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<https://reachmd.com/programs/cme/connecting-science-psoriatic-arthritis-patient-care/10918/>

Released: 10/17/2019

Valid until: 10/17/2020

Time needed to complete: 30 Minutes

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### Connecting Science to Psoriatic Arthritis Patient Care

Dr. Birnholz: Science is moving forward in understanding the key inflammatory pathways involved in psoriasis and psoriatic arthritis, leading to development of targeting, effective therapies for patients with these diseases. It is becoming more and more important for clinicians to understand what the available treatment options are, how to use them appropriately and how to discuss them with patients. This is CME on Reach MD and I am Dr. Matt Birnholz.

Joining me to help address the topic of targeted therapies for psoriatic arthritis, is Dr. Phillip Mease, who is Director of Rheumatology Research with Swedish Medical Center and Clinical Professor at the University of Washington School of Medicine, and Dr. Allan Gibofsky, Professor of Medicine at Weill Medical College at Cornell University. Dr. Mease and Dr. Gibofsky, thanks so much for being here today.

Dr. Mease: Thank you.

Dr. Gibofsky: Thanks, Matt, good to be with you.

Dr. Birnholz: Dr. Mease, to start, can you walk us through the inflammatory mechanisms and pathways operative in psoriatic arthritis and how understanding these pathways connects to therapeutic approaches for this disease?

Dr. Mease: In psoriatic arthritis, activity of the innate immune system is largely driving the path to the etiologic process as compared to rheumatoid arthritis, where there is more adaptive in the insistent function. The key cells involved include dendritic cells and other frontline immune cells that are present, not only in the skin and the gut, but also in other places in the body, where they normally serve as first line of defense against microbes and also in tissue repair. They just happen to be overly active in psoriasis and psoriatic arthritis. One of the phenomenon that we see in both of these conditions is activation of these pathways, wherein both TH1, as well as TH17 cells are activated and produce TNF, interferon gamma, but importantly interleukin 17, which is a key product of TH17 and other cells. For example, we know that there is a strong role for tissue micro injury and infectious antigens to stimulate the production of several cytokines, including interleukin-23, that in turn stimulates the activation of TH17 cells and other cells. What are some of these other cells? Neutrophils, mast cells, natural killer cells, and a group of cells that we call resident innate immune cells that are living in areas such as the enthesium where when there is micro injury, they are activated and turn on the production of interleukin-17. These observations help us understand why drugs which work in the IL-17 and IL-23 pathway, can be so significantly effected in both psoriasis and psoriatic arthritis. We also know, based on almost two decades of experience, that inhibition of TNF is very important and across many autoimmune diseases, including psoriasis and psoriatic arthritis, drugs which inhibit TNF can be very effective. So in addition to my comments about IL-17 inhibitor, we know that TNF inhibitor is very important as well.

Dr. Birnholz: That is a great overview Dr. Mease, thank you. And I also think that is a nice springboard for helping us understand the logical choice of therapies in psoriatic arthritis. So, with that said, what do we know about the comparative efficacy and safety of agents that are currently in use to treat patients with psoriatic arthritis?

Dr. Mease: The number of agents that are being approved for the treatment of PSA are growing and this is based on, not only the testing of drugs that have traditionally been used in the treatment of rheumatoid arthritis, such as the class of TNF inhibiting medications, but also newer ones that I was alluding to earlier such as the interleukin-17 inhibitors or the IL-12/23 inhibitor risankizumab. Now, we have a

number of observations that have been aggregated over the past two decades for TNF inhibitors that show their efficacy in both the skin disease, as well as all of the musculoskeletal aspects of psoriatic arthritis, including the arthritis component, enthesitis, dactylitis, but also spine disease of psoriatic arthritis. One of the newest trials to be conducted and presented was the so-called SEAM study, in which one of the older TNF inhibitors etanercept, was tested with monotherapy against methotrexate monotherapy and against the combination of etanercept and methotrexate. Now in rheumatoid arthritis, we have learned that it was important for the best efficacy of TNF inhibitors to add methotrexate both for clinical and radiographic outcomes, but in the SEAM study it turned out that the combination of methotrexate and TNF was not that important that both methotrexate, as well as TNF inhibitors, worked well as monotherapy. Etanercept certainly worked better than methotrexate, but methotrexate did pretty well in all of the musculoskeletal aspects as well as the skin aspects. So, on the one hand it gives us some confidence that methotrexate can work when we use that medication for psoriatic arthritis, but it also gives us confidence that the new ACR guidelines, which recommend a TNF inhibitor being used ahead of methotrexate, also makes sense, because the TNF inhibitors work very well and their safety is relatively equivalent to methotrexate. After the TNF inhibitors became available and widely used, the next agent to become approved was the IL-12/23 inhibitor, risankizumab. This showed efficacy in both the musculoskeletal domains, but also very effective in the skin domain of psoriatic arthritis and long lasting, up to three months of effectiveness. This drug has a relatively good safety record and so it is very popular with dermatologists as well as rheumatologists. Next, after this came the IL-17 inhibitors and this class of medications, as I mentioned before, was very specifically targeted to being effective in psoriasis and psoriatic arthritis. They were not quite as effective in rheumatoid arthritis and with greater specificity we also have possibly a slight advantage in terms of safety without as much broad immunosuppression. We have seen very good effects in arthritis, enthesitis, dactylitis spondylitis and very good effects in the skin and nail disease of psoriatic arthritis. We also have abatacept, a TC modulator, which has shown effectiveness in all domains of psoriatic arthritis and batacept has been used for quite a long time by rheumatologists for the treatment of rheumatoid arthritis and we know very well its relatively safety profile from that indication.

There are also some oral medications that have been approved including the PDE 4 inhibitor of apremilast, which has shown efficacy in arthritis, enthesitis, skin disease. It's a bit more modest in effect than what we have come to know with the biologic medications, but the safety profile of the drug is very good with virtually no serious infection rate, malignancy signal or other major problems, although the drug does have some tolerability issues in its initial phase of use, including nausea, diarrhea or headache in some patients, so we usually use a very low dose initially until we get to the standard dosage of the medications so the patients can tolerate the introduction of the medication better.

There is a new class of drugs for psoriatic arthritis which have been previously approved for rheumatoid arthritis known as the JAK inhibitors. The first one for approval in psoriatic arthritis is tofacitinib, which has shown efficacy again in all of the clinical domains of psoriatic arthritis as well as skin disease. One of the clear advantages of oral medications is their convenience. With tofacitinib there is a safety profile that we know well from rheumatoid arthritis and there is really no difference in safety in treatment of psoriatic arthritis. So in summary, we've got a smorgasbord of options in front of us and as we move along and depending on patient response to treatment, and we know that sometimes patients may lose efficacy after several years being on a drug, it is very helpful to have different medications, both within the same class, but also different classes of medication to try to gain our goal of low disease activity or remission.

Dr. Birnholz: And Dr. Mease, staying with you for a moment, I would like to get a better sense for how the most current professional society guidelines should be used in choosing therapy. And I am considering the recent ACR/NPF guidelines and maybe the recent EULAR psoriatic arthritis guidelines. Can you take us through those guidelines and give us some tips on how we should be using them to define therapy for patients?

Dr. Mease: I would like to start with the evaluation of the treatment guidelines in psoriatic arthritis, which go back about a decade and the first guidelines were produced on the one hand by the GRAPPA Organization, which stands for Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, which I am a member of, and also there were EULAR guidelines that were published. These guidelines were overall very similar, but there were some differences. For example, the EULAR guidelines recognize that there were many drugs that had efficacy and so they put them on an equal footing and allowed clinicians to make choices, depending upon the patient in front of them, what the patient's preferences were and so forth, and so giving more of a choice. Whereas the EULAR guidelines were a bit more linear at that time, starting people off on methotrexate and then after a while being able to move on to a TNF inhibitor and so on. Then, with the updated EULAR guidelines, they have become a little bit more graph like with more choices at the front end, so including TNF inhibitors and IL-17 inhibitors in similar footing, as well as use of methotrexate. Of course, with all of these guidelines there are overarching principles that emphasize the importance of the clinician and the patient working together to make decisions based on the individual patient preferences and also depending upon how the patient presented. Are they arthritis predominant, are they skin predominant, are they enthesitis predominant, are they spondylitis predominant, and then making choices

appropriately. The newest set of guidelines are the ACR/NPF guidelines. These are very interesting, in that they are the first guidelines to clearly suggest that a TNF inhibitor should be used before methotrexate and this is based on the clear evidence for efficacy as well as relative safety. Otherwise, there are many similarities to the EULAR and the GRAPPA guidelines, including further down the road use of IL-17 inhibitors, IL-12/23 inhibitors and so forth and giving specific recommendations, depending upon whether the patient has issues such as inflammatory bowel disease, or predominant skin disease and so forth. With all of these guidelines, it is a helpful guide for clinicians in helping them make choices between the increasing number of medications that we have, can achieve significant efficacy with relatively good safety.

Dr. Birnholz: Dr. Gibofsky, let me turn to you. What is your experience with using clinical practice guidelines in treating your patients with psoriatic arthritis?

Dr. Gibofsky: Well first Matt, let me compliment Phil on his excellent summary in response to your last question. But in answer to the one you just posed, I tend to lean more towards the GRAPPA guidelines. I think they have much more practical and real-world value. The GRAPPA guidelines don't just make recommendations based on clinical domains, they also ask us to think about the comorbidities that the patient may have and to me, that is a much better approach. The point of the guidelines that Dr. Mease outlined are certainly well stated and certainly appropriate as well, but I think though that we are seeing a significant rationale from moving away from methotrexate, particularly in certain phenotypes of the disease, especially enthesitis and the axial disease phenotypes.

Dr. Birnholz: For those just joining us, this is CME on Reach MD and I am Dr. Matt Birnholz. Today I am speaking with Drs. Phillip Mease and Allan Gibofsky about the treatment of psoriatic arthritis. So Dr. Gibofsky, given the pathologic mechanisms involved in this disease, which we have discussed, what factors play into the choice of agents for the treatment of psoriatic arthritis?

Dr. Gibofsky: So Matt, I think there is a six-equation calculus that a physician uses in approaching any patient with any clinical problem and this is used for choosing therapy for any agent in any disease. Sometimes the factors are solved directly, sometimes it's the back of the physician's mind, but all of these factors go into the selection of therapy and particularly in psoriatic arthritis. First, there is the question of efficacy. Does the drug work? Because if the drug doesn't work, there is really no sense in prescribing it. The second is safety. Does the drug have an acceptable safety profile because we never want a patient to be worse off when they are treated, then when they are untreated and we have seen already several agents that may have demonstrated efficacy, but which have several concerns because of the safety profile. Next is tolerability and this refers to agents that, while not specifically unsafe, they don't necessarily make the patient feel well and so the tolerability of an agent becomes particularly important, if not more so than its efficacy to safety ratio because even if a drug has a good efficacy to safety ratio, if the patient can't or won't tolerate it, it is not one that is going to result in a good outcome. The next factor is adherence and that is important. We want to use agents that are easy for the patient to remember to take in simplified schedules and whether we are talking about oral agents or injectable agents or infusible agents, we are concerned about issues related to the frequency of administration, which is a particular concern to many patients that we treated, especially those with psoriatic arthritis. Individual patient characteristics are the next factor and those are important as well because in the course of a day, we treat a spectrum of patients from those who may weigh 60 or 65 kilograms soaking wet, to those who may weigh 200 to 220 kilograms bone dry. Each of these individuals are individuals with different schedules and preferences of administration. And so we have to consider all of these factors in the choice of therapy, particularly with respect to psoriatic arthritis when things like the weight of the patient, the comorbidities of the patient become important in defining what agent to use as I outlined earlier. Finally, there is cost or more broadly expressed, perhaps access. As much as we may want to use a particular agent in a given patient based on our desire to use it and the patient's desire to take it, we often find that there are significant impediments put in front of us by the patient's payer. We find things like step edits or requirements that multiple agents of different classes be used first and all of these are the kinds of things that make it difficult in some instances to give the patient the most appropriate and personalized therapy. In psoriatic arthritis, we also have to consider that we are not just dealing with arthritis, although as rheumatologists, that is our primary focus, but we also have to be cognizant of the activity of the disease of the skin as well. Many patients tell us that their quality of life is impaired by the arthritis and other patients tell us that their quality of life is impaired more by their skin. So to the extent possible, we would like to choose agents that can give us efficacy in both, depending upon which one is of most importance to the patient. Now it turns out that the patter of arthritis may be important and whether or not there are extra or near articular manifestations such as enthesitis. The pattern of arthritis is such that it may not just be relevant in terms of peripheral manifestations and the number of peripheral joints involved, but whether the patient has axial disease, which may also be a particular clinical determinant of what we are going to select. Now, I alluded to the fact that in some of our patients the skin relief may be important, in others they may be seeking relief from their joint discomfort and others may be seeking a combination of the two with a different emphasis on both. And so the proper use of patient outcome measures that help us gauge the effectiveness of therapy in several of these domains becomes critical and particularly important in selecting an agent for the individualized treatment of a specific patient with psoriatic arthritis.

Dr. Birnholz: Dr. Mease, turning to you. What are your thoughts on this?

Dr. Mease: Allan, very eloquent and you highlight the complex matrix that gets our thinking processes going when we enter the room with the patient. One other thing just to mention and it is a metaphor that I often use with patients, is that the disease process is a bit like a symphony orchestra performance of a complex piece, where at times the whole orchestra is playing, but at other times there may just be the violin section or the wind section and PsA is a bit like this, where a person may have everything going on at once, arthritis, enthesitis, spondylitis indexes or there may be times when there is predominant skin activity, predominant spine activity, predominant enthesitis, so we have to be attuned to this, not only in our assessment of the patient when they are in the clinic, but also in guiding our treatment choices.

Dr. Birnholz: Dr. Gibofsky, let's shift gears for a moment and talk about shared decision making. Now what is meant by the term in your clinical arena and how do you use the concept and its techniques in your discussions with patients about choice of therapy?

Dr. Gibofsky: Great question Matt. Shared decision making is a particularly important concept that really emphasizes the collaborative process in which patients and clinicians make treatment decisions together by integrating the evidence that we present in the context of individual patient preferences and values. Now, shared decision making goes behind the simple concept of informed consent. Shared decision making means that the information given to the patient not only includes the traditional information about risks, benefits and alternatives of therapy, but that the factors that we are providing the patient are consistent with the patient's values as expressed to use because this means that the therapeutic choice will ultimately be acted upon by the patient. If the decision isn't shared, then it's really difficult to anticipate that the patient is going to adhere to the regimen that we are trying, in that instance, to impose. So fundamentally what we are doing is defining a set of medically reasonable options, given that there usually are more than one medically appropriate option, but in the end the choice is being made by the patient. I can't stress that enough. It is the patient's choice made by the patient, weighing the importance of the option attributes or preferences for them. This is our way of giving the patient the information that they need to make a decision consistent with their own individual value system. Each patient is an individual and the same information to two different patients, may result in different decisions about the therapy to be used. Now the patient shares their values, their preferences about treatment attributes, the treatment concerns, their concerns about route of administration and after that, after all of their concerns are addressed, then the decision is made which is mutually agreed upon. Now let's not be naïve and let's recognized that there are issues related to access that may in many instances limit shared decision making, but fundamentally what shared decision making means is that you're trying to make the patient as knowledgeable as possible about the risks, benefits and alternatives of numerous options available to them and allow them not just to passively accept the decision that you have made, but to be an active partner in the decision making process. And so shared decision making becomes very important in helping patients to understand what they are getting, why they are getting it and what they can reasonably expect from being on that therapy.

Dr. Birnholz: Dr. Mease, what are your thoughts on shared decision making from the vantage point of your practice.

Dr. Mease: One of the things that I will often suggest to a patient with whom I have had a very meaningful discussion about therapy choice, is to go home and sleep on it, to reflect and be thoughtful about the choice in front of them, rather than making a snap decision. Sometimes that isn't always so easy, especially if they come from a long distance, but I think a thoughtful decision making process is very important.

Dr. Birnholz: Doctors my last question to you both. Any additional thoughts or takeaways you would like to share for our audience on this topic of psoriatic arthritis? Dr. Gibofsky, let me start with you.

Dr. Gibofsky: You know, this is a very exciting time to be a rheumatologist and it is a very optimistic time to be a patient with psoriatic arthritis. We have a multitude of therapies based on the understanding of the pathology that Phil outlined for us earlier, and that has led to the rational development of multiple agents that can inhibit different pathways of inflammation and may be acted in different facets of phenotypes of the disease. And we have so many and have so many different mechanisms of action, that if a patient doesn't respond to one after an appropriate trial, we can certainly try them on another. And finally I would stress that importance of getting the patient's input at every point so that they can educate us as to whether what they are experiencing is most important to them in terms of efficacy of the drug and having them, not just as a passive receiver of a medication, but an active participant and partner in the therapeutic decision making process.

Dr. Birnholz: And Dr. Mease, your thoughts.

Dr. Mease: I completely agree Allan at all of the points that you have made. Additionally, This a terrific time for us to be able to potentially achieve remission or low disease activity state in our patients with psoriatic arthritis. We have a number of highly effective medications. If patients lose benefit to one of them or have safety issues, then we have drugs to transition to and this is a wonderful opportunity to get patients back into a normal state of work productivity, family enjoyment, outings with relatives and friends, the things that are important to patients; very different than in the old days before we had such objective therapies when basically all we could do was just hold the patient's hand while they continued to have progressive joint damage and ongoing dysfunction and pain and fatigue.

Dr. Gibofsky: Yeah, I guess I would just like to remind our listeners of famous axiom of Sir William Osler, that he articulated over a century ago, when he told us that the role of a physician is to cure few, to help most, but to comfort all and while we had been focusing on the comfort aspect, we now in a much better position to provide cure and certainly help to our patients with psoriatic arthritis.

Dr. Birnholz: Well on that note, I would like to thank Dr. Mease and Dr. Gibofsky for taking us through the current treatment options for patients with psoriatic arthritis and sharing their perspectives on shared decision making with our audience today. Doctors, it was great having you both on the program.

Dr. Gibofsky: Happy to participate Matt. Hopefully it was worthwhile for our listeners.

Dr. Mease: Thank you so much for having me. I very much enjoyed participating in today's discussion.