to include some black box warnings regarding venous thromboembolic complications, malignancies, and cardiovascular complications. I want to clarify for our colleagues that all of these changes – all of them – came from a single post-marketing safety study done in rheumatoid arthritis patients who were older than age 50 and had preexisting cardiovascular disease. In that specific high-risk group, they saw in the doses of tofacitinib, compared with rheumatoid arthritis patients who were randomized instead to receive etanercept, that the people who got tofacitinib had these complications more often. That has not been seen in the ulcerative colitis population or in the psoriatic arthritis population that also received tofacitinib. Ozanimod, the mechanism of that is it actually inhibits lymphocytes from leaving lymph nodes and traveling through the lymphatics to get to the bowel. So you recall vedolizumab inhibits white blood cells from getting through the bloodstream to the bowel. S1P receptor modulators, and specifically ozanimod, inhibit lymphocytes from trafficking through the lymph nodes and lymphatics to get to the bowel. And the one thing we see is an expected drop in the lymphocyte count, not to the point where patients are lymphopenic or at risk for infections otherwise. That's an expected measure that seems to correlate to efficacy, although there's still some work going on to prove that.

Dr. Nandi:
We've discussed a lot of great things, Dr. Rubin, on this episode in terms of the plethora of therapies, their safety profile and mechanisms, and hopefully we're going to guide Tabitha to the next best step.

Before we conclude, are there any key takeaways you want our listeners to take home?

Dr. Rubin:
Well, I appreciate the opportunity to chat with you. I always love talking to you, Neil. So I'll end with a few takeaway messages. The first one is benchmark a biomarker in all your patients with IBD so you know how to follow them over time, both to measure response to therapy as well as to anticipate loss of response and certainly to assess if they do have a loss of response. The second message is that we are really using a treat-to-target strategy, which combines the patient feeling better with objective measures that their disease is truly under control, because we know that'll lead to sustained control over time. The third message is don't leave patients on therapies too long when there are other options available. And the last one, which I really hope starts to help folks use these newer treatments, is understand the potential benefits of small molecules in patients who have extensive inflammation or who may not be responding as well to a monoclonal antibody and consider those therapies earlier, and don't leave them just for the end or as salvage because they're new and you haven't yet learned how to use them. Hopefully, this has introduced you to some of those principles, and you'll be more inclined to be thinking about it for the next patient like Tabitha who's in your practice.

Dr. Nandi:
Dr. Rubin, thank you so much for joining us on the program. I always learn some new, important point when I hear you speak. I think our audience will take away a lot of high-yield points about the different options that we have in our ulcerative colitis armamentarium, and I thought we did a great review of treat-to-target strategies. All of this will help our patients, and all of this will empower clinicians to have more confidence so they can take advantage of these different treatments.

Dr. Rubin:
As always, it's my pleasure. Thank you.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Prova. Thank you for listening.