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Tailoring Inflammatory Bowel Disease Care: Selection Criteria and Timing

Dr. Buch:
This is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and today I'm joined by Dr. David Fudman to discuss positioning of advanced therapies for inflammatory bowel disease, or IBD. Dr. Fudman is an Assistant Professor and Director of Inflammatory Bowel Disease Clinics at the University of Texas Southwestern Medical Center.

Welcome to the program, Dr. Fudman.

Dr. Fudman:
Thank you very much for having me.

Dr. Buch:
It's truly a pleasure. Dr. Fudman, with limited head-to-head studies among advanced therapies, how do we choose the best medication for our IBD patients?

Dr. Fudman:
That's a great question, and fortunately for our patients, it's becoming a little bit more difficult as we have more options. There are many factors that we want to take into account. I think the first thing we want to think about, of course, is efficacy. We also want to assess the patient's risk of disease-related and therapy-related complications and balance those things, because we want to choose a therapy that's going to be optimally effective for that patient's disease and that will reduce their overall complications from their disease but also assess what that individual patient's factors are and what their patient characteristics are that might portend that they could have a higher risk of treatment-related complications. We, of course, need to take into account very importantly patient preferences with regard to mode of delivery, whether that's subcutaneous, IV, or oral, how frequently the medication needs to be used, or other patient values. Then, we skirted over efficacy, but that's very important. We have an increasing number of head-to-head studies, but of course, we're still lacking in these, and accumulating observational data as well as the strategy called network meta-analysis, which tries to combine the pivotal trials, the phase three studies of drugs together into a meta-analysis to see which ones seem to be better. These techniques all have their own strengths and weaknesses, and so we have to be careful to integrate these data with an eye to each type of study's advantages and disadvantages. And then lastly, we have to really be careful to consider efficacy and specific disease phenotypes. So the most common one we think of would be perianal disease or fistulizing disease and Crohn's disease where the evidence for some agents is much stronger than for others.

Dr. Buch:
And moving on from there, what additional criteria, like safety and time of induction, should influence our medication decision?

Dr. Fudman:
Well, of course, safety is really important to take into account. I like to think of safety in two components. The first, of course, is how effective the drug actually is, because in general, the more effective the drug, the safer it will be, because it will reduce the risk of disease-related complications, and in some cases it will also decrease things like infection, especially in the case of Crohn's disease. There's a relatively recent meta-analysis that showed, for example, that in patients with Crohn's who were treated with vedolizumab versus with an anti-TNF, there wasn't any difference in serious infections where we might expect to see some and that we hypothesize would be driven by the higher efficacy of the anti-TNF medications.

So if that's the first piece, the second piece is the intrinsic safety of the drug, and that's essentially if we gave the drug to a bunch of healthy people, what would happen, because we can't avoid disease-related complications in those people, and so that's the intrinsic safety of the drug. And we kind of put these two together. We integrate these two concepts in a personalized way for each patient because the risks are different for each patient. You also talk about how long it takes to get an effect from a drug, and that can be really important in certain cases. Some therapies definitely work faster than others. So, for example, JAK inhibitors have a very fast onset of action, so they might be used to avoid systemic steroid exposure in someone who really needs to do that, or to get patients quicker when that's really the very top priority for that patient. And actually, that's led to some use of JAK inhibitors in the hospital for patients hospitalized with ulcerative colitis, for example.

Dr. Buch:
So let's now move on to specific scenarios. What medications should we use for the initial treatment of moderate to severe ulcerative colitis, and are there advanced therapies that are less effective?

Dr. Fudman:
Well, we're lucky now that we have an increasing number of great options for treating patients who are naïve to advanced therapies for their ulcerative colitis. For patients who are still presenting very much on that severe side of disease—maybe we're thinking that they're at risk of needing to be hospitalized—infliximab is still really a good option. We'll often use this in conjunction, at least initially, with an immunomodulator based on the data that outcomes are better doing so. We might pull that immunomodulator off later.

The FDA label for upadacitinib and JAK inhibitors in general states that those should be used after an anti-TNF, but the data from the pivotal trials for these drugs in this setting for a very sick patient is still good, and so off-label use of a JAK inhibitor could be a good option in a very sick patient as well that's biologic naïve. But for patients who are sort of on the more moderate side of moderate to severe, or even on the less severe side of severe, aside from infliximab, we have a lot of other good options, and we can choose from really any of them. Those would be vedolizumab, ustekinumab, or any of our IL-23 selective agents, so that would be mirikizumab, risankizumab, or guselkumab. And our S1Ps ozanimod or etrasimod—those would all be good choices.

There's one choice that we would avoid here, and that's adalimumab. Adalimumab is just less effective for ulcerative colitis than our other choices. And actually, the AGA guidelines, which are based on an updated network meta-analysis, put adalimumab in the low efficacy category for drugs for patients who are both bio-naïve and bio-experienced.

Dr. Buch:
And if this initial treatment is unsuccessful, what do you then select?

Dr. Fudman:
Sure. So the next medicine you would choose would very much depend on what the first medication was. So if the first medicine was infliximab, then the most efficacious therapy next is probably upadacitinib. Upadacitinib seems to also be more effective than tofacitinib, the other JAK inhibitor approved for ulcerative colitis. We do have other options, and if we're really concerned about a therapy-related adverse event—for example, maybe we have a patient who's older, who has a history of atherosclerotic disease or of other concerning issues—then maybe we would choose ustekinumab or an IL-23 in that setting.

The one that we probably wouldn't use here is vedolizumab. It doesn't seem to work as well in anti-TNF-exposed patients. And S1Ps in general don't work as well in patients who are advanced therapy exposed, and so we probably wouldn't choose that here either. If the initial treatment, though, was vedolizumab, which it commonly is, we would typically go to infliximab, but it would still be very reasonable to go to something that hits IL-23, so either ustekinumab or any of the IL-23 selective agents.

Dr. Buch:
Great. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. David I. Fudman about advanced therapies in inflammatory bowel disease.

And following through with this thought process, Dr. Fudman, what do you recommend as initial medication for moderate to severe Crohn's disease?

Dr. Fudman:
So although our options are expanding, they're not as expanding as quickly for Crohn's as they are for ulcerative colitis. So in Crohn's disease, traditionally, we would start with an anti-TNF, either infliximab or adalimumab, probably favoring infliximab in more severe disease presentations and phenotypes, but those are still great options. But there's been somewhat of a shift to starting to use agents that hit IL-23, particularly now the newer selective IL-23s in first-line, and so for patients without the most severe phenotypes, these really are becoming a go-to, at least in our practice. This is favorable for patients with regard to their intrinsic safety as well as

subcutaneous dosing; although, subcutaneous dosing of infliximab, which is more frequent than IL-23, is also now available. I would say on average our bio-naïve patients who are not super sick now are starting on IL-23 rather than anti-TNF, but anti-TNFs are still a very good choice here.

Dr. Buch:
Great. Dr. Fudman, what should we know about combining more than one advanced therapy for our IBD patients?

Dr. Fudman:
That's a great question. This is a strategy that seems to be very promising, particularly for patients with disease that's refractory to multiple therapies or patients who have more than one immune-mediated disorder for whom getting just one agent to work effectively for both diseases can be difficult. So if we employ this strategy, we typically pick one or two drugs with very high intrinsic safety, so those would be medicines like vedolizumab, ustekinumab, or an IL-23, and we would combine them either with another medicine from that group or a medicine—an anti-TNF or a JAK inhibitor.

There are some limitations to this strategy. The main limitation, really, is access. Of course, payers are reluctant to approve two different advanced therapies simultaneously. Sometimes that can be overcome or, alternatively, sometimes manufacturer assistance programs can be used to get one or both of the agents. The other limitation is that the data for this approach is still actually pretty sparse, and I think it's important to acknowledge that. The data that does exist though is very encouraging. There's been multiple systematic reviews of observational data and they show very high rates of clinical remission. And this is in a very treatment refractory population, so I think that means a lot, and those data haven't shown any real new safety signals.

There's also increasing interest among industry partners in combination therapy. So, as an example, the phase 2 VEGA study compared guselkumab versus golimumab versus the combination of the two drugs in ulcerative colitis, and the combination of the two was the most effective. So because of this interest, there are multiple ongoing industry studies looking at combination therapy and more in development, so I think there's more to come in this space, and it's an exciting space, one that hopefully will be able to get more patients into remission.

Dr. Buch:
So just honing a little bit into side effects, are there any particular concerns when we're talking about two advanced therapies?

Dr. Fudman:
That's a great question and one that we, at this point, have limited data on. Our data is mostly limited to observational data in terms of adverse effects because the VEGA study is our only modern published randomized trial—at least in UC—for combination therapy. There's also the EXPLORER trial in Crohn's disease. Overall, none of these studies have found new safety signals. In general, combining an anti-TNF and a JAK inhibitor is a little bit controversial, but is done at some centers, and that combination is probably the one that is most prone to increasing adverse effects. But the fact that the intrinsic safety of vedolizumab and anything hitting IL-23 is so very high theoretically, we don't have huge concerns about doing this and also, we don't have concerns that have really spouted up in the data thus far.

Dr. Buch:
Thank you for that information. As we approach the end of our conversation, Dr. Fudman, do you have any final takeaways you'd like to share?

Dr. Fudman:
Well, I think we talked a lot about what therapy to choose for patients. I think another main takeaway is that overall in IBD care, we're not treating patients as aggressively as sometimes they would benefit from. We know, for example, in Crohn's disease, early effective therapy really helps them avoid complications. So the PROFILE study, which actually was a study of biomarkers but also looked at, in randomized patients, an accelerated step-up strategy where patients needed to flair to quickly get an immunomodulator and flair again to quickly get infliximab versus getting infliximab and an immunomodulator up front with early diagnosis Crohn's disease. The patients who had early aggressive therapy or early infliximab plus an immunomodulator did very substantially better over time in terms of their clinical outcomes and their complications than the step-up group, so I think one of the key things is we shouldn't get too caught up on which therapy to choose and perhaps need to concentrate also on which patients need to get therapy and how we get it to them early and effectively.

Dr. Buch:
So just you intrigued me a lot. So how can we explain the fact that we're not getting to the patients that we need to get early enough? Mostly, it's gastroenterologists who are going to be providing these medications. What seems to be the problem?

Dr. Fudman:
I don't think there's any one answer to that question. I think there can be reluctance on the part of patients to start therapies that are not familiar to them. I think that the disconnect, particularly in Crohn's disease, between symptoms, inflammation, and disease complications can be something that requires a substantial amount of both physician and patient education. I think that there are access issues to these drugs where it can be very time-consuming on the part of physicians and their staff and offices to overcome payer barriers to get drugs to patients. I think also there are delays in diagnosis that are a result of a variety of different issues. So I wish there was one problem that we could tackle in order to get patients on a therapy that's effective for them and get it done close to their time of diagnosis, but I think we have to look at it from multiple different angles.

Dr. Buch:
Thank you for that clarification. I want to thank my guest, Dr. Fudman, for an excellent discussion of advanced therapies for inflammatory bowel disease.

Dr. Fudman, it was a pleasure speaking would you today.

Dr. Fudman:
This was great. Thanks so much for having me.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you again very soon.