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Emerging Science in the Personalized Pursuit of Remission in Ulcerative Colitis Patients

Narrator:
Welcome to CME on ReachMD. This activity, entitled “Emerging Science in the Personalized Pursuit of Remission in Ulcerative Colitis Patients” is provided by Prova Education and is supported by an independent educational grant from Genentech.

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Dr. Rubin:
This is CME on ReachMD, and I’m Dr. David Rubin.

Dr. Ha:
And I’m Dr. Christina Ha.

Dr. Rubin:
Together we’ll be reviewing some of the newer therapies, including the second-generation anti-integrin therapies, our JAK inhibitors and S1P receptor modulator therapies as well as some of our existing treatments and thinking about how together we can work to take better care of our patients with ulcerative colitis.

Tina, I’m really excited to talk to you about this topic because, as you know, this is a daily struggle for us and our patients.

Dr. Ha:
Yes.

Dr. Rubin:
Take us through some of the reasons patients don’t respond to their therapies, what we call primary nonresponse, and maybe start by just telling us what that means. What is primary nonresponse?

Dr. Ha:
So the first thing is, primary nonresponse means that you start a treatment and you don’t see a clinically meaningful result after initially starting the therapy, and we usually gauge that after about 8–12 weeks of being on the treatment. So there are a lot of factors that may influence response or nonresponse, and I think the first step is choosing the right agent for the right disease activity and the

right disease severity for patients, particularly if they have high-risk features.

Dr. Rubin:
So the right agent, the right disease severity, the right patient, there's a lot of things there, right?

Dr. Ha:
Exactly.

Dr. Rubin:
No wonder we're having so much trouble.

Dr. Ha:
Right. And I think that it's about identifying these features early on. We know, for example, people who have extensive colitis, deep ulcers or require steroids, that category of patients will probably require more assertive treatment earlier on in order to lead to a better outcome and hopefully lower rates of primary nonresponse.

Dr. Rubin:
Yeah, that's a very good point, so thinking a little bit about clearance or understanding more about what might happen. So, who's the patient that's going to have rapid clearance of a monoclonal antibody?

Dr. Ha:
Those are going to be the patients who have probably the most severe forms of colitis. Those are the patients who have what we call the Mayo 3 disease, which is really characterized by just extensive spontaneous bleeding or the deep ulcers, but the primary predictor is really just having that low albumin because that low albumin indicates they're going to be wasting or losing a lot of the biologics or the protein-based monoclonal antibodies that we use.

Dr. Rubin:
What are some of the mimickers that can throw us off that will give us somebody with symptoms—we know they have ulcerative colitis but make it harder for a treatment to work?

Dr. Ha:
Yeah, great question, and it's really important that we rule out these mimickers, and probably the 2 most common that we need to be aware of are infections such as Clostridioides difficile as well as CMV, or cytomegalovirus infection.

Dr. Rubin:
Is there a way that we can predict which therapy we should be using? Are we at that point yet? How do you make a decision about a patient's treatment? What's the first thing you use if somebody... Let's say that they're not mild but they're more moderate or severe. How do you make that initial decision?

Dr. Ha:
Well, it's based on a variety of factors. It's based on how aggressive or how symptomatic they are at that time, it's based on their endoscopic features, and to a certain degree it's also based on their labs, because if I know that they have, for example, the low albumin that we were talking about, I want to choose a treatment that may not necessarily be as influenced by the albumin or I can adapt or adjust the dosing earlier on in the disease course so I can potentially overcome it.

Dr. Rubin:
So, in the secondary loss of response, which is somebody who responds initially and then loses response, we have to re-evaluate that patient. So, let's start by just defining what secondary loss of response or secondary nonresponse is.

Dr. Ha:
So, for me, it's exactly as you say. They had an initial robust response to the induction treatment, and they've noticed some clinical benefit, but over time what they've noticed, particularly for some of the biologics, is by the time they receive their next dose, there's

increase in symptoms or they start to develop some adverse reactions, whether it be infusion reactions or injection reactions, site reactions, and that's where you want to utilize therapeutic drug monitoring to see if it's because their levels are too low or if it's because they have antibodies, and if that's the case, then you re-evaluate to see if there's another agent either within that class of medications that you may want to use or if their response is insufficient and you want to switch out of the class.

Dr. Rubin
My general approach to somebody who has a secondary nonresponse is first to make sure that they're actually inflamed because sometimes their symptoms are due to other things. The second, though, is to make sure they don't have that infection that you taught us about, so I want to make sure that that's not complicating all this. And the third one is to really figure out where the drug is, just like you said. So I do something very similar to what you're saying. And then the question is: How do you know what to use next?

Dr. Ha:
Mm-hmm.

Dr. Rubin:
That's a big challenge. So, how do you know what to use next?

Dr. Ha:
And it's tough, and this is where the idea of having biomarkers that can help predict what the next best treatment should be is very exciting. Are those currently available? Not yet, but I think that there are some areas where there may be some future opportunities. And I think that what you decide next is really dependent on how well they responded to that initial agent, how they are doing currently, how active their colitis is on the scope and what's the most likely next best regimen.

Dr. Rubin:
So the important thing is first to make sure the patient is actually inflamed. Sometimes patients with bowel problems have symptoms that are not due to their recurrence of the disease. Secondly is to make sure there's no infection. And then thirdly is to figure out where the drug is. And the different scenarios that can play out here is that in the case of a monoclonal antibody, for example, there may be no drug detectible and they may have neutralizing anti-drug antibodies. In that case sticking with the same class makes good sense because you showed that it worked initially and the reason the patient isn't responding is because of neutralizing antibodies. And the reality is that really only applies to anti-TNFs right now because that's the only class where we have more than 1 option. But the second scenario would be, if there's plenty of drug present and no anti-drug antibodies and the patient is inflamed and not infected, that's where we might think: Is the mechanism failing?

And the theory behind this has to do with the fact that we're really not treating the cause of colitis; we are treating the result of it. And the human body is amazing, and it finds a new pathway of inflammation. So at least in theory what we're doing by blocking 1 pathway is that it may work for a while, but the human body has a collateral inflammatory pathway because it thinks it's protecting us, or maybe it really is protecting us, and therefore, that results in a loss of response, and we call that mechanistic escape. And in those scenarios, that's when you have to think about a completely new mechanism.

Dr. Ha:
Right.

Dr. Rubin:
And that's what drives us to make decisions. Fortunately, we have lots of mechanisms, but unfortunately, they don't all work as well as we need them too, and there's still room for a lot of improvement.

And so let's look at a video animation to understand a bit more about some of our existing and future therapies and how they work in ulcerative colitis.

Narrator:
Novel mechanisms of action have the potential to change the landscape in ulcerative colitis by achieving sustained remission rates.

The α4β7-MAdCAM-1 and α4β1-VCAM-1 pathways, as well as TGF- β induced expression of αEβ7 on T-cells in the gut play important roles in the pathophysiology of IBD.

The anti-integrin vedolizumab blocks the α4β7-MAdCAM-1 pathway thus blocking entry of these cells into the lamina propria. Natalizumab blocks both the α4β7-MAdCAM-1 pathway and the α4β1-VCAM pathway preventing new T cells from entering the gut.

In addition to blocking the α4β7-MAdCAM-1 pathway, Etrolizumab, a novel gut selective anti-integrin, has a dual mechanism of action by also blocking the αEβ7 integrin on the leucocyte that allows it to bind E-cadherin on intestinal epithelium, disengaging the T-cell from the endothelial cell thus preventing further epithelial damage from inflammation.
Macrophages and dendritic cells release cytokines such as interleukin 12 (or IL-12) and interleukin 23 (or IL-23), which induce a T-helper 1 (or TH1) and T-helper 17 (or TH17) cell response, respectively.

Ustekinumab inhibits the p40 subunits of IL-12 and IL-23, thus blocking TH1 and TH17 stimulation of pro-inflammatory cytokines.

Newer agents such as mirikizumab, risankizumab, brazikumab, and guselkumab inhibit the p19 subunits of IL-23, preventing activation of the JAK/STAT pathway.

Naïve T lymphocytes play a key role in immune surveillance. Activation of these lymphocytes occurs in secondary lymphoid organs, such as the lymph nodes. The chemoattractant sphingosine 1-phosphate (S1P) guides lymphocyte circulation through these lymphoid organs in a gradient-dependent manner.

There are five S1P receptors subtypes (S1P1–S1P5) that modulate the various actions of S1P.
Investigative S1P1 agonists such as ozanimod and etrasimod block the S1P gradient-dependent egress of lymphocytes from the lymph nodes.

Ozanimod is an oral S1P1 and S1P5 agonist
Etrasimod is an S1P1, S1P4, and S1P5 agonist

Dr. Ha:
That was fascinating. So, based on that video and knowing what we know about primary and secondary nonresponse, Dr. Rubin, let's focus on some of these second-generation anti-integrins. How will these agents help overcome some of these issues that we're facing today for some of our UC patients?

Dr. Rubin:
The newer anti-integrin therapy, specifically a drug called etrolizumab that is in development, is a therapy that blocks alpha E and has a more selective approach in some ways but also has a possible second mechanism of action. So on the one hand it still blocks trafficking to the bowel, which is important, but it may also have an impact on the active inflammatory cells that are already in the intestine and help them egress out of the intestine. So, what we've come to appreciate is we think that this therapy may actually have 2 mechanisms of action and additionally provide benefit to our patients.

The clinical trials for this are ongoing. Some of them have finished recruitment, and a couple phases are actually done and have been analyzed, and what we've learned about etrolizumab is that this therapy works very well in both UC and Crohn's, as we would expect it to. And in the ulcerative colitis trial, they actually looked at patients who had already been on anti-TNF, so a harder-to-treat group of patients, and the therapy looks very promising. And the safety profile, as we've come to expect with anti-integrin therapies, is quite good as well. Now, etrolizumab is dosed as an injectable therapy, so it offers that mode of action or mode of delivery and, therefore, has some convenience to it as well.

So this offers a promising new therapy that we're looking forward to, and we can add it to our list of options. And we have to start thinking carefully then about: Would we use this primarily for an induction in maintenance strategy in new patients? Will we position it after failing other drugs? This is the whole conversation we have about everything that we get.

Dr. Ha:

So, Dr. Rubin, you had mentioned that one of the differences between vedolizumab and etrolizumab is that etrolizumab works on alpha 4 beta 7 as well as alpha E beta 7, so does that mean it's still gut-selective, which is one of the primary reasons why vedolizumab is so appealing to a lot of our patients?

Dr. Rubin:
We believe it is, and we think that by hitting those 2 targets we may have a broader action. It's very interesting because our observation with natalizumab, which we were using primarily for Crohn's when it was available and when it was the only anti-integrin we had, was that it seemed to work better in some ways than what we've seen with vedo; and, of course, there's never been a head-to-head, so this is my observation. Similarly, we're hopeful that therapies that offer, um, a similar safety profile but maybe a broader action may cover more of what we need in the bowel. And we recognize that it's complicated. Whenever you try to knock off one pathway, you're probably missing others, so we have to find this balance between doing more and not affecting the safety profile, and that's the hope of at least this therapy.

Dr. Ha:
Mm-hmm. So that's very fascinating and encouraging that we have another integrin that's potentially going to be very useful for our UC patients. But what about some of the newer JAK inhibitors or maybe even the S1P agents that are currently being studied in trials?

Dr. Rubin:
Right, so a very exciting time and a lot of new treatments coming. So the JAK inhibitors and the S1P receptor modulator therapies are small molecules.

Janus kinase is an enzyme that is involved in cellular activation, and when a cell is exposed to environmental triggers, it's what turns it on to start producing inflammatory cytokines and trigger a variety of other pathways. When you block janus kinase, you knock down multiple pathways. There are 4 different janus kinas, um, molecules, specifically JAK1, JAK2, JAK3 and something called TYK2. Tofacitinib, the one JAK inhibitor currently available for ulcerative colitis but did not work in Crohn's disease, blocks JAK1 and 3 and overlaps a little bit into JAK2, so it's a nonselective, broadly-acting JAK inhibitor. There are several JAK1 inhibitors that are in development that seem to work well in Crohn's and probably work well in UC, and we've had some data to suggest that as well. They work fast, but we shouldn't confuse their convenience for their safety because they knock off a lot of inflammatory pathways, and there may be things that we have to keep an eye on and we're learning about. One of them, for example, what we've learned from tofacitinib is that it increases the risk for activation of herpes zoster and causing shingles, and that seems to be a signal that we've seen with some of the other JAKs as well.

Dr. Ha:
Mm-hmm.

Dr. Rubin:
The S1P receptor modulator therapies are very interesting as well. There's 2 that are currently in development in the IBD space, and what these do is they actually trap activated lymphocytes in the mesenteric lymph nodes. Um, by doing so it has a similar action as what we talked about with anti-integrins but works slightly differently in that it traps these activated cells in lymph nodes. The cells that aren't activated, or at least not being driven for the IBD process, can still respond. So you have a preserved, adaptive immune system, but you have an inhibited, um, immune response that's going on with the IBD. So this offers another potentially novel mechanism that would offer safety and is cellular-based.

Dr. Rubin:
I think the takeaway messages for our colleagues are that we have a lot of good options already available. There are promising drugs that are in the pipeline that are near term. I mean the next year or 2 we're hopeful they will come. And that in order to use our current drugs most effectively, they need to be monitoring patients, they need to pair the dosing of the drug with the disease activity, and they need to be thoughtful about approaching patients who are losing response, uh, to make sure they understand why that

might be happening and then choose another option. And behind all this, of course, has to be an ongoing dialogue with payers so that they don't drive us into the ground and that there is some rational decision-making that is not all about cost but also includes some medical facts that will help us.

Dr. Ha:
And hopefully we'll be part of that discussion.

Narrator:
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