JAK Inhibition in Inflammatory Bowel Disease

Announcer

This is CME on ReachMD! You’re listening to Updates in Autoimmunity and Chronic Inflammatory Disorders: Think You Know JAK? The following activity will discuss JAK inhibition in inflammatory bowel disease.

This activity is jointly provided by Global Education Group and Integritas Communications, and supported by an independent educational grant from Gilead Sciences, Inc.

Before beginning this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Allan Gibofsky, MD

Hello, and welcome to this program, in which we will look at the JAK [Janus kinase] pathway in the treatment of inflammatory bowel disease. I’m Dr. Allan Gibofsky, attending physician at the Hospital for Special Surgery, and Professor of Medicine and Public Health at Weill Cornell Medical College in New York City.
I’m joined today by Dr. Bruce Sands, Professor of Medicine and Chief of Gastroenterology at the Icahn School of Medicine at Mount Sinai in New York.

Bruce, describe for us your perspectives on the treatment of inflammatory bowel disease (IBD).

Dr. Bruce Sands

Sure. As you know, the perspectives have changed quite a bit in the last few years. It used to be that we were quite content with asking a patient, “How are you feeling?” and getting the answer, and if the patient said they were doing well, you know, we took for granted that they were well. But what we’ve learned is that we can’t really just direct treatment at symptoms. Symptoms in IBD can be quite unreliable. You can have patients who have very active bowel inflammation who seemed to have very little in the way of symptoms and, conversely, patients who have no appreciable bowel inflammation and they will be extremely symptomatic for a variety of reasons, such as irritable bowel syndrome overlay, and so on. So we’ve learned that we have to ask the patient how they feel, but we also have to look for objective evidence that the state of their bowel inflammation is well controlled.

We’ve learned to distrust symptoms and recognize the disconnect. We also, therefore, like to go in cycles of treatment, and this is a treat-to-target approach, which should be very familiar to a rheumatologist because we stole it directly from the rheumatology playbook, like all of our good ideas.

Dr. Gibofsky

And we stole it from the cardiologists and the endocrinologists. So at least we’re in good company.

Dr. Sands

Maybe for all of medicine, we’ll get there someday. But essentially, the cycles of care focus not only on getting the patient to feel better, but also getting the bowel mucosa to heal up. About 3 years ago, the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), which is an international organization of experts, created the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) paper, a position paper, for which many experts in the field were asked what the goals of therapy should be in the modern era of treatment, where we have effective treatments that can heal the bowel.

What these experts came up with was a series of 12 different recommendations and goals, but we can boil it down to very simple targets for ulcerative colitis (UC) and slightly different targets for Crohn’s disease. For UC, we essentially have a patient-reported outcome (PRO), which looks for no diarrhea and no rectal bleeding, the cardinal symptoms of UC. So that’s the part of the patient feeling well. But the second component that has to be there is endoscopic remission. We’re looking for healing of the
mucosa on colonoscopy. For Crohn's disease, the PROs are slightly different. We don’t want to see diarrhea and we also want abdominal pain to be remitted. Those are the 2 cardinal symptoms of Crohn's. Because Crohn’s disease can also affect the small bowel, we can’t necessarily rely only on ileal colonoscopy, which may be adequate to assess the state of mucosal inflammation, so we can also depend to some degree on cross-sectional imaging. Then there’s some adjunctive goals that help us along the way: biomarkers such as C-reactive protein or fecal calprotectin. There’s also some interest in histologic remission, which is yet a deeper stage of remission, and all of those are appropriate goals of care.

All of this is incorporated into cycles of care, in which when you start a new therapy, whatever it is; you wait an appropriate amount of time, generally 4 to 6 months is what we think is about right for most therapies to really achieve consolidated mucosal healing. If there’s a good response, we keep on going generally with the same regimen. If there has been no response or an inadequate response, then it’s time to adjust the therapy or move on to a different, more effective therapy. In this way, we have cycles of care that get us to the goal of getting the patient feeling well and also healing their mucosa.

Dr. Gibofsky

It occurs to me that if I were walking into one of your lectures or you were walking into one of mine, in the middle, you would hear terms like **objective metrics, link therapy to the metric**. In other words, don’t settle for being comfortable with qualitative terms like **doing well**, but actually measure joint involvement. Actually measure bowel involvement objectively, either by examination, which for us is the external joint evaluation or for you is the internal endoscopy, and these principles seem to permeate both of our disciplines, which probably ultimately leads to better care and understanding the therapeutic agents that we use, and how they’re going to work.

Dr. Sands

I think that’s right. The evidence base for this approach is probably much more robust in the rheumatology space, but we do have examples of trials that now demonstrate this. The CALM study that was just published showed that if you direct therapy toward objective evaluations of mucosal healing or at least 2 biomarkers along the way, you actually do achieve higher rates of mucosal healing and higher rates of remission.

Dr. Gibofsky

Yes. And we have something similar called TICORA, which is steady tight control of rheumatoid arthritis [RA], where the application of an active metric together with the therapy does better than the therapy alone, because you’re defining the disease activity that you’re ultimately going to be seeking to
resolve. Bruce, you’ve alluded to this, but tell us about the trial data and your thoughts on some of the newer, nonbiologic targeted therapies, in particular, the Janus kinase (JAK) inhibitors in IBD.

Dr. Sands

Right. So whereas we’ve become accustomed to using biologic therapies, and these really have revolutionized the care of patients with IBD, we’re eager to start using more oral, small-molecule–based therapies just for their convenience and for their lack of immunogenicity, which is a problem with basically all biologic therapies ultimately. Just this year we had our first approval of a JAK inhibitor, tofacitinib, which you have been using for a while, in May 2018. There are 2 other agents in active investigation for Crohn’s disease, upadacitinib and filgotinib, which are entering phase 3 studies. Peficitinib was explored in UC, and it’s probably a pan-JAK inhibitor, but it did not prove to be efficacious for that disease.

Dr. Gibofsky

One difference I think worth highlighting that you’ve recognized that my field hasn’t, is the difference between induction and maintenance, the concept that you might want to give a drug at a higher dose to begin with, then lower the dose as you move along. Certainly that’s the dosing that was approved in UC for tofacitinib, which was not approved in RA, wasn’t even sought in RA. Just standard dosing all the way across, no matter whether you’re using it for induction of disease activity remission or maintenance of the current state.

Dr. Sands

Yes; the approved indication and the labeling language for tofacitinib is remarkably flexible, but basically it starts with 10-mg twice-daily dosing for 8 weeks. However, it was also observed that for patients who had not yet achieved a response by 8 weeks, you could achieve an incremental gain in response if you waited another 8 weeks, still on 10 mg twice daily, and after the patient achieved a response or, hopefully, a remission, you would have the choice of either continuing on 10 mg twice daily, which might be more appropriate for patients who have refractory disease, for example, people who have been on anti–tumor necrosis factor (TNF) blockers in the past might choose to remain on 10 mg twice daily, or you can de-escalate a little bit to go to 5 mg twice daily.

Dr. Gibofsky

It may be that the approval of the higher dose for a period of time in your disease reflects the increasing comfort with tofacitinib, and our diseases and the fact that we didn’t get approved for the higher dose even though there may be a rationale or justification for doing so. Tell us a little bit about
the granularity of the data in UC, for example, the OCTAVE studies with tofacitinib.

Dr. Sands

The OCTAVE studies were the pivotal induction studies, with maintenance follow-up after that. The remission rates were clearly superior to placebo remission rates. You saw treatment effect size over placebo of something like 10% to 12%, which may not seem overwhelming, but you have to keep in mind that half of these patients were TNF blocker-experienced patients. Interestingly, we talked before about the disconnect between symptoms and what’s going on at the level of the mucosa in terms of the inflammation. If you look for mucosal healing at week 8, you see about twice the rates of mucosal healing as you do clinical remissions. You see mucosal healing rates in about a third of patients. And the third important point is that, regardless of whether patients had prior experience with TNF blockers or not, you saw the same effect size for the naive patients as for the experienced patients.

Dr. Gibofsky

That’s an interesting point in our diseases: what we generally see is that the more agents patients have been on, the less likely it is that the next one they’re given is going to elicit as good a response. We never expect as much from our train wrecks, so to speak, as we do from the patients getting their first medication.

Dr. Sands

It’s exactly the same in IBD. In fact, if one looks at just the absolute rate of response, it is higher in the naive patients. But if you adjust that for the placebo response rates, which are quite low in anti-TNF-experienced patients, you still see the same kind of effect size.

Dr. Gibofsky

We always have to temper our enthusiasm for efficacy with concerns about adverse events. Tell us a little bit about your experience with tofacitinib in UC.

Dr. Sands

Sure. My personal experience has been very good but also very limited in terms of commercial use because we’ve only had it in our hands for a few months at this point. The clinical trials clearly show us the same kinds of signals of safety that you’ve seen; for example, in the realm of infections, the one thing that comes out very clearly is a risk for herpes zoster. We know that certain types of patients are more susceptible; it appears that Asians may be genetically more susceptible to herpes zoster, but it is also a dose effect. So at the higher dose of 10 mg twice daily that we use, we do see higher rates of
herpes zoster than with the lower dose, which might be one reason to choose to de-escalate therapy.

In terms of cancer risk, the main concern is nonmelanoma skin cancers, although there is certainly a smattering of other cancers reported; at least in the UC experience, they did not occur at higher rates. In contrast to what has been observed in RA, we have not seen increased risks for gastrointestinal (GI) perforation, which would be an obvious concern for us, but we clearly do see changes in lipids, namely a rise in a total cholesterol, both HDL [high-density lipoprotein cholesterol] and LDL in proportion to each other. Very few patients seem to need to go on antilipid therapy; some do, but not many. It is recommended that at least you check lipids 4 to 8 weeks after starting therapy.

Dr. Gibofsky

Certainly with the exception of GI perforation, as you’ve noted, all those concerns about infection, malignancy, and lipid elevations have occurred and continue to be a concern in RA and psoriatic arthritis as well. Bruce, what about the differences in therapeutic efficacy of tofacitinib in UC and Crohn’s? Anything we need to be aware of?

Dr. Sands

Yes; it’s interesting. There have been not one but two phase 2 studies of tofacitinib in Crohn’s disease, and both of those studies were negative. Whether that was a mechanistic failure of the drug, or failure to dose adequately, or some design issue with these studies, which does happen because of high placebo response rates in some Crohn’s studies, we really can’t know, but suffice it to say that the drug is not approved for Crohn’s disease, and this stands in contrast to 2 other JAK inhibitors that are in development that do seem to have some promise of efficacy in Crohn’s. Filgotinib is the first one of these. And as we said, it is more of a JAK1, relatively specific inhibitor, and at least in Crohn’s disease, there are clearly benefits in terms of clinical remission.

There was also evidence of endoscopic response, meaning the mucosa seemed to heal up. Prior anti-TNF exposure does reduce the rate of mucosal healing and of clinical remission. But even in the anti-TNF-experienced patients, you do see response rates that are important. So, at least in phase 2, filgotinib seems to be very promising in Crohn’s. The second agent is upadacitinib, which is a little bit more JAK1 specific and, like filgotinib, appears to have great promise of efficacy. It actually had very important rates of mucosal healing and endoscopic response, meaning 50% change from baseline. These are up-and-coming agents and suggest that not all JAK inhibitors are exactly the same in their disease profile responses.

Dr. Gibofsky
Bruce, we’ve talked about a lot of material for our listeners and our viewers today—let’s wrap it up. Give me your top 2 takeaways that our listeners and viewers should walk away with.

Dr. Sands

I think we’ve talked about 2 really big points, the first of which is that we are embarking on a treat-to-target type of approach to treating patients to get the best results from really effective therapies. It means really targeting therapy to heal the mucosa, not just the symptoms, and to iteratively go through the process of making sure that drugs are working and continue to work for a patient. And the second big point is that the influx of new agents that are small-molecule agents, particularly the JAK inhibitors, which show promise both for UC and for Crohn’s disease, appear to work for patients who may have had failure of TNF blockers to treat their IBD. So, we think these will be really useful agents in years to come.

Dr. Gibofsky

Yes; I completely agree. Thank you.

Dr. Sands

My pleasure. It’s been fun.

Dr. Gibofsky

And thank you, the audience, for joining us for this CME program. Please remember to complete the CME posttest and fill out the evaluation. For additional CME opportunities, please visit us at ReachMD.com, and at www.ExchangeCME.com.

Announcer

This activity was part of a series jointly provided by Global Education Group and Integritas Communications. To receive your free CME credit, please be sure to complete the post test and evaluation by going to ReachMD.com/JAKInhibitors.

ReachMD: Be part of the knowledge.