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JAK-STAT Signaling and Disease Pathogenesis in RA and IBD

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-STAT Signaling and Disease Pathogenesis in RA and IBD.

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Allan Gibofsky, MD

Hello, and welcome to this program, in which we will look at autoimmunity and chronic inflammatory disorders, focusing on the JAK pathway. 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.

This CME activity will explore insights into the immunopathogenesis of both rheumatoid arthritis and inflammatory bowel diseases, with a focus on Janus kinase—or JAK—inhibition, as a target.

So to begin, Bruce, let's take a look at the immunopathogenesis of both rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), and let's start with IBD.

Bruce Sands, MD

We've known for a long time that the 2 inflammatory bowel diseases—Crohn's disease and ulcerative colitis (UC)—are immune-mediated diseases, as is RA. There is a whole variety of immune cells that are activated: macrophages and neutrophils are involved; T cells, we know that they secrete a variety of substances that are proinflammatory, basically cytokines and chemokines, and that these, in a coordinated fashion, recruit these cells into the mucosa, where they're actually destroying the structure of the gut. And that's what causes the symptoms of diarrhea and abdominal pain, all the things that our patients suffer from. So, a lot of the interventions that we've employed really are directed against cytokines, particularly the biologic therapies. We also know there's a strong genetic component to these diseases. In fact, there are well over 200 genetic susceptibility loci. These give us various themes that relate to how the mucosa handles the microbiome in the gut; how it reacts to a nonpathogenic bacteria and to immune mediators being aberrant.

Dr. Gibofsky

We can say many of the same things for RA as well. The overriding hypothesis, I think, for both our sets of diseases, is that they occur in genetically susceptible individuals who encounter the appropriate environmental trigger or triggers, which may be in the body or which may be outside of the body. That interaction is what begins the cascade of cellular, humoral, and other events, which leads to the

production of the inflammatory mediators that result in perturbation—in your case, of the gut; in my case, of the synovium—but the overriding hypothesis remains the same.

It occurs to me that perhaps at some point in the future we may not have divisions into gastrointestinal and rheumatology as much as divisions that are mechanistically based, and the diseases are phenotypes of that mechanism.

We've alluded to pathways, so let me begin by talking about the so-called Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway, in both of the inflammatory conditions that we're focusing on. In RA, we have several years of experience with JAK inhibitors in targeting the pathway rather than the individual cell signaling that results. And we've learned that the JAK family includes 4 specific members of the family, JAK1, JAK2, JAK3, and tyrosine kinase, or TYK, 2.

Cytokines—proinflammatory or anti-inflammatory—bind to surface receptors that activate JAK pairs, which dimerize, causing their phosphorylation, and then cleave to the complex with another molecule, called the STAT partner protein, which itself also dimerizes then goes to the nucleus, leading to production of additional inflammatory mediators.

Dr. Sands

It's a complex system of molecules, but basically what you're describing is a system of intracellular signaling downstream of the proinflammatory cytokines that activates these immune cells to secrete a whole variety of other proinflammatory cytokines contributing to the cascade. We get clues from the genetics of IBD, and I assume from RA as well, that the JAK and STAT molecules are implicated as loci for genetic susceptibility for these diseases, so, it makes sense that these should be targets. We also know it is an interesting system because it's sort of a mix-and-match system. You mentioned the 3 JAKs—JAK1 to JAK3—and TYK2, combining with themselves or with each other in a binary fashion, and that's what produces specificity for a cytokine. For example, downstream of binding of interleukin 2, you would have JAK1 and JAK3, and those are the ones that are being activated, which has implications for the profiles of these JAK inhibitors and where they're actually hitting in the cascade, as well as for what occurs downstream.

Dr. Gibofsky

Yes; we have selective inhibition. We have nonselective inhibition and what that means for downstream production is still being teased out. Let's talk a little bit about the agents that we have available to us, both in my diseases and now yours, and those agents that may be up and coming for your diseases and mine.

Dr. Sands

I think it's important to point out that while all of these agents are JAK inhibitors, they are not all the same molecules. They have slightly different profiles. It's probably true that all of them touch upon any of the JAKs, that is, but they have different specificities. For example, the agent that is approved in UC in IBD is tofacitinib, which is a pan-JAK inhibitor with relative specificity for JAK1 and JAK3. We are starting to look at other agents, such as filgotinib and upadacitinib, which are more JAK1 specific.

Dr. Gibofsky

The differences among the JAK inhibitors may not just define how they work, but what they work on and what they are responsible for controlling, as we've seen. Given that, are there potential differences we should be thinking about in terms of whether there is homodimerization or heterodimerization in the context of JAK activation?

Dr. Sands

I don't think we're sophisticated enough to really predict what is going to happen downstream. We might look at these profiles and the relative selectivity and, for example, we might be concerned that something that hit JAK2 more might actually inhibit erythropoietin, which might give you more anemia. In fact, probably all these agents hit JAK2 to some degree, but at least for tofacitinib in IBD, for example, we don't see any significant anemia.

Dr. Gibofsky

What do you think it may mean, since we're kind of speculating at this point, that we have a common system that appears to be operative in the gut, in the joint, in the skin, perhaps in bone, perhaps in hair loss, perhaps in a bone marrow activation? What does that mean in terms of thinking about what inhibition of that pathway may mean?

Dr. Sands

I think it means that these are systemically active medications and there will be desirable effects and undesirable effects. We've become very accustomed to using biologic therapies, which generally have very exquisite specificity for one cytokine or one target. These

medications are not like that. They actually target a lot of different cytokines all at once. Therefore, they will be useful for a lot of different immune-mediated conditions. They will also have a variety of possible adverse consequences.

Dr. Gibofsky

It seems to me that when we go from extracellular inhibition or surface inhibition to intracellular inhibition, we have to be concerned about the fact that it may not just be the cells in the target organs that are being affected but other organs as well, and we may not yet have defined all of these, given our relatively early experience with these agents, even in the disease conditions that I've mentioned. With that in mind, Bruce, what are your top 2 takeaways from this activity so far?

Dr. Sands

I think it's important for the audience to understand that the JAK inhibitors are a new class for those of us who are treating IBD, less new to those treating RA, but, advantageously, they are oral agents, so immensely convenient for patients, and they are also highly effective.

Dr. Gibofsky

Are there concerns about their use that we should have in mind other than the general effect on multiple cells of the body? Are there unique things that we should be concerned about when using these agents that we haven't yet seen in the use of our other therapeutic agents in these diseases?

Dr. Sands

There are specific safety concerns. For example, one infection that we do see clearly increased, and it seems to be a class effect for the JAK inhibitors, is herpes zoster infection. There can be other serious infections, but they're not as common. There is increased risk for nonmelanoma skin cancers, potentially for other kinds of cancers, although that's less clear. There are risks for lipid profiles: you see elevation of both LDL and HDL in proportion, at least in patients with UC treated with tofacitinib. There are also rare instances of cytopenia that you may see; you may see anemia, low neutrophil counts, or lymphopenia, but that's actually been very uncommon, at least in UC treated with tofacitinib.

Dr. Gibofsky

One of the buzzwords in medicine today, both for professionals and for the public, is *precision medicine*, or targeted therapy. Do you think that the implications of JAK selectivity that we've spoken about will really, or are really, leading to targeted therapies?

Dr. Sands

In one sense we are targeting something but not as precisely as biologic therapies do. I think when we get to the point of really understanding what, specifically, is driving disease for one individual, we might be able to choose one JAK inhibitor instead of another, but at this point we don't really have that luxury.

Dr. Gibofsky

I think it would be great if we had a way of predicting who would respond to a given agent or, alternatively, who would not respond or who would become toxic.

Dr. Sands

You're describing the holy grail, absolutely.

Dr. Gibofsky

We have to choose wisely when we approach it. I think that, as much as we've learned, there's still a long way to go, particularly given the infancy of this class of molecules and its therapeutic application.

Dr. Sands

I agree.

Dr. Gibofsky

Let me take a minute to review the available and emerging JAK inhibitors in RA. Then I'll ask you to do the same for IBD. In RA currently, we have 2 approved agents in the United States. We have tofacitinib and baricitinib. Tofacitinib was, as you know, originally touted to be JAK3 selective, then maybe JAK1 selective; or, maybe it's 3, 1, and 2 selective. So I think we now refer to tofacitinib as a pan-JAK inhibitor and it's been approved for RA. It's also been approved for psoriatic arthritis (PsA) in my part of the world.

Then we have baricitinib, which is another oral agent, thought to be a JAK1-selective inhibitor, with maybe a little bit of JAK2 thrown in as well. And it's been approved for RA. Now, it's of interest that tofacitinib is approved worldwide for RA and PsA at 5 mg twice a day or 11 mg once a day with another formulation. Baricitinib sought approval for 4 mg once a day, which is the approved dose in Europe. But in the United States, it was only given a 2-mg dose approval in RA. I think our experience with baricitinib is certainly nowhere near as long as it is with tofacitinib in RA, so we have to tease out what that difference in dosing is going to mean in terms of efficacy.

Regardless of what we've seen in terms of efficacy, there is another holy grail to consider and that is whether JAK selectivity can result in differences in mechanism of action that can translate into, if not differences in efficacy, differences in the adverse event profile. To date in RA and, to an extent, in PsA, although you probably shouldn't make comparative statements in the absence of a head-to-head study, the fact is that we've really not seen significant differences in efficacy in terms of the JAK inhibitors at the doses that were approved, with the possible exception that maybe the lower dose of baricitinib may have a little bit less efficacy. As to whether selectivity has translated into efficacy differences, maybe not. But there may be some differences in terms of adverse event profiling, such that we have seen differences in the incidence of thromboses, certainly in the clinical trials of baricitinib, which is what in part led to the US Food and Drug Administration not approving the 4-mg dose but rather the 2-mg dose, and the suggestion that this adverse event in particular may be unique to baricitinib and not a class effect. What's your experience in the IBD world, Bruce?

Dr. Sands

It's interesting. Of course, our experience is more limited than the experience in RA and we do not have experience with baricitinib. Most of our experience is with tofacitinib, the one approved agent, but, interestingly, the approved dose, at least for induction, is the higher 10-mg twice-daily dose, and in fact, earlier studies even explored as high as 15 mg, which did seem to be more effective in the phase 2 studies. But there were concerns about higher risks for infections, in particular, herpes zoster. So the dose that was pursued for approval in phase 3 was the 10-mg twice-daily dose, which can be used for 16 weeks of treatment or longer. Especially for patients who are tumor necrosis factor experienced and, therefore, probably more refractory, there is the option potentially of continuing indefinitely on that 10-mg twice-daily dose.

When you look at efficacy and safety and really are talking about different doses for different indications, it gets a little bit complicated. And when we're thinking of the other agents, it's interesting that, so far, upadacitinib appears to be highly effective in Crohn's disease, and filgotinib in the phase 2 studies also appears to be highly effective in Crohn's disease. By contrast, tofacitinib explored at the same doses that seemed to work in UC, was not effective in Crohn's disease, suggesting that potentially there are differences in JAK inhibition profiles that may have an impact on the differential efficacy in these 2 diseases.

Dr. Gibofsky

Certainly. To round out the discussion of emerging or investigative inhibitors, we see upadacitinib in RA has a very good efficacy profile. Filgotinib has an acceptable and good efficacy profile. Peficitinib was studied in RA, as well, with an acceptable efficacy profile. So we're really not seeing, as I said before, significant differences in efficacy at their appropriately selected dose.

Dr. Sands

It's a little bit different for peficitinib in UC, in which it was studied. It did not prove to be effective at doses that were, I believe somewhat similar to what were used in rheumatoid arthritis.

Dr. Gibofsky

Thanks, Dr Sands, this has been a very informative discussion.

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.

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