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Diagnosis, Management, and Monitoring of IBD: Treat-to-Target and Therapeutic Drug Monitoring

Announcer:
Welcome to CME on ReachMD. This activity, titled *"Diagnosis, Management, and Monitoring of IBD: Treat-to-Target and Therapeutic Drug Monitoring,"* is provided by the American Gastroenterological Association and Partners for Advancing Clinical Education, in partnership with Practicing Clinicians Exchange and Clinical Care Options, LLC.

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Dr. Sands:
Hello, and thank you for participating in this educational program entitled IBD Resource Center for Primary Care and Gastroenterology Professionals: Your One-Stop Shop for Managing IBD. This module is part of a core IBD curriculum provided by the American Gastroenterological Association, and Partners for Advancing Clinical Education in partnership with Practicing Clinicians Exchange, and Clinical Care Options. This activity is supported by educational grants from Amgen, Ferring Pharmaceuticals, and Takeda Pharmaceuticals USA.

I'm Bruce Sands, Chief of the Dr. Henry D. Janowitz Division of Gastroenterology at Mount Sinai Hospital, and Chief of the Division of Gastroenterology at Mount Sinai Health System, and the Director of the Digestive Disease Institute at the Icahn School of Medicine at Mount Sinai in New York.

This is the second of six Medical Minute presentations, and today I'll be discussing diagnosis, management, and monitoring of IBD, treat-to-target and therapeutic drug monitoring. The objectives for this Medical Minute are for you to be better able to apply the treat-to-target approach in patients with IBD and to detail how therapeutic drug monitoring is used to assess patients for appropriate drug concentrations.

So let's talk about treat-to-target. Let's begin with a case study of Kate who's 25 years old and has a one-year history of Crohn's disease. She has been on infliximab 5 milligrams per kilogram every 8 weeks since her diagnosis, and she calls her office with concerns that she's having a Crohn's flare with worsening symptom over the last month. She's experienced 5 pounds of unintentional weight loss, as well as abdominal discomfort, frequent bowel movements with pain and bleeding, fecal urgency as well. She is not feeling well. What steps will you take to assess symptoms? What are the evidence-based treatment targets for Kate? And would your process or targets change if Kate had ulcerative colitis instead of Crohn's disease?

Well, we have many different layers of goals of therapy for our patients with inflammatory bowel disease. We can think of early diagnosis where we need to distinguish between disease activity which is how they present in the moment in terms of their symptoms, and disease severity, which is the course of their disease over their entire career as an IBD patient. We can think of rapid induction and remission as a goal of therapy because we want the patient to feel well. And also we want to see objective evidence of healing of the bowel inflammation, as we would call mucosal healing. We want to see not just rapid induction, but also stable and sustained maintenance and prevention of relapse that occurs if there is not adequate healing. We also want to treat in such a way that we not only

prevent disease complications, but also complications of drug therapy. And so we can do this by looking at vaccination, cancer prevention, and monitoring. And ultimately, we want to decrease hospitalizations and surgery.

We also have to be aware of the effect of IBD on patient's psychosocial status. These are pervasive conditions that affect how they perform and feel emotionally. And patients with IBD are subject to increased risk of anxiety and depression, as well as sexual dysfunction. And finally, we all need to keep in mind that we want to have good adherence to care and have effective and durable therapy so that care can be cost effective over time.

STRIDE-II outlined a series of treatment targets in Crohn's disease and ulcerative colitis, and divided these into short-term targets, intermediate targets, as well as long-term targets. In the short term, we want to see symptomatic response. And not only that, we want to eventually see symptomatic remission, as well as normalization of biomarkers, such as C-reactive protein. We want to see a decrease in fecal calprotectin as another biomarker into an acceptable range. And particularly for children, we want to see normal growth trajectory. Finally, over the long term, we want to see endoscopic healing, normalization of quality of life, and an absence of disability. Notably, these were considered but not formally added as targets. We would consider transmural healing to be a potential target in Crohn's disease and histologic to be a potential target in ulcerative colitis.

Specifically in Crohn's disease, we are looking at a composite endpoint for patient-reported outcomes of clinical remission and objective endoscopic remission. And so we define a patient-reported remission as resolution of abdominal pain and normalization of bowel habits assessed at a minimum of 3 months during active disease, but individual goals need to be addressed. For the endoscopic side of things, we want to see resolution of ulceration, and think of assessing this roughly 6 to 9 months after starting therapy. And when endoscopy is not adequate to assess inflammation, we can and should use cross-sectional imaging, such as CT enterography or MR enterography. As adjunctive measures, we would include C-reactive protein or fecal calprotectin to help us get to where we eventually need to go with these diseases. But histology is not considered to be a target of treatment with Crohn's disease as yet.

In ulcerative colitis, our patient-reported outcomes include resolution of rectal bleeding and normalization of bowel habit, as well as individual goals such as improving fatigue, mood disorders, quality of life, and work productivity. And endoscopically, we're looking for resolution of both friability in ulceration, which basically correlates with a Mayo endoscopic sub score of 0 or 1, and this should be assessed more like 3 to 6 months after the initiation of therapy.

Here again, biomarkers like CRP and fecal calprotectin are adjunctive measures that help us measure progress along the way, but they're not adequate targets in their own right. However, histopathology is a more sensitive measure of inflammation, and while not initially considered to be a target of therapy, is increasingly being considered for that reason.

A good example and proving that a treat-to-target approach can work in Crohn's disease is the CALM study, where we looked at tight control in Crohn's disease. Your patients were randomized either clinical or management based on symptoms alone, or tight control that was driven therapy with escalation according to CDAI, fecal calprotectin, C-reactive protein, and the use of prednisone. And you can see with tight control approach, that patients had higher rates of deep remission, higher rates of biological remission, and a trend toward improvement in endoscopic remission, which is very hard to achieve. And no difference in complete endoscopic remission, which may be just too difficult to achieve. But in all, you can see the benefits of a tighter control approach, a treat-to-targeted approach that incorporates biomarkers like fecal calprotectin and CRP, not just symptoms.

Let's turn from treat-to-target to consider therapeutic drug monitoring and its role in personalizing therapy. Turning back to our case study, Kate has a one-year history of Crohn's disease and she's been on infliximab since diagnosis, and she calls your office with concerns of a Crohn's flare with symptoms over the past month. She says that she has been adherent to her therapy; she hasn't recently traveled or had any other illnesses, and she has not had any other medications added recently. So what are your next steps in your evaluation?

Well, you can consider laboratory data, such as chemistries, complete blood count, inflammatory markers, ruling out Clostridium difficile, or performing stool ova and parasite. And you can consider MRE and/or ileal colonoscopy. But would you order drug and/or antibody levels to assess Kate's therapy? That's another question.

In our armamentarium, to tailor therapy to a patient, we have this concept of therapeutic drug monitoring, or TDM. And TDM can be divided into reactive TDM and proactive TDM. Reactive TDM is measurement of drug concentration, as well as anti-drug antibody levels in the setting of primary non-response or secondary loss of response to a biologic agent. And the purpose of reactive TDM is to inform about reasons for loss of response or lack of response, and to facilitate therapeutic decisions. On the other hand, proactive TDM incorporates measurement of trough concentrations of drug and anti-drug antibody levels, with the goal of optimizing biologic therapy to achieve a therapeutic drug concentration, regardless of how the patient is doing, even if they're doing well. And the purpose is, over time, to improve response rates and prevent secondary loss of response.

So, if we consider the use of reactive or proactive therapeutic drug monitoring and biologics, reactive approaches rationalized as then better directs the management that you would take in addressing primary non-response or secondary loss of response, it's proven to be more cost effective than empiric anti-TNF therapy dose optimization based on the occurrence of symptoms, and it's also been shown to be associated with better therapeutic outcomes, compared with empiric adjustments of anti-TNF dosing.

Proactive therapeutic drug monitoring is thought to be associated with better therapeutic outcomes compared with empiric optimization and/or reactive TDM, although the evidence for this is largely lacking to date. You can also optimize monotherapy instead of combination therapy with an immunomodulator if you're very assiduous about doing proactive adjustment of drug dosing. And proactive monitoring also allows for the potential to slightly decrease or de-escalate dosing, or even discontinuation when in clinical remission. So they really serve different purposes.

Unfortunately, there are high rates of primary non-response and secondary loss of response, despite anti-TNF therapy being highly effective therapies. Here, you're seeing a whole spectrum of estimates for primary non-response in IBD, to different anti-TNF agents, ranging from as low as roughly 10%, to as high as about 70% in some cohort studies, and secondary loss of response being much higher, on average, about 40% across a whole range of cohorts.

There are mechanisms associated with primary non-response and secondary loss of response, which include mechanistic failure of the drugs; simply that the IBD is not responding to the biology of the drug, despite optimal dose and drug trough concentrations. And the disease is probably driven by inflammatory mediators that are not blocked by a particular drug, therefore unlikely to respond to other drugs in the same class. On the other hand, you have what you might call non-immune mediated pharmacokinetic failure, which means that the IBD is not responding because the drug is actually in a subtherapeutic trough range, even though there are not anti-drug antibodies. And this results from rapid drug clearance, often in the setting of a high inflammatory burden.

And finally, the most common reason for a secondary loss of response would be immune-mediated pharmacokinetic failure, where the patient has a low or undetectable trough concentrations of drugs and high anti-drug antibody levels, leading to clearance of the drug very rapidly. And this is the result of immune-mediated formation of neutralizing anti-drug antibodies to the drug. And this occurs quite often, particularly with anti-TNF antibody.

There are many factors that are thought to influence pharmacokinetics, not only the presence of anti-drug antibodies, but also the use of concomitant immunomodulators which can decrease the risk of forming anti-drug antibodies, as well as decreased drug clearance in their own right, leading to better clinical outcomes. Patients with high baseline TNF, not that we measure this clinically, may have increased clearance. Patients with low albumin have increased clearance of immunoglobulins in general, and this is often seen.

Patients with a high baseline C-reactive protein have a high inflammatory burden, and therefore likely increased drug clearance. In patients with high body mass index may increase drug clearance as well, as well as men having higher clearance. And finally, the HLA-DQA1*05 haplotype, if patients have a specific haplotype of this, are at increased risk of forming anti-drug antibodies. Still, it is actually very hard to predict how the drug pharmacokinetics will operate in a single individual. And there are not good individualizable models for targeting dosing initially of a drug to a particular patient.

The AGA offers a clinical decision support tool for therapeutic drug monitoring that focuses on a reactive TDM approach. It begins with identifying whether the patient truly has inflammation objectively driving their symptoms. And if they do, you want to check for adequacy of trough levels. If the patient has adequate trough levels and inflammation, then they're not responding to this mechanism of action, and you'll want to switch to a different class of drug. If the patient doesn't have adequate trough levels, you need to determine whether this is because they've developed anti-drug antibodies or not. If they've developed anti-drug antibodies, then you could optimize therapy by adding an immune modulator or switching to a different agent in the same class. And if there are no detectable anti-drug antibodies, and there's a low trough, then this is not an immune-mediated pharmacokinetic failure, and you can potentially increase the dose, or again add a immune modulator to also boost the level.

People also consider the possibility that proactive TDM may be useful during therapy and even early after induction therapy. But this is really conceptual at this time, because adequate evidence is really lacking. There's a thought that with proactive TDM, you could actually improve clinical outcomes by reducing primary non-response as well as subsequent secondary loss of response, and also have less occurrence of inappropriate switching out of class or presumed primary non-response. There may also be pharmacoeconomic benefits, hypothesized improvement to quality of life with improving the rapidity of achieving remission and less corticosteroid exposure, and also potentially avoiding the need for combination therapy with an immune modulator. But all these benefits as well as the pharmacokinetic benefits themselves, are still at this point, hypothesized but not substantiated in clinical evidence to date.

Returning to our patient, her laboratory workup reveals an elevated C-reactive protein, a low albumin level, C. difficile negative, and doesn't have any ova or parasites positive in her stool. Her MRE shows 20 centimeters of active ileal inflammation, and she has low

infliximab levels, and no detectable anti-drug antibody. So how do you assess her laboratory results? And what factors were likely contributors to her symptoms? What is the next best step for her therapy?

Well, it's important to know if you're going to measure drug levels, what the targets are for a therapeutic threshold. And these may differ for different drugs. For infliximab, it's thought to be levels of 5 or higher, for adalimumab, 7.5 micrograms per mL or higher, for certolizumab, pegol, 20 milligrams - micrograms per mL or higher, and for golimumab, it's thought to be more than 2.4. There's some studies that would suggest still higher levels achieve a little bit better benefit as a threshold. But above these levels, generally, there's roughly a 10% chance for further improvement with dose escalation.

What about therapeutic drug monitoring for non anti-TNF agents? Well, in studies of ustekinumab and vedolizumab in their pivotal trials, with both agents we saw very low rates of anti-drug antibodies in both Crohn's disease, and in the case of vedolizumab, Crohn's disease and ulcerative colitis. And so it's not really clear that therapeutic drug monitoring is going to be useful with regard to the concern of anti-drug antibodies which are a concern with anti-TNF antibodies. The low rates of immunogenicity with vedolizumab and ustekinumab really suggest that monitoring of anti-drug antibodies with these agents is not going to be useful. Furthermore, prior immunogenicity to an anti-TNF biologic is not associated with increased risk of anti-drug antibodies to vedolizumab or ustekinumab, suggesting that prior experience is not sufficient to suggest that TDM would be useful. Or I would add that combination therapy with an immune modulator would be useful with those newer agents. In fact, if you look at vedolizumab concentrations, there are some thresholds that have sort of been proposed. But you can see the differences between patients who achieve remission and no remission with regard to their median vedolizumab concentrations are very, very little in between. So the dynamic range for drug levels between remission and non-remission are very narrow. So, it makes it very difficult to draw a line for where you want the threshold to be.

There are many issues to consider in the use of reactive and proactive TDM. You should think about what the relationships are between drug levels and response. How might that be different in different subpopulations? For example, also looking at population level data and real-world use in individual patients may be very different things. And it's not always the case that more drug is necessarily better. We discussed the role of non anti-TNF agents and the use of TDM in those patients, and it seems that that's very unclear. And how established is reactive TDM at this point? I would say pretty well established. But there are still some data gaps in understanding the precise thresholds for different goals of therapy. We can consider the strength of the evidence for proactive TDM, and note that there are many data gaps supporting that. And also, there's a concept of very early proactive TDM. And there's some growing evidence for that, really adjusting dosing immediately after initiation of therapy. But again, that is probably for the future.

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