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Biomarkers for Ulcerative Colitis Management: A Review of the AGA Guidelines

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and today we're joined by Dr. Siddharth Singh, who will be discussing an article he co-authored, titled "AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis," which was published in *Gastroenterology* in March 2023. Dr. Singh is an Associate Professor of Medicine at the University of California-San Diego.

Welcome to the program, Dr. Singh.

Dr. Singh:
Thank you for having me.

Dr. Buch:
Let's dive right in, Dr. Singh. Can you share some key insights from your article?

Dr. Singh:
Yes. So first of all, I do want to emphasize this was a group effort. We had a whole guideline panel with content experts and methodologists in developing these practice guidelines. The intention with these guidelines was to focus on the role of biomarkers in the management of patients with ulcerative colitis. There has been an increasing recognition that symptoms may not always correlate with endoscopic activity, and we realize that if we treat patients to a target of achieving endoscopic remission, they tend to have better outcomes. That said, endoscopy is invasive and costly, and patients may not always like it, and that's where biomarkers can be informative wherein a combination of biomarkers in the context of patient symptoms can inform us pretty well about how the endoscopic activity may appear.

So the key take-homes from these guidelines were basically trying to identify how do we use biomarkers optimally when we're treating our patients with ulcerative colitis. We listed out several recommendations. The first of them was focusing on combining the utility of biomarkers in combination with symptoms when we are following our patients with ulcerative colitis in routine practice rather than relying on symptoms. The subsequent set of recommendations focused on what cutoffs should we use or think about when applying these in clinical practice. We focus on three main biomarkers: stool C-reactive protein, stool lactoferrin, and serum C-reactive protein. And we looked at different patient scenarios, a patient who's asymptomatic, what cutoffs you use for these different biomarkers; a patient with mild symptoms, do biomarkers perform pretty well or not; and finally, in patients who are calling in with symptoms, such as a flare of our ulcerative colitis, how do we use biomarkers to confirm or refute the presence of significant inflammation and make subsequent treatment decisions.

Dr. Buch:
And what can cause false-positive results when considering biomarkers for monitoring of ulcerative colitis?

Dr. Singh:
There are certain instances, these biomarkers are not perfect and do not always imply the presence of significant inflammation if they are elevated. Some key factors that can contribute to false-positive results, perhaps the most important one is the presence of gastrointestinal infections, so infections like C. diff infections and gastroenteritis can cause some elevation in biomarkers, which can be confusing in certain situations, and that is why we suggest that almost always if you're thinking about a patient who's flaring up, perform stool test to rule out infections in conjunction with stool biomarkers of inflammation.

Dr. Buch:
And similarly, what can cause false-negative results?

Dr. Singh:
There is a subset of patients who may never mount a biomarker response. We know that is true for C-reactive protein in a multitude of other conditions, but for some stool biomarkers, for patients who have a limited segment of disease—for example, some patients with ulcerative proctitis involving a small portion of the colon—they may not mount adequate response, even if they are symptomatic, so in these patients, the results may be false-negative and these tests may not be reliable. For these reasons, what we suggested in the guidelines is in general, we should anchor these biomarkers against endoscopic evaluation for a specific patient. So a patient who's feeling well, if you're planning on doing an endoscopy to evaluate endoscopic disease activity, try to anchor your fecal protectin and C-reactive protein in that situation. Subsequently, if that same patient were to flare up and you were to perform and endoscopy, try to measure the calprotectin and other biomarkers at the same time so you know what is a typical range for the patient and if they mount adequate responses and at the same time those biomarkers come down when a patient is asymptomatic and there is no evidence of endoscopic disease activity.

Dr. Buch:
So, Dr. Singh, what role do biomarkers have in assessing endoscopic remission?

Dr. Singh:
That's an excellent question. What we realized is for a patient who is asymptomatic, maybe about 10–15 percent of patients may actually have significant endoscopic inflammation going on. If on top of those absence of symptoms, if we were to identify and say the fecal protectin is less than 150 or the fecal lactoferrin is normal or the serum C-reactive protein is normal, our confidence in saying that the patient is truly in endoscopic remission goes up significantly higher, up to 95–98 percent likely that a patient who is asymptomatic with normal threshold for biomarkers as we have defined in these guidelines, and that patient is very likely to be in endoscopic remission, and we may be able to forego routine assessment of endoscopic disease activity in those patients.

Dr. Buch:
And that leads to this additional question: Are there certain patients for whom the use of biomarkers may not be very helpful?

Dr. Singh:
That is an excellent question. Clearly, there are some patients like we talked about where their endoscopic activity may not correlate with their biomarkers, so there may be a subset of patients where, even if they have significant endoscopic inflammation, they may just never mount a biomarker response, and in that situation checking the biomarker to inform treatment decisions is not going to be helpful. Similarly, there may be patients who are asymptomatic, but if you do a stool test and their calprotectin is significantly elevated, you should follow it up either by repeating a calprotectin just because there is individual variability as well as intra-individual variability over time, but if the repeat biomarker continues to be elevated, confirming an endoscopy in a situation like this, if the endoscopy does not show evidence of inflammation even though the biomarker is persistently high, in those situations that may be a patient where that specific biomarker is not very informative for subsequent treatment decisions.

Dr. Buch:
Thank you for that. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Siddharth Singh about the role of biomarkers in ulcerative colitis.

Now switching gears a bit, Dr. Singh, the AGA makes no recommendation for or against a biomarker therapy or for an endoscopy-based strategy. From your vantage point, do you have any recommendations that would utilize both endoscopy and markers?

Dr. Singh:
Yes. So our current treatment paradigm is when a patient with ulcerative colitis is flaring up, we generally would check biomarkers as well as an endoscopy to confirm the presence of inflammation. We start them on a specific treatment, and subsequently, generally about two to three months out we would follow up their symptoms as well as interim change in biomarkers, and we're generally excited if a patient is doing well clinically as well as there has been a significant decline in biomarkers. What we identified is if a patient like this has a fecal calprotectin of less than 50, we can be pretty confident that that patient may be achieving endoscopic remission. However, endoscopic changes typically take about six months or so, so our current treatment paradigm suggests that after a treatment adjustment for a patient who's flaring up, we should perform an endoscopy to take a look at things and confirm that somebody is in endoscopic remission.

What we try to look at is whether we can rely solely on biomarkers to continually follow these patients and only perform an endoscopy in a subset of patients where there's discrepancy between symptoms and biomarkers. Unfortunately, there are no such clinical trials that

exist that can help us choose one approach of using a biomarker-based strategy with triaging of endoscopy for only a selected group of patients versus routinely performing an endoscopy for all patients. As a result, we call this a knowledge gap at this point, but this is an area ripe for future studies which can inform an optimal way of using biomarkers for all our patients with ulcerative colitis.

So in essence, at this stage, we combine a strategy of interim use of biomarkers to make some treatment adjustments but eventually confirm that endoscopic remission outcomes have been met in that situation.

Dr. Buch:
And we're looking forward to those future studies, and I'm sure our patients are absolutely looking forward to those future studies. So how does the CALM study on Crohn's disease compare with the information available on ulcerative colitis?

Dr. Singh:
That is an excellent question. So for the audience who may not be aware, the CALM study was a study in patients with early Crohn's disease comparing a treatment strategy that focused only on treatment adjustments based on symptoms versus a treatment adjustment strategy based on a combination of symptoms and/or biomarkers, including fecal calprotectin and C-reactive protein. So these patients at the time of a flare-up were started on a specific treatment, and the patients who were randomized to the biomarker-based monitoring strategy typically at every 12 to 16 weeks had their biomarkers checked, and if the biomarkers were elevated or if the symptoms were still ongoing, their index treatment was adjusted so that the biomarkers are normalized. In contrast, the comparator arm treatment was only adjusted in response to presence of significant symptoms. And what the investigators there observed is at the end of one year, the patients where treatment was adjusted in response to both symptoms and biomarkers were much more likely to achieve a deeper remission or endoscopic remission at the end of 48 weeks as compared to treatment adjustments based only in response to the presence of symptoms.

There are no such studies that, unfortunately, exist for ulcerative colitis, but what our guidelines are, in fact, suggesting is that perhaps an interim biomarker-based treatment adjustment may be helpful in improving clinical outcomes down the line for our patients with ulcerative colitis also. Future clinical trials comparing these two treatment strategies in ulcerative colitis would significantly enhance the quality of evidence to support such a recommendation.

Dr. Buch:
And again, we're looking forward to that study. Lastly, Dr. Singh, are there any final thoughts you'd like to share with our audience today?

Dr. Singh:
Yes. What I want to emphasize is that as we are increasingly becoming more aware and utilizing biomarkers in our clinical practice, our hope with these guidelines is to help standardize practice, inform people of biomarkers; and all the complex decision-making that happens when using these biomarkers, how we interpret the results of a biomarker in the context of your symptoms is extremely important; and how you respond to those biomarker results similarly is extremely important. What we realized during the development of these guidelines is that it's not black or white here where one approach fits everybody, and people need to get comfortable with using biomarkers and apply their experience, and importantly, engage patients just because there's always been some level of uncertainty when checking a biomarker in a patient with ulcerative colitis, and so how do you respond to that biomarker. It is, perhaps, easier to make some relatively minor treatment adjustments based on the presence of elevated biomarkers, but some key decisions like switching to a different medication all together there will be some inherent level of discomfort in making some of those treatment adjustments based only on biomarkers. These guidelines were not intended to replace endoscopy, which still remains the gold standard for evaluation of endoscopic remission as well as a multitude of other things that we use them for in our patients with ulcerative colitis, such as dysplasia surveillance, prognosticating patients who are flaring up in terms of how severe their disease is and what is their extent of disease.

Dr. Buch:
This was an excellent review of biomarkers in the management of ulcerative colitis, and I want to thank my guest, Dr. Siddharth Singh, for sharing his insights. Dr. Singh, thanks so very much for joining us today.

Dr. Singh:
Thank you again, and I hope you enjoyed this.

Dr. Buch:
We certainly did. For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Thanks for listening.