

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/new-perspectives-on-biologic-therapy-in-moderate-to-severe-ulcerative-colitis/10946/>

Released: 09/13/2019

Valid until: 09/13/2020

Time needed to complete: 15 minutes

ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

New Perspectives on Biologic Therapy in Moderate-to-Severe Ulcerative Colitis

Announcer:

Welcome to CME on ReachMD! The following activity, New Perspectives on Biologic Therapy in Moderate to Severe Ulcerative Colitis, is provided in partnership with Prova Education and supported by an educational grant from Takeda.

Prior to beginning the activity, please review the faculty disclosure statements as well as the learning objectives.

Your host is Dr. Neil Nandi.

Dr. Nandi:

Thanks to recent advancements, strategies for treating ulcerative colitis have evolved from simply controlling symptoms to treating patients to achieve objective measures of inflammation control, sustained remission, and to prevent progression of the disease. Biological therapies and small molecule DMARDs have played a part in this shift, but what real-world data are there to support the use of these therapies earlier in the treatment paradigm?

This is CME on ReachMD, and I'm Dr. Neilanjan Nandi. Joining me today to discuss these advances in the management of ulcerative colitis is Dr. David Rubin, Professor of Medicine, and Chief of the Section of Gastroenterology, Hepatology, and Nutrition, and the Co-Director of the Digestive Diseases Center at the University of Chicago Medicine. Dr. Rubin, welcome to the program.

Dr. Rubin:

Well, thanks Dr. Nandi. I'm really happy to be here to discuss these advances.

Dr. Nandi:

I'm so glad that you could join us. So just to set the stage for our audience, this past March of 2019, the ACG, the American College of Gastroenterology, released much awaited practice guidelines in ulcerative colitis. I'm hoping you can further elucidate; what are the major recommendations that were updated? And what have we seen in clinical practice since their publication?

Dr. Rubin:

Well, the American College of Gastroenterology's ulcerative colitis practice guidelines that came out in March 2019 were long overdue. The prior guidelines that the College had published were from 2010. And in those 9 years, there were some significant changes in the way we think about ulcerative colitis, and many new therapies that were approved by the FDA. So this was an important document to bring everyone up to speed. One of the most significant changes we made in this new guideline was the definition of activity of disease and separating it from severity of disease. Activity of disease means how inflamed or how sick the patient is at the time you are evaluating them. And severity really refers to prognosis. What's the likelihood that this patient will end up in the hospital or need surgery for their ulcerative colitis based on a variety of other factors? And by separating these out, we try to clarify for our colleagues how to make treatment decisions based not only on what we are doing in the short-term, but also having your eye on the long-term. The other major advance in the guidelines was the introduction of a new activity index that not only includes the usual markers of clinical activity like number of bowel movements, but also added something that's very important of patient; the symptom of urgency, which can be quite disabling, and of course is due to the inflamed rectum. And we also added to that activity index measures of the endoscopic activity or measures of the inflammation as measured by a stool test called fecal calprotectin.

Dr. Nandi:

You know, one of the most important pieces that I see honed in on the guidelines is this definition of mucosal healing. Can you help us understand better; how do we define and identify what is the meaning of mucosal healing, and the significance as a targeted therapy in ulcerative colitis?

Dr. Rubin:

One of the major advances, as well in these guidelines is the adoption of a goal of management that includes healing the mucosa, the lining of the bowel. And this is because we now have sufficient evidence to show that patients with ulcerative colitis who achieve a healed bowel, and I'll tell you how that's defined in a moment. Patients who have a healed bowel are less likely to need steroids, are less likely to have a relapse within the next year, are less likely to be hospitalized, and are less likely to have surgery for their colitis. So we recognized for quite awhile that achieving a healed bowel is associated with better outcomes. What we've gotten better at understanding now is which treatments can get up there, and how we might move the needle so that individual patients who are not healed can actually get to that level of control. Many people are surprised to hear that 50% of patients who are in symptomatic remission, in other words are healing well, are still walking around with active inflammation if you look with a scope into their bowel, or you measure it through a blood test or stool test. We recognize that the discordance between feeling well and walking around with active inflammation offers an explanation as to why some patients who seem to be doing okay, end up having a flare or doing poorly later down the line. So the mucosal healing in our goals of management is a goal that we think is very important. We recognize that it actually can't be achieved in everybody, but we know that most patients should be able to achieve some level of endoscopic improvement, and ultimately a healed bowel in many situations. It's defined primarily by how the bowel looks using a scope, and there are a couple of different scoring systems. The one that most people are familiar with is called the Mayo Endoscopic Sub Score. The Mayo Endoscopic Sub Score goes from a score of 0, which is totally normal, to 3, which is very severe. So understanding the degree of endoscopic severity gives you some guidance as to whether you should address therapies a certain way, but also how you can stratify patients to come back for earlier follow-up.

Dr. Nandi:

Absolutely. That was wonderful. When I tell my patients I want them to look as good on the inside as we want them to feel on the outside, this is one way we try to illustrate the importance of mucosal healing. Now, let's talk about treat-to-target; treating to that target of mucosal healing. There are several classes of medications that can be used to achieve this goal such as biologics and small-molecule DMARDs. How can we best position these agents, particularly in the bio-naïve or treatment-naïve patient?

Dr. Rubin:

That's a very important question. I think one of the biggest challenges we have right now is in sequencing our therapy. Some of this can be determined based on understandings the severity of the patient. In other words, the patient who has a high risk for colectomy or hospitalization, or who has already been hospitalized, even if they responded to your steroid treatment, really is somebody who should be getting a moderate to severe treatment strategy. But in terms of how do you choose between one of the three anti-TNF therapies that are FDA-approved for ulcerative colitis, or the anti-integrin therapy, the vedolizumab, which is leukocyte trafficking inhibitor, or even tofacitinib are small-molecule like the Janus kinase inhibitor. How do you make those decisions? And it really ends up being somewhat patient-specific. In other words, whether they have certain features of their disease like extraintestinal manifestation, which might drive us to think about one therapy over another. It ends up being payer-specific, as all the listeners know, even when we have the best intentions and some thoughts about what we want to do. Payers may not allow us to go in that particular order. And it also may end up being much the patient's decisions that help make these choices. Our job is to think carefully about the different mechanisms within the limits of what we have, and to make recommendations based on what we understand the efficacy and safety of those therapies may be. When we don't really know which treatment might be best, which is often, we start with a therapy that's within the class of treatments we're trying to use. And an important part of a treat-to-target strategy, which is the general principle of how we're trying to do this now, is that after you use that initial therapy at some pre-defined time interval, maybe three months, maybe six months, not longer than that, you reassess to see if you truly obtained the control you were trying to get to. Is the patient feeling well? Have they obtained clinical remission? And secondarily, are the objective measures of their disease actually under better control? Is the mucosa improved or even healed? Are their labs normal? Is their weight restored? Et cetera. And when they do obtain those targets, we then shift it to a monitoring strategy where we keep an eye on things and schedule follow-up. When they haven't obtained those targets, the next question of course is why haven't they. Was it a dose issue with the therapy you chose? Is it a mechanism that you need just a completely different strategy? Or is this something in the real-world like the patient can't get the medicine? You know, they got one prescription or one dose and couldn't refill it, and they're not actually taking what you've recommended. So you make an adjustment based on what you find out might be going on, and then you reassess. This has been explored in the real world, and in a retrospective assessment from the University of California in San Diego by our colleague, Bill Sandborn, patients with ulcerative colitis who felt well but had inflammation on their scope, had their treatments adjusted. And usually the first adjustment was simply raising the dose of their existing therapy. And

the second adjustment was adding a second treatment to what they're already on. So it's not always as complicated as taking a patient who feels well and making a major change to their medicine or switching them up to a different class. I think it's important for people to understand that. But the other part is for patients to understand why we're trying to do this; what's the goal and why would we do it. I think I very much like what you said, Dr. Nandi, that you want patients to look as good on the inside as they feel on the outside. That's a wonderful way to describe it. I sometimes think that symptom control is necessary to feel well, but endoscopic healing or mucosal healing is necessary to keep it that way.

Dr. Nandi:

Thank you, Dr. Rubin.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Neilanjan Nandi, and today I'm speaking with Dr. David Rubin from the University of Chicago Medicine about how we can apply a treat-to-target strategy in ulcerative colitis treatment with the use of our modern therapies.

So now that we've discussed what we've learned through several clinical trials, Dr. Rubin, can you help us apply some of this knowledge to the concept of real-world post-marketing data? Can you help further define what this means to our audience? And can you also relate what you've seen since the approval of these biologic therapies in real-world daily clinical practice?

Dr. Rubin:

When patients get enrolled in clinical trials, they end up being a quite limited group of individuals who satisfy a variety of inclusion and exclusion criteria. And the trials are very controlled and there are a variety of factors that are important in order to understand whether a therapy is safe and effective. And, in fact, with vedolizumab, there is a multi-center US consortium – I'm not part of it, but it's called VICTORY. And the U.S. VICTORY group has explored the real-world of vedolizumab. For the most part, what they have found is, number one, the safety matches what was seen in the clinical trial. Vedolizumab by nature being a gut-selective therapy has a very favorable safety profile, and it really only works on the bowel, and does not seem to have any systemic immune-suppressive properties. So what has been seen in the VICTORY papers and analyses is a safety profile that continues to look reassuring. The other things that some listeners need to remember is that the first drug that was in the anti-integrin class that was involved in IBD, was an old drug called natalizumab, which treats both multiple sclerosis and Crohn's disease. And because it affected the central nervous system, natalizumab had a brain infection that was related to this. One of the other things we've been interested in is whether vedolizumab, by nature, being only in the gut, would ever have that problem and, in fact, it has not. And now we have both the follow-up of VICTORY, we have the follow-up from our own center at the University of Chicago, and we also have follow-up that was mandated and then studied by both the FDA and Takeda Pharmaceuticals. So we've learned quite a bit. The steroid-free remission rates, the mucosal healing rates, the clinical remission rates are all similar to what was seen in the clinical trial, which is a very nice thing to know, and it's actually quite remarkable when you get out into the real world; that the results seem to match what was seen in the clinical trials.

Dr. Nandi:

So, you know, this is very interesting that we have all this real-world data to help us guide patient decision-making in terms of adverse events long-term on therapies. How do you see these data in defining future practice algorithms and treatment positions going forward?

Dr. Rubin:

It's a big challenge, but there are some practical considerations. The first is to acknowledge that we have our first head-to-head biological therapy trial. And that study is called VARSITY, and that was presented earlier this year. The VARSITY trial took patients who had moderate to severe ulcerative colitis, and they randomized them to either adalimumab at standard dosing, or vedolizumab. And the primary endpoint was clinical remission at one year. And at the end of the VARSITY trial, more patients had achieved clinical remission with vedolizumab than they did with adalimumab. It was an interesting study, and the results were of great interest to the field. And it suggested that vedolizumab was better for this group of patients and should be considered as a first-line therapy. So a very important study because it was head-to-head, and it was the first one to do this, but there are some questions that are remaining unanswered and we are of course waiting for the full manuscript to be published.

Dr. Nandi:

Thank you, Dr. Rubin. This has been a very thorough and wonderful discussion. Before we wrap up today, are there any messages, Dr. Rubin; any take-home messages you'd like to leave our audience with today?

Dr. Rubin:

Well, I think that the message for our colleagues and for any patients who happen to listen, as well, is one of optimism and appreciation for the progress that we've made. In the 9 years since the last time the ulcerative colitis guidelines were published by the ACG, and now we have some new AGA guidelines that are coming, we have, in fact, made some great progress in understanding how to predict outcomes, and how to focus on not just short-term getting our patients feeling better, which is of course important, but keeping them

where they need to be. And then of course once we do that successfully, we start to see that we can actually change the natural history of the disease. So while we're waiting to discover cures for this type of inflammatory bowel disease, we certainly know now much more about how we should be moving our patients to achieve these types of goals, and use our new therapies, not necessarily in a pre-specified order, but at least know to move through them to achieve our goals and understand how to do that in a more systematic way. I really appreciate the opportunity to explain this to the listeners.

Dr. Nandi:

Thank you so much, Dr. David Rubin, for sharing your invaluable insights on how these new therapies are providing more options, and also changing the way we approach the treatment of ulcerative colitis. I can't thank you enough for your time. For CME on ReachMD, this is Neilanjan Nandi, MD, and have a wonderful day.

Dr. Rubin:

Thank you, again.

Announcer:

This activity has been provided in partnership with Prova Education. To receive your free CME credit, be sure to complete the post-test and evaluation by visiting ReachMD.com/Prova.

This is CME on ReachMD: Be Part of the Knowledge.