Postoperative Crohn’s Disease: Pittsburgh’s Treatment Trial: A Model for Understanding IBD. Our program is presented by Dr. Miguel Regueiro, Clinical Head and Codirector of the UPMC IBD Center. By participating in today’s program and completing the electronic post-test evaluation you will receive one CME CEU credit. Dr. Regueiro will address questions following the presentation. You can submit questions at any time throughout the program using the Ask A Question Link on the lower right hand side of your screen. And now Dr. Regueiro.

Thank you and good evening. Welcome to the program discussing the treatment trial for postoperative Crohn’s disease. I know that this is an audience that includes primary care internists as well as gastroenterologists and surgeons so what I plan to do in the next 40 to 45 minutes is provide an overview on inflammatory bowel disease but then really focus on postoperative Crohn’s disease as a model for understanding IBD but also for understanding postoperative prevention and management.

So I think that most of us know that inflammatory bowel disease has been on the rise in North America and specifically in the United States. Point estimates approximately 25 years ago were that there were approximately 500,000 in the United States with inflammatory bowel disease, now rates have been estimated as high as 2 million Crohn’s and ulcerative colitis patients in the U.S. This has been increasing over the past two decades, it’s still a disease of primarily younger patients however anybody can be diagnosed, the most common age of onset is between 15 and 40 years. We still do
not have a medical cure for inflammatory bowel disease and surgery is common, and I’ll come back to this obviously in a minute.

Well what are the geographic distributions? We know that like most autoimmune or immune mediated inflammatory bowel diseases, Crohn’s disease and ulcerative colitis are most common in North America and the Northern European countries. So on this map of the world the red, the dark red includes Crohn’s disease and ulcerative colitis prevalences and a higher rate than in Asia, Africa and Latin America. Interestingly if you were to parallel this to other autoimmune diseases like rheumatoid arthritis, multiple sclerosis, lupus and others there’s a similarity. This may be explained by what we consider a hygiene hypothesis in that patients and people who are exposed to parasites at a young age may protect against inflammation and autoimmune diseases, so places like Asia, Africa and Latin America where this is prevalent this has been a common protectant against autoimmune disease where in North American and Scandinavian countries this is less common.

Where ulcerative colitis can come in different forms, but is an inflammatory bowel disease process that involves at least the rectum and then different parts of the colon. And you can see in the left hand panel proctitis, left sided colitis in the middle and pan colitis on the right. This is a contradistinction to Crohn’s disease which is an inflammatory process that can occur anywhere in the gastrointestinal tract from the mouth with patients often presenting with mouth ulcers or aphthous ulcers of the mouth, skipping around in the intestine all the way down to the rectum and anus. In the dark red is the most common are for Crohn’s disease which is the terminal ilium or right colon. You
can see the appendix in the right lower quadrant of this picture and many patients will present with appendicitis like symptoms.

What’s the current etiology or why does anybody get inflammatory bowel disease? Well, this really is a paradigm that would apply to all of inflammatory conditions but also probably all medical conditions that we understand today. So at the bottom of this slide you see IBD, but pick your disease de jour and this probably would apply to that. In essence there is a genetic susceptibility that may explain 20 up to 30, 35% of patients so it’s not the entire story, there has to be some environmental factor that leads to a dysregulated immune response. So that’s our current understanding of IBD.

We do know that there are certain environmental factors that can trigger inflammatory bowel disease, this has been well described from infections to nonsteroidal anti-inflammatory medicines, antibiotics, diet has received a great deal of attention and there are several studies that are up and coming looking at diet as it impacts on IBD, smoking is interesting and most of the audience probably knows this, but smoking and cigarette smoking is actually protective against ulcerative colitis, it’s probably one of the only things in medicine we can find good about smoking is that it prevents ulcerative colitis; where smoking is horrible and very harmful for Crohn’s, where patients who smoke with Crohn’s often require surgery and have other problems. Our group here in Pittsburgh and others have now been exploring stress as a potential factor for inflammatory bowel and there’s clear evidence now that stress increases inflammatory, increases cytokine production and essentially stay tuned for more on that subject to come.
There is also a large North American consortium looking at genetics and inflammatory bowel disease, our group in Pittsburgh but certainly several others across North America are essentially taking blood samples on every patient we see in our clinics with Crohn’s and ulcerative colitis and in essence what we do is we phenotype these patients, we describe what we see. Where is the inflammation, how severe is the disease? Do they smoke? What medicines are they on? We take blood samples, extract the DNA and essentially identify loci. At last count there were over 150 loci that have been identified with Crohn’s and ulcerative colitis, and this is probably one of the most rapidly understood inflammatory conditions based on genetic analysis. So there could come a day where we have if you will the entire genetic map sorted out for IBD and I think that day is probably not too far in the future. What we do with that information still remains a question.

One of the pivotal studies was looking at certain genes and I don’t expect anybody to read this slide, but this is just one of many genetic explorations that have been done looking at the IL-23 gene and now I think what we are learning from these genetic understandings is that we are finding targets by which we can apply treatment to help inflammatory bowel disease patients.

The immunology of IBD has also been worked out, this is a somewhat busy slide that was published in the New England Journal of Medicine back in 2004 but on the far left hand side are the bacteria and then the intestinal epithelium are the barrier next to it and then essentially a mucosal immune response to bacteria. So our current understanding is that normal antigens and bacteria somehow in a
genetically predisposed host leads to an array of autoimmune and immune dysfunctional responses that we now know as inflammatory bowel disease.

Well how would we put this together as a story? And it’s interesting, there’s a family I saw about a year ago and if you look at the person on the left hand of the panel what we now realize is that our immune system is in constant attack by millions of antigens we take in by our mouth every day. So dietary antigens, different bacterial antigens and we are constantly down-regulating this response and it’s a wonder that we don’t all walk around with severe inflammation all of the time. But when you look at this it’s not uncommon for a common infection to trigger inflammation and it’s how the host responds to that infection what happens in IBD.

So for example, about a year ago I took care of a family that went off to Mexico, they had a great time, they drank the water, all of them came back with traveler’s diarrhea. All of them got better on their own, they didn’t require any treatment however the daughter in the family began to have more diarrhea after a week, and the diarrhea ultimately turned bloody and ultimately she went on to have a diagnosis of ulcerative colitis. So if you look at this slide, the family was exposed to a pretty common pathogen. In her case she was unable to down-regulate the immune system to lead back to a normal gut, so the rest of the family ended up in the bottom right of the slide where she ended up in the top left – I’m sorry, top right of this slide in that her gut was inflamed and probably with an autoimmune response to a common bacteria.
Well what’s the typical treatment? And I’m not planning to take us through all of the medications and treatments for inflammatory bowel disease, but typically the question is should we look at a top down or a bottom up approach? But in essence the groups of medicines are still the same regardless of which one we put on top, from aminosalicylates to antibiotics to steroids to immunomodulators and then most recently in the last decade the biologic therapy, most known are anti-TNF agents, and then surgery often will sit on top. Now one of the questions is whether or not we can look at surgery possibly earlier or use some of the more aggressive biologics earlier and change the natural course of disease.

So there has been the question, we’ve seen a change with an increase in use of immunomodulators and anti-TNF and especially in the last decade, and we’ve seen a change in the need for surgery. And the simple answer is that this is – we have limited prospective studies, we do have a couple of retrospective studies and in fairness there have been some other studies that I’m not going to present today that may show that earlier use of these treatments will prevent the short term surgery, the question is long term is that possible. But based on the retrospective data we have not found that there has been a decrease in overall surgical rates in a cohort population, at least not yet. There was a study by the Cosnes Group out of France that was published in 2005 which looked at the increased use of immunosuppressants in the form of 6 Mercaptopurine, Azathioprine and to a letter extent Methotrexate, and actually found that the surgical rates were still as high in the increased use of these immunosuppressants as prior to this treatment.
Our group in Pittsburgh also looked at this and published this in 2010 and we found that the small bowel resection rates were the same in the pre anti-TNF era as the post anti-TNF era. And just to briefly mention the study, what we looked are different time periods, so this is somewhat of a busy chart but if you look at the bar graph, the light or I should say the purple on the left is time period 1, 1995 up to the light blue is time period 4, 2007. And we looked at different medicines, 5 ASAs on the left, immunomodulators the second column, anti-TNFs the third and then finally corticosteroids. And I think it’s interesting, we can see that our corticosteroid use has decreased certainly from 1995 to present. Immunomodulator use also trended up, our use of 5 ASAs for Crohn’s disease trended down, kind of what we would expect. And our anti-TNF use also increased.

So the question is did the increase of immunomodulators and anti-TNF impact on our surgical rates, and what we found is that there was a low percent, about 1.5 to 2% of patients required surgery each year and it did not alter based on the increasing use of anti-TNF and Azathioprine. Now in fairness this was a retrospective study looking at a single site but it was interesting to see at least in our data that we did not see a difference. So that we know now that despite inflammatory bowel disease medicines still nearly 2/3 to 3/4 of our patients with Crohn’s disease will at some point in their lifetime require an intestinal resection, at some point require a surgery. We also know that surgery is not a cure. So now I’m going to transition the talk from the background of overall IBD to focus on our understanding of postoperative Crohn’s disease and I’ll submit along the way some ideas as far as how postop Crohn’s may actually parallel the understanding of inflammatory bowel disease in general as far as disease presentation, symptom presentation and overall treatment.
So what do we know about postoperative Crohn’s disease? Well I mentioned a minute ago that surgery is not a cure, so if you think for a minute of the patient that you send to the surgeon who does an ileocecal resection and takes out all of the active Crohn’s disease, so for that split second when the normal healthy ileum above the resection is attached to the normal healthy colon below the resection in a primary ileus chronic anastomosis, that patient is essentially in a remission or a surgical cure. But we know over time that the clinical recurrence rate will openly represent, so that by 60%, I should say by 10 years 2/3, 60% of patients, will have symptoms that come back suggestive of active Crohn’s disease.

When you look at the endoscopic recurrence rates this is somewhat more alarming. When you take a patient, whether they have symptoms or not, and one year after a resection with a primary anastomosis, do a colonoscopy, look at their anastomosis but look at the neoterminal ilium, the last part of the small bowel right above the surgical anastomosis up to 90% of patients will have recurrence, and this has been shown by Rutgeerts and his colleagues and published back in 1990. But probably most alarming is that what happens one week after surgery. So forget about macroscopic, endoscopic recurrence, forget about symptoms, if you take a patient who has an anastomosis and you biopsy the normal appearing small bowel above the anastomosis histologically we can already start to see Crohn’s disease recur at that early time point. So clearly surgery is not a cure.
Paul Rutgeerts’ group I mentioned a minute ago really was the pioneer to look at the postoperative course of Crohn’s disease and essentially came up with a scorecard on endoscopic recurrence as it may impact on future clinical recurrence. And in essence and not to spend too much time on this, the scorecard looked at a score of 0 all the way up to a score of 4 with 0 being normal, 1 being less than 5 ulcers, 2 being more than 5 ulcers, and 3 more moderate to severe inflammation and then finally 4 severe inflammation but also now starting to have stenosis or stricture. These are just pictures to show you some of the examples, so an endoscopic score of 0 in the top column would be everything normal if you were to erase that one small aphthous ulcer. A score of 1 is up to 5 of those ulcers and then a 3 you can see in the bottom left and a 4 on the right with a stricture.

What his group showed is that based on the endoscopic recurrence within the first year you can predict the clinical recurrence and the surgical recurrence long term. So this is a Caplan-Meier curve looking at what happened to patients who had endoscopic scores. The top bar is a score of 1, and most of these patients are symptom free and surgery free out to 8 years. So a score of 0 or 1 may predict that the patients will do well long term. A score of 2 having more ulcers, 20% recurrence at the end of 8 years, but then look what happens in the patients who have a score of 3 or even 4. So the patients with most severe endoscopic recurrence, even if they do not have symptoms, ultimately these are the patients who will come to another surgery at some point in their lifetime. So this endoscopic score has really revolutionized the way we look at postoperative Crohn’s disease and stratify treatment based on the score system.
So the question is how do we manage postoperative Crohn’s disease? Should we put patients on treatment after surgery, and if so what should we use? 5-ASA, should we use antibiotics, steroids or immunomodulators? What’s the role an anti-TNFs or biologics, how do we follow these patients? I mentioned a minute ago that many of these patients are clinically silent, they feel entirely well but if you do a colonoscopy you see disease recurrence within a year. So the question is when do we do a colonoscopy after surgery? Are there better methods? So fecal cal protectants, small bowel ultrasound, are there other noninvasive ways to look for recurrence? And then finally are there predictors of disease recurrence that we can use to stratify patients as to who we treat after surgery and which medicines we use?

So there have been several randomized controlled trials looking at the prevention of postoperative Crohn’s disease, and originally when I made this talk several years ago there were nearly 200 slides that followed it, and I promise you I will only show a few based on these data. But the data really we are looking at 5-aminosalicylates, Budesonide, the Nitroimidazole antibiotics, so for North America Metronidazole, in Europe they also use Ornidazole, and then finally the immunomodulators 6-MP and Azathioprine. We put together a systematic review and we looked primarily at endoscopic end points.

I think it’s important to look at the data, and this is the – really the only data slide that I’ll show from these studies, looking at 5-aminosalicylates. I think that in general most of us now realize that 5-aminosalicylates for treatment of any Crohn’s disease is somewhat limited. Now granted Crohn’s
colitis 5-ASA may play a role, but for Crohn’s in general 5-ASA therapy is probably largely ineffective. Unfortunately what we found postoperatively is essentially the same thing. So this is a difficult slide to read but if you just focus on the right hand side of the slide of the risk ratio, the line going down the right hand side, and then you look at all the lines crossing that line. The bottom line is that for the Sulfasalazine trials on top and the Mesalamine trials on bottom any time the line touches the risk ratio of 1 there was no difference between the control, which is on the right hand side of the slide and 5-ASA on the left. However when the metaanalysis was done and the publication came out in the American Journal of Gastro just this year the very black diamond all the way at the bottom is still fairly not touching the line so the conclusion was that 5-ASA treatment works in postop Crohn’s prevention.

When you look at the data tough and when you look at the evaluation of the study, there were 11 eligible randomized control trials, so this is a large group of patients, but you really need to look at postoperative studies and define the relapse or how recurrence was defined. So 7 of the studies used clinical recurrence, 1 used radiologic and only 3 of the studies bundled clinical with endoscopic. I’ll say that the endoscopic data did not show an benefit from 5-ASA treatment and when you look at the clinical data the number needed to treat was 13, which means that for every 13 patients put on 5-ASAs after postoperative Crohn’s disease only 1 patient had a clinical benefit, not an endoscopic benefit. So I think the utility of the 5-ASA treatment is something limited.
This was our systematic review that we published in 2009, we looked at all clinical recurrence rates, all endoscopic recurrence rates on the left and right and then we looked at different treatments, placebo, 5-ASA, Budesonide, Nitroimidazole and the immunomodulators. If you focus on the endoscopic recurrence, which I think most would argue is the more robust factor in determining postoperative recurrence and future surgery, there was not statistically a difference between most of the treatments and placebo. There were 4 Azathioprine 6-MP studies, 2 showed a benefit, 2 did not and the metaanalysis showed a slight benefit however endoscopic recurrence was no different.

So this leaves us wondering what do we do. So at best the endoscopic recurrence rates with the standard medicines at best are about 45%. What does this mean? Well this means that nearly half of the patients we put on postoperative prevention treatment will ultimately come to endoscopic then clinical recurrence and come back to surgery. And you see this in your clinics all the time, these are the patients who have surgery, they feel great, they do wonderfully well but 5 to 10 years later they come back with symptoms and ultimately they need another surgery.

So the question is, is there a better way to treat postop Crohn’s disease and prevent postoperative recurrence? So several years ago our group came up with a study looking at postop anti-TNF and we used Infliximab and we developed a randomized control trial to evaluate this. I will start by saying before I go into the slides that this was not meant as a proof of concept study, this was really a pilot study by which we intended to see if there was any signal if you will for anti-TNF postoperatively. And I’m happy to say that there is a large international study that will hopefully position anti-TNF
postoperatively and we need to wait for those data. But in the meantime we’ve published this data in Gastroenterology in 2009, the study we designed was a small randomized two-arm double blind placebo controlled trial. We did do a sample size calculation and what we assumed was, based on the Rutgeert data that if we did nothing, if we had a patient on placebo 80% would have endoscopic recurrence at one year, and we assumed that 20% in the Infliximab group would have a recurrence. So that came up with a sample size of 24 patients.

So we divided the 24 patients randomly in a blinded fashion to either receive Infliximab at the standard 026 induction and every 8 weeks thereafter at 5 mg/kg or placebo. Our primary outcome was to determine endoscopic recurrence. We were interested in clinical recurrence and remission but these were secondary outcomes, and I think that’s important. Our primary outcome was an endoscopic end point not a clinical end point. We did use the Rutgeerts score and just to recap our endoscopic remission was defined if the patient had a score of 0 or 1, and our endoscopic recurrence rates were a score of 2, 3 or 4.

And we – these are the baseline demographics, and again the numbers are slightly small but if you look at it, Infliximab is on the left and placebo is on the right, for gender, age, duration of disease, location, type of disease, prior Infliximab, yes there were patients who received Infliximab prior to the study, the number of surgical resections, there were patients on immunomodulators who came into the study and continued and prior 5-ASA. There was no difference between the two groups. Interestingly, and this is the problem with a small study, we actually found that there were more
smokers in one group than the other and I would dare say that if the numbers were reversed in the spread bar, if the numbers were reversed I would not be presenting these data. But what we actually found, if you will, is that active smoking was stacked against treatment with Infliximab, meaning there were more smokers on Infliximab than on placebo, which if anything would mean that the endoscopic recurrence and clinical recurrence would be higher in the smokers than the non-smokers.

And these were the bottom line data from the study. So for this graph yellow was Infliximab, placebo was red and this is looking at endoscopic recurrence, and again the numbers are small but over 85% of the placebo patients had an endoscopic recurrence at 1 year, whereas only 1 patient with Infliximab treatment had an endoscopic recurrence. And I don’t have the slide as part of this stack but we also looked at individual scores and all but 2 of the Infliximab patients had a score of 0, which was perfectly normal; whereas over 50% of the placebo patients had a score of 3 or 4. So what does this mean? This means that patients not treated with Infliximab had endoscopic recurrence at 1 year, not just mild but scores of 3 or 4. What was most alarming is that most of these patients did not have symptoms, they actually felt well. They were clinically silent. Well, the conclusions that we drew from this were that at least in this pilot study that Infliximab was effective at preventing endoscopic clinical and histologic recurrence. We also went on to publish our data looking at adverse events and we did not find an increase in adverse events despite using Infliximab within 4 weeks of a abdominal surgery.
Well this is all well and good, but this is one small 24 patient study and I would dare say I would not hang my hat on this study to say that this should change our treatment paradigms. But there have been several other small studies on postop anti-TNF, and if you look at this graph there are 4 studies, ours is the one in the second line, the top 2, Sorrentino and ours looked in Infliximab, the bottom two in the dark blue looked at Adalimumab and these all looked at starting anti-TNF postoperatively within 4 weeks of resection and then looked at an endoscopic recurrence. Placebo or 5-ASA are on the right side. And what you can see at least, and granted these are small, all but ours was an open label study, but you can see that the trends looked about the same, 0% in one anti-TNF, Infliximab, 0% at the bottom in Adalimumab treatment and then 9% in our study and 10%, so fairly small recurrence rates compared to placebo and 5-ASA. So now if we were to look at the overall totality of the data and include Infliximab at the bottom of our systematic review, at least I think we are starting to see a signal that maybe anti-TNF postoperatively is effective treatment.

The question is where do we position anti-TNF after surgery? And this is a postoperative treatment algorithm that we came up with, I know that other groups are adopting a fairly similar algorithm. We are in the process of now looking back at our 25 years of data within the University of Pittsburgh system to see if we can validate this but this is – in essence this is how I practice on a daily basis and I will start by saying that you will notice in two of the arms I do not start anti-TNF immediately after surgery. So let me make it clear that even though we showed that anti-TNF therapy may be highly effective postoperatively, this is not an agent that we are using in all patients automatically after surgery.
So how do we approach this? Well we risk stratify patients based on their likelihood of having postoperative recurrence. So patients with a low risk for postoperative recurrence, so who are those patients? These are the patients who have had Crohn’s disease for a long period of time who ultimately come to their first surgery for a small or short stricture. I will say that these are rare patients in our overall consortium, there’s probably only about 10% that would fall into this group. However if I have some of these low risk for recurrence patients I would not necessarily recommend putting them on any treatment postoperatively, however within a year of the surgery I would recommend a colonoscopy with identification of ilium. And if there is recurrence then I would step up treatment to at least immunomodulator, if not an anti-TNF as I think that that represents an early postop recurrence within a year.

Well what about the moderate risk patients? And I think these are the patients that are more common for us to see in our practices. So these are patients who have had disease for under a decade, so relatively new diagnosis who come to surgery for maybe an obstruction but have a definitely inflammatory component to their stricture who maybe have not been on much treatment at all or this is really their, their first presentation. These are patients that I would recommend an immunomodulator postoperatively, either 6MP or Azathioprine. And I think based on the European study that combined Metronidazole upfront with these agents, Metronidazole would be a very appealing medicine to use. The only thing that I found is that Metronidazole at at least 1 gram a day is very difficult to take long term, the patients in at least the study looked at taking this for at least 3
months, probably the effect of antibiotics are long term, meaning that patients probably need to continue this. So things like peripheral neuropathy, dysacusia, some of the other symptoms, obviously Metronidazole also reacts poorly to alcohol so patients would need to abstain from alcohol for a long period of time, this makes this challenging. But I do have patients who are motivated who have been on antibiotics postop combined with 6MP and done quite well.

Well what’s the group of patients that I would consider anti-TNF? These are the high risk patients, and let me define that by – for a minute, and I include that at the bottom of the slide, but I’m going to expand on that a bit as well. So these are the patients who come to surgery who don’t just have a stricture or inflammation but actually have fistula or penetrating perforating disease complicated by an abscess. These are the patients who are not just having their first surgery but this represents their second, third, fourth, fifth surgery. So the natural course of disease is such that these are patients who have had disease for a period of time and required multiple surgeries.

Two other groups that I would include in this high risk group are cigarette smokers. So those patients who refuse to quit postoperatively are at a very high risk for recurrence. Now ethically I’m not saying that we can tell them to continue to smoke and then put them on anti-TNF, however our study at least did show that anti-TNF prevented postop recurrence even in our smokers. That’s not the message of this talk, but if you have patients who cigarette smoke after surgery they are at a particularly at a high rate of recurrence.
And the final high risk group that I would consider, although there are not much data on this, I am curious to see if this is a group we should consider anti-TNF postop are those patients who you’ve had on immunomodulator treatment already who continue to have disease that ultimately progresses to surgery. So maybe they’ve been on weight based Azathioprine 6MP, or they’ve been on an adequate dose of Methotrexate and despite this their inflammation is a galloping disease that continues at least to surgery. And I should make the caveat that these aren’t the patients who were thrown on Imuran 3 months before surgery as a last ditch and probably needed a surgery a year ago for an obstruction, I’m talking about the patients who truly are refractoried immunomodulators. Postoperatively time will tell, we need more data but maybe that’s a group that would be considered for an anti-TNF therapy as well.

So I think the course of postoperative Crohn’s disease if I were to summarize in the next two slides and then I’ll leave plenty of time for any questions and I may have some additional slides that I could add in at the end, I think that postoperative Crohn’s disease interestingly offers a glimpse into the natural course of all of undiagnosed Crohn’s disease and maybe other immune mediated diseases. And what do I mean by that? Well, this is a disease where we can actually wipe the slate clean. We can actually do a resection of the area of inflammation, reattach to healthy parts of the bowel and essentially start over again. In rheumatology obviously we can’t cut out the joints with rheumatoid arthritis and start over again, but we can actually do this with Crohn’s and see what happens. So we have the opportunity to wipe the slate clean. We also know that postop Crohn’s until there is a recurrence that patients will feel symptomatically is clinically silent. So patients have postop
Crohn’s recurrence at a very high rate but don’t feel it, they don’t have symptoms. Well again think about the patients you see in your offices and you do a colonoscopy and you see horrible disease for the first time, so forget postop Crohn’s, just a patient coming to you for the first time, you do a colonoscopy and you see horrible disease and you look at them and you think your symptoms cannot have lasted this 2 to 3 months, they probably had disease for years but it’s finally reached a critical point by which they have symptoms because of transmural inflammation or a complication and then ultimately placed on treatment to try to prevent a further progression. The same thing happens postoperatively.

We also know that once symptoms develop surgery is often required. So why in all of Crohn’s disease are the surgical rates still so high? Why are they still 2/3 to 3/4 of the patients? Well, probably because the disease progresses to a point that there is tissue restricting and remodeling that is irreversible with medications. We know that with postop Crohn’s, we know that if we wait postoperatively patients feel great for 3 to 5 years, but once they start to have symptoms again they often require another surgery. I think the postoperative model also is unique in that we know that disease detection really requires mucosal inspection, so again we can’t rely on clinical symptoms, often things like sedimentation rate and C reactive protein may be good Seracult markers but really looking at the mucosa, identifying the score is probably the best we have at determining the course of Crohn’s disease.
We now know that at least in the postop setting biologic may prevent recurrence. This kind of parallels what we are seeing in medical treatment, meaning the earlier use of biologic therapy in certain patients with high risk Crohn’s disease may prevent the natural course of disease that’s more destructive and damaging. Similarly postoperatively the high risk group of patients for recurrence after surgery started on a biologic may ultimately prevent a recurrence.

So where do I think we are going in the future? I think that this represents a unique model like I said and we may be able to extrapolate this to the undiagnosed or newly diagnosed patient, and in essence we may have the opportunity to really look at the true top down model with surgery on top that induces the deepest remission. We talk about deep remission with mucosal healing and I realize what I’m saying is somewhat controversial, but if you think about a patient who has Crohn’s where you look on a CT or colonoscopy and they have 6 to 12 cm of horribly inflamed or stenotic ilial disease and that’s the first presentation I sometimes wonder if these are patients that probably should go to surgery early followed by medical treatment, so truly the deepest remission and then altering the natural course.

We are actually now in Pittsburgh and I know other groups are looking at this postoperative model to try to understand the pathogenesis of IBD. Maybe we can extrapolate this to other immune mediated diseases where we know that genes, the bacteria that we come in contact with or our body’s own normal bacteria and the immune responses that occur, we can actually target the area where we know there is going to be a recurrence. And then finally there is a large international study looking at
postoperative prevention with anti-TNF treatment, and I think we need to wait for those data before we uniformly apply anti-TNF treatment. However I did mention a minute ago, in my group of patients that I see those with the highest risk I do consider for postop prophylaxis with anti-TNF. I think the Prevent study will hopefully give us more answers. I just wanted to thank our IBD group that I work with here in Pittsburgh and at this point they are going to turn it back over to Ron and see if there are any questions.

This concludes Dr. Regueiro’s presentation, at this time we will begin a question and answer session. Again, you can submit questions at any time using the Ask a Question link on the lower right hand side of your screen. And it looks like we’ve had a couple come through already.

You talk a lot about starting medicines immediately after surgery to prevent Crohn’s disease recurrence, but what about waiting for recurrence? Would it be okay to wait for recurrence and then start medications?

So I think, I think that’s an excellent question and this, this really comes up quite a bit is that you know we, we all have patients who go to surgery and they feel great after surgery and they, they really honestly will tell us I don’t want to take a medicine, I feel very well. Is it reasonable to wait for clinical recurrence or an endoscopic recurrence? And I think the honest answer is we don’t know yet but we do have some data on this and I do have some extra slides I’m going to try to pull up here now looking at this question. So in our study, I mean Rutgeerts has already shown that if we wait for
a clinical recurrence most of the time after surgery they are clinically silent until the disease has progressed and it’s too late.

In our study if you look at the CDAI, the Crohn’s Disease Activity Index, the patients whether they were in remission endoscopically with a score of 0 or 1, or recurrence with a score of 2, 3 or 4, they all were in remission with their symptoms. So the majority of the patients felt well, so I don’t think that waiting for clinical recurrence is a good idea. What about delaying treatment until there is an endoscopic recurrence? Well I think this is a really important point, and the honest answer is we don’t know but we have some data to look at on this.

And this is a table that’s somewhat busy but focus on the yellow if you will for the, for the first part of my answer. Endoscopic remission is on the left, endoscopically active or mucosally active disease is on the right. There are three postop studies, Yamamoto, our study where it’s not been published yet, at least these data, and then Mantzaris with Adalimumab, looking at waiting until there is endoscopic recurrence. So in essence what they did in these studies is patient went to surgery, had a resection, felt great and then at some point, 6 months to a year later, had a colonoscopy and then only if they have a recurrence were they started on an anti-TNF. The top two Infliximab, the bottom one Adalimumab, and then a year later they had another colonoscopy to see what the remission rate was, so the score of 0 or 1.
And interestingly what you can see on the top, 38% in Yamamoto, 2/3 of our patients, about half of the Adalimumab patients were able to achieve an endoscopic remission. Endoscopic reactive Crohn’s disease was still quite high, and interestingly if you look at it the majority of patients that once they start to develop endoscopically active lesions they are not able to recover. So this is a very interesting concept and we do have data from the medical treatment trials.

So look at SONIC, which is probably our best study looking at combining Infliximab and Azathioprine early on, only 44% of the patients were able to completely heal the mucosa. So I would submit that maybe if we were to do a colonoscopy 3 to 6 months after surgery and maybe if we pick-up the earliest sign of disease and treat maybe we could recover. However the only thing that concerns me is that once we start to get mucosal damage I do wonder if there is an irreversibility to it and I think more study is done, but that’s a great question.

Okay, our next question is if a low risk patient has a colonoscopy at one year and has no disease how often are you doing repeat scopes to look for return?

Right, so you know the reality is do we really need to do colonoscopy repeatedly in all of these patients? I think for the patient, that rare patient who has a stricture, undergoes a resection and one year later or in any group you do a colonoscopy you see absolutely no disease at all, I think for that lowest risk group patient I’m not necessarily doing yearly colonoscopy. I know on the algorithm it says every 1 to 3 years, generally what I do is I’ll do 2 colonoscopies a year apart. If they are both
entirely normal, I’ll wait 3 years. If the third is entirely normal, I’m not necessarily doing regular colonoscopy because I think that’s the patient that has a very rare risk for recurrence.

Okay. For high risk recurrent patients do you recommend combination therapy? I think your study looked at Infliximab monotherapy after surgery. Would you recommend monotherapy or combination therapy?

Yeah, that’s another absolutely outstanding question and in essence what the person asking the question is getting at is do we – should we take a SONIC-like approach after surgery, meaning should we use combination treatment? The person asking the question is correct in that we do not apriority start both Infliximab and an immunomodulator. We did have patients who had been on an immunomodulator and that’s obviously a different scenario, and then the Infliximab was added. My honest answer is I don’t know. In clinical practice I am starting patients postoperatively if they have not been or they are not on an immunomodulator I am using a small dose of an immunomodulator in combination, probably not for the short term. And I think most of the studies have shown a short term combination treatment at a year is probably not going to make much of a difference, but more for the long term durability.

Now I do have plenty of patients who have been intolerant to 6-MP Azathioprine and Methotrexate, and I have had them on monotherapy postop anti-TNF and my sense is about 2/3 of them have done well and we will publish our 5 year data hopefully within the next year, I’m collecting that now. But
we actually have had patients on monotherapy which goes against what every standard thinking we have, done well long term. But the majority I would recommend using a small dose of an immunomodulator if they can tolerate it.

The next question is do you have any long term data on what happened to the patients in your study beyond one year?

Right, so as I mentioned a minute ago and I think that this is a question we are asked quite a bit is you know what are the 5 year data? And without giving away the details I can talk in generalities because we are just starting to look at this, and we are just having patients now reach their 5 year mark so I don’t have complete data although we do have all 24 of the patients, we do have follow-up on.

And the bottom line is this, that the patients who are on Infliximab who are in remission who continued Infliximab out to 5 years, we have not seen an endoscopic recurrence and obviously not a clinical recurrence. Interestingly the patients who have been on placebo who were started on Infliximab for recurrent disease at 1 year and continued on Infliximab and some of them were also on Adalimumab after a year and then we had one patient on Certolizumab, these patients actually have 2/3 of the patients have continued to do well, 1/3 of the patient actually another surgery, which gets back to the question of if we wait too long can we recover?
And then finally the group of patients who were on Infliximab in remission and stopped treatment, over 50% of the ones we’ve looked at so far have had recurrence. Now the flip side is 50% of them continue to do well, however the majority of them are on an immunomodulator. The sample size is very small, so I think that what I just said realize that we are looking at a total sample of 24. And I’m not sure we can make much of that, but we will publish this data in the near future.

What risks are associated with long term use of Infliximab?

So you know the question of safety comes up and I think our patients have access to the web and looked at safety all the time. As physicians we are concerned with this. There was a recent presentation of the American College of Gastroenterology just a couple of weeks ago, it was called the TREAT Registry where the long term data were looked at. And the bottom line is that the long term safety with anti-TNF treatment is pretty good, so the biggest concern patients have are will I develop a lymphoma, a cancer, a bad infection, an opportunistic infection like tuberculosis? The experience has been that many of these will occur within the first year or two, but when you look longer term, 5 years, 10 years, now some patients have been in trial initially up to 15 years, the overall risk is less than 1% for severe infection, lymphoma, cancer.

The question comes up quite a bit what about combinations? So young males there was a higher rate, although the total rate is still less than 30 total patients of this hepatosplenic T-cell lymphoma, and I think that scared away a lot of people, especially young males for using combination. I have
used Methotrexate more, I’ve not had complications. I think Methotrexate also works very well in combination, but the bottom line is long term. Actually if anything the safety looks better, I think many of the signals are once you get beyond a year or two if there is going to be a problem again only we see it at that time. The one caveat, and sorry for the long answer, is that there has been recent publications on nonmelanoma skin cancers, and I think that this is important and I think the dermatologists are becoming more of our friends in that we are seeing higher rates of basal cell and squamous cells. Probably more in the immunosuppressed, 6-MP Azathioprine, but anti-TNF may have a signal as well, so skin care and skin examinations long term need to be considered.

Do you use the Prometheus Prognostic Labs to help decide on postop treatments?

I mean that’s – so that’s another good question, are there other surrogate markers or ideas as far as prognostication diagnostically. So I will tell you that personally I do not generally use the Prometheus Labs to help me prognosticate my patients only because generally I’m looking and I also have to admit I have a biased population, so usually these patients have seen several gastroenterologists, they’ve been through multiple treatments, they are coming to me already with a fairly severe course. But forgetting that caveat, I think patients and there have been studies by Bugerett and others looking at predictors of severe course, and these are somewhat intuitive. So a patient with pan intestinal involvement, fistula, patients with deep ulcers, patients who are smokers, young age of onset, these have all been factors that I will use.
Now it is to say that there may come a day where the accumulation of these Prometheus or these autoantibodies that come back—or I should say these autoantigens that come back very high or triple positive, double positive may play a role. I personally do not, I think it’s reasonable if you need help in pushing you towards more aggressive treatment, but I would consider the patient and how they are presenting with their symptoms and overall phenotype and disease behavior.

Are we really wiping the slate clean if many patients have microscopic disease within a week of surgery? And should we have pathologists check margins of resection for evidence of microscopic disease?

So my answer is absolutely yes, and that was—it’s a very good question. I think also when you read the postoperative studies that are being done, read the methodology to see how they define margins. So whoever is asking this question is right on target. What we did in our study is the patients had to have macroscopically clean margins but also histologically we looked at if they had clean margins. Granted, if you have a patient who does not have a clean margin, meaning that the Crohn’s is cut out but there is still remnant Crohn’s at the anastomosis when the suturing is done, that’s a patient who has remnant disease that’s not recurrent. In the studies that have been done on histologic recurrence the patients had clean macroscopic and histologic margins, so as best we can tell they were clean, they also have had studies looking at biopsies at 5 and 10 cm above where the surgical site was with no disease recurrence and then a week later when the bowel was reconstituted that there was disease recurrence. So I think these data are pretty compelling.
How do you proceed with a patient that required surgery and was on a TNF for say a year when surgery became necessary?

Yeah, and I think that’s a tough call. So the question is is the patient failing the anti-TNF and will they fail it postoperatively? Or is there anti-TNF somehow going to work better postoperatively? And I think it’s depends how we define this. So a year I think is a pretty good timeline. If the person asks a patient who has been on a TNF for 3 months and goes to surgery probably the disease was too late to begin with and they needed surgery anyway. At one year you could argue well, and my feeling is when you look at some of the structural damage data that’s coming out, patients newly diagnosed will get a sense early if their disease is irreversible. What I do with those patients are I do continue the anti-TNF postop. I don’t think that’s necessarily a primary failure. I think probably many of the patients we treat for the first time probably already have tissue remodeling and damage that’s irreversible, so we do continue postop treatment. If you think it’s a true primary nonresponder of anti-TNF, then I think that becomes a challenge, but that’s probably only about 10% of the patients.

That about wraps it up for the question and answer session, I’d like to thank Dr. Regueiro for his time this afternoon, and one final announcement before we close.

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