



**Balancing the Risks and Benefits of Treatment  
For Inflammatory Bowel Diseases  
June 9, 2009**

**Slide 1: Balancing the Risks & Benefits of Treatment For Inflammatory Bowel Diseases  
Operator:**

Hello, everyone, and welcome to today's free educational teleconference and webcast – *Balancing the Risks and Benefits of Treatment for Inflammatory Bowel Diseases*. It is my pleasure to introduce your moderator, Kimberly Frederick, Vice President of Patient and Professional Programs at the Crohn's & Colitis Foundation of America.

**Kimberly Frederick:**

Thank you. On behalf of the Crohn's & Colitis Foundation of America, welcome, and thank you to all of you who are attending today's program that is sponsored by UCB. I want to thank all of you who submitted questions in advance of this program. After the presentation, we will start taking questions from both telephone and webcast participants, answering as many questions as time allows. If we are not able to take your question today, please call our information resource center at 888-694-8872, as we are available from 9 AM to 5 PM eastern time Monday through Friday.

Also, to help us improve our teleconference webcast program, we would like to remind you to fill out the program evaluation form, which is available online or in the registration packet. Beginning tomorrow, you will be able to view an encore of today's presentation online at [ccfa.org](http://ccfa.org). The program will be available for one year. We encourage all of you to share this information with your friends and family members and colleagues who were not able to attend today's live program.

**Slide 2: Balancing the Risks & Benefits of Treatment For Inflammatory Bowel Diseases**

And now I have the pleasure of introducing today's speaker, Dr. Corey Siegel. Dr. Siegel graduated from Tufts University School of Medicine in Boston and went on to complete his residency in internal medicine at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire. Dr. Siegel served as Chief Medical Resident at Dartmouth from 2001 to 2002, where he also completed a fellowship in gastroenterology. From 2004 to 2005, he completed a fellowship in inflammatory bowel disease at Massachusetts General Hospital in Boston, Massachusetts.

Currently Dr. Siegel is Assistant Professor of Medicine at the Dartmouth Medical School and Director of the Inflammatory Bowel Disease Center at the Dartmouth-Hitchcock Medical Center, Section of Gastroenterology and Hepatology.

Dr. Siegel's research interests include understanding risks and benefits tradeoffs in IBD and improving risk communication for patients. Dr. Siegel also lectures both nationally and internationally, has been published in various journals and currently serves on the medical and advisory board for CCFA.

Welcome, Dr. Siegel, and thank you again for being with us today. I'll now turn the call over to you.

**Dr. Siegel:**

Thank you, Kim, and thank you to CCFA for making this possible. I've been looking forward to this to have the opportunity to talk to you about something which I think is critically important, which is not just what are the medications for Crohn's disease and ulcerative colitis, but really balancing the risks versus the tradeoffs of the benefits for the treatment of these diseases.

So, first off I'd like to say that I wish we had treatment for IBD that was 100 percent effective with no side effects, and I think that's the goal of everybody at the CCFA and everybody doing research in IBD. But that's simply not the case now. However, it's an incredibly exciting time with new meds. We're learning to use the current medications that we have better, and we've come an extremely long way just in the past four or five years from where we were. Every year we make more progress and we have more effective and safer treatments. But today is really focused on what we have available now; giving you a clear description of what we know and what we don't know, and to let you know how effective they are and also the associated side effects.

Side effects turn out to be a very difficult conversation and I think scary for many people to talk about, both patients and physicians and families. And it's hard to know where you get all of our medication information from. It's from friends, it's from families. A large part these days is from the internet. And a large part should be from your doctors. But unfortunately doctors have less time than ever, the treatment choices are even more complicated than ever. So I hope today to leave you at least with some understanding of what we know so that you can make informed choices with your providers about your own treatment.

This webcast isn't about convincing you to use certain medications. It's really about making you comfortable and understanding what the options are that are available. Thank you for sending in the hundreds of questions we received in preparation for this. I've tried to address at least the main themes, but I'm sorry if we don't get to everything.

### **Slide 3: The IBD Medicine Cabinet**

So let's get started. First off, what do we have in our IBD medicine cabinet? If you are a patient with Crohn's disease or taking care of a patient with Crohn's disease or involved in any way, you've probably heard of, if not all, at least most of these medications.

Starting at the top, we have the 5-aminosalicylates or what we call 5-ASA drugs. Antibiotics are used primarily for Crohn's disease. Corticosteroids and prednisone, as most of you know of and most of us think about, is somewhat of a bad word, and we can talk about that a little bit. And then most of this will be really dedicated to talking about the immune modulators or immunomodulators and biologic medications. The reason I focus on these is they are the most effective medications that we have for most patients with Crohn's disease and ulcerative colitis. It's often the medications that have the side effects that are most concerning to patients, families and their physicians. So I want to focus on those, and if there are questions about the others at the end, hopefully we can address them.

### **Slide 4: Benefits & Risks of Immunomodulators**

So let's start off with the benefits and risks of immunomodulators, and then we'll move onto the class of drugs called the biologics. We'll talk about trade-offs and how we can understand where our trade-offs need to be made, and then finally finish with some ideas about what you should be asking your doctor about the risks and benefits of disease, and ways that we physicians sometimes miscommunicate information, which unfortunately happens all too often.

### **Slide 5: Immunomodulators**

So first, the immunomodulators. There are other names for these called immune suppressant medications or antimetabolite medications. When you look for information on these, search the Internet responsibly. If you Google or any other search engine azathioprine or 6-mercaptopurine, which are the medications I'm primarily speaking of, and methotrexate as well is included here, you'll find a lot of information on there that may or may not apply to patients with IBD at all.

First, they were used as chemotherapy treatments many years ago and still are. So you might be reading about cancer treatments, which is certainly *not* what you want to be reading about and learning about. They're also used for transplant patients, liver transplants, kidney transplants. Again, that's a totally different dosing of drugs and different group of patients. So you want to make sure that you're reading about inflammatory bowel disease patients.

Also, just to note on the Internet, you also want to make sure unless you're on a site like the CCFA site, you're not exactly sure where the information is coming from. Most people don't go and post stories about how well they're doing on the Internet, so it's really filled with some scary stories more often than not.

These medications, however, have been used since the 1970s for the treatment of Crohn's disease and ulcerative colitis, and really we've learned a lot more about how they work by quieting down the immune system and their effectiveness and also side effects.

### **Slide 6: What Is the Efficacy of 6MP/AZA?**

So how effective are these medications? And, again, although methotrexate is a medication we commonly use for Crohn's disease, 6-mercaptopurine and azathioprine really are the most commonly used immunosuppressant medications for both Crohn's disease and ulcerative colitis.

Some important points that always need to be remembered. First off, these medications don't work right away. They can take two to four months to fully kick in. So if you've been on these medications for a few days or a few weeks or sometimes even a few months, they may not have had enough time to start working fully, and they might need a little bit more time. Because of that, they're usually taken along with another medication to get patients into remission or get you feeling better. So it might be reasonable to take 6-MP or azathioprine along with a short course of prednisone with a plan to get you off of prednisone very quickly as soon as these medications kick in. And there are a variety of other short-term medications that we can use along with this as well.

How well do they work? Well, once you can get into remission on these medications, the majority of patients stay in remission on these medications. Approximately 70 percent, or 70 out of every 100 patients who take it stay in remission for at least that next year, and if you look out many years later, if you stay on the medications at the same dose, most people continue to do well. The question always comes up, and there were a number of questions that I received, about how long do you have to be on the medications, and can you stop? There've actually been some pretty good research studies on this, and if you look at groups of patients who stay on the medications versus those who stop, those who stop almost invariably start having flares of their disease again, whereas the majority stay in remission if they stay continued on the medication.

### **Slide 7: What Are the Side Effects of 6MP/AZA?**

So what about side effects? A lot of this conversation over the next 30 to 40 minutes is about balancing this. So what are the main side effects of 6-MP and azathioprine? Well, some of them are not so serious and some are more concerning. Allergic reactions, if any of you out there have had one, it's certainly not something you want. But very rarely does it become a serious or even close to a life-threatening thing – but it does occur about 3 percent of the time in patients who take these. Typically it's a rash, fever, and you just don't feel great.

I typically tell my patients when they ask me, "How do I know if I have pancreatitis?" And I tell them that they'll know and they'll probably be cursing me all the way to the hospital when they have it, because it's really not a pleasant experience. It's a severe abdominal pain that typically radiates right through the back. The nice thing about any allergic reactions, if there is a nice thing about having a side effect, is that it goes away – and it goes away on its own when you stop the medications, and almost always it's not a long-term problem.

Serious infections are certainly something we worry about, and the reason is is that these medications suppress your immune system. So you might be at risk for having more infections, even more typical infections. I'll often times tell patients that you might have three colds a year instead of one or two colds a year, and it might last seven days instead of three or four days. But there are also these risks of very serious infections that you wouldn't get typically because we are suppressing your immune system. These are very rare. And although serious infections might occur 5 percent of the time, life-threatening infections – something we call sepsis – occur very, very rarely. And if you see on that slide, the denominator goes from 100 to 10,000 because out of the 10,000 patients who take these medications, approximately 15 might actually have life-threatening infections. Who are those 15 people? Usually you think it's *you* when you're worried about taking these medications. However, if you look at the patients who get into big trouble with these medications, it's typically those who are also taking high doses of steroids, often times taking narcotics or pain medications, and often have multiple other medical problems. So although we have to pay particular careful attention to those patients, it doesn't mean we can't use them. And the majority of patients who are taking these really are at a much, much lower risk than that of serious problems.

The next couple lines in there refer to cancers, something specifically called non-Hodgkin lymphoma. I think, at least in my practice, when I'm prescribing these medications, this is where I spend most of my time talking with patients and their families about the real risks of cancers that are associated with these. And I find when I look around the Internet for information, this is what pops up most often. So we do have to put things in perspective here. The risk of developing lymphoma or non-Hodgkin lymphoma, which really is the main cancer that we worry about with these medications, is only about 4 people out of 10,000 people who take it. To keep that in perspective, on no medications, just a random person walking around the street in the United States has approximately a risk of 2 people out of 10,000. So although if you were writing a news article, you might write that these medications double your risk of cancer, really what we're talking about is 2 people out of 10,000 and increasing that to 4 people out of 10,000. I did put a line there because of course having lymphoma is not the only thing you have to worry about. Is it treatable? Can you make it through? Fortunately, more than two thirds of people who develop these lymphomas are actually treated completely, and it's not a further problem. So, again, not something you want, but treatable if it develops.

### **Slide 8: A Risk Palette**

This next slide that I'm bringing up – give me one moment here, sorry – is called a risk palette, and you're going to see this come up a couple times over the course of the talk. I like to use this because the small numbers – 2 per 10,000; 4 per 10,000, 0.04 percent are very hard, I think, to conceptualize. I like these risk palettes because it gives you an idea of really how small these numbers are. If you can see the little dots there, those are supposed to represent 10,000 people.

### **Slide 9: Risk of Dying From a Serious Infection**

If you think about some of the numbers we went through, this is that risk of dying from a serious infection. Although I wish it was zero, it's about 15 people out of 10,000 who take it. And, again, those 15 people typically have other things going on other than their inflammatory bowel disease.

### **Slide 10: Annual Risk for Developing NHL**

Here's that risk of developing non-Hodgkin lymphoma without any medications. It's about 2 people out of 10,000.

### **Slide 11: Annual Risk for NHL While on 6MP/AZA**

So there's a lot of fear about these medications, 6-MP and azathioprine, causing lymphoma, it goes up to about 4 people out of 10,000. So four of those little people are lit up with red as opposed to two.

### **Slide 12: Benefits & Risks of Biologics**

Now let's move on from the immunomodulators to the biologic agents, and there are a lot of similarities. There are some differences. Then we can talk about towards the end how we can use these in combination and if that's a safe thing to do, is it more effective than using them on their own.

### **Slide 13: What Is Biologic Therapy?**

I always like starting with the definition of biologic therapy. So what's the technical answer? Why do we call these biologic therapies? It makes them sound fancy and new. But really it's referring to any therapy or medication that is actually made from a living organism. So it's not a synthetic process of making up a medication that doesn't already exist in your body. Here the medication is similar or identical to the actual biologic chemical that your own body makes. So the practical answer for inflammatory bowel disease, these are really designer drugs made to specifically block inflammation or actually stimulate anti-inflammatory processes in your body, as opposed to medications like prednisone, which is globally suppressing your entire immune system – and to some extent, 6-mercaptopurine and azathioprine may do the same thing.

### **Slide 14: Smart Bomb**

These medications really are more like a smart bomb where they focus in on an individual chemical in the body to help suppress Crohn's disease or ulcerative colitis.

### **Slide 15: IBD Biologic Treatment Made Simple**

This is a simple side approach of the chemicals that we're dealing with. On the left side of the seesaw are chemicals that float round your body that cause inflammation, and on the right side are chemicals in your body that are there to help prevent inflammation. I've circled TNF-alpha all the way to the left as that's the chemical that the biologic drugs that we use most commonly, the anti-TNF drugs called infliximab, adalimumab or certolizumab pegol – you might know as Remicade<sup>®</sup>, Cimzia<sup>®</sup> and Humira<sup>®</sup> are focused on. All of those other chemicals on this have already been used in research studies and are actively being studied as other alternative methods of also treating Crohn's disease and ulcerative colitis.

### **Slide 16: Antibodies Block Chemicals**

So if we think about TNF-alpha, the medications that we're giving are actually antibodies. If you look at those yellow Y-shaped symbols there, those are antibodies that are trying to bind onto active inflammatory chemicals or cytokines in the body. And those pink thumb-shaped objects there, which are trying to land in the center of that chemical receptor, are trying to cause inflammation. There's something in the body of patients with Crohn's disease and ulcerative colitis that want to cause this inflammation. So medications like the anti-TNF medicines, such as Remicade, Humira and Cimzia, are these Y-shaped type materials that are given to patients to try to block the inflammation to prevent that from occurring.

### **Slide 17: Differences Between the Biologics**

So does it matter which one we use? We've had three now. Infliximab was the first; adalimumab was the second, and now certolizumab pegol is now available just over this past year. They all work by very similar mechanisms. They're slightly different in their design and how long they last. Infliximab is given intravenously through the vein every eight weeks. Adalimumab is an injection that's subcutaneous that's given every two weeks. And then certolizumab pegol is a subcutaneous injection that's given every four weeks. The newest biologic drug, and working by a different mechanism – it's called an anti-adhesion molecule and was just recently approved over the past year as well for Crohn's disease is natalizumab. This is given intravenously every four weeks, and typically you have to be registered through a program called TOUCH<sup>™</sup>. And we'll talk about the benefits and risks of this medication as well in the next couple of slides.

### **Slide 18: How Effective Is Anti-TNF Treatment?**

So let's start with the ones we've used over the past 10 years now and are really gaining a lot more experience with the anti-TNF drugs. So how often do they work? There are really two questions when you're thinking about these medications. How often does it work right away, and then is it going to keep working after that? So I've broken down these slides to show you what the initial chances of responding to the drug. Here, about 60 percent of people feel better pretty quickly when you start and anti-TNF drug. My suspicion is this number is higher as these are taken from clinical trials. And as you may know, clinical trials typically involve some of the

sicker patients that we treat, and I would think, in general practice, that's if this number is a little bit higher.

### **Slide 19: Anti-TNF Therapy Effectiveness Over Time**

So if you focus on those 60 percent, what happens to them later? At the end of a year, just over a third or 34 percent of those patients are in complete remission. Meaning that they don't feel that they have any symptoms of Crohn's disease. So to me, as I started with in the very beginning, I wish these medications worked 100 percent of the time. But when you're on steroids and sick and you need a medication that's going to help, there's a very good chance that you're initially going to respond to the anti-TNF drugs, and there's a pretty good chance that you'll continue on and actually go into remission. In addition to those 34 percent who stay in remission, there's still a number of patients who feel a lot better but haven't quite reached that level of remission – meaning they just don't feel that they have any symptoms. If you compare it to those in the placebo group, and again we're not talking only about clinical trials, but just to make a point that there are a lot more patients getting better on the medications than if you don't receive the medications at all.

### **Slide 20: Side Effects of Anti-TNF Drugs**

let's address the side effects of anti-TNF drugs. There's a long list. And if you open the package insert that comes with this, it's impossible to read and decipher and understand really what the most important things are to look at. So I've tried to put here what I think are the most important ones, and then we're going to focus on infections and these risks of lymphomas and cancers as we mentioned with the immunomodulator drugs.

So starting with the hypersensitivity reactions, these are injection-site reactions or infusion reactions where you have an immediate allergic-type reaction. Again, these are scary. They're fortunately not life threatening. Sometimes it's just a little welt from an injection. Sometimes it's feeling short of breath during an infusion. But they typically go away very quickly and are not a long-term problem. Immunogenicity really refers to the idea that...although I told you these are biologic medications and they're very similar to medications in your own body, it's still possible to have allergic immune-type reactions to these medications, because despite the fact that they might look like chemicals in your body, they're not exactly the same. Headaches are common and go away typically fairly quickly. Rash occurs every so often and – usually not a major problem.

I'm going to skip to the serious ones, of infections and then if you look all the way down that row to malignancy. Let's focus in on those a little bit.

### **Slide 21: Main Side Effects of Anti-TNF Treatment**

So going to malignancy first. And, again, I think these are the most concerning to both patients and providers and families when you think about starting a medication that might actually cause cancer, which is a scary thing to think about. But to remind you of the baseline risk, meaning



those people walking around on no medications at all of non-Hodgkin's lymphomas, about 2 people out of 10,000. On the immunomodulators, it's about 4 people out of 10,000, as I mentioned a few slides ago. If you're using anti-TNF medications along with immunomodulators, although the risk is a little bit higher, it's still about 6 people out of 10,000. So, again, the new story would be a triple risk from 2 to 6, but still a very, very small number.

I'm going to mention hepatosplenic T-cell lymphoma over the next few slides, and I'll come back to that. Here's that issue again of very severe infections – because we are suppressing the immune system, you are at risk for developing infections that are worse or possibly worse than they would be off the medications.

In one series looking at patients from the Mayo Clinic and looking at a bunch of other research studies and put them all together, the rate that I was able to come up with of actually being at risk of dying from a severe infection is about 4 people out of 1,000. But I'll show you on the next slide that that's a specific group of people. And for younger patients, the majority of patients we're treating, that risk is much, much lower.

That number for tuberculosis, 5 people out of 10,000, is low. It was a lot higher before we got smarter about this and understood that tuberculosis was a risk of using anti-TNF therapy. In the majority of patients when this occurs, although it's still very rare, again is a treatable process. Just to be clear, these medications don't *cause* tuberculosis. In people who have been exposed to tuberculosis at some point in their lives, this medication takes away that mechanism to prevent it from coming back. So giving the medication sometimes allows tuberculosis to rise again. But if you've never been exposed to tuberculosis or haven't lived in a place where it might be at risk for exposure, it's incredibly unlikely that this would ever be a problem for you.

## **Slide 22: Risk of Dying From a Serious Infection**

Let's talk about this risk of very serious infections or even dying from infections. So although that number seems high, 40 per 10,000 treated patients, again, if you look at the 10,000 little people there, it's still an incredibly rare event.

Now here it's even more important. The people who had these infections were a specific subgroup of people where their average age is in their 60s, they were taking both steroids and many times narcotics or pain medications. If you wonder why your doctors are being so mean and not giving narcotics for pain, this is one of the reasons. There actually seems to be a higher risk of dying from serious infections if you're taking narcotics. In addition having disease for a much longer period of time and having other medical problems. So if you look at people from clinical research studies who have actually died from infections, having diabetes, having liver problems, having cirrhosis with liver problems, kidney problems are all risk factors for serious infections to get out of control. That doesn't mean that if you have these problems you can't use these medications. It just means that we have to be even more careful and be right on top of any fevers or new things that come up during therapy. With younger patients, patients without all these other medical problems, the risk is much, much lower.

### **Slide 23: Annual Risk for NHL on Combination Therapy**

Going back to that issue of non-Hodgkin's lymphoma, again, it's about 6 people out of 10,000 if you're using these medications in combination. Meaning an anti-TNF therapy along with an immunomodulator like azathioprine or 6-mercaptopurine. For some people, the 6 per 10,000 may be intolerably high and any increased risk of cancer may be unreasonable. But in my mind at least, and I think most of the patients I've talked to about this, that's a very reasonable risk to take, particularly if you're not feeling well.

### **Slide 24: What Is Hepatosplenic T-Cell Lymphoma?**

So hepatosplenic T-cell lymphoma has only been something on our radar screen over the past couple of years. It's a subtype of non-Hodgkin's lymphoma. Signs and symptoms of this are fevers, chills, night sweats that don't go away, enlarged liver and spleen that your doctor can feel on examination, and blood counts that are dropping. The diagnosis isn't easy to make, as it requires a biopsy typically of the liver, the spleen or the bone marrow. It happens to be a particularly nasty type of cancer that's very difficult to treat.

### **Slide 25: Hepatosplenic T-Cell Lymphoma and IBD**

So why do we care about this with inflammatory bowel disease? Well, there are a few more now but initially there were 9 reported cases of this type of cancer with taking a medication called azathioprine. Probably can occur with 6-mercaptopurine alone. And then over the past few years there were 16 cases, and I believe 1 or 2 more now, of patients taking infliximab in addition to azathioprine or 6-mercaptopurine. Typically this affects young patients. The average age is 23 and interestingly most are male. Something we don't really understand, but we know that lymphoma in general is something that affects males more than females.

Now here that denominator or out of how many is incredibly important. This isn't out of 10,000. This is out of probably 400,000 patients who've been treated with infliximab for IBD and over a million patients who've been treated with infliximab throughout the United States. And although I've been focusing these numbers on infliximab, I should say that it's probably fair to assume that it also applies to adalimumab, which is Humira, and certolizumab, which is Cimzia. We simply don't have enough information on these newer drugs to say that they're any safer or any less safe than infliximab. We just have 10 years of information about infliximab. So if I keep referring to that it's only because that's what we're basing our estimates on.

### **Slide 26: Natalizumab**

So let's change course a little bit to our newest drug which is called natalizumab. As I mentioned, this is a totally new way of treating Crohn's disease. And interestingly it works very well for the treatment of multiple sclerosis as well. For now the only patients with Crohn's disease who can receive this are patients who have already been on an anti-TNF agent and have not done well. So this is really specific for a subgroup of patients who have tried almost everything and have no other options.

The concern with this medication, and the reason that it requires a lot of discussion, is this risk of a serious neurologic problem called progressive multifocal leukoencephalopathy or PML, so I don't have to say *that* over and over again! I'm going to come back to the risk of PML in just a moment.

### **Slide 27: Treatment With Natalizumab**

First let's talk about how effective natalizumab is. So, in patients who have failed anti-TNF therapy – and I always hate saying that. It's really that the medication has failed you, not that you have failed the medication – but in this group of patients that have gone through almost all of our treatment options, I think we do pretty well. So as mentioned start off with what's my chance of initially responding. And initially just over half of patients got better in the clinical trials with natalizumab. So 51 percent of patients responded and started feeling better within the first 10 weeks of treatment.

### **Slide 28: Effectiveness of Natalizumab Over Time**

Well what happened after that? If you focus on these 51 percent of patients, that almost half of those stayed in remission, were free from symptoms over the course of the next year. So, again, although I wish this were 100 percent, if you take all those patients out there who have not done well on anti-TNF therapy, this is a very reasonable alternative for treatment.

### **Slide 29: Natalizumab**

So if you think about the trade-off with this, what it comes down to is, we worry about PML. Well, PML is an infection that involves the brain that's related to a virus that's called the JC virus. To date, and this was just updated very recently, there have been 10 cases in the world reported associated with natalizumab. Nine of them were with multiple sclerosis, and there's just been a single patient in the world with Crohn's disease who's had this problem. I can't say for sure that that means Crohn's patients are more protected than MS patients, because many, many more MS patients were treated with this drug. But perhaps because it involves the brain and not the gut that maybe MS patients are at more risk. But that might be wishful thinking.

So out of how many are these 10 cases? Well over 52,000 patients now have received natalizumab. So that's a much higher number than we had in the past, and almost 7,000 patients have received this for over two years.

### **Slide 30: Estimated Risk for PML**

If you look back at our risk palette and – what that means, again, we're at a very small number. These are 7 patients out of about 10,000 who were treated. So if you think about what your chances are of having PML while receiving natalizumab, the chances are very small. And you can see the characteristics of patients who've had these problems.

### **Slide 31: Treatment Pyramid for Crohn's Disease**

So let's put this all together and think about the treatment options for Crohn's disease. Starting on the bottom are really treatments for patients with mild symptoms. As you move up, for patients who have more moderate symptoms. And as you go up the chain, really, as your symptoms become more severe. With that said, we're learning a lot now and we're finding that using these stronger medications earlier on in the course of disease before complications develop actually might be much more effective than waiting until problems occur.

### **Slide 32: Treatment Pyramid for Ulcerative Colitis**

I want to make a quick distinction between ulcerative colitis, as ulcerative colitis is very different, as you may know, because taking out the colon in a surgery is a cure of that disease. Although I agree that's not the first option for most people, it is an option earlier on for others. And some patients, after hearing what I've told you about side effects of these medications, might say maybe surgery is an option now and not only after I have failed every single medical therapy that's out there. So I think about this a little bit differently for ulcerative colitis than Crohn's disease.

### **Slide 33: Are Two Drugs Better Than One for CD?**

Now, coming back to Crohn's disease, I did mention earlier that we've put a lot of thought into if it's safer to use one drug versus two drugs at a time. Is it more effective to use two drugs as opposed to one drug? So there's a very important recent research study that was presented initially about six months ago and just updated this past week at our national meeting that compares azathioprine used on its own to infliximab use on its own to a combination of the two.

### **Slide 34: After 6 Months of Treatment**

This is what happened after the first six months of treatment. And if you can follow along on top, just over 30 percent of people went into remission on azathioprine as compared to 44 percent of people with infliximab. And then look at that number for combination therapy. It jumps up to 57 percent. The bottom row relates to how many people had a completely normal colonoscopy after treatment. As you can see, azathioprine alone had 17 percent and skipping over to combination therapy was 44 percent. So it does seem to be that using these medications together increases the likelihood of going into remission and having complete healing during that colonoscopy, which is nice to see. I leave it with a question to you really, is that worth it? Is that jump in 13 or 14 percent chance of remission worth what might be a possible higher rate of side effects by taking the two medications together?

### **Slide 35: Learning & Making Trade-Offs**

Now, the last few slides really relate to making tradeoffs and understanding the numbers here.

### **Slide 36: Patients' Willingness To Take Risk**

So this is an interesting research study that maybe some of you were involved with. This involved almost 600 patients with Crohn's disease where we asked you, are you willing to take the risks of these medications for the chance of feeling better? The message from this slide is that as patients were sicker and felt sicker in this study, by reading the descriptions of patients, they told us that they would be willing to take a higher chance of side effects. And I think this is very intuitive. That red line is showing you that as patients were sicker and obtained better benefit of therapy, that they were willing to take higher risks. As a matter of fact, almost up to a 1 percent or 1 in 100 risk of cancers or lymphomas. The white line where it says "here is 1 per 1,000," all the risks I've already told you pretty much are below that line. So at least in this survey of patients, we learned that most patients are willing to take the risks of side effects of these medications despite the fact that we are concerned about them and are scared about them.

### **Slide 37: Putting Risk in Perspective**

We also need to put this in perspective, that just being alive and walking around the planet, we have risks of bad things from happening to us. Although very few of us have either been struck by lightning or know somebody who's been struck by lightning, it happens. But look at these numbers for other things that we do every day. The chance of dying over your lifetime from a biking accident is 1 per 5,000; drowning, 1 per 1,000. And believe it or not, in the US, the chance of dying in a car accident is about 1 out of 260. The chance of dying from cancer is 1 out of 8, and the chance of dying for heart disease is 1 out of 5. Now, remember this isn't patients with Crohn's disease. This is people in general. So when we're talking about side effects of medications on the order of 1 per 10,000, 6 per 10,000, we're taking extremely small risks to help make you feel so much better and get the quality of life back to where it should be.

### **Slide 38: Decoding the Numbers Game**

Now, the last couple of slides are talking about numbers and thinking about how you should interpret numbers – and really demand that your doctors communicate with you about numbers too.

### **Slide 39: This Is Doctor Talk**

This is doctor talk. This is how we write medical papers and describe things to each other. To be honest, I don't know that we understand when we're talking about these numbers very well either. Small numbers are very, very hard to interpret – 0.01 percent, and SIR is a standardized instance ratio of 3.23, or relative risk or statistically significant *P* values. Even terms like "common" or "rare" mean incredibly different things to different people.

### **Slide 40: This Is Doctor Double-Talk**

This was shown very nicely by some colleagues of mine here at Dartmouth where they use the term called "framing." Now this happens every day in almost everything we do, but it shouldn't

happen in the doctor's office. If a doctor tells you, as they did in this research study here talking about heart attacks, that a medication might reduce your risk of heart attacks by 34 percent, that sounds very appealing. However, if it was said that this medication might reduce your risk of heart attacks by 1.4 percent, you might not be so excited. Or you know what, mathematically speaking, these are exactly the same thing. And we use these relative terms sometimes to either purposely mislead people or, I think, just to confuse the issue a little bit, not on purpose at all. And although no doctors are out there trying to mislead patients or families or each other, sometimes we get caught up into the fact that these relative risks sound more impressive. So for instance, as I told you, there's a double or 100 percent higher risk of lymphoma with immunomodulating drugs. But what that really translates to is 2 people out of 10,000 to 4 people out of 10,000. So I would suggest that if you're hearing these numbers or reading about medical information, look for the *absolute* risk, not the relative risk which can be very confusing.

#### **Slide 41: Weighing the Risks Against the Benefits**

So summing this all up, these are really very individual decisions, and I realize very much so that everyone has a threshold of how much risk they're willing to take and how much benefit they expect to get from therapy. We have to worry about disease, as well, progressing on its own. Without proper treatment, we're talking about medications like prednisone, which I don't have a slide on. I'd be happy to talk about that a little bit at the end here, but long-term corticosteroids like prednisone have a very, very high chance of side effects. Almost everybody has side effects, and some of them are irreversible. In addition, the chance of the disease itself progressing without proper treatment is very high. In Crohn's disease, about 80 percent of people, or 80 out of 100, will need surgery for their Crohn's disease over the course of their disease without proper treatment. With ulcerative colitis 20 percent or 20 out of 100, otherwise said 1 in 5 patients, will need their colon removed without proper treatment. So the idea here is making decisions about effective therapies but understanding that there's a scary but very, very rare chance of some serious side effects.

#### **Slide 42: Summary**

So in summary, immunomodulators and biologic medications can dramatically improve the quality of life in IBD. There are some very serious but very rare side effects associated with these medications. In general, if you need the medication, the benefits most often times outweigh the risks. To clearly understand the trade-offs is important so that you leave the office feeling that you're making a decision with your physician and not that somebody is making that decision for you.

#### **Slide 43: Life Is Full of Risks, Some Worth Taking**

So thank you very, very much for attention. I hope that I have addressed many of the questions you have. And I look forward to and glad that we have time for questions. So thank you.

## **Slide 44: Question-and-Answer Session**

### **Kimberly Frederick:**

Thanks, Dr. Siegel, that was such a thorough and informative presentation. And I'm excited that we're going to now begin the question-and-answer session with the audience. We know many of you have questions and we will address as many questions as possible. Okay, so we have one from Valmar. And the question is, can you discuss the long-term effects of Remicade?

### **Dr. Siegel:**

Sure. Well that's an important question. I think it's important to point out that the numbers I gave you really are related to what we understand over these first years that we've had Remicade and the other anti-TNF medications available. So although the medications and numbers I gave you of the effects are related to one- or two-year risks of these drugs, it's probably pretty close to the long-term side effects. Other than the major risks that I've already noted, there are not other long-term side effects that we know about. Granted, we've had these medications available for 10 years, not 50 years. But I would be surprised if any new long-term side effects arise because 10 years is a pretty long time to be able to follow patients and understand what potential rare side effects occur. And if there are long-term side effects, I think they're going to be much, much less frequent than the ones I've already shown you, since none of them have really reared their heads already. So I think it's fair to say that the side effects I showed you are probably about the long-term side effects. Whether it increases over time, year by year do they accumulate, I don't think that's the case. I think that most of these risks are probably up front and early on. And if you make it through that first year without having major side effects, chances are you'll do very well. But to be honest, that's not something that we know with medical research quite yet. I hope that helps.

### **Kimberly Frederick:**

That's great. We'll take a phone question now.

### **Operator:**

The first question comes from Carrie in Massachusetts.

### **Kimberly Frederick:**

Hi, Carrie.

### **Carrie:**

Hi. Yes, I had a question in regard to the 6-MP. I get a lot of colds during the year as it is right now. I get a lot of – like 15 colds a year. Is it too risky for me to go on 6-MP or something like that?

**Dr. Siegel:**

How often do you get these colds? Are they clustered together in the wintertime? Are they spread throughout the year?

**Carrie:**

It's kind of spread out through the year. I mean I'll get colds, upper respiratory infections year-round. Mainly fall and winter, but I can get them spring, summer – a couple of them during the spring and summer.

**Dr. Siegel:**

Are they serious? Do they last more than a few days?

**Carrie:**

Oh yeah.

**Dr. Siegel:**

Are you out of work for them?

**Carrie:**

They'll last sometimes two weeks, four weeks. I'll have to go on antibiotics.

**Dr. Siegel:**

And if I have this right, you're not currently on 6-MP, is that correct?

**Carrie:**

No, right now I'm on Entocort<sup>®</sup>.

**Dr. Siegel:**

I think it's a valid concern. There are some people, and you may be one of them, who are at more risk for infections than others. But there are actually some ways that this can be evaluated now. And seeing how long and how effective your immune system is might be a reasonable thing. So seeing somebody like an immunologist might be a good idea before starting 6-MP to make sure that there's nothing that is a little different about your immune system. With that said, chances are you'll be okay. And I've actually had a number of patients who are like you who used to get a number of infections and interestingly, once we treated their Crohn's disease or ulcerative



colitis effectively, something happened to reset their immune system in some way and they stopped getting those. So I wouldn't say that you absolutely can't use it, but in your case it might be reasonable to consider looking into it a little further before jumping in.

**Kimberly Frederick:**

Okay, we'll move onto a Web question asked by Daphne. And the question is, can good lifestyle choices – diet, exercise, hygiene, etc. – help limit risk of serious infections when on immunomodulators?

**Dr. Siegel:**

I think globally the answer is yes. Anything to keep yourself healthier and keeping away these other diseases that I mentioned, like diabetes, liver problems, kidney problems, are all helpful in keeping your immune system healthier and keeping you well. So exercise, eating well, taking care of yourself, getting some sleep are all things that in general keep your immune system functioning better and therefore will protect you against some of these side effects. So, again a very important question.

**Kimberly Frederick:**

Okay, and I'm going to take another one from the Web, and this is asked by Dan. Does starting and stopping treatment with biologic drugs reduce their effectiveness?

**Dr. Siegel:**

Dan, thank you for asking this. This is something that I had wanted to cover and didn't quite have enough time for. The biologic drugs, as mentioned, are antibodies. And although the antibodies are given to you to try to attach onto other chemicals in your body, you could actually develop antibodies against those drugs. But starting and stopping the medications probably does increase the chance of your body developing antibodies against the drugs and therefore making them less effective. So in general, we like to start biologic drugs and then keep them going for as long as they're effective.

**Kimberly Frederick:**

Great. Let's take a telephone question.

**Operator:**

Yes, your next question comes from Chris in Idaho.

**Dr. Siegel:**

Hi Chris.

**Chris:**

Hi. Part of the question has already been answered, but I'm not responding to anything. I'm not being treated except for the symptoms. My question is, where do you go outside of an immunologist? And who do you – with all the other medications, I've tried Remicade and I got an infection immediately on Remicade. They had to pull me off of it, and there was just nothing left. So I'm sort of left –

**Dr. Siegel:**

And you have Crohn's disease, Chris?

**Chris:**

Yes. I've had it for four years.

**Dr. Siegel:**

I'm sorry to hear your troubles. Four or five years ago, I would have said once you try Remicade and it didn't work, you were getting into some very difficult choices. However, now there are three new medications out there, including Humira and Cimzia and Tysabri<sup>®</sup>, that might be an option. Sometimes if you develop an infection on Remicade, that may not mean you can't use it at all. It may mean we just have to use it at a different time, or use antibiotics along with it. So I don't think that it means that you're out of luck completely with the biologic medications. Furthermore, and I don't know exactly where your disease is, I want to make a comment that I think is very important.

**Chris:**

I can tell you, it's right at the juncture.

**Dr. Siegel:**

So if it's right at the juncture, surgery is no longer considered really a bad word for patients with Crohn's disease. When I was learning about this in medical school, I was told that the last thing in the world you want to do for a Crohn's patient is have surgery. However, these days the surgeons are so good at what they do, often times it can be done laproscopically and just a few days in the hospital that segments of Crohn's disease can be taken out. Although that doesn't mean you're cured, usually it's much easier to treat when you're starting fresh, and you get to reset the clock in a way where you can start a medication at that time and then go forward. So sometimes I feel like we push way too hard on the medical therapy, where we have to enlist our friends the surgeons to help us. We shouldn't use every single medicine that we have and experience side effects in particular before doing that. So I think meeting with a surgeon, if it is right at the juncture of where your bowel comes together there called the ileum, which is the most common site of Crohn's involvement, it might be worth talking to a surgeon. And that goes

for everyone out there with Crohn's disease. Surgery is not something that we absolutely need to avoid, and certainly for ulcerative colitis as well. For you, Chris, though, I think it's still worth considering some of these other biologic medications if you haven't had a real shot on them.

**Kimberly Frederick:**

Okay, great. Dr. Siegel we've got a bunch of questions on the Web related to naltrexone. This question is from Josh. How effective is naltrexone for UC?

**Dr. Siegel:**

Sure. Well, the study of naltrexone was actually published in 2007 in something called *The American Journal of Gastroenterology* on patients with Crohn's disease. I don't know of much on its use in ulcerative colitis, although there may be something out there I haven't seen. The study in Crohn's disease generates a lot of interest, and a lot of patients ask me about this. It's because the response rate was incredibly high, something like 50 or 70 percent of patients or even higher felt better with naltrexone. But an important point is this wasn't what we called a randomized control trial where we have a large number of patients who either get treatment or get placebo. Although I hate the idea that we have to use placebos in these clinical trials, it's really the only way and best way to understand if these medications really work. For instance, if you just treat patients with placebo in clinical trials, because of the nature of Crohn's disease that it gets better and it gets worse on its own, sometimes up to 60 percent of people can simply get better. So although the naltrexone study was very impressive and many, many people got well, it only involved 16 or 17 patients total and didn't have a comparison group to know if people would have gotten better on their own anyway. So I'm excited about the future possibilities of naltrexone. It's not something I would use in my practice typically now, but I look forward to seeing more information on it in the future.

**Kimberly Frederick:**

Okay, great. We'll take a telephone question now.

**Operator:**

Your next question comes from Camilla in North Carolina.

**Camilla:**

Yes, good afternoon. I'd like to know if there's a low-maintenance dose of prednisone with probiotics that would help at all.

**Dr. Siegel:**

Thanks, Camilla. That's really two questions rolled into one sort of. I'll mention the prednisone issue first. Your body makes an equivalent of about 7.5 milligrams of prednisone a day. So

although we like to not give any extra prednisone, if there are some patients where if we can get you down to about 5 milligrams of prednisone a day, although there still are some side effects – specifically risks of osteoporosis and cataracts and even some people develop diabetes on that dose – a dose 5 milligrams or lower is reasonable to consider in some people; although it’s certainly not my first choice.

Probiotics are also very promising. I feel that we have a long way to go in understanding how they work and how to make them work better. I think in the next few years we’re going to understand a lot better how to use probiotics. But right now it certainly is not quite the magic bullet to cure Crohn’s or ulcerative colitis. And I often times will use them in conjunction with other medications. But on their own I’m just not confident that they’re powerful enough to keep the disease under control.

**Kimberly Frederick:**

Okay, great. We’ll take another phone question.

**Operator:**

Your next question comes from Yvonne in Alabama.

**Yvonne:**

Yes, I had a ileostomy, most of my large intestine has been removed. Am I considered cured or just in remission?

**Dr. Siegel:**

Yvonne, how long ago was the surgery?

**Yvonne:**

Eight years.

**Dr. Siegel:**

Eight years?

**Yvonne:**

Uh huh.

**Dr. Siegel:**

And has there been any evaluation since? Meaning a scope to look inside the ileum to see if there's been any recurrence?

**Yvonne:**

No.

**Dr. Siegel:**

Well, sometimes that's worth doing. The reason being, when you have an ileostomy, it's sometimes hard to tell if you're having symptoms of Crohn's or not. And you probably know what I mean, but when you move your bowels normally you know that you're having diarrhea and looser stools. So with an ileostomy, it's sometimes difficult to know if things are acting up. However, with that said, if you've made it eight years and if you had a scope to look in there and there was no recurrence of disease, you might be in the lucky group of about 20 percent of people that after surgery have a long-term remission without needing medications at all. Although I mentioned 20 percent, 80 percent of people do have some recurrence and need medications. You might, again, be one of those lucky people who do quite well. So my suggestion would be to talk to your doctor about maybe taking a look in there. And the reason to do that, even if you're feeling well, is that if it's starting to come back, it's always easier to treat Crohn's disease before symptoms are serious or before complications can occur. So it might be reasonable to start a medication now that prevents symptoms from occurring as opposed to waiting for something to happen, and that might be a reasonable way to predict. If they look in there and nothing is seen, then I would feel pretty confident that you're going to do well over a longer period of time. But you'll still have to keep a close eye on things in the future.

**Kimberly Frederick:**

Okay, let's take a Web question. This question comes from Demini, and the question is, what are the irreversible side effects of prednisone?

**Dr. Siegel:**

Well, thanks Demini. Prednisone and – I would bet that out of all the people logged on still can answer this question even better than I. The side effects that I most worry about are osteoporosis. We do have some medications now that can help reverse the effects of weakening bones from prednisone, but still osteoporosis is the most common and one of the most difficult to take care of. Cataracts are something that occur. As you know, they occur more frequently as people get older. But even in young patients taking prednisone they can occur. Fortunately surgery is fairly routine now for cataracts, but it's still something you don't want to go through if you don't have to. Diabetes is something I also worry about. Usually if you have diabetes on prednisone, it goes away when you stop prednisone, but not always. But that's one of the main long-term side effects that I do worry about. And those are the main long-term side effects. The irreversible

ones, again, I would imagine the majority of people listening know about, which are weight gain, acne, difficulty sleeping, irritability. All that go away when you come down on the dose or stop the medication.

**Kimberly Frederick:**

Dr. Siegel, this question comes from the Web again from Jennifer. And the question is, are risks and benefits different in pediatric patients versus adults?

**Dr. Siegel:**

Yes, they are. Children are probably at risk for certain things a little differently. For instance, as I mentioned, the people at the highest risk of severe life-threatening infections are older people, older than the age of 60 who have other medical problems, on other medications for those medical problems. Where children might be at a higher risk of other things. Now, the two slides I showed in hepatosplenic T-cell lymphoma, when that first came to be was really only involving pediatric patients. We thought that our adult patients were immune from this problem. Although the average age is in the 20s, there are some younger patients and fairly young patients who've been affected by this. Really, as a subgroup, that is one of the main risks of the medications, specifically azathioprine and anti-TNF therapy when used together, that we worry about. Now, with that said, kids are probably at a higher risk of untreated disease. So although in adults the risks we think about are surgeries and complications, in kids we also have to think about growth failure and lack of proper development. So I think if there's any group of people who we need to treat well and need to treat really effectively is the children, and, therefore, I think that in most cases the benefits far outweigh these very small risks.

**Kimberly Frederick:**

All right. Let's try a Web question. This question is from Cheryl. And the question is, now that we know the risks of drugs, do you feel surgery is a better option for UC, or are there risks and likely complications with surgery also?

**Dr. Siegel:**

Well thanks Cheryl. That comes to be a very personal question, and it really has to do with how frightened are you about these rare side effects, and what do you think about having a major surgery to take the colon out? With two major options either being an ileostomy or a bag or having a J-pouch surgery where you can reconnect the small intestine to the anus and create a pouch inside. You still move your bowels the same way, go to the bathroom about five or six times a day, and many people prefer surgery to having these medications lifelong. But the majority of people probably would rather try medications and see if they work. So this isn't something I can answer globally for everybody. I – really, in my patients try to lay out very clearly what the options are of the medications and at the same time, have our patients meet with the surgeon so that they can hear what surgery might be like and what they can expect. I feel overall, again, most patients want to try the medications and see if they work. But there have

actually been some interesting research studies on this, and about one third of patients would prefer to go to surgery and jump over the medications and not use those at all. So it's a very important question and something that I think is really individual based on patients.

**Kimberly Frederick:**

All right. We'll take a question from our telephone audience.

**Operator:**

Your next question comes from Melvin in Florida.

**Kimberly Frederick:**

Hi Melvin.

**Melvin:**

Hi guys, I appreciate you taking the question. I'm actually the dad of a daughter who has just started with the Cimzia and was wondering...and I didn't hear the specific reference to Cimzia, how long it might be before you know whether it is working or not. What is the expectation for feeling better? First shot? Second shot? What does experience show?

**Dr. Siegel:**

Right. So let me take that, Melvin, using these biologic drugs in general and then I'll specifically mention Cimzia, because they're all a little bit different. Cimzia is given initially the first shot and then a shot two weeks later and then two weeks after that and then monthly. With Remicade you get three infusions right within six weeks, and then Humira you get a larger dose initially and then two weeks later a smaller dose and then two weeks after that they use the regular dose. So this period is called the *induction period*, where we give higher doses up front to get up those drug levels and get things going. I typically use that induction period as the period of understanding if it's going to work or not. So it's not within the first few days or even within the first week or two. I really feel like in those first, sort of, three to four weeks you should have an idea if it's going to work or not. And Cimzia, because you get the first couple shots all within that first month, I would think by that fourth week, really that third dose of Cimzia, typically is where we would like to see that there's at least some response.

**Kimberly Frederick:**

Okay, great. Let's take another question from our telephone audience.

**Operator:**

Your next question comes from Sherry in Rhode Island.

**Kimberly Frederick:**

Hi Sherry.

**Sherry:**

Hi. I had a question concerning Asacol<sup>®</sup>. About a year ago, I was reduced from three times a day to once a day, but I'm still getting pain occasionally. Is that just based on information? Should I look into maybe having the dose increased again?

**Dr. Siegel:**

Thanks, Sherry. How many pills are you taking of the Asacol once a day?

**Sherry:**

Two.

**Dr. Siegel:**

Two pills. So that's a pretty low dose. When I started the talk earlier, I mentioned there are a lot of new medications out there. And we're also learning how to use the current medications we have in a better way. We used to use all of these medications like Asacol, sulfasalazine, Colazal<sup>®</sup> – I'll try to get them all – Rowasa<sup>®</sup>, Lialda<sup>™</sup>, and Pentasa<sup>®</sup>. I think I got most. They're all of the classic drugs called mesalamine or 5-ASA drugs, and we used to initially believe that these had to be taken three or four times a day to work. But now we're realizing that once-a-day dosing actually is pretty effective. With that said, it needs to be a high enough dose. And Asacol, just two pills a day may not quite be a high enough dose for your treatment. So I think it's worth considering that. And also remembering that pain in patients with inflammatory bowel disease isn't always the inflammatory bowel disease. There can be other things causing that too. So when I see patients who are having symptoms and I'm not sure it's from their Crohn's or colitis, something like a colonoscopy or CT scans are other ways to understand how much inflammation is present might help direct which therapy and where I go next.

**Kimberly Frederick:**

Okay, I'd like to ask you a Web question from Laura. She says, how do you know when it's time to try some other medications? How long should you give them to work before you try something new?

**Dr. Siegel:**

Well, thanks, Laura. It's somewhat dependent on the medication. As I mentioned, the anti-TNF agents, sometimes within the first few weeks you know if they're going to work or not. The



immunomodulator medications really do take a few months. The average, I say, is three or four months. That means average. Some people are getting better in one or two months. And in some people I don't see the effects until five or six months. So it really does take a few months for the immunomodulator drugs to work. I would say that whichever medication you're on, talk to your doctor about how long they take to kick in and show their full effects. And if you're beyond that period of time, the next question is, am I on the right dose? And if you're not, to go to the right dose. And then if you are on the right dose and things don't seem to be going as well as they could be, then maybe at that point it's time to think about switching medications.

**Kimberly Frederick:**

Okay, and another question from the Web audience. This is from Barbara. Can you discuss the immunizations that one should get before starting 6-MP?

**Dr. Siegel:**

Thanks, Barbara. That's a really important question. I don't know that I have time to go into all the details of this. Briefly, patients – really all patients on immunosuppressant medications, so most of the medications we've talked about today – should receive annual flu shots and should receive a pneumonia shot probably once every five years. We used to think these were reserved only for older people, but the recommendations typically now for patients on immunosuppressive medications is to get them, again, flu shots on an annual basis at any age and a pneumonia shot really at any age every five years or so, in addition to all the childhood typical pediatric vaccinations.

Now, there are a couple that I want to mention that you *can't* get. And this is important because not all primary care physicians are thinking about what medications you're on for immunosuppression, especially if you're receiving medications like Cimzia or Humira or Remicade that may not be on their medication list. And if you are immunosuppressed, you can't receive *live* vaccinations. So there is an influenza vaccination that's intranasal, which is live, and that can't be used. Also, the vaccinations for chickenpox and for herpes zoster are live vaccinations and can't be used. There are some others that are out there; however, those are the main ones to think about.

**Kimberly Frederick:**

Dr. Siegel, there's several questions on the Web, and I'm going to try and sort of lump them together around pregnancy and the risks and benefits of these medications. Basically, the question is, what are the risks and benefits of these drugs as they relate to pregnancy as well as to breast-feeding?

**Dr. Siegel:**

Again, another great idea for Kim, maybe a future topic for one of these webcasts, because this is a really long question. Let me address this somewhat globally as opposed to specific

medications. The highest risk to the baby and mother during pregnancy is out of control inflammatory bowel disease. So by hoping to stop all medications and get through, that's probably the worst possible scenario. Because we know for sure that active uncontrolled disease is really at high risk for causing trouble with a newborn baby. With that said, we can't completely say that all these medications are risk-free during pregnancy. But we now have many years and many, many patients experience using the medications like 6-mercaptopurine and azathioprine in pregnancies that seem to be very safe, well tolerated and don't, at least as far as we can tell, don't cause any significant abnormalities in children. Then the newer medications, the biologics as well, we're gaining more information that these medications again seem to be very safe and used in pregnancy if used in the proper ways. Some of these medications I like to hold in the third trimester of pregnancy, and some others you can keep using. So I think it's worth talking to your doctor about the specific medication, but in general we like to keep our patients on the medications that are working. Some that are absolutely contraindicated during pregnancy is methotrexate. And if you're on methotrexate and thinking about pregnancy, that's something that we would have to change. In addition, thalidomide, which we use sometimes in Crohn's disease, absolutely can't be used at all. So, again, Kim, we should keep this in mind. This would be another great topic.

**Kimberly Frederick:**

Definitely. Let's take a telephone question now.

**Operator:**

Your next question comes from Anne from New Hampshire.

**Kimberly Frederick:**

Hi, Anne.

**Anne:**

Yes, I just wanted to know if there have been any studies yet regarding Remicade, the percentage of total healing in a colonoscopy for say the 10 years that it's been on the market.

**Dr. Siegel:**

That's a great question. I alluded to this. Are the Web slides still up Kim?

**Kimberly Frederick:**

Yes, they are.

## **Slide 45: After 6 Months of Treatment**

### **Dr. Siegel:**

So I'm showing a slide now Anne that gets to this somewhat. And if you look at that second column, these are patients who've had a colonoscopy before and after treatment. And you can see with infliximab, which is Remicade, that about 30 percent of people had completely normal colonoscopies after the six months of treatment. So pretty exciting that we can get things looking completely normal; although, as I noted a few times now, I sure wish that were 100 percent. But compared to no healing at all, I think we're making some good progress. Long term is something that we don't quite understand, but I would bet that the numbers are probably a little bit lower than this and drop off somewhat over time, but I would hope that we're doing a better deal than certainly not using these medications at all.

### **Kimberly Frederick:**

Okay, great. Thank you again, Dr. Siegel, for your time, your warmth and your expertise. We truly appreciate you being here with us today and for all of your work on behalf of patients with ulcerative colitis and Crohn's disease. A special thank you again to UCB for making today's program possible. And most importantly, on behalf of the Crohn's & Colitis Foundation of America, thank you all of you who participated in today's program. We hope you enjoyed it, and please remember to fill out and return your evaluation forms. You can also do that on the Web site. For those of you in the teleconference audience who received a confirmation packet in the mail, you can send back the evaluation in the self-addressed envelope provided.

One more thing. For more information on how you can join the fight against IBD, please join Take Steps or Teen Challenge, which is our national walk and our national endurance events. Or to get additional educational information, call our IRC 9 to 5 Monday through Friday at 888-694-8872, or check out our Website at [ccfa.org](http://ccfa.org).

Thank you again for sharing this time with us, and goodbye.

END