Adding Tools to the Toolbox: New and Emerging Treatments for Psoriatic Arthritis

CMEO Podcast Transcript

Allan Gibofsky:

Hello and welcome. On behalf of CME Outfitters, I'd like to welcome and thank you for joining us for the second in a series of three CMEO cast podcast titled *Adding Tools to the Toolbox: New and Emerging Treatments for Psoriatic Arthritis*. This is supported by an educational grant from Janssen Biotech, Inc, administered by Janssen Scientific Affairs, LLC. I'm Alan Gibofsky, professor of medicine at Weill Cornell Medicine and attending rheumatologist and co-director of the Clinic for Inflammatory Arthritis at the Hospital for Special Surgery in New York, New York. I'm joined today by my dermatology colleague, Dr. April Armstrong. April is professor of dermatology and Associate Dean of Clinical Research at the Keck School of Medicine, University of Southern California, where she's also Director of Clinical Research Support for The Southern California Clinical and Translational Science Institute and vice chair and director of Clinical Trials and Outcomes Research, and director of the psoriasis program in the department of dermatology at the Keck School of Medicine, part of the University of Southern California in Los Angeles, California. Welcome. April

April Armstrong:

Thank you, Allan. It's a pleasure to be here.

Allan Gibofsky:

For our listeners, today's activity is eligible for American Board of Internal Medicine Maintenance of Certification credit, and also as a CME for MIPS improvement activity with the CMS. You can obtain CME Maintenance of Certification points by completing your post-test and evaluation at the conclusion of the activity. Be sure to fill in your ABIM ID number and date of birth on the evaluation so it can be submitted by CMEO to the ABIM. Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation. In approximately three months, you will receive a follow-up survey from CMEO and CMEO we'll then send you confirmation of your participation to submit to CMS attesting to your completion of a CME that you can submit for MIPS Improvement activity credit. Our learning objective for this podcast is to apply key clinical efficacy and safety data for novel and emerging agents to treatment decisions in patients with psoriatic arthritis. April, let's start off with the principles of treatment for psoriatic arthritis. Indeed, the principles of treatment for any disease that impacts the musculoskeletal system.

April Armstrong:

Absolutely. A few principles of treatment I see my rheumatology colleagues as well my dermatology colleagues really live by our number one, obviously to reduce pain in our patient's joints. Number two is think of ways in which we can really improve their quality of life. It's very important to prevent as much as possible the structural damage and its complications because these structural damages, when progressive, can really lead to irreversible consequences and damage. In addition to that, it's important to note that oftentimes management by a multidisciplinary team can be very helpful and we want to engage our patients as stakeholders in our treatment decision-making process. Then finally, it's important to identify comorbidities as they can impact our treatment choice.

April Armstrong:

Now, when we look specifically at the multiple different factors that can influence our treatment decision, let's take a look at this funnel. As you can see, on the left hand side of the funnel are what clinicians, what we bring to the table, and they are, for example, our clinical experience, our interpretation and knowledge of the guidelines by the professional societies, and our knowledge of the evidence, the new literature that is constantly updated. Then on the right side of the slide, what we see are these patient factors that are super important in terms of treatment decision process, and that is assessment of patient's disease severity, their comorbidities, discussion with them regarding their side effect concerns. Not only their side effect concerns, but the likelihood of a patient who may experience certain side effects. Then finally, we want to take a patient preferences into consideration as well. As you can see, all these different multiple factors can play an important role in terms of the ultimate treatment decision.

Now let's talk about the various therapeutic classes that we have with regards to treating PSA. First, you're starting with non-pharmacological therapies, and these can include physical and occupational therapy, recommending our patients to stop smoking, weight loss and exercise. These can be very helpful in terms of adjunctive therapies that can help reduce the disease burden.

Now, there are also symptomatic treatments and primarily treatments that are directed at joint pain. Those can include non-steroidal anti-inflammatory drugs as well as local glucocorticoid steroid injections. Now going on to talk about small molecules and DMARDs the pharmacological therapies in the class of oral small molecules include methotrexate, sulfasalazine, cyclosporine, leflunomide, and apremilast. Not all of them are FDA approved. In fact, only apremilast is FDA approved for PSA at this time. Then we're going to talk about our classes of biologics and they include TNF inhibitors, as you can here. Examples being etanercept, infliximab, adalimumab, golimumab, and certolizumab. We have our then one in class that's IL-12,23 inhibitor, ustekinumab, also FDA approved for PSA. Then we also have IL-17 inhibitors and in the US, FDA approved therapies include a secukinumab and ixekizumab. Both bind to and antagonize IL-17A. Then we also have antibodies against CTLA-4, and that is abatacept.

Continuing on that, a newer class of medications in the treatment against PSA includes JAK inhibitors and [inaudible 00:06:38] inhibitors. Those are either approved or in late stage development, and they include tofacitinib, upadacitinib, deucravacitinib, and then finally we have our IL-23 inhibitors, such as guselkumab, risankizumab and tildrakizumab. Some of them are being studied for PSA and other such as guselkumab is approved for PSC. As you can see, we really have this large toolbox of different medications to choose from for our PSA management.

Allan Gibofsky:

Yeah. It's interesting to me, as a rheumatologist, that what we're seeing is that many of these drugs are being studied first in psoriasis and then because patients with psoriasis have inflammatory joint disease, the studies are then being done for psoriatic arthritis. We're often seeing the approval in psoriasis first, and then the carry over into psoriatic arthritis. That's not a uniform observation because there are certain agents that, as you know, are approved in psoriatic arthritis but not psoriasis, but it seems to be that those agents are first studied in psoriasis and then move over into psoriatic arthritis. Now April, in 2018, the American College of Rheumatology and the National Psoriasis Foundation got together and issued a guideline for the treatment of psoriatic arthritis, because it is both a dermatologic and a rheumatologic disorder. I know you were involved with this process, so can you shed some light on it for our listeners and viewers?

April Armstrong:

Yes. I think this is a process where it's really a perfect example of how two specialties can work together for the good of our patients, and also evaluating data so that new agents and new targets and new treatments can really be synthesized in terms of guideline formation. As you said, Allan, it's a collaboration between rheumatologists and dermatologists and through ACR and the National Psoriasis Foundation. The goal of this is primarily to really develop guidelines that can reduce oftentimes the large variation in care that we see in the real world. These guidelines are helpful because it helps to synthesize evidence-based medicine up to that point and then put them into guidance where the clinicians can look at and really think about how to apply them in the individualized way to their patients.

Now, Allan, one thing is that in order to understand efficacy data well we oftentimes need to understand the measures that help us really inform these results. One of the key measures, as you can see, that are used that we talk about all the time is ACR20, ACR50, ACR70; just this ACR scoring measure. Can you talk to me a little bit about how this measure was formed most importantly, and what are the domains in this measure so that as a dermatologist and primary care physicians and other non-rheumatologists, we can have a good appreciation of what ACR measures?

Allan Gibofsky:

Well, the ACR responder index was established to include a number of domains; a visual analog scale of pain, a patient global assessment, where the patient describes and determines their own assessment of their progress, a physician global assessment, the health assessment questionnaire, and finally, an objective metric of inflammation, either the sed rate or the CRP. These are all added up, and one looks for either an ACR20, which is a 20% improvement in the number of tender and swollen joints, an ACR50, a 50% improvement in the number of tender and swollen joints, or an ACR70, which is a 70% improvement in the number of tender and swollen joints. The domains are the same. We're just looking at a different quantification of the measure of difference.

The other important thing is that you're looking at the measurement as a percent improvement. If someone starts off with 10 tender and swollen joints and gets down to eight tender and swollen joints, they have an ACR20. If someone starts out with 20 tender and swollen joints and gets down to 16 tender and swollen joints, they still have active disease, more active than the first patient, but they also have an ACR20. It's the percentage of improvement. Now, we can put all of the data for all the agents you've mentioned on a slide side by side, but this is more for illustration and not for direct comparison. There've been very, very few head-to-head studies done, particularly in psoriatic arthritis. I also need to point out that the ACR responder index was initially done in rheumatoid arthritis and only then validate psoriatic arthritis, as opposed to another metric, which I'll get to in a minute.

What you see in this slide, in this illustrative slide of comparative efficacy versus placebo, not comparative efficacy versus each other, is that all of the agents you've mentioned, whether it is the oral agents, the JAK inhibitors, the class of TNF inhibitors, the IL-12,23, the IL-17, the CTLA-4 IG, or the IL-23 inhibitor that's been approved, have shown significant improvement in the ACR20 as compared to placebo. That's the only point of this slide. They all work, but we can't say from this slide which one works better.

Allan Gibofsky:

Now, I mentioned that the ACR responder index was defined in rheumatoid arthritis and then validated in psoriatic arthritis. In contrast, there is a very nice metric called the MDA or minimal disease activity criteria, which was looked at specifically for psoriatic arthritis by my good friend Laura Coats and others, where they've looked at tender joint count, swollen joint count, the skin areas measured by the PASI or the body surface area, patient pain, patient global activity, both of those on a visual analog scale, the health assessment questionnaire, and finally tender symphyseal areas. A point count was assigned to each of those. If the patient had five of those seven domains, then they were thought to have a MDA, which was quantitated based on the number of points assigned.

Now April, the bar graph that I went over, looked at a lot of different types of agents, but an agent that has come into particular interest as members of a class and also on its own, or the agent representing the class of IL 23s, namely guselkumab. Take us through the data on this newest FDA agent, guselkumab.

April Armstrong:

Absolutely. Allan, as you know, Discover-1 is a trial evaluating guselkumab in patients with active psoriatic arthritis who are biologic naive or had previously received TNF alpha inhibitor treatment. What was found was that ACR20 at week 24 was achieved by significantly greater proportions of patients who are in the guselkumab every four week group. In fact, that's nearly 60%. In those who were randomized to guselkumab every eight week group, 52% of them achieved ACR20. This is compared to 22% in the placebo group. What this amounts to is really a difference between the placebo group and the every eight week guselkumab group; a difference of 30% difference in terms of achievement of ACR20. I highlight the every eight week group because that is the FDA approved dosing for guselkumab in PSA, which is the same as the FDA approved dosing that was used in psoriasis for its maintenance therapy.

Now, let's take a look at other efficacy end points. Compared to the placebo, both guselkumab every eight weeks and every four weeks group were also superior to placebo in terms of achievement of excellent efficacy in the skin, as well as a level of functioning as measured by [inaudible 00:15:48] and SF-36. Now, if we take a look at the data here, dactylitis and enthesitis, we will understand a little bit more about the effects of guselkumab on those two aspects. Among patients who had dactylitis or enthesitis at baseline, regardless of whether the patient has had prior TNF treatment, nearly 60% of patients on guselkumab every eight week achieved complete resolution of dactylitis, and 50% of them achieve complete resolution of enthesitis going on to look at a bit long-term data, now we're going to take a look at one year data with guselkumab in psoriatic arthritis. What we see here on the graph is a longterm efficacy of guselkumab on ACR20 over one year.

In these biologic naive patients with PSA, with the most stringent and conservative analysis method of non-responder imputation for this one-year data, what was found was that the proportion of patients on guselkumab every eight weeks achieved ACR20. That proportion was 74% at one year. Now this is important because this data shows that the ACR response, ACR20 response, after 24 weeks, which was a primary endpoint actually continued to improve through one year. This was used again... this was calculated with the most stringent method of understanding the efficacy, long-term efficacy. It's very important when we talk about efficacy we also think about adverse events, the safety profile. When we look at the guselkumab data, what was founded that few AEs resulted in study drug discontinuation, and there were minimal elevations in liver enzymes in the Gus or the placebo group. There were no serious infections, no IBD and no malignancy signal. Now, Allan, now that we reviewed a bit about guselkumab data, can you share the data for two of the emerging IL-23s?

Allan Gibofsky:

Well, sure. Let's begin with tildrakizumab, which is being studied in active psoriatic arthritis. I think you can appreciate that at the doses studied and at the intervals that were used, tildrakizumab did better than placebo in this 24 week trial. The most frequent treatment emergent adverse events through week 24, which was the primary endpoint of the trial, were nasal pharyngitis and diarrhea. There were no reports of candidiasis, inflammatory bowel disease, no major adverse cardiovascular events or malignancy, no patients discontinued treatment due to treatment emergent adverse events, which is important for a tolerability of the drug. No deaths were reported. Serious treatment emergent adverse events occurred in 2.2% of patients treated with tildrakizumab combined versus 2.5% of patients treated with placebo.

The second agent is risankizumab, also looked at an active psoriatic arthritis. This was another double-blind parallel design dose ranging phase two trial, which went out to 16 weeks. You can appreciate the significant improvement in psoriatic arthritis ACR20 and the patients who were getting risankizumab versus placebo. Here the most frequent treatment emergent adverse events through week 16 were infection pooled arms of 35.6% versus 28.6%. The most reported adverse event were upper respiratory tract infections, but there were no reports of tuberculosis. Adverse cardiac events only occurred in one of 143 patients, malignancy in one of 143 patients, patient discontinuation due to adverse events was 2.8% versus 4.8%. No treatment related deaths were reported and serious treatment emergent adverse events occurred in 2.8% of patients treated with risankizumab versus no patients in the group treated with placebo. This is a phase two study. More to come.

Finally, just to round things out, let's look at upadacitinib, which was also looked at in psoriatic arthritis. This is not an IL-23. This is a JAK inhibitor. Here you can appreciate for upadacitinib that the percentage of patients achieving an ACR20, an ACR50 or an ACR70 was higher in the group taking upadacitinib, whether it's 15 milligrams a day or 30 milligrams a day or versus placebo. The primary endpoint of the study was of course the ACR20 at week 12 for the population studied versus placebo. You can appreciate the significance of upadacitinib at both doses versus placebo at that point in time.

I always like to tell our colleagues that there's no such thing as a free lunch. Every drug that we use needs to be factored into the construct of the risk benefit relationship. To be equally fair to upadacitinib as to the other agents we've discussed, let me briefly go over the adverse events seen in the upadacitinib psoriatic arthritis study. There you can see that there was a higher incidence of adverse events, serious adverse events, adverse events leading to discontinuation, serious infection, herpes zoster, panic disorder, anemia, non-melanoma skin cancer and CPK elevation at the 30 milligram dose than the 15 milligram dose, but AEs in the 15 milligram dose versus the placebo were pretty much the same. Serious AEs were higher in the 15 milligram upadacitinib group than the placebo group, AEs leading to discontinuation slightly higher, herpes slightly higher, anemia slightly higher, but nothing else of major significance in comparing upadacitinib at 15 milligrams versus placebo.

April Armstrong:

Great. Well, thank you, Allan, for that wonderful review of the new IL-23 inhibitors and their efficacy and safety for treating PSA, as well as the data for upadacitinib. Now in a podcast when we talked about axial manifestations of psoriatic arthritis, can you talk a little bit about how axial involvement in PSA-A may impact our treatment choice?

Allan Gibofsky:

Well, it may. As I indicated in our first podcast, there may be differences but also similarities in axial psoriatic arthritis phenotype versus the idiopathic axial spondyloarthritis. People have been trying to tease this out in terms of response to therapy as well. This is a study of tofacitinib in patients with psoriatic arthritis of the axial variety. It is not approved for the treatment of axial spondyloarthritis, although it is approved for the treatment of psoriatic arthritis of all phenotypes. Here you see that when a very different measure, ankylosing spondylitis ASAS score was used to look at improvement in these patients treated with tofacitinib. You find significantly higher ASAS 20s and ASAS 40s at 20% and the 40% improvement in these patients treated with tofacitinib than with placebo. There may be differences in how patients respond as a function of their phenotype, as well as a function of the agent that we give them.

Here is a study looking at guselkumab in patients with active psoriatic arthritis, but with imaging confirmed sacroiliitis. Again, you can appreciate that when looking at the ASDAS marker, the Ankylosing Spondylitis Disease Assessment Score in this population of patients, you can appreciate that guselkumab did better than placebo, and the patients who were switched from placebo to guselkumab achieved good responses as well. Here we're looking at the number of patients who achieved a major improvement versus a clinically important improvement versus those who actually became inactive with their disease.

At this point, April, I think we can summarize and bring our SMART goals into the picture. What we've tried to do is apply the principles of psoriatic arthritis treatment to optimize outcomes in our patients. We've acknowledged, as you did in the opening slides, that many factors contribute to the important decision-making and more important, as we discussed back to back, the toolbox for psoriatic arthritis is expanding and we need to be able to evaluate and apply clinical efficacy and safety data to our treatment decisions when faced with a patient with psoriatic arthritis. That may include knowledge of their phenotype, knowledge of their comorbidities, knowledge of their disease activities, knowledge of their preference, and so on.

This podcast is one of a three part series. We hope that you'll take advantage of all of the episodes in the series and these activities and a wide variety of other activities and resources on inflammatory disorders for both healthcare providers and patients are available on the CME Outfitters psoriatic arthritis evaluation education Hub. These activities, and a wide variety of activities and resources on inflammatory disorders for both healthcare providers and patients, are available on the CME Outfitters Psoriatic Arthritis Education Hub.

To collect credit for today's activity, please click on the link to complete the post-test and evaluation online. Be sure to fill in your ABIM ID number and your date of birth on the evaluation so we can submit the credit to the ABIM, and participants can print their certificate or statement of credit immediately. Thank you, April, and to the listening and viewing audience for joining us today as today, as today the treatment landscape is growing and will continue to grow. It's a very exciting time to be a rheumatologist and a dermatologist treating these patients, and hopefully this gives us the ability to personalize treatment for our patients based on their needs and their preferences. Thank you.