Overview

Russell D. Cohen, MD, and Thomas A. Ullman, MD, summarize clinical data on JAK inhibitors in Inflammatory Bowel Disease (IBD). In addition to discussing the rationale for targeting JAK-STAT signaling pathways, faculty discuss the clinical implications of new research for patients with IBD.

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Target Audience
This activity was developed for gastroenterologists, gastroenterology fellows, and other health care professionals who have an interest in inflammatory bowel disease (Crohn's disease and ulcerative colitis).

Learning Objectives
At the conclusion of this activity, participants should be better able to:

• Describe the relationship between the Janus Kinase-STAT signaling pathway and pathogenesis of inflammatory bowel disease
• Summarize the latest research developments in treatment of inflammatory bowel disease with Janus Kinase (JAK) inhibitors
• Incorporate evidence-based research into clinical practice

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Module 1: Rationale for JAK Inhibitors in IBD

Russell Cohen, MD: Hello and welcome to today’s program, Office Perspectives, The JAK-STAT Pathway in Inflammatory Bowel Disease, Expert Insights and Discussion of the Latest Research. I’m Dr. Russell Cohen. I’m a professor of medicine and director of the Inflammatory Bowel Disease Center here at the University of Chicago. Joining me is Dr. Thomas Ullman.

Hi I’m Dr. Thomas Ullman, MD professor of medicine and gastroenterology at Mount Sinai School of Medicine.

Today’s learning objectives are the following. First, describe the relationship between the JAK-STAT signaling pathway and pathogenesis of an inflammatory bowel disease. Second, summarize the latest research developments in treatment of an inflammatory bowel disease with JAK inhibitors. Third, incorporate evidence-based research into clinical practice.

Our goals, whenever we are treating these patients, are to induce and maintain a remission, and this remains challenging with these current therapies. You know, on average, about a quarter of our patients fail to achieve response that’s appropriate or sufficient for them. It’s probably a number that’s far less than that once we throw in more challenging or difficult to treat patients with more moderate and severe disease.

There’s also, with many of these medications, as you know, a decrement of therapy over time. So even our best therapies really aren’t sufficient to account for all of the illness that we’re seeing. Illness, as you know, is associated with the decreased quality of life, substantial morbidity, even some minor increase in mortality, and a number of complications that result in hospitalizations, surgical procedures, emergency
room visits, and probably most important of all, loss of time at school, loss of time at work. These are real challenges to us as treating physicians for these patients, but really much more importantly, these are big challenges to our patients.

Now the pathogenesis of the inflammatory bowel disease, as you are aware, it’s really multifactorial. Under normal conditions, a gut homeostasis is obtained through a multifactorial bit of work that’s done all behind the scenes. The intestinal mucosa involved gut epithelium, the gut associated immune system, and as we’re learning more about it, the gut-like microbiota, the flora. All of those 3 things—and particularly the epithelial defenses and the immune system, in reaction to the gut flora that are there—all of that has to work in a very nice finely tuned dance, almost, that occurs between all 3.

In patients with inflammatory bowel disease, genetic and environmental pressures end up leading to a failure in single or multiple components of this mucosal homeostasis that results in a dysregulated immune and bacterial interaction pathway. It’s characterized, really, by the persistence of pro-inflammatory pathways. Current therapeutic paradigms in IBD generally involve the manipulation at various steps along this pathogenetic process.

Environmental and genetic factors—there’s very little we can do and these things act early in the preclinical stages of inflammatory bowel disease—can be modified really only in selected subpopulations who suffer from these illnesses, and we really haven’t been able to fully target our therapies there just yet. So we’re spending much more time with the epithelial barrier, with manipulation of the immune system, in an effort to correct the dysbiosis that’s there. We’ll try and do things with floral manipulation as well.

The majority of treatments really aim at reducing the overactive and pro-inflammatory pathways that take place in the inflamed mucosa. It’s generally accomplished by blocking pro-inflammatory cytokines, primarily but not exclusively TNF-alpha, we also can block IL-12 and 23, and can also block the trafficking of inflammatory cells into the intestinal mucosa. That’s largely where we stand at this point in time. It’s very limited. We do well, but we can certainly do a whole lot better. Russ, I’m hoping that maybe you can discuss with us some of the things that are going on with respect to the JAK-STAT signaling pathway, and how manipulating that system might be of benefit.

Russell Cohen, MD: Well, Tom, you know the JAK-STAT signaling pathway is really a fascinating pathway, and it’s multiple pathways depending upon which particular JAK kinase or Janus kinase that we’re talking about. So we believe that the Janus kinase, JAK plays a role in regulating many things. We believe that JAKs play a role in regulating many things: cellular proliferation, differentiation, and immune cell functioning, as well, too.
on the other end of the receptor, on the inside of the cell, that’s where the action is really happening. The JAK-STAT pathways are responsible for the subsequent consequences, in many cases, inside of these cells. The JAKs serve to transduce the signals from the cytokine receptors.

So, the idea behind JAK inhibitors is to interfere with the JAK-STAT signaling. This interference is not done outside of the cell, but actually inside the cell itself. For example, the JAK may compete with ATP for binding to the kinase domain of the JAK, and inhibit the various JAK proteins. So we know about JAK1, JAK2 and JAK3, primarily, that have been the focus of much of the research, at least that which has reached the clinical realm. Their STAT family has 7 transcription factors that subsequently are stimulated or, in case of the medicine, blocked from JAK.

Now this is not a foreign idea right now. In fact, there already is a JAK inhibitor on the market, tofacitinib, which is used in rheumatoid arthritis and under research in psoriasis and also in inflammatory bowel disease. These are small molecules. In other words, they’re pill medications, which is also interesting because most of the breakthroughs we’ve had in the treatment of Crohn’s and colitis in the past 10 to 20 years have been through injectables or intravenous agents. So now we’re moving into the realm of the small molecules which are oral agents, and that changes the game in many different ways.

JAK inhibition has been shown to be potentially therapeutic in IBD, especially JAK1 and JAK3, by blocking interleukin 2 receptor, interleukin 6 receptor actions inside of the cells. Now a very nice model is shown where we can see various of the interleukin receptors at the top, along the cell wall, if you will, and then the receptors going through into the cytoplasm where you can see a number of different JAK proteins might be involved. For example, interleukin 2 and interleukin 7 through the receptor may involve JAK1 and JAK3, while interleukin 10 is JAK1. Moving along, you can see interleukin 6, for instance, might have 3—JAK1, JAK2 and tyrosine kinase 2, and IL-12 may also have a different pathway.

Many of the investigators have been looking into either a nonspecific JAK inhibitor, which tofacitinib generally is. It’s JAK1, JAK2 and JAK3, but primarily JAK1, JAK3, or there also are investigational-specific JAK inhibitors against 1 or maybe 2 of the Janus kinases. Then, as you can see on the picture, that subsequently you have the activation of the STAT and then the transcriptional changes. These are very potent signals that, upon blocking, may have a profound influence and beneficial impact in decreasing inflammation that may result from patients who have Crohn’s disease, ulcerative colitis and other conditions.

Now, as I mentioned, there are some ongoing studies of small molecule inhibitors of the JAK-STAT signaling IBD, and I’d like to highlight 2 in particular. The first one, which I’ve referred to already, is tofacitinib, which happens to be on the market, and the primary inhibition is JAK1 and JAK3, more so than JAK2. There’s ongoing studies in ulcerative colitis, as well as Crohn’s disease, and they’re in phase 3 studies moving quite readily along. A second agent I want to concentrate on is filgotinib. Filgotinib is a selective JAK1 inhibitor and it is actually looked [at] in
Crohn’s disease now phase 3 and ulcerative colitis phase 3 studies as well. There are a few other JAK inhibitors that are in phase 2 or phase 2 to 3 testing, which are highlighted, GO634, peficitinib and upadacitinib—so try saying that multiple times! I’m sure that given the efficacy we’ve already seen in some inflammatory diseases, this list will certainly just grow longer.

I did mention that we have clinical data on the JAK inhibitors. Dr. Ullman perhaps you can give us a little overview of the results so far.
Module 2: Efficacy

**Thomas Ullmann, MD:** Sure. That was really an outstanding review of what was heretofore, for me, at least, a complicated pathway of how these agents work. I really appreciate the effort that went into that. I’m going to try and review for you and our audience, some of the data that we have for these JAK inhibitors for the treatment of ulcerative colitis as we move into this world of Mabs to Nibs.

So, as you mentioned, some of the early work that has been done in IBD has been with these 2 particular agents—tofacitinib and filgotinib. Tofacitinib is the one that’s pretty well studied, at this point, within the world of ulcerative colitis. Tofacitinib, as you mentioned, is an oral JAK inhibitor with specificity in theory, and probably in reality, for kinases 1 and 3. It modulates the signaling of a large subset of pro-inflammatory cytokines by inhibiting JAK1 and JAK3. These cytokines include IL-2, IL-4, 7, 9, 15 and 21. These are integral to lymphocyte activation, function and proliferation.

The phase 2 study of both safety and efficacy in patients with moderate to severe ulcerative colitis was performed. There were 194 patients in the study. It was demonstrated to show superior rates of clinical response, remission and endoscopic remission, with a response rate of 70% in the highest dose group. Again, these are all patients with moderate to severe UC. They were randomized to 4 tofacitinib regimens or placebo, twice daily, over 8 weeks.

The measures that they used for response were decrease of Mayo score of at least 3 points, and a decrease in the rectal bleeding subscore of at least 1 point, and an absolute subscore of 1 or zero at the end of the study. The statistical difference in these groups is really quite impressive. I think we’ll have a figure up here about now that’s going to show that it’s a 78% clinical response rate for the group that received 15 mg twice daily over these 8 weeks as compared to only a 41.7% response rate in the placebo group. There’s really a very nice dose response curve that’s present with the low dose of half a milligram twice daily, 3, 10 and 15, all showing an increase with dose over time. A nice looking figure that’s there and as you can see, statistical significance was achieved for that high dose, that comparison of 77.6% vs 41.7%.

You can also see that there’s a little difference in the proportion of patients who are able to achieve a clinical remission using the Mayo indices. Again, 10 mg twice daily and the 15 mg twice daily, both showed impressive results and statistically significant advantage vs placebo, with greater than 40% in both of those arms receiving or achieving clinical remission compared to just 10% in the placebo arm.

So, ongoing phase 3 OCTAVE studies, which include not only the OCTAVE Induction studies that have been done, OCTAVE Induction 1 and 2, but the OCTAVE Sustain studies. One was that long-term extension trial, which is OCTAVE Open, were recently presented, and show that there’s really impressive duration of effect over...
time, and this has been very, very encouraging, I think, and really adds to the notion that these could potentially be very, very successful therapies in the treatment of ulcerative colitis.

Whether we’re talking about mucosal healing endpoints, or efficacy, these were very impressively similar both in anti-TNF treated and anti-TNF naïve patients, over time. These are very impressive data, at least they seem so to me. As you can see in the Induction 1 study, we have a 50% or 60% clinical response rate compared to 33% for placebo, and similarly, 55% vs 28.6% in the OCTAVE Induction 2 study. These are really terrific studies. Unpublished data in the OCTAVE Sustain study showed that the proportion of patients in remission at week 52, which was the primary efficacy endpoint, was significantly greater both in the 5 mg twice daily and 10 mg twice daily studies when compared to placebo.

What’s very interesting about this is that opposed to the early 8-week study that I previously showed you, these are very nice data using the lower doses of 5 mg and 10 mg twice daily. Really similar to what is out there for patients with rheumatoid arthritis, in terms of dosing. So very impressive data over time and really nice results, I think, for tofacitinib in the treatment of ulcerative colitis.

Russell Cohen, MD: Dr. Ullman, one thing that you mentioned on the OCTAVE Sustain trial, which I don’t believe has been published yet, but has been presented, is that while the 10 mg twice a day group seemed to be the most effective in the induction for this agent, the tofacitinib, in ulcerative colitis, for the maintenance—the 5 mg twice a day—did quite well, too, which brings the possibility of inducing with a higher dose, 10 mg twice a day, and then maintaining with 5 mg twice a day, and of course they remain to be seen what doses get approved. In the rheumatoid arthritis current practice they use the 5 mg twice a day, at least until recently, too.

Thomas Ullman, MD: I also did want to point out that there is an ongoing study for filgotinib in ulcerative colitis, the SELECTION trial, one of the longer acronyms that we’ve had to deal with here over time, and I won’t go into the details of that acronym. This is already in a phase 2b and 3 clinical trial investigating the efficacy and safety of filgotinib at 2 doses, 100 mg and 200 mg, really with the usual kinds of endpoints and the usual kinds of design that’s there. They’re currently recruiting and the primary endpoint will be the proportion achieving remission at weeks 10 and week 58. Like you, I’m certainly looking forward to having these data presented to us.

Perhaps, Dr. Cohen, we can spend a little bit of time and you can take us or guide us through some of the data that we’ve been able to see in the JAK inhibitors and their utility in Crohn’s disease.

Russell Cohen, MD: You know, Tom, I think you gave a really great summary for ulcerative colitis, particularly with tofacitinib, where we have a lot of information. I do recall the 2012 publication and the presentation of the data, and we’re very excited to use it as an agent in Crohn’s disease. The data with the Crohn’s disease, though, was a little disappointing, although I really want people to understand one of the caveats. That is that the placebo response rate was unusually high.
Module 2: Efficacy

In the phase 2 study, which is, if you see pictorially the blue bars are the placebo rate, you can see that the placebo response rate was 47.1% by the clinical response 70, which is a decrease in 70 points in the CDAI which had been the standard since the biologics had been introduced for endpoints. So how do you beat a placebo rate of 47%? Well, the 5 mg dose as you can see by the bright yellow bars, were 57.6%, but statistically there really wasn’t seen—if you look across all these endpoints—a dose response. The dose is seen to go up and down. It may be down and who knows. It took a little air out of our balloon although it also made us wonder why, once again, the placebo response rate is trying to kill our Crohn’s drugs. What is important is that even though these endpoints didn’t show statistical significant difference in dose response, if you look at inflammatory markers, there was a big impact on that. I think that’s what has stimulated our interest in pursuing this agent further in Crohn’s disease.

More recently, there was just a publication looking at a phase 2b tofacitinib efficacy in Crohn’s disease study looking at the 10 mg twice a day, 5 mg twice a day, or a placebo. I want to point out that the clinical response rate for placebo—if you look at the blue bars—was 55.6%, again, which makes it difficult, even though you have efficacy rates where the active drug around 70%, it’s hard to show a big difference there. The remission rates in the 36.7% placebo, slightly over 43% for the drug, and then going down the line.

The maintenance of remission perhaps was a little bit better. It’s really perplexing why we’re getting such a big placebo response rate. I think that tofacitinib’s role in Crohn’s disease, while it’s still being studied, certainly isn’t as advanced as for ulcerative colitis, and it may be because of differences between the conditions. But it also may be because, in studies, the endpoints that were required to use may not be very accurate in Crohn’s disease, while they’re more so in ulcerative colitis, which is also understandable because in ulcerative colitis you can just stick a sigmoidoscope in someone and you see if the mucosa looks normal, and the end of the bowel, or not, too. For those of you who don’t do IBD research, welcome to our world. It’s very frustrating.

However, I do want to point out that there was some more exciting information with the selective JAK inhibitor, the filgotinib, in Crohn’s disease. The FITZROY study, which was published in 2017, showed that while the placebo response rate was 41%, the response rate for the drug was 59% and remission rates were twice as high with the drug than with the placebo. So again, this is a selective JAK1 inhibitor. It looks certainly promising and certainly justifies doing further studies. Some people say, “Well maybe the selective JAK1 is the way to go with Crohn’s and the JAK1 and 3 is really with ulcerative colitis.” I would be a little hesitant to come to that conclusion until we get more data, because I
still find it surprising that the tofacitinib, which worked so well in ulcerative colitis, doesn’t seem to have those numbers in Crohn’s disease. I think it may be more of an outcomes [issue] in the studies than truth. So hopefully we’ll be able to get one or both of these agents into the marketplace for one or both of those conditions.

So one of the parts of the FITZROY study looking at filgotinib in Crohn’s disease compares the outcomes in patients who are anti-TNF treated vs anti-TNF naïve. You can see just as in virtually any other study with the biologics or other agents, patients who previously had anti-TNF—as shown in the bright yellow here—have lower rates of response in remission than those who are anti-TNF naïve. While it may be due to a change in the patient’s environment as a result of the TNFs, or, as we are learning now, may be even a change in the microbiome. It also may be in some patients just the fact that they’re tougher patients and that’s why they fail the TNFs or no longer on the TNF and eligible for the trial. I do want to point out that the results in the anti-TNF treated [group] are still quite impressive. Corresponds in over 50% in clinical remission, and over a third of the patients, which is quite good. Many of the other trials looking at anti-TNF experience patients had noticed a huge drop-off in efficacy and it is not the case in this agent. It may be, again, the issue of small molecule vs a biologic. I don’t think we know for sure, but certainly it’ll be something to look forward to in other studies as well.

Now we have been talking about efficacy in ulcerative colitis and in Crohn’s disease with tofacitinib and filgotinib. One other area that clinicians and researchers, and patients, of course, are very interested in, are the safety data. So Tom, can you tell us a little bit more about what we know, so far, about the safety of these JAK inhibitors in BID or in other conditions?
Module 3: Safety

Thomas Ullmann, MD: Sure. Thanks very much for that turnover and very, very interesting with the more favorable filgotinib data that are out there with respect to Crohn’s disease. I heartily echo your sentiments with respect to really just how challenging some of the indices that we deal with are. The challenges of dealing with the placebo response rate that sometimes turns out to be so much higher than we would have expected, rolling into a study. It really presents a number of enormous challenges. Thanks for reviewing those kinds of issue.

As for safety data, as in so many agents in our past—particularly oral agents—we have the benefit of talking about drugs that have already been approved in other conditions. Tofacitinib is such a drug. It’s already approved in rheumatoid arthritis (RA). The safety data had been very encouraging there. Primarily following those phase 3 and extension trials in RA, and again as you had mentioned before, that’s typically with dosages of 5 mg or 10 mg twice daily. We’ve seen changes in lipid profile that have been slightly significant, but nothing else that’s been overly dramatic, I’ll say. In terms of what we have seen in the clinical trial arms within IBD, the adverse event (AE) rates are similar in the treatment and placebo groups. Granted, in the ulcerative colitis studies, we’re waiting for publication for those more prolonged extension trials as we spoke about before, and the one-year trials. At least over the short term, there’s a dose-dependent hyperlipidemia, and there is a bit of an increase in viral infections that have been noticed, particularly in the highest dose of tofacitinib. Other adverse events really differ from monoclonal antibodies that are currently in use in ulcerative colitis in that sometimes we also see some anemia that’s present. We have to avoid the use, in some patients probably with this hyperlipidemia, particularly those with multiple cardiac risk factors. Phase 2 studies in ulcerative colitis and Crohn’s disease, of course, as you’re aware, are not particularly powered for safety. The most commonly reported adverse events have been influenza and nasopharyngitis, 6 patients each in those arms, and the absolute neutrophil count was less than 1500 in 3 patients who received tofacitinib. Overall, as you know, a figure that I suspect will be up as you’re hearing my voice, has been able to demonstrate the adverse event rate really looks very, very nice. Again, the 6 patients who had SAEs from infection are a cause for concern, and we’ll pay more attention to that over time. It’s looked very encouraging in the RA literature, so far through.

In terms of tolerability that have been out there and the tofacitinib arms and safety and in Crohn’s disease, adverse events were similar among all groups. As we had seen in ulcerative colitis, and as well as in the RA literature, there are these dose-dependent increases in lipids, particularly low and high density lipid protein cholesterol, that have been noticed. Eighty-three patients did experience one or more treatment emergent AE,
40 of which were considered by the investigator to be related to the studied medication. The most commonly reported of these emergent AEs were nausea in just under 9% of patients, abdominal pain at 8%, specifically worsening Crohn’s disease in 6.5%, and vomiting in 6.5% as well. So again, hard to tease out what is necessarily drug-related and what may also be the effect of under treatment of Crohn’s disease as well. Fourteen patients experienced 26 different serious adverse events and of 2 patients, these are considered by the investigator to be treatment-related. Worsening Crohn’s disease in 1 patient in the milligram twice daily group. Severe abdominal pain, diarrhea, ileus, chills and pyrexia in one patient each amongst the 5 mg twice daily group.

The most commonly reported event really could be attributed to worsening of Crohn’s disease. I think that the bottom-line here is that we’re really talking about what appears to be a really nice safety signal. Five infections were considered to be severe. An anal abscess was noted in 1 patient on the placebo arm. Pneumonia in the placebo arm. Sepsis in placebo and then vulvar abscess in 1 patient who was receiving the 5 mg twice daily. So that’s the clinical trial experience with tofacitinib that we have so far.

Filgotinib has also been investigated in the FITZROY study that you reviewed over 20 weeks. From parts 1 and 2 of the combined study, when we put them together, it really appears to be quite safe and well tolerated in this patient population. Similar instances or incidences of discontinuation, serious adverse events and adverse events overall, including infections, were observed, and the majority of these events, as it was with tofacitinib, and is always the case in all of our clinical trials, is worsening of the underlying disease.

There was an increase in mean hemoglobin concentration that was observed, but really without a difference between filgotinib and placebo. So maybe there’s something there with the doses that we’re using, at least in filgotinib, that don’t seem to promote anemia, which is certainly good news. There’s no clinically significant change from baseline in the mean neutrophil count or liver chemistry testing that was observed in filgotinib. Overall, filgotinib showed a favorable lipid profile with an increase in HDL but no change in LDL. So certainly good for those patients perhaps, or better than we had seen in tofacitinib, whether this is a real effect or just sort of more of a random amalgamation that’s there in these trials, which, again, are smaller and not particularly designed to find these kinds of differences. Similar incidences of early discontinuation were seen. The majority of these were related to worsening Crohn’s disease in this trial, and an increase in hemoglobin again observed. I think we’re really talking about an overall favorable safety profile that’s here. We certainly need more data and we’re not really at a position yet where we can talk fully about the safety of these agents, but so far, so good. It’s certainly been very encouraging. That’s certainly good news for our patients. We’re talking about the potential use of an oral agent with an excellent safety profile. I think this is the kind of agent, in generality, that our patients are looking for.

So maybe, Dr. Cohen, you can take some moments and guide us through what you think
the clinical implications are of where we stand right now with the JAK inhibitors and perhaps where you think the future is going to take us and how we’re going to end up positioning these medicines should they become approved.

Russell Cohen, MD: Well, you know, Tom, that was a fantastic review. One thing I learned at a recent meeting was that the JAK2 is responsible for erythropoiesis and that may be why a more nonselective JAK inhibitor that inhibits JAK1, JAK2 and JAK3 may have anemia associated with it, while a selective JAK1 inhibitor would not. But I do want to point out that while tofacitinib does inhibit JAK2, it inhibits JAK1 and 3 primarily. So the JAK2 impact seems to be quite minimal, and the incidences of anemia were extremely small. The other thing I just wanted to point out is that whenever people talk about, “Oh, increased cholesterol” everyone gets nervous. Well the increased amount was very, very slight. I can even imagine that if I have my cholesterol taken multiple times it might even be that much of a change, too. This is not a big change in cholesterol, and I agree entirely that we’re very excited about the safety.

So your question to me was, who would you use it in? So now let’s presume that we do get approval in patients with inflammatory bowel disease. I think ulcerative colitis is further along that path than Crohn’s disease, but hopefully for both. So who could you use it in? Well let’s look at the studies. These are for patients with moderate to severe ulcerative colitis so on moderate to severe Crohn’s disease. It’s not very hard to get to moderate disease. Active ulcerations on endoscopy, requiring corticosteroids…you’ve already got moderate disease. As you pointed out, the fact that these are pill medicines makes it a lot easier to convince the patient, and perhaps even yourself, that that might be something you’d use sooner rather than later. The possibility of having patients who have not been on biologics before they go on to a JAK inhibitor, is real. You weren’t required to be on a biologic in all of these different studies. Often, they’ll look at some that were and some that weren’t, but certainly we would want to break out of any shell where we would be constrained saying, “Well you have to fail 4 different therapies first.” Because people who fail 4 therapies are going to fail the fifth therapy in most cases, too.

So what are the possibilities? First, you can use it as a first line in patients who have moderate to severe ulcerative colitis or moderate to severe Crohn’s disease, depending upon the FDA approval. The second is you might you use it sooner in patients, let’s say, that maybe they’re responding to steroids but you see that they are coming down off steroids and already having relapse. Third, perhaps you will have the patient already try and fail a biologic whether an FDA approved biologic, the anti-TNFs, the anti-integrin therapies in Crohn’s disease. We have an anti-IL-12 IL-23 that’s currently FDA-approved. The mechanisms for the JAK inhibitors are different, so often we get lots of questions and say, “Well, my patient is failing this therapy. What should I do next?” Commonly, if someone is failing a pathway—let’s say anti-TNF with good drug levels and no antibodies—then we are advocating moving to a different pathway of information. I mean hopefully, one day, maybe soon, we’ll have maybe genetic information to know what would be the best pathway for each patient. At least for now, if you do have patients who are on one pathway, a pathway being anti-TNF, an anti-integrin, or anti-IL-12 IL-23 or even a JAK inhibitor, if they’re failing one pathway, probably with the drug levels, it’s probably a good idea to switch to a different pathway for that particular patient. The other thing to consider is some of our patients are plagued with making antibodies against the injectable or infusible agents. Patients who make
antibodies against one are unfortunately more likely to make antibodies against the second one. So you could also foresee an instance where you have a patient who has made antidrug antibodies to one of the biologics that they’re on and now instead of going to another biologic that’s injectable or feasible, you might go to an oral agent, whether it’s a JAK inhibitor or other oral agents if they’re available in the future as well, too. There are certain patients who might not be suitable to get a biologic but say an anti-TNF because of a particular infection they may have had or particular history of a type of tumor. Well that might be someone who is more suitable for one of the other agents that I mentioned, including perhaps a JAK inhibitor. Luckily, as I mentioned, even the issues with anemia and with lipid profile changes are so slight that I don’t think it’s really going to sway you away from using a JAK inhibitor in these patients. Tom, what do you think?

Thomas Ullman, MD: Yeah, I think you’re right. I definitely want to echo the notion here that we’re not talking about an immunologically active—in terms of antibody formation—medicine here. We’re talking about oral agents in which there is no particular immune tolerance that we have to induce and maintain here. I think, again, as you mentioned, and I certainly didn’t mean to overstate it, but might have, these small lipid changes are not all that dramatic. As I’m sure you’ve had the really great experience of dealing with over time, when our patients get better, they have the opportunity really to put on a lot of weight and this is a great thing. I always find when a patient comes to me, he says, “What are we going to do, I put on 30 pounds since you started me on this treatment?” Provided that that treatment is not corticosteroids, I’m usually thrilled. Small, subtle increases in lipids is certainly nothing that particularly scares me. I think that the safety profile that is emerging with these agents, the efficacy that we’ve seen, I think that we’re going to have to think about positioning these agents very, very early in a number of different patients. I think to some extent these discussions with our patients that roll around shared decision making and the market force is really, if you will, that that will engender …will tell us where to present these medicines to patients over time. I think that these particular agents look sufficiently promising in efficacy and safety that we’re going to want to move them in very early. We’re definitely not going to want to go down that pathway of just trying to force a square peg into a round hole when patients have adequate drug levels, as you mentioned, with whatever agent they’re on and aren’t making antibodies, you really don’t want to use anything else from that class of medicine that’s out there. It’s certainly very encouraging that we don’t have to position this first, either, because it looks as though those who failed anti-TNFs, and those that were naïve to anti-TNFs, seem to do just about as well at least in the tofacitinib trials, and what was presented at DDW, again, hasn’t been fully peer reviewed yet, but I suspect that it’s on its way.

I think we’re going to position these medicines early. I don’t know that that’s going to be for sure. We’ll see what our experiences are with these over time. I know that my rheumatology colleagues have been very encouraged by these agents in their use in rheumatoid arthritis, but we’ll see how things go over time. It’ll be very interesting. Curious to hear more from you and what you might think about it.

Russell Cohen, MD: I think that, too, they’re all very good points that you bring up, too, and I agree that medical professionals are very excited about the emergence of the small molecules. So, Tom, maybe you can provide us with a summary for today’s program?

Summary
- JAK-STAT inhibition is a promising therapeutic target in IBD
- Tofacitinib has shown efficacy in UC and CD
- Filgotinib has shown efficacy in CD
- Both agents demonstrate tolerability
  - Dose dependent hyperlipidemia w/tofacitinib
- Several trials are ongoing
- Shared decision-making with patient will be key to effective use in clinical practice
Thomas Ullman, MD: Thanks so much for doing this with me Dr. Cohen. It’s always a pleasure and whatever you’ve been able to smooth over that I’ve gotten wrong or done in a very haphazard fashion, I appreciate all the help here. I think that between what we’ve been able to discuss, so far, and what data are out there, clearly the JAK-STAT inhibitors are a promising therapeutic group of medicines with really an appropriate therapeutic target for our patients with inflammatory bowel disease.

Tofacitinib has shown really nice efficacy in ulcerative colitis. It beats the pants off placebo, particularly at the higher doses, and the Crohn’s disease story is emerging. It looks like filgotinib might be very helpful there as well. Both agents, I think, really demonstrate some very impressive tolerability and safety over time, and we’ll certainly get more information, over time, both in the rheumatoid arthritis world, and should these agents get approved, within the IBD world as well. There’s several ongoing trials that are going to further educate us over time as to the true placement that will come once approval—if approval comes—and I look forward to seeing those data, as I know you do, as well.

Then the point that we touched on toward the end is that this business of shared decision making that we have with patients only going to be effective not only for the JAK inhibitors but for all of our medicines over time. It’s really a balanced decision about safety, about efficacy, about lifestyle. It’s really about making our patients get the most out of their lives. I sometimes—perhaps too often—discuss the analogy with my patients about what it is that we’re trying to achieve with the medicines we’re giving them. I want their Crohn’s disease, I want their ulcerative colitis, to be as inconvenient to them as thinking about cavities is to all of us. You take your medicines a couple of times a day. You do some flossing. Hopefully it doesn’t bother you more than that. That you’re able to go to work, go to school. To paraphrase a great ad and a great tagline, “So that they can really be all that they can be.” That their lives can be as rich and as unburdened from these illnesses as they can possibly be. My sincere hope is that these medicines become a step toward that, and I think we’re making great progress. I turn it over to you to give the last word here, Dr. Cohen, because I’m sure that there are things you’d love to say that I didn’t touch on and the floor is yours.

Russell Cohen, MD: Well, Tom, you’re a true gentleman scholar. I always like to say thank you to the participants and people who have joined us today. I hope that we have been able to provide to you what is truly expert insights, as well as discussion of the latest research in the exciting small molecular JAK inhibitors and hopefully that we’ll be hearing more in the near future. Thanks for joining us.