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Key Considerations for Treating Ulcerative Colitis

Dr. Buch:
With the addition of new medications and lack of comparative studies, the difficulty of how to accurately position them for the treatment of ulcerative colitis continues to increase.

Welcome to *GI insights* on ReachMD. I'm your host, Dr. Peter Buch. And joining us today to discuss insights on this topic is Dr. Sara Horst, who is an associate professor at Vanderbilt University.

Welcome to the program, Dr. Horst.

Dr. Horst:
Thank you so much for having me. I'm really excited to talk about this today.

Dr. Buch:
To start us off, Dr. Horst, what are the greatest barriers standing in the way of successful ulcerative colitis therapy?

Dr. Horst:
That's a great question. And, you know, there are a lot of barriers, but the one that comes to mind to me is right now we have this increasing landscape of treatment modalities for patients with moderate to severe ulcerative colitis. We have biologics, you know, at least three mechanisms, we now have small molecules, but figuring out which medication to use for which patient and in what order I think is still very difficult. I know we're going to be doing a lot of research on this in the future, and I really look forward to us helping providers and patients understand that a little bit more.

Dr. Buch:
And that's a perfect segue into my next question. If we have two anti-TNF failures in general, how do you decide between using upadacitinib and tofacitinib?

Dr. Horst:
Yeah. So, you know, this is a difficult question. So, we're talking about a patient who has ulcerative colitis who's failed an anti-TNF, and this is the situation that currently, according to the FDA, we are allowed to use a JAK inhibitor. And, you know, in a lot of cases, this is the drug I would go to next because if someone's failed anti-TNF, they're not feeling well, they're flaring, they have moderate to severe disease and, they're increasingly at risk for having medications not work and, you know, you're in the position where you're having to talk to a patient about, "If this doesn't work, are we going to think about another drug, or do we need to talk to the surgeons and, you know, think about a colectomy?" So, in this case I'd want to use a drug that I know has some reasonable efficacy for someone who's failed an anti-TNF.

And, you know, in particular, I think upadacitinib has some good data about this. When you look at the phase 3 clinical trials and look at the people who failed anti-TNF and then look at this delta in between placebo and response in both induction and remission, upadacitinib—and they had two phased induction studies—really had a strong delta in between those two groups.

Tofacitinib is very reasonable as well. I will say the best way to answer this question is a head-to-head clinical trial, which does not exist, so I'm trying to talk a little bit about apples to oranges. And I do think the safety between the two medicines—I have not seen any data that really is different between the two. So, if I really had to pick, you know, I do think that based on the phased trials, upadacitinib has, you know, some strong data, but I also think that if I'm going to a JAK inhibitor, I'm going to use the one that the patient's insurance is going to cover. Right? We have to think about that. And so, you know, I don't think we have enough data to say I can for sure tell you

which one to use over the other.

Dr. Buch:
Perfect. So, this is also a wonderful segue into the next question. What do we need to know about the risks that come with using JAK inhibitors?

Dr. Horst:
So, there was, you know, a little bit of concern that there may be increased risk of cardiovascular event and lipid increase with tofacitinib when it came out for rheumatoid arthritis and ulcerative colitis, and so the company was asked to go back and look at this question, and they looked at patients who had increased risk of a cardiovascular event. So, the patient population were patients with rheumatoid arthritis, who are older who had a cardiovascular risk factor, and a lot of those patients were on methotrexate as well just by the nature of how rheumatoid arthritis is treated.

They then compared another group of patients, very similar at baseline, who were on anti-tumor necrosis factor therapy and looked at patient events over a period of time to see if there was an increased risk of cardiovascular events or thromboembolic events or death in the two groups, and there was an increased risk with tofacitinib for cardiovascular events and thrombotic events in this large patient population of rheumatoid arthritis patients who were older and had a cardiovascular risk factor. So, because of that, you know, because of this concern, the FDA decided that we needed to position this medication behind anti-tumor necrosis factor therapy.

So you know, when you think about overall risks, all of these events are very low. It is very unlikely that your patient is going to have this happen to them. The likelihood they're going to have an adverse complication from their ulcerative colitis is much higher than any risk that we would talk about that I just talked about for the patient, so I end with that. The risk of having uncontrolled disease for you is not rare. The risks that I just mentioned to you are.

Dr. Buch:
Very useful, and 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. Sara Horst about ulcerative colitis therapy.

So, Dr. Horst, turning to ozanimod, where does this fit in the treatment of ulcerative colitis?

Dr. Horst:
Yeah, so ozanimod is a really interesting medication. So, this is a new mechanism of action that we haven't had access to before, and when I think about ozanimod, it's a sphingosine receptor modulator. What it's doing is sort of modulating how a lymphocyte leaves the lymph node.A very simple view of this, it's sort of trapping some of these lymphocytes that might be affecting downstream inflammation for our patients with ulcerative colitis.

And I think, what's exciting about this medication is it does not have a restriction. You do not have had to fail anti-tumor necrosis factor therapy to start this medicine. This is an oral medicine that can be used for moderate to severe ulcerative colitis first-line. When I look at the phased clinical trial data, the best efficacy of this is in patients who have not been on any biologic medication, or we would sort of term bio-naive, and so this, to me, is a great medication and option for someone who's really interested in oral medication, who has moderate to severe disease but may be more on that moderate end of ulcerative colitis.

Dr. Buch:
And as a quick follow-up for that, what should we know about the safety profile of ozanimod?

Dr. Horst:
Yeah. So that's a great question. I think when you talk about inhibiting lymphocyte trafficking, you know, it might make us worry that the patient might have an increased risk of serious infections. And while that's a little bit elevated over placebo in the phased clinical trials. And actually, when they collated, they used their safety data and looked at both MS patients, so multiple sclerosis patients and UC patients and put them together, so we have more patients to kind of look at safety. We really did not see very high rates of serious infection, which is great to see.

Because it is sort of inhibiting lymphocyte trafficking, you may see a drop in lymphocyte count, but that did not increase the risk of serious infection in this patient population.

The other thing that sphingosine receptor modulation in other drugs, not ozanimod itself but in others, this mechanism with other medications in multiple sclerosis, it can affect heart rate, so you do have to think about the patient who may be at risk for having a cardiovascular risk factor as, in particular, any kind of conduction defect.

And it is recommended that you get an EKG prior to starting this medication, although in the phased trials heart rate was very minimally

affected in patients with ulcerative colitis and even multiple sclerosis.

The other thing to think about is anyone who would be at risk for macular edema. So, this medication does have a slight increased risk of macular edema, so anyone who has diabetes or a history of uveitis, it is recommended that the patient get an ophthalmologic exam.

And then the last thing to think about is pregnancy. So, this medication has not been studied in pregnancy. There is a little tiny bit of data, from a from an animal model that it might cause spontaneous abortion. We don't really know if that's the case or not in humans at all in any way, shape or form, but because of that, using it in pregnancy you know is not recommended, and that's the same with the JAK inhibitor class as well.

Dr. Buch:
Thank you. And just changing direction a little bit, if we are to achieve even better mucosal healing, there is an indication for treatments that need to be added to either vedolizumab or ustekinumab?

Dr. Horst:
I think some of the great things about these newer biologics, which is a little bit different than anti-tumor necrosis factor therapy, is do we need to use immunomodulator therapy, and that would be like azathioprine or methotrexate. And, you know, a lot of the reason that we did that, where we've done that classically for anti-tumor necrosis factor therapy is that we're, number one, trying to prevent immunogenicity because anti-tumor necrosis factor can have high rates of immunogenicity. Up to 1/3 of patients can develop antibodies to the drug, which makes it much less likely to work. And there is some synergistic data especially in Crohn's disease that the medication—using azathioprine with, in particular, infliximab might have better rates of remission, and whether that's from drug levels, you know, I think some of—some newer data may suggest that.

But with these newer medications, they have very low rates of immunogenicity, less than 5 percent in both of these drugs, and so, for me, using immunomodulator therapy and that quote "combo" therapy with these newer biologics is probably not as necessary. And there is one review that sort of collated some of this data together and really found that in patients who are on immunomodulator therapy compared to those who aren't and on these newer biologics, there was really no differential improvement in rates of response or remission, so in those medications, I'm really trying to use them by themselves.

Dr. Buch:
Thank you. And before we close, Dr. Horst, are there any other thoughts you'd like to share with our audience today?

Dr. Horst:
I think one of the big takeaways for me when I think about a patient who has ulcerative colitis, and I kind of alluded to this earlier, is I think it's important not to just think about them when they're sitting in front of you with current symptoms, but think about them as in a larger picture. So, if they really have risk factors for having severe ulcerative colitis, meaning high risk of colectomy, those are the patients that you really need to think about treating early and treating aggressively. So, if they're young, they've been hospitalized, they have severe disease on their endoscopy, they have high CRP, low albumin, you know, those people, they may feel okay when they're sitting in front of you right at that moment, but you need to think about them and what their disease is going to look like 5 to 10 years down the line.

Dr. Buch:
Thank you. This was an excellent discussion on ulcerative colitis. I want to thank my guest, Dr. Sara Horst, for sharing her insights. Dr. Horst, thanks so much for joining us today.

Dr. Horst:
Thank you so much. It's been a pleasure.

Dr. Buch:
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, and see you next time.