

# TRANSCRIPT

Crohn's & Colitis Foundation of America

## Inflammatory Bowel Disease: Why Should I Take My Medications?

Sunanda V. Kane, MD, MSPH

MARCH 6, 2008

### Slide 1

#### Introduction

Good afternoon, everyone, and thank you for joining us for the presentation *Inflammatory Bowel Disease: Why Should I Take My Medications?*

### Slide 2

#### Introduction

I am Dr. Sunanda V. Kane, and I am a gastroenterologist and Associate Professor of Medicine at the Mayo Clinic College of Medicine in Rochester, Minnesota.

Before I begin, I'd like to thank the Crohn's & Colitis Foundation of America for presenting this very exciting teleconference, and also Procter & Gamble for their generous support of this educational program.

### Slide 3

#### The Spectrum of IBD

I'd like to begin by setting up the stage for the spectrum of inflammatory bowel disease, or IBD. One to two million Americans have IBD. This disease can be separated into approximately two categories: ulcerative colitis and Crohn's disease. Features of ulcerative colitis include continuous inflammation, involvement only of the colon, inflammation that's superficial to the lining of the colon, and an increased risk of cancer.

Crohn's disease is a little bit different in that the inflammation can be patchy rather than continuous. The involvement isn't just with the colon but anywhere between the mouth and the anus. The inflammation is considered full thickness rather than just the superficial inner lining of the colon. There's also an association with fistulas, which are abnormal tracks between the affected intestine and other parts of the body, and strictures, which are narrowings of the inflamed and affected intestine.

Approximately 10 percent of patients fall into a category that's somewhere in between. We call that *indeterminate colitis*, meaning that there are features of both ulcerative colitis and Crohn's disease. It doesn't change the way that we treat you; it just means that there's an overlap of some of the symptoms and features of both of those conditions.

## Slide 4

### Potential Causes of IBD

A lot of people ask me, “What is the cause of IBD?” We don’t really know, but we do understand that it’s a combination of different things. There is a genetic predisposition, meaning that somewhere in the genetic profile of a patient, there is the predisposition or the set-up for possible development of IBD. But this isn’t a genetic disease like we think of Tay-Sachs or Huntington’s chorea, where there’s a specific gene that causes Crohn’s disease or ulcerative colitis. We understand that there’s a genetic component.

Another component is the immune system, and that we believe that the immune system is overactive. We don’t understand how the immune system became overactive, but rather that it is inappropriately attacking the body.

Those two things have to be added into also the environment of the patient, and not necessarily the environment meaning where you live, but the environment of your gut, meaning the kinds of bacteria that you see, as well as the environment of the body in general, meaning your diet as well as whether or not you smoke. Because we know that cigarette smoking can often affect whether Crohn’s disease is made worse or whether ulcerative colitis can be made better. So it’s a combination of three different things that we think cause this; it’s not as easy as just saying it’s a gene or a certain bacteria or bug.

## Slide 5

### Environmental Triggers

When we talk about environment, again, we are talking about the environment of your gut, but also the environment with which you live. We know that there are triggers that can trigger either the disease to come to light in the first place, or triggers that will make existing disease flare. Some of those triggers include infections. If you were to get travelers’ diarrhea or food poisoning, certainly that can set off a flare of your disease. Regarding antibiotics, we often say that the “-illins are the villains.” So penicillin, amoxicillin, ampicillin, any of the antibiotics that end with the term *-illin* are known to cause GI [gastrointestinal] upset and can cause a flare of disease. So we try to avoid those *-illin* medicines and pick antibiotics that have other properties to them.

What do we understand about diet? Well, we have an apple sitting there because while an apple a day may keep the doctor away, apples in the setting of active disease can actually be somewhat detrimental. And it’s not because of the apple itself, it’s because of the peel of the apple. The peel is where there’s a lot of indigestible fiber. And if you have active inflammatory disease, that peel that is not digested or broken down can just sit there and layer on the inside of the intestine. And sort of like a beaver’s dam, where there is build up of sticks and leaves and twigs, you have build up of pieces of apple skin, and pieces of corn, and pieces of celery, things like that, that can actually cause some partial obstruction or just cramping and bloating because of the food that’s sitting there that’s undigested.

Smoking is particularly controversial right now. We do know that smoking will make Crohn’s disease worse. I think it’s important that, as part of the management of any patient with Crohn’s

disease, smoking cessation becomes an aspect of their care, because of the effect of smoking on the disease activity itself.

I get a lot of questions about stress and can stress cause IBD. We don't believe that stress causes IBD per se, but that certainly when you are going through a stressful period in your life or an episode that you're not getting enough sleep, that you are not eating correctly, and that your immune system goes awry when there's a lot of stress. So certainly all of those factors play into how active your disease is.

Then the last category that we talk about is that of the nonsteroidal anti-inflammatory drugs, or NSAIDs. NSAIDs are commonly available over the counter in the form of Aleve<sup>®</sup>, Naprosyn<sup>®</sup>, Motrin<sup>®</sup>, not Tylenol<sup>®</sup>, but the other anti-inflammatory drugs that we use for headaches and aches and pains. Taking those on a regular basis at high doses can cause GI upset, ulceration, and a flare of disease. So it's important to speak with your doctor about the medications that you're taking over the counter or what other physicians may be giving you, because they can affect your IBD.

## **Slide 6**

### **Diagnosing IBD**

I'm going to take a few minutes to explain how we diagnose IBD. Certainly a clinical history is very important, a physical examination, laboratory tests—and I'm going to talk a little bit about that in a little bit—endoscopy, which would include looking at your stomach, which is called a gastroscopy, or colonoscopy, where we look at your colon.

There are certain x-ray films that we like to do, whether that's a small bowel x-ray where you drink a certain kind of barium, or a CAT [computed axial tomography] scan where you drink a different kind of barium, or an MRI, where you don't drink any barium because we use a magnetic field to look at your insides.

And then tissue biopsies. That's where we send pieces of your tissue that we collect from the endoscopy to a special physician called a pathologist, who can then look at the inflammation under the microscope.

## **Slide 7**

### **Questions Frequently Missed During History-Taking**

Certain questions are frequently missed during history-taking. It may be helpful if you know what questions to ask your physician, or what physicians and healthcare extenders should be asking in terms of making a diagnosis. It's interesting that family history, not just for first-degree but second-degree relatives, becomes important to consider whether a patient has ulcerative colitis or Crohn's disease.

We've already talked about the NSAIDs, that regular use of these can cause ulceration or inflammation, and can certainly take an underlying inflammation, make it worse, and have disease come to light.

When there is use of an antibiotic, you develop a little bit of diarrhea and the diarrhea doesn't get better, then that could be the trigger that sets off that initial flare and then leads to the diagnosis.

And then also infections. Infections—whether a cold, whether the flu, whether salmonella poisoning from food—we definitely want to know about infections. It's interesting that there have been links to previous infections with measles and with mumps; however, over the years those have not necessarily panned out. But certainly, if you had a recent or a previous infection, then that is something that becomes important as part of your history.

## **Slide 8**

### **Clues in the Physical Examination**

What is a physician looking for in the physical examination? I said that you were going to have a physical examination. Clues are present from head to toe. In the mouth, we often look for oral ulcers. Where you may think that's a cold sore, it's actually the same kind of ulcer that we may see with our scopes in your stomach or in your intestine. We look at the whites of your eyes and also at the eyelids to see whether they are pale, to suggest anemia. We're going to look at your skin to look for special kinds of rashes. We're going to feel your abdomen to make sure that there isn't a mass or any inflammation of the fat or the colon. Then we are going to look at your bottom, because we want to check for hemorrhoids and particular growths called *skin tags*, which may suggest either Crohn's disease or ulcerative colitis.

## **Slide 9**

### **Ulcerative Colitis**

Let's focus on ulcerative colitis for a few minutes. There are certain terms that we use to describe the extent of disease. Let me first say that in ulcerative colitis, the small intestine is not involved. This is a condition that involves only the colon. When you hear the term *proctitis*, that means that only the rectum or the last part of your colon is involved. We could certainly call it *rectitis*, but for some reason we use the Latin, so it's called proctitis. *Left-sided disease* means that it's the left side of your colon that's involved. *Pancolitis* means the entire length of the colon is involved. All of those conditions still relate to ulcerative colitis; we are just referring to which parts of the colon are involved.

## **Slide 10**

### **Symptoms of Ulcerative Colitis**

What are some of the common symptoms of ulcerative colitis? The symptoms are going to depend on the extent and the severity of the inflammation inside. So certainly rectal bleeding is very common, as is the urgency to evacuate. There can be diarrhea and abdominal cramping. Then we also ask about what we would call *extraintestinal symptoms*, meaning things that are occurring outside of the intestine itself. These would include joint pain or swelling, eye inflammation, and again those skin rashes or lesions.

## **Slide 11**

### **Common Symptoms of Crohn's Disease**

If we focus our attention on Crohn's disease, diarrhea is very common. But rather than cramping, we actually hear about abdominal pain and tenderness when we press on the abdomen. And, again, that's because it's not just the superficial inside lining that's involved, but all the

layers of the intestinal wall. Patients with Crohn's often have a loss of appetite because of their illness and because it hurts when they eat. So they don't eat and that leads to weight loss. There can be fevers and certainly fatigue because of their illness or also because of any anemia that they have. There can be rectal bleeding, but less often than in ulcerative colitis. There may be anal ulcers like the oral ulcers, because this is a disease that affects any part of the GI tract from the mouth to the anus. It's interesting that in children, they can have none of the above symptoms but just stunted growth. That's the way they manifest their Crohn's disease.

## Slide 12

### Laboratory Tests

So what are we looking for in laboratory tests? That a lot of blood can be taken out of a patient. And what are we looking for? Routine labs are ordered first, and that would include what we call a complete blood count. And that looks at the white blood cells and the red blood cells to rule out infection and anemia. There's a certain protein called C-reactive protein, and the presence of that C-reactive protein assesses how active the inflammation is. The higher the C-reactive protein, the more active the inflammation.

We do chemistry panels, because we want to look at electrolytes, which would include potassium, sodium, and bicarbonate. Those are the electrolytes that become deranged or upset or abnormal when there is a lot of diarrhea. And certainly we want to look at the other protein levels to make sure that patients are not malnourished.

We also check the thyroid hormones when patients complain of weight loss, because we want to make sure that there's not some other explanation for their weight loss.

And then sometimes we test patients for celiac sprue, or celiac disease, because of the overlap that can be seen between those symptoms. Sometimes patients may have both of those conditions.

We definitely want to check the stool and make sure that there are no infections there, which would be with parasites. Unfortunately, the yield for those is very low, because it's cumbersome to get enough stool to the lab quickly enough. There certainly can be false-negatives, but we do want to check the stool. We want to check the stool for a certain kind of toxin that is produced by a bacteria called *Clostridium difficile*. This bacteria can overgrow in your colon, and it's the toxin, not the bacteria itself, that can lead to diarrhea and illness.

Also in the stool we look for white blood cells, which would suggest inflammation, and other proteins that may be shed into the stool; those are called *lactoferrin* and *calprotectin*. These very sensitive proteins are not present in the stool of patients who have irritable bowel syndrome or from diarrhea that is caused by medications, but is in the stool of patients who have inflammation.

### Slide 13

#### Diagnostic Studies: Small Bowel Series

When we have patients drink barium for a small bowel x-ray or series, we are looking for changes in the bowel wall that are indicative or represent very long narrowings or inflammation. Here is an example, where the red arrows show someone's small intestine that is very, very narrowed. It's called a *string sign* because the narrowing is such that it actually looks like a piece of string rather than the normal width of a small intestine.

### Slide 14

#### Endoscopy

When we do endoscopy—again, that's just a generic term for scoping a patient—we're looking at the inside of the colon. On the one side labeled *ulcerative colitis*, you can see that there are some white splotches there, a little bit of green, and intervening with that is some reddish pink. That's ulcerative colitis. This is because to the trained eye we can tell you that that is inflammation that is involving all of the wall of the intestine, and that it is diffuse and continuous, and that there are small, superficial ulcers there.

As compared to the other side of the slide, *Crohn's disease*, you can see that there are white ulcers there, but then you see that there is what looks like divots or indentations of the wall, and that they are pink. Crohn's disease gives you ulcers that are much deeper into the wall, and that's why they look like divots. And there are areas that are completely normal compared with the surrounding ulcerations. It can be very easy to tell the difference between ulcerative colitis and Crohn's disease when we put a scope in, but sometimes it's not so easy.

### Slide 15

#### Endoscopy

Sometimes we have to do a video capsule endoscopy, in which a patient swallows a video camera, and we take pictures and we can see ulcerations. This is a picture of a very typical small intestine, rather than a colon, with three ulcers that are fairly deep and thus indicative of Crohn's disease.

### Slide 16

#### Management Goals for IBD

Now that we've talked about how we diagnose IBD, let's talk a little bit about management goals for IBD. Obviously, as shown in the center, the main goal is to establish the correct diagnosis. And, like I said, sometimes that can be difficult if you have overlapping symptoms of both ulcerative colitis and Crohn's disease. We would call it indeterminate colitis, but basically the goals are going to be the same.

First and foremost is to try to relieve patient symptoms. Whether we do that short term or long term, that's obviously goal number one. In order to relieve the symptoms, that means we have to try to induce remission. How do we induce remission? That's by treating inflammation. We'll talk a little bit about medical therapies in a minute. But along with inflammation we want to try to treat complications that have occurred because of the inflammation. Like the nutritional deficits, which would mean replenishing sodium and potassium and any proteins that may have

been lost. Certainly we want to make sure that patients are eating a balanced diet with enough protein and calories in order to help them gain back any weight that they may have lost.

In doing all of these things, we must try to minimize treatment toxicity. So it may be that there's a medicine that may seem appropriate, but in a certain specific patient, that medication may be just so toxic that the risk is not worth the benefit. So we're always trying to first do no harm with the understanding that we're trying to relieve symptoms.

If we relieve symptoms and induce remission, we try to maintain that remission. Meaning that it's not enough to get you feeling better for 1 or 2 weeks; you've got to feel well for 6 months, 1 year, 2 years, 3 years. Because you have to remember that inflammatory bowel disease is a chronic condition that is not curable. It is treatable. So the goal is to keep you well as long as we can while trying to minimize toxicity.

In minimizing toxicity and maintaining remission, we're also trying to improve daily functioning. Sometimes that goes back to relieving symptoms. Some of those symptoms are going to be directly related to how bad the inflammation is or how bad some of the complications have been in terms of chronic pain issues or scarring.

Addressing psychosocial issues also becomes very important. This condition affects younger people who are trying to raise families, who are trying to get through school, who are trying to hold down jobs, and it can certainly be very overwhelming if you're trying to take care of yourself and a family and trying to hold down a job. So those are all things that we have to take into consideration when we're picking therapies and when we're trying to map out what symptoms have to be relieved first and where we are going with long-term management.

One of the things that we have to worry about long term, not short term but after a long period of time, so we're talking about years to decades after the disease has been present, is to identify what we call *dysplasia*. Dysplasia is the term for precancer. These are abnormal cells that are prone to continue to grow and turn into cancer, but at the time that we find dysplasia is only abnormal cells. For the women in the audience, you can think about a pap smear, where they talk about atypical or abnormal cells on a pap smear. That is not cervical cancer, but it is abnormal tissues or cells that then lead to another procedure. So we look for the same thing in the colon and in the small intestine of patients who have ulcerative colitis and Crohn's disease, where we're looking for abnormal cells that may be precancerous and intervene for that dysplasia before we find cancer, but certainly finding cancer at its earliest stages that we possibly can. That's a long-term management goal along with making sure that we've maintained remission and replenished any nutritional deficits long term.

## **Slide 17**

### **Medical Therapies for IBD**

Let's talk then about some of these medical therapies that we use. The 5-aminosalicylic acid agents, or 5-ASA, quite a mouthful I know, come in different flavors. The most commonly used one is mesalamine. Mesalamine is a 5-ASA and comes in delayed release tablets, and there are two of those: Asacol<sup>®</sup> and Lialda<sup>®</sup>; in controlled release capsule form, which is Pentasa<sup>®</sup>; in

enema form, which is Rowasa<sup>®</sup>; and then in suppository form, which is Canasa<sup>®</sup>. All of those are the same ingredient, which is mesalamine, just in different packages.

Another 5-ASA, which is similar but not identical, would be sulfasalazine, and it's sold under the brand name Azulfidine<sup>®</sup>. Another one is balsalazide [Colazal<sup>®</sup>]. The last one is olsalazine [Dipentum<sup>®</sup>].

A way to think about all of these different drugs is like Coca-Cola<sup>®</sup> and Pepsi<sup>®</sup>. They are both colas, but they're sold under different brand names and just a little bit different from each other, yet essentially the same product. So that's how you should think about the 5-ASA agents.

5-ASAs work at the lining of the intestine. So they do not suppress the immune system. They are not steroids. They are used for mild to moderate disease at the level of the inflamed intestine, used specifically for the colon and just the last part of the small intestine. And these, again, are drugs that work not by suppressing the immune system, but by mopping up the proteins that the immune system is making that are causing the inflammation.

## **Slide 18**

### **Medical Therapies for IBD**

We also use antibiotics to change the environment of the colon, and also for patients with Crohn's disease who may have abscesses or fistulas. Most commonly we use Cipro<sup>®</sup> [ciprofloxacin] and Flagyl<sup>®</sup> [metronidazole].

Now, if we think about patients who have more active disease who may require steroids, there are different steroid preparations, but the one most commonly used is prednisone. Hydrocortisone is given either intravenously in enema form or in foam form. And it is indeed prednisone that is used most frequently in the oral form for adults. Methylprednisolone is used for children. Budesonide [Entocort<sup>®</sup>] is FDA [Food and Drug Administration] approved to treat Crohn's disease.

## **Slide 19**

### **Medical Therapies for IBD**

Steroids are very good at suppressing the immune system, but those of you who have been on steroids know the very significant side effect profile and toxicities. So instead of suppressing the immune system with steroids, we suppress the immune system with other agents. Those include azathioprine and its cousin 6-mercaptopurine and methotrexate. Cyclosporine is used less often these days, but is available intravenously and orally to treat both Crohn's disease and ulcerative colitis. The reasons that cyclosporine is not used as much now is because it is quite toxic and has to be carefully monitored by laboratories and physicians who have experience with cyclosporine.

Some of you may have heard about or may even be on biologic agents, which are proteins that have been manufactured in a test tube, if you will, and that are given to treat Crohn's and ulcerative colitis. The first one that was available, which has been on the market for about 11 years, is Remicade<sup>®</sup> [infliximab]. Remicade is intravenously given every 8 weeks, if you respond to the short courses that are given initially. Humira<sup>®</sup> [adalimumab], which recently got FDA approval for just Crohn's disease, not ulcerative colitis yet, is available in a shot form and is

given every 2 weeks. Then the last one that actually has FDA approval for Crohn's disease, but isn't quite ready yet for administration to Crohn's patients, is Tysabri® [natalizumab]. That is also intravenous and will be given once a month.

## **Slide 20**

### **C. Everett Koop, MD**

Circling back to the major theme of this presentation, "Why Should I Take My Medications?", it's interesting that the former US Surgeon General once said, "Drugs don't work in patients who don't take them." So I can tell you about all of the different options that we have to treat inflammatory bowel disease, but if you don't take the pill, if you don't come for your IV [intravenous] infusion, then you're never going to be better.

## **Slide 21**

### **Factors that Affect Adherence**

So let's talk about adherence and factors that affect adherence. If we talk about a definition of adherence, it's taking medications over a long period of time. It's not enough to take a medication for a week and thus you're doing it fine. It's what happens in 6 months, what happens at 1 year. The extent and the duration and the severity of the disease certainly affect adherence. Meaning that the more severe one's disease has been, the more motivated one is to take the medicines. But then certainly as patients go into remission and are feeling well, the likelihood that patients take their medicine goes down, because they don't feel as motivated that there's a reason to have to do that.

People who are more likely to adhere to therapy are those who have more aggressive disease, in whom there are more flare-ups. Or patients who are knowledgeable about their treatment and aren't afraid of it or who understand why they're taking it and how it works. Patients who are knowledgeable understand why they're taking it in the short term and why they're taking it in the long term.

Clear instructions and educational materials are available through healthcare professionals and pharmaceutical companies that help increase the knowledge about the importance of treatment and the risks of non-adherence. So saying that you don't understand your medicines or how to take them is no longer necessarily acceptable, because there is help out there to understand what's going on.

## **Slide 22**

### **Risk Factors for Non-Adherence**

Let's talk about what we know about non-adherence and who is at risk for being non-adherent. This is a study that I helped conduct when I was at the University of Chicago. We followed patients who had ulcerative colitis and who were all prescribed 5-ASAs to treat their ulcerative colitis. What we found was, after talking to their pharmacies, who really was taking their medication and who wasn't. It turns out that patients who were married, who had had a recent colonoscopy, or who had a greater extent of disease, meaning more of their colon was affected, were the patients who were more likely to be adherent. Those patients who were male and those who were taking more than four other medicines besides their 5-ASA were over two times more likely to be non-adherent. So a single male is most at risk for not taking the medication. If you

take more than four medicines, you are 2½ times more likely to not take your ulcerative colitis medicine than someone who is taking fewer than four other medicines. What's interesting is that those four other medications could be anything from multivitamins to other supplements to prescription medications for other conditions.

### **Slide 23**

#### **National Quality Forum Report**

It's interesting that your tax dollars went to a very large National Quality Forum Report to study the effect of non-adherence on the health of Americans. The goals of the forum report were to improve medication adherence by creating some standards to change the way that healthcare professionals interact with patients. So basically the government is saying that it's the physician's fault that you're not taking your medicines correctly, and that we need to develop standard performance measures that could be implemented in patient care settings to help improve adherence. It's not enough that there's educational information available; we must actually provide it to our patients and make sure that you understand what you're reading.

So one of the recommendations from this report was that adherence needs to be evaluated just like your blood pressure, your weight and your height. Every time a patient is seen by a physician or a nurse, we ask, "How is it going with your medicine? Are you taking it? Are you having problems with it?" Thus, adherence becomes another what we call *vital sign*. And as part of that, as part of the history, every time you come in you should be asked, "Are you taking your medicine? How are you taking it?" "What's the dose that you're taking?" We think that reminding you about your medicine every time that you're seeing a healthcare provider gives the kind of positive reinforcement to help you take your medications.

### **Slide 24**

#### **Significant Factors Associated with Risk of Not Refilling 5-ASA at 3 Months**

This slide shows more data that we have provided and studied. Again, this is looking at a very large database of prescriptions. More than 3,000 ulcerative colitis patients given 5-ASA prescriptions were looked at for 3 months to see what happens with patients who are not refilling their 5-ASA prescription. It turns out that at 3 months, those patients who were less likely to refill their medication were those who are male, who have a mail-order prescription service, who have to pay a copay, who actually have a lower daily pill load, and those who have a psychiatric history.

Who are more likely to refill? Those patients who have been on steroids and those who have been using rectal 5-ASA therapies. We think that's because we know that steroids are bad and that patients want to be off of them. So the impetus to be off of the steroids is to refill those 5-ASA therapies and to stay on them. It's interesting that if I were to show you a graph of what the percentage was of patients not refilling their medications at 3 months, it's about 40 percent. So right off the top there are patients who are not going to refill their medications at just a small short interval like 3 months.

## Slide 25

### **Adherence Decreases Risk of Relapse**

We know that patients are at risk. We know who's at risk, which are basically the single males. And we know that they are not refilling at 3 months. But who cares? Does it *matter* if you don't take your medicine?

This next slide is a graph. This is from work that we performed, again, at the University of Chicago, where we followed a group of 100 patients with ulcerative colitis for 2 years. We watched them and tracked how much medicine they were taking over that timeframe by talking to their pharmacies and getting refill data.

Now, of course we were asking the patients also how much they were taking. And it was very interesting, as a side note, that the patients were stating that they were taking a lot more of their medicine than what the pharmacies were telling us that they were refilling.

So our interest here was to look at patient outcome at 2 years based on how much medicine patients were consuming. We were able to show that the patients who were taking at least 80 percent of their medicine as prescribed had approximately a 90 percent chance of still being in remission after 2 years. And that's in complete distinction to the patients who were non-adherent, meaning taking less than 80 percent of their medicine. And only 33 percent of them were still in remission at the end of 2 years. So between these two lines there's a fivefold difference. So basically in English what that means is that if you don't take at least 80 percent of your medicine, you have a fivefold increased risk of having a disease flare within 2 years, compared with someone who does take their medicine.

I show this graph to all of my patients when they get bored with or sick of taking their medicine. I say, "Well, here's what we know: that you can have a high chance of still being in remission if you can just stick with this, or you're bound to have a flare of your disease if you stop taking it." That's the kind of education and discussion that we need to have with each one of our patients.

## Slide 26

### **Adherence Decreases Risk of Relapse**

So, again, here on this slide, we are putting in words what I just showed you on a graph. That in this prospective study—so we are following patients in a prospective manner over time—those who were adherent, meaning taking 80 percent or more of their medicine (so we're not even asking for 100 percent of therapy here, we're asking for on average 80 percent of your medicine), that 89 percent were still in remission compared with those patients who have a 39 percent chance of still being in remission at the end of 2 years.

## Slide 27

### **Non-Adherence is Associated with Recurrence**

So we have here just by follow-up timeframe over 6 months, 12 months, and 24 months, who is having recurrence and who is not. What's interesting here is that if you look at the 6-month data, those patients who have had no recurrence were filling or taking on average 80 percent of their medicine versus those who were having a recurrence were taking about 25 percent of their

medicine. The same thing held true at 12 months and 24 months. So this is actually looking at the same data in a different way. Those who did not have recurrence, how much medicine were they taking versus those who did have a recurrence, how much were they taking? And there's a direct correlation to how much medicine you take and how likely you are to still be in remission and not have a recurrence.

### **Slide 28**

#### **Non-Adherence is Associated with Recurrence**

So 82 percent of patients with recurrence had not taken their medication. Similarly, 34 percent of patients remaining in remission had not taken their medication. There are still some patients who don't take their medications who remain in remission, but it's the minority and not the majority. It's the majority of patients who don't take their medicine who suffer a recurrence. So, again, this is another way to talk about the data that we showed you, that taking your medicine is associated with remission, and not taking your medicine is associated with disease recurrence.

### **Slide 29**

#### **Other Factors that Affect Adherence**

There are certainly other factors that affect adherence. Some of those factors include adverse reactions to medications, whether it's an allergic reaction or a side effect that's known versus a reaction that you're having that maybe you don't tell anybody; the need for many medications, the effectiveness of the treatment itself, and certainly the convenience. For patients, it's really important to understand when you need to talk to your physician about a side effect versus an adverse reaction to the medicine. If you experience something and stop taking the medicine, but don't tell the doctor that you stopped taking it, then that healthcare provider, whether it's the doctor who prescribed it or the nurse who is seeing you on that next visit, they're going to assume that you're taking the medicine. So it's important to tell the healthcare provider that you're no longer taking that medicine relatively soon after you stop it, and not wait until your next appointment, when there's been an assumption that you've taken it and now maybe your disease is not under control.

It's important for healthcare providers to try to minimize the number of medications given. It's interesting that now there are several different therapies out there that combine two drugs into one pill. So you may have seen the commercials for the medicines where there's a high blood pressure medicine in the same pill as your cholesterol medicine. That's called a *polypill*. Polypills can actually decrease the need for separate medications and make it easier or more convenient for you to take your therapy. And certainly effectiveness, whether that's true or perceived, is going to affect how often that you take your medicine. If you don't think a medicine is going to work or your healthcare provider doesn't think that the medicine is going to work, of course you're not going to take it. By the same token, if you believe that this is really going to help you, then there is a higher chance of it actually helping you.

### **Slide 30**

#### **To Increase Treatment Adherence**

Okay, so how do we increase treatment adherence? This is a two-way street between physicians, healthcare providers, and the patient. Clearly, simplifying the treatment regimen is important. There are a lot of medications that were studied in large trials that were given as three times or

even four times a day, but we have follow-up data now to suggest certainly for the 5-ASA medications, whichever one you're taking, that they can be given in a twice-a-day regimen. There's no reason that it has to be three times a day if you are taking a 5-ASA therapy. The longer that you take the medicine, the more likely you are to continue taking it. So, again, that success begets success, that taking it on a regular basis and making it part of your daily routine makes it more likely that you're going to adhere to the therapy.

And then lastly is finding support for emotional and social issues regarding your disease and your therapy. So what I often do with my patients is I turn their medication consumption into a family event. It may be that mom or dad has the condition, but they have to take their medicines. If I can make it once a day, they take it in front of their family at dinnertime and everybody else takes something too. So the kids are taking a multivitamin, the spouse is taking a multivitamin, and everybody takes something by mouth all at once. That actually can supply quite a bit of emotional support for that medication-taking behavior.

### **Slide 31**

#### **Patient-Centered Self-Management Training**

Some colleagues of mine in Europe asked, "What if we make the self-management of inflammatory bowel disease *patient-centered* rather than *physician-* or *nurse-centered*?" So they put together a program in which half of the patients served as the controls, where they got normal care (meaning that when they got sick they had to call their doctor's office, they had to come in and be seen) versus a group that was given education and self-guidance materials in order to know how to treat their disease and their relapses and what to do in terms of their therapy. It turns out that the time to treat a relapse in the self-guided group was significantly shorter. It was less than 50 percent of the time as compared with the control group. That the number of visits that the self-guided group had to make to the doctor was 1 day versus 3 days in the control group. And time spent visiting a doctor was 1 hour in the self-guided group compared with 6 hours in the control group. So clearly, education was a big component here and that patients can be taught how to manage their disease and be more adherent with an improved outcome.

### **Slide 32**

#### **Why Take Your Medications?**

Why take your medicines? This is the crux of the entire conversation that we're having today. I've already showed you the data for long-term, at least 2-year data that suggest that taking your medicine decreases your risk for active disease. Now we believe that there are three other very good, compelling reasons to take your medicine.

The first is that regular use of 5-ASA products has been associated with a decreased risk for developing cancer. There have been six studies done over the past two decades from different places around the world, different kinds of patients, different investigators, that consistently have shown a decreased risk of cancer development in patients who take regular amounts of 5-ASA compared with those patients who don't. The one cumulative study that put all of that data together shows at least a 55 percent reduction in the risk for cancer if you take 5-ASAs on a regular basis long term. We think that the amount that you have to take is 2 grams per day, which is equivalent to about five tablets of Asacol, about two to three capsules of Lialda, and about six

tablets of Pentasa, or eight tablets of azulfidine. So in that rough area, 2 grams per day of any of those medications will decrease your risk for colorectal cancer.

The second compelling reason is that we believe that with regular and early use of the 5-ASAs in particular, as well as the biologic agents and with the immunomodulators, you can decrease the risk of disease progression. Meaning that you can keep it from getting worse by taking medicines on a regular basis early on in the disease course. Which makes sense that if you treat it early and you treat it consistently, you won't allow it to progress. Now we actually have prospective data to show that that's true.

The third reason is a corollary to that: with regular use of medications on a consistent basis, you can increase your chance for disease regression. Meaning that wherever the disease is, you can actually cause it to decrease, particularly in ulcerative colitis. That if you have it throughout your entire colon, that you can actually make it regress and that you can heal parts of your colon and so the extent of your disease declines. That has been shown also in prospective fashion.

So there are four reasons to take your medications: one is to prevent relapses; two is to decrease the risk of disease progression; three is to increase your chance for decreased regression; and four, and maybe the most important reason of all, is to decrease that risk for colorectal cancer down the road.

In conclusion, I hope that I have given you four very good reasons why you should take your medications. First, I showed you the graph that showed how you can decrease your chance for disease activity. We've talked about decreasing your risk for disease progression. We've talked about the increased chance for disease regression. And certainly, and maybe most importantly, over time decreasing your risk for colorectal cancer.

Now, having shared all of these data with you, it's really important for me to stress that if you have specific questions about your own care and about your own medicines that you're taking, that you discuss this with your healthcare provider, whether it's the nurse practitioner, whether it's a nurse, or whether it's a physician prescribing the medications, that you voice your concerns and your questions regarding your own personal issues and risk factors for adherence and non-adherence and for complications of your disease long term.

And with that I'd like to conclude today's presentation. I hope that you found the information useful, and I'd like to thank you for your attention.

## **Question and Answer Session**

Operator:

Our first caller is David from Canada.

David:

I was wondering, given the sort of overwhelming evidence that Crohn's may be caused by *Mycobacterium paratuberculosis*, what sort of basic research or clinical trials the Mayo Clinic might be doing?

Dr. Kane:

David is asking about very intriguing data that's mostly come out of Australia and a lab in Florida, looking at—and I wouldn't use the word overwhelming, but I would say intriguing, and they are very actively looking into this—looking at a specific strain of *Mycobacterium* that may be the cause for Crohn's disease. There have been a few small trials; they are not controlled trials, but they are being done in a scientific manner, using different combinations of antibiotics to treat Crohn's disease. There's been some very encouraging preliminary data, but here at Mayo Clinic, we are not engaged in any of those trials because we are not convinced yet that there is a true cause-and-effect relationship there. Some of these antibiotics are potentially very harmful, and so at least here at Mayo Clinic we are not involved in those trials as of yet. We are still waiting for others who are more convinced of this relationship to show us that it's safe to do it.

Frederick:

Great, we're ready for our next caller.

Operator:

The next question comes from Edith in Georgia.

Edith:

Hi, thank you, Dr. Kane. I have a question pertaining to those who've already had surgery to remove part of their colon or small intestine. In preventative maintenance, between Pentasa<sup>®</sup> or Purinethol<sup>®</sup>, which one would probably be the most effective in preventing the progression of the disease?

Dr. Kane:

Edith has a very good question: I've already had surgery, how do I prevent it from coming back or having more surgery in the future?

This is actually the one area that is probably the least satisfying to IBD specialists around the world, because we don't know the perfect formula. Because there are lots of reasons why patients go to surgery in the first place. And that while there have been studies looking at different agents, these studies were all done before we had Remicade available to us, and so if I were to quote you what the guidelines are in the literature right now, that a patient who has had an operation, we recommend that they go on Imuran—if they tolerate it—after their surgery. That they can go on high doses of metronidazole, but that is short term. We don't know yet about Remicade or Humira, but what we all agree on is that in patients who are smokers who have Crohn's, that smoking accelerates the disease progression to another operation sooner. So we all agree that smoking cessation should be part of the treatment regimen. But otherwise it's really an individual sort of scenario as to which is the best medicine following an operation.

Frederick:

Thank you, Dr. Kane. We have many questions in the queue, so I think we're ready to take the next question.

Operator:

The next question comes from Karen in Michigan.

Karen:

Hi, Dr. Kane. I have had ulcerative colitis for the last 16 years and I'm wondering if I have to have the one known ulcerative colitis susceptibility gene in order to have gotten this disease. Because none of my relatives have ulcerative colitis. So is it true that I must have a whole string of ancestors who were carriers with this gene?

Dr. Kane:

So the question is about where we are with genetics in this condition. That's another very good question and a very intriguing area for research.

What we understand right now about ulcerative colitis is that there are what we call candidate genes, meaning that if you have one of these genes you are more likely to get ulcerative colitis. But having said that, the majority of patients who have ulcerative colitis don't have a family history and don't carry this candidate gene. So what we understand now about genetics is all in its infancy and is not the kind of genetics work where we know that for sickle cell anemia or for Tay-Sachs, that there is a specific gene—or for cystic fibrosis—that if you fix the gene, you fix the condition. It doesn't work that way for ulcerative colitis or Crohn's.

What we do know for Crohn's is that there are a few other genes that are not related to the ones that we see for ulcerative colitis, that are found more frequently, but at this time we certainly do not recommend genetic testing for any patient, nor do we say that just because you don't have a family history, then that means that you don't have a risk for the disease.

Frederick:

Great. We're ready for our next question.

Operator:

The next question comes from Peter in Pennsylvania.

Peter:

I notice that the research that you reference about the decrease in the rate of relapse through adherence to a drug regimen is based on ulcerative colitis patients. Is there parallel research on Crohn's patients?

Dr. Kane:

So far the parallel data for Crohn's patients comes from the very large controlled trials that have been done by the pharmaceutical companies. And the problem with those studies is that everybody is getting medicine all the time and that there's a nurse there to tell them when to take it. So we don't have the same kind of data for Crohn's and I'm trying to figure out how to do that study. The problem with trying to do it for Crohn's disease, as you know, is that there are some patients with Crohn's disease who have fistulas, some who don't have fistulas, some have it in their small intestine, some in their colon, and it's really hard to gather a group of patients who are similar enough that it would make sense at the end of a year to figure out what happens to

them if they do or don't take their medicine. But it's absolutely something that I think needs to be done.

Frederick:

Great question. Can we have another one, please?

Operator:

The next question comes from Nancy in New Jersey.

Nancy:

Good afternoon. I just wondered, is there specific evidence to show that antibiotics can be one of the causes to trigger Crohn's disease?

Dr. Kane:

So what we know about antibiotics is that they can disrupt the normal bacterial environment of the GI [gastrointestinal] tract; that's enough to be the straw that breaks the camel's back, so to speak, and to bring out the inflammatory bowel disease that was harboring there in the first place.

We don't have any direct evidence that taking an antibiotic will cause Crohn's disease, but we certainly know that it can be one of the factors that brings it to medical attention.

Frederick:

Next question, please.

Operator:

The next question comes from Florence in Texas.

Florence:

Good morning, Doctor. I was wondering about a new medication called balsalazide, generic for Colazal. I was wondering if you're familiar with that new drug. And also is it as effective as the Colazal?

Dr. Kane:

Florence is asking is about one of the generic forms now of a 5-ASA called balsalazide, and it's the generic form of Colazal. Colazal has been available to treat ulcerative colitis for a few years and now the generic form is out. There have not been head-to-head trials of Colazal versus generic balsalazide, but we believe because balsalazide generically is just the same medicine without all of the window dressing, it's not any less effective than Colazal. And that it certainly wouldn't be available if we thought it was more harmful. So whether it's better or not, it's certainly cheaper, and that's why some physicians are switching over to it.

Frederick:

Great. Can we have the next question?

Operator:

The next question comes from Mundep in New York.

Mundep:

Hi, Dr. Kane. Actually I just have a question about my son. He's 8 years old and he has ulcerative colitis. I just want to know if the 6-MP [6-mercaptopurine] did affect the growth.

Dr. Kane:

In the pediatric population, pediatricians have a clock that's ticking in terms of getting a patient better. That the stakes are much higher to treat active inflammation earlier than in adults. Because you will stunt the growth of patients if they continue to have active disease. So stunted growth in children is related to active disease and not due to the medicines that they're taking. So 6-MP is not associated with stunting growth, it's associated with actually the opposite, of helping to decrease the inflammation, so that the children can grow.

Frederick:

Great. Next question, please.

Operator:

The next question comes from Natalie in Florida.

Natalie:

Hi, how are you? I've had ulcerative colitis for 10 years. Now the doctor says I should have a colonoscopy every year.

Dr. Kane:

This is a very important part of management for ulcerative colitis and also for Crohn's disease when it's predominantly in the colon, and I'm glad you brought this up.

What we understand about ulcerative colitis is that when patients have ulcerative colitis that involves their entire colon, more than 10 years, that's when they increase their risk for colon cancer. The way to monitor for this is to have regular periodic colonoscopies. There is debate in the literature about how frequently this has to be, but we all agree that after 10 years of disease, if it involves the entire colon, that patients have colonoscopies every 1 to 2 years until they've had disease for 20 years, and then after 20 years everybody agrees they need it yearly.

So it also depends on that patient's own family history for polyps and for cancer, as well as their history with how inflamed their colon has been and how aggressive their disease has been in terms of how frequently that surveillance colonoscopy should be done. So some physicians are particularly concerned about catching things early and recommend once a year. Others are a little bit more lenient and say we can do it every 2 years.

Frederick:

Great question. Can we have our next question, please?

Operator:

The next question comes from Paul in Massachusetts.

Paul:

Hi, Dr. Kane, thank you for your time. I have a question regarding the therapy. Currently I take Pentasa and azathioprine for Crohn's disease. I'm 53, I've had Crohn's disease since I was age 14. But I'm also steroid-dependent. I need 10 milligrams a day. Do you find this is typical?

Dr. Kane:

No, I don't. The reason that we put people on azathioprine is to get them off of steroids. And that if they are unable to get off of steroids, then we usually get a little bit more aggressive about finding alternate therapies that will actually get them off the steroids. Now there are some people who have been on steroids for such a long time that they literally can't get off because their body has become so used to them and they need them. But that's, hopefully, a situation that doesn't occur in the majority of patients.

There's always an exception to the rule and that your body makes somewhere between 7 and 8 milligrams of prednisone a day, so somebody who's on 10 milligrams, that physicians may feel comfortable that that's a "low dose." I don't subscribe to that same philosophy. But I certainly do know of patients who are completely well on some amount of prednisone per day, but it scares me because long-term use of prednisone has been associated with so many bad outcomes, in terms of infection, if you need surgery for other things, bad wound healing, osteoporosis, cataracts, and also diabetes. We try really hard to get patients off of steroids.

Frederick:

So certainly it's important to take this information, wouldn't you say, Dr. Kane, and go back to your physician and talk to him about your concerns?

Dr. Kane:

Right, right.

Frederick:

Great. Can we have the next question, please?

Operator:

The next question comes from Julie in Washington, DC.

Julie:

Hi. I wanted to ask you about the safety of taking 12 Asacol a day during pregnancy.

Dr. Kane:

Julie has a good question about the safety of some of these medicines during pregnancy. In the mesalamine products, whether it's Asacol or Pentasa or Colazal, these are all considered very low risk during pregnancy and that we actually have prospective data to show that these are not harmful to the fetus and actually keep the mom well. So the issue of being on a 5-ASA during pregnancy, it's like taking a multivitamin in terms of its safety. So definitely recommended.

Frederick:

Thank you. Can we have the next question, please?

Operator:

The next question comes from Angela in New York.

Angela:

Hello. In your chart you have followed patients for 3 years and after 3 years of complete adherence and patients are symptom-free for half that time, what is the likelihood while following doctor's orders that the patient can slowly reduce the antibiotics, and how slow should be the rate that is the safest?

Dr. Kane:

Your question is about if somebody's been well for 3 years and you want to try to taper their regimen of their drugs?

Frederick:

I think she's on mute now.

Dr. Kane:

In general, patients who are well for long periods of time, trying to minimize the exposure to whatever medicine they're taking is a reasonable thing to do. It sort of depends on which drug it is, and Angela had mentioned antibiotics and since they're all so different, it would be hard to answer that specifically. But when patients are well for extended amounts of time, so 3 to 5 years, and they have been taking their medicine, then yes, I do discuss with them on an individual basis what's the lowest amount you can be on and still be well. So I'll leave the answer in that frame.

Frederick:

That's a great answer. We're ready for our next question.

Operator:

The next question comes from Rhonda in North Carolina.

Rhonda:

Hi, Dr. Kane. I've had Crohn's for about 4 years and I've actually been on every medication on your list, one type of each of your medicines. Currently on Remicade, it's not working for me because of the side effects of the medicine. The medicine is working, but not the side effects. If the 6-MP drug that I took increased my liver count, would another drug of that nature possibly do the same thing?

Dr. Kane:

Yes. What Rhonda is asking is about certain adverse events that occur with drugs. And so 6-MP and azathioprine, which are the two cousin drugs, which are very tightly associated with each other, that if you get a particular side effect on the 6-MP, you will get the same side effect with azathioprine. That's true specifically for liver issues, and pancreatitis. Those are the two that we see. If you get one of those with one of them, you'll get it with the other.

Frederick:

Okay. We have many questions in queue still. We'll take the next one.

Operator:

The next question comes from Kimberly in Texas.

Kimberly:

Hello, good afternoon. I have been diagnosed with Crohn's and I wanted to know what your thought was on the use of Colestid<sup>®</sup> long-term to control the diarrhea.

Dr. Kane:

So good question about Colestid, which was one of the drugs that we didn't talk about. Colestid is a medicine that does not affect the immune system and is not used per se to treat Crohn's. What it is used for is to treat the diarrhea that can be associated with Crohn's. So some patients who have bad diarrhea and particularly of a certain age group and certain amount of disease in their small intestine do very well on Colestid because it binds bile. Bile is irritating to the GI tract and will cause diarrhea. So in certain patients Colestid as an adjunct or an addition to therapy to treat the Crohn's can work very well as an anti-diarrheal.

Frederick:

Great. Let's take our next question.

Operator:

The next question comes from Kristie in Alabama.

Kristie:

I was diagnosed with Crohn's in December and my doctor is telling me that stress is the main cause.

Dr. Kane:

As we talked about, stress does not cause the disease. What stress does is it can make it worse and can bring out the symptoms that weren't necessarily there beforehand. So managing what's going on in your life can certainly help with putting everything into perspective and helping you on the right track to getting better. But there's no evidence for causation of stress, causing your actual disease.

Frederick:

Okay, our next question.

Operator:

The next question comes from Phyllis in California.

Phyllis:

Hi, Dr. Kane, thank you for taking my question. It's also about medication. I've been on Remicade for just over a year now and I'm still taking 6-MP and Asacol. I'm wondering if I need both of these on an ongoing basis.

Dr. Kane:

That's a very good question, too. Sometimes what happens is that we as healthcare providers, we can lose track of what our patients are taking and we think that we've stopped one medicine or we assumed that we told our patient to stop something because we switched them to something else. That may not be the case. Any time that you are on multiple medications, it's always a nice idea to make a specific appointment and that the whole agenda of that appointment is not to talk about your diarrhea or your actual health, but to say, "Listen, we're going to spend 10 minutes to talk about my medicines. Here's what I'm on." And a lot of times the doctor or the other healthcare provider will say, "Really? I thought we stopped this." It can be very educational to just spend that 10 minutes and not talking about anything else, but saying here are my medicines, why do I need to be on this one and this one and this one. A little bit of education and communication can go a long way.

Frederick:

So don't assume your doctor knows what you're taking at all times.

Dr. Kane:

And that's a horrible thing to say, but I'm certainly guilty of that myself.

Frederick:

That's important. Can we have the next question, please?

Operator:

The next question comes from Miles in New Jersey.

Miles:

Hi, Dr. Kane. Concerning the frequency of the 5-ASAs and being able to take it less often, is there also a dosage change?

Dr. Kane:

No. So when you're changing the frequency of the 5-ASAs, we just change how often you're doing it. So if you've been prescribed eight tablets of something or six and you're supposed to do it two, three times a day, we just say take three of them twice a day. So we don't change the dose, we just change the frequency.

Frederick:

Can we have our next question?

Operator:

The next question comes from Elaine in Maryland.

Elaine:

Hi. After being in remission with ulcerative colitis for a few years, I know that taking one ibuprofen brought me into another flare-up. And no matter how much Asacol I take, whether two tablets a day or six, I'm always very sick in the mornings and fine the rest of the day. I don't want to have a buildup of Asacol in my liver or kidneys, so do you have any advice for maybe what time of day I should take it and how much to prevent the morning sickness?

Dr. Kane:

Elaine brings up two very good points. One is that a lot of you find that there's like this "morning rush hour," where most of your symptoms are in the morning, and that's because nature has set up our bodies to basically work with the sun. The way that we're supposed to work is that you get up in the morning when the sun rises, you have something to eat and your stomach tells your colon it's time to evacuate, so that we can get on with the rest of our day. And when there's inflammation, whether it's Crohn's or colitis, that message or that signal is exaggerated and that you can't have just one formed bowel movement and get on with your day, it's multiple during the morning. There's not a lot that we can do about that morning nature call.

What I can tell you, point number two, is that the medicines, that mesalamine 5-ASA medicines, they don't build up in your kidneys or in your liver to cause toxicity that way. These drugs are metabolized very efficiently and are not absorbed. So you could even take up to 4 grams in whatever formulation that you have prescribed, all at once, and it's not going to do any more damage to your liver or your kidneys, as if you took it three or four times in a day.

So that morning rush, really we try to just acknowledge that that happens and figure out what you may be able to take at night to sort of slow down that morning rush in the morning.

Frederick:

Thank you. Can we have our next question, please?

Operator:

The next question comes from Beverly in Michigan.

Beverly:

Hi. I'm an elderly lady, I'm 72. I got Crohn's disease in my 30s and I've had only one surgery and I've been very well through the years. I did have one flare-up with the blockage in the colon and had to have that done, but it wasn't anything from the Crohn's, it was from the scar tissue. My question is, I'm back on the Pentasa and I've been taking nine a day and when I'm feeling good, the doctor told me I could take six a day. But the last year I've been suffering from a fistula on the left side of my rectum and he's put me on Cipro 1,000 milligrams a day. And I do very well, it closes up. But the minute I go off the Cipro, or go down to 500 milligrams on his instructions, it starts up again. I have no other symptoms of the Crohn's coming back. I have the regular bowel movements, I don't have cramping any more. It's been about 7 years.

Frederick:

Your question is, Beverly?

Beverly:

Being on the Pentasa and the Cipro, is it hurting my liver or my kidneys, and why does the fistula keep coming back?

Dr. Kane:

Like I said to the other caller, Pentasa is not going to harm your liver or your kidneys long-term; these are extremely safe medications.

Fistulas will never necessarily go away. We can make them dry out, but they will never go away. If you have persistent drainage when you stop the Cipro, then maybe you need to talk

to your doctor about the fact that, hey, look, every time I go off the Cipro, this comes back, is that what you want me to stay on or is there something else we can do? Because fistulas are a different kind of scenario than just straight Crohn's that's in your small intestine.

Frederick:

Okay, can we have another question, please?

Operator:

The next question comes from Richard in California.

Richard:

Hi. I was wondering, if you take Remicade, once you're on Remicade, is that it, are you always on Remicade?

Dr. Kane:

What we understand about Remicade and the other biologic therapies is that once you start them, that we continue them as long as they are working because if we stop them, then that's when you become at risk for developing antibodies to the therapy and developing an immunity to them; and that if we were to reintroduce them at some time, you would have a very bad allergic reaction. So we know now that somebody who has been started on these therapies needs to continue and that's what they take to treat their Crohn's or their ulcerative colitis.

Frederick:

Thank you very much for that question. And thank you to everyone. This concludes today's program. Thank you again, Dr. Kane, for your time and expertise. We truly appreciate you being here, thank you, you were great.

Dr. Kane:

I'm very happy to have been here.

Frederick:

Great. Also a special thank-you again to Procter & Gamble Pharmaceuticals for making today's program possible. And most importantly, on behalf of the Crohn's and Colitis Foundation of America, thank you to all of you who participated in today's teleconference. We hope that you enjoyed the program.

Please remember to fill out your Evaluation forms. They really are very important to us in driving future programs.

For more information about today's program or for disease-specific information as well as for upcoming teleconference programs like the one you just heard, please call our Information Resource Center at 888-MY-GUT-PAIN. Also if you would like to get involved in our spring Take Steps for Crohn's & Colitis Walk, or our Team Challenge Half Marathon, or to chat with an Information Specialist, please visit our website at [www.ccfa.org](http://www.ccfa.org).

Again, thank you for sharing this time with us and have a great day. Good-bye, everyone.

Operator:

This concludes today's conference call. You may now disconnect.

END