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Clinical Challenges of IBD Management: Biologic Failure and Advances in Surgery

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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, Chief of the Division of Gastroenterology at Mount Sinai Health System, and Director of the Digestive Disease Institute at the Icahn School of Medicine at Mount Sinai in New York, New York.

Today in the fourth of six Medical Minute presentations, I'll be discussing clinical challenges of IBD management, biologic failure, and advances in surgery. The objectives for this Medical Minute are for you to be better able to apply strategies to optimally manage patients with IBD who are not responding to biologic therapy, and to detail recent advances in IBD surgery and the impact on patient outcomes.

Well, let's consider how we might address biologic failure. And we'll start with a case study, namely of Frank who's 32 years old, and he's had ulcerative colitis for 7 years. He is frustrated that he's continued to have flares despite the use of adalimumab therapy. He presents today with active severe disease despite adherence to that therapy. We note that his adalimumab levels are below goal and anti-drug antibodies are present. So what are the next steps in therapy for Frank? Well, according to a reactive therapeutic drug monitoring framework, you could do a number of things in the scenario. You might change to a different anti-TNF agent, preferably accompanied by combination therapy with a thiopurine or methotrexate to prevent recurrence of anti-drug antibodies. Or you might change out of class to a different type of mechanism of action.

According to the AGA Clinical Decision Support Tool, you might choose a few different things as second-line therapy and moderately to severely active ulcerative colitis. They suggest for adult outpatients with moderately to severely active ulcerative colitis, and prior failure of infliximab, particularly primary non-response to infliximab, that you would ustekinumab or tofacitinib preferentially over vedolizumab or adalimumab. So let's look at some of the data behind that recommendation.

We can look at the ULTRA 2 study which looked at the efficacy of adalimumab after infliximab exposure in patients with ulcerative colitis. And this was a randomized double-blind placebo-controlled phase 3 trial in patients who had moderate to severely active ulcerative

colitis, nearly 500 patients were studied here. And what you can see is that while patients who had prior TNF inhibitor exposure, namely infliximab exposure, had lower clinical response and clinical remission rates at week 8 and week 52, there still are substantial proportions of patients who are responding and remitting. Namely, you could see clinical response at week 52 in 1 out of 5 patients, and clinical remission in about 10% of patients. Of course, earlier on, those rates are somewhat higher, and you do see some decrease in the rates of response and remission over the course of a year.

If we look at the data on vedolizumab from the GEMINI-1 study, which was a randomized phase 3 study, there is a post-hoc analysis of patients who were divided as either being TNF inhibitor naive, or TNF alpha inhibitor exposed. And while it's clear that patients who had prior TNF inhibitor exposure had lower rates of clinical remission, clinical response, and mucosal healing, what we now call endoscopic improvement, then we're seeing with the patients who are TNF inhibitor naive, there's still substantial rates of these outcomes. About 10% of patients achieve clinical remission, despite TNF inhibitor exposure in the past, about 39% achieve clinical response, and about 30% achieve endoscopic improvement or mucosal healing. While these effect sizes are much smaller than are seen in the TNF naive patients, they still are important for some patients.

The VARSITY study was a head-to-head comparison in a blinded fashion of vedolizumab to adalimumab, and these were largely TNF alpha inhibitor naive patients, but about 20% of the patients in this study had prior exposure to infliximab, and typically, these were mostly failure patients. So it's interesting to note that when you compared the outcomes at the end of the year for the patients with prior TNF alpha inhibitor exposure, that vedolizumab and adalimumab were about equally effective, about 16% achieved clinical remission at the end of the year with adalimumab, and about 20.3% achieve clinical remission with vedolizumab. While this was numerically superior for vedolizumab, actually it was not statistically significantly different. We should also note that in the main study, vedolizumab was superior to adalimumab for clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission. But that primary outcome really looked at the majority of patients who were naive to either of these types of agents.

Turning now to ustekinumab, the outcomes were explored in the UNIFI study in ulcerative colitis. And if you look at the patients who had prior biologic failure of any of a number of different classes, once again, you see that ustekinumab achieves an effect size over placebo for clinical remission of about 11.5%, for clinical response and effect size over placebo of 29.9%, and endoscopic improvement, the effect size is about 14.3%. And these effect sizes actually are quite similar to what are seen in biologic naive, even though the absolute rates of the outcomes are slightly lower, meaning that the placebo clinical remission, clinical response, and endoscopic improvement rates were overall lower as you would expect in the biologic failure patients. So this is the first example where the effect size after failure of a biologic is the same for biologic naive patients, an important finding.

In the OCTAVE 1 and 2 studies, tofacitinib was looked at as an induction and maintenance therapy. And here too, the effect sizes were well preserved, even if patients had failed TNF inhibitors. You can see clinical remission superior to placebo after TNF inhibitor failure in 11.5% benefit over placebo, and mucosal healing, or again, what we would now call endoscopic improvement, with an effect size of 16.7% over placebo. And this is very similar to the effect sizes that you see with TNF alpha inhibitor naive patients. So this would be a second example of where the drug does about as well in the TNF inhibitor exposed patients, as it does in the naive patients.

We have newer agents that are not accounted for in the AGA guidelines, and have not yet been incorporated. Ozanimod is one of those agents, and the study that led to the approval of the drug, the pivotal trials, really had interesting outcomes at week 10. The drug was overall effective as an inductive agent at week 10, and also maintenance through a year. But there has also been a post-hoc analysis, looking at biologic naive patients, patients who had failed one biologic therapy, or patients who had failed two or more therapies. And interestingly, patients who had failed only one biologic therapy did about as well at week 10 in terms of clinical remission and clinical response as the biologic naive patients, whereas patients who had failed two or more biologic therapies did not do nearly as well in any of these outcomes of clinical remission or a clinical response. Interestingly, if a patient on two or more biologics achieved clinical response and was re-randomized in the maintenance phase to continue on therapy, those patients seem to do about as well at the end of the year. So it's unclear at this point in time, how often we would want to use ozanimod after failure of a biologic agent. But certainly, these data would suggest that failure of just one prior biologic, ozanimod, can be effective.

And we have a still newer agent in our armamentarium, which is upadacitinib, a JAK1 selective inhibitor, and with some similarities to tofacitinib, which is a pan JAK inhibitor. And the data presented here, demonstrate that regardless of whether a patient has bio-inadequate response or non bio-inadequate response, essentially naive or adequate responders in the past, that all of the effect sizes are preserved for a number of different outcomes, suggesting that this particular JAK inhibitor like tofacitinib, will also be an effective second-line agent after failure of another advanced therapy or biologic.

And this is nicely displayed in a network meta-analysis, which seems to show that after failure of another biologic, the most superior agent for this subset of patients would be upadacitinib, followed by tofacitinib, and subsequently lower rates but still effective for ustekinumab, vedolizumab, and ozanimod.

For Crohn's disease, a number of other approaches have been proposed for a second-line therapy in high-risk patients. For patients with severe disease and prior exposure to infliximab or adalimumab, it's suggested that ustekinumab would be the preferred agent for most patients in combination with thiopurine or methotrexate. And it is also possible to use a second TNF alpha inhibitor, which you might consider for patients with loss of response due to immunogenicity to the first TNF alpha inhibitor or because of intolerance.

For patients who are more risk averse, meaning they might have prior serious infections, prior malignancy, advanced age, multiple comorbidities, or just don't like the idea of possible side effects of agents, for patients with moderate disease severity, ustekinumab monotherapy is suggested. And for higher disease severity, infliximab or adalimumab monotherapy, which would be very safe, or vedolizumab in combination with thiopurine or methotrexate. And here, I have to say that generally studies do not find added benefit of a thiopurine or methotrexate to either ustekinumab or vedolizumab. So I do question this recommendation a little bit based on the available evidence now.

If you look at a systematic review of the efficacy of second-line agents for Crohn's disease after infliximab, we generally find that all of the agents of adalimumab vedolizumab, and ustekinumab seem to be effective with positive effect sizes, although with vedolizumab, and this does not achieve statistical significance. So it really would be preferred to move to a second-line TNF inhibitor agent, or to ustekinumab as is seen in this study.

One might also wonder, what is the efficacy of a TNF alpha inhibitor after failure of a drug like vedolizumab? Once you fail vedolizumab, what are the likelihoods of responding to other TNF inhibitors? And we don't have much data on this question, but there is at least one study which was a retrospective analysis of patients with ulcerative colitis or Crohn's disease who were treated with first-line TNF Alpha inhibitor or second-line TNF alpha inhibitor, after discontinuing first-line vedolizumab. And after initiation of first-line treatment, TNF alpha inhibitor patients and vedolizumab patients who went on to switch to a second TNF inhibitor had similar disease characteristics. And in combined ulcerative colitis and Crohn's disease analyses, cumulative rates of treatment persistence, clinical response, and clinical remission were comparable between first-line and second-line TNF alpha inhibitor patient cohorts. And the similar results were observed when patients were stratified by ulcerative colitis and Crohn's disease. So these results suggest that first-line vedolizumab does not have a negative effect on the effectiveness of subsequent TNF inhibitor therapy in real-world clinical practice.

We have a newer agent in our armamentarium, and this is the anti-IL23 antibody risankizumab, now approved for the treatment of Crohn's disease. And in a subanalysis of patients enrolled in the pivotal trials, the phase 3 trials, who had prior biologic failures, it's apparent that this drug is effective for a range of outcomes, even if patients had failed one, two, or even three or more prior biologic therapies with well-preserved effect sizes across the spectrum of prior failures. And this is true for clinical remission, as well as for endoscopic response.

And very importantly, another subanalysis which suggests that even for patients who have failed ustekinumab, which is an inhibitor of both IL12, and IL23, risankizumab, which blocks only IL23, might work for 20 to 30% of patients despite prior failure of an agent with some similarity of mechanism of action, namely ustekinumab.

So in conclusion, all agents are less effective in second-line use after failure of a TNF alpha inhibitor, including a second TNF alpha inhibitor. A second TNF alpha inhibitor, tofacitinib, upadacitinib, vedolizumab, or ustekinumab may be effective after failure of a first TNF alpha inhibitor in ulcerative colitis, and a second TNF alpha inhibitor, risankizumab, ustekinumab, or vedolizumab may be effective after failure of a first TNF alpha inhibitor in Crohn's disease.

Now, let's turn our attention to advances in IBD surgery. We'll turn back to the case of Frank, who's our 32-year-old who has ulcerative colitis, and he's inquiring about the need for surgery to help with his ulcerative colitis. What information will you share about surgery as an option for him? What is the likelihood he will require surgery? What benefits or risks would you discuss compared with other approaches? And this is a complicated topic to broach with any patient. But some patients, by recent estimates as many as 10% with all ulcerative colitis, may require colectomy at some point within the first 15 years of having their disease. And of course, patients with Crohn's disease are at even higher risk of requiring at least one bowel resection. Older data would suggest that 70% of patients may require a bowel resection during their course of disease.

So what are the indications for surgery in IBD? For ulcerative colitis, we may see indications that are urgent, like colonic perforation, life-threatening GI bleed, or toxic megacolon, or fulminant colitis refractory to medical treatment, or even acute severe ulcerative colitis that's not responding to medical therapy, persistent treatment, and symptoms despite medical management. And finally, neoplasia is another reason why patients require colectomy. For Crohn's disease, we might see complicated disease behaviors, like perforation of the bowel. Rarely might we see hemorrhage, symptomatic fistulae, or abscesses and certainly symptomatic bowel obstruction. And finally, rarely neoplasia may be a reason for surgery as well.

Why is early medical therapy that's effective important in IBD? And this is especially true in Crohn's disease. Well, it's been

demonstrated that there's likely a window of opportunity early in the course of the disease, before there has been persistent inflammation and the development of stricture, fistula, abscess, all things that eventually require surgery. So if you can intervene early, the hope is that you're going to prevent these disease complications that will lead to the need for surgery. But this requires not only early treatment, but also tight control of the disease, and aggressive monitoring of the disease to make sure that you're achieving goals of mucosal healing and maintaining it over time. And this can be assisted not only by assessing symptoms, which are sometimes deceptive and don't tell you whether there is or isn't active inflammation, but also looking objectively for inflammation by endoscopy or by biomarkers, or both. Similar principles are hypothesized in ulcerative colitis, but this aggressive nature of the disease is not quite as clear. Still, effective treatment is needed both in UC and Crohn's disease, even if only to provide adequate control of symptoms and the mucosal inflammation that we see in a treat-to-target approach.

Now turning to surgery, one of the main questions that comes up is, when we treat our patients with medical therapies and then they end up needing surgery anyhow, how concerned should we be about the risk of having a patient on immune-inhibiting medications like TNF inhibitors? The PUCCINI study definitively answered this question about whether TNF inhibitor exposure increases the risk of infections, like surgical site infections, or deep incisional infections, or organ space infections. And essentially, it's very clear that regardless of prior exposure to TNF inhibitor, when balancing for multiple other risk factors for these infections, there's no additional risk imposed by the TNF inhibitor itself. So this concern really goes by the wayside, and what we really learn is that surgical site infections or any infection after surgery is really associated with preoperative use of corticosteroids, smoking status, previous bowel resection, and history of diabetes primarily.

Another interesting idea is the notion that for some patients with small bowel Crohn's disease, early small bowel resection may be an alternative to medical therapy. And here, we're looking at the data from the LIR!C trial, and - which was a randomized controlled trial of just that, small bowel resection versus anti-TNF, namely, infliximab, as a treatment for ileal or ileocolonic Crohn's disease of a limited length. And the cohort with initial ileocecal resection did quite well, surprisingly well; 42% did not require treatment for flares despite 5 years of follow-up, and only about 26% ended up being on anti-TNF therapy anyhow, whereas the patients who were treated with anti-TNF therapy, 48% of them required resection anyhow over the 5-year follow-up, and 52% maintained on anti-TNF therapy. So this is an intriguing idea, and raises the question whether we should be offering surgery earlier and more often to our patients with limited ileal Crohn's disease.

So some key takeaways about surgery and IBD include that early treatment of Crohn's disease is imperative to reduce surgery risk. Surgery rates for IBD have declined since the increased use of anti-TNF therapies. But about one-third of Crohn's patients will still require surgery within a 5 to 10 year period after diagnosis, and about 10% of UC patients will require surgery within 10 years of diagnosis. Patients exposed to a TNF inhibitor within 12 weeks of intraabdominal surgery are not at higher risk for postoperative complications or infections.

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