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New Ulcerative Colitis Paradigms in the Personalized Pursuit of Remission

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

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Dr. Rubin:
A common challenge we face in managing patients with ulcerative colitis is knowing which therapy to choose and whether or not the patient’s going to respond to the therapy. We also have difficulty making decisions about how to sequence our therapies when the patient doesn’t respond to their first therapy or when they lose response to a therapy that was previously working. One of the promises that we hope for the future is to develop better biomarkers that tell us whether the drug is working, and even better would be predictive therapeutic biomarkers that tell us what drugs to choose or even which drugs not to choose for specific patients.

I’m Dr. David Rubin. This is CME on ReachMD, and I’m talking with my colleague Dr. Christina Ha.

Dr. Ha:
Hello.

Dr. Rubin:
So, Tina, let’s talk a little bit about some of the biomarkers we use. Let’s start with the ones that are currently available. Then we’ll talk about some of the possibilities for the near-term future. So, what biomarkers do we use in ulcerative colitis to know that a patient is sick and that they are responding to treatment?

Dr. Ha:
Well, the 2 most common are the C-reactive protein as well as the stool marker fecal calprotectin. However, those are really only helpful if they were abnormal during the time of flare to begin with. But if they are, those are markers that you can follow over time. And in the treat-to-target strategy, which recommends that at select intervals, usually at every 12 weeks, we assess to make sure patients are responding based on clinical symptoms like: Are their stools less frequent, more formed? Are they still having rectal bleeding? Are they still having urgency? Those are important clinical symptoms that we have to monitor. And then you want to make sure that the C-reactive protein is normalizing and their fecal calprotectin is decreasing or normalized.

Dr. Rubin:
It’s important that we’ve gotten to a point in our field where we’re finally matching the objective measures of disease activity with patients’ symptoms. And, in fact, in the new ACG guidelines for managing ulcerative colitis and in the AGA guidelines, we’ve gotten to the point where we acknowledge that, of course, symptom improvement is essential, but it’s not sufficient, that we have to also be looking for these improvements and objective measures of inflammation. Why is that so important?

Dr. Ha:

Well, I think that, you know, you've actually looked at this quite a lot, and patients don't always tell us exactly how they're doing. And you know, I'd love for you to elaborate a little bit more on some of your work using studies such as the UC:NORMAL study, but we know that in addition to patient's symptoms, we do need to follow these objective markers to make up the difference from the lack of transparency that can sometimes occur in clinical practice.

Dr. Rubin:
Yeah, I think that's exactly right. I mean, it's taken us a while to get here, and we're always lagging behind our colleagues in rheumatology, but we've learned that if we want to modify the disease process and change the natural history of the disease, we need to have objective measures, and so using CRP or the neutrophil-derived calprotectin can be a very useful way to do that. But what we really want are markers that tell us who will respond to which therapies. Are we getting there? What's around the corner?

Dr. Ha:
Well, I think that some of our newer agents are giving us some clues as to maybe some predictors for our patients who may be more likely to respond to one treatment versus another. I think a great example is with etrolizumab. There are a few, um, studies that looked at some of phase II data that suggest maybe some patients who have higher alpha E expression on their colon biopsies may be more likely to have enrichment with etrolizumab and potentially response or remission, so that may be a biomarker that we can follow to identify which patients should have etrolizumab positioned a little bit earlier. I think with some of the p19 antagonists—looking at IL-23, for example—there are some studies showing that there may be decreases in certain proinflammatory cytokines like IL-17 and IL-22 that may be lower after they receive those agents. I think they are still very preliminary, and we need to see if they are replicated, not only in the phase III clinical studies but in clinical practice. But it gives us optimism that there may be clues that allow us to fine-tune from all the different options that we have in the future.

Dr. Rubin:
Yeah, I mean, I think that that's very promising. And one of the messages that I've had with folks who are developing these markers and therapies is it doesn't have to be perfect.

Dr. Ha:
Mm-hmm.

Dr. Rubin:
You know, we just want to be nudged in the right direction.

Dr. Ha:
Right.

Dr. Rubin:
Show us a way that we can go and help us choose. There's even old data that suggests that patients who have high P-ANCA titers with colitis are less likely to respond to anti-TNFs, so we can use some of these things in our daily practices so we can make good decisions about how to manage our patients.

Dr. Ha:
Absolutely.

Dr. Rubin:
And it's definitely necessary because we can't keep having new mechanisms and new therapies coming to market and being available without knowing how to choose any of them. And we're people who spend most of our time with IBD patients. Our colleagues who take care of patients with many other gastrointestinal disorders can't possibly know how to refine therapies without some guidance. It's just definitely necessary.

So I'd like us to take a moment now and just look at a video of biomarkers and how they may influence clinical decision-making.

Narrator:
Studies showed ulcerative colitis patients, with similar prior treatments achieved different levels of clinical remission with etrolizumab therapy

Those patients with an αE (ITGAE) gene expression in their baseline colonic biopsies achieved nearly a 3-fold higher clinical remission rate at 10 weeks compared with patients with low αE gene expression.

In addition to αE gene expression for etrolizumab, other potential predictive biomarkers under investigation include: granzyme A, IL-22,

IL13Rα2 or TREM1, each indicated to a specific therapy.

IL-22 is a potential biomarker to predict clinical remission with brazikumab use in ulcerative colitis, true or false? True

TREM-1 is a potential biomarker to predict clinical remission with infliximab use in ulcerative colitis, true or false? False

Integrin alpha-E gene expression is a predictive biomarker for clinical remission with etrolizumab in patients with ulcerative colitis, true or false? True

Dr. Ha:
So that video really puts into perspective how we could potentially apply some of these clinical biomarkers. But knowing what we have right now, how do you put it all together in a suggested approach to address our patients who have moderate to severe UC?

Dr. Rubin:
Well, I often remind patients and I try to teach my colleagues that we're not treating the cause of ulcerative colitis; we're treating the result of it. I wish we knew the cause. We're getting closer to understanding some possibilities. But in the meantime what we do know is that there is an overactive immune response in the intestine, that it's continuing without being otherwise turned off, so our treatment strategies have been aimed at that inflammatory response with the idea that if we can turn it down long enough, we hope that the body takes over, restores homeostasis and heals the bowel. That's the general principle here.

So, in the absence of knowing which treatments to choose, we end up looking at markers of the disease activity as a way to know that we're on the right track, and not just when their patient is sick to know they're responding to therapy but also after they're well and when they're in remission. And one of the things people have neglected and I think we need to spend more time on is the concept of disease monitoring. So, when we think about our goals for ulcerative colitis, symptom-wise it's the absence of rectal bleeding; it's reduction in stool frequency; very importantly is the elimination of urgency, which drives people crazy. Right?

Dr. Ha:
Crazy.

Dr. Rubin:
It's a terrible thing. And we've included urgency in the new ACG UC guidelines.

Dr. Ha:
Mm-hmm.

Dr. Rubin:
From the standpoint of knowing whether the disease is objectively under control, there are a number of different things we can look at. The now almost out-of-date STRIDE consensus statement that came from some of our colleague experts said that we should look at objective measures with endoscopy. We've now said calprotectin and CRP, as you mentioned, are reasonable ways to know that this is under control as well.

So, in a general approach to this to put it into practice, the patient gets started on their first therapy with some baseline measures of disease activity as well as acknowledging what their current symptoms are. We expect they're going to get better quickly. We'd like them to be feeling better within a couple weeks, but we really officially reassess them between 6 and 12 weeks depending on the treatment, not only based on: How are you feeling? Have you achieved clinical remission with the absence of bleeding and urgency? but also objectively. Is the calprotectin less than half of what it was or even normalized? Is the CRP, if they make it, down to normal, or do we do a scope even at 3 months or at 6 months to see the bowel is improved? When it's not, when any of these markers or symptoms are not, we move along. Often that only means adjusting the dose of the current therapy, but what it might mean is adding a second drug or switching classes all together. And it's complicated, but the point is you don't stop. You don't wait for the patient to have a complication. You don't wait for them to call you that they're worse. You schedule these things. You build it into your analysis and your management of these patients.

And with our newer therapies, we must have ways to do this in a more predictive manner. We have to have markers that make sense for new mechanisms of action, and we need to be able to not only know if the drug's going to work but ways to predict when it's not going to work so that we can be ahead of the game here with this disease so we know that somebody is starting to have a relapse before it occurs—very important. So that whole thing of treat-to-target of getting a patient to where we need them to be, or at least actively trying until we get to a point where we or the patient don't want to move on or we run out of options, and then once you're at the target, monitoring them over time. Stable maintenance also requires using similar targets.

Dr. Ha:

Mm-hmm. And part of this, though, is to make sure that the patients are active participants in this discussion. So, while the treat-to-target conversation is very easy for us to understand, how do you as the clinician get your patients to buy into the concept of treat-to-target—and to be quite honest, more frequent monitoring?

Dr. Rubin:
Well, we know from previous work that patients think we're already healing their bowel. When they are feeling better, they assume their bowel must be healed. When we give them a therapy, they assume that's what it's supposed to do, so educating them that that's not always what happens or that they might feel better but not be under good control is part of this conversation we have. So we tell them that, "When you feel better, when your symptoms are improved, your quality of life will be improved, but if we want it to last, we have to have an objective control of your disease, and we need to use more objective measures." When they hear that from us and then we schedule them for specific follow-up or communicate about adjustments we may make in their treatments because of it, they really buy into this. There's a balance though because you can get patients who are very focused on these outcomes, and we can't always get there in many patients, so you don't want to drive this into the ground where if they can't achieve that goal they're going to be miserable and focused on that. What will change this and what I think will be paradigm- shifting for all of us will be at-home testing.

Dr. Ha:
Mm-hmm.

Dr. Rubin:
The at-home calprotectin testing is around the corner. It's already available in Europe and Canada. And when we have that and we can tie that to our treatments and encourage patients to be adherent to their therapies, we'll be able to actually move a lot of patients along this route. I think we have to raise their expectations, and we have to raise the bar on what we try to do as clinicians as well.

Dr. Ha:
So, with that strategy, though, does the first target when you're starting a treatment have to be healing?

Dr. Rubin:
I don't think that that's the first target. I think that improvement, um,is sufficient, both endoscopic or biomarker improvement, along with symptoms, but you also want to make sure that you're moving along and that this is going to be stable. And it's not going to be perfect in 12 weeks. It may take longer. So, if a drug is working, you don't want to give up on it too soon. You want to make sure you give it enough time and keep monitoring the patient, but you also don't want them getting worse or being unacceptably ill and not responding.

Dr. Ha:
So, what I'm hearing is, essentially, whenever you're starting any treatment, you just need to come up with strategies for effective partnering with the provider as well as the patient, and hopefully it will lead to better outcomes.

Dr. Rubin:
So, one of the things we've learned about treat-to-target is that often patients only need to make an adjustment in the dose of their existing therapy, and they can actually achieve improvement.

Similarly, we may be able to do that with many of our other treatment options when we're working through a treat-to-target, but understanding the mechanism of action of some of our other therapies may be key. For example, if we have a patient on a monoclonal antibody and they haven't achieved their target with the first dosing of it, we may realize, do you know what, they're losing protein in their stool; we should pick a different mechanism of action. So maybe a small molecule is going to be better where we don't worry about protein loss like a JAK inhibitor or one of the emerging S1Ps. In a patient who has comorbid illnesses where we worry about either their age or something else that puts them at higher risk for infections, maybe the mechanism of action when we add another therapy will be an anti-integrin treatment, so we'll actually add therapies in a more logical fashion rather than just substituting one for another.

Dr. Ha:
Mm-hmm.

And I think what we're going to learn is that by paying attention and by adjusting doses and adding therapies but being thoughtful about the mechanism of action, we're going to be able to get many patients where we need them to be. This is not a failed attempt to escalate therapies. It can be very successful in, um, short order, usually with just 1 or 2 adjustments, so that's an important message, because I think for many of our colleagues, the concept of treat-to-target means jumping to another class of therapy, putting the patient at risk when they're already feeling well. That's not the message. The message is adjusting so that they stay well and that we do so safely.

Dr. Ha:
Mm-hmm. Very important points.

Dr. Rubin:
That's what we want, right? And I think that even with our existing therapies we're able to do that more often than we've acknowledged. Uh, and with our newer options we're going to have some great and very safe and actually convenient options for our patients as well. It's an exciting time, but we really have to keep pushing so we can get our patients where they need to be.

Dr. Ha:
Well, optimism but more room to grow.

Dr. Rubin:
This has been a great dialogue. What would be the one take-home message you'd have for our colleagues?

Dr. Ha:
I think that the most important thing is to come up with a strategy for monitoring. Don't start a treatment and let the patient go on their own. You have to identify certain time points, certain variables you're going to follow, and communicate that piece with the patient, their caregivers and the entire care team, and hopefully we'll have better responses.

Dr. Rubin:
I agree completely with you, and I think the biggest take-away message is that we should be raising the expectations of our patients to achieve not just remission in the short-term but disease modification and long-term control, and we really can do that with our existing therapies. The newer treatments that are on the horizon will add to that, no doubt about it, and hopefully we'll continue to get all these patients feeling better, and we'll work hard to keep them where they need to be.

Dr. Ha:
That's the goal.

Dr. Rubin:
Great, thank you so much for this conversation

Dr. Ha:
Thanks for having me, its been fun!

Narrator:
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