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Achieving Long-Term Success in the Management of IBD

Announcer:
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Dr. Nandi:
Can we achieve remission and improve long-term outcomes in IBD? The answer is an emphatic yes. With a proactive treat-to-target strategy, we can make that difference.

Welcome to our discussion on Achieving Long-Term Success in the Management of IBD. I am Dr. Neil Nandi, and I'm joined today by Dr. Gary Lichtenstein, distinguished professor of medicine at the University of Pennsylvania. Welcome to the program, Gary.

Dr. Lichtenstein:
Thank you, Neil. It's an absolute pleasure to be here today with you. I look forward to our discussion.

Dr. Nandi:
Gary, I'm glad you could join us. We both know that ulcerative colitis and Crohn's are lifelong illnesses that are currently without cure. However, thanks to novel biologics and small molecule therapies, we are finally beginning to demonstrate that we can heal the mucosa and impact both quality of life and potentially decrease complications such as intestinal cancers and complications that require surgical interventions. Whereas some patients may be committed to life with prednisone, many are benefiting from immunotherapy. In this context, clinicians are continuously asked what are the cumulative lifetime risks of being on immunosuppression for their patients? What's your take? And how do you approach this conversation with your patients?

Dr. Lichtenstein:
That's a very important question that we deal with on a daily basis. And whenever assessing something directly, we have to say, what's the alternative? What's the benefit? What's the risk? The disease progressing, we recognize, Neil, is a very bad outcome. So we have to look at this in the context of malignancy, infection, complications, morbidity, and mortality. And we recognize certain things. Severe disease activity is a higher mortality. Use of agents such as corticosteroids may increase the death rate and severe infectious complication rate. So given these are our “enemies,” we look at therapies that alter these and lessen the use. And we'll talk about that more in the near future.

Dr. Nandi:
I think that's really great how you phrased that. You talked about broad immunosuppression, such as with corticosteroid therapy versus a more targeted approach with our newer agents. You know, with the advent of anti-TNF therapies, which was a miraculous turning point for all our IBD patients, that was truly revolutionary in how we treated or managed these patients. And it was more focal immunosuppression. Now we know that over time, some patients may develop secondary loss of response to TNFs by developing antibodies. Is this to be expected across all of our various biologics? And does it apply to small molecule therapies as well?

Dr. Lichtenstein:
So very, very important point. And we really learned a while after using anti-TNFs, initially infliximab, that antibodies that are used do – can have immunogenicity come about. The anti-TNFs are perhaps the most immunogenic of the agents we use in clinical practice, and we often use them in combination with an immune modulator in an effort to lessen immunogenicity. Anti-integrins and also anti-interleukins, the IL-12/23s which are now approved for use in the United States, have much less immunogenicity. The small molecules – and we'll talk about those, azathioprine, 6-MP, methotrexate, and tofacitinib – really, we don't have to worry about that. That's not an issue that comes about. So, yes, it's a problem. We've overcome that in a big way, and we still have many more molecules in the pipeline that we're looking at, many of which are not that immunogenic at all.

Dr. Nandi:
And I think this is really honed in when we look at some of these long-term extension studies, the long-term – the LTE data, if you will, for ustekinumab or even vedolizumab in contrast to anti-TNF therapies. Can you give us some idea for our listeners, what does the long-term extension data show for our anti-IL-12/23s and integrins in comparison to anti-TNFs when it comes to efficacy and durability of that response?

Dr. Lichtenstein:
So it's an interesting question given the recent data presented on ustekinumab in ulcerative colitis, for example. Individuals do well up front. And when we look at the durability, if you get into a state of remission, the chance of remaining in remission after the initial year remains about a straight line across. Overall, about 80%, if we look at the data – and this was presented recently at the European meetings, as well as the American College of Gastroenterology meetings, and I would estimate that it was not formally analyzed – about an 80% overall rate, once achieving a state of remission, of remaining in remission. And that's the number that we have, for example, for ustekinumab for Crohn's. That was the initial studies that look at this. But the UC data, we now have 2-year follow-up to date. Immunogenicity is low. The durability is good. And that's an important thing when we talk to patients. Patient care, we can say if you do well initially, you'll continue to do well. And that's an important component of clinical care, is durability.

Dr. Nandi:
Absolutely. I couldn't agree with you more. And I think patients, they get that buy-in especially, right, when they hear that, look, if you respond to this medication, you're going to continue to respond. And that's a buy-in on their part.

How does the type of or extent of disease affect the agent that you pick for the patient? And at what point does systemic versus gut-specific immunosuppression come into play when you're talking to a patient about risk?

Dr. Lichtenstein:
When we see a patient, we initially look at them and say, what are the factors that they have that portend a good and a bad prognosis? If someone has, for example, isolated aphthous ulcers in the ileum, only a few, 2 or 3 perhaps, we might observe that patient. And if they have symptoms, we might use enteric-coated budesonide, for example, to treat them, which is more a local therapy, if you would, because it's topical delivery. If someone has perianal disease, they have ileocecal disease, they have a bad prognosis. Let's say there's smokers, which makes them have a worse prognosis. That person needs a systemic immunosuppressive agent, such as a biologic initially, which targets these specific pathogenetic abnormalities that have been recognized, for example, in Crohn's. So that's how we prognosticate, you know, when we look and we see the patient. And then we assess. And we'll talk about that more in the near future.

Dr. Nandi:
Very good. Does it matter in terms of how you talk about risks when you specifically talk about TNFs and anti-IL-12/23s versus lymphocyte trafficking inhibitors like anti-integrins? How do you explain this to the patient, and how does that come into your decision-making?

Dr. Lichtenstein:
I think the biggest concern of the patient is, besides are they going to do well, how safe is a medication? And when we look at the agents we have, steroids are really the worst. We have double the death rate, double the severe infectious complication rate, which has been published in numerous series. Those are the agents that we try to avoid. Anti-TNFs, we have side effects which can come about, congestive heart failure, optic neuritis, multiple sclerosis, lymphoma. We estimate about a 3-fold risk of lymphoma based on – some of the studies suggest this. Whereas, if we look at black box warnings for vedolizumab and ustekinumab, there's no black box warning for malignancy or infection. So safety is really paramount when we talk to patients. Those patients with prior malignancies, many gastroenterologists, for example, would choose vedolizumab, which is more gut selective, if you would, and less systemic.

Dr. Nandi:
For those just joining us, this is CME on ReachMD. I'm Dr. Neil Nandi, and I'm here today with Dr. Gary Lichtenstein. We've been

reviewing lifetime risks of IBD treatment immunosuppression and recapping the long-term durability of our current therapies.

So, Gary, you know clinicians are always utilizing these therapies, hoping that they work for their patients but wondering how long the therapy will last. What do real-world studies, such as VICTORY with vedolizumab, illustrate to us about the long-term durability of vedolizumab, or even long-term data for ustekinumab and TNFs?

Dr. Lichtenstein:
So I think it's important to first define what's real-world data. And these are where it's not a prospective randomized trial. There are many different sources of this. Registries, consumer data, wearables, clinical outcomes, lab data, mortality data, social media data, EMRs, prospective enriched studies, claims data, hospital data, and pharmacy data, and a host of other things. So this tells what happens in real life. And the VICTORY consortium is interesting. It's a conglomerate of many groups getting together and saying, what happens in the real world? Because we can look at mortality in clinical practice, but you can't look at that in a clinical trial as an endpoint. It doesn't go over well with many IRBs. In addition, there's differences in the population, the intervention. You can have a multifaceted and can have harmful exposures in real-world data, not in clinical trials. You can compare to other therapies in practice, often the standard of care. And you have long observation periods. The sample size is larger, and you overcome the population heterogeneity as well. Long term, even death can be fought. So I think there's many benefits to observational studies, but the RCTs, the randomized controlled trials, are equally as important.

Dr. Nandi:
No, that's great. Have we seen that real-world studies for these different therapeutic agents are mirroring clinical trials, or are they surpassing them or not standing up to snuff?

Dr. Lichtenstein:
I think we learn from them. Each is unique. I'll give an example, there's a recent – the BioLAP Multicenter Study from the GETAID study group looking at ustekinumab in patients with Crohn's. And in this particular scenario, you could see that if you failed an anti-TNF before, your chance of success was less. And in addition, success was about 38.5% in this population. And patients with setons at an initiation, a third had successful removal. So you get real-world experience, the probability of recurrence-free survival of 86.2% and 75.1% at 26 and 52 weeks. So it gives you what's going to happen in the real world. Protocols are protocolized, and they may not represent what happens in clinical practice. For example, dose adjustment. Elevation of the dose of a drug in a clinical trial may not come about. In real-world data, that happens, and we increase the dose, shorten the intervals in clinical practice.

Dr. Nandi:
Now, Gary, let's focus our attention on a topic that is probably becoming more challenging each time a new therapeutic class is approved. And that's an exciting and great challenge to have. Also, the challenge of what is the next agent to use when we know we need to switch. Gary, what are your thoughts, and how do you approach knowing when you've used the medicine as maximally as you can? And how do you make the decision as to what they should go on next?

Dr. Lichtenstein:
Great question and one that's extremely relevant. And, Neil, what we do is a treat-to-target approach. We look to see what's the area that is abnormal, whether it's an intestinal target or an extraintestinal target that's troubling the patient and is problematic. So, for example, the patient with luminal Crohn's, ileocecal disease, we treat them. Whether we start with an anti-TNF or another agent such as vedolizumab may depend on the presence or absence of extraintestinal manifestations. Do they have pyodermic gangrenosum, erythema nodosum, arthropathy, things of that nature? And if they do, one might target with an anti-TNF. If they don't, then perhaps either agent would be acceptable. But what's the risk to the patient? And how safe is it, and how effective is it? The severe colitic, in-hospital we typically would use infliximab. So again, the punishment has to fit the crime, as we say. In other words, the severity of the disease and the prognosis dictates what we use and how we use it, and the extraintestinal manifestations also come into play in a big way.

Dr. Nandi:
And, you know, certainly Crohn's, it really causes punishment, sadly, to our patients. Right? Especially those patients who suffer from perianal fistulizing disease, which can not only affect the area around the anus, of course, but the bladder, the genitals, or enterocutaneous fistulas to the skin. How do you approach treatment when you think about treatment therapies for acute fistula versus chronic fistula?

Dr. Lichtenstein:
So the first question we have to ask is, does the patient have a pyogenic complication? Do they have an abscess? And that will typically present with pain, and that would be perianal pain. If they do, then a careful external examination and a digital rectal exam

would be an important thing to do. And if question, cross-sectional imaging is of paramount importance. CT scans will often miss perianal abscesses. So a cross-sectional imaging with an MR scan and working close with colorectal surgery or GI surgery or wherever it is familiar with Crohn's is important. An examination under anesthesia may be necessary. If that's excluded, then use of the appropriate agent is appropriate to consider. And all the agents we use, ustekinumab, vedolizumab, all the anti-TNFs work to treat fistulizing Crohn's.

Dr. Nandi:
Dr. Lichtenstein, it's been wonderful having this conversation with you. Before we wrap up, do you have any last take-home messages for our audience?

Dr. Lichtenstein:
Well, thank you, Neil. I think it's important to recognize that we've come a long way in our treatment of patients with inflammatory bowel disease. We now have better ability to predict the future in many, but not all, of our patients. So we recognize that early intervention truly makes a difference in the outcome, not only of the disease itself, but quality of life of our patients. We recognize, as well, how to better use the agents that we have. I recall when anti-TNFs were introduced, we really just gave one initial dose and we watched the patient. So we've evolved in many ways. Patients' quality of life is really at the center of this, and also overall avoidance of non-targeted therapies.

Dr. Nandi:
Folks, that's our time. I want to thank our listening audience and my esteemed colleague, Dr. Gary Lichtenstein, for sharing his wisdom and insights for us today. It was wonderful speaking with you, Gary.

Dr. Lichtenstein:
Thank you, Neil. I appreciate the opportunity to talk with you. And hopefully this is helpful for clinical practice for those who are listening.

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