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Small Molecules in IBD: JAK Inhibitors and S1P Modulators

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Dr. Odufalu:
Hello, I'm Dr. Odufalu, and here with me today is Dr. Rubin. Small molecules are reshaping inflammatory bowel disease care by giving clinicians effective oral options that work through targeted intracellular and immune-trafficking pathways. In this episode, we will break down where therapies like JAK inhibitors and S1P modulators fit in ulcerative colitis and Crohn's disease and what makes them different from biologics. We'll also highlight the key clinical pearls, safety considerations, and emerging data that matter most in everyday practice.

So, Dr. Rubin, in today's treatment landscape, where do JAK inhibitors fit in the sequence of therapies in IBD?

Dr. Rubin:
Well, thank you so much. I have said for a while now that the arrival of targeted synthetic small molecules has been a revolution in the inflammatory bowel disease space because small molecules avoid one of the challenges we have with monoclonal antibodies, and that is that protein-based therapies like our monoclonal antibodies may be subject to an exposure problem. What I mean by that is in patients with an inflamed bowel, they can leak protein, so when you give a monoclonal antibody, you may end up with increased clearance due to protein loss through the wall of the bowel, and therefore, even if the mechanism were right, it may not work as well as you need.

Small molecules address this by having rapid and predictable absorption in the small intestine, and also because they are able to do that, they're also delivered orally. JAK inhibitors include a number of therapies that inhibit the enzyme Janus kinase, and there are several different Janus kinase enzymes that are related to activation of inflammation in a variety of different pathways.

And in the United States, we specifically have two JAK inhibitors that have been approved for treating IBD: tofacitinib which is a pan-JAK inhibitor, meaning it inhibits JAKs 1, 2, and 3 and is approved for moderate to severe ulcerative colitis, and upadacitinib, which is a selective JAK1 inhibitor which is approved for the treatment of moderate to severe Crohn's disease or moderate to severe ulcerative colitis.

These are very rapid-acting therapies in the clinical trials and in the real-world experience. Many patients experience symptom improvement within 1 day. Certainly by day 3, many patients can tell these therapies are working. They also work extremely well in the spondyloarthropathies, whether they're axial or peripheral. So for a patient who has IBD with joint pain, the number one extraintestinal manifestation, they're a very nice option. And if they have a separate diagnostic indication of inflamed joints, whether it's in their spine, their pelvis, or their peripheral joints, it's a very good choice as well.

Because these therapies work so well and bypass the challenge we have with proteins, they have also been studied in the patient hospitalized with severe ulcerative colitis, and there's emerging data to suggest they may be beneficial in that setting and may help us get control of patients with severe UC.

There are a number of things to keep in mind, however, about these therapies. The first one is that in a different patient population—patients with rheumatoid arthritis who had known cardiovascular disease—there was a study performed with tofacitinib comparing it to anti-TNF and led to the somewhat unexpected finding of venous thromboembolic complications and major adverse cardiovascular events in those patients. It ends up being that it was mostly people over 65 and those who were smoking cigarettes and some who even had previous history of venous thromboembolic complications. So there is a black box for the JAK inhibitors to consider that in our patient population.

Having said that, the label for upadacitinib has been updated more recently, and what we have learned from studying tofacitinib and upadacitinib in the IBD space is we have not seen those same risks among our patients.

Another thing we've learned about with these therapies is that inhibiting Janus kinase also affects lipid transport, so the lipids may go up in some of our patients by about 10%. However, interestingly, the low-density lipids, the high-density lipids, and the triglycerides go up in the same ratio that they are at baseline, so the cardiovascular risks are overall thought to be stable.

The risk that we do know these patients have when they're on these therapies is an increased risk for shingles, and so it is recommended that once you have someone on one of these therapies that they be vaccinated for varicella zoster. Having said that, that's a recommendation we have for other therapies within the IBD space, and this is not necessarily different, but it's very important since that can protect people from having shingles.

Finally, with our JAK inhibitors, the data on these therapies in women who are pregnant is quite limited, so it's been advised that we avoid them in women who are planning imminent conception or who are already pregnant. Having said that, the global consensus on pregnancy and IBD says that you can weigh the risks and benefits when you're considering using those therapies in pregnant women. In my own practice, I would consider using the therapy later in the second trimester after the very important first trimester is over, and it's something to keep in mind for your patients.

So to summarize, these are rapid and effective therapies that offer new mechanisms in our patients. We have options in both Crohn's disease and UC and importantly for patients with acute severe UC in the hospital setting. But we need to keep an eye on their lipids, we should vaccinate against zoster, and we should also keep in mind that there are warnings against the possibility of venous thromboembolic or major adverse cardiovascular events. But they have not been seen in the IBD population. And overall, in that one study with tofacitinib in RA, we believe that that was a very high-risk population and a different disease state.

These are therapies that have been very available now and effective for the patients who need them, and I want our colleagues to be comfortable recommending and using them.

Dr. Odufalu:
Wow, Dr. Rubin, thanks for that really thorough review of JAK inhibitors. And I really like that you touched on how rapid they work and especially in hospitalized patients. And so I remember when the first JAK inhibitors came out and they talked about really how quickly people saw symptomatic response. I was a little skeptical, but that's been shown across the board with patients that do respond in my practice.

And I think you touched on where we can position this therapy, especially in patients that are very sick who have low albumins because of their severe disease, that this might be a good alternative and really positioning that early on in the treatment course instead of waiting for maybe some other therapies when they are very, very sick.

Dr. Rubin:
Yeah, I agree with all those comments. I was equally skeptical when it first became available that it would work that fast, but I certainly have observed it myself.

I've also observed that I think upadacitinib may be a bit more effective than tofa, which is a bit counterintuitive since we think of tofacitinib inhibiting three of the Janus kinase isoforms, and upadacitinib just JAK1, but maybe it's a dosing thing. But regardless, we certainly appreciate that. The other dosing difference is, is that tofacitinib is generally dosed twice a day, although there is an extended-release once-daily formulation. Upadacitinib is once a day. Both drugs start with a higher dose for induction in their treatment of Crohn's disease or UC— tofacitinib just for UC. And then in maintenance we either continue that dose or we drop them to a lower dose in maintenance once people are doing well.

So we've certainly learned a lot about these. I think that they've been a game changer for many of our patients, and we should continue to think about how to use them effectively and certainly monitor people carefully.

Dr. Odufalu:
Great. Can we move the conversation to the next small molecule, S1P modulators, since this is another newer mechanism of action that we're using in the IBD space?

Dr. Rubin:
Sure. So the sphingosine-1-phosphate receptor modulators is the other new class of therapies that are small molecules, meaning they're also oral, but they have a different mechanism. And there are two drugs that are available in the US and increasingly around the world that specifically treat ulcerative colitis. We do not have an S1P receptor modulator for Crohn's disease.

The first one is called ozanimod, and the second one is etrasimod. Both drugs modulate the ability of activated lymphocytes to detect the signaling molecules called sphingosine-1-phosphates, and there's five different forms of the sphingosine-1-phosphates numbered 1 through 5. So there's a bit of a distinction between ozanimod and etrasimod in that regard, but they both generally target the activated cells that are going to be on their way to the bowel and have to do with inflammation in our bodies.

They are once-daily oral therapies, and the way they work is by preventing those activated lymphocytes from egress out of the lymph nodes in which they're made and where they're activated. So it's essentially a cellular-trafficking inhibitor that keeps those cells in the lymph nodes, and then they don't go to the colon. And actually, although some people think a cellular mechanism is slower than an anti-cytokine mechanism, the reality is that it works pretty quickly. Patients who respond to these therapies can usually tell within 2 weeks.

The nice thing about these therapies, in addition to being oral, is that they have a very nice safety profile. Unlike the JAKs that we just discussed, these do not have any black-box warning. And in the additional analyses of these therapies in patients with moderate to severe UC, it's been clear that they work better in patients with more moderate disease or after 5-ASA therapies have not worked, or certainly after 5-ASAs and a single course of steroids. And you don't have to have failed conventional therapies to get to these drugs, and you don't have to be thinking about downstream other therapies before you get to these therapies.

On the contrary, these are a perfect option to consider after a 5-ASA treatment trial in a patient, and I've even had a couple patients more recently who prefer this—taking one pill a day instead of getting started on four pills or an enema of their 5-ASA treatment.

Now, there's a couple things to keep in mind about these therapies that we want to make sure you understand. The first one is that by the nature of the mechanism, the circulating lymphocyte count in patients who are taking these drugs will drop. This is not a side effect. This is the effect of the medicine. So again, by keeping those white blood cells in the lymph nodes and they don't enter the circulation, you'll actually see the white count drop a little bit, and the lymphocyte count is the part of that that is dropping.

This does not drop to the level of infection. With both drugs and in all their clinical trials, there was not an increased risk of infection. Actually, when you look at the studies, the drugs were incredibly safe. There was a very low risk of adverse events.

The other thing to keep in mind is that one of the S1Ps—one that is not targeted by ozanimod or etrasimod—is related to cardiac conduction, and therefore you do see when you start these therapies a transient asymptomatic bradycardia in about 10% of the patients who start the therapies. Let me say that again: transient and asymptomatic. And it drops by only a beat or two. And the only reason we knew about it is because they looked for this off-target effect and they measured it in the clinical trials. But patients who start these therapies do not need to be on a monitor, and they don't even know that this is happening.

Ozanimod has a dose titration, so you get the first week, it starts on 1/4 of the dose, then 1/2 the dose, then the full dose. Etrasimod starts with the full dose once a day, and this is not a clinically significant problem. However, because of that, it is recommended that you get an EKG before you start therapy, or at least know that your patient's in normal sinus rhythm and that they don't have a second-degree heart block that you didn't know about. And I don't know about you, but the last time I saw a patient with second-degree heart block was when I was a resident rotating on cardiology. So I do check it, but I'm not overly worried about it.

The other thing that we've learned is that some patients have mild elevation of liver enzymes. This is not uncommon for many of our therapies, but that tends to resolve over time.

Similar to our JAKs, we just don't have enough data using these drugs in pregnant women. So it is advised that women planning pregnancy in the short term or who are pregnant are off the therapies, but they have a short half-life, and so usually you can stop etrasimod and within a week or 2 somebody can become pregnant if that's the plan. Ozanimod has a slightly longer half-life, but these are drugs that can wash out, and we're pretty comfortable with this.

There are no serious infections that are really reported, no opportunistic infections. This is not considered a systemic immune

suppressant, and overall these are very nice therapies. But again, they work better earlier in our treatment algorithm in ulcerative colitis, and they work better in people with more moderate disease than severe disease. So another important option for people to know about. And I've said for a while now that I think we're underutilizing this therapy.

There are other S1P receptor modulators that are used for multiple sclerosis. They're broader acting, but the neurologists often say that this is the safest therapy they have. And a couple of my colleagues will tease me and say, “Why aren't the GIs using this in many more patients?” So I think there's room for us to learn more about this and to offer it to our patients.

Dr. Odufalu:
Wow, again, thank you for going over the S1P class as well as the mechanism, and I particularly like your discussion on the safety. I agree with you. I think that this is definitely underutilized, and specifically in my young patients with mild-to-moderate disease where going to an infusion center or getting a self-injectable is a challenge sometimes, and in my older patients where sometimes dexterity is a problem, being on a pill is just easier versus being on infusion or a self-injectable. So thanks for touching on that.

Dr. Rubin:
Yeah, we haven't learned enough yet about extraintestinal manifestations with these therapies. My anecdotal experience with the patients we've treated with these therapies is that people who have arthralgias, if we control their bowel inflammation, the joints are usually better, so that's a nice thing to know. But people with inflammatory skin or joint problems, this is probably not the right treatment for those individuals.

I also just started a patient a few weeks ago on one of these drugs, and she had just been diagnosed with ulcerative colitis. So I went through, here's what mesalamine is, and you'll take four of these pills, and for now because you're having some urgency maybe we'll use an enema. And then I described the other option of being on an S1P, and I said it's one pill once a day and you might feel better within a couple of weeks. And she said, “Well, who would ever choose four pills and an enema over one pill once a day?” And in fact, just coincidentally, I heard back from her today that she's feeling amazing, and she's very happy with her choice.

So I think we can challenge what we've long done as long as you understand a bit more about the therapy and the safety and start thinking about how to get these to our patients.

Dr. Odufalu:
Awesome. Well, thanks for sharing that.

So with that, this has been a great bite-sized discussion. Our time is up. Thank you for listening.

Dr. Rubin:
Thank you.

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