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New Viewpoints in the Management of IBD

Announcer:
Welcome to CME on ReachMD. This activity, entitled “New Viewpoints in the Management of IBD” is provided by Prova Education.

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Dr. Nandi:
The 21st century has seen the advent of multiple novel steroid-sparing therapies in the management of Crohn's disease and ulcerative colitis. Patients may demonstrate variable efficacy depending on their unique IBD phenotype or may lose response over time. Fortunately, we are learning not only about how to best wield our existing armamentarium, but also how to exploit what we have learned in regards to new and emerging therapeutic targets currently under investigational study. In this program, we will review what are these newer targets? What role will these agents play in managing IBD? And most importantly, how do you select the right therapy at the right time for your patient? These are just some of the key questions that we will aim to answer here today.

Welcome to our discussion on New Viewpoints in the Management of IBD. I'm Dr. Neil Nandi, and I'm joined today by distinguished IBD specialist, Dr. Russell Cohen, Professor of Medicine at the University of Chicago. Welcome to the program, Russ.

Dr. Cohen:
Thank you, Neil. It's a real pleasure to be here with you today.

Dr. Nandi:
We're very privileged to have you. Russ, we currently recognize that lymphocytes communicate the pro-inflammatory cytokines and that many of our current and emerging therapies aim to block and/or antagonize this action. Can you please provide our listeners an overarching framework for how clinicians should categorize these different mechanisms of action and what this means for related emerging therapeutics?

Dr. Cohen:
Absolutely, Neil. You know, I think it's very helpful to think of these therapies as families. And each family has a different mechanism. Many, if not all, of the listeners are probably familiar with the anti-TNF family. Anti-tumor necrosis factor-alpha. TNF has been found to be a very important pro-inflammatory mediator for many diseases, and blocking TNF-alpha by various mechanisms of antibodies or fragments of antibodies, depending on the particular formulation, has been shown to be effective in both Crohn's disease and in ulcerative colitis.

A completely different approach, one which can be, you might say, more gut-specific and customized, is using anti-integrin therapies by selecting for the integrins that are involved with transmigration of the leukocytes into the gut or keeping them out of the intracellular space. There are available and investigational therapies that are looking at this unique family.

Many of us are familiar with blocking anti-IL-12 and 23 through the p40 antibody that's available for both psoriasis and Crohn's disease and now ulcerative colitis. There are some exciting breakthroughs more on the IL-23 blockade within this same family.

Oral JAK inhibitors, or Janus kinase inhibitors, hit the world a few years ago for inflammatory diseases, initially rheumatoid arthritis and now at least commercially available for ulcerative colitis and under investigation for Crohn's disease. These are very different in that they interfere with the signal transduction from the cell membrane after the receptor has been stimulated by whatever the cytokine is and then block the message getting to the nucleus and transducing the signal and eventually transcribing the protein.

S1P inhibitors have been breakthroughs in multiple sclerosis and now are under great investigational studies in inflammatory bowel disease. Their mechanisms, while these are oral therapies, are somewhat more complicated in that they cause modulation of the various receptors on leukocytes that are in the lymph nodes, preventing them from leaving the lymph node and then causing inflammation. And then finally, there are a few other areas that we may discuss later on in today's program.

Dr. Nandi:
I think that was a great way to go ahead and categorize in families, as you said it, the different types of mechanisms of action. We're learning how to exploit different pro-inflammatory cytokine pathways. We know that it doesn't always work. In the case of exploiting IL-17A monoclonal antibody with secukinumab, we know that can sometimes promote or exacerbate ileal disease. But we know that we have learned quite a bit from what are the most promising mechanisms for our patients with IBD. I'm hoping that we can review each of them in further detail.

So can you please enlighten us a little bit more on some of the real-world data on the efficacy of ustekinumab, the IL-12/23 inhibitor, but also perhaps reference some of the other agents that are related, that are upcoming, that are focused on IL-23 alone, namely risankizumab and guselkumab?

Dr. Cohen:
Absolutely, Neil. You know, it's fascinating. So IL-12 and 23 have the same p40 subunit. Ustekinumab is actually an anti-p40 antibody. It binds to both IL-12 and 23 through the p40 subunit and prevents inflammatory signals from potentiating down into the immune system. Now what's interesting is that one of the main mechanisms is felt to block IL-17, but as you mentioned, if you block IL-17 directly in inflammatory bowel disease, it may have undesirable effects. So it maybe goes to show that we don't understand these things as much. Now breakthroughs in psoriasis have shown that the IL-23 blockade through the different subunit, the p19 subunit, is certainly the more successful approach in psoriasis and maybe so in Crohn's disease. So the investigational ones that you mentioned already risankizumab, guselkumab, as well as a number of other ones that are working through clinical trials, target the p19 subunit of interleukin-23. What we're hoping, and so far seeing, is that the safety profile of the anti-IL-12/23 ustekinumab, and these anti-IL-23 blockers are not only efficacious, but also very, very safe.

Dr. Nandi:
It's pretty fascinating how far we've come along, graduating from just IL-12/23 blockade to only IL-23 blockade. Like you said, we don't know everything, all these crazy negative feedback loops in the immune system that we're learning to better manipulate. That was a perfect summary.

Let's turn our attention to therapies that actually target leukocyte migration. Whereas cytokines can help leukocytes communicate with one another, leukocytes must still physically migrate along arterial highways, if you will, to the intestinal bed to cause that inflammation. What can you tell us about some of these anti-integrins?

Dr. Cohen:
Well, Neil, you know, the way I describe it to my patients is imagine you're sitting in the clinic room and there's a hallway. The hallway outside my room is the blood stream, and each room is a different organ. The room we're in is the gut room. The next room, the cardiologist's in is the heart room; the next room is the pulmonologists, the lung room. Well, the way that these anti-integrins, such as vedolizumab work, is they block the white blood cells from getting out of the bloodstream into the gut selectively by blocking alpha 4 beta 7 integrin, which is pretty much on the gut exclusively with only small amounts in other parts of the body. As a result, it's as if the door to my room is locked while the white blood cells in the hallway could easily get into the heart room or the lung room. Let's say a patient had a pneumonia or some other infection outside of the gut, their white blood cells would not be prevented from going there. As a result, it does not seem to be as a systemic immunosuppressant. And the safety trials so far have actually proven that to be the case. Vedolizumab is commercially available, approved for both ulcerative colitis and for Crohn's disease. We're looking also at some experimental similar medications that block these type of mechanisms. Etrolizumab, for example, blocks the beta 7 subunit. So while it will block the beta 7 that's seen on alpha 4 beta 7, as with vedolizumab, it also blocks alpha E beta 7, which may be responsible for retaining the white blood cells in the intraepithelial space. In other words, if you block it, the white blood cells can't stay in the epithelial space. They have to leave. And as a result, you might have a double-barreled way of blocking inflammation.

Dr. Nandi:
So this is fantastic because it sounds like our treatments, at least along this modality of lymphocyte trafficking inhibitors, is getting a little

smarter, right? We're getting more gut-specific as this research carries through.

For those just joining us, this is CME on ReachMD. I'm Dr. Neil Nandi, and I'm here today with Dr. Russ Cohen. We're discussing current and emerging therapies to manage inflammatory bowel disease.

Now, Russ, the first small molecule to market in the IBD space has been JAK inhibitors tofacitinib, which you mentioned earlier. Can you please review some of the OCTAVE clinical trial data and call upon any real-world efficacy data for tofacitinib as it relates to ulcerative colitis?

Dr. Cohen:
Absolutely. So tofacitinib was the first JAK inhibitor approved for inflammatory bowel disease, and it is effective in patients with ulcerative colitis. This trial is done in moderate to severe ulcerative colitis. And one of the nice things is that it does show efficacy in patients who have failed an anti-TNF, which not all the other investigational drugs do very well in those patients. As an oral agent, it may be more appealing to patients. It does not have to suffer from the problems that may occur with immunogenicity, with starting and stopping therapies, which has plagued us, at least with the anti-TNF agents. And while it is an immune suppressant, since it is an oral agent, it can be easily stopped rather than, let's say, an IV drug that you gave and has to be given 8 weeks later; you may have 8 weeks of drug on board that you might not want. So for those reasons, it's good. Unfortunately, the clinical trials in Crohn's disease failed, so we're looking towards investigational members of the family. So investigational agents such as upadacitinib, which is already available for patients with rheumatoid arthritis, is being studied in Crohn's disease and ulcerative colitis. This is a JAK-1 selective agent which may have a better safety profile, or may not, and may have better efficacy, or may not. We'll find out as we move along. Filgotinib is another JAK-1-specific agent that is also going through clinical trials. The idea being that if you are more specific for the JAK-1 rather than a pan-JAK inhibitor, as tofacitinib, you may have lower levels of toxicity, but the proof is going to be in the pudding when we get the final results.

Dr. Nandi:
So yes, these new agents are more selective JAK inhibitors. So far we've covered 3 monoclonal antibodies that we call biologics which are each approved for ulcerative colitis and Crohn's disease. And we've covered 1 small molecule – a commercial molecule, tofacitinib – only approved for ulcerative colitis. We have another exciting mechanism of action to discuss, which are the sphingosine 1P, or S1P, receptor modulators such as ozanimod and also etrasimod. What have we learned thus far about the current efficacy of these agents from investigational studies?

Dr. Cohen:
Well, the first S1P on the market for MS, multiple sclerosis, was fingolimod. Now it has been joined by 2 others, siponimod and ozanimod. Most recently, ozanimod has been well studied for inflammatory bowel disease. It is an oral agent and as an S1P phosphate modulator, it is felt to be one that you can use in someone who already has MS, unlike patients who are on anti-TNF therapies. You can't use them in MS patients. And it may have some of the other benefits I mentioned for an oral agent of not having immunogenicity problems, being able to stop the medicine, and having the immune effect wear off quicker than perhaps some of the other agents. There are some more specific S1P inhibitors that are under investigation right now similar to – as I mentioned before, it remains to be seen if these are things that will advance – and such as etrasimod, which blocks the subreceptors 1, 4, and 5. And there's another, amiselimod, similar as well, too. We're hoping to be more specific. They may have better efficacy and lower toxicity.

Dr. Nandi:
You know, this is phenomenal because it's nice to know that we have so many other molecules in the pipeline. It wasn't that long ago, 6, 7 years ago, where we only had 1 type of therapeutic agent. But now we have 4 different commercial options, which is exciting for our patients. At the present time, in 2021, how do you position these biologics and small molecules in terms of treatment or choosing the right treatment for our patients?

Dr. Cohen:
Well, it's a great question. So the first thing you can do is cheat. If someone already has another inflammatory disease that there is FDA approval for, then go with that. So if someone already has rheumatoid arthritis or psoriatic arthritis or psoriasis or MS, then you would choose the agent that not only covers that indication, but also covers their inflammatory bowel disease. Another factor may be, well, do they have any contraindications to one of the therapies? I mentioned patients who have MS cannot get anti-TNF therapy, so you would not be choosing that. There may be some other contraindications that also may impact. Most of these medicines the biologics, are IV or shot formulation, while the orals are pills. So patient compliance, patient insurance coverage is very important, particularly patients who are on Medicare, where there's a difference with coverage for IV infusions and injections that are administered by healthcare provider compared to those that one gives themselves. So balancing out who the patient is, what other conditions do they have, believe it or not, where they are. If they're in the United States, their insurance coverage may actually impact your choice.

Dr. Nandi:
Absolutely, and you know what you're also illustrating there, it's multifactorial in the decision, but it's also shared decision-making is critical to helping to find out what's the right treatment at that time for the patient. Now, Dr. Cohen, this has been a fantastic synopsis of not only the available therapies that we have today, but of the exciting emerging therapies that are most promising on the horizon. Before we wrap up, do you have any takeaway messages you want to leave our listening audience?

Dr. Cohen:
Absolutely. You know, these therapies are, for the most part, very safe and effective therapies. They're far safer than steroids. And it's very important that we move patients away from steroids and completely off of steroids onto these exciting biologic or novel small molecule therapies.

Dr. Nandi:
Thank you very much. Folks, that is our program. I want to thank our audience for listening, and I want to offer a sincere and special thank you to my colleague, Dr. Russ Cohen. We truly appreciate your time and your commitment to educating our IBD community.

Dr. Cohen:
Thanks, Neil. Thank you so much.

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