

Ulcerative Colitis: The A to Z of Treating UC



TRANSCRIPT

Program Overview

Operator

Greetings, and thank you for joining us today for the Ulcerative Colitis: The A to Z of Treating UC Teleconference/Webcast.

It is our pleasure to introduce today's moderator, Ms. Kimberly Frederick, LCSW, MSW, Vice President of Patient and Professional Services for the Crohn's & Colitis Foundation of America (CCFA).

Thank you, Ms. Frederick, you may now begin.

Kimberly Frederick, LCSW, MSW

Hello, everyone. On behalf of the Crohn's & Colitis Foundation of America, welcome, and thank you for attending today's program, Ulcerative Colitis: The A to Z of Treating UC. It is sponsored by Centocor Ortho Biotech Inc.

We chose today's topic based on the feedback that we have received in the program evaluations of our previous teleconferences and webcasts. Many people have requested this particular topic, and we are delighted to be able to deliver a program completely dedicated to ulcerative colitis (UC).

To help guide future program topics, we would like to encourage you all to fill out the program evaluation form, which is available online and in the registration packets.

We would also like to thank all of you who submitted questions in advance of today's program. We have worked hard to address many of those content areas.

After our keynote presentation by Dr. Ullman, we will then open up the program for your questions. We will take as many questions as time allows, from both the telephone and webcast participants. If we're not able to take your question, our Information Resource Center can be reached at 888-694-8872. The Information Resource Center is open Monday through Friday from 9:00 AM to 5:00 PM Eastern Time.

An archive of today's program will be posted on the CCFA website where you will be able to listen to the presentation, view presenter slides, and download a transcript of the program.

I now have the distinct pleasure of introducing Dr. Thomas Ullman. Dr. Ullman is an Associate Professor of Medicine, Director of the Center for IBD, Division of Gastroenterology, at the Mount Sinai Medical Center in New York.

Dr. Ullman received his undergraduate degree from Brown University and continued on for his medical degree from Cornell University Medical College, and completed a postdoctoral fellowship at Yale University School of Medicine.

Dr. Ullman has conducted studies detailing the natural history of dysplasia in ulcerative colitis, the influence of inflammation on carcinogenesis in IBD (inflammatory bowel disease), and relative

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chemopreventative effects of a number of therapies used in UC. Additionally, Dr. Ullman is pursuing research into biomarkers of disease diagnosis and activity in IBD.

Now, I'd like to turn the time over to Dr. Ullman for the presentation.

Presentation

Thomas Ullman, MD

Thanks very much, Kim, and I want to thank not just Kim, but the entirety of the CCFA, for putting on this and previous webcasts. These have all been such terrific programs; I am hoping very much that I don't break the string of terrific webcasts that the CCFA has had to offer. I want to thank all the technical support people as well, who have done a great job in priming me so that, hopefully, this will go off flawlessly. Most of all, I want to thank all of you out there on the Web or on the phone listening to this, who are really taking some time out of what I am sure are busy days, and I hope that together we can make headway in our mutual education about the diagnosis, care, and treatment of ulcerative colitis.

Kim gave a nice introduction, so this is all just a little bit of extra business here and we will jump right into it here. The goals of today's presentation are to provide an overview of ulcerative colitis, to discuss treatment options, and to review the impact of ulcerative colitis on quality of life. We will also identify questions to ask your doctor, and the possibility and the certainty that some questions I'll be able to answer for you guys at the end.

Ulcerative colitis, as most of you probably know, is a type of inflammatory bowel disease. It is a chronic and relapsing disease of the large intestine. The large intestine is sometimes called the colon—those two things can be used interchangeably—that causes inflammation and ulceration in the lining of the bowel. About half of the cases are mild and that certainly means that the other half are not so mild. Flares may be alternating with periods of symptom-free remission. It usually requires treatment to obtain a remission, and we commonly use treatment not just to obtain that remission, but to maintain it as well. There are certainly some similarities between the inflammatory bowel diseases, ulcerative colitis and Crohn's disease. You see that nice little photograph with the big white arrow pointing to some ulcers that are there in the lining of the colon in a patient with ulcerative colitis.

In terms of what distinguishes ulcerative colitis from Crohn's disease, they both certainly are inflammatory bowel diseases, as I mentioned, and their prevalence is about equal. Prevalence is a term that some scientists, called epidemiologists, use to describe how many patients out there in a population have the illness. We think, in the United States at least, that there are about the same number of patients with ulcerative colitis as there are with Crohn's disease.

Ulcerative colitis affects the colon, starts at the rectum, and moves some distance north within the colon or large intestine. Crohn's disease can involve the colon but may also involve the small intestine, or really any other place in the gastrointestinal tract from mouth to anus.

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The lesions in ulcerative colitis—that is what we see that is abnormal in the lining—usually are shallow ulcerations in ulcerative colitis and are more commonly deep ulcerations in Crohn's disease, but it is often very difficult for a gastroenterologist or a radiologist to truly distinguish what he or she sees on either a colonoscopy or an x-ray test. Even if it is shallow versus deep, it is sometimes very difficult to distinguish ulcerative colitis from Crohn's disease.

In ulcerative colitis, that pattern of ulcers tends to be continuous and doesn't have areas that skip, whereas Crohn's disease may be patchy. Following treatment, that can all change and ulcerative colitis can appear to be patchy but, usually, at its presentation, and for most of its course with or without treatment, it tends to be continuous.

There are different surgical approaches to ulcerative colitis than there are with Crohn's disease. Approximately 25% to 40%—and this number needs to be relooked at in the twenty-first century—of patients with ulcerative colitis will have surgery at some time to treat their ulcerative colitis. In Crohn's disease, that proportion is much, much higher; in part because it sometimes includes segmental, or short segments, of small intestine requiring that surgery.

There is an increased colon cancer risk in both ulcerative colitis and Crohn's disease, though it is slightly higher in ulcerative colitis because when the disease involves the colon, it seems that is a much more common area for cancer than the small intestine, which can be involved with Crohn's disease. We are going to speak a little bit more about cancer and cancer risk in the upcoming slides, but before I freak anybody out, let me just say that the risk seems to be, in the twenty-first century at least, almost equal among patients with ulcerative colitis who are followed by a gastroenterologist, as it is in the general population. That seems to be one of our larger achievements, though we do not know exactly how to credit that achievement. Whether that is due to colonoscopy, medicines, or some other factors that we have not yet figured out or understood is really unclear.

Another thing that I love to do is dispel myths in general and, specifically, one I would like to dispel is that inflammatory bowel disease, in general, and ulcerative colitis, specifically, are caused by stress. Now sometimes stress can make the symptoms worse or can seemingly trigger a flare, and it certainly can make the symptoms worse, but the disease itself and the underlying inflammation that goes on with this disease is not caused by stress alone.

What does cause it? I would love to tell you that I have the answer to that, but I don't really know. It turns out that there are certainly genetic influences into the cause of ulcerative colitis. There are environmental cues and triggers that seem to be apparent in terms of it, and you need to have some genetics, you need to have some environment, and you need to have some sort of defect or change in the immune system, meaning that what we really have here with ulcerative colitis is a disease of an inappropriate immune response to normal conditions.

The way that I would like for all of you to think about this, and you probably have at some time, is that under ordinary circumstances everyone is at risk for a colonic infection. When we have an infection, what we are talking about, is some sort of bacteria or virus or other bug that the body needs to get rid of and really replace it with the normal bacteria that live there.

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What happens, or what seems to be happening in ulcerative colitis, is that the normal bacteria are there but what we have is an inappropriate immune response to what otherwise is normal. And, again, we think that has to do with some genetic factors, some environmental factors, their combination, as well as some immune system factors that are independent of those features.

The connection of these factors is very important and lots of research is certainly ongoing to better define these things. We are still on a certain level scratching the surface. The environmental factors that we believe to be triggering this robust, or overly robust, inflammatory response include infectious agents; the immune system, as I mentioned, over-responds to this kind of environmental insult. It gets turned on and, unfortunately, cannot get turned off. Some people liken this to the Energizer® bunny kind of metaphor that we have seen in advertising to say it just keeps going and going and going. This is certainly part of the deal with ulcerative colitis.

What's going on there is that the immune cells are attacking normal tissue, causing inflammation and tissue injury, and those ulcers that I mentioned before and those changes that we saw in that one image of a colonoscopy, seem to really be about this over-robust immune system attack that is there.

This same inflammatory process can affect other parts of the body, and sometimes there are these symptoms that go on in joints, in skin, with rashes, some eye inflammation, occasionally some oral inflammation, and oral ulcers as well, though that is more typical for Crohn's disease. These kinds of symptoms, outside of the large intestine in ulcerative colitis, they are collectively called extra-intestinal manifestations.

In terms of genetic research and genetic mapping that has occurred, a number of genes have been identified as being part of the process. Sadly, this has not yet, at least, led to any discoveries for potential therapies for ulcerative colitis. It seems that the genes involved somehow turn on certain inflammatory pathways giving rise to ulcerative colitis. We are hoping that someday we will be able to really harness what we have learned from these genetic studies and turn them into therapies.

It is also possible that some of these genes will predict all sorts of things about the disease and potential response to therapy. Instead of something of a one-size-fits-all or nearly-all approach to treating patients, we can actually, over time, potentially develop more individualized therapies.

The symptoms that so many of you have, unfortunately, become familiar with, that are characteristic of ulcerative colitis, include diarrhea, often mixed with blood and mucous; the blood and mucous coming from the abnormalities to the lining of the colon or large intestine. The thing you have to remember is that the large intestine, on a relative basis, is something of a dumb organ and the things that it really does are help to absorb water as well as some electrolytes and provide a convenient storage place for feces. Diarrhea mixed with blood and mucous tends to be the hallmark symptom of ulcerative colitis. As would be the case with any kind of inflammation involving the large intestine; abdominal pain and cramping are often present. There is an urgency to have a bowel moment, in part because, with all that inflammation that is there, including to the very bottom part of the rectum, there is an uncertainty as to whether that rectum is empty or full, and sometimes the brain receives really incomplete or inappropriate signaling from the diseased rectum. Often, because of the ongoing active inflammation,

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there can be appetite loss, fatigue, and weight loss. While sometimes these symptoms can herald one of these flares when there is more active disease, sometimes there is more of an up and down or cycling course to the disease.

In children who get this, because of the chronic inflammation, this can give rise to growth impairment. There can also be these nonintestinal or extra-intestinal complications that we spoke about before with joint pains and swelling, skin rashes, oral ulcerations, and eye inflammation. Every now and then there are some liver problems where the bile ducts that exist in the liver can become inflamed, and there are some other less common extra-intestinal or noncolon symptoms that can happen as well.

As for the disease pattern, the rectum is almost always involved. To a certain extent, it really is almost universally involved. It is very uncommon that there is no involvement of the rectum. Sometimes it is a little decreased in the rectum as opposed to the rest of the large intestine.

We tend to classify the disease based on how much of the colon or large intestine is involved, and we have a nice figure coming up in a future slide about that. Patients usually report a gradual onset. It is not so much like a light switch kind of trigger where symptoms come on and all of a sudden; folks are terrifically, terrifically, sick, whereas the day before they felt fine. Usually, it takes sometimes days or even a week or weeks for things to sort of linger before attention is sought, because it seems to be, or can be, a little slow and insidious in its onset. The return attacks go along with complete remission and so it has this waxing and waning property to it in many, many patients.

There you see another great image from a colonoscopy and, usually, ulcerative colitis, as it says there, has these continuous but superficial ulcerations. The white that you see there, those are the ulcerations, and the red is the regenerative or new tissue being laid down on this ulcer bed that is there as the colon tries to heal itself over time.

Triggers for disease activity or symptom worsening include psychological stress; even though we said before it doesn't particularly cause it, it can certainly make symptoms that are always there seem a little bit worse or maybe even become a little bit worse without actually affecting inflammation that is there. This whole brain/gut interaction is something that is being explored on an everyday basis in research labs around the globe.

Nonsteroidal anti-inflammatory drugs—and these include aspirin, ibuprofen, naproxen, Aleve[®], really almost all of the over-the-counter pain medicines except for Tylenol[®] and acetaminophen, can all give rise to disease flares, though they don't always. This is not really a one-to-one kind of pattern. Patients who receive these drugs are just at a somewhat greater risk for developing or perpetuating a flare than patients not on these drugs.

There is an interesting association to having had an appendectomy; patients who have had an appendectomy are at slightly higher risk for the development of ulcerative colitis over their lifetime, although, again, not even close to a one-to-one kind of relationship. It is just a subtle increase that will take good research to figure out what is going on there.

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Remission rate declines with disease severity. Relapse rate appears to be higher in younger patients as opposed to older patients. We are not really sure why that is. The important thing to always remember with this is that ulcerative colitis primarily affects quality of life but does not really shorten one's life span. This is really important to keep in mind when you are thinking about that or if you are attending this on behalf of a loved one.

We tend to characterize the severity of disease based on the ongoing symptoms. This does not always associate with how much damage there is to the large intestine, but that is something of an academic kind of discussion. We think of mild disease as involving up to 4 loose bowel movements per day, often bloody, with perhaps some mild abdominal pain.

We think of moderate disease when it involves 4 to 6 bowel movements a day and there seems to be more pain associated with it. There may be some other symptoms like anemia, which just means a lowered red blood cell count. This can certainly be apparent in patients with moderately active disease.

We think of the disease as being severe when there are more than 6 bowel movements a day. Most of these will be bloody in a patient with severe disease, and there may be some, what we call, constitutional symptoms, and these are the things like fever, appetite loss, and the like; anemia is often present here as well.

We tend to think of fulminant disease when there are more than 10 bowel movements a day, there is continuous bleeding, abdominal pain, sometimes distention, meaning that the abdomen starts to fill up with air. If left untreated, fulminant disease can have the severest of severe consequences, you can see on the slide, sometimes being fatal. So a patient with fulminant disease really needs very intensive monitoring and often will need to go to surgery if there is not something of a rapid recovery in a hospitalized setting.

We also tend to define the disease, as I mentioned before, based on how much of the large intestine is involved. If the disease only involves the rectum, we call this proctitis. If it involves the rectum and some part of what is called the sigmoid colon, that is the part of the large intestine that sits just above the rectum, we tend to call that proctosigmoiditis. Left-sided colitis occurs when it extends all the way up on the left side to that part in the left upper abdomen; on that figure there, that is someone facing you, so it goes from the rectum up on the left. If it gets to that corner that is up there and extends no further, that is left-sided colitis. If it crosses over that corner, we tend to call that extensive colitis.

Again, the extra-intestinal features: oral ulcerations, which you can see in the picture. It is the little, sort of punched-out ulcer underneath the patient's finger, with the yellow arrow pointing to it. There can be eye inflammation; there can be arthritis with swelling and inflammation of the joints involving hands, feet, lower spine, and just about any joint in the body. There can be different kinds of rashes or skin manifestations as well. Sometimes there are some bumps on the shins, sometimes some rashes or skin lesions that involve ulceration that looks not too different from what you see there on the patient's mouth, as well as what we saw on the pictures of the colonoscopies.

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The risk factors that we have been able to identify and certain things that go along with this disease include the fact that it can occur at any age, though it does tend to affect younger people more commonly, or at least the initial presentation happens in younger people. Patients in their teens, in their twenties, in their thirties, those are sort of the peak years for developing the disease. There is, however, a second peak that seems to occur in patients when they reach 50 years to 60 years of age. It can affect all ethnic backgrounds. For reasons that are unclear—and it is uncertain whether this is genetics, environment, or other features—it does tend to be a little more common in Caucasians as well as in Ashkenazi Jews (those are Jews mostly of a European background). It seems to be a little more common in women than men, and there seems to be familial clustering as well. The risk of having this is a little higher when you have a first degree relative, and that means a parent, sibling, or child, who has ulcerative colitis. Although only about 5% to 30%, depending on which study you take a look at, do have a first degree relative with ulcerative colitis or with Crohn's disease.

The overall rates that are out there, we think we have about 700,000 people in the United States who are affected with ulcerative colitis, and that works out to be about 35 to 100 people per 100,000 in the population. There is a good deal of uncertainty in this number, but we tend to think that there are somewhat more than half a million people, so 700,000 in the United States is our best guess based on more recent studies.

As I mentioned before, there is this potential risk for colon cancer. That risk does not seem to occur, nor does not seem to increase above the generic or general population until the disease has been present for 8 or 10 years. Although it can occur earlier; it seems that the risk does not get above the general population's risk until then. It seems to be more common as the severity of ulcerative colitis increases. Other risk factors that are there seem to be the presence of the liver disease called sclerosing cholangitis; that is sometimes associated with ulcerative colitis but only in about 3% or so of ulcerative colitis patients. Patients who have disease when they were younger in age seem to be at a slight increased risk as well.

We do screening colonoscopies on patients once they hit 8 to 10 years of disease, and then we tend to perform them every 1 to 2 years afterwards. In so doing, or at least since we have been doing this, it seems as though we have been able to reduce that risk over time and it tends to look a whole lot like the general population's risk for colon cancer.

A common test that we use to diagnose and potentially make certain that a patient has ulcerative colitis, and make sure that they don't have something else that might look like ulcerative colitis, often we will do stool cultures and other stool tests to look and see if there are bacteria, parasites, or products of bacteria present. We, similarly, might do some blood tests to look at markers of chronic inflammation or acute, or just recent onset inflammation, as well as to look to see if there is anemia or the presence of an infectious organism.

The gold standard test in making the diagnosis, of course, is a biopsy of the intestinal lining, usually obtained at the time of a sigmoidoscopy or a colonoscopy. A sigmoidoscopy is just an abbreviated portion of a colonoscopy where the doctor only takes a look at, usually, the last third or so of the large intestine. Sometimes we will look at liver and kidney tests as well to see if something else is going on.

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As I mentioned, colonoscopy or endoscopic examination is the gold standard. The way we do it, and have done it now for the last 30 or so years, involves the use of a flexible scope or tube that has a light going through it as well as some sort of imaging device. These things used to run on fiber optics, they now work on this cool technology of video chips. We can take a look directly at the lining of the intestine and take a look at it on a monitor or a screen. We insert that into the rectum and then examine the rectum and then some distance behind the rectum to see what is going on in the large intestine.

We sometimes can do radiography tests, including barium x-rays, where an amount of something that x-rays don't go through, it is called radio-opaque, gets inserted into the large intestine and we can indirectly look at the lining that way. Sometimes we will do CAT (computerized axial tomography) scans on patients with ulcerative colitis to take another look at certain amounts of inflammation that might be found there as well, as well as to look at organs, not just the colon.

Moving on to treatment, which, I think, is probably most relevant to what is going on here today, we tend to take a look at a number of different kinds of medications that are out there. While we have had this disease pretty well defined for a good amount of time, our number of treatments that have been available and are available, has not changed so much over time; at least not so much in the last 5 years or so, and we have a lot of things that have been very effective over time, though I do think we are on the cusp of really making some important breakthroughs going forward.

Most commonly, we treat patients with a group of drugs called aminosalicylates, sometimes called 5-ASA, because it is technically a 5-aminosalicylate. These include drugs like sulfasalazine, mesalamine, balsalazide, and olsalazine. You might know these from some of their trade names, including Azulfidine[®] (sulfasalazine); I don't want to lead anybody here, obviously, and I am hesitant to give an order here. This is not an order of endorsement; it is just a general group of the medicines that are out there. There is Asacol[®] (mesalamine), there is Lialda[®] (mesalamine), there is Pentasa[®] (mesalamine), there is Colazal[®] (balsalazide), and Apriso[®] (mesalamine), as well as Dipentum[®] (olsalazine) and some others. Those drugs all basically work the same way and they all contain mesalamine or 5-aminosalicylate, and that is the basis for the way that they work.

Other anti-inflammatories that we use include corticosteroids—primarily prednisone and hydrocortisone—and these can be given, as can the mesalamine or the aminosalicylates, in both oral and rectal preparations. We sometimes will use immunosuppressant drugs, sometimes called immunomodulator drugs. It is worth pointing out, however, that the corticosteroids are terrifically immunosuppressing, but the immunosuppressants, or those that get classified that way for the treatment of ulcerative colitis, include what are called the thiopurines, and this is azathioprine and 6-MP; they are intimately related to one another. 6-MP is also 6-mercaptopurine or Purinethol[®]. Azathioprine also goes by the name of Imuran[®], and these drugs all work via the same mechanism and can be very helpful for avoiding corticosteroids over time.

We reserve the drug cyclosporine, that you see there on the list, for the treatment of patients who are in the hospital by and large, who are not doing so well with oral or intravenous corticosteroids.

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Methotrexate can be used, certainly, in Crohn's disease. Its track record in ulcerative colitis is still somewhat unproven but it is suspected to be of benefit, and there is actually a large Crohn's & Colitis Foundation of America, or CCFA-sponsored study that is going to take a look at its utility in the treatment of ulcerative colitis.

There are also biologic therapies. Most biologic therapies get their name because they are really protein-based therapies. These are very, very large molecules and have to be given either intravenously or under the skin. They cannot be given orally or rectally for that matter, and the only one that is approved for use in ulcerative colitis at this point is infliximab, which also goes by the name of Remicade® and it certainly has been shown to be effective in this situation.

We use antibiotics primarily to treat infections related to ulcerative colitis. There are very few studies, if any, that support antibiotics as primary therapy for the treatment of ulcerative colitis itself.

I drew up this slide, which reveals the old New York real estate expression of location, location, location being important. The rectum is really responsible for most of the nagging symptoms I mentioned. The urgency before, frequency because you don't know if you are full or empty can give rise to nighttime bowel movements and an expression you may have heard of called "tenesmus." You want to think of tenesmus as dry heaves of the rectum, and patients very frequently report they don't know if they are full or they are empty. They sit down, they stand up, they sit down, they stand up, and it is really a very nagging symptom, which really owes most of its presence to the presence of rectal inflammation.

It is important to point out that rectal therapy can really, really be effective in minimizing these nagging symptoms, so we tend to give enemas, suppositories, or sometimes spray foam in the form of Cortifoam® (hydrocortisone acetate rectal aerosol), which is a steroid-based foam, that can be very, very, very helpful at minimizing these symptoms. When the rectum is really sick, of course, patients cannot hold on to an enema, and that is when we tend to use the suppositories and foam.

Another option is surgery, and we want to think of surgery as a treatment option and not necessarily the failure of treatment. Too often we get suckered into believing that surgery is really just failure of treatment. It is, in fact, a treatment, and it is an option that about a quarter or more of patients will ultimately end up getting. We consider it a cure for ulcerative colitis but the anatomy does change when we do this. We talk of a proctocolectomy with removal of the entire colon, and sometimes this leads to a permanent ileostomy, where a segment of small intestine is brought out to the abdominal wall and the waste is then caught in an appliance that is worn across the abdominal wall. There is also something called an ileoanal anastomosis, and that is when the small intestine is then brought down to the anal canal and connected there. The sphincter muscles are still there and so there is still continence, though there are something to the tune of anywhere from 5 to 10 trips to the bathroom per day. It tends to preserve normal bowel function and can be very helpful, but it is not necessarily for everyone.

The diagram that you see there shows the J pouch, or what looks a bit like a J, down at the bottom of the figure. Sometimes because this surgery is done in multiple steps, the diagram of this patient shows

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not only a J pouch down at the bottom, but across the abdominal wall, which is there, or supposed to be there on the left side of that sort of sliced body, what you see there is a diverting ileostomy, so you see the small intestine going out there to the wall. This is very frequent—an ileoanal anastomosis sometimes can be done in 1 stage but is often done in 2 or 3 stages with a temporary ileostomy as part of the program.

The primary goals of treatment are remission and the avoidance of a recurrence or a flare. We want to control any complications and prevent them, either from the disease or from the treatment of the disease, and in so doing, we hope to maximize the quality of life. And it is really important to remember that we can do all these things, but if we are not improving the quality of life, we are really not doing anything. It is important to keep in mind that the treatment can sometimes be just as bad as the disease over time, and we always have to think about that.

Sometimes we can achieve remission and maintain a remission just with a single medicine. Sometimes we need multiple medicines to do that. The choice of strategy really depends on the severity of the disease as well as the patients' considerations of just how many medicines they are willing to take and whether or not their perception or their understanding of risk will allow them to take lots of medicines that might have side effects, or no medicines that might have meaningful side effects. It is an important thing for you guys to explore with your physicians, and it is really not a one-size-fits-all kind of treatment strategy here, and we all have to keep in mind whether you are a risk taker or not. Some people will say, "Darn it, I just really want to get better," and will accept lots of risk, and some patients won't accept any risk. It is really an important balancing act and always really important for you to discuss these concerns with your doctor or, in the case of those of you who do not have the disease but have a friend or relative or loved one with the disease, it is a very lengthy discussion and a really important part of the process in determining what kind of therapy to pursue.

We like to think that all these medicines work, and many of them do, and they can prolong a period of remission. There are the possible side effects but it is always important to keep in mind that these medicines are not as fast-acting as we would like them to be, so you really have to gauge things based in that context. You do not want to expect that the next day after starting some of these medicines, you will feel better. Even the medicines that often work the best in the most patients—the mesalamine or 5-aminosalicylate medicines that we spoke of before—on average, they can take anywhere from 2 to 4 weeks to become truly effective. We would like to see some benefit prior to that, but sometimes it does take a while and it is an important, discussion to have with your physician before you start on any medicine, when you might expect to see a response.

It is really unclear whether we need to get super aggressive early or more aggressive medicines, and I tend to use that term "aggressive" metaphorically here. Some of these aggressive medicines have more side effects. It is not clear whether an aggressive early strategy is better than trying the least toxic things and ramping up over time. A really important part of science that is going on now is to figure that out.

The practical consequences of a flare-up include the lack of predictability for those symptoms that we mentioned before, particularly the urgency and the rectal-based symptoms and, unfortunately, many

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patients will try to avoid travel or activity as a result of this. It is also important to point out that the medicines, not surprisingly, work best when you take them. Patients who adhere to their medicines are less likely to have flares or recurrences once they are in a remission. A very nice study demonstrated that there was almost 50% difference in flare rates between patients who were adherent to their medicines versus those who were not adherent. It seems as though it is possible that some of these medicines that we use to minimize inflammation may, in fact, result in decreased development of colon cancer, though that seems to be something of an area of controversy.

The potential side effects of these medicines are listed in the right-hand column that is here. This is important to point out, particularly for the medicines that we use probably too frequently, and those are the steroids, the prednisone-based medicines. We really only listed a few of the potential side effects here, including weight gain, changes in body fat distribution with a moon face, increased blood pressure, suppression of the immune system, loss of bone, sometimes loss of joints—it is important to remember that patients can sometimes need joint replacement surgery as a function of steroid-based medicines. Not shown on this figure are the potential side effects of Remicade or infliximab, as well as 6-MP and Imuran; those include infections; very, very, very, very rare, to the tune of 1 to 4 in 10,000, risk of lymphoma, but that is a little bit higher than it is in the general population. So, it is either an increase of 2 to 3 per 10,000, or a 300% to 400% increase, depending on how you want to spin it, and it is really an important part of the discussion before anyone starts on those medicines.

In terms of long-term impact on the quality of life for the management of any kind of chronic illness, it becomes the responsibility of patients and their family to do a bit of advanced planning. Make sure you do not run out of medicine, perhaps pack some additional personal supplies when on a long trip of some sort, maybe sometimes knowing bathroom locations on the days when you are not feeling well. It is very important to overcome certain features that otherwise are quite debilitating. Many ileostomy patients have certain burdens to bear that, over time, are very much eased as folks learn to live with it, and there are all sorts of different support groups. The CCFA is wonderful for this in being very, very helpful for such patients, and it is very important for patients to know that they are not alone out there and there is lots of help. Among us in day-to-day living, there are lots of patients and lots of folks who live with these illnesses and are such wonderful stand-up and inspiring people. It is important to maintain social interaction and enhance self image throughout the course of this disease, as it is with any chronic illness.

In terms of other parts of day-to-day living, exercise is always helpful. I always feel funny saying this because, as opposed to Kim Frederick, I am not much of an exercise maven, but exercise is always very, very helpful. Always think about starting any exercise program initially with some low-impact activities, and then advancing based on how much you can do. Really pay attention to yourself. You never want to overdo things in any exercise program.

Diet is probably the single most asked question that I get about the treatment of this disease, and it is probably the thing that we know the least about. I am certainly hopeful that that will change over time but, even though it makes no sense, currently, there is no link between diet and flare-ups of disease. I tell patients to individualize as best they can. I often tell them to keep something of a diet diary so that we can sometimes pull out what might affect their disease that may not affect others, so you want to

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play around with that. If you are lactose intolerant, obviously, avoid dairy, and you want to experiment with fiber. Always drink ample amounts of fluid; consider nutritional supplements if you feel like you are not getting as well-balanced a diet as you otherwise would. It is always worth considering probiotics. They have not really been established in their treatment or prevention of disease or disease flares, but there really is very, very little downside to them except for their effect on the wallet.

There are great resources that are available to you. I personally believe, and I am obviously biased, but the Crohn's & Colitis Foundation of America's website, www.cdfa.org, is really tremendous and you should all take advantage of the real wealth of information that is out there, very frequently updated. There are research updates that are patient-oriented that are there on the site, as well as all sorts of explanations about medicines, their potential side effects, relative benefits, and everything that is new, and also wonderful access for getting involved. It is really such a great organization. I think something of a unique organization in that it does so much for patient education, professional education, supports research and does great, great advocacy work as well. There is a helpful links site that is there and there is, as Kim mentioned earlier, the Information Resource Center available via phone, and their many, many local support groups and local chapters that are out there. Even when a chapter's office is far away, the CCFA recognizes that and is doing all sorts of things to expand its coverage all across the United States. Just a wonderful organization that is really there for you to provide information, not just today, but throughout time.

It is always important to have a terrific channel open to your doctor. A frequent question that is worth asking and knowing, just for your own education if you have ulcerative colitis, is how much of your large intestine is involved. Always thinking about what treatment plan is best suited for you, your doctor's opinion on probiotics could be different from mine, maybe strongly in favor or even potentially strongly opposed. I am a fairly neutral, middle-of-the-road, I-don't-know-yet kind of guy. That is something that certainly could change over time and something that we should all be keeping our antenna open or available for.

You always want to have a discussion about potential side effects of your medicines and you want to know just how long any of these medicines might take before you see any kind of benefit, and if you do develop benefit, how long it is likely to be effective. It is certainly worth having discussion on whether you should alter your diet or take supplements. Our group here has a nutritionist associated with it; not every institution does but, certainly, your gastroenterologist, who would be taking care of you, will have access to or know a nutritionist who can help you out. You should have a frank discussion about whether there should be restriction of activities, but I would suggest to you that all doctors will want their patients to be as active as possible without going over the edge. You always need to know when your next colonoscopy should be for the purposes of cancer prevention. We did not discuss that at great length, but it is something that I am particularly interested in, and it is worth having that discussion.

I did fail to mention that how much of your colon is involved is an important risk factor as well. So patients with just proctitis really are not at any increased risk, and it is only for patients with the left-sided disease and more who are at risk for colon cancer.

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That is all I have for you for now, and we are going to move on to the question-and-answer part of today and we will get going on that. Thanks very much for your attention on this, and we will look forward to doing the question-and-answer session now.

Question-and-Answer Session

Kimberly Frederick, LCSW, MSW

Thank you, Dr. Ullman, for that highly-detailed and wonderful presentation. We are now going to begin the interactive question-and-answer session.

Operator

We will begin the question-and-answer session with a Web question.

Kimberly Frederick, LCSW, MSW

Thank you. The question is, for someone diagnosed with UC for 25 years, does the number of years that the disease has been in remission, meaning asymptomatic with no dysplasia, decrease the possibility of developing colon cancer or is the percentage the same as someone whose disease has been more active?

Thomas Ullman, MD

This is something near and dear to my heart for the very first question. Our group actually tried to take a shot at studying that question and it seems as though more inflammation begets more dysplasia and more cancer. The flip side of that coin is that less inflammation probably results in less cancer.

It is also important to point out that having regular colonoscopies continues throughout this time and we have not yet figured out how to reduce the number of colonoscopies over time, though I suspect, in the future, we will be able to demonstrate that patients who have had really robust and long remissions are at slightly less risk and maybe will be able to spread out the number of colonoscopies over time. For now the recommendation continues to be every 1 to 2 years if you have left-sided disease or more for more than 8 years.

Kimberly Frederick, LCSW, MSW

We are going to skip to a Web question really quick, and then we can go back to the phone. The question here is, what is your point of view on recommending surgery for a dysplastic or high-grade dysplasia biopsy?

Thomas Ullman, MD

There is great variability with that but I think that most folks agree that if dysplasia is removed in its entirety, the next colonoscopy should be in about 6 months and probably with sort of fanciful techniques, high optic scopes, or a practitioner who is comfortable using spray dye to highlight things. If the dysplasia was not removed or it was found in a nontargeted biopsy, those patients probably should have their colons removed because they have something—they may already be harboring a

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cancer and, therefore, the risk becomes too high. We do not have really great ways of separating who does and does not harbor cancer in that situation.

Kimberly Frederick, LCSW, MSW

Okay, great. We will take a phone question now.

Operator

Thank you. Our next question comes from the line of Hazel from South Carolina. Please proceed with your question. Your mic is now live.

Hazel from South Carolina

Thank you. I have a question about fish oil. I know that it is an anti-inflammatory and I had suggested that my son, who has had ulcerative colitis for 16 years, that he try it. He has had some success with it but he is taking a large amount. He is taking like 20 capsules, 1000 mg each, and he is taking 20 a day, which seems like a lot to me, but what can you tell me about that?

Thomas Ullman, MD

As you mentioned, anti-inflammatory activity has certainly been ascribed to and demonstrated with fish oil. Its effect in ulcerative colitis, however, is a bit in the realm of the unknown. It has not been ideally studied. It was studied reasonably well in Crohn's disease recently and, unfortunately, did not turn out to be of any great benefit. Whether that is true in ulcerative colitis or not is still something of an open question, though I suspect not. Twenty capsules a day, or that much fish oil, as you described, seems to be an awful, awful lot. Then again, if he has developed a benefit since starting it, I, to some extent, even though Kim pointed out that I went to Cornell University School of Medicine, I really went to the Yogi Berra School of Medicine, and so, I often say, "If it ain't broke, don't fix it." I think you and your son should talk to his doctor about the possibility of reducing that over time to see if the effect is maintained without taking so much.

Kimberly Frederick, LCSW, MSW

Thank you. I am going to ask this Web question because I think this is really an important question that we get a lot here. Why is there such a large gap between those on the Internet and with holistic and alternative medicine practices who advocate aggressive supplementation and diet versus mainstream medicine and all the doctors I have talked to. Have supplementation and diet been proven useless or have they simply not been tested yet?

Thomas Ullman, MD

That is a great question, one that I get nearly every day, either via e-mail from my patients or on the phone, just as you guys do, too, at the Information Resource Center.

I think it is much more the latter. I think this really is an area that has been somewhat underexplored. What separates, and I mean this not in any minimizing or belittling way, but what seems to work in a few patients and has the potential to be thought of as complementary and alternative medicines, or

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folk medicines sometimes called, if that substance has been around for a real long time, and sort of being put through the crucible of an appropriately scientifically performed study. There is a wide chasm that is there and I think we need to study many, many more of these things, whether we are talking about supplements, dietary therapies, and other complementary and alternative medicines. Unfortunately, there is just not a lot to hang your hat on that is out there yet. I think that we will get there eventually but we are just not out there yet.

Again, for things that do not have much by way of side effects, my tendency is to tell my patients to try and go ahead and go for it. If it becomes costly do not do it. I always cringe when I hear patients spending an extraordinary amount of money on some of these complementary and alternative medicines that are not yet proven, and it is just important to keep your doctor informed to what is out there. Every now and then, some of these things really are not safe but, unfortunately, it is just this big gap between what the questioner reported as mainstream science, and complementary and alternative therapies. Eventually, we will be able to bridge the divide for many of these things. We are just not there yet.

Operator

Our next question comes from the line of Tina from Illinois. Please proceed with your question. Your mic is now live.

Tina from Illinois

Yes. My question is, is bleeding present for weeks normal during flares, even if you are on 3 different types of medications during the flares?

Thomas Ullman, MD

Bleeding, like any symptom, can be present when there is not a lot of damage to the lining. It does not take a large amount of damage to the lining for bleeding to exist and so bleeding is one of many of the symptoms that are out there with ulcerative colitis. I actually have a number of patients with proctitis who have 1 or 2 formed bowel movements per day and have some blood that is still there and we just cannot get rid of it. Sometimes it is worth upping the ante to more aggressive therapy, and sometimes it is really just such a small change in the lining, that it is really not worth the risk to the patient to pursue that line of therapy. Bleeding can happen and can be persistent, even in the absence of what we would ordinarily call a flare. It is really just one of many symptoms that is part of this larger constellation of disease activity.

Kimberly Frederick, LCSW, MSW

We have a question on the Web, and it is, since UC can lead to malabsorption, how can a person ensure he or she is getting the right dosage of medications, vitamins, and nutrients?

Thomas Ullman, MD

This is one of the areas that sometimes are misconceived, and this is really one of the things that can separate Crohn's disease from ulcerative colitis. In ulcerative colitis, and, as I mentioned earlier in the

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webcast, the colon only absorbs water, some minerals, and not the minerals that are important from a nutritional point of view, but just really sodium and chloride, and it does not really work toward absorbing any of the nutrients in our diet. Patients with ulcerative colitis do not have malabsorption of nutrients. Patients with Crohn's disease can and, certainly, plenty of other, mostly small intestinal illnesses, can have problems with absorption.

That said, some patients require more of a medicine than others. That has nothing or very little to do with absorption, but rather the way their body metabolizes or converts the drug into either an active or inactive agent and it is always important to keep that in mind. There is no true malabsorption that occurs with ulcerative colitis.

Operator

Thank you. Our next question comes from the line of Alan from Wisconsin. Please proceed with your question. Your mic is now live.

Alan from Wisconsin

All right, thank you. I just recently saw Dr. Weil on a TV show and he talked about other inflammations of the body, and he suggested we only use an olive oil as opposed to corn or any of the other oils that are out there.

Part two is, how about acupuncture and chiropractic?

Thomas Ullman, MD

Thanks for the question and, while I certainly prefer foods cooked in olive oil, I am certainly unaware that diets that are richer in other forms of vegetable oil, whether it is corn, soy, or other oils, I am not aware that that has been well examined or well studied, and I think that this speaks to that gap that exists between complementary and alternative medicines and true clinical science, or what we like to call clinical science. That may or may not be true. It may or may not be true for a population of patients with ulcerative colitis. It may or may not be true in you. I just cannot say.

I apologize, Alan, I forgot the second part of the question while I was focused on olive oil.

Alan from Wisconsin

Acupuncture and chiropractic.

Thomas Ullman, MD

Again, this speaks to some of the same issues of complementary and alternative medicines. I actually have a couple of patients who swear by the acupuncture that they receive and I have some patients who have undergone acupuncture and found it to be not helpful at all. I think this is one of those areas that is terrifically understudied at this point in time, and so it is hard to make a formal recommendation one way or the other. I think it is one of those things where if it works for you, you should certainly

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pursue it, and time will tell if it is going to turn out to work for a population of people with ulcerative colitis.

Kimberly Frederick, LCSW, MSW

Okay, great. I am going to take a Web question and it is, a couple were asked, Dr. Ullman, about children and colonoscopies. This one is a little bit more specific, but if you want to answer it in a general way that is fine. I have an 11-year-old who was diagnosed with IBD last year. She is on Pentasa (mesalamine) and has not had a flare-up since. Are the recommendations for colonoscopies the same for children?

Thomas Ullman, MD

In general, they are, and it turns out that colonoscopy is a great tool for taking a look at the lining of the large intestine, and frequently we get a peek at the very last part of the small intestine as well. The only times we need to do that are to diagnose what is going on; so at the time, where in this case we are talking about ulcerative colitis, when we are looking to see if ulcerative colitis is present or not. Every now and then there are some other reasons that have to do with bleeding and other things, where we will want to take a look to see if the symptoms that are present are a function of colitis activity or not.

For the cancer prevention and colonoscopic surveillance, we begin that after patients have had the disease for 8 years or more, the special exception being patients who also have that liver illness that I mentioned, sclerosing cholangitis. Those patients start immediately and then have a colonoscopy every 1 to 2 years while under surveillance. Those recommendations are, in fact, independent of age.

Obviously, it is a bigger deal to have a colonoscopy in someone who is younger, due to the issues of sedation and completion of preparation and the like, but, basically, the recommendations are the same.

Operator

Thank you. Our next question comes from the line of Pauline from Nevada. Please proceed with your question. Your mic is now live.

Pauline from Nevada

Thank you. I am currently on my third treatment of Remicade. I am also taking 10 mg of prednisone and a 50 mg of 6-MP, along with a probiotic; Asacol, I take 12 pills a day. I am currently up at night with 3 to 4 movements, during the day it seems to calm down and I am having possibly 2, so a total of 6 to 7 movements a day.

Now taking all of this treatment, when am I going to see results?

Thomas Ullman, MD

I certainly wish you well and improvement on what sounds to be a very tough quality of life right now for you. We do not always see results after 3 treatments of Remicade, and sometimes it does take that

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fourth treatment for it to kick in, but, Remicade does not work in everybody. It works in more people than a placebo does, and these are patients who are on medicines like the medicines that you are on, patients also on Asacol, 6-MP, and prednisone. It is certainly possible that Remicade will not work in you.

I would certainly give it another treatment. I would certainly talk to your doctor about alternatives. Sometimes an increased dose of Remicade can prove to be helpful to patients, sometimes it just does not do much. Sometimes, as I mentioned before, particularly with the night-time bowel movements and the urgent bowel movements, the addition of rectal therapy—and when you are active, rectal spray foam—sometimes can be a real lifesaver and difference maker. That is a metaphoric lifesaver, but it can be a real difference maker and be very, very helpful for patients with nagging rectal symptoms.

Those are the kinds of things that I am going to encourage you to talk to your doctor about: how many more doses of Remicade before we either up the dose or try something different, and whether or not the addition of some rectal spray foam could be helpful.

Kimberly Frederick, LCSW, MSW

Okay, I am going to take a Web question. The question is, for those with a J pouch, are there suggested strategies to keep the pouch healthy, such as diet, probiotics, etc?

Thomas Ullman, MD

There are good data for probiotics in the treatment of pouchitis, that really means, in the prevention of pouchitis after antibiotic treatment to get rid of a flare of pouchitis.

Many patients who have a J pouch never get pouchitis and we are not certain that it is worth doing anything to prevent that first flare, though it has been suggested that probiotics might be helpful in that situation as well, provided that they were started right after the surgery. No one knows beyond that.

We do not really know what the dietary influences are over the possibility or probability of the development of pouchitis or some other pouch complication, and so a lot of this is a mystery. This is a surgery that has been around for 20-plus years but not in big numbers until about the last 15 to 20 or so, we really do not know as much as we need to. A lot of the great centers out there, including the Cleveland Clinic, the Mayo Clinic, Cedar Sinai in Los Angeles, our center to some extent here at Mount Sinai, are really busy trying to explore this, but there is not a lot of reliable information out there yet. Just, stay in touch with your doctor, treat flares of pouchitis, should they develop, and we will all await more information as it comes.

Kimberly Frederick, LCSW, MSW

Okay, another Web question is, how do you decide what medication is the best for the patient, anti-inflammatory versus immunosuppressants?

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Thomas Ullman, MD

We tend to try in most everyone, except for the patients who show up with their very first flare being a severe flare, those aminosalicylate- or mesalamine-based medicines that I mentioned before. Unless they are intolerant to them, or if those medicines prove insufficient, then those become the medicines that we will tend to rely on.

Unfortunately, the buzz word that is out there is this thing called “personalized medicine,” but it has not taken over yet. We tend to, because those medicines in particular have such a low rate of meaningful side effects, we tend to use a lot of those. We tend to reserve prednisone for patients who develop flares, while on those aminosalicylates or in whom aminosalicylates are insufficient to bring a flare to rest or remission.

We tend to reserve the immunosuppressants, things like 6-MP and azathioprine, and to a certain extent even Remicade, for those patients in whom there are either too many flares or too many times on steroids, or who cannot seem to be able to get off of steroids. That is generally how we approach those sort of more advanced medicines.

As I mentioned in one of those slides, it is not clear. Maybe we really need to be giving the immunosuppressants upfront to lots of people, or even the infliximab or biologic therapies upfront to people, but we are not really ready to pull the trigger on that yet. That time could come, but it really has not yet been fully explored.

Operator

Thank you. Our next question comes from the line of John from Ohio. Please proceed with your question. Your mic is now live.

John from Ohio

Thank you very much for taking my call. My question concerns anal fistulas and leaking anal fistulas. Is there any treatment besides surgery that could alleviate this problem?

Thomas Ullman, MD

Strictly from an ulcerative colitis standpoint, anal fistulas are not a particular part of the picture. They are very much associated, however, with Crohn's disease. There are, certainly, medical treatments for anal fistulas related to Crohn's disease, chief among them include steroid avoidance, as well as the use of the immunomodulators and, as well as the use of infliximab and the other anti-TNF (tumor necrosis factor) medicines as well. But not particularly associated with ulcerative colitis.

Kimberly Frederick, LCSW, MSW

Okay. A Web question. Do you recommend taking antidepressants or anti-anxiety medication to manage the emotional aspects of the disease?

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Thomas Ullman, MD

The short answer is, yes. The long answer is, that is an area where I think we are really starting to make a bigger move when it comes to personalized medicine. Not all anxiety is the same, not all depression is the same, but often these medicines—the typical antidepressants and the typical anti-anxiety medicines—can really have great effects in helping people who have disease-related anxiety or disease-related depression.

We are starting to learn much, much more about these things. We actually have a psychologist who is associated with our center. I think that if your doctor is uncomfortable in prescribing those medicines, I would press him or her to refer you to a psychologist or psychiatrist who might have or might be able to offer a more firm opinion on whether or not there is utility to the individual patient.

Summary and Conclusion

Kimberly Frederick, LCSW, MSW

Just to add, the Crohn's & Colitis Foundation has more than 200 support groups around the United States and you can find out about one that is in your area by contacting your local chapter or calling the IRC, the Information Resource Center, at 888-694-8872.

With that I would like to thank you, Dr. Ullman, for your insightful presentation and your thorough answers to our questions. On behalf of the Crohn's & Colitis Foundation of America and everyone on the phone and on the Web, we would like to thank you all for the work that you do every day to support patients and families who are touched by UC.

To all the patients, caregivers, and family members on the line, if your questions were not answered, you can call the Crohn's & Colitis Foundation's Information Resource Center. Again, the number is 888-694-8872.

We would also like to give a special thank you to Centocor Ortho Biotech Inc. for sponsoring today's program.

Please, complete and return the evaluation in your meeting packets. This is really what drives these programs and how we decide what topics to select and make them meaningful for you.

On behalf of the Crohn's & Colitis Foundation of America and Dr. Ullman, thank you for joining us.

Thomas Ullman, MD

Thanks very much everybody. Really appreciate it.