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### New Perspectives on Biologic Therapy in Crohn's Disease

#### Announcer:

Welcome to CME on ReachMD. The following activity, titled New Perspectives on Biologic Therapy in Crohn's Disease, is provided in partnership with Prova Education and is supported by an educational grant from Takeda.

Your host is Dr. Neil Nandi.

#### Dr. Nandi:

There's an ongoing dialogue on shifting expectations of care in the management of Crohn's disease because it isn't just about controlling symptoms anymore, it's about controlling inflammation. That's why today we'll be exploring what we mean by treating to target, the benefits of early initiation of biologics and how real-world data is stacking up to clinical trial evidence. This is CME on ReachMD, and I'm Dr. Neil Nandi. Joining me to discuss the advances in the management of Crohn's disease is Dr. Millie Long, Associate Professor of Medicine and Physician of Gastroenterology and Hepatology at the UNC School of Medicine in Chapel Hill, North Carolina. Dr. Long, thank you for joining us for the program.

#### Dr. Long:

Thank you. Pleased to be here.

#### Dr. Nandi:

So, you know, it's a rapidly changing era in the management of Crohn's disease. Can you please tell us how, in our approach, have the last five to ten years changed?

#### Dr. Long:

I think it's changed a great deal, and we think for the better outcomes for our patients. I think the biggest change in the last decade has been a change of goals of therapy; whereas, previously, we would treat with medication to help to improve symptoms, which still remain a very important goal, we want our patients feeling better, our treatment landscape has really evolved that it becomes very important to also treat in order to improve inflammation because what we have found over the past decade, is that we have much better outcomes for our patients when we actually heal up the inflammation and heal up the bowel lining. And so, our goals have now become dual-fold where we want patients feeling better, but we also want the bowel lining healed. The other aspect I would say that has changed a great deal over the past decade is appropriate selection of patients and when we need to intervene in terms of treating with biologic agents. And we're starting to understand that we need to treat somewhat more aggressively earlier in the disease course. What we think is that if we can treat the inflammation in Crohn's disease before structural damage occurs, before a patient has a complication such as a bowel obstruction or an abscess associated with fistulizing disease, our medications A) are more effective; and B) have more of an ability to prevent downstream complications for our patients. And so, this idea of treating to a target of healing inflammation and treating appropriate patients with risk factors earlier in the disease course has helped us to improve outcomes in Crohn's disease. There are interesting data that actually show that in the biologic era, we actually seem to have a lessening rate of surgeries for Crohn's disease and we find that reassuring that potentially we're helping to impact some of these downstream consequences.

#### Dr. Nandi:

Absolutely, and we know that, like you said, the natural history of Crohn's, if we wait too long, there's too much damage done to the bowel wall and we're inevitably going down the line of surgery; we have to treat earlier. Are there any particular clinical trials that we can cite or that might be useful for our listeners to gauge that can give evidence to how we can treat more aggressively?

Dr. Long:

Absolutely. I think one of the more recent landmark studies was the CALM study that Jean- Frederic Colombel and colleagues published in Lancet last year, and this was the first study to demonstrate kind of two aspects of Crohn's disease management. The first being that they treated to a target and then the second aspect was that they tried to maintain tight control, meaning that they used more than just clinical symptoms to actually titrate therapy so that issues such as elevated fecal calprotectin or elevated CRP markers of inflammation came into play that if these were still elevated, medications would be titrated. This was actually a randomized control trial of the kind of standard, which is to use clinical symptoms to help to guide therapy as compared to this kind of tight control paradigm using some of these biologic markers. And, importantly, when we do use this tight control and really kind of monitor biologically as well as symptoms, it actually allows us to have better endoscopic outcomes. We actually get more healing of the bowel over the long-term. So, I think this has really changed some of the paradigm of how we manage Crohn's disease.

Dr. Nandi:

You know, I think you brought up a really important point for our listeners which is the importance of mucosal healing. Are there any suggestions about making – or any data about endoscopic assessment and how endoscopic healing does or doesn't predict long-term prognosis ?

Dr. Long:

Absolutely. So, we have data that if we actually can heal that bowel – it's comparing the people who actually are healed at that first endoscopic assessment as compared to those that are not – that we look at more of a long-term outcome such as surgery, hospitalization, and kind of that long-term mucosal healing rate, and we actually have improved outcomes if we can achieve this early mucosal healing. So, it has really changed my practice. For example, in Crohn's disease, one of the things we know is that clinical symptoms don't always correlate with inflammatory burden , and so what the concern is, is that we actually may be under-treating some of these patients or potentially even over-treating. Sometimes there're symptoms where there's not inflammation. And so, what I have done in my practice is I have really started reassessing. Typically after I start a therapy from a Crohn's disease perspective, I'm actually performing a repeat colonoscopy within six months after initiating that therapy and then, at that time, I'm adjusting therapy based on what I find, and this has become a very important tool in the management of Crohn's disease.

Dr. Nandi:

Absolutely, so this is very insightful and I'm hearing you loud and clear, Dr. Long, we need to be very aggressive about initiating therapy early on in the disease course to prevent these complications, and it sounds like we need to be very aggressive about monitoring treatment response, proving that there's mucosal healing. Let me shift gears in just a second here with treating aggressively, with that in mind, how do we predict or identify which patients we should be more aggressive with who have Crohn's disease?

Dr. Long:

Well, that's a great question and we wish we had very specific, exact criteria, but we do have some risk factors that we can use to help to triage patients and for those that have more of a risk of disease progression as compared to those that don't. But when we look at what are the prognostic factors, those people that will have a much more complicated disease course, first off it's very young. People who are quite young really do seem to have a more aggressive form of Crohn's disease . Second, if they have extensive bowel involvement. For example, when Crohn's disease affects the upper GI tract, that is a Crohn's disease that seems to be more aggressive and that's someone that we should be treating with a biologic earlier. Another example would be a patient that has perianal disease or severe rectal inflammation. Those are characteristics associated with a more complicated disease course. And then, finally, it's at diagnosis. A patient presents and, you know, perhaps they were diagnosed late, and they actually already have penetrating or stenosing disease, certainly, that's a patient that we need to treat more aggressively up front. In the newest Crohn's disease guidelines from the American College of Gastroenterology, they also recommend using endoscopy to re-stratify. Meaning if a patient does have quite deep ulcerations on endoscopy that this is someone that also has poor prognostic factors and someone that we should be considering treating more aggressively up front. I think by taking those characteristics under advisement, it will help us to select the appropriate population to use biologics earlier in the disease course.

Dr. Nandi:

Yeah, so, if we just take a step back and look at the patients that we see in clinic everyday who come in for that initial consultation, and we just go down the list of those very typical risk factors you just identified – age, duration of disease, complications of the disease, and location – a significant portion of our patients I feel in my practice are going to benefit from biologics, but it's very easy – we don't need a fancy scoring system, right? It's just clinical risk factors if we step back and look at the patient as a whole, and I think it makes it easy to

identify what we have to do to get this patient from this point in time to a better point in time. So, you know, it's 2019 at the recording of this podcast, and it wasn't that long ago that we didn't have many options for Crohn's. Now, Dr. Long, we have at least three different classes of monoclonal antibodies – biologics, anti-TNFs, anti-integrins, and anti-IL-12/23s. Can you help our listeners understand the key differences between the individual classes and share how the patients differ for each biologic therapy?

Dr. Long:

Absolutely. I think what the key aspect that we have to say up front in this conversation is that for Crohn's disease, unfortunately, we don't have any head-to-head clinical trials. We don't have any trials that compare an anti-TNF to an anti-integrin or an anti-integrin to an anti-IL-12/23. I hope that those studies will be done in the future. And so the data we're using are indirect data – observational cohort level data, even things like network meta-analyses to try to compare these drugs indirectly in terms of efficacy. So, really it makes it very difficult to say you should use A over B. I will say that, obviously, anti-TNFs are a long-standing agent that really we've used since 1998, so over 20 years of data in terms of treatment of Crohn's disease. The one comparative effectiveness study that has been done is actually a study – the SONIC trial – that actually looked at anti-TNF use alone as compared to azathioprine, obviously an immunomodulator, as compared to combined therapy with anti-TNFs and immunomodulator. In that particular study, those on combined immunosuppression had better efficacy outcomes, at least over the short-term. And so, that study is one that I do use in my practice and that, particularly up front, if someone has quite aggressive disease, I am using combination therapy with an anti-TNF and azathioprine. Certainly, obviously, our listeners, over the long-term, may have some safety concerns and other concerns, but I think it's very clear from an efficacy standpoint that, certainly, at least in the first 6 or 12 months that that combination for our most aggressive disease may be more efficacious than either of those drugs alone. Other drugs, the newer drugs – anti-integrins, vedolizumab – we have had this since 2014. This drug has really demonstrated excellent safety. The therapy itself is one that I preferentially use when I am trying to come up with the safest combo – safest therapy for my patients. It actually, obviously, has demonstrated efficacy in Crohn's disease. A little bit slower in onset than the anti-TNF agents, potentially more like week 14, where we would expect to see clinical response, potentially clinical remission, as compared to somewhat earlier with the anti-TNF but clearly has shown efficacy in this population. And then, ustekinumab, they've only approved anti-IL-12/23, approved in 2018, has also demonstrated efficacy in Crohn's disease and seems to have very good safety signals as well. So, in my practice, I certainly use clinical characteristics, comorbidities to help me to determine which of these therapies I am going to use first and, certainly, if someone is a primary failure of that class of drug, I'm moving onto another class of drugs, and each of these agents have been very effective for the treatment of Crohn's disease.

Dr. Nandi:

That's very helpful and that's a really great type summary of the kind of different agents and what we have available. You know, you brought up, there's not a lot of – there's really little to no head-to-head trials, maybe with the very, very recent exception of VARSITY vedolizumab and adalimumab, do you have any guidance for our audience about that one head-to-head trial that we have between anti-integrins, vedolizumab, and anti-TNF adalimumab?

Dr. Long:

Yes, of course. And so, in ulcerative colitis, there was a recently published New England Journal of Medicine paper that looked at a head-to-head comparison of adalimumab as compared to vedolizumab and this was actually a 52-week study, where they induced with standard dosing of both agents. At 52 weeks, it actually demonstrated improved efficacy for vedolizumab as compared to adalimumab for clinical remission and also for endoscopic endpoints. What was interesting is for the endpoint of steroid-free remission, it actually seemed that adalimumab may have been better. But, again, for the main outcomes, vedolizumab was superior to adalimumab. And so, that's very important. I think it really will inform ulcerative colitis landscapes. I do think that from a Crohn's disease perspective, it's hard to infer data specifically from that trial and so I think we do need data within Crohn's disease populations to help to make some of those decisions, but I think it was a huge movement forward in our field to have a comparative effectiveness trial of biologic agents in ulcerative colitis and, as I mentioned, I'm really looking forward to further data in Crohn's disease.

Dr. Nandi:

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Neil Nandi and Dr. Millie Long is here with me today to talk about the latest treatment strategies for Crohn's disease.

This has been really insightful. Dr. Long, before we depart, do you have any particular take-home message that you want our learners to take away at the end of this discussion?

Dr. Long:

I think that the key thing is we have to look at each patient as an individual and really use those risk factors that we discussed early on to help us to treat the right patient earlier. I think that for too long in the inflammatory bowel disease world, we've been waiting for complications to occur in order to be more aggressive with management. I think we need to change that trajectory. I think these recent

guidelines and some of the more recent studies have helped us to understand this. The sooner we can incorporate that into our practices, the better outcomes I think we'll have for our patients.

Dr. Nandi:

That's perfect and I think that is definitely the take-home message; individualized therapy and early aggressive use.

Dr. Long, thank you so much for spending your time and sharing your valuable insights with all of us. We truly appreciate it. For CME on ReachMD, this is Dr. Neil Nandi. Until next time.

Announcer:

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