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This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/crohns-colitis-foundation-perspectives/innovative-treatment-approaches-in-ibd-a-look-at-how-far-weve-come/11194/

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Innovative Treatment Approaches in IBD: A Look at How Far We've Come

Dr. Simmons:
The evolution of therapies for inflammatory bowel disease over the past decade has been nothing short of remarkable. Now, as we look into the 2020s, we'll take stock of the latest treatment targets, disease mechanism updates, drug pipeline developments, and patient safety considerations clinicians should know. Welcome to the Crohn's and Colitis Foundation Perspectives on ReachMD. I'm Dr. Jen Simmons, and joining me to discuss the current and emerging treatment landscape for IBD patients is Dr. Jill Gaidos, Associate Professor of Medicine in the Division of Gastroenterology, Hepatology, and Nutrition at Virginia Commonwealth University. Dr. Gaidos, it's great to have you with us.

Dr. Gaidos:
Thank you so much for inviting me to do this.

Dr. Simmons:
Of course. So to get us started with the frame of reference, what kinds of changes have you witnessed or taken part in within the last several years that have innovated our treatment approaches to IBD?

Dr. Gaidos:
So when I initially started in training in IBD, the mantra for treatment at that time was step-up therapy, where the idea was to start with what we considered the safest or mildest medication, and work up to the strongest medication, which at the time was anti-TNF. And that was based on whether the patient's clinical symptoms had improved. We then progressed to treating to symptom resolution, so not only were they feeling better, but were they feeling back to their baseline, how they felt prior to their IBD diagnosis. Since that time, we've really figured out a few more things about IBD and the medications to treat IBD. We now know that the anti-TNF, though not completely without risk, are much safer long-term than the immunomodulators in regards to possible side effects or complications. We also know that IBD symptoms don't always correlate with active mucosal inflammation, which is the cause of many of the disease-related complications we seen in IBD, such as the development of fistulas, strictures, or colon cancer. So instead of treating this symptomatic improvement or remission, we're now treating towards a goal of mucosal improvement to try to prevent the potential long-term complications that result from ongoing active mucosal inflammation. We also now use risk factors to try to identify patients who are more likely to have more complicated disease, and we treat those patients with the medications that have been shown to be more effective for severe diseases. So some of these risk factors include patients who are diagnosed at a younger age, patients with more extensive involvement of their inflammatory bowel disease, and patients who have required surgery at the time of diagnosis.

Dr. Simmons:
So would you say it's more customized therapy?

Dr. Gaidos:
It's more customized, but we're also treating early based on risk factors to again try to prevent these long-term complications from ongoing inflammation, and then were also really targeting the inflammation and not just symptoms.

Dr. Simmons:
So just to level-set the playing field, can you overview the main therapeutic classes for IBD, and how they compare or contrast from one another?

Dr. Gaidos:

So over the past several years, the treatment options for the management of IBD have really exploded, which is extremely exciting. Our main therapeutic classes for the treatment of IBD now include corticosteroids, 5-aminosalicylates or methylamine medications, immunomodulators, biologics, and small molecules. The immunomodulator class includes azathioprine and methotrexate. The biologics class now includes not only anti-tumor necrosis factor agents, but also anti-integrin medications, which include, vedolizumab and, less commonly used is natalizumab. And then, we have the interleukin IL-12/IL-23 inhibitor, ustekinumab. The small molecule class – the small molecule agent that's currently available on the market in the U.S. for the treatment of ulcerative colitis is, uhtofacitinib, which is the pan-JAK inhibitor but there are several other, JAK inhibitors and other, small molecules that are currently under investigation. So selecting the current medication for each patient still remains a challenge as we have really no means to determine which mechanisms of action will work best for a particular patient. We now know that, some of our older therapies are not quite as effective for IBD as we had previously thought, so we're now no longer regularly using methylamines to treat Crohn's disease, or methotrexate to treat ulcerative colitis. We do know to avoid long-term steroid use. We try to get them off steroids as early as possible because of the associated severe complications associated with steroids, such as severe infections. For the biologics, we have a better understanding now of their pharmacokinetics, and are monitoring drug levels and antibody levels more closely to try to prolong the efficacy of the medication in patients. The drug and antibody levels are somewhat less useful for the newer biologics, vedolizumab and ustekinumab, as there seems to be less immunogenicity or antibody development with these medications. Tofacitinib is, in the small molecule class are not monoclonal antibodies, so we don't worry about immunogenicity with the development of antibodies against the drugs. Some further differences between these new medications include the need for infusions or injections with the biologics, while tofacitinib is an oral agent. Regarding combinations of these therapies, right now there have been discussions about combining, some of these or multiple of these agents. The concern is combining immunosuppressant therapies and what are we putting the patients at risk for if we combine those. And another eliminating factor right now is the cost of these medications. So without studies showing that they're significantly more effective together, right now, it would be cost prohibitive to combine, the newer biologics with the newer agents.

Dr. Simmons:
So let's specifically talk about the biosimilars that have made an entrance into treatment plans over the past few years. Can you talk about the impact that they similarly have had, and what impact they're projected to have in treating IBD, and their obstacles in their use compared to the biologics?

Dr. Gaidos:
So initially the biosimilars were very big news in the IBD community. We, in the IBD community, were really concerned about their expedited FDA approval. So one of the ways that they were able to get to the market so fast is they were able to test their drugs in just a few of the disease states where the originator product was approved, and then once they met the endpoints for several disease states, they were able to extrapolate, efficacy in all of the, disease states where the originator drug, is approved. So the first, biosimilar for infliximab was actually not tested in IBD, yet was approved for the treatment of IBD. So our concern was, is it really going to work in IBD, because we know there's multiple medications that work for rheumatoid arthritis that don't work for Crohn's disease or ulcerative colitis. The other concern is once these medications became available, there was a lot of mandatory switching that was going on in, pharmacies and hospitals across the country, and then again when the second, uhinfliximab biosimilar was available, there was another switch. So for us, we were worried that there was enough of a variability in the formulations to trigger antibody formation and then the patient would lose response to the treatment. A lot of people confuse a biosimilar with a generic, and they're actually not the same. With a generic medication, the medication has the exact same structure. With a biosimilar, they have a similar, structure of the active component of the medication, but there are at least one side chain that varies. So with any monoclonal antibody, if you have variability in the structure, there's a risk that your body will see that as a foreign protein, create an antibody to it, and then it won't work for you anymore. I think as far as, improving care of IBD, the promise with the development of the biosimilars was that these medications would expand access to biologic agents to patients who can't afford them due to a significantly decreased cost through this expedited FDA-approval process; however, in reality, this decrease in cost isn't quite as significant as what we had hoped and, in some cases it's only temporary. And then further, it's really not the patient who is seeing the cost benefit; it's the insurance companies. So to the patient, they don't see a benefit at all.

Dr. Simmons:
For those of you just tuning in, you're listening to Crohn's and Colitis Foundation Perspectives on ReachMD. I'm Dr. Jen Simmons, and today I'm speaking with Dr. Jill Gaidos about the current treatment landscapes for IBD. So, Dr. Gaidos, let's consider safety issues that often follow the use of several IBD treatments, such as immune suppression effects from biologics. Are there any treatment advances or lines of research looking at ways to mitigate these and other drug-related risks for patients?

Dr. Gaidos:
There are several ways that, we work to prevent infections, which is always a concern when we start a patient on, immunosuppressive

medications. First of all, with any immunosuppressive therapy, it's very important to make sure your patient is up to date with their vaccinations. There are several serious infections that are potentially preventable with vaccines such as herpes zoster, shingles, influenza, and pneumococcal pneumonia. So a professional education committee for the Crohn's and Colitis Foundation have recently updated the health maintenance recommendations for IBD, and these are available online. Our idea was to make it easier for IBD providers to determine what vaccines their patients may need or other, screenings patients need, and then get them up to date. We also work to minimize immune suppression as much as possible. So for example, we're no longer routinely keeping patients on combination therapy with anti-TNF and immunomodulators such as azathioprine or methotrexate. Previously, patients were started on this and kept on it indefinitely, but now, we're learning that we can, reserve that combination for patients who have risk factors for more complicating disease. Another way to lower risk for infections is really to limit the duration of steroid use. Most people; patients and providers, think of steroids as very safe because their pills, and for some reason that makes them safer, and they've been around for a long time, but steroids are immunosuppressive and they increase the patient's risk for infection. In addition to other, possible adverse side effects that we worry about with long-term steroid use or recurrent episodes if used for long periods of time.

One of the things is some of the newer agents, such as vedolizumab and ustekinumab we haven't really seen a trend toward increasing infections with these agents. I mean, we still monitor patients closely, but, overall in the clinical trials and as well as in the post marketing, there hasn't been a trigger towards any particular increase in infections, or an increase in any particular infections in our patients. With tofacitinib, however, the studies have clearly shown an increased risk of developing herpes zoster or shingles, as well as lipid abnormalities, and a risk for venothromboembolism or blood clots was seen in the RA population, being treated with the higher dose of the medication. So vaccination with the attenuated herpes zoster vaccine can help to prevent zoster infection in patients being treated with tofacitinib. And the current recommendation with UC patients is to try to treat at the lower dose.

Dr. Simmons:
I also understand that modes of delivery for IBD treatments are a hot topic for innovation to help improve patient compliance and adherence. Can you talk to that?

Dr. Gaidos:
Sure. So some of the new medications that are coming out, the small molecule agents, are oral agents. These include the JAK inhibitors, which we talked about with tofacitinib, but there's also several other JAK inhibitors, with different mechanisms of action that are under clinical investigation that are all going to be oral agents. That is helpful to improve compliance, but oral agents don't always improve patient compliance. There are some patients that you actually want them to come in for an appointment at an infusion center to make sure they're truly getting their medications. But for others, having these oral agents, is much more convenient, there are multiple patients who have to drive several hours to an infusion center, they have to take off work for that period of time, so, really it becomes a burden for them. In addition, there are some patients who simply can't or won't self-inject, which can further limit your treatment options. So oral agents do provide, a great benefit, for those particular patients. Some of the other perks with oral – the small molecule agents is the cost. You don't have the cost of an infusion center and a physician fee or a hospital fee associated with that. And then also they are not monoclonal antibodies, so we don't have to check the drug levels and see if antibodies are present. And if the patient does, for whatever reason, stop the medication for a period of time, you can safely resume it without having to worry about it no longer working in them.

Dr. Simmons:
And lastly, Dr. Gaidos, as we carry this forward-looking theme to a close, are there any other developments or lines of investigation that you're excited about for potentially taking IBD standards of care to another level?

Dr. Gaidos:
Yes, there are several developments in IBD that I am particularly excited about. First of all, all of the new therapies that are being investigated currently. There are many, many new drugs in various stages of testing that are extremely encouraging. And hopefully as people are investing time and money and energy into this disease state, we can hopefully soon have better, safer and hopefully less costly treatments for our IBD patients. Some of the drug companies, as part of their clinical trials, are looking at, additional testing that could help to predict, if the patient will respond to that mechanism of action, and that would be really nice for us in the clinical setting if we could do some type of additional testing to predict which, mechanism of action would treat that patient. That would allow us to eliminate a lot of trial and error, and really expedite the recovery process in our patients, potentially, helping to prevent these disease-related complications, but also improving the patient's quality of life, which is really the patient's main goal of treatment. The third thing that I'm really excited about is our better understanding of pregnancy in IBD, and the safety of IBD treatment in pregnancy. Through the, Prospective Registry of Pregnancy and IBD and Neonatal Outcomes study, or the PIANO study, we've really been able to get a better idea of, patients with IBD, their pregnancy outcomes, so can they safely have children? And then too, the impact of their medication use on the pregnancy, as well as on, their children. So that's been really helpful to explain to patients that they can safely have children, they

can safely continue, most of the IBD therapies during pregnancy, as well as in lactation.

Dr. Simmons:
Well this has been an extremely valuable discussion about where we've arrived thus far in IBD care, and a glimpse at the road ahead. I'd like to thank my guest, Dr. Jill Gaidos, for joining me today. It was great to have you on the program.

Dr. Gaidos:
Thank you so much for inviting me to participate in this important discussion on the current treatment of IBD. I really enjoyed our conversation.