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Navigating Treatment Choices for Crohn's Disease & Ulcerative Colitis

Dr. Buch:
There are many treatment options for moderate to severe Crohn's disease and ulcerative colitis, but they come with several side effects. How do we know which option will work best for our patients? This is *GI Insights* on ReachMD, and I'm Dr. Peter Buch. Here to help me answer this question is Dr. Philip Ginsburg, an assistant clinical professor at both the Yale New Haven School of Medicine and the Frank H. Netter M.D. School of Medicine. Dr. Ginsberg is also the Medical Director of Research and the Director of the Inflammatory Bowel Disease Center of Connecticut. Dr. Ginsburg, I'm delighted to have you join us here today.

Dr. Ginsburg:
Thank you for having me.

Dr. Buch:
It's a pleasure. Let's get right into it. Many of our colleagues are moving away from the use of anti-TNFs and towards other products for newly diagnosed Crohn's and ulcerative colitis patients. Is it time to abandon anti-TNFs?

Dr. Ginsburg:
That's a great question. I don't think that it's time to abandon anti-TNFs. Anti-TNF agents clearly have a role for induction and maintenance of remission in moderate to severely active Crohn's and ulcerative colitis that have failed conventional therapies. And they also especially have a role for specific phenotypes, for example, in Crohn's disease with penetrating complications such as perianal fistulas, anti-TNFs clearly have a very defined role. Infliximab, for example, has a separate FDA indication specifically for fistulizing disease. It's the only biologic that has that indication. There are other specific circumstances, such as the post-operative model for relapse after an ileocecal resection, for example. So I definitely don't think it's time to abandon anti-TNFs. I love the fact that we have a number of newer therapies with different mechanisms of action and we should definitely be willing to individualize our therapy and use other MOAs, but anti-TNFs are still here to stay.

Dr. Buch:
Thank you. The other big elephant in the room, of course, is side effects. Would you kindly elaborate on the side effects of anti-TNFs compared to the newer medications?

Dr. Ginsburg:
Yeah. So, anti-TNF agents include, among other things, infliximab, adalimumab, certolizumab, golimumab. These are the commonly used anti-TNF agents in inflammatory bowel disease. And there are several others. As a class, they all tend to share similar sort of side effect profiles. And what I tell patients, and this is a very sort of clinically oriented discussion, is you can be allergic to any medication and with the infusion-based anti-TNF agents that can take the form of an infusion reaction with injection-based medications that can take the form of an injection site reaction or any allergic or hypersensitivity reaction. There can be bone marrow suppression, including decreases in the white blood cell count, leukopenia as well as increased susceptibility to infectious complications. And those include not just the usual viral but also bacterial, fungal, atypical, and even opportunistic infections have occurred. As a class, there is a concern for reactivation of latent tuberculosis and other mycobacterial infections, and so we always want to very carefully screen our patients for any history of latent TB or previous exposure. We will sometimes see liver function test abnormalities, so it's important to monitor our patients who are on all biologic agents, including anti-TNFs. There are some things that are sort of unique to anti-TNFs as a class that we don't necessarily see with other agents, such as worsening of demyelinating disorders or multiple sclerosis and worsening of congestive heart failure. So these are definitely specific, considerations with anti-TNF agents. We wouldn't want to give infliximab or adalimumab, for example, to someone who has, decompensated class IV congestive heart failure. And then there are some more

esoteric side effects, like the so-called lupus-like syndrome and other autoimmune complications. And, that's pretty much it. You know, there is much discussion about concern of lymphoma and hepatosplenic T-cell lymphoma and other non-melanoma skin cancers. Fortunately, these are quite uncommon.

Dr. Buch:
Talking about the hepatosplenic T-cell lymphomas, have the numbers gone up in the last few years?

Dr. Ginsburg:
So the risk has remained the same as it's very uncommon to see. It's very uncommon. And hepatis lymphoma is generally driven by treatment with thiopurine, such as Imuran, azathioprine, or 6 mercaptopurine. So we generally see hepatosplenic T-cell lymphoma only when given in combination. So it is in the label for infliximab and adalimumab, and certolizumab, and golimumab, and all the anti-TNF but it's generally driven by concomitant thiopurine use. The numbers haven't gone up. The numerator and the denominator has remained, you know, the overall risk is the same. But we have identified at least a few hundred now in the entire literature. It's still very, very rare.

Dr. Buch:
Based on the SONIC and SUCCESS studies, we know the benefits of adding anti-metabolites to anti-TNFs for the treatment of Crohn's and ulcerative colitis. Will we get an improved response when combining anti-metabolites to vedolizumab or ustekinumab?

Dr. Ginsburg:
So the short answer is no, it doesn't appear so. We don't have the same type of data as SONIC with anti-TNFs, so we don't have a prospective study that is specifically designed to answer this question. That's the disclaimer. That said, we do have post hoc analyses and subgroup analyses from the pivotal trial data for both vedolizumab and ustekinumab that don't appear to show any benefit of combining thiopurines or methotrexate with either of these agents as it relates to clinical response or remission. That said, if you really drill down into the data sets, it is also true that patients who were on concomitant immunomodulators in both studies had higher serum trough levels associated with decreased anti-drug antibody formation. Again, these were subgroup analyses, and so there are questions about power and whether, you know, in the absence of a dedicated study that specifically looking at this question. But the general consensus in the IBD community is that vedolizumab and ustekinumab don't appear to be as antigenic as anti-TNFs as a class, and therefore the role of combination therapy seems to be less important. And so I find myself giving vedolizumab and ustekinumab a lot as monotherapy. Primarily as monotherapy, unless there's a special circumstance.

Dr. Buch:
Thank you. For those of you just joining us, this is *GI Insights* on ReachMD. I'm Dr. Peter Buch. And joining me today is Dr. Phillip Ginsburg, who is discussing medicine choice for the treatment of IBD. How do you choose the optimal treatment strategy for your patients?

Dr. Ginsburg:
So this is a difficult question. We all have different ways of treating our patients and I don't have one particular sort of pathway that I follow. I tend to individualize therapy based on unique patient circumstances. That said, the current state, if you will, of how we choose medications is to start by staging our patient to understand the extent and the severity and the distribution of their disease, and then to choose a medication based on risk. So we want to understand to risk stratify our patients based on the risk of future progression and complications, and then to treat accordingly. So you might sort of expect that if we have someone with mild, newly diagnosed ulcerative colitis, that might be fairly limited in extent to just the rectum and rectal or rectosigmoid who may have a couple of extra bowel movements over their baseline, you know doesn't impact their quality of life significantly. They're still working. They don't have horrible biomarkers and not a lot of abdominal pain that we're going to treat that patient perhaps a lot differently than someone who has had several years of aggressive, penetrating, you know, ileal Crohn's disease with perianal fistulizing disease, etc. So, you know, we do individualize our therapy. So, for example, for someone with mild ulcerative colitis, the first person I talked about, we may choose a first line, 5-amino salicylate and/or topical therapy. But for the latter patient, we may go straight to an anti-TNF agent, for example. So, that's a very difficult question to answer. There's no one size fits all. I think it's important to individualize our treatments to understand the extent and the severity and the distribution of disease to exclude complications and most importantly, to risk stratify our patients and treat accordingly.

Dr. Buch:
As we know, third party payers play a huge role in medication strategy. How do you get what you need for your patients?

Dr. Ginsburg:
What I find that works for me, and this is very individual for me, is documentation. And I have a lot of help because it requires a lot of help. And just that paperwork alone can extend extensive resources in an office setting. I also find that really thoroughly documenting the

need has really been very helpful. So when I see a patient, I make a point of developing a narrative of their disease, and I document all of that in my office notes. So that way, when my staff sends the office note to the payer, the payer has everything that they need. And if it's denied, then it's very easy for me to dictate an appeal. There is a lot of back and forth that goes on with third party payers. There's no magic recipe for how to do it, but it oftentimes requires, you know, really being proactive and chasing down the payers and not being afraid to appeal and jumping through hoops. And that's what we have to do on behalf of our patients.

Dr. Buch:
Before we conclude, is there anything else you would like to share with our audience today?

Dr. Ginsburg:
I would just say that now is a very interesting and really fun time to be taking care of patients with Crohn's and ulcerative colitis. We've seen from the first anti-TNF agent that was approved over 20 years ago now the development of several follow-on anti-TNF agents and multiple other classes of biologic medications, and now coming full circle back to small molecules; all of which we sort of touched upon. And so we have several different strategies that we can employ for our difficult to treat patients which makes things very interesting as we start to think about, you know, different ways to help our patients.

Dr. Buch:
That's all the time we have for today. I wanted to thank Dr. Ginsburg for helping us to understand medication choices in the treatment of inflammatory bowel disease. Dr. Ginsburg, thanks very much for your insight.

Dr. Ginsburg:
You're very welcome,

Dr. Buch:
For ReachMD. I'm Dr. Peter Buch. To access this episode and others from *GI Insights*, visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Thanks for joining us today.