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Raising the Bar in PsA: Integrating Structural Assessment to Improve Long-Term Outcomes

Announcer:
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[CHAPTER 1]

Dr. Schwartzman:
Welcome to our discussion today on integrating the structural assessment of psoriatic arthritis, or PsA, into clinical practice. In this first chapter, we will discuss the role of imaging and assessment of structural change in incorporating these factors into clinical trials.

This is CME on ReachMD, and I'm Dr. Sergio Schwartzman.

Dr. Mease:
And I'm Dr. Philip Meese.

Dr. Armstrong:
And I'm Dr. April Armstrong.

Dr. Schwartzman:
Let's dive right in. Dr. Mease, can you tell us about some of the clinical trials that demonstrated the importance of conventional radiographic analysis when assessing structural damage in patients with PsA?

Dr. Mease:
Thank you, Sergio. Yes, assessment of structural damage progression has been an important part of psoriatic arthritis trials. Starting with the first trials with etanercept in PsA conducted around the year 2000, 2001 and then infliximab and the other anti-TNF medications. We borrowed a chapter from assessment of structural damage progression in rheumatoid arthritis using the Sharp/van der Heijde method of analysis, in which we look at both erosions, bone damage, and joint space narrowing, cartilage damage in the structural damage progression assessment.

What was shown was that the anti-TNF medicines all inhibited structural damage progression. And furthermore, it has been shown that even in patients who don't have a complete clinical response, may have inhibition of structural damage progression, implying that the TNF inhibitors have the capability of inhibiting structural damage even when there is smoldering clinical disease activity.

We then had a similar efficacy in preventing structural damage shown with the interleukin-17 inhibitor medications, and indeed with one of them, ixekizumab, it was shown as early as week 16 to separate from placebo.

There have been assessments in other drug classes as well. For example, in the studies with ustekinumab, there was assessment of radiographic progression. However, the results were mixed, and so there is not an indication for ability to inhibit structural damage

progression with this medication, nor with the T cell modulator abatacept, nor with the JAK1 inhibitor, JAK1 and 3 inhibitor, tofacitinib. X-ray changes were assessed in the tofacitinib trials, but the trials were not designed to specifically look at getting the indication of structural damage inhibition.

The JAK inhibitor upadacitinib, which has recently been approved for psoriatic arthritis, studied structural damage progression in SELECT-PsA-1, which were patients who had not yet been exposed to biologic treatment. And in that particular study, there was separation between the placebo arm and the upadacitinib treatment arms favoring inhibition of structural damage progression with upadacitinib.

Most recently we've seen data with the IL-23 inhibitors. And what was shown with the DISCOVER-2 trial is that with guselkumab, when given every 4 weeks, was able to statistically separate from placebo. But in the every-8-week dose, which is the approved dose, it was not.

And then finally with apremilast, which has also been approved for treatment of psoriatic arthritis, they did not assess structural damage progression in their trials, so we don't have a sense of that. And similar to our older conventional synthetic DMARDs [disease-modifying antirheumatic drugs] in this regard.

So we have – by and large, many of the trials have assessed structural damage progression using conventional radiography of X-rays of the hands and feet and demonstrating inhibition of erosions and joint space narrowing.

We have prepared a short video to help you better visualize the PsA pathology seen on radiographs of patients with PsA.

Announcer:
Radiographic features of psoriatic arthritis, or PsA, include: erosion; ankylosis or fused bone; joint space narrowing; flexion deformities; arthritis mutilans, in which there is joint and bone destruction; and the “pencil-in-cup” deformity. Ankylosis and flexion deformities are shown here. Note the bone fusion at the joints and the complete deformity of the hand indicative of flexion deformity. Joint space narrowing, erosion, and pencil-in-cup deformity are shown here. These images depict arthritis mutilans of the hands and of the feet. Finally, these images demonstrate asymmetric syndesmophytes, often indicative of PsA of the spine, and fusion of the sacroiliac joint. The radiographic images shown typically represent long-standing PsA disease. Nonetheless, many of these issues may be apparent at baseline due to the long lead times before diagnosis.

Dr. Mease:
We hope that the video has helped you visualize the types of structural changes in PsA that we're discussing.

I'd like to also touch on the point that there are advanced imaging techniques that have been used as well, in addition to conventional radiography. These include ultrasound, which is typically done in the exam room with the patient and gives us a good sense of changes that may occur in the small joints of the hands and feet and some of the other peripheral joints as well. But it's not good at capturing information about the spine. We can not only see changes in what we call grayscale or amount of synovitis, but we can also see through power Doppler the degree of inflammation by assessing vascularity.

MRI is most helpful in assessing the spine. This gives us granular information about inflammation in the bony structures of the spine, as well as ability to show us structural changes as can the advanced imaging technique of CT.

Speaking of the spine, we generally have not in phase 3 clinical trials in PsA addressed the spine from an imaging point of view. Oftentimes, that's done in trials of axial spondyloarthritis, and we use that as a surrogate for how the spine might be in PsA. The only trial to assess axial PsA specifically is with the one of the IL-17 inhibitors, secukinumab, which showed a significant improvement in patients treated with this medication. And there is a study that is just getting underway with an IL-23 inhibitor, guselkumab, known as the STAR study, in which there will be a specific look at axial PsA.

Dr. Armstrong:
Those are great points, Philip. From my perspective, in clinical trials, the radiographic progression scores, such as the Sharp/van der Heijde score, are typically not normally distributed. And what we see is that only a small fraction of treated patients show progression, with the majority showing no progression at all, for example, for some of the IL-17 inhibitors. And I think those are important points to recognize. And the implication of that is that small outliers can have a big impact on the data that we see.

And also, the scale itself may be prone to some measurement errors. Oftentimes, it requires at least 2 trained readers, for example, blinding to the sequence, etc.

And I oftentimes think about the powering of these studies, of these clinical trials, because of some of the difficulties in terms of potentially detecting the differences. Sometimes it can be difficult to power the study for progression, so oftentimes we will see the use

of enrichment criteria such as a CRP [C-reactive protein] or baseline erosion, for example, being incorporated into the eligibility criteria.

Dr. Schwartzman:
In terms of clinical trials, in addition to those concerns expressed by Dr. Armstrong, there are other issues. At what point do you actually take a reading? Is it at 16 weeks? Is it at 24 weeks? Is it at 1 year? Is it at 2 years? The longer the follow-up, obviously, the greater the strength of the data. But it's impossible to carry these trials on for that period of time.

The other question is also whether or not clinical trial data with a very unique group of patients with very active disease actually reflect real-world changes. And if they do, what is the meaning of a Sharp score change of less than 3 from a clinical perspective?

In Chapter 2, we will evaluate the different therapies that are available as well as their impact on the progression of PsA as seen on imaging. Stay tuned.

[CHAPTER 2]

Dr. Schwartzman:
Welcome back. In the first chapter, we discussed [integrating] clinical trial data and structural assessment of psoriatic arthritis into practice. In Chapter 2, we will be comparing the impact of different therapeutic approaches as conventional radiographic progression in PsA.

This is CME on ReachMD, and I'm Dr. Sergio Schwartzman.

Dr. Mease:
And I'm Dr. Philip Mease.

Dr. Armstrong:
And I'm Dr. April Armstrong.

Dr. Schwartzman:
Dr. Armstrong, can you tell us about the various therapeutic approaches to PsA and which have been shown to impact conventional radiographic progression? Also, are there current guidelines and best practices when leveraging imaging techniques to evaluate the progression of structural damage?

Dr. Armstrong:
When we're thinking about the various treatment approaches to PsA, typically for the systemic therapies, we consider, for example, the biologics which include the TNF inhibitors. And in that class, we have adalimumab, certolizumab, etanercept, golimumab, and infliximab. Among those that I mentioned, golimumab is the only one that is only approved for PsA. The rest are approved for both psoriasis as well as PsA.

And we also have our IL-12/23 inhibitor, ustekinumab. Our IL-17 inhibitors include ixekizumab and secukinumab for treatment approaches to PsA. In dermatology, we also use brodalumab as well, which is not approved in the US for PsA but is approved elsewhere for the treatment of PsA. And when we're thinking about our IL-23 inhibitors, we have guselkumab, which is approved for PsA, risankizumab and tildrakizumab are our other IL-23 inhibitors not approved for PsA yet, but are used pretty widely in dermatology for the treatment of psoriasis.

We also have our CTLA4 immunoglobulin abatacept, used for PsA. And then when we're looking at targeted therapies, we have our JAK inhibitors, such as tofacitinib upadacitinib, among others. And also we have PD-4 inhibitors such as apremilast.

Of course, we cannot forget about our traditional DMARDs, such as methotrexate, in our treatment approaches.

With regards to the guidelines question, there's currently no guidelines governing the use of treatments that are specifically for inhibition of radiographic progression. But I would refer the audience to the GRAPPA guidelines, which are looking at the overall treatment approach for peripheral arthritis for psoriatic arthritis. And it's nicely divided into populations for DMARD naïve versus DMARD inadequate responders and biologic inadequate responders.

With regards to which therapies are effective in terms of inhibiting radiographic progression, there are several things to be aware of. It is unclear to date, at least in my opinion, if any of the radiographic progression inhibition abilities of methotrexate, and methotrexate may have, therefore, little influence on the progression.

There are the studies, as both Philip and Sergio have mentioned, on radiographic progression in PsA for TNF inhibitors, for IL-17 inhibitors, and also more recently we are also discussing the emerging data in the area of JAK inhibitors.

For example, for SPIRIT-P1, which is the study for ixekizumab looking at radiographic progression after 52 weeks of ixekizumab in patients with PsA, what we know is that 82% of those patients do not have progression of joint damage at 1 year. And looking at the 3-year data, which I know both of you are authors on this study, we also saw that inhibition of radiographic progression also persisted to about week 156 in about 61% of patients on the q2 dose and 71% on the q4 dose of ixekizumab.

And lastly, I just wanted to mention guselkumab, which is an IL-23 inhibitor. And we have learned, for example, from their pivotal studies in psoriatic arthritis, that the q4-week arm of guselkumab at week 24 have shown a statistically significant difference with regards to the placebo at week 24 in terms of inhibition of radiographic damage. There were no statistical differences with a q8-week dosing; however, I do think that further studies are necessary to tease that out a little bit.

Dr. Mease:
Even though the FDA does not require that a drug show ability to inhibit structural damage progression in order to be approved for PsA, increasingly both clinicians as well as patients are very interested in this outcome. I think in the future, we'll see that most drugs that are ultimately approved, have as part of their database the data on not only peripheral joint changes but also in the spine as well.

Dr. Schwartzman:
Okay, thank you. In Chapter 3, we will be discussing how to incorporate the routine structural evaluation of PsA into clinical practice. Stay tuned.

[CHAPTER 3]

Welcome back. In Chapter 2, we discussed the impact of different therapeutic approaches and guidelines with regards to conventional radiographic progression in psoriatic arthritis. In Chapter 3, we are addressing how to implement routine structural evaluation for PsA into clinical practice.

This is CME on ReachMD, and I'm Dr. Sergio Schwartzman.

Dr. Mease:
And I'm Dr. Philip Meese.

Dr. Armstrong:
And I'm Dr. April Armstrong.

Dr. Schwartzman:
Dr. Mease, let's focus on implementing what we have just learned. What are your thoughts on how we can incorporate routine structural evaluation for PsA into clinical practice?

Dr. Mease:
Thank you, Sergio. What I'd like to do is just give a little bit of history about the assessment methods and then how we incorporate that into practice. In our first trials with the biologic agent etanercept, the person that was involved with the radiographic aspect of that trial was Désirée van der Heijde, and she did a modification of the original rheumatoid arthritis Sharp's radiographic score and modified it for psoriatic arthritis.

In that first trial, we not only looked at erosions and joint space narrowing, but we tried to look at the issue of osteoproliferation, which can also be seen in psoriatic arthritis. We found that the erosion and joint space narrowing aspect worked well, meaning we could discriminate between placebo and treatment arms. But the proliferative changes in bone were so glacial that those were ultimately dropped. And so one of the other assessment methods known as the Ratingen score from Germany, which did include osteoproliferation, but was otherwise so complex that it was never used in clinical trials.

There's also something called the modified Steinbrocker which is used in, for example, in Dafna Gladman's long-term registry in Toronto. But by and large, the modified Sharp/van der Heijde scoring system for psoriatic arthritis is what is used.

Now, these [radiographic scorng systems] are great for clinical trials where you can really spend the time and effort to do this. But in clinical practice, this is not really practical. And so the way we typically do it in practice is when a patient first comes in with this, we get what we call baseline films of hands and feet, look to see if there are any erosions or joint space narrowing. And then, over time, we may periodically get updated films of the hands and feet, let's say at a 2- or 3-year interval, in particular in patients who are showing ongoing active disease despite our treatment efforts. These are the ones that we're most concerned about. If a patient is doing very well clinically, we may not necessarily measure this as frequently.

The other and very sensitive way to look for this kind of damage progression is to look using ultrasound in the clinic. And that's

something that is increasingly used in rheumatology clinical practice. It's more younger rheumatologists are trained in ultrasound technique.

Dr. Armstrong:
In terms of how to implement routine structural evaluations for PsA into a dermatologist's practice, I think this will definitely be one of the key challenges. I think that we do look towards our rheumatology colleagues for their guidance in this regard.

I really like what Philip said about the newer models of imaging such as more rheumatologists incorporating ultrasound into their clinical practice. I think that for dermatologists, this may be something quite a bit a ways down the road for a number of different reasons. But I think at the current time, what will be very helpful for dermatologists to understand is recommendations for the frequency and the type of optimal imaging, be it X-rays or in-office ultrasound, in order to detect the clinically relevant change.

And also, I will say that reporting, when we look at the radiologist's report, for example, as many dermatologists, we don't do a primary read of the X-rays, for example. I think having some kind of structured reporting, no pun intended, that can be very helpful. I see in my clinical practice a bit of varied reporting depending on who is reading the images. And also more detailed description on changes from last evaluation can be very helpful to inform us when we are thinking about the different therapies.

Dr. Schwartzman:
So in this chapter, Phillip started with a historical perspective on the different scoring methodologies and how they have become popular in clinical trials. I'm going to add one other important, I think, historical note. And that is that if we look back 3 to 4 decades ago, rheumatologists were very consistent about doing X-rays, particularly on the hands, in patients with rheumatoid arthritis, and not only at baseline but every year thereafter. And that was taught to all of the fellows. Many of us initially grew up with that. Unfortunately, at that time, we did not have therapies that could modify that progression. And that practice has completely fallen out of favor in rheumatoid arthritis.

So I think one of the questions that's in front of us is whether that type of an approach, now with new therapies that can impact on that, should be adopted. And I suspect that that will not happen because it's fairly time intensive. And as April mentioned, there's an issue about who reads the X-rays. In fact, even for some of these scoring methods that have been described, even in academic centers there are very few people who could do a modified Sharp score. So I think that ultimately that responsibility will fall on the rheumatologists if we are to move forward with that type of an approach.

Dr. Mease and Dr. Armstrong, any final thoughts on this chapter?

Dr. Mease:
I think that efforts to assess structural damage progression are very important in clinical practice. I think it's something that patients are interested in and want us to do.

Dr. Armstrong:
I couldn't agree more. And also we have data showing that improvement in structural damage is intimately associated with improvement in function and patient's overall quality of life. So I think examining this issue is very important as we approach patients with psoriatic diseases with both skin as well as joint disease and thinking about the patient in a comprehensive manner.

Dr. Schwartzman:
Thank you. In Chapter 4, we'll be discussing strategies to optimize PsA outcomes for our patients. Stay tuned.

[CHAPTER 4]

Dr. Schwartzman:
Welcome back. In Chapter 3, we discussed implementing structural evaluations for PSA into clinical practice. In Chapter 4, we're exploring strategies that minimize radiographic progression and maximize patient quality of life to optimize PsA outcomes for our patients.

This is CME on ReachMD, and I'm Dr. Sergio Schwartzman.

Dr. Mease:
And I'm Dr. Philip Meese.

DR. ARMSTRONG:
And I'm Dr. April Armstrong.

Dr. Schwartzman:

Dr. Armstrong, what are some strategies we can use to better optimize outcomes for our patients with PsA?

Dr. Armstrong:
I think we can consider several approaches. And I will be very interested in hearing both Philip and your perspective on this as well, Sergio. To me, first of all, once the diagnosis is confirmed and the accurate assessment is done, selection of a therapy that has proven efficacy in halting radiographic progression is very important.

And then, importantly, long-term monitoring in a regular frequency is also very important. And I will be interested in hearing if there's agreement on the frequency of monitoring. And many dermatologists will rely on the expertise of our rheumatology colleagues on understanding and translating data on inhibition of radiographic progression to clinical practice.

So rheum/derm collaborations will be key with regards to management of patients with a potential structural damage and in the PsA setting.

Dr. Mease:
I agree that it's important for clinicians to understand the data from clinical trials on structural damage progression so that they can optimally choose medications with a proven track record in this regard.

And furthermore one of the points that's important to make to patients is even if they have occasional flares of disease or some grumbling symptoms of pain or stiffness, that many of these medications have the ability to inhibit structural damage progression, regardless of these ongoing symptoms through separate mechanisms on bone in addition to their effect on inflammation.

Dr. Schwartzman:
Although we didn't go into too much detail about the individual therapies that are discussed, and there are clearly advantages and disadvantages to every single one of those proposed therapies for individual patients, the question about how much radiographic progression should drive the choice – or halting radiographic progression should drive the choice of a therapeutic agent remains open. And I think as we look forward in time, with more and more studies, particularly studies that are seen in dermatology much more so than rheumatology, head-to-head studies, that we will be better able to answer that question.

Dr. Armstrong and Dr. Mease, any final takeaways on this chapter?

Dr. Armstrong:
I completely agree about head-to-head studies. I think that's what's keenly needed in psoriatic arthritis. We have many of them in dermatology in psoriasis that have really guided our therapeutic choices. I think in the absence of head-to-head studies, the network of meta-analysis can be helpful when it's done with rigor.

And lastly, the collaboration between derm and rheum is really critical in this regard because oftentimes the patient may come to a dermatologist first. And our choice of therapy could make a big difference with regards to their joint – structural damage in their joints as well as other aspects such as enthesitis and dactylitis, which I know we didn't have so much time to talk about. Therefore, this key collaborative piece will be critical to patient outcomes.

Dr. Mease:
Taking off from the collaborative subject that April just referred to, many patients may have been in the office of a dermatologist for years with their psoriasis before they developed psoriatic arthritis. So they've got a certain trust that's been developed with the dermatology physician and staff. I think it's very important, when the patient develops PsA, for the dermatologist and rheumatologist to speak with each other, either on the phone or through the electronic medical record or ideally in a combined clinic so that there can be an incorporation of the goal of inhibition of structural damage progression into the treatment plan. And this is one area where I think rheumatologists can really contribute to the discussion between derm and rheum to optimize picking and monitoring drugs that can inhibit damage.

Dr. Schwartzman:
Thank you, both Phil and April, for joining me and for sharing all of your valuable insights.

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