Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/identifying-and-managing-patients-with-ibd-at-risk-for-progressive-disease/8575/

Released: 03/17/2017
Valid until: 03/17/2018
Time needed to complete: 1 hour

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Identifying and Managing Patients with IBD at Risk for Progressive Disease

Narrator:
Welcome to CME on ReachMD. This segment, “Identifying and Managing Patients with IBD at Risk for Progressive Disease,” is brought to you by Albert Einstein College of Medicine, Montefiore Medical Center, and MCM Education, and supported by an educational grant from Takeda Pharmaceuticals U.S.A., Inc. For a program description, learning objectives, credit statements, and disclosures, please review the front matter for this activity.

Dr. Sandborn:
Hello. I’m Dr. Bill Sandborn from the University of California San Diego. Welcome to today’s presentation, “Identifying and Managing Patients with IBD at Risk for Progressive Disease.”

Our learning objectives are to review risk and severity assessment for patients with IBD as it relates to treatment decision making; to discuss the treatment strategies for the management of patients with low-risk and high-risk IBD, including the benefits and the safety profile of biologic therapy; to discuss the guideline recommendations and quality measures related to preventative care and screening needs in patients with IBD; and finally to describe practical approaches to patient engagement to optimize shared treatment decision making.

Let’s start with the epidemiology of IBD. There’s approximately 3.1 million cases in the United States. This was based on a 2015 National Health Interview Survey. It’s higher than previous estimates. We now recognize that about 1.2 percent of the population in the United States has IBD. The peak incidence is in late adolescence and early adulthood but onset can be at any age, and the prevalence is slightly higher in females.

With respect to pathogenesis we think of sort of the interface of genetic susceptibility and altered response of the immune system, particularly the mucosal or intestinal immune system, and a number of environmental triggers, some of which have been identified and likely some of which have not.

We’ll transition now to thinking about the approaches to measuring the risk and severity in IBD and start with ulcerative colitis. So for ulcerative colitis there were care pathway guidelines published in *Gastroenterology* by the American Gastroenterology Association in 2015 that look at the diagnosis and risk stratification that can be used to guide treatment selection. So, you initially make a diagnosis and assess the inflammatory status, you stratify the patient according to their risk of getting colectomy and you assess for comorbidities and therapy-related as well as disease-related complications, and then you put patients into low-risk or high-risk groups. In the low-risk group they get induction and then maintenance therapy where you’re looking for something that’s effective but you’re really mindful of the side effects of the therapy. And in high-risk patients you’re looking for patients who are at risk for hospitalization, but maybe are not yet in the hospital. You have to decide if you put them into the hospital and you’re going down the path of induction therapy for an inpatient or they’re kind of high-risk but still an outpatient and you’re looking for induction and maintenance therapy in that high-risk patient.

With respect to making the diagnosis and assessing inflammatory status, first you look at the signs and symptoms, those things that you’re used to, things like bloody diarrhea, tenesmus, urgency, abdominal pain, fever, weight loss, etcetera. You perform laboratory

testing looking for anemia, high CRP and sed rate. Make sure the patient doesn't have *Clostridium difficile*. Typically, we'll perform some sort of endoscopic procedure and if there's any concern about abdominal complications sometimes a CT scan. And then you look for comorbidities and therapy-related complications. So, you want to understand the patient with respect to their psychosocial support system, whether or not they have depression, how much they know about the disease, you know, to make sure they don't have infections like *Clostridium difficile* or other bacterial infections, CMV or parasites. Make sure they're not taking nonsteroidal anti-inflammatory drugs which can lead to flare of colitis, ensure that they're taking medications; look for adverse events related to medical therapy. Realize that patients have at least a three-fold excess of both arterial and venous thromboembolic or hypercoagulable risks. So, watch out for that. And if they're in the hospital prophylax against it. Be mindful of the colorectal cancer and dysplasia risk patients with long-standing ulcerative colitis. And in the hospital setting be mindful of the development of toxic megacolon and fulminant colitis. [Slide 10] So how to stratify patients for their risk of colectomy and hospitalization and that sort of thing, low-risk patients would be patients who have more limited anatomic extent, proctitis, proctosigmoiditis and more mild endoscopic disease. High-risk patients would be patients with extensive colitis, deep ulcerations, younger age, relatively higher CRP or sed rate values, patients who require oral or intravenous steroids, patients who have required hospitalization, concomitant *Clostridium difficile* or cytomegalovirus.

Transitioning now to Crohn's disease, same sort of idea. You want to diagnose and risk stratify patients to guide treatment, so you assess for inflammatory status, you look for comorbidities and therapy-related complications. You assess the current and prior disease burden, put patients into low- or high-risk categories and then treat them accordingly.

So with respect to inflammatory status you look at signs and symptoms, things like fever, abdominal pain, GI bleeding, physical exam, abdominal tenderness, weight loss. You'll do lab testing again looking for anemia, C reactive protein elevation, hypoalbuminemia. Fecal calprotectin can be used in some cases, sedimentation rate. Um you'll typically perform colonoscopy and figure out whether the patients have inflammatory markers that kind of track with the colonoscopy. Potentially you'll do a CT or MRI enterography for patients with small bowel disease. Similar to the situation with ulcerative colitis, you'd look for infections. With Crohn's disease which tends to progress from luminal inflammatory disease to the complications of stricture, fistula and abscess, you'll be using both colonoscopy and MRI or CT to look for bowel obstruction, or fistula and abscess.

Be mindful of the prior surgical history and the risk for terminal ileal resection leading to bile acid diarrhea, bacterial overgrowth; if you have enough ileal resections steatorrhea or fat malabsorption. Watch out for drug side effects. Again be mindful of the risk of abdominal abscess or fistula. Abdominal pain, fever are common findings. And then perianal fistula/abscess which is heavily driven by physical exam and then a pelvic MRI.

In terms of stratifying patients, low-risk patients or patients that are over 30 or more, have limited extent of anatomic involvement, don't have involvement of the perianal or rectal area to any significant extent; their ulcers are more superficial as opposed to deep. They haven't had prior surgery and they haven't developed complications of stricture/fistula/abscess. In contrast, patients with moderate- to high-risk are younger patients, extensive amount of anatomic involvement of the perianal or rectum to a significant degree, the presence of deep ulcers at colonoscopy, a history of one or more surgeries and current or previous complications of stricture, fistula and abscess.

So how do we turn those risk stratifications into treatment strategies? First let's think about our broader IBD management goals. These would include inducing a remission which can include clinical remission, endoscopic remission, also called mucosal healing, histologic remission, and in the case of Crohn's disease radiologic remission. You would also like to maintain remission to avoid progression to disease complications, to maintain quality of life and to prevent hospitalization and surgery.

So thinking about some of those goals, why would endoscopic remission or mucosal healing be important? It's a more objective endpoint than clinical remission with respect to assessing disease activity. There's growing evidence mucosal healing is an important goal because it appears to be associated with improved long-term outcomes. These can include a decreased likelihood of future disease flares, a decreased progression to disease complications, particularly in ulcerative colitis where unchecked inflammation leads to complications of stricture, fistula and abscess and a decreased need for hospitalization and surgery. So let's focus a little bit on the treatment of ulcerative colitis. So remember we had gone through this algorithm of diagnosing the patient, looking for comorbidities and then stratifying them into high-risk or low-risk groups. So for the low-risk patients, these are the patients with low endoscopic activity and more often with more anatomically limited disease. For induction therapy the mainstay is going to be oral or rectal mesalamine products; budesonide is also an option, either oral or rectal; and then oral or rectal conventional steroids. And then the maintenance therapy would be typically oral mesalamine, although rectal mesalamine is also a possibility. If patients fail to respond to induction therapy, then you would move them over into the high-risk algorithm which we'll come to next. And if they relapse under a maintenance therapy then you would again move them over to the high-risk algorithm.

So let's switch over then to the high-risk algorithm for ulcerative colitis. For induction you have a couple of different options. You could give a short course of steroids and then a maintenance therapy with thiopurines or anti-TNFs plus or minus thiopurines or vedolizumab.

You could induce with an anti-TNF agent with or without a thiopurine and then if it is effective continue that as maintenance therapy. You could induce with vedolizumab with or without an immunosuppressive agent and then continue that as maintenance therapy. And then we'll come in a minute to what to do with refractory patients that are high-risk.

So let's think about some of the drugs, so 5-amino salicylates; we know that they are effective for induction and maintenance of remission in patients with mild to moderate ulcerative colitis. There's a variety of formulations, both oral and rectal, no clear differences across the formulations for efficacy for induction. Some of the formulations have been studied and are indicated for once daily dosing, and there's not strong evidence for dose response above 2.4 grams per day. Note that one agent, sulfasalazine, is not as well tolerated as balsalazide or various delayed and sustained-release formulations of mesalamine. Side effects can include sort of general intolerance, rare instances of idiosyncratic nephrotoxicity, rare instances of transaminitis, rare cardiac hypersensitivity, headache and sometimes pulmonary symptoms or pancreatitis.

Steroids, very effective for inducing remission. There's a number of conventional steroids, which can be given orally or rectally and then more recently there's been availability of colon-release oral budesonide and budesonide foam. The downside to steroids is they can't be used for maintenance, and we know that as patients wean off steroids there's a fairly high risk of relapse so you need some kind of post-steroid maintenance therapy that's not a steroid. And with conventional corticosteroids if you use more than 20 milligrams for more than 60 days there's an increased risk of mortality from serious infection. Side effects can include increased risk of infection, as we just said, elevated blood pressure, glucose, adrenal axis suppression, osteoporosis, steroid myopathy, glaucoma and a variety of other steroid side effects which you are familiar with.

What about thiopurines, azathioprine and 6-mercaptopurine? These are really slow-acting drugs, not very effective for inducing remission, have some benefit for maintaining steroid-induced remission, so typically they're given as a concomitant medication with either a tapering course of steroids or with a biologic. Some patients, about 10 percent of the population, don't metabolize these drugs well and so it's recommended that genetic testing for thiopurine methyltransferase enzyme activity or genotype be undertaken before patients receive thiopurines to avoid overdosing the 10 percent of patients with low metabolism. Side effects from these drugs can include bone marrow suppression, liver toxicity, lymphoma, including the more rare hepatosplenic T cell lymphoma that tends to occur in young males, non-melanoma skin cancers and opportunistic infections.

And then we have anti-TNF drugs for ulcerative colitis. There are three drugs that have been approved for moderate-to-severe disease including infliximab, adalimumab and golimumab. Biosimilars are emerging into practice for infliximab and adalimumab. Patients uh need to be screened for tuberculosis and hepatitis B prior to treatment because anti-TNF drugs can reactivate latent infections. These drugs have been associated with various opportunistic infections including tuberculosis, fungal infections and bacterial infections. You can see immunogenicity to these biologic drugs and the immunogenicity, which is associated with both adverse events and loss of efficacy can largely be prevented by coadministering an immune suppressive like azathioprine or mercaptopurine or methotrexate. Hepatosplenic T cell lymphoma has been reported, although the majority of the cases have occurred in patients who are also receiving azathioprine or mercaptopurine and again mostly in young males. And there is some association with melanoma. [Slide 26] Looking at the efficacy of these three drugs, we'll start with infliximab on the left. You can see that infliximab over 8 weeks was effective for inducing remission in over 30 percent of patients at two different doses, compared to closer to 10 percent for placebo. And then at 54 weeks about 35 percent or so of patients were in remission compared to about 15 percent of placebo-treated patients. With adalimumab at 8 weeks it was about 17 percent versus about 8 percent, and then out at week 52 about 15 percent versus again about 9 percent or so. And golimumab at 6 weeks, about 18 percent versus 9 percent or so, and then at 54 weeks—but this is restricted to patients who had initially responded to golimumab—then about 28 percent or so versus about 15 percent.

What about cyclosporine? This is typically used only in the hospital setting for rescue. It's really a short-term intervention to try and avoid colectomy. A comparative effectiveness study showed that cyclosporine and infliximab had similar efficacy in the hospitalized patient failing IV steroids. It's a potent immunosuppressive and has a number of side effects including infection, lymphoma, hypertension, nephrotoxicity and seizures. It's still used in selected patients but not very widely used these days. Most patients would get rescued with infliximab.

What about some of the other biologics for the higher risk patients? These can include vedolizumab, which is an antibody to the alpha-4-beta-7 integrin that blocks lymphocyte trafficking to the gut. It's effective for both inducing and maintaining response and remission in patients with moderate to severe ulcerative colitis. It can be used in patients who have failed anti-TNF drugs and patients who are naïve to anti-TNF drugs. It has quite good safety profile, generally not associated with opportunistic infections or malignancy. There is some signal for nasopharyngitis. Tofacitinib is a Janus kinase inhibitor that uh has recently completed phase III trials. It is effective for both induction and maintenance of ulcerative colitis. It's an orally administered medication; it has some potential risk of lymphoma, opportunistic infections and there does seem to be a signal for herpes zoster.

Here are some of the data for vedolizumab. You can see the efficacy of vedolizumab for inducing clinical response and clinical remission in patients who've previously failed anti-TNF drugs on the left and in patients who are naïve to anti-TNF drugs on the right. And you can see that the drug is effective in both patient populations, but the absolute magnitude of effect is somewhat greater in patients who were naïve to biologic anti-TNF therapy.

And then among patients who initially responded to vedolizumab, if you continue it out over the course of a year you can see that continuing vedolizumab 300 milligrams either every 4 weeks or every 8 weeks is more effective than stopping vedolizumab and switching over to placebo for the outcome measures of clinical remission, durable clinical response, both in anti-TNF failure patients and in anti-TNF naïve patients.

And then we had talked a minute ago that tofacitinib or the Janus kinase inhibitor have some efficacy in ulcerative colitis and here you can see two clinical trials, OCTAVE 1 and OCTAVE 2, where tofacitinib was effective for inducing remission and mucosal healing in both patients who had previously failed anti-TNF drugs and those who had not. Similar to the situation with vedolizumab, the magnitude of effect is somewhat greater in patients who had not failed anti-TNF drugs than in those who had.

What about the treatment of Crohn's disease? So, we'll switch gears here.

So thinking first of low-risk patients we have a targeted steroid, budesonide, which is a delivery system that releases in the distal ileum and the right colon. It's administered in a 9-day dose and can be quite effective for mild-to-moderate Crohn's disease of the ileum and right colon. For that anatomic area, as well as for more distal Crohn's colitis patients, can also receive a tapering course of prednisone either alone or with azathioprine, to be continued as a maintenance therapy. And the patients with extensive colitis or left colon Crohn's disease then you would use a tapering course of steroids with or without follow-up treatment with azathioprine.

For high-risk patients typically patients would receive anti-TNF therapy as opposed to thiopurines or not being treated. And then we know from the SONIC trial that anti-TNF therapy in combination with a thiopurine is more effective than anti-TNF therapy alone or a thiopurine alone. So combination therapy, anti-TNF plus a thiopurine, is the most effective treatment strategy. And methotrexate can be used in place of a thiopurine in patients who have some contraindication or intolerance to thiopurines.

Thinking about the individual drugs mesalamine in Crohn's disease has minimal efficacy and is not FDA approved for Crohn's disease, as compared to ulcerative colitis where mesalamine is clearly effective and is the platform first-line treatment for ulcerative colitis. There's some evidence that sulfasalazine as opposed to mesalamine may have a very modest induction benefit in Crohn's disease.

Steroids are useful as we've discussed previously but really just for induction of remission. They're not maintenance agents and they have a number of side effects as we had discussed previously for ulcerative colitis. Thiopurines, similar to the situation with ulcerative colitis, slow onset of action so they're not really induction drugs, their role if they're to be used is more as a maintenance agent and combined with either a tapering course of steroids or biologics. We talked previously about the need to test for TPMT enzyme activity or genotype before prescribing and we've talked about the side effects of the thiopurines in the ulcerative colitis section. [Slide 37] So here's the SONIC trial that I referenced earlier showing that combination therapy with the anti-TNF drug infliximab and azathioprine is more effective than infliximab monotherapy, and both of those strategies are more effective than azathioprine. So this really gives that the basis for the hierarchy that I showed earlier, that the most effective strategy is combination therapy; the anti-TNF monotherapy is intermediate; and the least effective strategy is the thiopurine-based maintenance strategy.

What about methotrexate? There are data from Brian Fagan showing that methotrexate is effective for inducing and maintaining uh clinical remission in patients with Crohn's disease. It's a moderately potent immune suppressive, has some drug interactions with NSAIDs, it cannot be used during pregnancy because it's teratogenic and leads to spontaneous abortion, can have liver and lung toxicities. Occasionally you'll see myelosuppression, occasionally infection, probably not as much as what you see with azathioprine or mercaptopurine, and occasionally you can see skin reactions.

Anti-TNF drugs, we've talked a bit about this already in the setting of ulcerative colitis. The three FDA approved anti-TNF drugs for Crohn's disease are infliximab, adalimumab and certolizumab pegol. Biosimilars again are coming in the near future for infliximab and adalimumab, and we've already talked about the need to screen for TB and hepatitis B and the potential side effects. So how effective are these drugs on a relative basis?

Here you can see the results of some of the pivotal studies for infliximab, adalimumab and certolizumab compared to placebo and you can see that in general the placebo induction rates range from 4 to 12 percent and the active treatment rates range from 21 to 48 percent for induction of clinical remission. So, in general I think about 10 percent on placebo and 25 or 30 percent on active drug across the different doses and agents for week 4 induction of clinical remission.

What about maintenance of remission? So this is taking patients who have responded to induction therapy with an anti-TNF and then

get randomized to continued maintenance therapy with either placebo, so a drug withdrawal or continued anti-TNF therapy. And if you look out at 6 months you can see that initially about 60 percent or so of patients will respond to induction therapy with an anti-TNF and then continuing the anti-TNF leads to maintenance of remission in about 40 percent of patients compared to about 20 percent or so of patients who withdraw the anti-TNF and switch over to placebo.

What are some of the newer drugs? So vedolizumab, an anti-integrin agent, we've talked about that already. It's effective for both induction and maintenance of remission in patients with Crohn's disease. It can be used in patients who have previously received anti-TNF drugs or who are naïve to anti-TNF drugs. Ustekinumab is a monoclonal antibody that targets the P40 subunit that is shared by interleukin-12 and interleukin-23. It is effective for both induction and maintenance of remission in Crohn's disease. You need to screen for tuberculosis prior to initiating treatment with this agent and, although you can see some infections, there are not black box warnings for infection with this drug.

So here is some of the data. The induction effect is relatively stronger in patients who are naïve to anti-TNF therapy and a little bit less so in patients who have had prior exposure to anti-TNF drugs, although it was effective for inducing clinical remission in that setting. And then for maintenance you can see that 300 milligrams of vedolizumab administered either every 4 weeks or every 8 weeks was effective for maintaining clinical remission, clinical response in both anti-TNF failure patients and anti-TNF naïve patients out through week 52.

What about ustekinumab? Here you can see two induction trials. UNITY 1 is an anti-TNF failure population and UNITY 2 is an anti-TNF naïve population. You see that ustekinumab particularly at the 6 milligram per kilogram dose is more effective than placebo for inducing clinical remission over 8 weeks and you can see that the drug is effective in both patient populations but the absolute efficacy is greater in the anti-TNF naïve population.

And then if we look at the maintenance therapy you can see that continuing ustekinumab every 8 or 12 weeks is effective for maintaining clinical remission, clinical response, steroid-free remission and sustained clinical remission out through week 44.

Okay, well let's now transition to thinking about the prevention and screening in patients with IBD.

So you want to have on your radar screen some of the vaccine-preventable illnesses such as influenza, pneumococcus, Tdap and herpes zoster. In general the influenza injections are not live virus. Pneumococcus is not, and Tdap is not. Up until now the herpes zoster vaccine is a live virus vaccine, which means it can't be given in patients who are receiving steroids, immune suppressives or biologics, but there is an inactivated or non-live herpes zoster vaccine that's coming out this year that could be administered to patients who are taking these medications.

There's also HPV and this affects both males and females in various ways and so vaccination is recommended. Meningococcus, hepatitis B and hepatitis A, and these are all non-live vaccines.

How do we measure quality in IBD? The AGA has taken some steps in this regard. One is to clearly define the type of IBD the patient has, anatomic location and the activity. We've talked a lot about that today. To initiate corticosteroid-sparing therapy, we've certainly outlined the strategies for doing that. To monitor for corticosteroid-related bone loss, to vaccinate patients for influenza and pneumococcus, to assess for latent tuberculosis before starting anti-TNF therapy, and similarly to assess for hepatitis B before starting anti-TNF therapy. To monitor when patients have flared for concomitant *Clostridium difficile* especially in the hospital setting. To prophylax for venous thromboembolism in the hospital setting and to ask patients to stop smoking.

The Crohn's and Colitis Foundation of America has taken a similar sort of approach and they've recommended performing TB and hepatitis B testing before anti-TNFs; to initiate to steroid-sparing therapies; to check thiopurine methyltransferase before starting thiopurines as we've talked about; to test patients who are flaring for *Clostridium difficile*; to look for CMV colitis in patients who are hospitalized with ulcerative colitis; to recommend smoking cessation; educate patients about getting vaccinations; to monitor for dysplasia and cancer in patients with long-standing ulcerative colitis, including periodic colonoscopic surveillance with biopsies and recommending colectomy or close surveillance for patients where dysplasia is found. And then they've further evolved to looking in terms of measuring these things to looking at the proportion of patients who are in steroid-free remission for a year; the proportion of patients who are currently taking steroids; the number of days per month or a year lost from school or work attributable to IBD; the number of days in the hospital attributable to IBD; the number of emergency room visits per year for IBD; the proportion of patients who have malnutrition, anemia, the number of patients who have normal disease-related, health-related quality of life; the proportion of patients who are requiring narcotic therapy; patients with nighttime bowel movements or incontinence; and the proportion of patients who experience any incontinence in the last month.

So finally how does one approach patients for engagement related to shared decision making?

So we know that there's a number of predictors of poor patient adherence. These can include patients who have low symptoms, so they sort of forget about the disease or there's a chronic condition, any element of cognitive impairment, if the treatments are complex, if the medications are costly, if patients feel like they're stuck taking the medicines, if they have any fears that the medication might be dangerous. Sometimes people just forget if they don't have adequate follow-up from their provider, if there's any background mental illness, a new prescription's sometimes hard to get in the groove. If the patient is not convinced that the drug's going to be beneficial, if the patient doesn't really understand their illness, if there's not a therapeutic relationship with their provider or if they experience side effects from the medicines. [Slide 55] So a model for shared decision making has this acronym SHARE. So, Seek your patient's participation; Help your patient explore and compare treatment options; Assess your patient's values and preferences; Reach a decision in collaboration with your patient; and then afterwards Evaluate your patient's decision.

So let's look at a couple of cases. Number 1 is a patient with ulcerative colitis, 56-year-old male with a history of hypertension, hypercholesterolemia, diagnosed with moderate ulcerative colitis, improved with steroid therapy, could not tolerate azathioprine, became steroid-dependent. A year ago he was placed on infliximab and was able to taper and discontinue steroids. He was well on infliximab maintenance therapy until a couple of weeks ago. Currently he having 4 or 5 stools in the morning, occasional bleeding, doesn't have nighttime stools. He'd gained about 30 pounds over the last year and his blood pressure has been more poorly controlled. He had a colonoscopy which showed a featureless left colon with decreased haustrations, there's diffuse inflammation of the rectum and the left colon to the splenic flexure and then a cut-off to normal bowel.

So how do we think about this? What are the causes of treatment failure in patients with anti-TNF agents? There can be poor adherence in up to a third of patients, suboptimal drug concentrations resulting from patient variability and pharmacokinetics and exposure. In general weight-based dosing helps with that but it doesn't always solve the problems, and the way you get at this is to actually measure the drug concentration and to assess for the presence of anti-drug antibodies which tend to clear the drug. Sometimes patients will get a concomitant infection with *C. diff* or CMV which makes them appear to be a treatment failure but they actually have an infectious colitis. So when a patient develops recurrent symptoms while receiving maintenance therapy with an anti-TNF drug you want to rule out *C. diff*, kind of confirm the flare with labs plus or minus a sigmoidoscopy or colonoscopy and then check the anti-TNF drug levels and test for the presence of anti-drug antibodies to assess for the adequacy of exposure of the patient to the therapeutic drug.

So here's what the algorithm kind of looks like. If patients have a subtherapeutic drug concentration and positive anti-drug antibodies you'd probably switch to another anti-TNF. If they have a therapeutic drug concentration then probably switch to a different mechanism of action, so you could switch to vedolizumab or tofacitinib in the setting of ulcerative colitis or vedolizumab or ustekinumab in the setting of Crohn's disease. And if they have a subtherapeutic concentration without the presence of antibodies then the most beneficial thing is actually just to increase the dose of the drug that they're on rather than switching to another anti-TNF or switching out of class.

What about this question of what to use as your first-line biologic in a patient with steroid-dependent ulcerative colitis? Would you use an anti-TNF or the anti-alpha-4-beta-7 integrin vessel, vedolizumab? So, with anti-TNFs you have both subcu and IV options. Currently vedolizumab is only IV. We know that anti-TNFs can have a rapid onset of action and infliximab can be given intravenously in the hospitalized patient. With anti-integrins the onset of action seems to be slower. It's not so clear that they are useful for rescuing patients with severe steroid-refractory ulcerative colitis failing IV steroids. With anti-TNFs you get the best results if you combine with a thiopurine; less clear about that with anti-integrins, although it hasn't been well studied. And then there is some risk of opportunistic infection and lymphoma in patients who get anti-TNFs. Then we don't have those black box warnings with vedolizumab.

So back to our patient; what's the follow-up? Active disease was confirmed, infections were ruled out, trough concentrations of infliximab demonstrated the absence of drug and positive antibodies to infliximab. This of course was in the setting of monotherapy and you recall that we had discussed that the best treatment strategy with infliximab and other anti-TNFs is to give combination therapy. So the patient was switched from infliximab to adalimumab and he regained his clinical and endoscopic remission. And I'm going to add a little editorial here that he also had a thiopurine put in place to prevent the same thing from happening again.

Then we have another case. This is a patient with Crohn's disease. So it's an 18-year-old male, no significant past medical history, presents with about 6 months of progressively worsening abdominal pain, diarrhea, fatigue and a more than 10-pound weight loss, has some perianal irritation symptoms. On physical exam there's abdominal tenderness in the right lower quadrant, some fullness. On perianal exam there's a skin tag and a small fistula, no fluctuation or pain to suggest an abscess. White count is normal, hematocrit's normal, platelets are a bit elevated at 500, ESR is elevated at 40 and CRP is elevated at 50 milligrams per liter.

The patient had MRI enterography that shows more than 40 centimeters of terminal ileal inflammation and thickening as well as involvement of the right colon. Colonoscopy shows significant ulcerations in the ileum, cecum and ascending and transverse colon and patchy, more minor involvement in the rectum.

So what should we do with this patient with Crohn's disease? Well we want to determine the disease severity, risk stratify the patient

low-risk versus high-risk, review our medical options using the SHARE decision making to ensure patient engagement. Think about vaccinations and screening strategies.

So this patient based on the significant ulcerations, the large length of small bowel involvement is more in the moderate to severe category, so some of your treatment options would be to use an anti-TNF agent, and as we discussed earlier combination therapy would be the most effective over anti-TNF monotherapy which would be still preferred over thiopurine monotherapy.

The SHARE decision making, you want to discuss with the patient these various treatment options including the benefits and the risk of the different options.

So ultimately the patient decided to start therapy with a TNF blocker and azathioprine, TPMT was checked and was normal, hepatitis B and QuantiFERON Gold for tuberculosis were negative. And so he was able to start combination therapy.

So, in conclusion, just to make some key points, be diligent and sort of obsessive with your patients about assessing risk factors for severity of disease, establish therapeutic strategies based on the individualized patient's risk of progression. You can use the AGA Care Pathways to put patients into low- and high-risk buckets. Don't forget to vaccinate for preventable illnesses and monitor for the risk associated with the various classes of drugs, and try to routinely engage in shared decision making with your patient to increase the chances that they will adhere to the treatments that you've recommended.

So, with that we'll close the presentation. Thank you for your attention.

Narrator:
This segment of CME on ReachMD was brought to you by Albert Einstein College of Medicine, Montefiore Medical Center, and MCM Education. To receive your free CME credit click on the Advance to Post Test Button below. Thank you for listening.