

TRANSCRIPT

Managing IBD: Taking Charge of Your Disease

Dr. Miguel D. Regueiro

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Operator:

Hello, everyone, and welcome to *Managing IBD: Taking Charge of Your Disease*, a free telephone and web education program. It is my pleasure to introduce your moderator Laura Wingate, Senior Director, Field and National Programs, of the Crohn's and Colitis Foundation of America.

Laura Wingate:

Hello, everyone. On behalf of the Crohn's and Colitis Foundation of America, welcome and thank you for attending today's program, which is supported by a charitable contribution from Shire.

We would also like to thank all of you who submitted questions in advance of the program. After Dr. Regueiro's presentation, we will open the program up for your questions. We will take as many questions as time allows from both telephone and webcast participants. If we are not able to take your question, our Information Resource Center can be reached at 1-888-694-8872.

Today we are simultaneously interpreting our program into Spanish. Dr. Regueiro will be speaking a little bit slower to allow for simultaneous interpretation.

We encourage you to complete the online evaluation form after the program.

In addition, to help us further our understanding of IBD, we encourage you to join CCFA Partners, our national registry of patient-reported outcomes. Simply complete an online evaluation survey to be part of this exciting research initiative. Patients will receive research updates and information on IBD. Visit www.ccfapartners.org to learn more and to participate.

I now have the distinct pleasure of introducing our speaker for today's program, Dr. Miguel Regueiro. Dr. Regueiro is Professor of Medicine, Associate Chief for Education, and Clinical Head and Co-Director of the Inflammatory Bowel Disease Center at the University of Pittsburgh School of Medicine. Dr. Regueiro's main clinical and research interest is inflammatory bowel disease. He currently serves on CCFA's National Scientific Advisory Committee.

And now it is my pleasure to turn the program over to Dr. Regueiro. Dr. Regueiro, we are so grateful to have you with us today.

Dr. Miguel Regueiro:

Thank you, Laura, and thank you to CCFA for allowing me to spend time with you

today. I believe that this will represent a very informative and educational program. The title of the talk is *Managing Inflammatory Bowel Disease: Taking Charge of Your Disease*. I will provide an overview on inflammatory bowel disease as well as treatment aspects and also leave time at the end for your questions.

We have a fairly full educational program and these are some of the topics and goals of today's educational forum. To provide an overview on inflammatory bowel disease, to describe the overall goals of IBD management, and to discuss the different treatment options and management strategies. We will also explore the complexities of remission in inflammatory bowel disease and discuss what support is available as far as adherence and maintenance of adherence in treatment.

Many of the slides are slides that we use as physicians in our educational programs. And I will do my best to translate, if you will, many of the slides into practical terms. But I think one of the advantages to this program is that it really gives you a very high level understanding of inflammatory bowel disease in the year 2011.

So what is the spectrum or what are the different types of inflammatory bowel disease? On this slide you can see that over one million Americans have inflammatory bowel disease and recently the point estimates are as high as two million Americans have inflammatory bowel disease. The two main categories of inflammatory bowel disease are ulcerative colitis and Crohn's disease. Ulcerative colitis and Crohn's disease encompass 99% of inflammatory bowel disease.

In the middle of the slide is the term indeterminate colitis and just simply put, these are people who have inflammation in the colon or ulcers in the colon and the physician cannot distinguish between ulcerative colitis and Crohn's disease.

On the next slide, the key features and differences between ulcerative colitis and Crohn's disease are outlined. Many times people come in and they'll see us as physicians and say well, what's really the difference between Crohn's and ulcerative colitis? And I'll mention again that these are all under the spectrum of inflammatory bowel disease.

So what's ulcerative colitis? Ulcerative colitis is inflammation in the colon (also known as the large intestine) only. The inflammation is continuous and symmetric. That means that there's inflammation that coats and lines the colon entirely, but may stop at a certain point. For example, there are patients who present with ulcerative colitis, who just have inflammation in the rectum and then the inflammation stops. That's what we call ulcerative proctitis. Conversely, there are people who have inflammation throughout the entire colon, throughout the entire large intestine, and that's called pan-ulcerative colitis.

As far as the depth of inflammation, with ulcerative colitis it's a mucosal inflammation. What does that mean? That means that if you imagine drinking a very hot cup of coffee or a hot drink and burning the inside of your mouth, that raw irritated feeling, that's on the mucosa, that's the top layer of the colon. That's what we call mucosal inflammation. As far as ulcerative colitis, this is inflammation or ulcers that only occur in the colon. It does not travel or does not extend up into the small intestine. And then finally the rectum, the lowest part of the colon, is always involved with inflammation.

So now if you look at the right side of this slide under Crohn's disease, the dark red color signifies the most common area of Crohn's in the gastrointestinal tract, and that

is the last part of the small intestine called the terminal ileum or the upper part of the colon. You may hear the term ileocolonic Crohn's disease, that usually means the last part of the small bowel and upper part of the colon.

Unlike ulcerative colitis, Crohn's disease may skip around in the intestine, meaning there may be an inflamed segment of small bowel or large bowel, and then a normal segment of intestine, and then again ulcers or inflammation. That's what we call skip disease.

Unlike ulcerative colitis, the mucosa is involved, but the Crohn's disease can also lead to transmural inflammation, meaning that the inflammation actually penetrates or goes into the wall of the bowel.

I mentioned already that Crohn's, unlike ulcerative colitis, may involve any part of the gastrointestinal tract, anywhere from the mouth all the way down to the anus. Interestingly, unlike ulcerative colitis, the rectum may not be involved, but it is not uncommon for people with Crohn's to have anal involvement, meaning inflammation around the anus with skin tags, fistula, and fissures.

Where does inflammatory bowel disease occur in the world? Even though this slide says geographic distribution of ulcerative colitis, it is really geographic distribution of IBD, and to that matter any autoimmune disease. So interestingly, if you think about rheumatoid arthritis, lupus, multiple sclerosis, other immune-mediated or other autoimmune diseases, the pattern is identical and we think there are similarities between these.

For example, if you look at the map of the world, where you see the dark red, that is the most common area for inflammatory bowel disease to occur, which is North America and the Northern European countries. You'll note that Asia, Africa, and Latin America are less common for inflammatory bowel disease, however, those are on the rise as well.

So the question comes up, why is this? Well, some of it may be the great American diet and unfortunately some of the things that are processed in foods may lead to inflammation. But it may also be what we call the hygiene theory, meaning that North American and Northern European countries are very sanitary when it comes to cleaning and at a young age our bodies need things to react against, the immune system has to fight off foreign things. So if we live in too clean of an environment, sometimes we see autoimmune diseases.

Finally in Asia, Africa, and Latin America, historically there's been a greater incidence of parasite infections at an early age. And interestingly parasites or worms, although it's somewhat disconcerting to think about, may actually protect against autoimmune diseases. There's now been some research looking at parasites as a treatment for inflammatory bowel disease. And maybe in the question and answer segment, we can come back to that.

So I mentioned some of this already, inflammatory bowel disease in terms of time trends. This is a slide that's about ten years old, but there is an increased incidence and now we're actually seeing a second piece, we're seeing more rates and more common onset.

Who gets inflammatory bowel disease? This is a disease that's primarily of young

people, 15 to 30 years of age is the most common. It had been once thought that females were more common than males, but now we see a fairly even distribution in gender between females and males. And finally this is more common in Caucasians and Jewish populations. However, as I mentioned a minute ago, we are seeing an increase worldwide in all racial and ethnic populations.

Why do people get inflammatory bowel disease? If you look at the bottom yellow circle on this slide that says IBD, you probably could substitute any disease that we have today and this same theory will exist. Meaning that on the left hand side there's a genetic susceptibility and on the right hand side there are environmental factors, such as infections, different medicines, NSAIDs (ibuprofen), diet, smoking, stress, and antibiotics. A genetic susceptibility combined with exposure to an environmental factor leads to an immune response that's dysregulated, meaning an autoimmune response that ultimately leads to inflammatory bowel disease.

I'll pause for a minute to discuss smoking because smoking is one of the interesting environmental factors with IBD in that cigarette smoking has been associated or makes Crohn's disease worse. It's interesting that the smoking makes Crohn's worse, there's more surgery with Crohn's, but there's also an interesting thing that we can find that smoking makes ulcerative colitis better. Now while we do not recommend smoking in our ulcerative colitis patients, patients who have ulcerative colitis often quit smoking or never have smoked. So that's an interesting feature.

I already mentioned that IBD might have a genetic influence. We've seen different racial and ethnic variations, but there have also been twin studies that have shown this as well, where there's a concordance, meaning if one identical twin has Crohn's or colitis, it's common that the other will as well. It's less common in fraternal twins, but certainly more common than the overall population.

There's been an explosion of research on genes and without going through all the acronyms of NOD2, HLA, and some of those other features, just know that there are over 150 genes that have now been identified with Crohn's and colitis and this may be the first disease where the entire genetic map is solved. So we have exciting possibilities on the horizon for not only understanding better Crohn's and colitis, but coming up with better treatments.

On the next slide you can see this says normal intestine versus intestine with IBD. If you look at the model of the person with a colon on the left hand side and start there, it's not uncommon for anybody, forgetting Crohn's and ulcerative colitis for a minute, to be constantly bombarded by different antigens or foreign products. So think about it, we eat lots of different foods, unfortunately we inhale and ingest many different things that we may not intend to, and our gastrointestinal tract is constantly fighting off those different types of antigens, those foreign products. It's amazing that more people don't have inflammation in the intestine, but the immune system is constantly regulating this, it's constantly saying this is good, this is bad, this is what we need to fight off.

Imagine somebody who then gets a common infection, say a food poisoning. Their colon might become inflamed temporarily, but if you look at the bottom of the slide the immune system in somebody who does not have IBD goes back to normal. In somebody who has a genetic predisposition or a dysregulated immune system, often they

cannot down-regulate and they go back up to that right hand side of the slide where there's inflammation.

So putting this together is a story that may be easier to understand. I took care of a family several years ago who all went to Mexico, they had a great time, they all drank the water. Unfortunately they came back with traveler's diarrhea, a very common problem. The family got better, but the daughter continued to have diarrhea a week later. She had stool cultures but nothing came back showing that there was an infection. She developed bloody diarrhea and ultimately was found to have ulcerative colitis. So she was probably exposed to a common infection, the immune system fought that off, but then the inflammation started because the immune system started to attack the colon. In summary, that is our current theory as to why people get IBD.

With ulcerative colitis, the most common clinical findings are diarrhea and bleeding. And this is an endoscopic picture showing an inflamed colon. There are a variety of rare, very rare complications that occur, but cancer and dysplasia is one that we'll talk about a bit later as well. And then there are some extraintestinal disorders that are listed at the bottom. So some people have skin, joint, sometimes eye inflammation that can also be related to the inflammatory bowel disease. But bleeding and diarrhea are common features of ulcerative colitis.

On the other hand, Crohn's disease, as you remember me saying a minute ago, is inflammation that can be anywhere in the gastrointestinal tract and often people with Crohn's disease come with more abdominal pain or tenderness for long periods of time. Weight loss can be a feature. There can be diarrhea, but there is not always diarrhea. Some people are mistaken to have irritable bowel syndrome for a long time, only later to find that they have Crohn's disease.

As far as testing for inflammatory bowel disease, really it comes in three main categories at this point, and I won't detail this too much, but there are three things that as physicians we check for in inflammatory bowel disease. There are some laboratory tests, which usually include blood work and we can get stool samples. There are endoscopies, like colonoscopy and upper endoscopy where we can take biopsies. And there are different radiographic tests or radiology, so plain X-rays, CAT scans, or MRIs. We use the totality of these tests to try to distinguish who has Crohn's or ulcerative colitis. We always want to make sure there's not an infection that can be treated with an antibiotic. And once we come up with a diagnosis, then we look to treatment.

So what are the main goals of treatment for inflammatory bowel disease? Really the top two lines summarize the main treatment goals. One is to induce a remission or response and another is to maintain a response or remission. And what does that mean? That simply means somebody comes in with symptoms of Crohn's or ulcerative colitis, we try to put them on a medicine that controls the inflammation and makes them feel better, but then maintain that well-being, so maintain remission, maintain response.

We're interested now in mucosal healing and healing the lining of the intestine, which again I'll come back to at the end. And we try to prevent complications, improve one's quality of life, improve nutrition, and as best we can, limit surgery. However, I will say often surgery is an important part in the treatment paradigm for Crohn's and ulcerative colitis.

As far as inflammatory bowel disease, what we are hoping to have on the horizon through genetic studies is the ability to actually measure genes that will target therapy for an individual person. Until we actually have that experience or that availability, how do we choose the right medicine for somebody with Crohn's and colitis?

So the old adage, in quotation marks, is when your only tool is a hammer, everything looks like a nail. What does that mean? That means that you can see a list of medicines that I have on this slide and often we will use medicines in people to try to control the inflammation and sometimes we don't know what the medicine is that will work for that person, so we'll try one, then another.

I will tell you that 20 to 30 years ago, we really only had prednisone and a medicine called sulfasalazine, so there's been an explosion of treatment options that range from the anti-inflammatory 5-aminosalicylates, medicines that work on bacteria, steroids, immunomodulators, and then finally the more recent category, biologic therapies.

Now I'm going to briefly outline all of these in the next few slides. All of the names of the 5-aminosalicylates or 5-ASAs listed are oral formulations, but they can also be given in ulcerative colitis as suppository or enemas to control the inflammation in the lower part of the gastrointestinal tract. These are all primarily used for ulcerative colitis but can also be used for Crohn's disease. They are much more effective for ulcerative colitis than they are for Crohn's disease.

We also have medicines that work on bacteria, which include antibiotics and probiotics. We think that bacteria in the normal intestine may actually play a role in inflammatory bowel disease, but also antibiotics have been used to treat Crohn's fistula, Crohn's disease, and an entity called pouchitis. An ileoanal pouch is when patients have surgery to remove the colon and the small bowel is made into a pouch that is hooked together inside, so there's not an ostomy bag. Antibiotics and probiotics are very effective for treating pouchitis. And then some people actually have too much bacteria in their intestine or bacterial overgrowth and we use antibiotics for that as well.

In addition to antibiotics, there are things called probiotics, which you may have heard of, because these are in yogurts and other healthy foods. And then prebiotics, which are essentially the natural ingredients that counterbalance the bad bacteria.

For historic purposes, the corticosteroids have been around for many years. These are used to mainly induce remission in ulcerative colitis and Crohn's disease. For example, prednisone is probably one of the most common medicines that we use to treat IBD. These medicines work very quickly to heal inflammation but they have lots of side effects and we try to avoid using these medicines long term. There is a newer steroid that has less systemic effects, meaning it's not absorbed throughout the body and the bloodstream, called budesonide or Entocort[®], and that's primarily used for Crohn's in the small bowel and upper part of the colon.

In the last 20 years, the immunomodulators have become a common medicine and I would say in the last ten years are used very early in treatment in some patients. We use these more in Crohn's disease than ulcerative colitis but we have experience now in both, so we use these in all IBD. So things like 6-MP or azathioprine, Imuran[®], are what we call steroid-sparing agents. What this means is a patient will be placed on

prednisone, feel much better, but then we'll transfer them onto one of these treatments to try to maintain remission. Methotrexate and cyclosporine are two other examples.

Finally, the newest treatments are the biologic therapies or biologic response modifiers. The group that is most well known are the anti-TNF agents. These include infliximab or Remicade[®], adalimumab or Humira[®], and certolizumab or Cimzia[®]. So they're kind of long complicated names, but they all work the same way to block an immune chemical to control inflammation. Remicade or infliximab is approved for both Crohn's and ulcerative colitis, where Humira (adalimumab) is just for Crohn's. Cimzia (certolizumab) is just for Crohn's as well. Finally, a medicine that's commonly used for multiple sclerosis, but is also FDA approved for Crohn's disease, is called natalizumab or Tysabri[®]. It is my prediction, based on the medicines that are in the research pipeline and those that the FDA is considering, that in the next five years we will have several additional biologic therapies.

So how do we approach somebody with inflammatory bowel disease from a treatment standpoint? This is the treatment pyramid that we have traditionally used. Just to simply state it this way, it was not uncommon in the past for all IBD, to use medicines like 5-aminosalicylates first, and work our way up the ladder to steroids, to immunomodulators, and then finally anti-TNF medicines. So we went from the least aggressive to the most aggressive.

You may hear from several sources that we are actually inverting the pyramid. What this simply means is that there are people who may benefit from more aggressive treatment earlier. Immunomodulators, 6-MP (Imuran), or things like Remicade, Humira, Cimzia, as first-line treatment. And it may be if we use these earlier, we can prevent problems long term and alter the natural course of disease.

Another big concept is how do we as physicians and researchers and for people who have Crohn's and colitis define remission and response. And this may be somewhat confusing, but if you look at the bottom of the slide, the 20th century answer, meaning what we had done for a long time, is really only focus on symptoms. For example, there's a Crohn's Disease Activity Index and other research indices that we use to measure symptoms. We had only based treatment and response on how somebody felt, which is of paramount importance. But now what we're learning in the 21st century is not only do we care how somebody feels, but we want to make sure that the tissue heals, that the mucosa heals, that the ulcers and inflammation ultimately go away. So this concept of mucosal healing has really become a forefront interest of ours as researchers and we're learning that this may help long term.

So why don't we just care about symptoms? And this is a slide that presents some of the problems if you were just to look at symptoms. Simply put, symptoms are disease-focused, but not disease-specific. For example, there's a common syndrome called irritable bowel syndrome that you may have heard of before. And just to pause for a minute, 70 to 80 million Americans have irritable bowel syndrome, but there's no sign of inflammation in the gastrointestinal tract. Irritable bowel syndrome often presents with diarrhea or constipation, fatigue, or abdominal pain. Look at the list of symptoms I just mentioned, those can also be seen with Crohn's and ulcerative colitis. So if we just looked at symptoms alone we may not be getting at the root of the problem for

inflammation, it may not impact prognosis, and also we do not use our symptom-based treatment scores that we use for research in our clinical practices.

This concept of mucosal healing is one that I would like to present to all of you today, to let you know that this is probably where we're headed in the future. So yes, we want to make somebody feel a lot better, that's obviously very important, but we also want to heal the tissue. What we're now learning through several research trials is if we heal the tissue, we have prolonged remission, we avoid hospitalization, maybe we can decrease surgeries and other complications, and certainly we can decrease the risk of cancer. So there's been an emerging trend towards looking at healing the tissue as well as making somebody better.

The problem is, and I won't belabor this point too much, is as physicians and researchers and as all of you as an audience that either know somebody or have Crohn's or ulcerative colitis, how do we do that, how do we define how to heal the tissue. Mucosal healing has been an area that we probably are best understanding through colonoscopy or endoscopy and taking biopsies. There are a lot of other possible techniques that are non-invasive in the future, whether it be on blood or measuring certain samples that do not require endoscopy to measure mucosal healing. So stay tuned on that.

What about the asymptomatic patient who does not have endoscopic healing? This is an interesting concept in that there are some people who come in that are under-reporters, not intentionally under-reporting, but they just don't feel the inflammation. The question is maybe they're used to their symptoms and they've lived with this for years and they say I don't have a problem and they're just used to it. Or maybe there are some people who really don't feel the inflammation. Then we look at are people taking their medicines regularly, should we as physicians increase the treatment if we see inflammation, or should we just say well, you're feeling okay, we'll leave it alone, can we really heal the tissue in everybody and what are the risks and benefits of trying to use more medicine to heal the mucosa.

We just got back from our CCFA national conference as physicians and researchers and this entire topic was a morning discussion. And I'm afraid we don't have the perfect answer yet, but healing the mucosa is probably of paramount importance.

Let's switch to maintenance therapy. Eighty percent of people who continue to take their medicines will stay in remission. So you have somebody who has Crohn's or ulcerative colitis, they're on a medicine, they get their disease under control, and if they're maintaining their medicines they do well. Interestingly, 20% of patients who stop the treatment may remain in remission, and the question is why do some people stop treatment. And this is a bit of a busy slide, but these are somewhat intuitive. Common reasons that patients stop medication are due to patient-related factors, i.e. being male, being single, and forgetfulness. If you have to take 20 pills a day, it's not uncommon that you're going to forget to take them. The other big thing is people who actually feel very well often say well, maybe I don't need my medicines anymore. Economic factors can also play a role. Obviously in the era that we're in right now, if a medicine costs a prohibitive amount of money, the insurance doesn't cover it, it's just not practical, it's not affordable. Medicine-related factors are important. Maybe there are multiple pills during

the day or maybe somebody's read something on the web and is worried about a side effect or maybe this impacts the daily schedule or maybe there are other factors involved. I think ultimately it's important to have a good relationship with your physician or healthcare provider in sorting through some of these details.

So what are the reasons for non-adherence and not taking medicines? Again I mentioned forgetfulness, that was the most common reason cited, but a second one is lack of perceived benefit or if people who get into remission feel quite well.

There was an eloquent study that was actually done looking at this and what you can see here, which is I think somewhat intuitive, is that 89% of ulcerative colitis patients who continued to take their 5-aminosalicylates remained in remission. For those patients who stopped their medicines or were non-adherent to the medicines, only 40% or 39% were still in remission. So even though this is intuitive, continuing to take medicines is important.

I think we can improve as physicians by educating people about the pros and cons of the medicine and really working with the patients. I think patients should let the physicians know some of the barriers to taking medicine as well.

Let me switch gears for a minute and talk a little bit about surgery. What we're realizing is that for Crohn's disease, nearly two-thirds to three-quarters of people with Crohn's will need surgery and about a third of people with ulcerative colitis will still need surgery. I would not look at surgery as a failure. Sometimes this is a necessary treatment to make people feel a lot better. For Crohn's disease, surgery is often required for a blockage or a stricture, sometimes for a fistula or infection. For ulcerative colitis, the most common reason for surgery today is for disease that's not responding to medication or if somebody develops a pre-cancer or a dysplasia. This is another common indication.

The most common types of surgery for ulcerative colitis are shown here. On the far left, what I think many people are concerned about is that they will have what's called an end ileostomy. That's where the colon is removed and there's a stoma or a bag applied. I will tell you that actually from an outcome standpoint many people with ileostomies do quite well long term, but there's now an alternative to that for some people, not everybody, called an ileal pouch-anal anastomosis, that's on the right hand side, where the colon is removed and everything's hooked together. I don't have a picture on the Crohn's surgery, but if you imagine a long piece of pipe where six inches is taken out in the middle and the two ends of the pipe are hooked back together, that's the most common treatment for Crohn's disease as far as surgery.

What about the role of stress in inflammatory bowel disease? I know this is a cartoon saying I think it's stress. Well, all of us know now that stress definitely does play a role in inflammatory bowel disease and we know that stress may actually make inflammatory bowel disease worse and management of stress can actually make inflammatory bowel disease better. There have been studies in our center and in other centers looking at how stress can impact on inflammatory bowel disease. If you look at that red dotted curve at the right hand side of the slide, where stress and anxiety is along the X or bottom axis, and performance and efficiency is along the Y, if you imagine athletes, or people who get nervous before a game, often the adrenaline flows and the stress actually is good to a point. But the problem is for somebody who has chronic

stress, when you come over the hump of the curve, it can have detrimental effect. So with Crohn's and colitis we now know that stress definitely can play a role and managing and coping with stress are often an important part of treatment.

There are ways that we can now look at managing and coping with stress. I'm not going to go through this too much, but even simple approaches such as exercise, yoga, different support groups that CCFA offers, biofeedback, cognitive behavioral therapy, and even things like hypnosis that have been used. So the days of saying stress is not important are over. We know stress is important. And as physicians and researchers and the CCFA, these are targets that we're looking at to better manage disease.

Nutrition is also important. We know that nutrition is important in healing and inflammation, and the immune system and energy levels. Unfortunately we don't have the perfect prescribed diet at this point. I know this a popular question and very common. There's a lot written on this and I have many people that I see with Crohn's and colitis and if you heard the diets that work for each one, they're very different from one person to the next. We definitely think diet plays a role. We just don't know exactly what the right diet is for each individual person. And I think that that's important.

We do know that generally carbohydrates with more soluble fiber are good. Fiber is often asked in inflammatory bowel disease, is that good or bad. Generally as long as a person doesn't have a stricture or a narrowing from Crohn's disease, eating fiber is okay. Now obviously if there are blockages or problems with blockages, then fresh fruits and vegetables, peanuts, corn, and popcorn can be difficult to digest. We often also use supplements. If you look at the table at the bottom, some people need injections of B12. We know that Vitamin D and calcium sometimes are low in our patients with inflammatory bowel disease and we need to supplement. In general, my recommendation is that everybody who has IBD takes a multivitamin. But there are some people who need supplements beyond that.

So I have just a couple of more slides to wrap this up and then I think we'll stay on time and be able to answer any questions in the remaining half hour. But I'd like to present a clinical vignette of a person with Crohn's disease I saw, which I think represents a fairly typical example.

So this was a 23-year-old female nursing student, who was taken to the emergency room with presumed appendicitis, meaning the inflammation of the appendix. She had pain in the right lower part of her belly. She actually had pain in regular bowel movements for years and originally was told this was irritable bowel syndrome. So a very common scenario in our patients with inflammatory bowel disease is that they've been told for a long time this is irritable bowel syndrome, it's probably just something you ate, or the diet. However, recently the pain became more severe. She also started getting fevers and she had some weight loss. So these are things that we would not expect to see with irritable bowel syndrome. And I'll mention to the audience that alarm symptoms, such as weight loss, fever, severe pain, certainly bleeding, these are things that should be addressed with a physician because these are not typical symptoms of irritable bowel syndrome.

When she came into the emergency room, I mentioned we often get blood work. There's something called a white blood count, that was elevated and showed there was

a problem with either inflammation or infection. So she had a CAT scan and the CAT scan showed that the last part of the small intestine, again that's called the ileum, the upper part of the colon called the cecum, which by the way, that's where the appendix is, so that's why at first it was felt that she had appendicitis, but these were inflamed. So we did a colonoscopy and we found inflammation in the ileum, the cecum, and the upper part of the colon, and biopsies confirmed Crohn's. Not everybody presents the same way, but this is a typical presentation of somebody with Crohn's disease.

I wanted to leave you with the last slide and that I think that really the future for inflammatory bowel disease is quite bright. We have more research, more knowledge, thanks to again groups like CCFA. We have a better understanding of not only the immune system, but the environment. And most importantly, genetics. Our center here has also looked at genetics and we now have over 150 genes that have been identified. So it may be that one day we get away from the only tool is a hammer, everything looks like a nail approach, and we can personalize IBD care, meaning we can do a blood test to measure the genotype and the phenotype and look at the presentation, what are their symptoms, where's the inflammation. I think that day will probably come very soon. It's actually probably coming sooner than we think. And I think what this will ultimately do is lead to better treatment that will alter not only the natural course of disease, meaning how somebody does with Crohn's or ulcerative colitis, but avoid unnecessary medicines, unnecessary side effects, and then ultimately at the end of the day what we all hope for, is that this will ultimately lead to a cure. I do think that that is in the future.

I would like to thank you as the audience for your attention to my talk. I certainly now will open it up to questions. I think Laura might have a few words to say as well, but thank you very much.

Laura Wingate:

Thank you very much, Dr. Regueiro, for your informative presentation. Now it's time for the question and answer part of our program. If you are hearing this program in English, the operator will soon be explaining how to queue yourself up for the questions. I have pre-submitted questions from our Spanish language audience and will be alternating with each of the live questions. So if you are hearing this program in Spanish, please disregard the following instructions stated by our operator. Operator, can you now please give the instructions to the telephone and webcast audience.

Operator:

If you are hearing this conference in English, to participate in the call by asking a question, please dial star-1 on your keypad. If you are joining us by web, simply click on Ask a Question, type your question, and then hit Submit. We will take questions in the order they are received. We can only take one question per person. Once your question has been voiced, the operator will transfer you back into the audience line. Again, to ask a question please dial star-1 on your keypad or click on Ask a Question, type your question, and then hit Submit.

Laura Wingate:

Dr. Regueiro, we will take our first question from the Spanish-speaking audience. Vilma from Venezuela writes I have been taking mesalamine for 18 years, are there any known side effects. And part two of her question is are there other effective medications to treat ulcerative colitis in the rectum.

Dr. Miguel Regueiro:

So that's an excellent question and thank you for that. The question is whether taking mesalamine for a long period of time, so that's a 5-aminosalicylate, what's the safety, and what is the best treatment for ulcerative proctitis or inflammation just in the rectum.

Well, mesalamine or the 5-aminosalicylate category has been around for a long time and is probably one of the most common and safe medicines that we have. Generally it's well tolerated and to answer the question, I think the safety profile of somebody who's been on it that long is very good. It actually may also help prevent colon cancer in patients with ulcerative colitis. Generally as physicians we do recommend that people who are on mesalamine get a yearly blood count, what's called a complete blood count, kidney function test, and liver function test. Very, very, very, very, very rarely we see an abnormality with that.

And the second part of the question, probably the best treatment for ulcerative proctitis or inflammation mainly in the rectum, is to use a mesalamine suppository or enema. Even though that sounds like a strange concept, sometimes applying a treatment directly to the rectum and healing the rectum is better than taking a lot of pills.

Laura Wingate:

Thank you. We're going to take our next question from the web audience. This question comes from Kathleen. What is the latest stem cell research for Crohn's disease?

Dr. Miguel Regueiro:

So what is the latest research for Crohn's disease. There are a number of different treatments that are available for Crohn's disease currently, but there are also many that are in the pipeline. Most of the research at this point is targeting biologic, what we call cytokines. And there are over 50 trials at this point looking at administering medicines that target certain immune chemicals in the body. Some are given as pills, some are given as injections, and some are given intravenously. I think probably in the next five years there are going to be several that will come out that will be readily available for Crohn's and ulcerative colitis.

Laura Wingate:

And what about stem cell research?

Dr. Miguel Regueiro:

And stem cell research is one of those treatments. Stem cell research is actually interesting in that there may be the ability to give stem cells and these can come as

mesenchymal stem cells, these can be autologous, from one's self, and these are often harvested in different ways. Just shortly put, if we administer those to the body, interestingly they may naturally heal inflammation in a way that does not suppress the immune system like some of the other medicines that I mentioned a minute ago. There are several ongoing trials on stem cells, we're awaiting their results. Preliminary studies look very positive and I do think at some point stem cells will be available for Crohn's and colitis.

Laura Wingate:

Thank you. Operator, we'll take our next question from the telephone audience.

Operator:

The next question comes from Julianne in Louisiana.

Julianne:

Yes, I'm steroid-dependent and I've done both Remicade and Enbrel[®]. I'd like to know more about the other biologic agents that Dr. Regueiro mentioned.

Dr. Miguel Regueiro:

Good question. Somebody steroid-dependent, has been on Remicade and Enbrel, what about the other biologic therapies.

Right now there are three commercially biologic therapies beyond what you mentioned. There's Humira, which is adalimumab, Cimzia, which is certolizumab, and natalizumab, which is Tysabri. Cimzia and Humira are similar to Remicade, except they're given as an injection. Humira is fully human. And certolizumab is what we call humanized. Both work like Remicade does. Unfortunately, Enbrel has not been shown to be effective in IBD. But if Remicade has worked, sometimes we'll try one of those other two. If none of those work, Tysabri has been approved for multiple sclerosis. It's given as an IV. Generally it's been very effective. There has been a rare complication called PML, which is an infection that can affect the central nervous system, and I think that somewhat tainted our enthusiasm, but I do have patients on it doing quite well. So those are the three other commercially available treatments.

Laura Wingate:

Thank you. We will take our next question from the Spanish-speaking audience. This question comes from SheylamarSheylamar from Puerto Rico. Can exercise aggravate Crohn's disease?

Dr. Miguel Regueiro:

Thank you for the question. Exercise has been interesting in that we've seen two things with exercise. For the most part exercise can improve Crohn's disease and ulcerative colitis. And sometimes symptoms, and we think maybe even inflammation can improve. However, there is a group of people who are runners or who exercise quite a bit, and actually notice that their diarrhea or their symptoms worsen. So forget Crohn's

and ulcerative colitis for a minute. There are elite athletes who run quite a bit, who will get problems with diarrhea without having Crohn's or colitis, and we think that it might be the way the blood circulates to the intestine in people who run long distances. So to answer your question simply, exercise will not worsen Crohn's or colitis, but some people who exercise quite a bit may notice that they get more diarrhea or even a little bit more bleeding and that probably has to do with those people, the way that the blood is circulating into their intestines.

Laura Wingate:

Thanks. We'll take our next question from the webcast audience and the question is from Marianne. In your experience how would you compare the effectiveness and side effects of mercaptopurine versus azathioprine and how often should blood work be done while on these medications?

Dr. Miguel Regueiro:

Right, so azathioprine and mercaptopurine, also known as Imuran or 6-MP, are essentially the same medicine, meaning that azathioprine, which is Imuran, is automatically converted into mercaptopurine in the body. So when you take the pill it's converted to mercaptopurine. The biggest difference is the doses, when you look at the milligram doses, are different. And we have to do a conversion. As far as blood work and how we monitor patients on mercaptopurine or azathioprine, every physician does it slightly differently, but I think all of us agree that routine blood work for the complete blood counts and liver function test is required. The reason for that is very rarely one of the side effects of these medicines is that they can lower the white blood count, which is involved in fighting off infection. Also these medications can increase the liver function test as a result of inflammation in the liver. The good news is if any of these problems occur, we stop the treatment and those problems go away.

Laura Wingate:

We'll take our next question from the telephone audience, Operator.

Operator:

Our next question comes from Rita in Florida.

Rita:

Yes, hi. This question is regarding the new treatments that you are saying will be becoming available in the next five years. Will any of these not be contraindicated if a person has latent TB that cannot be treated?

Dr. Miguel Regueiro:

That's a very good question. So the question is that one of the things we have found with some of these medicines, including the anti-TNFs, is that if a person has latent tuberculosis, there has been an increased rate of reactivation of tuberculosis. Without going into all the caveats of latent TB, there are actually some people with latent

TB that we actually can treat with these medicines, but it's somewhat complicated to go through how in detail. But to answer your question on the newer treatments, some of the newer treatments may be beneficial in people who have underlying TB or latent TB because they do not seem to target the immune system in a way that would promote TB. So some of these treatments may be available and may actually not cause problems with TB.

Laura Wingate:

Thank you. We're going to take our next question from the Spanish-speaking audience. This question comes from German in Spain. What are some of the general steps to follow for refractory patients who have received the conventional treatments?

Dr. Miguel Regueiro:

That's an excellent question and actually into itself that could be the topic of an entire conference, so thank you for that question. So I guess that there are so many caveats in people who fail traditional treatment, but one of the caveats, or I should say a couple of the caveats that we look for is if somebody is not responding to medicine, we try to figure out if it's a complication of the disease or if it's the disease itself. So for example with Crohn's disease, sometimes people seem like they're getting worse on treatment and we find out that they might actually have lots of scar tissue, a stricture, or a fistula or a penetrating problem that causes inflammation or infection. And actually in some of those people that we consider refractory, we'll recommend surgery. Also, we're seeing higher rates of infection. There's one called *Clostridium difficile* or *C. diff*, which has become really almost an epidemic. In some people who we see are refractory to treatment, we need to rule out other infections and make sure that's not the case. Finally, for those people who have active Crohn's or colitis and are not responding to treatment, we need to look to either some of the new biologics or if there's availability, to try to see if you would be eligible for a clinical research trial.

Laura Wingate:

Thank you. Our next question is going to come from our web audience. This question is from Rodrigo and he asks if you have Crohn's disease and have not reached mucosal healing, but are in remission, would you request that your physician keep increasing the dose or switch meds in order to reach mucosal healing?

Dr. Miguel Regueiro:

These are all absolutely outstanding questions and I wish all of you could have come to the CCFA physician conference this weekend because these are exactly the topics that we were talking about, so I really commend everybody on their questions.

I will give you my answer to this. So the question is if somebody does not achieve full mucosal healing, but they feel well, do we have to keep driving treatment to heal the mucosa completely. My feeling is that if we heal the mucosa to a point, but we can't heal it entirely, but the person has their life back, their quality of life is better, they feel better, their pain is less, their diarrhea is less, that if they're on what we consider maximal

medical therapy, that may be the best we can do and I'm not sure that without going through a drastic surgery we can take care of the problem beyond that. However, if somebody's not on what we would consider aggressive treatment, who maybe still has some mild symptoms and we still have active disease, I do think what we've learned now is that if we can heal the mucosa by stepping up treatment, whether it's to an immunomodulator or a biologic, healing the mucosa long term has benefit in preventing cancer, surgery, hospitalization, and future complications. So if we can heal the mucosa, great, and that's important. But I do think that there are some people that even with the maximal treatment, we just cannot fully heal. And that may be the best that we can do.

Laura Wingate:

Thank you. Operator, we'll take our next question from the telephone audience.

Operator:

Our next question comes from Sherry in California.

Sherry:

Hi, my question is when somebody has Crohn's disease, could osteoporosis be a result of Crohn's disease?

Dr. Miguel Regueiro:

So the question is osteoporosis in Crohn's disease. We do see a higher incidence and prevalence of osteoporosis or bone thinning with Crohn's disease. Some of that may be nutritional, so Vitamin D deficiency, calcium deficiency. Some of it could be a complication of medicines, specifically corticosteroids like prednisone, which accelerate bone loss in osteoporosis. Generally as physicians, it's our job to try to establish bone health. We often recommend bone densitometer, check Vitamin D and calcium, and try to limit steroid use for the reason that osteoporosis in Crohn's is common, but it's very common with steroids.

Laura Wingate:

Thank you. We're going to take our next question from the Spanish-speaking audience. This question comes from Maria in Ontario, Canada. My son suffers relapses every time he gets a cold, is this common?

Dr. Miguel Regueiro:

That's a very common scenario. So the question is somebody who gets a cold seems to get relapses of their Crohn's or colitis. Interestingly, even though you would think it's disconnected, so meaning having a viral cough or sinus problem or sore throat, we actually now know that upper respiratory infections have been linked to flares of Crohn's and colitis. Probably the reason for this is that as the immune system revs up, if you will, to fight off the infection or the cold, it cannot distinguish between the cold and the intestine. So as the immune system fights off the cold, often it can make the Crohn's or colitis worse. And that's a very common scenario. I'm afraid that's hard to avoid,

except we do recommend things like flu vaccines in people with inflammatory bowel because having the flu on top of IBD can be quite severe.

Laura Wingate:

Thank you. Our next question is from the web audience from Bruce. What can you tell me about calprotectin stool testing, why isn't it used more widely?

Dr. Miguel Regueiro:

So interestingly the biomarkers that have been looked at, there's a fecal or a stool calprotectin and a stool lactoferrin, and the question is why aren't these more commonly used. I think there are a couple of reasons for that. One is that as physicians and researchers we're trying to position them in clinical practice. I think to your point these probably will be used more commonly in the future. I do think that these correlate with mucosal healing and inflammation. And I would predict in the next five years that we'll probably see these tests ordered more commonly. The other thing, and each center is different in this, but I know at least where I am, sometimes when we order these tests, the insurance companies won't cover it and the cost of doing these can be quite expensive. Even though the test itself should not be very expensive, the bill that the person gets can be. So that has been a limitation. I think in the pediatric community, these are starting to be used with more frequency and I think in the adult IBD and GI communities we're going to certainly be using these more in the future because I do think that they are very good tests.

Laura Wingate:

Thank you. Operator, our next question from the telephone audience.

Operator:

Our next question comes from Annette in New York.

Annette:

I just recently had surgery for Crohn's disease. In fact I had it in March of 2010. Now since then I have not been on medication. I went for my check-up at the doctor and he said well, if you're feeling okay, perhaps you should just wait and see. They had given me some very strong prednisone when I was in the first two episodes before I had the surgery and I really can't tolerate that. I was on Asacol[®] for a good 16, 17 years. By the way, this is my second surgery, my first one was 17 years ago. And then he told me stop taking the Asacol, it's no longer effective for Crohn's. So now I'm up in the air, I really don't know what to do.

Dr. Miguel Regueiro:

I think the question is how do you manage postoperative Crohn's disease, is it something that we follow or is it something that we automatically treat. This is actually somewhat near and dear to my heart as we've actually researched this quite extensively in the last five years. And the answer that I'll give is that I think at the very least, if

somebody's had Crohn's disease surgery, within six to twelve months of the surgery, especially if one is not on medicine, it would be important to do a colonoscopy and look at where the surgery is done, to make sure that there is not early recurrence of Crohn's. Because what we've now learned is that Crohn's recurrence is not uncommon after surgery, but it often takes years before the person can feel it coming back.

The second is that we are now learning that in people who've had either multiple surgeries or have what we call fistula or penetrating disease, or those that smoke after surgery, have the higher rate of recurrence and there's now a push to possibly getting people on preventative medicines, things like Imuran, 6-mercaptopurine, even the anti-TNF agents, early, to try to prevent recurrence and the need for future surgery.

Laura Wingate:

Thank you. Our next question is from the web from Linda and she asks how do you feel about using a natural holistic type doctor in addition to your regular GI?

Dr. Miguel Regueiro:

I think this is an important topic and I think as a research and physician community, we're still trying to learn the best approach. My personal feeling is that there is a lot in medicine we understand, but a lot we do not understand. Therefore I think complementary medicine, certain holistic and natural approaches may have a role. As they say, the devil's in the details, meaning that there are certain things that can be done to supplement traditional treatment that I think make sense. Certain things like probiotics, which I mentioned that in my talk. Certainly those types of things would be of benefit. If somebody has severe IBD, stops all treatment, and tries a more natural approach, I would probably do that in concert with a gastroenterologist or physician to make sure that the person is on some type of treatment because we have seen people abandon treatment completely and later have problems. But to answer your question, I definitely think there's a role for complementary natural medicines. I think it just needs to be done in concert with the physician treating the IBD.

Laura Wingate:

Thank you. Dr. Regueiro, this is going to be our last question. And this question comes from Jean. What are your thoughts about the use of low-dose naltrexone as a way to manage IBD?

Dr. Miguel Regueiro:

So one of the interesting novel treatments that's been explored recently has been naltrexone and so for those that don't know what naltrexone is, it actually works on an opioid receptor or pain receptor to actually block the receptor. It's been traditionally used to combat some of the narcotics and reverse the effects of narcotics. But there's been an interesting research that's emerged, looking at certain nerve receptors in IBD that may lead to inflammation. And the question is if we give a medicine like naltrexone, can it block that. There was an early phase study that was published and looked quite promising with Crohn's disease. I would say right now I would still reserve it to more of a

research arena. So an academic center that's interested in researching this really should oversee it. It may be that in the future it's an effective treatment that we'll use as standard of care, but I think until then we really need to focus on the research centers looking at naltrexone.

Laura Wingate:

Thank you, Dr. Regueiro, for your insightful presentation and your answers to our questions.

To everyone on the line, if your questions were not answered, you can call CCFA's Information Resource Center at 888-694-8872. The center is available to assist both English and Spanish speakers.

To further help our understanding of IBD, we encourage you to join CCFA Partners, our national registry of patient-reported outcomes. Simply complete an online survey and be a part of this exciting research initiative. Visit www.ccfapartners.org to learn more and to participate.

I encourage all of you to complete the program evaluation. Your feedback helps us shape future programs.

We also want to give a special thank you to Shire for their charitable contribution for today's program.

On behalf of the Crohn's and Colitis Foundation of America, thank you for joining us. Good-bye.

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