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https://reachmd.com/programs/cme/strategies-for-achieving-mucosal-healing/15524/

Released: 06/08/2023
Valid until: 06/09/2024
Time needed to complete: 30 minutes

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Strategies for Achieving Mucosal Healing

Announcer:
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Dr. Ungaro:

Hello, everyone and welcome to Medical Minute One: Strategies for Achieving Mucosal Healing. This is the first in a two-part series called S1P Receptor Modulators in Ulcerative Colitis, an Evidence-Based Patient-Centered Approach to Optimizing Care.

I'm Ryan Ungaro, Associate Professor of Medicine at the Icahn School of Medicine at Mount Sinai in New York City.

These are my disclosures.

And this is our learning objective: identify and target objective measures of disease activity to achieve mucosal healing in patients with UC.

So to start our session, let's talk a little bit about the burden of ulcerative colitis. As you're all likely very aware, there are a number of symptoms that are classic in a clinical presentation of ulcerative colitis. Most patients will have diarrhea, rectal bleeding, cramping, patients will also frequently complain of urgency, having to rush to the bathroom, or tenesmus, having the sensation of incomplete evacuation. And also, in more severe cases where the disease is perhaps more markedly inflamed or extensive, may have more marked abdominal pain or decreased appetite, fatigue, and other systemic symptoms. So these symptoms obviously can be quite burdensome on our patients.

And when you survey patients about what is the impact of all the symptoms of ulcerative colitis and the disease on their lives, you can see that there is a major impact that our patients can have, that the disease can have on our patients. And you can see here a survey, internet survey, looking at a variety of different disease impact of the disease. And you can see on the left here, when you look at different chronic diseases, and you ask patients how they feel their condition, if it's controlling their lives, you can see that the actually ulcerative colitis patients on the top, are more likely to say that their disease controls their life compared to other chronic conditions like asthma and rheumatoid arthritis.

And on the right, you can see specifically when you ask patients with UC, the psychological impact, that many patients, the vast, vast majority, worry about the long-term effects of their disease, say that this disease makes their life more stressful, and they have feelings of being embarrassed or even depressed, so a major impact this disease can have on our patients lives. And in addition, both ulcerative colitis and Crohn's disease, the other inflammatory bowel disease that is on the spectrum of disease with ulcerative colitis, patients - and this is from a study from the Norwegian population-based cohorts, you can see that patients with ulcerative colitis are up to two times as likely to not be able to work due to their disease and actually have disability. So this is something that has a major impact and symptoms have a major impact. People feel that it can control their life, they can have lots of worry and depression due to this, and that it can lead

to actually leading disability and inability to work and lead the life that they want to live.

So with that, let's hear from our patient who's going to discuss his experience with UC before it was controlled.

Patient:
When my ulcerative colitis was not well controlled, my quality of life suffered pretty greatly. I had to be cognizant of, you know, if I was out shopping or doing something with family and friends, I always had to be aware of the bathroom situation, I had to be mindful of what I was eating or drinking to make sure that my symptoms didn't worsen. It does put you into a bit of depression as well. You know, you want to be like everyone else. But unfortunately, you are now tied to this disease. And that, you know, really does affect your quality of life. And so, it definitely takes a pretty significant toll on your emotional and mental health.

While most people who are 24, 25 years old are going out and hanging out with friends at bars and restaurants and enjoying life, you know, when your disease is not well controlled, you know, having a social life is pretty difficult because you have to really make your plans around your symptoms at the time. And you know, you have to really think about where you are going, what's on the menu, are there options that you can eat, things that you can drink that won't, you know, make your gut unhappy. And so, there's a lot more planning that goes into having a social life with friends. And unfortunately, a lot of time you're spent alone by yourself because of your disease progression, you're not allowed - you're not able to just enjoy life to the fullest like most people who don't have ulcerative colitis.

When my disease state was not controlled, my physical health wasn't great. Obviously, I'm, you know, experiencing symptoms from the disease which you know, can be painful and troublesome on its own. But just the inability to do normal day-to-day activities because of the disease, you know, I'm not able to work out, I'm not able to take care of myself as much because I'm not sure what, you know, I may do that could trigger a flare. And so, I have to be really careful about, you know, just everyday life and activities. And I have, you know, a lot of it was spent - you know, because of the disease was spent in bed, doing nothing. And obviously, my physical health was put on the backburner. At that point, I wasn't able to take care of myself like I had been before I was diagnosed.

Dr. Ungaro:
I would like to thank our patient for sharing their experience with us. I thought that was very informative.

And so, to continue on with our session here, let's talk a little bit about some of the health-related and quality of life issues we see with our patients with ulcerative colitis. And I think a key thing that needs to be discussed, and we need to think about when we're treating patients with ulcerative colitis is that the goals of treatment between the patient the physician are sometimes not well aligned. And we really need to make sure our goals are aligned in order to fully assess the burden and impact of this disease on our patients.

And what you can see here, this slide is giving you an idea of how in a patient's mind that – and a patient's goals, they may be different than for a physician. Because, you know, as a physician, we're oftentimes thinking about remission, what is the scope look like? What does their histology look like? We're thinking about the key objective metrics, say, that are often looked at in our clinical trials, as our outcomes are that our treatment is successful. And patients do see this as important, but they also may be oftentimes they're thinking as important or more important, are things like their ability to work, their ability to just go out and work and enjoy their lives, impact of some symptoms that sometimes we're not necessarily adequately addressing, like fatigue or urgency. And so, trying to align these things well, how the disease is impacting a patient's quality of life, with the objective metrics that we're thinking of as gastroenterologists, can lead to better outcomes to align our treatment plan and align our goals together with patients can improve outcomes.

This, to get at the idea that was just highlighted in that last slide, was a survey where they spoke to patients on the left and physicians on the right, and surveyed them and asked what are your top priorities for the management for UC? And interestingly, you know, the number one ranked actually did align the ability to perform daily activities. But after that, the goals really are very disparate between patients and physicians, where physicians, you know, maybe putting a higher emphasis on avoiding hospitalizations and surgeries, whereas patients are actually even more concerned about avoiding cancer, avoiding having to, you know - having to worry about urgency and where the bathroom is. And also concerns about side effects of medications. So these are things to keep in mind, that our goals as physicians and the goals of patients may not be directly aligned.

And again, just to kind of hit this idea of the burden of disease on our patients, this is another survey where you had 200 patients, and asking them, what patients are they suffering from at that moment in time, or have they ever suffered from. And in the red here, you can see patients, the vast majority said that they were suffering from diarrhea at some point, or bowel urgency, which makes sense. And many of these patients are saying that they were still suffering from these symptoms, even though, you know, it had been ongoing before that they - that is something that's lingering that is not being fully addressed. And so, the symptoms burden is something that for many patients, is very important and it's something that we need to make sure we're focusing on in our daily practice.

And here, you know, something to keep in mind when we're talking about some of the treatment goals for patients and physicians. You know, one of the things that as physicians we're really concerned about is avoiding surgery. And this is obviously an important objective

endpoint. You know, this is a nice meta-analysis that looked at rates of surgery over time. So in the prebiologic era before 2000 on the top and in the post biologic era, or in the current biologic and targeted therapy era after 2000. And you can see that our rates of surgery have declined over time. So 1-year risk of surgery going from about 5% to 3%, and a 10-year risk of surgery, going from about 15 down to 10%. So the rates of surgery have improved for our ulcerative colitis patients, but they are still high. So we still have a lot to do in terms of adequately addressing our patients' symptoms, addressing our patients' concerns about how the disease is affecting their lives, and also improving the overall natural history of the disease and helping our patients avoid outcomes like surgery.

So next, I'd like to just discuss the idea of controlling symptoms versus controlling disease activity. And I think the first thing to highlight here is that our patients, when they come to talk to us about their symptoms, we need to be cognizant that the symptoms and the objective metrics of inflammation may not always be lining up. It used to be that the treatment of IBD was focused on how patient symptoms were only. And if a patient was feeling well, we'd say, okay, great, come back if you're not feeling well, and you go on your merry way, and we'll see you if you have a flare in your symptoms. But what we realized over time and more and more research is highlighting for us is that the symptoms do not always correlate one to one with what is objectively happening on the - in a patient's colon, and the objective metrics of inflammation. This is one of many studies that got at this point. This is a post-hoc analysis of the ULTRA study, so adalimumab in ulcerative colitis, and they looked at the association of patient's PROs, so the patient-reported outcomes, which are frequency of stool and bleeding, rectal bleeding, and to see if you look at patients by their endoscopic score. So Mayo score of 0 or ES 0 on the slide on the X axis in the graph, up to a Mayo score of 3, which is more of a severe disease, and 0 being remission, there's a discordance between what you're seeing on the scope, and what the patient is reporting. And if you look on the right here, a Mayo score of 2 and 3, these are our moderate to severely active patients, so having erosions, ulcers, etcetera, you can see the blue bars are rectal score – a rectal bleeding score of zero, so the patient reporting no bleeding, that, you know, up to 1 in 3 patients may not be reporting bleeding at all, yet they have this active disease. So this is just a highlight that we need to be thinking about, you know, while the patient's symptoms are obviously one of the major important goals for us to improve, we also need to realize that the symptoms are not correlating one to one with the objective markers of inflammation.

And so let's talk a little bit more about this concept of symptom control versus these objective metrics of endoscopic healing. So as I mentioned, the treatment target in IBD, you know, for many years was symptom control. And that's at the top of this pyramid here, where you see PRO, so patient-reported outcomes, and that if a patient's feeling better, that you've met your target and move on. And what we've realized is that we want to get actually deeper levels of remission to improve outcomes for patients. So while we want their symptoms to resolve, we also want to be hitting more strict objective metrics. And this is what this slide is this pyramid is showing us that the next level of depth of remission can be endoscopic healing, so the patient is feeling better, at the top. But then also, we want to go a little bit deeper and say that, objectively, their colon is also healing as well. And you can see here on the right, a normal-appearing colon, so you want that colon to be, you know, as normal appearing as possible. And then there's actually now even a push and discussion about going even deeper than how the endoscopy looks, and looking at histologic healing, and even maybe eventually aspirationally molecular healing. So even if you look at a biopsy, what molecular pathways are still upregulated or not. So this is a slight the concept of that our goals for our treatment target have changed over time, and that we're looking at deeper and deeper levels of remission.

And this is just to remind you, when we're talking about endoscopic remission, that's that deeper level of remission, we're talking about looking at the colon on colonoscopy and doing a endoscopic score. Typically, this would be a Mayo endoscopic score is what's most commonly used. Just to refresh your memory, you can see here in the upper left corner is a Mayo score of 0, normal, all the way up to severe disease in the bottom right corner, which is a Mayo score of 3, where you have alteration and spontaneous bleeding. And so, incorporating these endoscopic scores into our routine practice, we're doing colonoscopies and using this as a measure of meeting our treatment targets, is critical in the care of ulcerative colitis patients.

So what are some of the data that show us that endoscopic healing leads to better outcomes? Well, this is one of many studies. One of the earlier studies, which was a post-hoc analysis of the ACT 1 trials, which is the phase 3 studies of infliximab for moderate to severe UC. And what they did was look at early timepoints, what the patient's colonoscopy looked like based on a Mayo endoscopic score of 0 to 3, and what was the patient's subsequent risk of having a colectomy over time. And you can see patients with a 0 or 1 in the blue and red bars at the top, compared to patients with a score of 2 or 3, so moderately to severely active disease, which are represented in the green and yellow bars. The patients who are healed with an endoscopic score of 0 to 1, did much better than those who continue to have active disease with a significantly decreased risk of subsequent colectomy. So meeting objective outcome of endoscopic healing, improved Mayo score, is associated with lower risk a later colectomy.

And this has also been replicated and built upon in a meta-analysis, looking at all studies that were able to provide this kind of data, looking at the early endoscopic endpoint, and later outcomes of clinical remission and colectomy over the longer term, 1 plus years. And this is 13 studies over 2,000 patients. And if you're meeting a endoscopic target of a Mayo score of 0 or 1 early on in ulcerative colitis, those patients are four times more likely to be in clinical remission after a year or more, and four times more likely to still have their

colon. So meeting those strict endpoints of endoscopic remission does lead to improvement in our hard clinical outcomes of remission, clinical remission, and even more importantly, or as importantly, not needing surgery.

And I mentioned before that are our goals for treatment, our targets have been going deeper and deeper levels of remission over time. And so, histology is something that has been proposed as a potential additional target. So your scope looks normal. But if you still have inflammation on your biopsy, how do those patients do? So you feel fine, your scope looks okay, you have a Mayo score of 0 or 1, but there's still inflammation on the biopsy and there's histological inflammation, how do those patients fare compared to those without histologic inflammation? And this is a data from a systematic review meta-analysis of multiple studies. And what they found was that if you have a endoscopic score of 0, but you still had histologic activity, your rate of clinical relapse was higher than if you had histologic remission as well. And that's the bottom row here. So a rate of 30% versus 5% at per year, risk of having a flare, was translated to about a 63% reduced risk of a flare. So patients who were at histologic remission, and having this more rigorous treatment endpoint, did have a substantially lower risk of clinical relapse in this meta-analysis.

So these data have informed our updated STRIDE-II guidelines. And this is a expert consensus recommendation about what our treatment targets should be for ulcerative colitis. This was done by the International Organization for the Study of IBD. So an international group of IBD experts. And what they proposed was thinking about these treatment targets in an intermediate target - intermediate target and a long-term target. So what are the immediate targets for ulcerative colitis? This is first clinical response. So you start a patient on the therapy, and are they having a decrease in their symptoms, and in this case, you know, at least a 50% decrease in their rectal bleeding score, or their stool frequency score, and that you're seeing some clinical improvement in what the patient has experienced, what they're reporting, this is in the short term in anywhere from that 2 to 8-week range. Intermediate targets, you know, more in that 3-month to 1-year range, these are where we're looking to achieve clinical remission, not just if they're feeling better, but that they're now actually normalizing their stool counts, their stool frequency, normalizing their presence of blood, so there's no blood in the stool, and also that their objective metrics of inflammation. So whether it is a blood test like CRP, or stool tests like fecal calprotectin, that these are also normalizing as well. So this intermediate target now is combining clinical remission plus normalization of your biomarkers of inflammation, whether it's CRP or fecal calprotectin. And then the long-term target, which we're talking in the 12-month range, 6 to 12-month range, we're adding on to that not only are you in clinical remission, but you're also at endoscopic healing, that your mucosa is healed as well. And this is defined as a Mayo endoscopic score of 0 so that the colon looks normal, no erosions, no ulcerations, no erythema.

And then also going along with things we said before about patient's goals, absence of disability, and normalizing quality of life. So we think if we meet these endpoints of clinical remission, endoscopic remission, we also can improve patient's quality of life, and the outcomes that are important to them as well.

And this is another, you know, figure showing what I just reviewed in a more visual sense where you have his immediate targets of a symptomatic response, intermediate where you want their symptoms to be in remission, and normalization of their non-invasive markers of inflammation like CRP and fecal calpro. And then the longer-term goal and then to scopic healing.

And right now, based on the current data, the IBD STRIDE-II guidelines say to consider but it's not yet affordable target, histologic healing. And I think this is because we're still waiting for more prospective data to say that treating to histology is definitely going to be better than treating to endoscopic healing. And also we do have lots of advances in our therapies, but we do have a limited armamentarium for our ulcerative colitis patients. So if we are treating to histologic healing, are we going to burn through too many medications too quickly? So histologic healing is, right now, a, I would say, almost an icing on the cake target. And really the target is clinical remission plus a endoscopic remission that on a colonoscopy, the patient's colon looks healed.

So how do we, you know, incorporate the - our assessments of patients into practice in terms of deciding how sick is our patient? What therapy do they need? So this is the ACG, American College of Gastroenterology Ulcerative Colitis Activity Index. So this is a post index that you can use in your daily practice to put a patient into a disease activity classification based on how sick they are at this moment in time. And I think that's a key thing to the concept, is that disease activity, is the patient sitting in front of you, how sick are they right at this, at this moment, a cross section at this moment in time? That's different from disease severity, which I'll talk about in a second. So you can see here from remission to fulminant, there's - I won't read through this ad nauseam here, but basically, there's a number of bowel movements, how urgent - how much urgency is the patient having, what their inflammatory markers are, and what their endoscopic score is, the totality of these metrics can then help you put a patient into a category of is this a moderate to severe patient, where I'm thinking if they're sicker, I need to think about a more targeted advanced therapy? Or is it a milder patient where I can do maybe a more step-up gradual approach? Or for the more extreme, is this a fulminant patient where they're very sick, at 10 plus bowel movements a day, very elevated inflammatory markers, lots of ulcers on a colonoscopy where I need to maybe even hospitalized them and get them better, more quickly? So this is one of many disease activity indices that you can refer to in clinical practice. So to give you a sense of where a patient is on their disease activity.

And as I mentioned, that we're now also going to incorporate the idea of severity. And what's different about the idea of severity is that we want to take into account the totality of a patient's history of their ulcerative colitis, and also what are their risk factors for having a poor outcome. So these are based on the AGA Care Pathway, where they were proposing to incorporate risk factors for colectomy in treatment decisions for patients. So high risk for colectomy are a number of risk factors listed here, extensive colitis, requiring steroids, having deep ulcers, having markedly elevated inflammatory markers, having a young age of disease onset, or low serum albumin, in comparison to patients who are low risk for colectomy, so more limited disease extent, or mild endoscopic disease. So you have someone who may be feeling okay, maybe been falling into more of the remission or mild bucket in that prior slide I was showing you. But if they have a lot of these risk factors for colectomy, that's something we need to be thinking about, maybe I need to have a more aggressive treatment strategy for this patient.

And this was something that we proposed in a review recently in gastroenterology how to try to incorporate these two ideas together, severity and activity. And so if you have a low severity patient who has mild disease activity, the risk of progression is likely low. But if you have a low severity patient, not many risk factors, but they're very sick at this moment in time, then we would say that person is probably more in the moderate risk, and we need to think about more aggressive therapy more quickly. And then someone who has a high severity, so someone who has a lot of risk factors for a poor outcome, regardless of how they're feeling at this moment in time, that's someone you're maybe thinking is more moderate to severely at risk for a poor outcome, and may need to be more aggressive with their therapy. So we're trying to marry these two concepts together of activity. How's the patient feeling right now with severity, and their overall risk factors.

So let's talk a little bit about management algorithms for ulcerative colitis. This is the classic step-up algorithm that you've probably seen in many talks, where you go in a stepwise fashion, where you start with the more milder treatment, and work your way up to a more targeted therapy. And, you know, this is still somewhat applicable, I would argue for ulcerative colitis patients who are maybe at lower risk for disease progression, or maybe moderate risk and they're not that sick, where you can start with a mesalamine and then reassess, see if they're getting better. If they're not getting better, step up to that next level of therapy. And typically, we want to be assessing to stay with mesalamines or if you're giving them a steroid, if they're not getting better within like 2 to 4 weeks, that you want to start thinking anything maybe move on to the next therapy. And so, you know, this is the classic step-up approach that many of us are also very used to insurance companies asking us you know what patients have failed before medication wise. But because of this idea of incorporating severity and activity to target our treatment, this is now becoming, not necessarily totally antiquated, but we're trying to identify patients who need to jump up to a higher level of more targeted therapy sooner, so we're not letting patients suffer with symptoms. And this is one conceptualization of how to approach treatment stratification and treatment selection for all sort of colitis patients based on the idea of how at risk is a patient based on how sick they are at this moment in time, and the risk factors for complications. So if a patient is more milder disease, no risk factors for complications, is, you know, somewhat sick, but not somebody thinking, you know, it has a high inflammatory burden potentially needing to be hospitalized. This is a patient where you can certainly start with a 5-ASA, oral plus or minus a topical, assess in 2 to 4 weeks. And then if they're starting to get – they're continuing to get better, having a response, continue that therapy.

More moderate patient who has more moderate symptoms, maybe some risk factors for complications, if they're not that sick, I think it's not unreasonable to start with mesalamine, but you want to rapidly move on, rapidly step up if they're not getting better in the short term in that like 2 to 4 weeks, maybe giving most 8 weeks to assess how they're doing with their mesalamine. And if they are not, they rapidly step up to another therapy. So if a patient is interested in a oral therapy, that would be ozanimod. Other therapy to consider in the more moderately severe patient would be vedolizumab or ustekinumab. You could also consider a thiopurine, although in general, you know, that is usually not used as commonly now as a monotherapy, particularly because it takes time to work.

If a patient is more on the moderate to severe side, this is where we're thinking going straight to a TNF antagonist, such as infliximab, adalimumab. And if the patient is not doing well on a TNF antagonist and has failed a TNF antagonist, this is where JAK inhibitor may play a role in the data as a second-line therapy after TNF antagonists failure for upadacitinib or tofacitinib. Those medications seem to work quite well in the TNF failure patient. And actually, it's important to note that the FDA has actually relegated these therapies of JAK inhibitors to second-line therapy only after failing a TNF. Obviously our more fulminant patients need to think about colectomy.

All the things to take into account here are other comorbidities. So if a patient has psoriasis or psoriatic arthritis, some of our therapies that work with colitis, also work for these conditions. So we may be able to kill two birds with one stone. If you use something, say, like ustekinumab, if a patient has psoriasis and ulcerative colitis. Or if a patient has other systemic, extraintestinal manifestations, things like TNF antagonists, or if they have, say, multiple sclerosis, something like ozanimod, where it's already approved for that as well, may push you more to that drug or another. So this is the idea that you're looking at how active and how severe is the patient's disease, and matching which type of therapy you'd want to use based on that.

And obviously, when we're talking with patients, everything is very individualized. I mentioned already that you're going to look at disease characteristics, concomitant diseases, other extraintestinal manifestations. You're going to think about the drug's route of administration, what does the patient want in terms of their lifestyle? What are their preferences? What's their risk tolerance in terms of safety of these medications? And so really, there's a lot of discussions that go in personalizing which treatment for which patient, and a lot of it is a, what we would call a shared decision-making process, where we discuss the pros and cons of each of these medications with the patients.

And this is just to give you a little bit more specifics of some ways in which this can work. You know, for example, a patient I mentioned before, who had long-standing UC and failed infliximab, an anti-TNF, this is something where you could go then to potentially a JAK inhibitor, upadacitinib or tofacitinib. If you have a patient who's newly diagnosed with moderate to severe ulcerative colitis, and they have a personal history of, say, a malignancy, such as lymphoma, you may then go for something that drug has not been associated with risk of lymphoma like an ustekinumab or vedolizumab. Or someone who, say, has very busy lifestyle, travels a lot for business. you may call for more injectable medication like adalimumab, ustekinumab, or, you know, an oral medication, such as ozanimod. So there's a lot of different nuances that go into, you know, the factors we're going to consider to selecting a specific medication. Since we are, right now, don't have any specific biomarkers that can tell us which drug will work best for which patient. We go with these, you know – these shared decision-making features and hints about what - if we can use a drug to help a second condition that a patient has as well as the ulcerative colitis.

So to finish, we have case; a 34-year-old man with ulcerative colitis. He's a gentleman named John, diagnosed with moderate UC. He's tried mesalamine now orally and topically for 4 weeks with no relief at all. He travels frequently and is interested in seeing if there's another oral therapy. You can see here that his vitals are okay. You know, not tachycardic, he's a little bit anemic. His albumin is in the normal range but his CRP and ESR are mildly elevated, as well as his calprotectin. The rest of his exam is normal with the exception of some mild left-sided tenderness. So you can see on his colonoscopy here, he has Mayo 2 disease. So you'd classify this person I think as moderate colitis.

So what therapy would you choose at this point for this patient? One option would be to consider mesalamine. But we've mentioned before, he's already been on this for 4 plus weeks. So at that point, you should already be seeing some benefit. So you want to move on at that point, if it's not having any benefit after a month. What about switching to a JAK inhibitor? An oral therapy, which he suggested or mentioned he's interested? The issue with a JAK inhibitor is that you have to wait until the patient has already had not had a TNF antagonists work for them. So in this situation, since he has not been on TNF, that is not the preferred option. And then the last option, which in this case would be I think the most reasonable one for this patient based on his goals of having oral therapy, would then be switching to ozanimod, which has good efficacy in biologic naive patients and is an oral therapy, which this patient wants.

So with that, I'd like to thank you for participating in this program. Be sure to click on the button below to receive your credit. And I also invite you to view Medical Minute 2, where my colleague, Dr. Jordan Axelrad, will be discussing putting it into practice where do S1P receptor modulators fit. And thank you again for your time.

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