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JAK Inhibition in Rheumatoid Arthritis

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 rheumatoid arthritis.

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Dr. Allan Gibofsky

Hello, and welcome to this program, in which we will look at autoimmunity in rheumatoid arthritis [RA], focusing on the JAK [Janus kinase] 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. Joel Kremer, Professor of Medicine at Albany Medical College,

and Director of Research at the Center for Rheumatology in Albany, New York.

In this program, we will discuss targeted synthetic DMARDs [disease-modifying antirheumatic drugs] that inhibit members of the Janus kinase family of enzymes (or JAK inhibitors) as treatment options for patients with rheumatoid arthritis.

Joel, let's begin with a brief discussion of how we should structure the treat-to-target concept in the context of what, as you and I have discussed so many times, is a mechanistically heterogeneous disease.

Dr. Joel Kremer

I think you and I feel passionate about treating to target. Why settle for moderate disease if you can get the patient to low disease, because there are a lot of comorbidities and implications with poor control. So why not treat to target? And the answer is, there is no good reason.

Almost half the time, patients who do not have adequately controlled disease will say, "Doc, I'm not ready to accelerate treatment." Now, I think if we just talk about treat to target without considering the psychological dynamic of the patient, we will not be as successful as if we integrate that into our thinking. Specifically, if a patient is doing okay but is not in remission and we, as the treating rheumatologist, want to do better, then it's easy for us. But that patient may be wedded to the status quo. That is, "No, it ain't perfect, Doc, but I've seen these ads on TV about a lot of these drugs, and they tell me about a lot of nasty things that can happen to me, so maybe the devil I know is better than the devil I don't know. Maybe I want to avoid side effects even though you're telling me I will do better." But we know that for many people, a loss is twice as important as a gain. Clearly there are gains associated with treat to target, but there are perceived losses in terms of a whole new set of side effects that I do not now have. If we are going to be successful, we have to do several things: 1) do a better job of describing the upside; 2) acknowledge the patient's fears; 3) develop trust. That trust is the key element. If we're going to establish that trust and acknowledgment that my treating physician cares, we will be more successful, I believe, in invoking the treat-to-target philosophy and utilizing it more, because we have such terrific drugs that we can use now.

Dr. Gibofsky

Let me take a minute and describe briefly the Janus kinase (JAK) signaling mechanism that we're going to be talking about for most of the conversation, and remind our audience what JAK inhibitors are and which ones are currently available for rheumatoid arthritis (RA). This molecule is bilaterally around an axis, and there are 4 alleles, or types, of it, JAK1, JAK2, JAK3, and a cousin named tyrosine kinase 2 (TYK2). These are involved in cytokine binding to surface receptors, which then activate JAK,

and the JAK dimers, the JAK pairs, cause phosphorylation then activation of another partner protein called STAT, or signal transducer and activator of transcription.

Those go to the nucleus after they dimerize, where they transcribe or act as transcription factors for the target genes, usually for the production of the inflammatory mediators that we seek to reduce the levels of in RA.

Right now in the United States, we have 2 available JAK inhibitors. We have tofacitinib, and we have baricitinib, and these are orally dosed low molecular weight agents. It's important that they're orally dosed, and small molecules, as opposed to the biologic therapies that we've been using. There are 2 other molecules in development in this family, upadacitinib and filgotinib, and it's thought that these 4 agents differ in terms of what their primary target is. So with that background, Joel, with the notion that we now have 2 agents available and at least 2 agents in the pipeline, give us some idea of how we are thinking about treating early RA and what, if any, the role of JAKs is going to be.

Dr. Kremer

My experience is, of course, primarily derived from tofacitinib. I have investigated other agents, but in terms of everyday use, tofacitinib has been around a number of years now. I think tofacitinib had a slow start, but I think people—that is, prescribers—began to recognize, this is a really valuable addition to our therapeutic armamentarium. I use tofacitinib a lot now in people who have failed everything, and I have migrated to using it even earlier. I think it's telling that the new American College of Rheumatology (ACR) guidelines do not distinguish between a mechanism of action that's relatively new, that has its own unique toxicities associated with it, from some of the drugs that have been around a lot longer. That is, at this point, it's really up to the doctor to determine, after a patient has failed conventional disease-modifying antirheumatic drugs (DMARDs), which drug would be best, and I think that as we gain experience with baricitinib at 2 mg and with upadacitinib, and filgotinib, which are in the wings, that the way we utilize these drugs in 2020, 2021, 2022, will evolve. My guess, because no one is perfectly prescient, is that we will be using a lot more of these drugs based upon their overall efficacy profile.

Having said that, there are side effects that clearly we need to be aware of in terms of what to expect, what to monitor, and how to counsel our patients as to what they may be experiencing with these agents.

Dr. Gibofsky

Is there an order in which we should be using these drugs? Is there a particular recommended sequence?

Dr. Kremer

In a patient with at least moderate disease who is new to my practice and who has not been exposed to methotrexate or other biologic agents, I usually start with methotrexate and I push it to tolerance. Hopefully I use it right; I use it subcutaneously and I watch for toxicity. The data have shown that roughly a third of patients will do okay with methotrexate. Then you can add other conventional DMARDs. I love adding hydroxychloroquine to methotrexate. I think it makes a better drug. Others will go to triple therapy; I'm not as big a fan of triple therapy primarily because of sulfasalazine and the frequency with which patients are unable to tolerate that. But let's say you've ideally treated with methotrexate and hydroxychloroquine, double or triple. Now you need to move on. You need to make a decision, and that's treating to target.

Which drug you use, per the ACR and European League Against Rheumatism (EULAR) guidelines, I think there's a level of arbitrariness to that choice at this point. We need real-world evidence to determine—whether a patient is anti-citrullinated protein antibody-positive, or seropositive, has failed prior biologic agents, all permutations and combinations of biomarkers in response, as well as age, and perhaps other biomarkers in development—which of these drugs to use.

It's possible that, as we gather experience from the European and US registries, that our thinking will evolve about how we use these drugs and in what order.

Dr. Gibofsky

I think that's right. I think we're leaning more toward multinational collaborations and the concept of European investigators, American investigators; you and I have done work with all of them, so it's more like a multinational collaboration leading, hopefully, to some international guidelines that can be applied regardless of the nuances of what doses are approved where.

So Joel, we've articulated great enthusiasm for this new class of agents, but we have to balance our enthusiasm over their efficacy with concerns about their safety, because no drug is without adverse events. As we've seen in our clinical practice, these drugs may have some concerns for the class, as well as some unique concerns for the individual agents. As with any of the agents we use, with the JAK inhibitors we're concerned about infections, particularly opportunistic infections; we're concerned about tuberculosis. We're concerned about malignancy. We're concerned about potential problems with the bone marrow, inhibition of various cell-forming elements, lipid elevations, liver enzyme elevations, gastrointestinal perforations. There is no "free lunch" here with these agents.

And that's for the class. Indeed, when it comes down to the individual agents, one of the concerns that the US Food and Drug Administration had with baricitinib, as opposed to tofacitinib, was the fact that

there was an increase in thromboembolic events in the randomized controlled trials, which led to the approval of only the 2-mg dose, not the 4-mg dose. It is a sense that that adverse event may be unique to that agent, as opposed to a class effect. Certainly, there are class effects for these agents that I've outlined, but there may be unique effects related to their profile of JAK inhibition. We don't know. We're still speculating from all of the data that we have, but clearly we have to be concerned about adverse events for the class of agents, as well as for the individual agents, and the things that require careful monitoring of these patients, whether they're being used as monotherapy or whether they're being used as combinations.

We're concerned about serious infections with these agents, in particular one serious infection, herpes zoster. We've seen an increase in herpes zoster cases in patients on the JAK inhibitors in the clinical trial and also in the postmarketing experience for them. That raises the issue of whether patients who are starting on a JAK inhibitor, whether tofacitinib or baricitinib, should be vaccinated. What's your perspective on that?

Dr. Kremer

My perspective is that I am concerned about zoster and my patients are concerned. Everyone has known someone who's had shingles or has seen pictures on TV and they're frightened. The killed vaccine that was most recently introduced is an excellent vaccine. My concern is the following: that it is highly adjuvanted and its adjuvanted status allows it to be more efficacious in terms of an immune response, but we're also giving patients with an autoimmune disease a strong adjuvant on 2 different occasions. So I need, personally, to see more data on safety relative to flares of an underlying autoimmune disease when patients are given an adjuvant on 2 different occasions. If I see reassuring data, I will undoubtedly use it universally.

Dr. Gibofsky

Tell us a little bit about what laboratory tests are important, how we should be monitoring patients, how often, and those kinds of things for our viewers.

Dr. Kremer

I think white blood cell counts, lymphocyte counts, neutrophil counts are important. Transaminase levels are meaningful. We have some rather arbitrary safety guidelines for transaminases: I've seen 2 times normal, 3 times normal, based upon my methotrexate experience. I don't like when transaminases there are elevated at all and I tend to repeat them. If they remain elevated, I would adjust the dosage for patients on a statin and patients who are on NSAIDs. If the patient is on methotrexate, I combine methotrexate with leflunomide. I think we have more flexibility with

methotrexate, and if that particular combination is used, I would back off of the methotrexate. If the transaminases remain elevated, I would probably adjust the dosage of the new agent, the JAK, so that the elevation went away.

I like to get labs monthly when I use these drugs for the first time. If a patient has demonstrated that they remain in the normal range for, say, 3 months—and it's arbitrary—I would probably back off and see the patient at the interval dictated by their clinical status rather than by my fear of the labs.

Dr. Gibofsky

That's a very nice summary for the people who are viewing us today. Let's now switch in the last minute or two that we have to the investigative agents that are on the horizon, filgotinib and upadacitinib.

Dr. Kremer

Filgotinib is really interesting and it is the least far along of all. To date, perhaps the safety profile of filgotinib is favorable. We don't seem to see as many serious infections, it's true, but in fairness, I think we haven't seen the entire picture. Upadacitinib has been studied in all the categories we described before. It's clearly an efficacious drug. It seems to have all the same laboratory challenges that we've described. However, for both of these drugs, there is no evidence of either thromboembolic disease or pulmonary emboli. But in fairness to baricitinib, I want to see how that drug does in the real world, because sparse events can occur in unpredictable patterns with any drug.

Dr. Gibofsky

I think if we can be reassured by anything regarding the new agents in development and what we've seen so far, it is that neither the DARWIN studies of filgotinib nor the SELECT in upadacitinib have shown us any new safety signals to be concerned about that we haven't seen from tofacitinib and baricitinib. So I think that's something we can take a little bit of reassurance from.

Joel, thanks a lot.

Dr. Kremer

Thank you.

Dr. Gibofsky

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

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