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Rheumatoid Arthritis: Challenges and Opportunities in the Evolving Treatment Landscape

Narrator:

Welcome to CME on ReachMD. This segment, *Rheumatoid Arthritis: Challenges and Opportunities in the Evolving Treatment Landscape*, is provided by Global Education Group and Paradigm Medical Communications, LLC. It is supported by an educational grant from Lilly.

Joining host Dr. Jennifer Caudle is guest expert, Dr. Allan Gibofsky, Professor of Medicine, Healthcare Policy and Research at Weill Medical College of Cornell University, and attending rheumatologist at the Hospital for Special Surgery. Here is Dr. Jennifer Caudle.

Dr. Caudle:

The importance of effectively treating patients with rheumatoid arthritis, or RA, cannot be understated. With several available agents to choose from, rheumatologists must determine the best therapy options for individuals at critical points during their disease course. Monitoring disease activity and progression and understanding how patient history impacts response are also crucial to treatment success.

I am your host, Dr. Jennifer Caudle, and I would like to welcome my guest, Dr. Allan Gibofsky, to the program. Dr. Gibofsky, thank you for joining us.

Dr. Gibofsky:

Thank you, Dr. Caudle. It's a pleasure to be with you.

Dr. Caudle:

Well, let's begin by defining early and established rheumatoid arthritis, as well as disease activity, both of which impact therapy selection.

Dr. Gibofsky:

Well, the 2015 American College of Rheumatology [ACR] Guideline for the treatment of rheumatoid arthritis does, as you mention, divide rheumatoid arthritis into early disease and established disease and then again by disease activity. Early rheumatoid arthritis is defined as disease with duration of symptoms of less than 6 months—where duration denotes the length of time the patient has had symptoms, not the length of time since rheumatoid arthritis diagnosis—since, as we all know, patients often wait with symptoms for quite some time before seeking medical attention. In contrast, established rheumatoid arthritis is defined as rheumatoid arthritis with duration of disease or symptoms of at least or greater than 6 months. Now, in addition to disease duration, we also categorize disease by disease activity as low, moderate or high according to the particular validated scale that the examiner is using.

Dr. Caudle:

According to the 2015 American College of Rheumatology Guidelines for the treatment of RA, methotrexate is recommended first-line for patients with early RA and low disease activity. Some patients, however, don't adequately respond to methotrexate. Dr. Gibofsky, will

you explain treatment selection for patients with RA who have an inadequate response to methotrexate?

Dr. Gibofsky:

Well, as you correctly point out, Jennifer, methotrexate is the anchor stone of therapy, and unless there's a contraindication, we almost always begin with that drug. However, as you acknowledge, patients don't always respond to methotrexate, and so we have other therapies to consider. And when the consideration of what other factors or therapies to use, we have to consider patient-specific characteristics such as the disease duration, disease activity, the age of the patient, the frailty of the patient, comorbidities, contraindications, and treatment history. Now, in addition, we overlay that with the treat-to-target recommendations, which mandate the use of validated composite measures of disease activity, including joint assessments. This is really what should be used in routine clinical practice to guide treatment decisions.

With that as our matrix, another general comment would be that while we hear about age as a contraindication to certain therapies, this is probably more age bias than anything else, because we're beginning to see data suggesting that many of the therapies we use, really don't have a significantly increased adverse event profile in older patients versus younger patients. And another point before we get more granular, is that when it comes to the comorbidity of malignancy, most authorities generally suggest that biologic agents should be avoided within 5 years after cancer has been cured, so if the patient has an active malignancy, biologic agents should definitely be avoided. Even if the cancer has been cured and the patient is considered to have no evidence of disease, we probably want to wait about 4 to 5 years before starting a biologic therapy. Finally, DMARDs [Disease-modifying antirheumatic drugs], methotrexate and leflunomide, are contraindicated in patients who are or may become pregnant. While the use of biologics in these patients is controversial, nevertheless that seems to be a good rule of thumb to follow in clinical practice. That said, certain of the TNF [tumor necrosis factor]-alpha inhibitors may, nevertheless, be a safe option.

So, rather than give you specifics, I've kind of given you some general principles that are used in the context of what therapies we begin to think about in the context of what to do after methotrexate, and these, of course, are going to be used either as monotherapy or in combination with conventional synthetics and so on.

Dr. Caudle:

Can you speak to the targets for biologic agents and how this factors into therapy selection?

Dr. Gibofsky:

I think what we've learned over the years is that there are a variety of cells and other structures and other tissues involved in the pathophysiology of rheumatoid arthritis, most of which can serve as targets for biologic therapy. The other thing that we have become particularly aware of is the amazing redundancy in these pathways leading to inflammation. In my cosmology, this is often like that old game of Whack-A-Mole. You suppress one and up pops another. You suppress that and up pops another, so there is no one target as much as there are multiple targets and multiple pathways that can be affected to reduce inflammation.

Now, general concepts that we should consider for the approved biologic agents targeting some of these pathways: the TNF inhibitors, infliximab, adalimumab, etanercept, golimumab, certolizumab pegol, and now fairly soon, if not already in some areas, the biosimilars to them are one class of agents; We have agents that work by suppressing B cell numbers and B cell activities such as the anti-CD20 antibody rituximab; we have agents such as abatacept, the T cell costimulation inhibitor. We have interleukin inhibitors, either against the molecule itself or, as we will soon have, the receptors, we now have one agent, tocilizumab. And, finally, the newest agent we have is the small molecule Janus kinase, or JAK inhibitor, and the JAK kinase inhibitors as a class have multiple agents, one already available to us, tofacitinib, and one on the horizon in 2017, and several others behind it.

Dr. Caudle:

So, considering the following case, how would you approach a 42-year-old woman with moderate RA diagnosed 1 year ago, who was initially started on methotrexate with good resolution of her clinical disease activity index, or CDAI, but has now had increased pain and swelling of her joints and a gradual increase of her CDAI score back to baseline levels?

Dr. Gibofsky:

Well, first of all, I'm very pleased that you alluded to the CDAI, or the Clinical Disease Activity Index, because this is an objective metric of disease activity, and an objective metric of disease activity should be done on every RA patient at every visit. This is the mantra: Every patient, every visit.

Now, there are several well-validated indices of disease activity— the CDAI, the SDAI [Simple Disease Activity Index], the GAS [Global Arthritis Score], the DAS [Disease Activity Score], the DAS-20, the DAS-28, the DAS-44, the DAS-66—but the CDAI seems to be the one

most commonly used in clinical practice. With that in mind, according to the 2015 ACR guidelines, in addition to methotrexate, this patient should receive another DMARD or a biologic such as a TNF inhibitor, which is usually the first type of biologic used in the treatment of rheumatoid arthritis. We've learned over the years that all biologics exhibit enhanced efficacy when combined with methotrexate and presumably any other DMARD. No biologic used as monotherapy, however, has shown consistent statistically significant clinical or functional superiority compared with methotrexate. Although there is some evidence from one trial that perhaps the newer JAK inhibitors may do so. Clinical efficacy, in patients with inadequate response to methotrexate, appears to be similar across all types of biologics as shown in meta-analyses, systematic reviews, and even a few well-designed head-to-head studies.

So, in this particular instance for this particular patient, among the biologic therapies I would consider, of course, would be an anti-TNF therapy, which is almost always the go-to medication, although abatacept, the T cell costimulation inhibitor, is also approved for first-line therapy. But given my druthers and given the long clinical experience with a TNF inhibitor, that's where I would probably start.

Dr. Caudle:

Well, what would you look for in follow-up?

Dr. Gibofsky:

Every patient on every visit should have a metric of disease activity, preferably the metric that was used when the initial determination of disease activity was done. So, I'm always going to be looking at the evolution of the disease activity metric to define my therapy, as to whether or not adjustments need to be made consistent with the treat-to-target paradigm, which I outlined earlier. The American College of Rheumatology recommends this previously-mentioned disease activity measure as important in defining remission, which is the goal for our therapeutic efforts; if not remission, then certainly low disease activity.

So, I've mentioned the metrics that are done primarily by the physician. We have patient activity scales such as the PAS-II [Patient Activity Scale]. We have the routine assessment of patient index data, with 3 measures, also known as the RAPID3 is widely used. These are my disease activity measures. In addition, I'm, of course, monitoring the patient for any evidence of intolerance or adverse events to the therapy that I've selected. So, laboratory follow-up such as a CBC [complete blood count], liver enzymes, serum creatinine level, depending upon the agent chosen, serum lipids, may also be important to monitor on the next visit and periodically thereafter.

One other concern is for potential adverse events. Now, biologics, in general, do increase the risk for serious infection, so certain screening efforts such as, for tuberculosis, hepatitis B and C are important before starting therapy. Vaccination should be done preferably prior to starting therapy for, or rather against, herpes zoster if the patient is going to receive any of the newer agents, which may predispose to an increased risk for reactivation of the endogenous virus.

So, while talking about vaccination, I should also say that the use of any live vaccine for a patient being treated with a biologic agent is contraindicated and should not be given. This is very important for the treating rheumatologist, and also for the patient to communicate to their primary care physician because most vaccines are going to be administered by the primary care physician as part of routine healthcare monitoring rather than by the rheumatologist.

Dr. Caudle:

Are there any new agents on the horizon that you would consider for this patient?

Dr. Gibofsky:

So, there is positive clinical study data for the JAK inhibitor baricitinib, which I alluded to earlier. Baricitinib will be, if approved, the second JAK inhibitor on the market. It is currently under review, and we expect that the approval will come later this year. Having made that statement, I am much better as a doctor than I am as a prophet, so please take that statement with a grain of salt. Next, we also have newer agents such as the IL-6 or IL-6 receptor inhibitors, namely sarilumab and sirukumab, both of which are also in late stages of development, one of which is also under review by the FDA [Food and Drug Administration] and may likely be available to us later this year if not early next year.

Dr. Caudle:

If you are just tuning in, you are listening to CME on ReachMD. I am your host, Dr. Jennifer Caudle, and I have the pleasure of speaking with our guest, Dr. Allan Gibofsky, on the topic of rheumatoid arthritis.

Dr. Gibofsky, earlier you spoke about therapy selection following inadequate response to methotrexate. You had said that a TNF-alpha

inhibitor is usually the first biologic agent used in rheumatoid arthritis. So, what would be your strategy for your patient 3 months later with disease that is still active following previous therapy?

Dr. Gibofsky:

So, if this is a patient that has been started on TNF therapy 3 months earlier, and assuming that they have already reached maximum dose of methotrexate prior to starting with TNF inhibitor, 3 months later I have a couple of choices. The first is, if appropriate, to change the dose of the TNF inhibitor that the patient is currently on. With agents, such as infliximab, which are weight-based, we often can get greater efficacy by increasing the dose. That is not always the case, however, for patients that are on fixed-dose therapy, such as adalimumab or etanercept. Next, there is the option of switching to a different TNF inhibitor and staying within class. We have all seen instances where a patient who did not respond to one TNF inhibitor may very well respond quite nicely to the second one that they're given. Finally, the third option is to go out of class and give either another biologic agent or tofacitinib, which is an agent of a different class. And those are our options available to us for the methotrexate-inadequate patient who has had an inadequate response after their first dose of a TNF inhibitor.

In making those therapeutic decisions, I would also consider the comorbidities that the patient may be experiencing such as renal dysfunction, diabetes, pulmonary disorder, liver dysfunction, and cardiovascular disease, because with whatever we use, it's important not to exacerbate comorbidities with additional therapies, and also to ensure that no new comorbidities have arisen in the course of therapy.

Now, the ACR 2015 Guideline has done a very good job of recommending specific agents or combination of agents for patients with certain high-risk comorbidities. In patients with an insufficient response to a TNF inhibitor, biologics that interfere with different target mechanisms are generally expected to be effective, but all agents, irrespective of their target, have lesser efficacy in TNF-experienced versus TNF-naïve patients. So, the more agents a patient has seen, the less likely it will be that they will have more efficacy with each successive agent. Less likely doesn't mean none, so we continue to go through the iterative mechanism as outlined by the ACR until we find the therapy that works for that individual patient.

And also, as I mentioned previously, we may use an IL[interleukin]-6 blocking agent such a tocilizumab; we may use a T cell costimulation agent; we may use a JAK inhibitor, all of which have been identified and deemed appropriate per the 2015 ACR recommendation for a patient with established rheumatoid arthritis.

Dr. Caudle:

Would you follow this patient differently this time around?

Dr. Gibofsky:

Not very differently because we still have the need for measuring disease activity at every visit and evolving our therapeutics based on the level of disease activity. We also have the requirement to monitor for adverse events, as I've outlined earlier. And so, it would be done at roughly comparable intervals. Now, if the patient's disease came under control such that we were able to see them less frequently, then we would be monitoring them less frequently. Less frequently does not mean never. Less frequently may mean every 6 months instead of every 3 to 4 months, but we would still be monitoring them for adverse events and for response to therapy.

It's another principle of therapy that the earlier the disease is caught, the more aggressive we may be, and, thus, the monitoring may be more frequent in the early stages of therapy. When patients have established disease or disease that comes under control, disease monitoring and assessment of disease activity may occur less often, particularly in patients with sustained low disease activity or remission.

Now, structural changes, functional impairment, and comorbidity should be considered when making additional clinical decisions in addition to assessing composite measures of disease activity. But at the present time, our validated metrics of disease activity do not include structural changes; yet those should be considered in parallel with the objective metric.

And just to wind up the paradigm of treat-to-target, I do have to remind you that until the desired treatment target is reached, we should be adjusting our drug therapy at least every 3 months. So, more often early in the disease process, at least every 3 months until we get the patient into our goal of low disease activity or remission, and then, perhaps, less frequently once they are there.

Dr. Caudle:

Are there promising agents that have recently been approved or are in development for this patient and others like her?

Dr. Gibofsky:

We are on the cusp of seeing several new agents available and introduced into our clinical practices. Agents such as different JAK inhibitors, like baricitinib, should reach us shortly. Different IL-6 inhibitors should reach us shortly. And those are the 2 classes of emerging agents that appear to be the most evolved and nearly ready for primetime for use in this and other patients like this patient.

Dr. Caudle:

Dr. Gibofsky, are there any final points that you wish to make?

Dr. Gibofsky:

I think I would leave our audience with the notion that while we've been talking about paradigms and we've been talking about a guideline, and we've been talking about the establishment of algorithms for care, the treatment of rheumatoid arthritis must be individualized. It is not one-size-fits-all. We can have 2 patients in our waiting room on the same therapy. One is swearing by it, and one is swearing at it, so we need to have choices and individualization of therapies that we're using.

I would also like to stress the importance of doing disease activity metrics, particularly the CDAI, which I find to be the easiest to use, in every patient at every visit. But more important than doing the metric, is linking the results of the metric to your therapeutic decisions. Don't just do a CDAI. Evaluate the results of the CDAI and determine whether or not the therapy needs to be adjusted based on whether or not the CDAI is moving in the right direction. And if you don't want to use a CDAI and you want to use one of the others, that's fine. So long as you're using a metric on every patient at every visit, and using the results of that metric to guide your therapy. The outcome ought to be good for that patient as well as for every patient that you're treating.

Dr. Caudle:

Well, with that, I would like to thank my guest, Dr. Allan Gibofsky, for speaking with me and our ReachMD audience.

Narrator:

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