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Emerging Therapies in UC

Announcer:
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Dr. Nandi:
This is CME on ReachMD, and I’m Dr. Neil Nandi. I’m here with Jean-Frederic Colombel, and together we will explore newer and emerging classes of agents and what role they will play in the management of ulcerative colitis.

Welcome, Jean-Frederic.

Dr. Colombel:
Welcome, Neil, and thank you for having me today.

Dr. Nandi:
Jean-Fred, we know that over time, many of our patients will benefit from an anti-TNF, but there is a substantial number that may lose response over time or not be primary non-responders for first-line therapy. Can you give us a brief overview that, beyond anti-TNFs, what are the new, emerging agents that are coming? What’s coming down the pipeline? What’s available now?

Dr. Colombel:
So in brief, following the anti-TNF era, there were, first, development of new biologics. And further, anti-integrin therapies like vedolizumab, which is still the most advanced treatment in this class. And then there were some studies about etrolizumab and abrilumab and ontamalimab. But still, the only one which is approved is vedolizumab, and we’ll, be talking about the positioning of vedolizumab, I guess. And then following the approval of ustekinumab, which is an IL-12/23 antagonist, we are seeing now the development of specific IL-23 blocker, which is also amazing. And there are several drugs in development not yet approved: risankizumab, brazikumab, mirikizumab, guselkumab.
And, what I think, frankly, is the most exciting, maybe, is the advent of new, small oral molecules. The first one is, of course, JAK inhibitors, and the first in class which is already approved for ulcerative colitis is tofacitinib, but we have great data now with more specific JAK1 inhibitors that we will be talking about, and a fascinating new class of adjunct, which are the S1P receptor modulators. One is already approved, which is ozanimod, and others are in development, such as etrasimod. So again, very exciting time, but little bit complex.

Dr. Nandi:
You mentioned S1P receptor modulator ozanimod that was recently FDA-approved. Can you please expound upon this, because this is still a relatively new agent to most gastroenterologists. Why is this class so intriguing for our community clinicians?

Dr. Colombel:
It’s very intriguing because it’s completely new, Neil. And so what’s the story? So S1P, which is for S, sphingosine 1-phosphate, was

originally discovered because it was expressed on endothelial cells. And then following the discovery of the first S1P receptor modulator, fingolimod, which is used in the treatment of MS [multiple sclerosis], we realized that actually it's also expressed on the lymphocytes, and then the excitement was growing.

So how does it work? There is a gradience of S1P from the blood and the lymph to the tissue, with higher concentration in the blood. And the cells which are expressing S1P receptors, such as lymphocytes, are thus following this gradient. So they are egressing, for instance, the lymph nodes, to enter tissues following this gradient and then causing inflammation and tissue damage. So the principle of modulation, which is S1P receptor modulator, is that they are leading to internalization of this receptor, meaning that the cells can't move anymore. They are trapped in the lymph node, and following this reduced egress, there are less circulating lymphocytes and then decreased inflammation and tissue damage. Very interesting with some important cells, which are involved in immune surveillance and not so much affected by this mechanism, such as memory T cells or natural killer cells.

So we need to understand that the S1P receptor – there are 5 S1P receptors, 1, 2, 3, 4, 5 – and they are ubiquitous. They can be expressed in many different parts of the body. And then the S1P receptor modulators are more or less selective. For instance, the ones that are of interest for us, ozanimod, is an S1P receptor modulator for S1P receptor 1 and 5, and then it's working in the gut but also in the brain, and actually it's also – it's already approved for the treatment of MS. The second one which is in development, etrasimod, is working on S1P receptor 1, 4, and 5, and it's currently developed in the treatment of GI disease and dermatological diseases.

Dr. Nandi:
When we think about prescribing ozanimod to our patients, what are some of the screening measures that we should take into account when embarking upon this medicine, and what is the monitoring recommended for this medicine?

Dr. Colombel:
You need to basically think about some very important points. First, S1P receptor 1 can be expressed in the heart, and it can lead to bradycardia. So meaning that you need an EKG before starting, and if you have any doubt about, for instance, some conduction disorders in your patient, you need to send the patient to the cardiologist. Second, S1P receptor 1 is expressed on endothelial cells, and then it can have an impact on the eye. And this is why, for instance, one possible side effect would be macular edema. So there are some ocular contraindications for the drug, such as, of course, macular edema, diabetes, and history of uveitis.

Dr. Nandi:
So, Jean-Fred, let's talk about efficacy. You know, what did the trials show in terms of efficacy for ulcerative colitis patients in ozanimod?

Dr. Colombel:
So the point that, first, the drug works, and it was shown in the phase 3 study – the True North study, which included both bio-naïve and bio-exposed patients. So I can give you basically the main result, which is clinical remission after induction, which was 18% after 10 weeks. And then maintenance, which is 37%. And this was, of course, statistically significant as compared to placebo. So this drug works, and there were a number of secondary endpoints, such as clinical response, endoscopic response, histological response, and mucosal healing, which were also met. So this drug is effective in the treatment of ulcerative colitis.

Dr. Nandi:
The data was excellent in terms of clinical response and remission and mucosal healing and steroid-free therapy. I want to kind of go into detail, though, about how to dose this medicine. There is an induction phase, but it's a pill pack that there's a slowly titrated dose and then the maintenance dose.

Dr. Colombel:
Why do we need to do that? In order to reduce the risk of bradycardia, to increase progressively the dose and so that you can progressively go up to the full dose, which is 1 mg daily. Then you are basically avoiding this risk of bradycardia. And then you will continue the treatment with the 30-day supply, but I think most of the problem may occur during the first week.

Dr. Nandi:
Now let's talk about JAK inhibitors, right? They're here to stay, and they've been proven to be effective therapies as well. Can you give us a brief overview of JAK mechanism of action but then review the current and evolving JAK therapies?

Dr. Colombel:
Again, I'm – so it's a little bit complicated. So, you know, JAK – so Janus kinase, they are tyrosine kinase, and basically what they do, they regulate the pathways, signaling pathways in the cells. So there are basically 4 JAK, so 4 tyrosine kinase – JAK 1, 2, 3, and TYK2. And what the JAK inhibitors do, they are binding to JAK, and basically they block the transduction of the signal from the surface to the nucleus. And then following JAK activation, there are a lot of pathways which are activated and which are blocked by a JAK inhibitor.

And depending on what JAK you block – JAK 1, 2, 3, or 4 – you will block a different function. For instance, if you are targeting JAK 1 and JAK 3, you will have an impact on maturation of lymphoid cells, homeostasis of T cells, B cell class switching, and inflammation.

Dr. Nandi:
And I think that's an interesting point, right? And I want to talk about safety of the JAKs in general, but I think to recap, you're illustrating that the different selective inhibition from one JAK inhibitor to another – for instance, tofacitinib or upadacitinib – may result in potentially different efficacy and safety profiles.

So let's talk about the JAKs, because that's gotten a lot of press recently. What are the key safety concerns of the JAK inhibitors so far, that we know of?

Dr. Colombel:
Let's start with what we saw in the upadacitinib development trial. You know, it's a phase 3, where there were 2 induction trials and 1 maintenance trial. What are the safety data? So we clearly saw a signal for increased risk of herpes zoster, and you know that, actually, we should vaccinate our patients – all our patients, actually, with the zoster vaccine. There was also – this is clear and a signal for an increased risk of DVT, of deep venous thrombosis. But in the clinical trial, there was no evidence of increased risk of serious infection or malignancy. And of course, I'm pretty sure you have seen this New England study comparing tofacitinib with anti-TNF. It was a noninferiority trial looking at safety over 5 years in patients with rheumatoid arthritis [RA]. And I'm talking about tofacitinib now. And the noninferiority was not actually met because there was a clear signal for an increased risk of a major cardiovascular event and concern associated with tofacitinib. So what was the consequence of that? The consequence is big, because then the FDA issued a black box warning, meaning that this drug has to be positioned not only after arthritis, but also after anti-TNF. We still don't know in IBD [inflammatory bowel disease] if the same will apply for upadacitinib, but in RA, the black box has been extended to JAK1, so upadacitinib functions as the same black box as tofacitinib in rheumatoid arthritis.

Dr. Nandi:
A lot of our tofa safety data, as you said, it takes years for us to amass enough clinical real-world observations to inform ourselves of true real-world safety and adverse event profile. But a lot of our data comes from RA literature, but conservatively, you know, we are gathering, you know, prospective long studies in UC-specific patients, but we have to be mindful and conservative with what we see from the RA patients and how we apply it to our IBD patients.

You know, in terms of monitoring response to therapy, our mantra in 2022 is treat to target and utilizing noninvasive markers and, you know, global assessment of how the patient's doing and, of course, endoscopic monitoring. Are there any other pearls or tips that you would share with our audience in terms of monitoring their response?

Dr. Colombel:
So far, according to the guidelines, we should target clinical and endoscopic remission. Histology is still in discussion. So once you have achieved this state of deep remission, then you can monitor the patient. And the monitoring path is very important. How do you monitor the patient? Of course you monitor based on symptoms. So blood is a red flag. And then there are of course biomarkers that I am using in clinical practice. Not so much CRP, which is not very reliable in UC, but calprotectin. So when you are doing your follow-up colonoscopy, you measure the calprotectin, which is associated with a state of deep remission. This is your baseline level, and then you can monitor your patient with calprotectin like every 3 months. And if the calprotectin is staying low, that very often means that the patient is still in deep remission – clinical and endoscopic.

Dr. Nandi:
Jean-Fred, thank you so much. We covered a lot of information – a lot of exciting information, in this episode. Before we conclude, are there any last take-home points that you want our clinicians there to know?

Dr. Colombel:
Yeah, so we didn't discuss positioning. It's still difficult to know, you know, because positioning is based on the efficacy, safety, convenience, and cost, of course. So very often, we are not the only one deciding, and we still don't have the level for some drugs such as upadacitinib. There is a lot of interesting personalization, you know, knowing which patient would respond to which drug, and there is an increasing interest in combination. I think the vedolizumab is a good drug as a first line. And then when the patient is failing, then you have a lot of choice.

As far as S1P, we still don't know. I think it's a good drug. So far, very often it's not positioned first line, but depending on the safety data that we will get in the future – not only with ozanimod but also with etrasimod – maybe this drug could be positioned actually before the biologics because of efficacy, safety, and convenience. You know, I think for our patients to be able to be treated with a pill once a day, this is a great advance.

Dr. Nandi:
Dr. Colombel, I appreciate you so much on this program. Thank you so much for joining us, and I really think that our listeners are going to leave excited to provide new medications for all of our patients.

Dr. Colombel:
Thank you, Neil.

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