Clinical Conversations: IBD aims to provide healthcare professionals with practical information on implementing evidence-based, guidelines-recommended care for patients.

In this podcast, we'll hear from internist Dr. Doron Schneider, Chief Patient Safety and Quality Officer for Abington Health, and gastroenterologist Dr. Sunanda Kane, Professor of Medicine at the Mayo Clinic.

DORON: Good morning. I'm here with Susie Kane, gastroenterologist from the Mayo Clinic. Welcome, again, Susie.

SUSIE: Well, good morning. Thank you. Welcome to you too.

DORON: Thank you very much. We're talking about inflammatory bowel disease and we're at the stage in this conversation where our patient has been referred to you and you've worked them up and have made a diagnosis of inflammatory bowel disease. Again, for this conversation, it's Crohn's or ulcerative colitis. At that point, there's a need to select the right agent for that patient. And I think for the primary care community, this is going to be very helpful for us to understand not only how you select which medicine, but how we can really work best with you to make sure that patients are adhering to their medicine and we can safely co-manage this patient together.

Let's start perhaps with that very first selection. How do you do it? Within the primary first care world, we certainly know steroids. We know that there are immunomodulators that have just exploded on the scene in the last decade and some of this is relatively new to us. Walk us through that process. How do you approach the newly diagnosed patients with IBD?

SUSIE: Right, so I appreciate the opportunity and I could give an hour lecture just on this topic alone, so I'll keep it at a really high level, not to confuse anybody, but to sort of giving you the ten-thousand-foot approach to this. So, we'll keep the conversation at this point limited to Crohn's disease because ulcerative colitis is really a different diagnosis. There are certainly medications that overlap and can be used for either diagnosis, but I think that the nuancing is much more prevalent for Crohn's disease.

The first thing that we do is we assess the location of the disease because that's going to drive the need for certain therapies over others – and why do I say that, if it involves two different organs? So the colon and the small intestines, that's a patient who's at greater risk for complications like fistula formation or stricturing and so we want to be more aggressive. The patient who has involvement with just one organ, meaning just the colon or just the small intestines, that you might have a little bit more wiggle room. So, you need to decide what the location is. If they have upper Crohn's disease, in the esophagus or the stomach or the duodenum, then actually you're going to trigger that location differently than the more distal GI tract and actually, acid suppression is usually how we treat the upper Crohn's disease.

Once you know your location, then you have to decide are they mild, moderate or severe. We have standard criteria for those definitions. But basically, from a clinician's standpoint, mild means that there is not any significant anemia, that they have symptoms that are not life altering per se, that they can still work fulltime, that their bowel habit is manageable without antidiarrheals, that they are not losing weight, and that they are not at risk for deep penetrating ulcers and complications.

The moderate patient is a patient who may be cutting back on their activities of daily living. They're losing productivity at work because they're missing days because of their symptoms and that you're already thinking, "Oh, goodness, this person is fairly sick and they need help."

And then the severe Crohn's disease patient is the one that we historically think about and we see in the textbooks, who are emaciated, who may already have a fistula either around their perianal region or even intracutaneous, that they are clearly malnourished, they may be febrile, they have extraintestinal manifestations and are people who are usually on either supplemental feeds or are in the hospital, who may be headed for the operating room.

DORON: Let me stop you there. That's very helpful. So, you really want to look at the disease activity. You want to look at symptoms. Make your decision-making about those. My understanding also is that we're moving to also thinking about suppressing the inflammatory response. So help us understand too in the context of, you've got the patient who's presenting with symptoms. Are you looking at inflammatory markers to help guide your thinking early on, somebody with milder symptoms, but very, very high inflammatory markers? Do you think about them differently or are we still pretty much focused mostly on symptoms?

SUSIE: That's a really good question because we do need some sort of objective criteria by which to monitor the patient for a response or worsening. And so absolutely, a CRP can be very helpful at the outset of your initiation of whatever therapy you're going to choose. A CRP at baseline is a nice objective marker that you can follow over time. You don't do it too frequently, but if it's an outpatient, every month or so, making sure that the CRP is dropping because you want it to control that inflammation. So that is a very good point. Yes.

DORON: I wonder if it's somewhat analogous for us in the primary care world to think about treating a target as it relates to diabetes for example. So, with our diabetic patients, no matter how they are feeling, we want to get their A1C down—some would say down to 8, some would say down to 7. There's argument about the right endpoint, but we know that there's a marker. So, is this somewhat analogous at this point given the range of symptom presentation? Are you treating, and we'll get to which agents here in a second, but are you treating towards trying to get to a particular target inflammatory level?

SUSIE: Yes, and I think that's a really good point. I like that analogy. I hadn't heard that one before. So yes, I would say that CRP could be analogous to that hemoglobin A1C, that you want it to be normal. Having said that, there are a couple of other markers that you can follow. So, the hemoglobin. Is it stabilizing? Is it increasing, meaning that you are stemming the loss of blood and allowing the body to then remake red blood cells and actually keep them in circulation? And then albumin. Is your albumin going up, meaning that you were actually absorbing the calories and the protein that you're ingesting and not losing them? So I think that there are a few different markers that are objective that you could follow and feel pretty confident that you're on the right track.

DORON: I'm wondering if that helps you at all with really looking at adherence as well for some of the regimens we're about to talk about. You probably have some expectation of some reduction in inflammatory markers in some of the meds that patients are taking and if they're not taking it, you may see that there's lack of movement in inflammatory markers. I know that we do that within the diabetes world and the blood pressure world. Things that we treat in a primary care space. Does that analogy extend to these agents as well to a certain extent?

SUSIE: That's interesting that you say because as we talk about immunomodulators, which historically have been the only class of therapy that we had prior to the introduction of biologics. So, if we talk about immunomodulators, these are agents that work on the DNA of the white blood cells and that's how they impart their anti-inflammatory mechanism. And so, you are suppressing the immune system in that way and an immunomodulator will cause a reduction in the white blood cell count, and it will also cause a macrocytosis. So, you can actually use a CBC for tracking adherence because you would expect the white cell blood count to hover around four or five and cause a relative glucopenia and you would expect an elevated MCV and you would expect on the differential a decreased lymphocyte count; and if those are all present then you know that the patient is taking their immunomodulators, i.e., a thiopurine, because those are the known effects and expected effects on the bone marrow of that agent. So, it's actually a nice trick.

DORON: Right. So, with no further ado, now that we understand the analogy somewhat to conditions that we treat in the primary care world, help us then understand the different classes. You already spoke just a moment ago about immunomodulators and really the role of monitoring. What are the different classes and what do we really need to know about them in co-managing these patients with you?

SUSIE: So, I would break it down into three different categories for therapy, or actually, there are probably four. The first category is what we call the topical therapies, which mean those therapies that only treat the mucosa. So, the medication imparts an effect only at the local level of the mucosa and not the immune system. And so that would include all of the mesalamine products. So when you have inflammation in your colon, you don't necessarily need, if it's mild enough, you don't necessarily need to suppress the immune system. You can use a local affecting therapy like a mesalamine to treat that. And then there are topical steroids, in particular budesonide. So budesonide imparts a steroid affect topically, not systemically, and could be very effective in the short term for treating Crohn's.

Then we move into the steroid category with the systemic steroids, so, prednisone, prednisolone, and those are quick acting and basically shut down the entire immune system and will be very effective to treat active, inflammatory Crohn's disease. They are cheap, they are simple to prescribe, you don't need any prior authorization or any other paperwork, and you can get them from the local pharmacy. So, I do see where the partnership with the internist is important because if I'm not available as a gastroenterologist to our mutual patient who may be having a flare and then they call you, it's not unreasonable for you to say, "Well, gosh, you sound really sick, let's get you better right now," and that you prescribe prednisone. The understanding and the contract there is that, "Okay, I'm giving you a limited amount and that we need to just treat the active symptoms right now, but this is not a long-term therapy."

The toxicity of steroids far outweighs the benefits long term and so we always have an anticipated exit strategy once we put that patient on steroids. So, that should be the mindset for the internist as well—that's terrific that you're available and able to take care of those patients' symptoms right then because they need to get to work and feel better, but it's not a long-term treatment or solution. So, we do have to worry about if a patient is on even after just a week they're going to become adrenally suppressed. They are going to have issues with glucose control, with acute psychosis, with AVN, and longer term with hypertension, with cataracts, with glaucoma, and osteoporosis. So, just the systemic effect is great for the inflammation, but then also systemic toxicity.

The immunomodulators we touched upon, the thiopurines, which are oral therapies, which makes them super convenient. They are also inexpensive because they've been around since the 1950s and are effective. But the problems with immunomodulators is that it takes three to four months for them to kick in because they have to impart their mechanism of effect on the bone marrow. And so, you've got some short-term toxicity that needs to be screened for, and sometimes that patient isn't going to call the gastroenterologist. They're going to call their internist. And so fevers, arthralgia and pancreatitis, if they develop that abdominal pain, nausea, vomiting, they may be calling their internist rather than the gastroenterologist and so, hopefully, there's been a conversation between the internist and the gastroenterologist to say, "Hey, I'm putting this patient on an immunomodulator. If they call you with these three things, have them stop it immediately because these are all reversible side effects."

And then the other immunomodulator in that class is methotrexate. Methotrexate can be a pill or it can be a shot. And so, it can be confusing if the patient calls you and says, "Well, I am taking these shots and they're not working" or "I'm having some sort of a reaction," and if they're not savvy enough to know that it's not an injectable biologic and it's just methotrexate, there can be some confusion in the kind of conversation you need to have.

So, I circle back again that hopefully, the gastroenterologist is doing their due diligence of having that communication and conversation with you so that you can anticipate what it is that that patient may complain of and what we should do about it if they call. Clear as mud, right?

DORON: It's extremely important, extremely helpful. I think that really what you've walked through so far is that the topicals, the steroid class, and the immunomodulators are that each one of them has its own immediate few toxicities longer term and impact on chronic health. I would simply offer that having clarity of communication in the consults that are coming in back and forth is an opportunity for all that are listening to consider, can we do better? So, simply putting a patient on a med without having clarity about the indication, the expected side effects, when to prompt a call to the GI doctor versus a PCP. All of that can really be part of the best kind of consult that would come from the GI doctor to the primary doc. And to bring that forward to the patient as well to make it exquisitely clear that these are the triggers, these are the red flags that should prompt a call to your doctors. I think I just wanted to highlight that because each one of these drugs is powerful, each one has its own set of issues, and the better we can partner with patients and really build a medical community around that patient is our opportunity.

SUSIE: I couldn't agree more.

DORON: Did you want to move into the next class—the bigger guns that are now in the biologic space? Tell us about them. What do we need to know?

SUSIE: Sure. So, of course, biologics are advertised on television now. So, I will use brand names and mention Humira, which is an injectable, Entyvio, which is IV and now Stelara, which is an IV dose for a one-time induction therapy and then it's injectable after that. In the late 1990s, the only biologic, and the first biologic class that came out are called anti-TNF agents. So TNF, or tumor necrosis factor, is a very potent proinflammatory cytokine and it was first discovered to be a protein that was produced by tumors and so that's how it got its name. But having said that, the body without having a tumor in it produces this marker. It's somewhat of an unfortunate nomenclature issue because patients will get very nervous and say, "I have a tumor? You didn't tell me I have cancer." But tumor necrosis factor is a factor that we make on our own. It was just initially described in rats and then in people who had tumors were making the protein. So, having said that, these are agents that are meant to block the activity of necrosis factor, which is a very potent pro-inflammatory agent and revs up the inflammatory environment, and because that's so non-specific that's why the anti-TNF agent, whether they are IV or whether they are injectable, treat a whole host of conditions—so, rheumatoid arthritis, psoriasis, psoriatic arthritis, ulcerative colitis and Crohn's disease, and ankylosing spondylitis. So, a lot of itises because of its very non-specific nature and it makes a very nice target as an inflammatory agent to go after. So, we had back in the late 90s the anti-TNF agents. Very well studied because they've been around for such a long time and very effective.

The things that I think an internist needs to know about anti-TNF agents is that one, that they do treat a myriad of different inflammatory conditions that range both GI and rheumatologic and now dermatologic worlds that really the side effect profile comes from the fact that these are biologics, meaning that they are proteins and not chemicals. So, anytime you introduce a protein into the body, that recipient or that patient can develop antibodies to that protein and have immune reactions or allergic reactions, or else build what we call neutralizing antibodies so that it basically makes the therapy inactive and no longer efficacious. So, immune phenomenon and then infection. So, if we are suppressing a major part of the immune system in order to get it to shut off to see the effects that we want, you're going to be at risk for infection and there are certain infections that are more prevalent and so that is TB and reactivation of hepatitis B and then certain viruses and funguses. So, not so much the bacterial infections, but the viruses, the fungus, and the TB. That's why it's so important for there to be updated vaccinations before we start these agents as well as annual flu shots. Now that we've got a non-live, non-attenuated shingles vaccine that's just really been a real game-changer in terms of getting our patients vaccinated for the preventable infectious diseases. I'm going to stop a minute, catch my breath and let you ask me questions.

DORON: How wonderful. It sounds like the biologics, there are multiple classes. You walked us through the history back in the late 90s with the TNF agents. Those are the infliximabs, adalimumabs, etc. Clearly, they do modulate the immune system so you're going to have a risk for infection, TB, hepatitis. This is critical for us in the primary care level to know this and to make sure that when patients are presenting with a fever that is on these agents, we take them extremely seriously. Just stopping there, the other classes of immunomodulators, are they any different just as it relates to the immune effects for suppression of the immune status? Can we lump them all together in a broad brush for the primary care community or are they in some way different as relates to their likelihood to lead to infection and other side effects?

SUSIE: Right. So, I think in a broad stroke, yes. With immunomodulators you're worried more about viruses and fungus, so those things that are not necessarily bacterial driven where antibiotics are needed. And so the important teaching lesson there is that, when a patient presents with upper respiratory symptoms that more than likely if they are on an immunomodulator biologic, it's going to be viral induced and not bacterial. And so, you really want to be prudent with giving these Crohn's patients antibiotics because they would be more at risk for C. difficile at this point, and just the GI effects of antibiotics in and of themselves can lead to just worse symptomatology.

But I will say that, you know, as we talk about the other two classes now with biologics, Entyvio, which is an alpha anti-integrin so it works differently than an anti-TNF. That could put you more at risk for certain kinds of viruses and that includes—and that's why the patients hear on the TV commercial certain brain infections, so that's PML or progressive multifocal leukoencephalopathy caused by the JC virus, and it's because what you are doing is disrupting the attachment of the white blood cells to the mucosal layer and when you do that you are disrupting other pathways that would set up this virus to get through into a place where it's otherwise been protected against. Particularly in the multiple sclerosis patient who get this biologic to treat their neurologic disease. It's a similar mechanism of action for Crohn's and, in theory, there is a risk for this brain infection. We have not seen it in the use of Entyvio. But its cousin compound, Tysabri, it is

a known potential side effect. So, from a medical-legal standpoint, the company has to say, "Well, this agent works like Tysabri and so there is this theoretical risk." That discussion is held with the gastroenterologist, and for reasons that are evident if you're not able to explain this properly, the patients don't want that therapy. However, if they are on Entyvio, the two things that we ask primary care physicians to watch out for actually are elevated liver enzymes and any kind of new neurologic symptoms that may develop, and that would be a trigger to do a workup to look for this possible mechanism.

DORON: So, let me just break that down for us. What you said is that for immunomodulators, patients are more at risk for viruses, so don't treat with antibiotics for bronchitis, for example. That's a very nice pearl. Anti-TNF agents and anti-integrin agents, patients are at risk for reactivation of TB. So annual TB testing would be of value. For the anti-integrin, really focusing on the neurologic systems for signs and early manifestations of PML and then liver functioning testing. So, I'm assuming that there is periodic monitoring that is going to need to be really discussed amongst the primary and GI doc as to who's doing what. Can you give us a sense if that's quarterly, every six months, and what is the blood work when you're on either an anti-TNF or an anti-integrin agent that we should be making sure that the patients get?

SUSIE: Right, right. So we discussed briefly the utility of a CBC and a sed rate. So, when you feel comfortable that the patient's symptoms and disease are under better control, then you're talking about monitoring their blood work. I think, for simplicity sake, we just recommend that for any agent that they're on, every three months they get a CBC and they get a comprehensive metabolic panel because that's going to show us their electrolytes and it's going to show us their liver enzymes and their albumin level. So every three months.

So the newest class of the biologics. So, in my career, I have seen us go from no biologics to now we have three classes of biologics. The newest one on the block, which is advertised, so I do think it's worthy of discussion because we watch television once and a while ourselves, so we need to understand what's out there. So there's Stelara, which is ustekinumab, which is yet another mechanism of action and it blocks interleukin now as opposed to TNF or working at the level of the mucosa lining. So, again another blockade of pro-inflammatory cytokines, but different than TNF so it's a little bit more targeted. And Stelara is FDA approved for psoriasis as well as for Crohn's disease. It's injectable and it does appear to have a little bit of a safer side effect profile than the anti-TNFs only because it is less global, if you will, but we still recommend that there are vaccinations before and then annually for influenza, and that there is monitoring of the CBC and liver enzymes every three months.

I forgot to mention that compelling argument to use Entyvio is that it is GI specific. So, I mentioned that the anti-TNF agents are very broad in their spectrum and Stelara is used for psoriasis and Crohn's. Interestingly, Entyvio only works at the level of the GI tract because it's the anti-integrin layer. So, it's the barrier function of the GI tract where this is targeted so it only works on the GI tract. So, you can't get it to use for psoriasis or rheumatoid arthritis. It doesn't work. It only works on the GI tract.

DORON: So, what a whirlwind in the last 20 minutes we were able to go over multiple classes. There's topical, there are steroids, immunomodulators. Now, there are three different classes of biologics.

Can you say, just in wrapping up, the importance of aggressively treating this disease? I do understand there are emerging data that suggest that the more that we use steroids early on and don't get people transitioned to some of these agents, their risk goes up for future strictures, fistulas, surgery, and other bad stuff to happen. So, really making sure that the GI doc is as aggressive as necessary and that the primary doc is ensuring follow up with the GI doc. It is increasingly important for us to get patients on the right agent given the data that's emerging about the overall impact in the quality of life and the complications. Can you, maybe in just thirty seconds or a minute to summarize that for us as we end this section?

SUSIE: Right. Yeah, so I thank you so much for bringing that up that it is so important for the partnership to be there because the messaging has to be the same. That as the primary care physician, that you guys understand the importance of early and aggressive treatment when appropriate because the patient doesn't understand that if they don't do this, that three years from now they're going to have a stricture and they're going to need an operation. As a gastroenterologist, I can say this, but they have an established relationship with you and if you can say, "Hey, you know what, Dr. Kane has prescribed this and I agree with that because…" and emphasizing and messaging the same points is so key.

DORON: Susie, thank you so much. What a great overview of the landscape of options that we have for our patients with IBD for us this morning, in particular, the focus on the Crohn's patient. So, we'll leave it there. Thank you very much.

SUSIE: Well, thank you it's been great.

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