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Released: 05/01/2026
Valid until: 05/01/2027
Time needed to complete: 1h 02m

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Targeting Inflammation in IBD: Localized vs Systemic Strategies

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Dr. Dolinger:
Hello. I'm Dr. Michael Dolinger, and joining me is Dr. David Rubin. We've already walked through the key inflammatory pathways driving IBD in an earlier episode, but understanding the biology is only part of the story. The knowledge that informs how we treat our patients will be given in this episode, and today we're going to take a closer look at the therapeutic landscape in IBD and examine where different treatments act along the inflammatory cascade, from broadly systemic approaches to more targeted and gut-selective strategies. We'll walk through how these therapies work and make them distinct mechanistically, and some practical considerations when you put them into clinical practice.

Let's start with the most systemic players, corticosteroids. Dr. Rubin, can you shed some light on how these act within the inflammatory cascade, and what should clinicians keep in mind when using them in IBD today?

Dr. Rubin:
I think everyone is familiar with corticosteroids for many conditions, and the inflammatory bowel diseases are no exception. The discovery that corticosteroids could treat Crohn's disease and ulcerative colitis was indeed a revolution in the 1950s, and they still have a role today, but limited. What we continue to see is that they are overprescribed and overused and associated actually with the worst outcomes.

Steroids work broadly on the body and affect many organ systems, even when you're trying to just target the bowel. And if you use a therapy like prednisone, it will have a variety of side effects that I suspect are well known to our colleagues who are watching this.

I want to emphasize that the general mechanism of corticosteroids is not fully understood despite 100 years of using them. But what we do understand is that they tend to have a lymphocytic effect, meaning that they affect the white blood cells that are a key component of the inflammatory cascade driving the acute and chronic inflammation of IBD.

The general rule in inflammatory bowel disease is that if you're going to use corticosteroids, you use them for as little time as possible and only as either a bridge to a maintenance therapy or to address an acute problem, with the idea that using them longer than 2 to 4 weeks maximum is not recommended. In our guidelines for Crohn's disease and ulcerative colitis, we recommend and we recognize that steroids are overutilized and are never to be used as maintenance therapy. The general rule in the GI field is that if a patient needs steroids more than once in a year for longer than 2 weeks, they need a different treatment strategy for their maintenance. I think it's a

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really important message.

My last point about corticosteroids is that we have new therapies for IBD that work so quickly that if we know a patient needs that other therapy to manage their inflammatory bowel disease, we can even avoid corticosteroids altogether. And I think that's an important point for everyone to understand.

So when someone has Crohn's or UC and they're not doing well, we really do need to work together to get them on a different strategy for their long-term management.

Dr. Dolinger:
Yeah, that's exactly my approach as well. I completely agree. If we're going to use steroids in that necessary evil, we need an immediate plan to move downstream into a more targeted therapy that's actually going to be the maintenance strategy for that patient's IBD.

From that aspect, how do you approach moving to a more targeted immune effective strategy for patients with so many options today? And in that setting, when do you consider some of our oldest biologics, the anti–tumor necrosis factor, TNF therapies, as first-line options for patients?

Dr. Rubin:
Well, the arrival of infliximab as an anti-TNF monoclonal antibody was the second revolution in managing IBD, and in fact it was the first drug approved by the FDA for the treatment of Crohn's disease. So it was a true advance in our field to recognize that we could use a monoclonal antibody to target a specific cytokine, tumor necrosis factor alpha. What we've learned subsequently is a whole bunch of information about how this therapy works, the potential adverse events that can occur, and when we should be using it.

In general, despite the fact that this therapy has now been around for more than 30 years, we recognize that anti-TNF is still an appropriate strategy for many patients with Crohn's disease and ulcerative colitis. Infliximab is the only drug in our field that has a separate label for penetrating perianal or fistulizing Crohn's disease, and it still has some of the best evidence for patients with ulcerative colitis who have acute severe ulcerative colitis and are in the hospital.

We've also learned, of course, from using infliximab and the subsequent other anti-TNFs like adalimumab, golimumab, and certolizumab pegol, that these treatments have a number of potential side effects. They can affect the ability to survey and maintain infections, so people with latent tuberculosis can have reactivation of their TB. It can worsen chronic hepatitis B. And TNF inhibition can also be associated with other bacterial and fungal or opportunistic infections. So it's important when we choose these therapies that we're thinking carefully about the patient and making sure that we're protecting them along the way.

We've also learned from our anti-TNFs a number of other important strategies, one of which is that these therapies work extremely well when there's inflammatory conditions of the skin or joints. So in the IBD world, when someone has Crohn's and an inflammatory arthropathy or joint pain, anti-TNF may be the right therapy for them.

I also want to emphasize that it's the anti-TNF therapies that are the only therapies that currently have enough evidence to recommend therapeutic drug monitoring, or what we sometimes just say is serum concentration assessment, to know whether patients are optimized and to assess what's happening when a patient is losing response.

All of our other subsequent monoclonal antibody therapies do not have sufficient evidence to use therapeutic drug monitoring as a standard approach.

So TNF is a really important therapy. It was a revolution in its arrival in managing IBD, and it has some significant considerations for the patient who might benefit, as well as how we protect them while they're on it.

Dr. Dolinger:
That is a fantastic summary of 30 years of history in 3 minutes.

Dr. Rubin, given that patients may not—we don't want them on steroids, we've talked about anti-TNF therapies, but there are other

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options. Can you inform our clinicians a little bit about the differences between those options and how they act, vedolizumab and maybe the IL-23 therapies, to give them some more information?

Dr. Rubin:
Yeah, I think that's important because it can be overwhelming. In general, we should acknowledge that all of our treatments currently in IBD are targeting active inflammation with the hope and understanding that removing the inflammation allows the body to heal and allows it to catch up and restore homeostasis. At least that's what we hope is happening.

So the strategies are either cytokine targeting, which is what TNF inhibition does or interleukin-23 inhibition does, or cellular targeting, which is what our vedolizumab or lymphocyte trafficking inhibitor does, or our S1P receptor modulators do by inhibiting the ability of activated lymphocytes to migrate out of lymph nodes.

Interleukin-23 is an interesting cytokine in that it is elevated in the tissue that is inflamed, but it is not otherwise constitutively active like TNF is. So when you inhibit IL-23, it tends to be more of a tissue-specific treatment strategy, whether it's the skin or the bowel, and therefore it has a very nice safety profile.

Similarily, when you think about vedolizumab as a lymphocyte trafficking inhibitor or the S1P receptor modulators, which also affect lymphocyte trafficking, those tend to be therapies that are only going to work where the inflammatory white blood cells are on their way to the bowel. So some of our treatments offer more selective targeting that enables safer treatments.

Now, on the other hand, you have to think carefully, because if you provide a therapy that's more selective, you may not be addressing other extraintestinal problems. So that's why you have to understand some of the basic immunology, as well as the other indications that some of these treatments will manage.

The last therapy I'll mention are the JAK inhibitors, a small molecule that inhibits the enzyme Janus kinase, and that is a enzyme that is in the cell membrane that is involved in activating multiple lines of inflammation. So Janus kinase inhibition, despite the fact that these are oral and convenient therapies, is a very potent and effective anti-inflammatory strategy because it affects multiple lines of inflammation. And so people need to understand some of the basics.

But the underlying strategy in IBD for all these years and all these therapies is still the same. We're trying to turn down an overactive immune response so the body can take over and get back to its resting state.

Dr. Dolinger:
That's a fantastic summary of hundreds of pages of mechanistic literature in 3 minutes. And well done, because I think I understand it better now myself.

Dr. Rubin:
Thanks, Mike.

Dr. Dolinger:
And despite that, anti-TNF therapies are the only approved therapies for children with IBD to date, which is a shame. But assuming we are treating adults, and most listeners are community gastroenterologists who treat adults, and we have other therapy options available today.

My practice is generally to say, as you had staged their IBD, do they have these extraintestinal manifestations, inflammatory arthropathies, and do they need anti-TNF, or is that the best first-line therapy for them? In the majority of cases, or many, it's not.

And so when it isn't, how do you decide between vedolizumab, IL-12/23 blockers, IL-23 blockers in patients with IBD, how do you differentiate first-line therapy options for patients?

Dr. Rubin:
Yeah, it’s a complicated question, but it also has a simple answer. The first point is, if you have a patient with Crohn's disease who is moderate to severe Crohn's, which is anybody who's really symptomatic or who has documented disease, frankly, this is somebody who

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any therapy that you're comfortable using that is not steroids is a therapy that's reasonable to get them on. Use what you know, just then of course make sure that you're achieving your goal of management.

So if you're most comfortable using an anti-TNF as one of your first treatment options and that's what you know and what you have available, okay. But otherwise, you can consider vedolizumab. You can consider our IL-23 inhibitors, and there's now three of them that are approved for moderate to severe Crohn's disease. And you can even consider the JAK inhibitor upadacitinib for some patients.

And the choice of therapy beyond what you're comfortable using should also incorporate your knowledge about any extraintestinal manifestations. If the patient has coexisting ankylosing spondylitis or sacroiliitis or frankly peripheral joint pain, then I'm going to favor an anti-TNF or a JAK inhibitor. I'm not as convinced that our IL-23s or vedolizumab is going to manage that as well as we might want.

Having said that, some of the peripheral joint pain is just due to bowel inflammation, so if you fix the bowel with any of these treatments, they might feel better.

If the patient has a history of skin inflammation, and in particular, psoriasis or plaque psoriasis, an IL-23 inhibitor is a wonderful choice. In plaque psoriasis, the IL-23 inhibitors have a 90% success rate. And so when you acknowledge that and recognize that the skin, as you said, Mike, might be a window to what's also going on pathologically in the bowel, an IL-23 inhibitor is a logical first choice. And so it's good to think about that.

And I'll end with one more point. It's not always about the medicine. In some patients, the first approach can be surgery. If it's a limited resection with a primary anastomosis that has 100% success rate in inducing remission, then you focus on preventing it from coming back.

And as hard as that conversation may be to someone, if you have someone who presents with a bowel obstruction or a dilated proximal lumen with stenosis downstream or a complicated penetrating abscess or phlegmon, it might be reasonable to take that out and get a fresh start and then focus on your subsequent therapies.

Dr. Dolinger:
Now, there's so many pearls wrapped up there. I think taking it as the clinician, if you have a clinical clue that matches your luminal disease, use that to pair with potentially the mechanistic therapy that matches those two things together. In absence of that, maybe it doesn't matter, and it's about getting your patient on an effective therapy that's safe as fast as possible that isn't steroids, as insurance and payers may dictate which therapy they're going to go on anyway, and so just getting them to that point as fast as possible and not delaying their care further may prevent that chronic bowel damage from occurring and change their life.

Dr. Dolinger:
Yeah.

So I will say that maybe it's not which therapy, but it's any therapy, and to not delay care and prevent the chronic bowel damage from accruing is maybe the best strategy overall for patients in IBD, as we avoid steroids, as you said from the beginning.

As we wrap up here, any last clinical pearls you'd leave our gastroenterologists with in the community to understand how they should treat Crohn's disease and ulcerative colitis in 2026 and beyond going forward?

Dr. Rubin:
One of my main messages in this modern era now is that we have enough treatments and we know enough about the natural history of Crohn's disease and ulcerative colitis to recognize that we need to provide patients with effective treatments for their disease. And too often we're undertreating by using mesalamine when it's no longer effective in UC or using mesalamine when it's not indicated in Crohn's disease, and we're overtreating with corticosteroids because they're cheap and easy to get but doesn't get the patient where they need to be.

So it's really time in our field and among our colleagues to make sure that our patients are getting advanced therapies when they're diagnosed with these conditions and that we work together to get them sustained remission free of steroids and to improve their quality of life, which ultimately is of course what we want for all of our patients.

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Dr. Dolinger:
I think that's perfectly said, and we'll wrap the episode up there. Thank you for listening, and we'll see you on the next episode.

Dr. Rubin:
Thanks, Mike.

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