Overview

Philip J. Mease, MD, and **Alexis R. Ogdie-Beatty, MD**, review the pathogenesis and a wide spectrum of clinical features, manifestations, and comorbidities of psoriatic arthritis; talk about classification criteria for PsA and different patient-reported and provider-assessed outcome measures; and discuss treatment recommendations and strategies, as well as various types of current and emerging therapies. Finally, they highlight some of the key issues and challenges of the management of PsA through reviewing patient case studies.

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Target Audience

This activity was developed for rheumatologists, dermatologists, primary care physicians, nurse practitioners, physician assistants and other health care providers who manage patients with psoriatic arthritis (PsA).

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Utilize validated tools to assess psoriatic arthritis (PsA) disease burden and response to treatment
- Summarize the clinical pharmacology, including mechanism of action, as well as safety and efficacy, of evidence-based medications for PsA
- Utilize a treat-to-target approach with individualized evidence-based therapy to reduce symptom burden and, when possible, achieve disease remission/low disease activity
- Identify and implement treatment of comorbidities of PsA in collaboration with the primary care provider

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Editor's Note

This is a transcript of the Alexis Ogdie-Beatty, MD, and Philip Mease, MD, presentation "Addressing the Burden of Psoriatic Arthritis: Moving Beyond the Joint."

Impact and Burden

Alexis R. Ogdie-Beatty, MD, MSCE

As physicians, we often think about psoriatic arthritis as an inflammatory arthritis that affects the joints. Psoriatic arthritis affects so much more than the joints. So, even if you think about the different domains of the disease, as it affects multiple tissues, the way the patients experience the disease is beyond the joints or the typical features of the disease.

Patients may experience decreased physical function or inability to do certain tasks. This may be as simple as having difficulty opening a jar or it may be having difficulty with walking. In addition, patients experience emotional effects of disease. When you're told you have a disease, it's going to last your lifetime and there's an unpredictability of the flares or different disease manifestations that may come, patients can become depressed or very anxious about what's happening with their disease. In addition, patients have poor sleep at times, and they may also have significant fatigue such as the feeling that the battery has run out, it's how some people describe it.

These maybe interrelated, and the fatigue may be related to the disease activity as well. Then, finally, this disease may impact how they relate to their family or to their friends. So, when patients have active disease, they may not want to schedule activities with their friends because they're worried about how they are going to feel; so, they can become socially isolated, and this can worsen depression.

Additionally, if they have small children or elderly parents that they're caring for, psoriatic arthritis gets in the way of those activities as well. It's hard to make lunch for the kids or get up early in the morning in order to get kids ready for school. I have parents telling me that they have to get up at 4 o'clock in the morning so that they can be ready by the time they're trying to get their 7-year-old out of bed at 7 o'clock in the morning. So, there's a variety of ways in which this disease affects patients and it affects each individual differently.

Patient Experience-Case Scenario

To illustrate the impact of psoriatic arthritis on a patient's life, I'll tell you about a case of one of my patients. I'm going to call him David. He's a 38-year-old man and a father of 3. He's married to his wife. He was diagnosed with psoriasis recently and was soon thereafter found to have psoriatic arthritis as well; it almost coincided in terms of their diagnosis. So, I'm going to come back to his specific disease features later but let me tell you a little bit about the impact of his disease.

As a father, he was walking around [an] amusement park with his kids and started to develop severe foot pain. The severe foot pain was actually dactylitis of 2 of his toes and that caused him not to be able to get around the park very well. So, he had to take a break from walking around with his kids and that for him was difficult because he's always been the dad that's been the fun dad doing things with his kids.

As this disease worsened, it began to involve his knees and his finger. So, he had trouble getting up the stairs to his office. It was having an impact in terms of getting to work, and he didn't want to look like the weak one that was having trouble going up the stairs. So, there's also this emotional aspect of someone seeing how he was interacting with the world around him.

He had a swollen finger and he didn't want other people to see his finger swollen, because it was quite obvious, if you looked at his finger, that he had dactylitis. In addition, David also had genital psoriasis. This was something that he didn't bring up in the visit, but I asked about. So, then it became clear that that had been more of an issue than he had let on.

His skin, while it didn't really bother him per se, he felt uncomfortable having a sexual relationship with his wife. So, this got in the way of their relationship. So, not only was he not able to be who we wanted to be as a father, but he was also having this new difficulty in his relationship that he hadn't had before. David was having a lot of suffering and a lot of burden from this disease. There are things that as clinicians, we might not necessarily pick up unless we ask about.

Patient Burden-Deane

Diagnoses

I was 57-years-old when I was diagnosed with PsA. I was a jogger. I used to go jogging every day after work, and it got to the point where I couldn't jog anymore. The more I jogged, the worse it got. So, a business associate recommended a rheumatologist to me, and I went to see him. And when he looked at me, he suspected psoriatic arthritis right away because I had a rash on my forehead at my hairline. He did some blood tests, and they came back and proved that I had psoriatic arthritis. At the time, he also told me, I think you may have some osteoarthritis in your knees, but we weren't worrying about that.

There was soreness in my hands, my right hand in particular, and my knees, and my feet. And it got just progressively worse and, in fact, it even became a chore to walk. That's how bad it had gotten in a short period of time.

Treatment

The initial treatment was methotrexate and prednisone, plus some cortisone shots. But I was on the methotrexate and the prednisone for 4 years, and then I changed doctors. I went to another rheumatologist, because the first one retired. The second one continued the methotrexate and the prednisone and added REMICADE (infliximab). He explained to me what a biologic was, and after a couple of treatments with the REMICADE I felt real improvement; but I was concerned about what it was. I did some research on my own. I went to

Janssen's website and read about it, and I read some other websites about it. And I didn't like the way the doctor's office was administering the REMICADE. They weren't weighing me, and the way they put the REMICADE in the saline bag worried me. It didn't seem to follow the Janssen protocol.

I asked my primary care doc for a referral. And I got a referral to a rheumatologist who I have been with since the year 2000. She's marvelous. She continued the REMICADE, but I would get it as an infusion at a hospital where they would weigh me first, and then the hospital pharmacy would prepare the dosage. I got some hand strength back, the swelling went down, feet improved. Didn't do anything for the knees.

I stayed on the REMICADE, methotrexate, prednisone combination until July of 2017, when the blood test came back. With the new doc, every time I had REMICADE, I would have a full set of blood labs done. She would monitor the results, and the creatinine level came back very high. She sent me to a nephrologist. He ordered a kidney biopsy and that came back showing damage to my kidneys from the methotrexate. We discontinued the methotrexate and continued with REMICADE and prednisone, and a little later added the leflunomide (Arava).

As of March 2019, I'm off the REMICADE because of the kidneys. Now I am just on prednisone and Arava. The blood tests revealed the only side effect that I experienced, which was the kidney damage, or high creatinine level. Other than that, there were none. I was very fortunate that I didn't experience any. Never had a problem with the prednisone, never had a problem with the REMICADE. The only thing that was a problem was the methotrexate, which we stopped.

Emotional Wellbeing

I'm a recovering alcoholic. I was in rehab in November of 2013 and haven't had a drink since. But that taught me a lot about myself, and I went to a psychologist when I came out of rehab, every Monday night for 2 years. He was also a recovering alcoholic and he helped me in my recovery and also to develop a positive attitude. AA is a very spiritual program, the psychologist is a very spiritual person also, and so that's played a big part of my life. But going to AA meetings is a support group, it's not an arthritis support group, but you're there with people having a struggle. You're helping them and you're getting outside yourself. That to me was more important. I did hook up to a couple of arthritis groups and, to be honest, I couldn't handle the negativity. "Woe is me, what am I going to do," that sort of thing. My glass is half full and I need to be happy. My wife is a happy person, a glass half-full person. But I think what I learned being a recovering alcoholic helped me deal with the arthritis pain because it's all about having a positive attitude. And there were days when they weren't so good. Back in January of 2017, I fell off the bed. My wife was in the hospital recovering from a heart attack, and I fall off the bed, land on my left hip, break the implant and break my femur. So, I was in rehab for a long time, and I was having a tough time emotionally with it. And then a friend of mine recommended a book called *Joni: An Unforgettable Story* by Joni Eareckson Tada. It's full of hope, and I haven't had a really bad day since I read that book. Even with this dialysis. I have diabetes, type 2, which is under control. Also, I had most of my stomach removed in 1980 due to bleeding ulcers, so now I don't have any stomach problems. And I had Hodgkin's lymphoma in 2000, and I had that fixed with surgery and chemo. And then the following year I had prostate cancer and they removed my prostate, with no follow-up, and that's been fine ever since. And the Hodgkin's has never returned. So, I'm a true cancer survivor.

As the patient, I had to be, as I said earlier, my own advocate. And talk to your doctor. Once you develop a relationship with your doctor, I think that that is a huge help in managing whatever your disease is, and I've been very fortunate. All my docs are associated with one hospital, so they can all see the electronic health record. They don't have to go and get permissions and all that sort of thing. I like that. I'm very comfortable. Everybody in the same place. And it's been a wonderful that I have great doctors, so I'm very fortunate to have good people all under the same roof.

Positive Outlook

You have to have a positive mental outlook to go forward. And I'm fortunate in that, [as] a recovering alcoholic, going to AA meetings. When I was in rehab, I turned my life over to God and I read the Bible constantly. I go to a Bible study class. It's all part of my being, of having this positive attitude and just not being down on myself.

It is what it is. I am what I am because I am not what I used to be. And, I'm happy here today. I'm happy with what I've got, and I don't look back, it's history. Tomorrow's a mystery, so let's deal with today. And I think if you can get through the PsA, you can get through osteoarthritis or rheumatoid arthritis if you've got a good attitude about it. If you're in charge, then you have a chance. And there's all kinds of places to get support. The Arthritis Foundation, your family, your church, wherever. But you need to be around positive people.

Extra-Articular and Extra-Cutaneous Manifestations and Comorbidities

There are a number of extra-articular and extra-cutaneous manifestations and comorbidities associated with psoriatic arthritis. Some are associated with the disease in general, such as inflammatory bowel disease and uveitis, and others are potentially a result of sustained systemic inflammation. They may include metabolic comorbidities such as cardiovascular disease, including myocardial infarction, as well as increased incidence of diabetes, increased incidence and prevalence of cardiovascular risk factors including hypertension and hyperlipidemia, obesity, and, also, fatty liver disease. In addition, depression and anxiety are also common in patients with psoriatic arthritis.

Ideally, the therapy should cover as many different domains of psoriatic arthritis as possible. However, as various constellations of extra-articular and extra-cutaneous manifestations of psoriatic arthritis and associated comorbidities respond differently to certain therapies–some comorbidities may even worsen with certain types of therapy–they are likely to have an impact on the choice of therapy. For example, it is important to know which therapies not to choose for a patient with psoriatic arthritis and inflammatory bowel disease.

Summary

Psoriatic arthritis is a complex disease that is more than just the disease of peripheral joints. It impacts patients in very different ways, and it is different from patient to patient. Not only is it heterogeneous in terms of the physical manifestations, including extra-articular and extra-cutaneous manifestations and comorbidities, but also in the way that it impacts patients' lives.

Thus, rheumatologists, dermatologists, primary care providers, and other health care professionals need to think about how each of the disease domains and individual comorbidities the patients may have is contributing to, not only the disease itself, but also to their overall life.

Diagnosis and Patient Assessment

Alexis R. Ogdie-Beatty, MD, MSCE

I'm going to talk about assessment of a patient with psoriatic arthritis. First, how do you diagnose psoriatic arthritis? Well, there are no diagnostic tests and there are no diagnostic criteria for psoriatic arthritis. However, there are classification criteria that are designed to help enroll a homogenous group of patients into a clinical trial. However, they have advantages, as this particular set of classification criteria also works fairly well as diagnostic criteria, or, at least, helps guide diagnosis.

CASPAR
ClASsification Criteria for Psoriatic ARthritis

Inflammatory musculoskeletal disease (arthritis, spondylitis, enthesitis) with 3 or more points from the following:

Evidence of psoriasis:	
a) Current psoriasis	2
b) Personal history of psoriasis	1
c) Family history of psoriasis	1
Psoriatic nail dystrophy	1
Negative Rheumatoid Factor	1
Dactylitis (current or recorded by a rheumatologist)	1
Radiographic evidence of **juxta-articular new bone formation**	1

These criteria are called the Classification Criteria for Psoriatic Arthritis or CASPAR criteria. In order to meet CASPAR criteria, a patient has to have an inflammatory arthritis. So, that would be a swollen joint or enthesitis, inflammation where a tendon, ligament, or joint capsule insert into the bone, or spondylitis, which would be consistent with inflammatory axial disease.

Once they've satisfied that portion of the criteria, they then need 3 points. First, you can get 1 set of points from the psoriasis box. If you have current psoriasis, you get 2 points. If you have a personal history of psoriasis, you get 1 point. If you have a family history, particularly in a first-degree or maybe a second-degree family member, you get 1 point as well. Then, if you have psoriatic nail dystrophy, specifically nail pitting or onycholysis, then you can get 1 point and negative rheumatoid factor gives you 1 point.

Dactylitis which is seen by a rheumatologist gets 1 point and that's because there is some differential ability to diagnose dactylitis. Finally, if you have juxta-articular new bone formation on x-ray around the hands or feet, that would be 1 point as well. So, if you get a total of 3 points from those criteria, then you meet the criteria for psoriatic arthritis. So, you can see how that would be fairly easy to meet with a peripheral arthritis and negative rheumatoid factor and a concurrent psoriasis.

Patient Assessment – Patient-Reported Outcomes

Now that we've talked about diagnosis, let's talk a little bit about how to assess the patient in clinical practice. First, I'm going to start with patient-reported outcomes, which is getting the patient's opinion about how things are going with their disease right now. There are several different outcome measures that are available for the measurement of psoriatic arthritis. There are some that measure specific domains of interest such as fatigue, and then there are others that measure kind of overall how you are doing, and then some that measure, specifically, function.

PsA Outcome Measures
PROs

- Health Assessment Questionnaire (HAQ)
- Short Form 12 (SF12) and/or 36 (SF36)
- Routine Assessment of Patient Index Data (RAPID3)
- Psoriatic Arthritis Impact of Disease (PsAID)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- PsA Quality of Life (PsAQoL)
- Dermatology Life Quality Index (DLQI)
- Work Limitations Questionnaire (WLQ)
- Work Productivity & Activity Impairment (WPAI)

Orbai AM, Ogdie A. *Rheum Dis Clin North Am.* 2016;42:265-283.

You would want to pick one that meets the needs of the patient, but also that you can use across patients. Some of the more commonly used ones, particularly in the United States, are the RAPID3 or the Routine Assessment of Patient Index Data 3 that's used for patients with rheumatoid arthritis and can be used for ankylosis spondylitis as well, and it's frequently used in practices across patients. The PsAID or the Psoriatic Arthritis Impact of Disease questionnaire is a relatively new index designed by EULAR and published in 2014, but it works really well overall in psoriatic arthritis.

You can use that one to monitor progress over time and to get a sense of how things are going. The advantage of PsAID is that you can see individual domains. For example, you can see fatigue, depression, and other elements that are specifically related to psoriatic arthritis.

Other outcomes measures include PROMIS (Patient-Reported Outcomes Measurement Information System) measures. So, these are more commonly used in the United States, developed by the NIH and embedded in many medical records systems, across academic health systems, in the United States. These are kind of general measures that are not specific to psoriatic arthritis but do function fairly well in PsA as well. Then, we have many more of the specific ones. The HAQ is commonly used across rheumatic disease as well, but specific to rheumatoid arthritis, it's also used commonly in psoriatic arthritis trials.

There are a variety of different versions of the HAQ, but, again, these are commonly used in clinical practice to manage arthritis, to monitor arthritis. The BASDAI, which is the Bath Ankylosing Spondylitis Disease Activity Index, is particularly relevant for patients with axial disease or ankylosing spondylitis but can be used as an overall global assessment as well.

Other measures are more specific to individual domains of psoriatic arthritis. For example, the Psoriatic Arthritis Quality of Life index, or the PsAQoL, is specific to quality of life. That one is also a licensed one, so it's harder to get. There's the FACIT, which is used to measure fatigue, or the PROMIS Fatigue, which also can measure fatigue. There are work impairment questionnaires like the Work Productivity and Activity Impairment (WPAI) questionnaire and the Work Limitation Questionnaire (WLQ). These are commonly used in longitudinal observational studies or randomized control trials, but not as commonly used in clinical practice.

Patient Assessment – Provider-Assessed Outcomes

We have gotten the patient's opinion, and often that's done prior to the patient coming into the room, and that may be directly embedded into the medical record or on a piece of paper in front of you. As we get to the physical examination, what should we assess in a patient with psoriatic arthritis? This will include a joint exam, and, typically, it's a 66/68 joint exam in psoriatic

arthritis. Often, in rheumatoid arthritis you'll do a 28-joint count, which will be the MCPs, the PIPs, the wrist, elbow, shoulders, and then the knees as well.

PsA Outcome Measures
Provider-Assessed Outcomes

- Swollen joint counts
- Tender joint counts
- Physician assessment of arthritis
- Physician assessment of skin disease (PASI, BSA, IGA, etc)
- Dactylitis
- Enthesitis
- Nails

Orbai AM, Ogdie A. *Rheum Dis Clin North Am.* 2016;42:265-283.

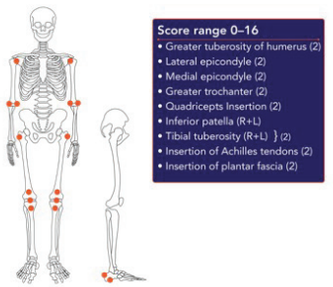
But that would miss a lot of joints that are involved in psoriatic arthritis, as the toes are commonly involved. The 66/68 joint count also includes the DIP joints, as well as hip range of motion. You only get tenderness in the hip, you cannot assess swelling. That is why it's 68, tender and 66 swollen. That also includes the ankles and MTPs as well.

In addition, the Physician Global Assessment is actually a good overall assessment of how the patient's doing. You can use a scale from zero to 10, where zero is doing extraordinarily well or really well and 10 is the worst level, highest level disease activity.

GRAPPA has a set of 3 global assessments, one that assesses the skin, one assesses the joints and one both. In addition, there's a variety of skin assessments that you can do. The easiest one I do in clinical practice is the body surface area (BSA). One percent of the patient's body surface area is their open palm. So, this is my 1% of my body surface area. The patient's open palm is 1% of their body surface area. If you estimate how many palms of psoriasis are involved that'll give you the body surface area, where less than 3%, in general, is considered mild and above 5% or 10% is considered severe, and somewhere in the middle is moderate.

The PASI or Psoriasis Area and Severity Index is a much more detailed assessment where you assess each quadrant of the body or each portion. The lower extremities, trunk, head and arms, and you give the body surface area for that particular body zone. Then you also give a score for erythema, induration and scaling. Together you calculate a weighted score for the PASI. The PASI is the primary outcome in psoriasis clinical trials. Then in addition to that, there are Investigator Global Assessments or position

PsA
SPARCC Enthesitis Index



Score range 0–16
- Greater tuberosity of humerus (2)
- Lateral epicondyle (2)
- Medial epicondyle (2)
- Greater trochanter (2)
- Quadriceps Insertion (2)
- Inferior patella (R+L)
- Tibial tuberosity (R+L) } (2)
- Insertion of Achilles tendons (2)
- Insertion of plantar fascia (2)

Maksymowych WP, et al. *Ann Rheum Dis.* 2009;68:948-953.

global assessments; there's a variety of these as well. The Investigator Global Assessment or IGA has a clear bottom tier. Zero is clear, one is almost clear, and that can go up to 5. Again, there's a variety of different anchors for those, but those are commonly used in clinical trials as well.

Beyond the joints and the skin, we also do dactylitis assessments. That's just a simple count, for example, [and] is one way to assess dactylitis. When we say a digit actually has active dactylitis, it's swollen from the base to the tip. Visually swollen but also feels swollen and it's generally tender. Sometimes erythematous as well, particularly when they first are kind of beginning, but it should be tender to be counted as active.

Then, in addition, there's an enthesis assessment. Again, entheses are places where a tendon or joint capsule inserts into the bone. There are a variety of different assessments for the enthesitis, you can have 16 spots or 6 spots. There's a Leeds Enthesitis Index, which is just the lateral epicondyle, the medial femoral condyle, and then the Achilles. The plantar fascia is another common area and that's included in the SPARCC assessment. Finally, we assess the nails in a variety of different ways. One is just a global assessment of nail disease. How bad is a nail disease from zero to 100 or zero to 10 or there's a lot of more detailed assessments, called the NAPSI (Nail Psoriasis Severity Index) or the modified NAPSI, as well.

Patient Assessment – Labs and Imaging

Finally, in fully working up a patient's level of disease activity, we have the patient perception of their disease, physician perception based on the physical examination, and, finally, laboratory and x-ray are kind of more objective data, if you will. C-reactive protein (CRP) is commonly filed in psoriatic arthritis, but it's actually only elevated in approximately half of patients. In those patients where it's normal, it's not that helpful to continue to follow up.

In patients with an elevated CRP, it may be helpful to follow, but if the patient is obese, they're more likely to have an elevated CRP anyway. So, you might not see much of a budge in the CRP with therapy, sometimes. Finally, x-rays of affected joints can show erosions or new bone formation. It's not necessarily helpful to follow x-rays more than once a year, and not all physicians follow them on a regular basis.

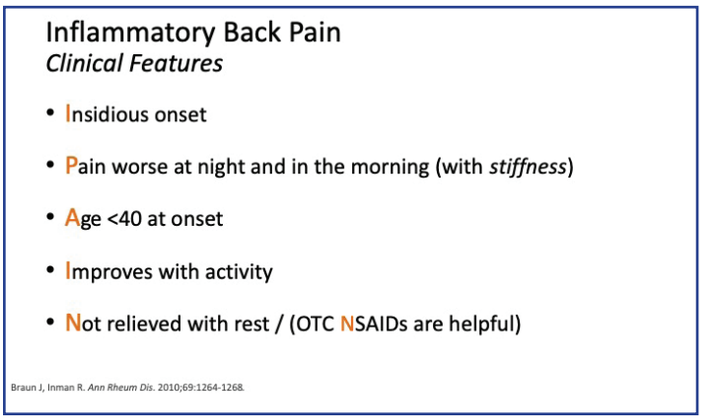
There are no specific recommendations about how often you get x-rays. It is helpful to get x-ray at a baseline because it can tell you whether or not the patient has erosions. If they have erosions, they're more likely to continue to progress or have more aggressive disease. Finally, assessment of the sacroiliac joints can be helpful in patients who particularly have low back pain because it can tell you if the patient has an axial disease as well.

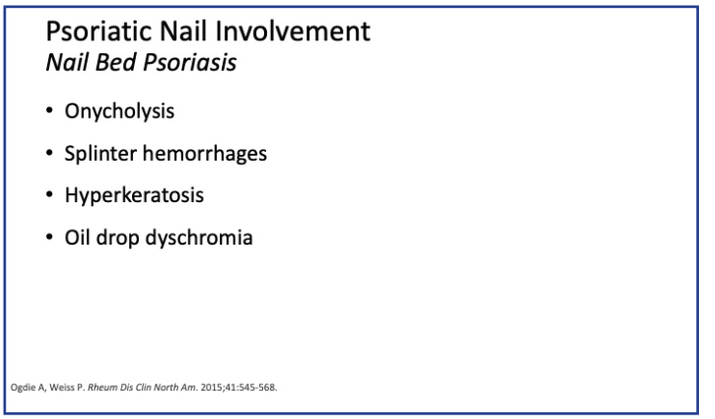
Sometimes, if the patient has low back pain that seems inflammatory, and they have psoriatic arthritis and a negative x-ray, you may go on to get an MRI of the pelvis to assess for active inflammation sacroiliac joints as well.

Inflammatory Back Pain

How do we know their back pain is related to their disease? So, features of inflammatory back pain include insidious onset; they don't know exactly when it started, as opposed to a mechanical injury. For example, a disc herniation, people can often point to a specific issue that'll cause that. Pain is generally worse in the second half of the night or in the morning when you first wake up, and it's generally associated with stiffness, like it's hard to move or hard to roll over.

Age is, generally, less than 40 at onset, or at least less than 45. Generally, inflammatory back pain improves with activity, whereas mechanical back





pain would be less likely to improve with activity–that is, it's not relieved by rest. So, people feel much better standing or moving than they do sitting or lying for a period of time. Finally, NSAIDs are generally helpful in improving the pain.

If you think your patient has inflammatory back pain, it's important to work that up because it does change therapy options as, when we get to therapies, we'll mention that in more detail. So how do you assess inflammatory back pain in a patient with psoriatic arthritis or presumed psoriatic arthritis? I mentioned you start with the x-ray at the sacroiliac joints. One of the common mistakes that I see is patients are sent for a lumbar spine film and that's unfortunately going to very often, depending on the radiology department, miss the sacroiliac joints.

We really want to know what's going on in the sacroiliac joints because that's generally where the disease will start. Let's say the sacroiliac joints are normal. Well, these days we catch a lot more non-radiographic axial spondyloarthritis and that means that the x-ray is normal, but there's actually inflammation on MRI, for example.

In that patient you'll go on to get an MRI if you really suspect that they have inflammatory back pain and their x-ray is normal. A common mistake I see is that patients receive a script for an MRI of the lumbar spine, which again will very rarely go all the way to the sacroiliac joints, depending on the radiology department. MRI of the pelvis without contrast, you're really looking at those STIR images or fat suppression images in order to see if there's inflammation there, as well, to look for; you can see bone erosions on the MRI sometimes more clearly than on the x-ray. If you have MRI evidence, then the patient is considered to have axial aspect of their disease as well.

Types of Psoriatic Nail Involvement

Finally, I did mention nail assessment, but I didn't mention what types of nail involvement can be considered to be part of psoriatic arthritis. Pitting, as noted earlier, as well as onycholysis , kind of crumbling or breaking away of the nail or eating away of the nail, are aspects of psoriatic arthritis.

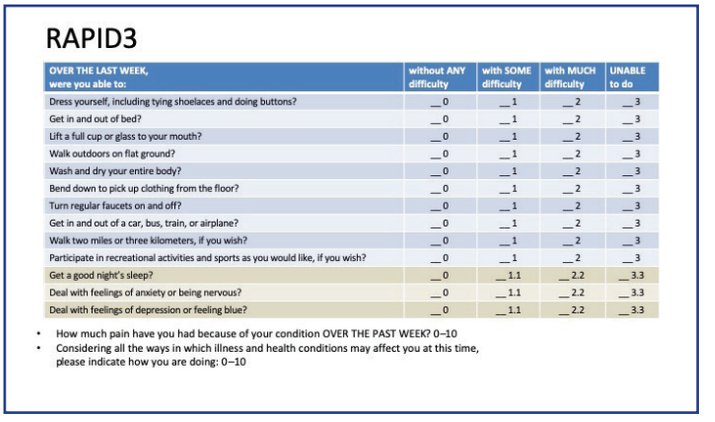
They're the most common aspects of nail diseases in psoriatic arthritis. However, there's a variety of different psoriatic nail dystrophy elements. So, splinter hemorrhages may be related or oil drop dyschromia and also hyperkeratosis. General ridges are not considered, especially longitudinal ridges, to be a feature of psoriatic arthritis, per se. Although when you ask about nail disease, patients will often bring that up.

PROs as The Primary Outcomes

In the beginning I began by telling you about all the different ways in which psoriatic arthritis can affect a patient. Diminish physical function, poor sleep, depression, anxiety, fatigue, work productivity, ie, diminished work productivity, difficulty with their family life, or difficulty with social participation, as well as other aspects. It is because of these reasons that patient-reported outcomes are particularly important to incorporate into practice, particularly in the care of patients with inflammatory arthritis like psoriatic arthritis.

If we don't have a way of asking patients systematically about how they're doing, it's hard to make sure that their voice is being heard in their care. Again, what are the reasons for which we follow patient reported outcomes? First, they reflect the patient experience. Regardless of the disease features, the patient may have different experiences that may help you tailor how you're going to treat that patient.

The ultimate goal is really to improve how the disease impacts the patients, so that they can get back to their regular life. Almost every patient will say one thing when asked, "What do you want?" It's, "To get back to my previous life before I got this disease." They also allow for an easy option for collecting data. For example, if you track your medical record, the patient reported outcomes, I have RAPID3 from each of the previous visits.



I can see how things have come up and down, so I can see when they flare because the number went up, and I can see when they've gotten better on therapy because the number went down. It is an objective way to track how the patient's doing. But not only that, it's helpful to demonstrate how a therapy is working. If you show that when you started the therapy, the day you prescribed the therapy the disease activity is high or the patient reported outcome score is high, and after therapy introduction, the patient gets better, that's good information for insurance companies when you're trying to get that drug reapproved.

Finally, they allow the patient to kind of reflect on their own experience with the disease, and this is really helpful before a patient comes in for a visit.

For example, in the RAPID3, there are 3 questions about sleep, depression, and anxiety. And by just asking those questions, it raises those questions as important to the patient, such that they will bring it up to discuss, when prior to doing that question they might not have thought about that as being a problem for them.

There are a number of different patient-reported outcomes used in clinical trials. In fact, in ankylosing spondylitis trials, the ASAS 20 or ASAS 40 are 40% or 20% improvement in a patient-reported score. It is a set of items from a patient-reported outcome. In the ankylosing spondylitis [studies] we're looking at trials mainly based on patient reported outcomes; the ASDAS also incorporates a C-reactive protein.

RAPID3

I am going to talk through a few individual patient-reported outcomes. One of the most common ones in the United States is the RAPID3 or the Routine Assessment of Patient Index Data 3. This is a well-known PRO to most rheumatologists in the US. It's really easily administered. It is a set of 10 questions about function and then 3 questions that are sleep, depression, and anxiety, as well as a pain assessment and a global assessment.

Routine Assessment of Patient Index Data-3
RAPID3

- Well-known PRO; easily and quickly administered; most commonly used rheumatology PRO in the United States
- Domains: physical function, pain, global health
- Range 0-30 (or 0–10)
- Developed and validated in RA; now assessed in AS and PsA as well

The 3 questions about sleep, anxiety, and depression are not included in the score, but the rest are average. The score of 10 can be quickly calculated into a score that is the average with the pain and the global assessment. So, this gives you an overall picture of how the patient's doing. But you can actually see 3 individual scores as well. The range is zero to 30 or some people divide it by 3 and make it a range zero to 10. This is developed and validated in rheumatoid arthritis, but there's a couple studies now validating it in psoriatic arthritis; one study examining this in ankylosing spondylitis tracked well with the BASDAI as well.

PsAID

I also mentioned in the beginning the Psoriatic Arthritis Impact of Disease (PsAID) Questionnaire. This is a questionnaire that was developed specifically for psoriatic arthritis by a patient panel. The patients decided on what was most important to measure for them and then there was a way of ranking all of those among the patients and then they developed a set of items for those different domains. In the clinical version of the PsAID there are 12 different items.

There's a 9-item version that's for clinical trial, so it's slightly shorter. Each item is rated on a scale from zero to 10 and then the items are summed to give a score. Each of the individual items is rated. So, you can actually see on a piece of paper how they're rating their pain, fatigue, skin problems, work or leisure activities, functional capacity, discomfort, sleep disturbance, coping, anxiety, fear and uncertainty, embarrassment or shame, social participation, and depression.

PsA Impact of Disease (PsAID)
Questionnaire (cont.)

"Circle the number that best describes the way you felt **due to your psoriatic arthritis** during the last week: 0–10 NRS"

- Pain
- Fatigue
- Skin problems
- Work and/or leisure activities
- Functional capacity
- Discomfort
- Sleep Disturbance
- Coping
- Anxiety, fear, uncertainty
- Embarrassment and/or shame*
- Social participation*
- Depression*

Gossec L, et al. *Ann Rheum Dis.* 2014;73:1012-1019.

Those are all important areas for the patients; if you can see where they're doing the worst, for example, you can target some different therapies. For example, if the patient is rating depression as quite bad, or coping or anxiety, you could refer them for mental health assessment or suggest therapy or refer them back to primary care for management of depression or anxiety. As these have a major impact on how patients respond to therapy, it's nice to be able to see each of those different items specifically laid out.

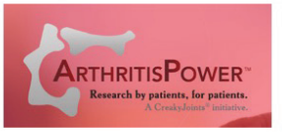
Additional Ways of Collecting PROs

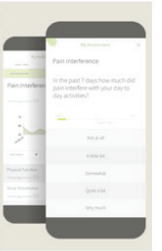
I mentioned a couple of different ways of using patient-reported outcomes. If you have large medical records such as the Epic electronic medical record system, these can be embedded right into the electronic medical record and sent to patients prior to their visit. For example, in our clinic, patients receive within 7 days of their visit, the RAPID3, they can go on, on their app with their iPhone and complete the questionnaire. It goes straight into my notes, and then I can see the trajectory over time.

If you don't have that opportunity, there's a variety of other opportunities for patients to collect that data. In the United States, a lot of patients are on ArthritisPower. So, ArthritisPower is an app they can download–and it is a study, so that they will have a consent because it does collect their information using studies, de-identified, as well.

They can track their own assessments there. They can do the RAPID3, they can do the PROMIS measures such as PROMIS sleep, PROMIS fatigue, PROMIS physical function or pain interference. They can track those and then actually show you a report of how they're doing. That is another way to track patient-reported outcomes, if you don't have them in your medical record.

Patient-Centric Way Forward
New Ways of Collecting Data and Conducting Trials





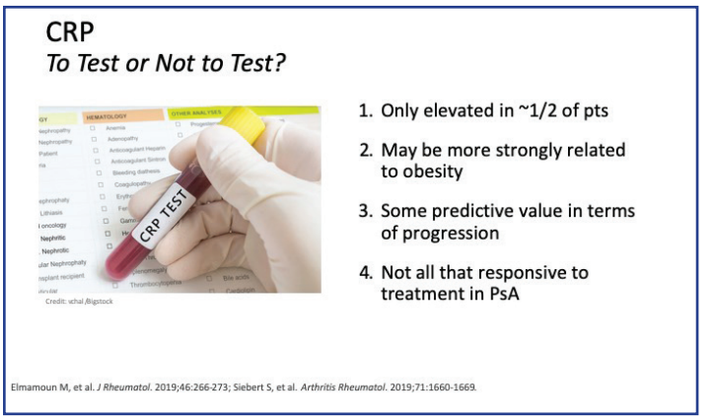
Finally, there's a good old paper option. So just having paper on a clipboard with the assessment that the front desk can hand to the patient as they're checking in.

Collecting PROs in Patients with Fibromyalgia

One of the common comments I receive from physicians about patient-reported outcomes is that if the patient has fibromyalgia, they don't feel that the patient reported-outcome is useful because patients with fibromyalgia are known to be prone to catastrophizing, so they might rate their outcomes really high. What I would say it's actually not part of the problem but part of the solution. Because if you can see that they're catastrophizing and they're having really high pain scores and really high impact from disease, that's a patient to treat the fibromyalgia because you can also bring down the scores in other ways. I would not tell a patient with fibromyalgia not to do it, I would actually continue to track this. Additionally, it can, as I mentioned, point out areas for particular improvement as well.

CRP – To Test or Not to Test?

I previously kind of touched on the fact that the C-reactive protein is commonly used in the assessment of patients with psoriatic arthritis, particularly over time. However , I also mentioned that about half of patients, or more, have a negative C-reactive protein or a normal C-reactive protein at baseline. There are other things that can influence the C-reactive protein. For example, if you have really severe psoriasis all over your body, then you're likely to have an elevated CRP just from the severity of psoriasis, or if you're obese with a BMI of greater than 30, your CRP is likely to be elevated as well.

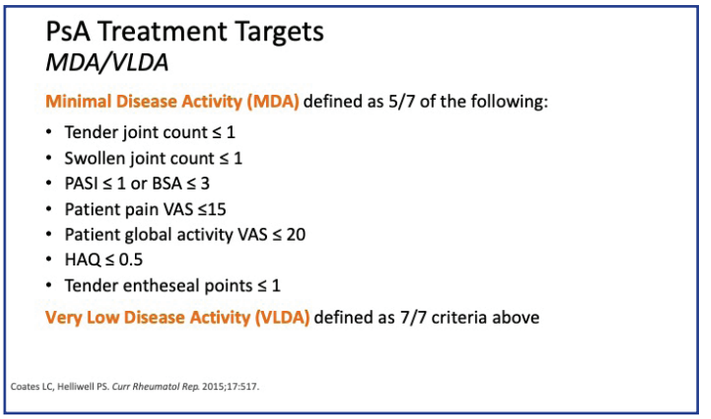


Do we test it or not? So, my general approach is to get the CRP in the very beginning, but then if it's normal, I won't continue to track it over time. However, [if] it's elevated, it can provide some benefit in terms of following it vis-à-vis a therapy. One of the other benefits of knowing the C-reactive protein is that if it's high it's a predictor for more aggressive disease. That can be helpful in the very beginning as well.

MDA/VLDA

There are a variety of different composite measures that can help you streamline what you should be following. One of the more commonly used outcome measures in clinical practice in psoriatic arthritis is called minimal disease activity (MDA).

This was developed for use as a treatment target in a treatment target strategy. The TICOPA study published in 2015 by Laura Coates, et al, in The Lancet examined whether or not getting patients to this target improved



their overall outcomes. As suspected, and as in rheumatoid arthritis, it does improve overall outcomes. What do the minimal disease activity criteria look like? This is an assessment of 7 different domains, and you get a point for each one that you achieve.

For example, if the tender joint count is 1 or less you get a point, and the swollen joint count is 1 or less you get a point, and those are both on the 66/68 joint count. The PASI or body surface area, which is easier to do in clinical practice. So, if you have a 3% or 3-palm body surface area or less, you get a point. There's a little debate around that, however, whether 3% is really okay because for some patients that would be still a lot of psoriasis.

If you did a RAPID3 for example, you would have each of the 3 patient-reported outcomes for the MDA. So those are the patient pain assessment, the patient global assessment, and the HAQ. These are a patient pain of less than or equal to 15 on a scale from 0 to 100, or 1.50 to 10, which would give you a point. Having a global assessment of less than 20 in a scale from 0 to 100 would give you a point and HAQ assessment of 0.5 or less on a scale of 0 to 3 would also give you a point toward minimal disease activity. Finally, entheseal points of 1 or less that are tender would also give you a point and this is on the Leeds Enthesitis Index as well.

If you have 5 of 7 of these points, then you would be in minimal disease activity. If you have 7 of 7, then you're in very low disease activity (VLDA), which has been demonstrated to be even better in terms of outcomes. However, most people don't get to be VLDA. This is a one easy way of assessing a patient and kind of streamlining what you need to get. If you did a skin assessment, 66/60 joint assessment, a Leeds enthesitis assessment of 6 entheses and then a RAPID3, you could actually satisfy all of these criteria fairly quickly in a visit.

DAPSA

Other targets for managing psoriatic arthritis include the DAPSA which is the Disease Activity Index for Psoriatic Arthritis measure. This sums the tender joint count, the swollen joint count, the patient pain assessment on a zero to 10 scale on a patient global assessment, from, sorry, one to 10 scale and CRP. There are a variety of different cutoffs for remission, low disease activity, moderate disease activity, high disease activity. This is an analogous to the CDAI in rheumatoid arthritis.

Summary

I am going to summarize some of the things that we talked about. First of all, patient-reported outcome measures are really important to incorporate into practice. I suggested that they're really important across rheumatic diseases, but I think they're also particularly important in psoriatic arthritis

because they help you focus your assessment and your management plan and treat the whole patient, in particular what the impact of the patient is experiencing.

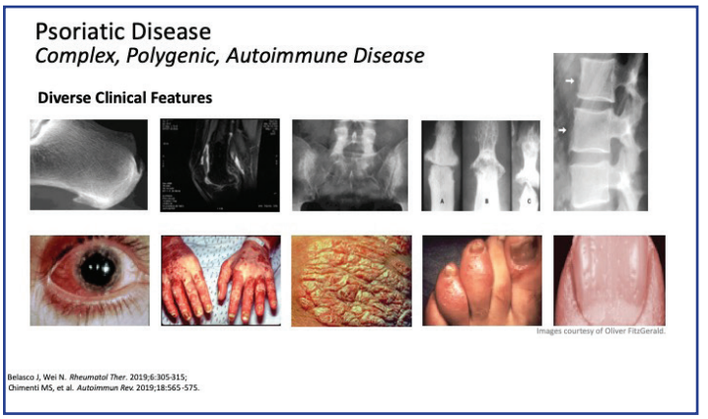
In addition, it's important to know the disease features of psoriatic arthritis and to do the assessment of features. This includes a peripheral joint assessment, dactylitis and enthesitis assessment, to know whether or not the patient has spine disease, particularly in the beginning, a nail assessment and skin assessment, as well. Finally, there is some clinical utility to labs and x-rays, particularly in the beginning, but they may not be something that you follow over time. In order to sum all this up, you can use treatment targets such as MDA or even DAPSA to kind of streamline your assessments in a day-to-day clinical practice, particularly after a full assessment at baseline.

Treatment Approaches

Philip J. Mease, MD

Psoriatic Disease – Overview of Diverse Clinical Features

Psoriatic disease, including psoriatic arthritis, is a complex heterogeneous disease with multiple clinical manifestations. Oliver FitzGerald, a researcher in psoriatic arthritis from Dublin, has put this photo montage together to get across the points. What you see are both images of the body in various locations, skin, toes, fingernail, eye, as well as images that depict the various ways in which psoriatic arthritis afflicts individuals. First and foremost is the skin disease, which typically precedes the development of the arthritis condition by, on average, 10 years. However, some patients may simultaneously develop skin and joint disease, whereas others may actually have the musculoskeletal manifestations appear before the skin disease.



In the middle and the lower panel of photographs you see the typical psoriatic plaque and, to the left of that, an individual's hands with very severe psoriasis, and you can imagine what a difficult time individuals with psoriasis have, especially when they're growing up, they're in their adolescent years or in their 20s and 30s and trying to get work, have family relationships and so forth. [For some people,] this is quite an embarrassing and depressing disease to have.

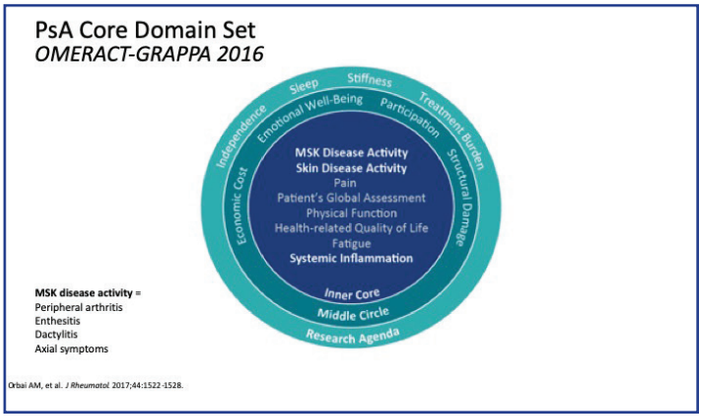
Also depicted are some of the aspects of the arthritis condition. For example, we see an image in the upper panel of a finger joint, the distal interphalangeal joint with a time-lapse sequence showing progressive erosive damage to the joint, which is quite severe. And this is going to show up as being quite painful to the individual. Just below that, there's a photograph of dactylitis, or sausage digit. This is where not only the joints, but also the tendons and the entheseal insertion sites of the ligaments into bone, along the course of the digit, are inflamed, leading to swelling of the whole digit. And when you see this, it's practically pathognomonic for psoriatic arthritis.

In the upper right-hand panel, you see a lateral view of the lumbar spine. And in the middle of the upper panel, you see a pelvis x-ray showing sclerosis around the sacroiliac joints. This is a depiction of the spondylitis that can occur in a patient with psoriatic arthritis, typically in 40% to 50% of patients, and can be quite impactful. On the far left above, you see enthesophytes at the heel on an x-ray, and this represents late stages of the enthesitis, inflammation where ligaments or tendons insert into bone. Again, very unique to psoriatic arthritis and this helps distinguish this condition from rheumatoid arthritis.

Just to the right of that is an MRI scan of the knee, which shows not only light-up in the synovium, but also in some of the bone tissue. So not only can we have synovitis, but also enthesitis and osteitis infecting the joins and bones adjacent to a joint. In the lower left-hand panel, you see an inflamed eye, and this underlines the point that there are often associated conditions, so besides musculoskeletal manifestations and skin manifestations and nail disease, we may see uveitis occurring, or we may see inflammatory valve disease. These are all conditions which are closely connected to psoriasis and psoriatic arthritis genetically, and thus more frequently seen in these patients than in the general population.

Core Domain Set

GRAPPA Group, working with OMERACT, has translated a core set of domains that need to be measured in clinical trials of patients with psoriatic arthritis. I should mention that GRAPPA stands for Group for Research and Assessment of Psoriasis and Psoriatic Arthritis. It's the major global education and research organization devoted to psoriasis and psoriatic arthritis. And OMERACT, which stands for Outcome Measures in Rheumatology Clinical Trials, is an international organization that has to do with developing outcome measures for assessing diseases in the rheumatology space. Ana-Maria Orbai, as the lead author for GRAPPA, published, in 2017, an article in which we summarized several years of work to come up with a core set of what has to be measured in clinical trials and what is good to measure in clinical trials. Starting with musculoskeletal disease activity as represented



by peripheral arthritis, enthesitis, dactylitis, and spine systems, skin disease activity, pain, patient's global assessment of the way in which the disease is affecting them, physical function, heath-related quality of life, fatigue, and systemic inflammation as represented by CRP or sedimentation rate. Those items that are in the inner circle are ones that we recommend be measured in every clinical trial and in long-term clinical registries in which we're assessing the disease.

Now, in some studies, it may not be necessary to measure structural damage. But somewhere in the clinical development program for a drug, it's important to see whether the drug can inhibit progressive structural damage in joints. That's why we include it in the second circle and usually it's done in the phase 3 program for clinical development of a drug. In addition, economic cost, assessing emotional well-being, and participation in meaningful life activities should be measured somewhere, but not necessarily in every study. And then there are some items in the outer circle which we consider to be part of the research agenda, and that's measuring independence, sleep, stiffness, and treatment burden.

Importance of Early Diagnosis

Now, if we don't diagnose psoriatic arthritis in a timely fashion, what happens? And that's why it's so important for us to have a recognition of the different ways in which the disease can present, as we've been discussing, and ways of assessing it with various measurement tools. But what happens if we don't do so in a timely fashion? There might be joint damage that occurs–more likely, joint deformity, physical disability. Extra-articular disease may develop more readily. And there will be greater morbidity and mortality, including the consequences of comorbidities such as cardiovascular disease and neoplasm. These are all things that we are trying to prevent by timely diagnosis and treatment of the disease.

PsA Manifestations and Comorbidities
Extra-Articular and Extra-Cutaneous

Need for teamwork with PCP, Ophthalmology, GI, Psych

- Uveitis (1.55%)[1]
- Ulcerative colitis (1.28%)[1]
- Cerebrovascular disease (7.32%)[1]
- Metabolic syndrome
  - Obesity (16.45%), hypertension (47.28%), hyperlipidemia (47.47%)[1]
- Fatty liver/NASH (5.77%)[1]
- Depression (21.2%)[1], suicidal ideation (0.48%)[1]
- Fatigue (15.8%)[2]
- Fibromyalgia (16.58%)[1]
- Osteoporosis (9.33%)[1]

1. Shah K, et al. *RMD Open*. 2017;3:e000588.
2. Kaine J, et al. *J Manag Care Spec Pharm*. 2019;25:122-132.

I've mentioned not only associated conditions, but also comorbidities, and I'd like to go into this in a bit more detail. As you will appreciate, this leads to the need for teamwork with not only the primary care physician, but also ophthalmologists, gastroenterologists, psychologists, as well as, of course, dermatologists who we closely work with in the management of patients with psoriatic arthritis. What are noted here are some of the common associated conditions such as uveitis, ulcerative colitis in Crohn's disease, but also comorbidities including cardiovascular disease, metabolic syndrome characterized by obesity, hypertension, and hyperlipidemia. Fatty liver, which is partly a consequence of obesity, depression, suicidal ideation, fatigue, fibromyalgia, and osteoporosis. All of these are important comorbidities that we need to attend to when we're caring for our patients, in addition to caring for the primary problems of psoriatic arthritis and psoriasis.

I'd like to come back to metabolic syndrome. This is something that is very common, as you can see. And it's often undermanaged in patients with psoriatic arthritis. We of course exhort primary care physicians and cardiologists to pay attention to these problems, to know that the patient is genetically inclined to have metabolic syndrome. So, they have to work even harder to control weight, blood pressure, and cholesterol. If we find, as rheumatologists or dermatologists, that PCPs or cardiologists are not taking adequate care of our patients in this regard, we need to step in ourselves and help the patient.

I'll also mention the fact that depression is a very important issue, and many times in clinical practice we don't attend properly to this comorbidity. It's sometimes embarrassing for the patient to talk about, they're reluctant to talk about it. So it's important for us to be proactive and to actually question the patient about it, because of the frequency when you have a bad skin disease, coupled with a bad musculoskeletal disease, it increases the impact on the patient's emotional well-being and is often the case that we need to enlist the aid of a psychologist or psychiatrist and consider the use of antidepressant medications.

I also want to highlight fibromyalgia. This is often not included in lists of comorbidities of a condition, but it's there whether we like it or not. Fibromyalgia is a condition in which a patient has an increased experience of pain, potentially fatigue, sleep disturbance as well, caused by an uptick of nociceptive peptides, neuropeptides in the central nervous system, and inadequate control of pain by the inhibitory neuropeptides such as serotonin and norepinephrine. There is a biological reason for fibromyalgia, as well as psychological, and oftentimes we may perfectly treat a patient's inflammation with one of our immunomodulatory medications, but the patient has residual pain and fatigue. So, we're thinking, well, maybe we're not quite doing an adequate job with our immunomodulatory medicine, when, in fact, heaping on the immunosuppression doesn't help us, but instead we need to be attending to the patient's concomitant fibromyalgia with either medications or other approaches to treating this condition.

Delayed diagnosis will lead to bad outcomes, and in a study from Dublin in which Muhammad Haroon has outlined that you have worse erosions, greater number of deformed joints, more sacroiliitis, more likelihood of arthritis mutilans, more functional disability, if there is a delay of more than 6 months in the diagnosis of psoriatic arthritis. It behooves us to be educating our dermatology colleagues as well as our primary care colleagues, orthopedists, podiatrists, and others who are perhaps seeing these patients, front line, to have them think about the possibility that psoriatic arthritis is present in a patient with psoriasis, and get them to us for appropriate treatment earlier.

Assessment Tools

There are a number of different measures that have been developed and used in clinical trials to measure the various domains that I showed you earlier in that onion diagram from OMERACT and GRAPPA. We're trying to summarize here some of these measures. Let's start with joint assessment. The first thing to note is that unlike rheumatoid arthritis where we can get away with just assessing 28 joints for tenderness and swelling, in psoriatic arthritis we strongly recommend assessing 68 joints for tenderness and 66 for swelling. This will include the feet and ankles, and the reason for this is that oftentimes, especially early on in psoriatic arthritis, the feet may be the predominant part of the body that are involved. And if you skip that area, you'll underassess the impact of arthritis for that patient.

There is an alphabet soup of other measures including the ACR20, 50, and 70 response measure that we borrowed from rheumatoid arthritis that has

PsA Clinical Trials
Outcomes Measures

Domains	Instruments
Joint Assessment	68/66 T/S joint count, ACR, DAS, PsARC, PsAJAI, DAPSA, cDAPSA
Axial Assessment	BASDAI, BASFI, BASMI
Skin Assessment	PASI, target lesion, global, PSI, PSD
Composite (holistic)	MDA, VLDA, PASDAS, CPDAI, AMDF
Pain	VAS, NRS
Patient Global	VAS (joint global, skin + joints global)
Physician Global	VAS (joint global, skin + joints global)
Function	HAQ, HAQ-S, PSAID
HRQoL	SF-36, PsAQoL, DLQI, PSAID
Fatigue	FACIT, Krupp, MFI, VAS
Enthesitis Assessment	Leeds, SPARCC, MASES, 4-point
Dactylitis Assessment	Leeds, present/absent, acute/chronic
Acute Phase Reactant	ESR, CRP
Imaging	X-ray (modified Sharp or van der Heijde–Sharp), MRI, US
Work/Home Productivity	WPAI, WPS

Mease P. *Arthritis Care Res.* 2011;63:64-85; Mease P, et al. *Ann Rheum Dis.* 2005;64:ii49-ii54; Mease P, van der Heijde D. *Int J Adv Rheum.* 2006;4:38-48.

worked well in psoriatic arthritis. The ACR20 is typically the primary endpoint of most psoriatic arthritis trials at the moment, although this may change in the future. There are a number of others that are listed, including the DAPSA score or the C or Clinical DAPSA that had been specifically adapted for psoriatic arthritis and used in clinical trials. These assess the tender and swollen joint count, but also patient global, for example, and sedimentation rate or CRP.

Axial assessment, we've listed several that are used in ankylosing spondylitis, now known as axial spondylarthritis trials, which can be used in psoriatic arthritis to assess the spine disease in the roughly 40% of patients with PSA that may have spine disease. Skin disease, in clinical trials we use the psoriasis area and severity index or PASI score. This is a complex scoring system that is not typically used in clinical practice. In clinical practice, we'll typically instead measure the body's surface area that measures the total amount of surface area that's involved where we know a handprint of the patient is 1% of body surface area, that allows us to get an idea of the degree of skin involvement.

There are some newer composite measures that take into account not only arthritis, but also enthesitis and skin disease, and these are the minimal disease activity (MDA) criteria, the very low disease activity criteria, something called the PASDAS, the CP-DI and the AMDF. These are more holistic measures that are proving to be very effective in measuring disease when used in clinical trials. Pain is simply measured on a BIS scale or NRS scale. Patient global, asking in all of the ways in which your arthritis condition, as well as your skin condition, affects you; physician global, same. And then function is measured by the HAQ score, which we borrowed from rheumatoid arthritis or something known as the PSAID, which is specifically developed for psoriatic arthritis.

Quality of life is measured by a general measure such as the SF-36, or more specific measure such as the PSAID, as well, which can measure quality of life. Fatigue, there are various indices that are used that are noted here. Enthesitis assessment, there's one specifically for psoriatic arthritis, known as the Leeds Enthesitis Index in which one assesses by palpating the lateral epicondyle area, the medial femoral condyle near the knee, and the Achilles tendon and insertion. And what we're doing is assessing for pain. The SPARCC is an instrument developed in Canada in which there are more sites, there are 18 sites that we press upon. It's proving to be a little bit more reliable in clinical trials than the Leeds index. And then the Maastricht, which is mainly used for axial spondyloarthritis clinical trials, but has been occasionally used in psoriatic arthritis.

And then an older measure, called the 4-point, where we just press upon the Achilles tendon insertion or the plantar fascia insertion. Dactylitis assessment, in older trials we just simply looked at the digits and assessed whether they had a sausage appearance or not, and thus present or absent. Along with assessing for tenderness, as well as swelling of the digit. And then there's a newer instrument, the Leeds dactylitis index, which is more complicated and actually requires measuring the circumference of the dactylic digits. Then we have a blood test, and unfortunately all we have at the moment are the sedimenation rate and C-reactive protein, and these tests are not as frequently elevated in psoriatic arthritis–typically, 35% or 40% of actively involved patients. But if these are elevated, then they can be used as biomarkers for disease activity as we're following a patient.

Imaging x-ray is typically used for assessing for structural damage progression. Looking at the hands and feet. But we also use ultrasound to look for evidence of inflammatory activity or MRI scanning, especially in the spine. And then, of course, assessing the ability for the patient to be productive in society with measures such as the WPAI for assessing this in clinical trials.

Treatment Recommendations – Core Principles

Let's talk about some of the treatment recommendations that have been developed over the past number of years. And we're starting with the GRAPPA recommendations, which were published in January of 2016. They're called the 2015 recommendations. And here are some overarching principles that have been suggested. These are kind of mom and apple pie kind of recommendations, but they're important to keep in mind, and that is that we're aiming to get the patient into the lowest possible level of disease activity in all clinical domains. Not just arthritis, but also enthesitis, skin disease, spine disease. We need to be measuring each of the areas that we've been talking about and to prevent structural damage progression.

PsA
GRAPPA Recommendations: 2015

Overarching Principles

- Achieve lowest possible level of disease activity in all domains of disease
  - Optimize functional status, improve QoL, and prevent structural damage
- Assessment requires consideration of all major disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease
  - The impact of disease on pain, function, QoL, and structural damage should be examined
  - In addition, activity in other potential related conditions and comorbidities should be considered including CVD, uveitis, IBD, obesity, metabolic syndrome, gout, diabetes, liver disease, depression, and anxiety
  - Patient-reported measures with a comprehensive history and physical examination, often supplemented by laboratory tests and imaging techniques, should also be included
- Therapeutic decisions need to be individualized
- Ideally, patients should be reviewed promptly
  - Early diagnosis and treatment are likely to be of benefit

Coates L, et al. *Arthritis Rheumatol.* 2016;68:1060-1071.

We want to be sure that we're doing the best we can to improve function and quality of life, and we should be measuring all of the aspects of the disease that go into impacting function, quality of life, pain, and structural damage progression. We should be doing so as comprehensively as possible. And we should be also addressing the comorbidities and associated conditions that I mentioned earlier. Each patient in front of us is unique. One of the things that I tell patients when they come in for the first time is that your disease is not going to be like any other patient with psoriatic arthritis. Given the heterogeneity of clinical domains, we need to individualize our assessment and treatments in order to effectively treat the patient.

All along the way, we should be engaging the patient with our assessments to tell us "how are you doing" and making sure that they're compliant with treatment. This often requires multidisciplinary treatment, including working with the dermatologist and possibly other medical specialties to best assess and treat the different clinical domains. There should be shared

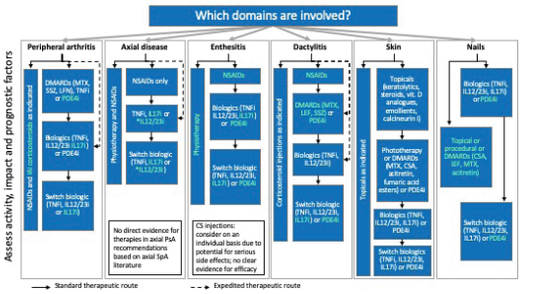
PsA
EULAR Recommendations: 2015 Update

Overarching Principles

- Treatment should maximize HRQoL through control of symptoms, prevention of structural damage, and normalization of function and social participation
  - Abrogation of inflammation is an important component necessary to achieve these goals
  - Aim should be best care based on a shared decision between patient and rheumatologist, considering efficacy, safety, and costs
- Because of its heterogeneity and potential severity, multidisciplinary treatment may be required
  - Rheumatologists should primarily care for musculoskeletal manifestations; in the presence of clinically significant skin involvement a rheumatologist and a dermatologist should collaborate in diagnosis and management
  - Extra-articular manifestations, metabolic syndrome, CVD and other comorbidities should also be taken into account

Gossec L, et al. *Ann Rheum Dis.* 2016;75:499-510.

PsA
GRAPPA Treatment Recommendations 2015



Coates LC, et al. *Arthritis Rheumatol.* 2016;68:1060-1071.

decision-making about treatment, including what is practical for the patient from a cost point of view, taking into account their relative aversion, or not, to safety issues, which may impact the treatment choice, and of course starting with efficacy and how efficacious the medication should be.

Rheumatologists should be at the center for managing the musculoskeletal aspects, but we should always be thinking about teaming with the dermatologist for optimal management of skin disease.

Non-Pharmacologic Management Approaches

Before getting into the pharmacological strategies for treatment, think about how the nonpharmacologic management approaches play out, starting with education of the patient, family, and other team members that are helping take care of the patient. We do this in the visit with the patient in the clinic. We hope that there will be family members coming with them. We give them reading materials to take home. We steer them to websites that are reliable, to learn about the disease. And of course, in our clinical notes, we are explicating what we're assessing, how we're assessing it, how severe is the disease activity, how are we going about treating it, so that we are educating our fellow health practitioners that may be taking care of the patient as well.

Psychological counseling is potentially very important, and then diet and weight loss. There are numerous studies now that show us that by controlling obesity, we can improve clinical outcomes with our treatments. Engaging physical and occupational therapy may be helpful. Exercise, conditioning exercise is important, and smoking cessation.

Pharmacologic Treatment Recommendations -- GRAPPA

Let's turn to the treatment recommendations, and we're starting with the GRAPPA psoriatic arthritis treatment recommendations that were published in early 2016. GRAPPA Group has divided the various domains of the disease into different buckets. Peripheral arthritis, axial disease, enthesitis, dactylitis, skin disease, and nail disease. Why have we done this? The reason is that depending upon the clinical domain, there may be differences in response to the different types of treatments that are used. A good example of that is looking at spine disease or axial disease where we know that nonsteroidal anti-inflammatories can be effective. But studies have shown that the conventional synthetic DMARDs (csDMARDs), such as methotrexate, are not effective in the spine. We leapfrog the csDMARDs and go right to a TNF inhibitor or an IL-17 inhibitor.

When these recommendations were published, we had an open label trial with the IL-12/23 inhibitor agent. But now we know from phase 3 studies with the IL-12/23 inhibitor that it does not work in the spine management. In the next iteration of the treatment recommendations, that drug class will be removed. But TNF inhibitors and IL-17 inhibitors work well and then we know that oftentimes patients may lose a response, so may need to switch. But if we go over to peripheral arthritis, which is one of the predominant issues, we have some evidence that the csDMARDs can be effective, so typically we'll start with one of those. But since there is evidence for a TNF inhibitor or a PDE4 inhibitor to work well even in patients that are virgin to use of csDMARDs, that's why those drugs can be used in that position.

The GRAPPA treatment recommendations–there are several drug classes, oftentimes, in each of these boxes. What we have done is said let's just put there any drug that we know to be effective and has been tested in that particular position of the treatment ladder, and not steer the physician to any one particular one, because there might be important issues around cost, feasibility, patient preference, safety, and so forth, that may guide the patient and the clinician to one or another class of medications. We'd like to be, if you will, more democratic about the choice that the clinician and the patient have in front of them.

Of course, with skin disease, there are going to be some topical treatments as well as UV light treatment that are part of the treatment ladder, and so forth. This is very individualized according to the clinical domains, and it requires that the clinician measure each clinical domain and treat the ones that are most active with the most appropriate treatment.

The other thing that the 2015 recommendations come out with is special attention to associated conditions and comorbidities. We've created a complex table in which you have the various drug classes, or specific drugs, and then a comorbidity or associated condition. There are situations, for example let's take Crohn's disease, where we know that a particular drug is approved for primary therapy, such as, adalimumab, or infliximab. That would be an example where we might actively choose a drug such as a

GRAPPA 2015 Recommendations
Therapy Considerations vis-à-vis Comorbidities

Comorbidity	NSAIDs	Glucocorticoids	Cyclosporine	Sulfasalazine	Methotrexate	Leflunomide	Hydroxychloroquine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
CVD	C	?												
CHF	C	C						C	C	C	C	C		
Obesity					C									
Metabolic syndrome		C			C									
Diabetes		C			C									
Crohn's Disease	?			A	OL				A	A	A			
Ulcerative Colitis	?		OL	A					A	A		A		
Uveitis		P*						?	P	P				
Osteoporosis		C												
Fatty liver disease	C			C	C	C								
CKD	C		SM		C	?								
Depression														?
Chronic HepB†	C				C	C		SM	SM	SM	SM	SM	?	
Chronic HepC†	C				C	C		?	?	?	?	?	?	
HIV								SM	SM	SM	SM	SM	?	
Malignancy								C	C	C	C	C	?	

C	Caution
?	Data insufficient, concerns raised
A	Approved for primary therapy
OL	Off-label use
P	Preferred therapy
SM	Requires special monitoring

*Corticosteroids used as preferred therapy for uveitis are most commonly given as topical and/or intraocular injections in preference to oral steroids.

†When treating patients with chronic infections that can affect the liver, consider consultation with providers having expertise in the area.

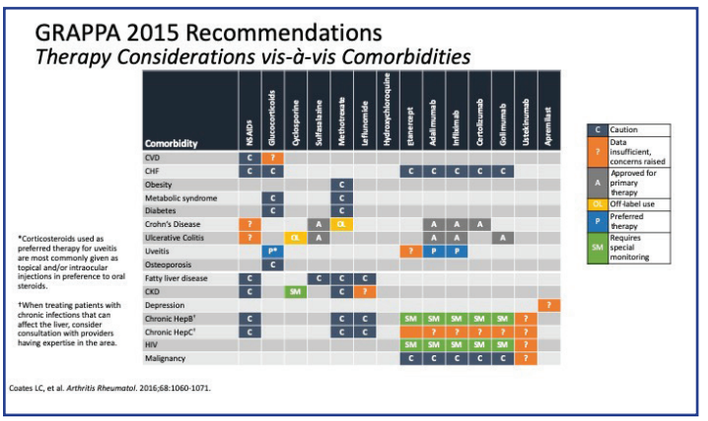
Coates LC, et al. *Arthritis Rheumatol.* 2016;68:1060-1071.

monoclonal antibody TNF inhibitor if the patient has concomitant Crohn's disease, because we could kill 2 birds with 1 stone.

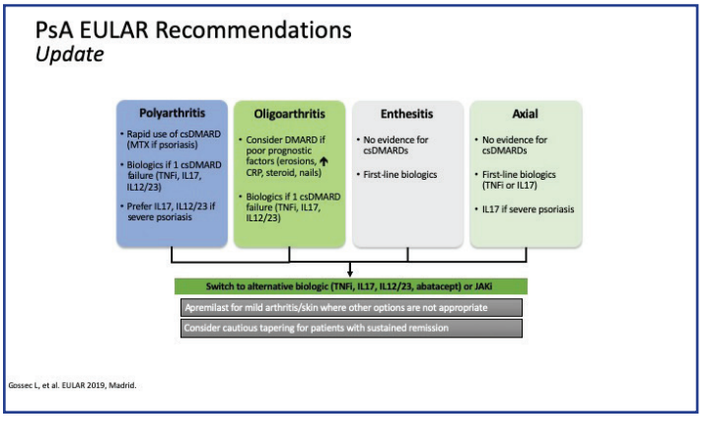
There are a number of Cs, where this represents caution about using the medication. Let's take, for example, the Cs that are under methotrexate. If the patient has obesity, metabolic syndrome, may have fatty liver as a result of that. They're more likely to have liver toxicity from methotrexate, so there should be extra caution used when using that medication. This is an important set of contextual factors to take into account when prescribing medications. This is a continuation of that same chart, in which more of the comorbidities are listed, and as you can see, for example, in the row for malignancy, there's some caution around the TNF inhibitors. This is because the TNF inhibitors have been associated with at least 2 malignancy conditions, one lymphoma and the other nonmelanoma skin cancer.

Pharmacologic Treatment Recommendations – GRAPPA vs EULAR

Let's turn to another set of treatment recommendations that have been published, the EULAR, which are the European recommendations. We're showing some comparisons between the EULAR 2015 and the GRAPPA 2015 recommendations. In a moment, I'm going to show you the updated EULAR ones, which correct what I consider some of the issues around the EULAR



2015 ones. One key point is that the EULAR recommendations really do suggest that a csDMARD should be used first, after a nonsteroidal, before going onto a biologic or targeted synthetic medication. They listed here methotrexate, leflunomide, sulfasalazine, and they were recommending quite a long assessment period, 3-6 months, before being able to move on to a biologic DMARD. This is partly because of cost considerations. There's also a strong preference after a csDMARD for either a second csDMARD trial

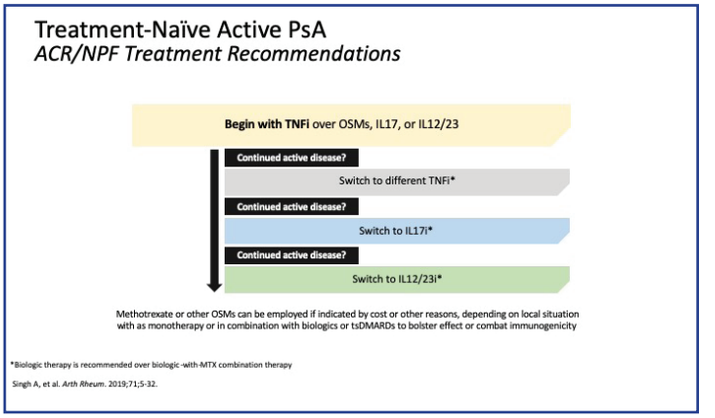


or a TNF inhibitor trial, whereas in the GRAPPA treatment guidelines, there's a more open choice amongst several of the types of treatments, including csDMARDs, TNF inhibitors, and the PDE4 inhibitor, before switching on to other biologics or targeted synthetic agents. Now , if we look at the updated PsA EULAR recommendations, they've moved a little bit more toward the GRAPPA ones. There is acknowledgement that biologics such as TNF inhibitor, IL-17 inhibitor, or the IL-12/23 inhibitor, can be used earlier, and especially in patients with severe psoriasis. They do highlight a difference that they feel is present between polyarthritis and oligoarthritis, and suggest that there should be more of a trial of csDMARDs in this group before moving on to a biologic agent. I'm not sure if I completely agree with this approach, since I have plenty of patients in my practice who have oligoarticular disease, that is 5 or fewer involved joints, but who are quite disabled by their arthritis. And so, I'm a bit more agnostic and don't tend to make the distinction between polyarthritis and oligoarticular as much as in Europe.

As with the GRAPPA treatment guidelines for enthesitis and axial disease, there is an acknowledgement that we don't have good evidence for the csDMARDs working in these clinical domains, and therefore to jump sooner to use of a first-line biologic. There's also increasing evidence for JAK inhibitor treatment, and that is acknowledged here in the update, and will be present in the updated GRAPPA treatment guidelines when they come out next.

Pharmacologic Treatment Recommendations – ACR/NPF

The third major group to get in on the act of treatment recommendations has been the American College of Rheumatology, collaborating with the National Psoriasis Foundation. There was a very interesting outcome, which was the recommendation to begin with a TNF inhibitor over an oral small molecule. That's the term that was used instead of csDMARD in this set of treatment recommendations. Based on review of the evidence and then the voting panel's discussions, the decision was made that the evidence was stronger for TNF inhibitors than with methotrexate, both from an efficacy and safety point of view, so thus the recommendation to use a TNF inhibitor first.



Then after that, depending upon response, one can move to an oral agent or move on to one of the other biologic agents, such as an IL-17 inhibitor or IL-12/23 inhibitor. Also within these recommendations, further down the road will be a JAK inhibitor. If the patient has already been on a csDMARD, such as methotrexate, then of course using either a TNF inhibitor, or an IL-17 inhibitor, or IL-12/23 inhibitor, if the patient has predominant enthesitis, there's acknowledgement that the oral small molecules may not work except for apremilast; so they would start, after a nonsteroidal, with a TNF biologic or tofacitinib, but also would consider use of an IL-17 inhibitor or IL-12/23 inhibitor.

Risks of Therapy

When we're thinking about treatment, we're not just thinking about efficacy. We're thinking about safety and tolerability, and we have to go over this with our patients. A common denominator amongst all of the immunomodulatory medicines is the risk for serious infection, so this has to be highlighted when we talk with our patients. With the TNF inhibitors, there is also the concern about the potential for TB or opportunistic infections, a little bit less so with the other medications. But still, there's a warning with each of the medications, about screening for TB before treatment and then surveilling for these as time goes by.

We need to talk about the potential for neoplasia or lymphoma. With TNF inhibitors, the potential for autoimmune disease, such as lupus or MS, being triggered, CHF, or congestive heart failure exacerbation, liver toxicity, especially with agents like methotrexate, hematologic toxicity, or inflammatory bowel disease with the IL-17 inhibitors.

Treatment Strategy Approaches – Treat-to-Target

We're also now developing treatment strategy approaches, including treat-to-target, and we like to aim for a state of low disease activity or remission in our clinic, and in clinical trials we're most often looking at minimal disease activity criteria or very low disease activity criteria. We also have tools such as DAPSA remission or low disease activity, PASDAS and cPDI remission low disease activity. I'm going to show you the results of the TICOPA treat-to-target trial in psoriatic arthritis.

Controlled taper is also a treatment strategy, and controlled withdrawal. This is more often done in Europe, where there's a bit more cost-consciousness about use of these medications, where we see, whether or not, after the patient has achieved remission, they can tolerate a taper of the medicine they're using, or a withdrawal, and have sustained remission.

Here are the minimal disease activity criteria that were developed by GRAPPA. There are 7 items, and if the patient meets at least 5 of them, then that means they are in a state of MDA and very acceptable. It includes arthritis, skin, patient pain, patient global, a function score, and enthesitis assessment. They are all very low levels, and the patient needs to achieve these by various measurements in order to be in this state.

Minimal Disease Activity (MDA)
GRAPPA Criteria

- A patient is classified as having MDA when they meet 5 out of 7 of the following criteria:
  - Tender joint count ≤1
  - Swollen joint count ≤1
  - PASI ≤1 or BSA ≤3
  - Patient pain VAS ≤15
  - Patient global activity VAS ≤20
  - HAQ ≤0.5
  - Tender entheseal points ≤1

Coates LC, et al. *Ann Rheum Dis.* 2010;69:48-53.

Treatment Strategy Approaches – TICOPA Trial

In the TICOPA trial, patients who were naive to a DMARD therapy were randomized to either a tight control arm, where they were seen on a monthly basis, and if they weren't in a state of MDA, they had had their treatment tweaked more aggressively. The other arm was a standard control arm, in which they were seen every 3 months, with no specific quantitation of disease activity, and no specific guidance about how the patient should be managed.

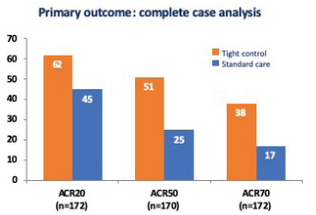
Here is the outcome for this trial. In orange, the patients are in the monthly visits, where they were striving for minimal disease activity, and as you can see, at the end of the year a greater number of patients had achieved ACR20, 50, and 70 responses than in the group that was seen every 3 months and did not have any specific quantitative goal to shoot for. The same was true for the skin responses. It looks as though we can get better disease outcomes by paying more attention to whether or not our patient has achieved minimal disease activity.

TICOPA: Tight Control/T2T in PsA
ACR Responses

Tight control was associated with significantly greater improvements in signs and symptoms of disease at week 48.

ITT with multiple imputations

Outcome measure	OR	Lower 95% CI	Upper 95% CI	P
ACR20	1.91	1.03	3.55	0.0392
ACR50	2.36	1.25	4.47	0.0081
ACR70	2.64	1.32	5.26	0.0058



Coates LC, et al. *BMC Musculoskelet Disord.* 2013 Mar 21;14:101.

This does come a slight cost, and that is that there were more serious adverse events that are drug-related, in the tight control arm, including a couple more infections than in the standard care arm. This just underlines the importance of surveilling our patients as we're treating them. There was also, as you can see, more GI upset. This was partly because of the fact that in this United Kingdom study, they did combine, in some patients, leflunomide with methotrexate.

Summary

To summarize, what we have gone through is a recognition that psoriatic arthritis is a complex autoimmune disease with multiple clinical domains. We've gone through the core set of assessments and clinical domains that should be looked at in our patients in clinical trials, assessing not only joints but also skin disease, enthesitis, fatigue, quality of life, function, and so forth. We've spoken about the risk of what happens in a patient with psoriatic arthritis over time, including progressive structural damage as well as loss of function and decrements of quality of life. We've emphasized the various comorbidities and associated conditions that may come with psoriatic arthritis and the importance of attending to these as well.

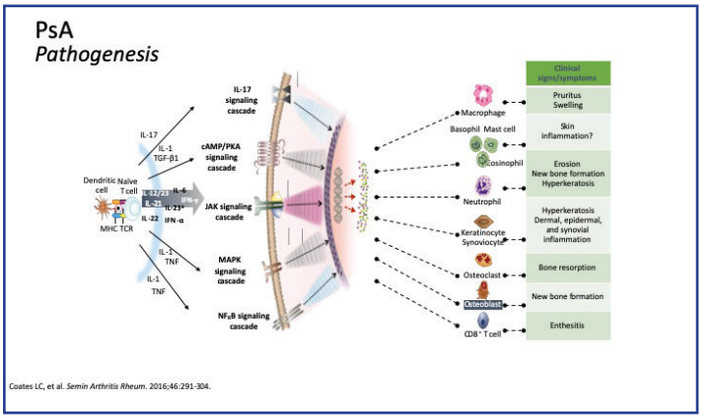
We have mentioned that delayed diagnosis is associated with worse long-term outcomes. We've highlighted a table of outcome measures that are used, especially in clinical trials, but some of them used in clinical practice. We've spoken about the various treatment recommendations and the overarching principles, including shared decision-making with patients, nonpharmacologic strategies, including physical therapy and exercise, weight loss, and we've gone through the 3 major treatment recommendations of GRAPPA, EULAR, and the ACR/NPF, which are largely similar, with some subtle differences between the different recommendations. We've spoken to safety issues, and then some of the treatment strategies, especially treating to the target of low disease activity or remission.

Treatment Options

Philip J. Mease, MD

Pathogenesis of Psoriatic Arthritis

The pathogenesis of psoriatic arthritis (PsA) is complex, because of the different clinical domains that are affected by the disease, including not only the joints, as reflected in synovitis, but also enthesitis, that is where tendons or ligaments insert into bone, osteitis, skin disease, as well as blood vessel involvement. What we find is that there is an activation, particularly of the innate immune system, but also the adaptive immune system, which then triggers a number of different cell types, including T-cells, macrophages, etc, to produce a number of proinflammatory cytokines, including TNF alpha, interleukin 17, interleukin 1, interleukin 22, interferon gamma, interleukin 6.



Coates LC, et al. *Semin Arthritis Rheum*. 2016;46:291-304.

When we are thinking about therapy of this complex disease–which is driven by a multi-cytokine, proinflammatory process, which affects immune cells that then go to the sites of inflammation, including skin, joints, bone, and so forth–we have to think about inhibiting a number of cytokines and cell types in order to effectively control the disease. There are certain cytokines that are depicted which have a very large role. TNF is an example of that; interleukin 17 is an example of that. We do find that with inhibition of these single molecules, we can have very large effects on the various clinical domains.

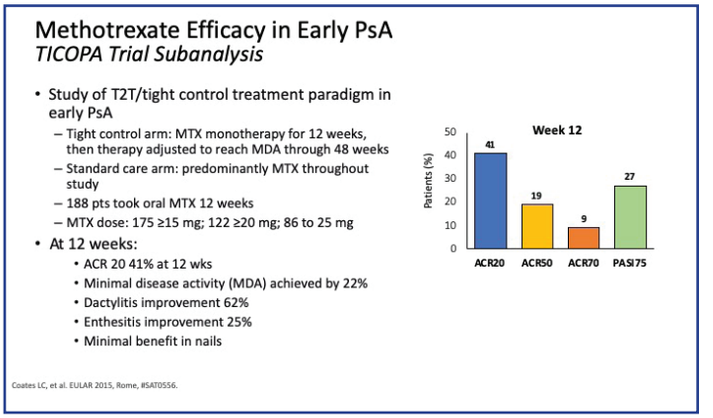
Pharmacologic Therapeutic Classes

There are various pharmacologic therapeutic classes that have been shown to be effective in psoriatic arthritis, starting with the conventional synthetic DMARDs, methotrexate, sulfasalazine and leflunomide, TNF inhibitors, etanercept, infliximab, adalimumab, golimumab, and certolizumab; the IL-12/23 inhibitor, ustekinumab; the IL-17 inhibitor, secukinumab, ixekizumab, brodalumab, and now the newest one, bimekizumab, which is both an IL-17A and IL-17F inhibitor; the IL-23 inhibitors that are specific for IL-23 inhibition through p19, brazikumab, risankizumab, and tildrakizumab; the T-cell modulator abatacept; and the targeted synthetic disease-modifying drugs, including the PDE4 inhibitor apremilast and the JAK inhibitors, of which tofacitinib, baricitinib, upadacitinib, and filgotinib are all in development, if not already approved for psoriatic arthritis.

csDMARDs

If we start with the csDMARDs, I'd like to acknowledge that unfortunately there've been very few trials, controlled trials, of methotrexate. The MIPA trial, or methotrexate in psoriatic arthritis trial was conducted in the United Kingdom. In this study, they tried to get patients to at least 15 mg per week of methotrexate. As you can see, looking at the *P* values of the various indices used to assess response, none of them achieve statistical significance in discriminating between methotrexate and placebo.

There were some mild successes, including improvements in patient and physician global and some of the skin scores with methotrexate, but overall the conclusion from this trial was that methotrexate was not effective. We all know from practice that methotrexate can be effective in a proportion of our patients. The problems with this trial were that about a third of the patients in each arm of the study dropped out during the course of the trial, so there may not have been enough patients to be able to detect a difference. The other is that investigators tended to put their most mildly involved patients in the trial as opposed to more significantly involved patients, who they were reserving for biologic treatment, so in many ways it was poorly conducted.



Coates LC, et al. EULAR 2015, Rome, #SAT0556.

In the TICOPA trial, which was a treat-to-target trial in psoriatic arthritis, in the first 12 weeks, patients who had previously not seen methotrexate treatment were treated with methotrexate in an open label fashion. Some of the results from that 12 weeks of experience with methotrexate alone, 41% achieving ACR20 response, 27% achieving a PASI 75 response, dactylitis improvements in two thirds, enthesitis in a quarter, and even a fifth of the patients achieving minimal disease activity. This is consonant with what we find with methotrexate, so not quite as good as from the various biologic agents, but nonetheless, with some patients, we can see reasonably good effect.

TNF Inhibitors

Then we come to the TNF inhibitors, and the molecular structures of the 5 of them are depicted. Across the board, the phase 2 and 3 trials with the various TNF inhibitors, and the results were largely similar, ACR20, 50, and 70 responses, excellent responses. This advent of TNF inhibitor therapy in PsA was a true breakthrough in our ability to control the disease and give the patients back their lives, with improved function, quality of life, improvements in pain, as well as inhibition of structural damage progression. And that's noted wherein not only do we get the good responses in arthritis, but also other domains, including the skin, enthesitis, dactylitis, function, quality of life, fatigue and structural damage progression.

The SEAM psoriatic arthritis trial, which is one of the newer trials, although it was with 2 older agents, etanercept and methotrexate. The way this trial was designed was, in essence, a head-to-head between etanercept monotherapy, etanercept in combination with methotrexate, vs methotrexate monotherapy. There were a large number of patients that were entered into the trial, 851, and these were patients with very early disease. The median duration of psoriatic arthritis was half a year, so we're getting at patients very early.

TNFi Therapies in PsA
Other Outcomes at Primary Time Point

- **Psoriasis**
  - ~60% PASI 75 response with monoclonal constructs; lesser with soluble receptor
- **Enthesitis**
  - ~60%–75% improvement
  - Assessment methods: 4-point, MASES, Leeds, SPARCC
- **Dactylitis**
  - ~60% improvement
  - Assessment methods: Count, score, Leeds dactylometer
- **Function**
  - Significant improvement achieved as assessed by HAQ
- **QoL**
  - Significant improvements in SF-36, PsAQoL, DLQI, EQ-5D
- **Fatigue**
  - Significant improvement observed
- **Structural damage progression**
  - Inhibited per Sharp-van der Heijde method

Mease P. *Ann Rheum Dis.* 2011;70:77-84; Mease P. *Arth Care & Research.* 2011:63;64-85.

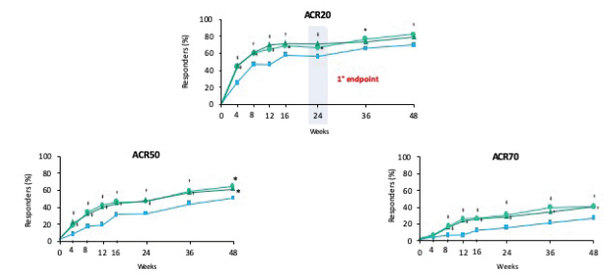
A very significant proportion of patients achieve this desirable state of MDA, with either the etanercept monotherapy or combination etanercept and methotrexate arms, almost identical. Then, these were statistically separated from methotrexate monotherapy. This supports the idea of use and efficacy of TNF inhibitors early on, more so than methotrexate, but methotrexate did a pretty good job in achieving MDA. So, if you're in a situation where you can use a TNF inhibitor first, great. This supports that.

If you're in a situation where you're required by insurance or by your government agency to use methotrexate first, then this gives you some confidence that in some patients, even minimal disease activity can be met. The other key point, though, from this is that there was no difference between an etanercept monotherapy and an etanercept plus methotrexate combination. This is very different than what we saw in rheumatoid arthritis where the combination of an etanercept plus methotrexate was really superior to an etanercept monotherapy and this led us in rheumatoid arthritis over the years to always recommend methotrexate in combination with TNF inhibitors when methotrexate was tolerated. However, in psoriatic arthritis, it's not at all clear that the combination is useful. Now keep in mind that this is an etanercept we're looking at. There may be less immunogenicity related to an etanercept therapy than another agent. And so sometimes we use methotrexate simply for the inhibition of immunogenicity. So that needs to be kept in mind in a separate context.

This shows you the ACR20, 50, and 70 responses from the same trial, very good ACR20 responses. Again, statistically superior in the etanercept step arms compared to methotrexate, and there was no difference between etanercept monotherapy and etanercept plus methotrexate.

If we look at the skin, this is one area where there might be some better results seen with the combination of an etanercept plus methotrexate as compared to etanercept monotherapy, and so this is one area where we might use the combination. And then in terms of radiographic progression there was clearly less progression with the etanercept arms as compared to methotrexate.

SEAM-PsA
Primary Results: ACR

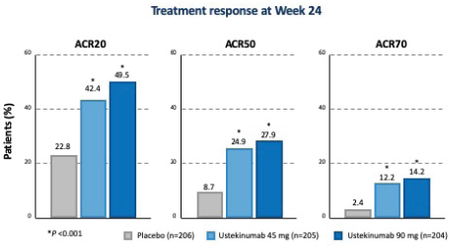


*P<0.05; † P <0.01; ‡ P ≤0.001; unadjusted. Observed data
Mease P, et al. *Arthritis Rheumatol.* 2019. 71:1112-1124.

IL-12/23 Inhibitor

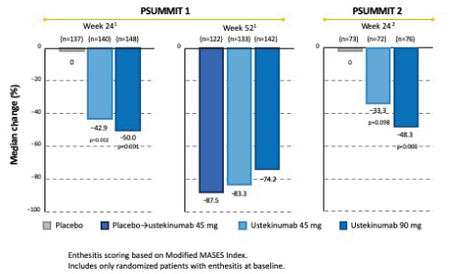
Let's turn to non-TNF approved and emerging therapies, and we'll start with the IL12/23 inhibitor ustekinumab. Here is a mechanism of action image in which we by inhibiting IL-12 and IL-23 by latching onto the p40 moiety of those molecules, which is what ustekinumab does. We can inhibit both the Th1 and Th17 pathways, which results in a reduction in interferon gamma, TNF alpha and IL-17. This is the result of the PSUMMIT 1 trial. These were patients that had not yet been treated with biologic agents and the ACR20 responses in the standard dose, 45 mg in 42.4% of patients and with the 90 mg dose 49.5% of patients, that higher doses were used in obese patients. These results are good and separated from placebo, although not quite as high as the results that we've seen with some of the other biologic agents. Here is the data in the PSUMMIT 1 and PSUMMIT 2 trials related to enthesitis using the Maastricht enthesitis index. The results were very good.

Ustekinumab
PSUMMIT 1 Trial



McInnes IB, et al. *Lancet.* 2013;382:780-789.

Ustekinumab
PSUMMIT 1 and PSUMMIT 2 Trials



Enthesitis scoring based on Modified MASES Index.
Includes only randomized patients with enthesitis at baseline.

1. McInnes IB, et al. *Lancet.* 2013;382:780-789;
2. Ritchlin CT, et al. ACR/ARHP 2012, November 10-14, Washington, DC, USA. Abs 2557.

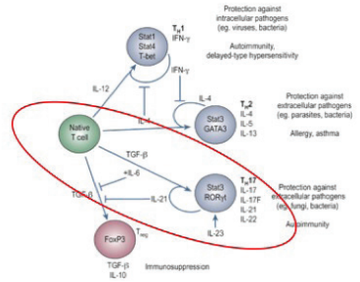
IL-17 Inhibitors

The next class of agents are the IL-17 inhibitors. There are 4 of these agents and we're going to focus on the first 2 data from the second secukinumab and ixekizumab trials.

This is a T cell differentiation pathway in which we see a naive T cell being stimulated by TGF beta and IL-6, as well as IL- 23, to become a Th17 cell and produce IL-17 as well as IL-21 and 22. We also know that there are a number of other cell types that can produce IL-17 and that's shown here on the left-hand side where other T cells, mast cells, neutrophils, for example, may all

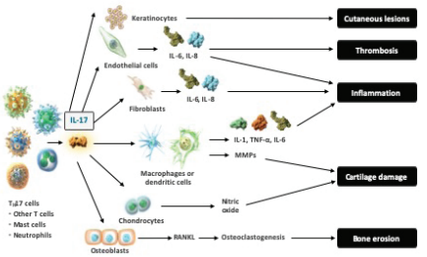
produce IL-17, some of these independent from IL-23 signaling. IL-17 then has an impact on a number of different effector cells including in endothelial cells, fibroblasts, macrophages, chondrocytes, osteoblasts and so forth, leading to the manifestations of disease in the skin, the joints, the bone, which are constituting psoriatic arthritis.

T Cell Differentiation Pathways
IL-17



McGonagle DG, et al. *Ann Rheum Dis*. 2019;78:1167-1178;
Bunte K, Beikler T. *Int J Mol Sci*. 2019;20:3394;
Sakkas LI, et al. *Front Pharmacol*. 2019;10:872.

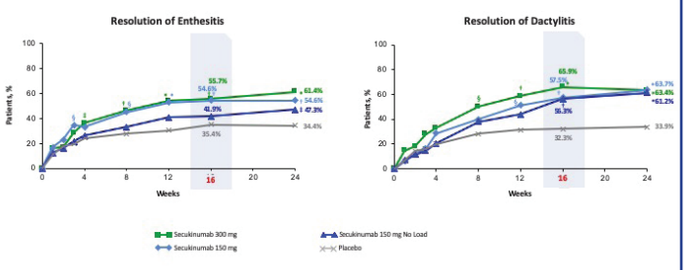
IL-17 Signaling
Role in Joint Inflammation and Matrix Destruction



Adapted with permission granted from Miossec and Kolls.
Miossec P, Kolls JK. *Nat Rev Drug Discov*. 2012;11:763-776;
Suzuki E, et al. *Autoimmun Rev*. 2014;13:496-502.

In the data in psoriasis trials with IL-17 inhibitors secukinumab showing very high rates of PASI response PASI 75% and roughly 80% as, and this is a clear, very beneficial effect that shows the important role that IL-17 plays in the pathogenesis of psoriasis. In regards to the data from the FUTURE 5 study, the largest trial with secukinumab, with 996 patients. Looking first at ACR20 responses where, with the 300 mg dose of secukinumab after a loading dose of 5 weeks, or 300 mg in the monthly administration of 300 mg sub-Q, we see 62.5% of patients at the primary endpoint achieving ACR20 response and then even with one 50 mg, either load or no load, we see very good responses clearly separated from placebo. Correspondingly, very good ACR50 and 70 responses with the best results being seen with 300 mg.

FUTURE 5
Resolution of Enthesitis and Dactylitis



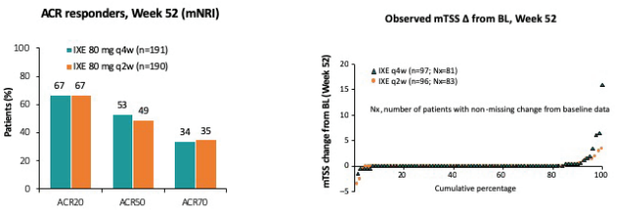
$^{a}P< 0.01$; $^{b}P< 0.05$ vs placebo.
Statistical analysis was based on a nonparametric ANCOVA. Linear extrapolation was applied if a baseline and week 16 value were available.
Mease PJ, et al. 2017 ACR Annual Meeting. November 3-8, 2017, San Diego, CA. P17L.

The FUTURE 5 study included two-thirds of patients that were naive to biologic treatment and then one-third of patients that had previously been on a TNF inhibitor therapy, and what we see are the results separating those 2 populations. In the anti-TNF naive group, which is those patients who have been less far along on the treatment pathway, we see even higher responses than we see within the overall group. So, 68.2% achieving an ACR20 response with the 300 mg dose and then slightly lower in the group that had seen previous biologic therapy with TNF inhibitors. An important outcome from the FUTURE 5 trial was demonstration of inhibition of structural damage progression and that was shown with this trial. We now know that secukinumab can inhibit structural damage progression. There was also very striking improvement of enthesitis and dactylitis, where we're seeing complete resolution of enthesitis and dactylitis in roughly two-thirds of patients with psoriatic arthritis with the 300 mg dose–slightly lower with the other doses of the medication.

Turning to ixekizumab, the other IL-17A inhibitor, and looking at data from the SPIRIT-P1 trial in which patients were enrolled who were naive to biologic treatment, and treated with either ixekizumab Q 2 weeks or ixekizumab Q 4 weeks. These are very good ACR20 responses. There was also in this trial an adalimumab reference control arm. This wasn't considered a head-to-head trial but instead it was used to make sure that the patient population was proper, and indeed, the adalimumab responses to this were as we would expect and clearly separated from placebo and similar to what we saw with ixekizumab . If we look at week 52 data, we see consistent results with very good ACR20, 50 and 70 responses and, as well, inhibition of structural damage progression. As with secukinumab, we see ixekizumab working across the board in different patient clinical domains. There was a study SPIRIT-P2 in which patients were all TNF inhibitor-exposed previously. And here we see the results from that trial, in terms of skin response, very high responses as well as ACR responses. Very similar to what we saw with secukinumab in this patient population.

Ixekizumab
SPIRIT-P1: IXE in TNFi-Naive Active PsA

- Radiographs analyzed for patients taking same IXE dose for full 52 weeks
- Little radiographic change with either dose



Mease P, et al. ACR 2016, Washington DC, 959; Van der Heijde D, et al. EULAR 2017, Madrid, OP0221;
Mease P, et al. *Ann Rheum Dis*. 2017;76:79-87.

There was a head-to-head trial between ixekizumab and adalimumab that was recently presented, called the SPIRIT-H2H (head-to-head) trial. This was powered to show a true comparison between ixekizumab and adalimumab. There was a novel primary endpoint, which was simultaneous achievement of a high joint threshold, that is an ACR50 response, and a very high skin threshold, that is a PASI 100 response. Simultaneous achievement of these 2 endpoints was achieved by 36% of the ixekizumab- treated patients and 28% of the adalimumab patients, which is statistically separated. So, in this primary and composite endpoint, ixekizumab bested adalimumab. It was predicted *a priori*, that the joint responses, as measured by ACR50, would be similar, that is noninferior between ixekizumab and adalimumab and, indeed, that

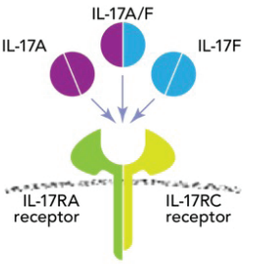
was shown, 51% of the ixekizumab arm, 47% of the adalimumab arm; so numerically better on the IXE side, but this was statistically insignificant, and then it was also *a priori* predicted that the skin responses would be better with ixekizumab and, indeed, that was shown. At week 24, 60% achieving a PASI 100 response and the IXE and 47% with adalimumab.

There were a number of other outcomes that were demonstrated, including using the SPARCC Enthesitis Index there was a statistical superiority of ixekizumab over adalimumab. Also, in terms of the PASI 75 and 90, as would be expected. Also, interestingly, several composite endpoints including minimal disease activity, very low disease activity, deaths, or remission and past deaths remission, where there was statistical superiority of ixekizumab over adalimumab. This trial helps support the overall efficacy of the IL-17 class of medications. We've been used to the overall efficacy of the TNF inhibitors for a long time. The IL-17s are newer to us, and this gives us confidence that in the various clinical domains of psoriatic arthritis, there is either noninferiority or superiority of the IL-17 medication vs the TNF inhibitor.

In terms of safety, there were no surprising signals. There was a slight increase of serious infection in the adalimumab group. And on the other hand, while we know that IL-17 protects the body against candida infection, we see a slightly higher frequency of candida infections in the IL-17 inhibitor arm, the ixekizumab arm. There were also more injection site reactions in the ixekizumab arm than with adalimumab. Note that the citrate-free, newer version of adalimumab was used in this trial, which we're learning yields less in the way of injection site reactions. And there were a very small number of inflammatory bowel disease players in the ixekizumab arm. None in the adalimumab arm.

Bimekizumab
Proof-of-Concept Study in PsA

- Monoclonal antibody directed against both IL-17A *and* IL-17F
  - *In vitro* human assay showed additive effects of IL-17A and IL-17F inhibition
- 4 doses at 0, 3, 6 weeks compared with placebo, primary endpoint ACR-N at Week 8
  - 40, 80, 160, 320 mg iv, with double dose at baseline



Glatt S, et al. EULAR 2016, London, #OP0108.

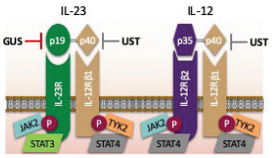
A newer agent that's in development, bimekizumab, is an IL-17A and IL-17F inhibitor, so slightly broader in its inhibition of IL-17. And this is data from a proof of concept study in psoriatic arthritis in which we saw very high ACR responses with this agent and also skin responses. We are anticipating this to have good effects and to be approved in psoriatic arthritis.

IL-23 Inhibitors

The next class of agents are the IL-23 inhibitors, which interact through inhibition of P19, which is specific to Interleukin 23 and thus this does not inhibit both IL-23 and IL-12. The first one is guselkumab and the results at week 24 with good ACR20, 50 and 70 responses, ACR20 at 58% and the guselkumab group clearly separated from placebo, very high skin responses, which we expect from an Interleukin-23 inhibitor class, and also very good responses with complete resolution of enthesitis and dactylitis and 57% and 55% respectively. The safety profile with the IL-23 inhibitors is proving to be a relatively good. The usual issue that we need to be cautioning about is the

Guselkumab
Phase 2 Trial

- Human monoclonal Ab against P19 subunit of IL-23
- Double-blind randomized placebo-controlled trial: 149 pts active PsA despite SOC, randomized 2:1 to GUS 100 mg sc vs PBO at 0, 4, then q8 wks
  - 9% received prior TNFi
  - 44% concomitant MTX



Deodhar A, et al. ACR 2016, Washington DC, #4L; Teng MW, et al. *Nat Med*. 2015;21:719-729.

Risankizumab (Selective IL-23p19 mAb)
Phase 2 Trial

- 185 patients, stratified by **prior TNFi use** and **concurrent MTX use** randomized 2:2:2:1:2 to RZB (4 arms) or PBO
- At **Week 24**, RZB-treated patients achieved:
  - Significantly higher MDA responses than PBO
  - SPARCC enthesitis score discriminated between RZB and PBO; LEI did not
  - No difference in Δ dactylitis count vs PBO
  - No new or unexpected safety issues

RZB effective in active PsA, including inhibition of damage; will proceed into phase 3

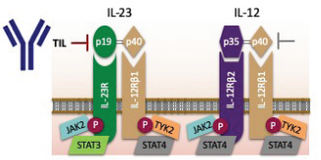
Mease PJ, et al. EULAR 2018, Amsterdam, OP0307.

potential for infection. The second agent to discuss is risankizumab. This has undergone a phase 2 trial in psoriatic arthritis and showed effectiveness not only in ACR and skin responses, but also inability to inhibit structural damage progression.

Third agent to mention in this class is tildrakizumab, a very similar mechanism of action by binding to P19, and we see high rates of ACR20 response at week 24 up to 79.5%, but also a relatively high placebo response, but statistically separated. Skin responses are very good with this agent PASI 75 and about approximately 80% and there was also evidence of enthesitis response.

Tildrakizumab (Selective IL-23p19 mAb)
Phase 2b Trial

- Double blind randomized placebo-controlled trial of 391 patients treated with 4 dose regimens TIL vs PBO
- Dosed through week 16, followed to week 24



Mease P, et al. EULAR 2019, Madrid, LB0002.

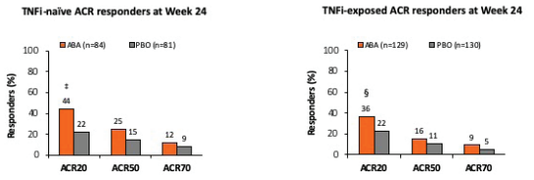
Co-Stimulatory T-Cell Blockade

The next agent is abatacept which has been approved in psoriatic arthritis. We know it well from rheumatoid arthritis. It works by co-stimulatory blockade with T-cell modulation. These are the results from a phase 3 trial showing modest ACR responses, separating out the TNF-naive and the TNF-

exposed patients that were approximately 60% of patients in this trial that had prior TNF exposure. This is a tougher crowd to treat than the TNF-naive population. And we also saw the linear response over time out to week 24 with 39% of patients achieving ACR20 response with abatacept treatment. Additional outcomes include the function response resolution of enthesitis and dactylitis and PASI at 75. Again, some effectiveness, although modest in these domains. And there was also some effect on radiographic progression.

Abatacept
Phase 3 Trial: ACR Responses

- 213 ABA 125 mg sc weekly vs 211 PBO (PBO 24 weeks → open-label ABA)
- ***~60% had prior TNFi exposure***



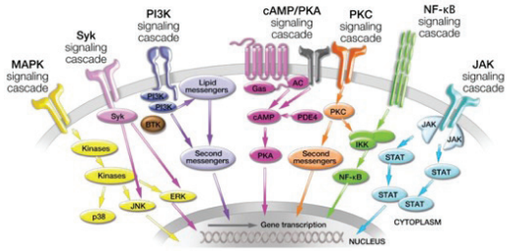
*P <0.001 vs PBO; †95% CI of estimate of difference in ACR50 response for ABA vs PBO did not cross 0 Nominal P-value 0.0034, 0.012§ vs PBO. Nominal *P*-values were not calculated for ACR50/70.

Mease P, et al. *Ann Rheum Dis.* 2017;76: 1550-1558.

Oral Targeted Drugs -- PDE4 Inhibitor

Now, turning to oral medications that have been approved or in development, first showing you the pathway by which these may act. The first drug we're talking about, apremilast, is a PDE4 inhibitor, which acts through the cyclic AMP/PKA pathway and reduces signal transduction in inflammatory cells. The second agent class we'll be talking about are the JAK inhibitors. In which the JAK inhibitor interacts with the JAK molecules on the inner aspect of the cell membrane and reduces a receptor, signaling into the nucleus of the cell and thus reducing activation of inflammatory cells.

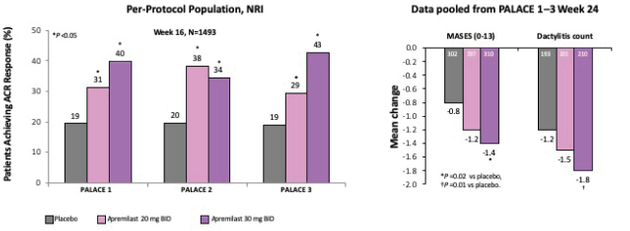
PsA
Cytokine Signaling Pathways



1. O'Sullivan L, et al. *Molec Immunol.* 2007;44:2497-2506; 2. Mavers M, et al. *Curr Rheum Rep.* 2009;11:378-385;3. Rommel C, et al. *Nat Rev Immunol.* 2007;7:191-201; 4. Tasken K, et al. *Physiol Rev.* 2004;84:137-167; 5. Baier G, et al. *Curr Opin Cell Biol.* 2009;21:262-267; 6. Ruderman E, et al. *Arthritis Res Ther.* 2011;13:125.

Here we see data with apremilast in psoriatic arthritis and we're starting with ACR response shown on the left and enthesitis and dactylitis response. These responses are statistically separated from placebo, are somewhat modest, so we target this drug early in use soon after methotrexate, if not right after methotrexate, and we target mild-to-moderate patients with this drug. The really exciting point about this drug, since it's efficacy on joints and skin is modest, is its relative safety. There is virtually no issue with serious infection, and no effect on comorbidities in an adverse way. If a patient is very averse to potential side effects and has mild-to-moderate disease, this is a good drug to try at that stage of the treatment ladder.

Apremilast in Active PsA
Effects on ACR Response, Enthesitis, and Dactylitis



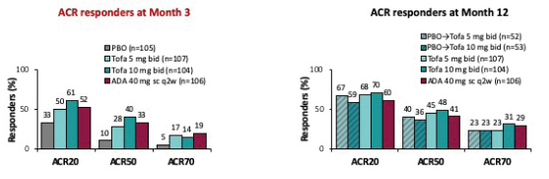
Gladman DD, et al. ACR 2013, San Diego, #816.

Oral Targeted Drugs--JAK Inhibitors

Turning to JAK inhibitors. JAK inhibitors have the ability to decrease the activity of a number of different inflammatory cytokines and so we think of it as a pan-cytokine inhibitors. With the drug tofacitinib, we've seen very good responses in the OPAL Broaden study, which are patients that are biologic naive seeing high rates of ACR20, 50 and 70 response and comparable to an adalimumab reference arm in this trial. There is climbing efficacy out through month 12. Patients were blinded to drug and to dosage, and this was an NRA analysis and so the fact that we're seeing higher responses actually reflects the true outcomes at this stage, even though not placebo-controlled. In terms of skin response, we see a modest response. This is up in the mid-40% range and, interestingly, comparable in this trial to adalimumab, we see improvements in physical function and there were very, very few radiologic nonprogressors in the trial, as noted. Enthesitis improved and there was a continued further improvement out through month 12, and the same was true for dactylitis.

Tofacitinib: Phase 3 OPAL Broaden (NRI)
ACR Responses

- 422 randomized TNFi-naïve pts (with an inadequate response to at least one csDMARD), 88% concomitant MTX
- **1° endpoints: Month 3 ACR20 and HAQ-DI**

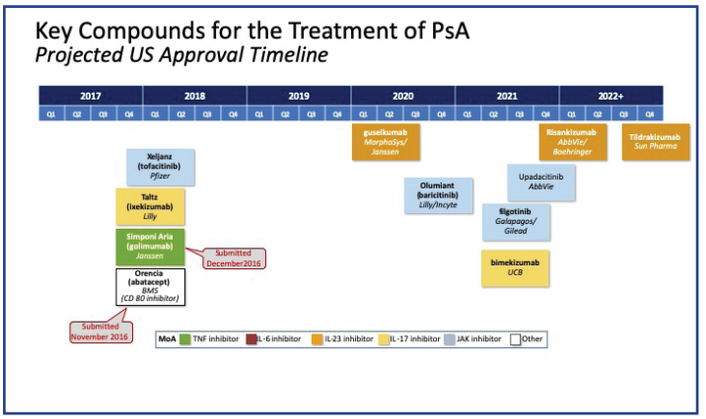


*P ≤0.05, †P <0.001, ‡P < 0.0001 vs PBO at Month 3

Mease P, et al. *N Engl J Med.* 2017;377:1537-1550.

Adverse events, serious infection, can occur, including herpes zoster, something that we've come to learn in rheumatoid arthritis trials. Otherwise, there was no new or different issue with tofacitinib compared to what we know as adverse-event profiles in rheumatoid arthritis. There was a second study called OPAL Beyond, enrolling patients that were previously exposed to TNF inhibitors. And here too, we saw good ACR20, 50 and 70 responses that were sustained over time, as well as improvement in function and skin scores. A newer JAK inhibitor that is more selective for JAK one, filgotinib, has been reported in psoriatic arthritis.

In a phase 2 trial, 80% of patients achieved an ACR20 response compared to 33% in the placebo arm. There were also good responses in terms of ACR50,



70, moderate responses in PASI 75. Minimal disease activity and Leeds Enthesitis Index responses. It looks as though this agent will be effective in psoriatic arthritis as it proceeds to phase 3, and might have a slightly better safety profile than the pan-JAK inhibitors. There are a number of agents, as mentioned, that are in development, including the Interluken-23 agents, and some of the JAK inhibitors, where we'll be seeing these introduced and approved for psoriatic arthritis, most likely in the relatively near future.

Summary

To summarize, we've walked through the pathogenesis of psoriatic arthritis, which involves a number of different proinflammatory cytokines, prominently TNF alpha and IL-17. Each affecting a number of different cells in different tissue compartments, including the skin, the joints, the bone and so forth. And so what we're looking at is the ability to reduce cellular activation in each of these clinical domains with a variety of medications, and especially of the TNF inhibitors, the IL-17 inhibitors, and then the currently approved IL-12/23 inhibitor, as well as some of the newer medicines that are coming along and likely will be approved in the near future, including IL-23 inhibitors and the ts DMARDs.

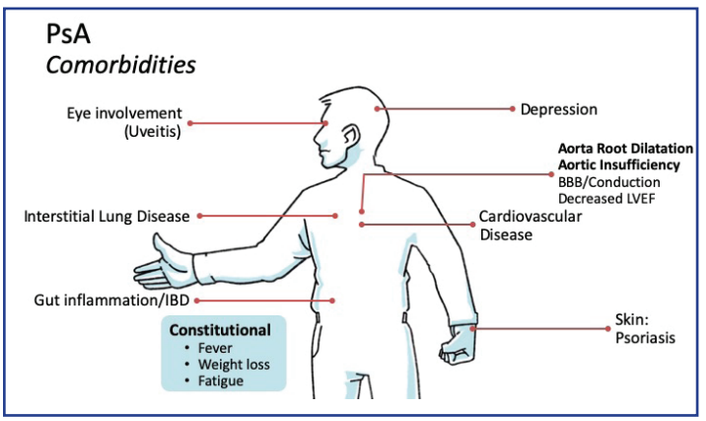
Comorbidities

Alexis R. Ogdie-Beatty, MD, MSCE

There are a number of comorbidities that are associated with psoriatic arthritis. Some of these are associated with the disease in general, such as inflammatory bowel disease and uveitis and others that are the result, potentially, of sustained systemic inflammation. These may include metabolic comorbidities such as cardiovascular outcomes, including myocardial infarction and increased incidence of diabetes, increased prevalence and incidence of cardiovascular risk factors including hypertension and hyperlipidemia, and obesity, and then, also, fatty liver disease.

Finally, I mentioned in our previous segment that depression and anxiety are also common in psoriatic arthritis. We are going to talk through some of these individual comorbidities. But as we think about the individual comorbidities, it's helpful to know why it's important to understand the comorbidities in psoriatic arthritis. First of all, they impact our selection of therapy.

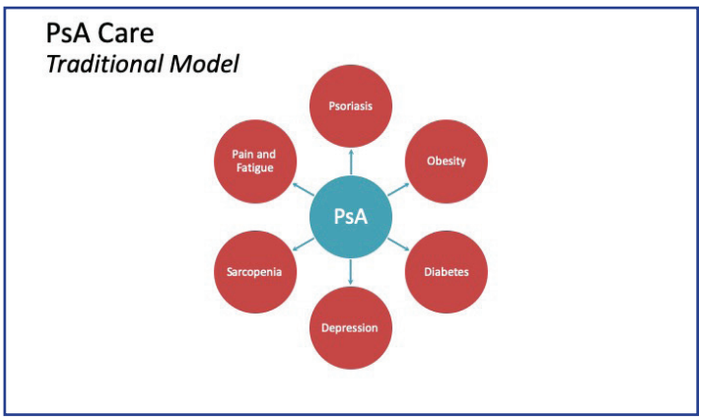
Some of these comorbidities may worsen with certain therapies. It is important to know which therapies not to choose in a patient with inflammatory bowel disease, for example. Additionally, we want the therapy to cover as many different domains as possible, both within the psoriatic arthritis and for the comorbidities. Finally, sometimes primary care doctors don't know about the comorbidities and the associations.



We have to be able to educate both the patient and the primary care providers about the potential risk for cardiovascular disease, for example.

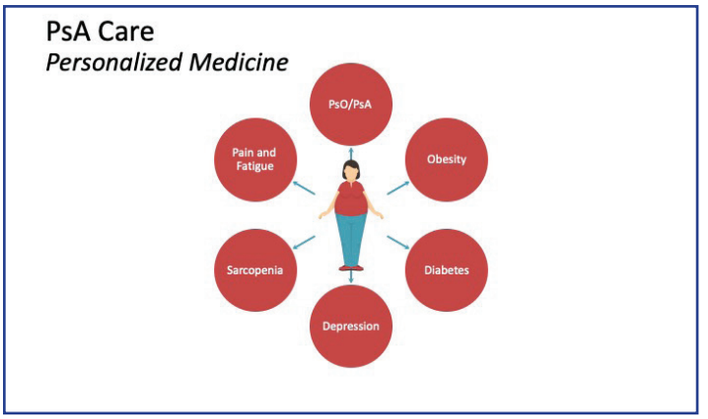
PsA Care – Traditional Model vs Personalized Medicine

As rheumatologists, one of the things that we commonly do is we think about the patient with psoriatic arthritis and we think, specifically, about their disease. In general, we don't have a lot of time to kind of think around the outside of the rim. We don't think about how each of these individual comorbidities that the patient may have is contributing to–not only to the disease the way that we see it–but also to their life.



In the traditional care model within rheumatology, we focus on the disease at hand. For example, when the psoriatic arthritis patient comes in with active disease we treat the psoriatic arthritis by prescribing a new therapy. But what I think we need to do, in order to get to better patient outcomes, is to put the patient in the center. In the traditional care model, psoriatic arthritis is in the center and the comorbidities are around the outside such that if you have psoriatic arthritis and you have a comorbidity, we think of the comorbidity being in the domain of the primary care physician.

In order to optimize outcomes and to truly have personalized medicine, if we put the patient in the center and think about all the different comorbidities, including psoriatic disease, and how they interact to encompass the patient

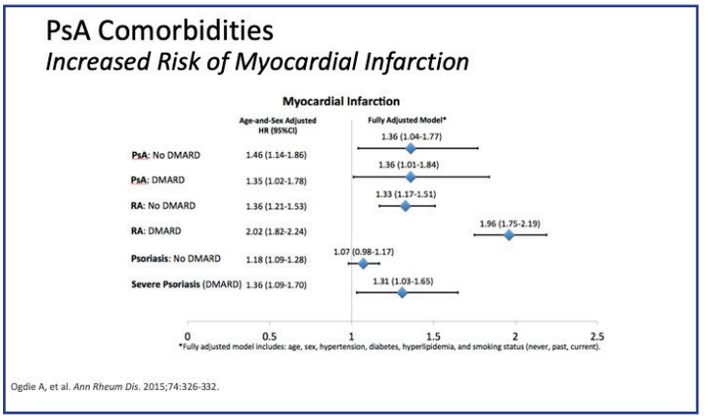


experience, then we can achieve those better outcomes through addressing the whole.

In this particular case, then, we need to be able to think about how can we address the patient's depression, even if that's so much as saying to the patient, please see your primary care doctor to discuss your depression, and sending the primary care doctor in their letter a note about depression as an item for discussion. It doesn't have to be prescribing for each of these individual problems but recognizing them and calling them out and suggesting both to the patient and the primary care provider that they are a problem that needs to be addressed.

Cardiovascular Disease – Myocardial Infarction

Let's talk through some of these individual comorbidities. I'm going to start with cardiovascular disease. This is one of the comorbidities that has the most publications available. It's been clear for a while that patients with psoriasis have increased risk for cardiovascular outcomes, particularly those with severe disease. Additionally, we've known for quite a while now that patients with rheumatoid arthritis have a significantly increased risk for cardiovascular disease as well. But it wasn't until about 4 to 5 years ago that it was also becoming more clear that patients with psoriatic arthritis had a significant increased risk as well.



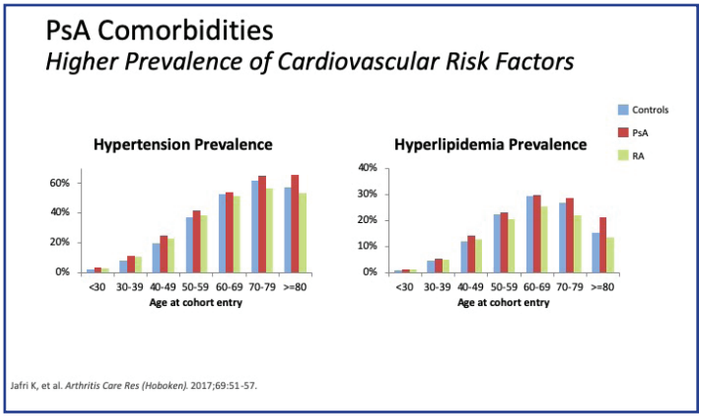
Ogdie A, et al. *Ann Rheum Dis*. 2015;74:326-332.

Some early studies demonstrate this risk in patients with more severe psoriatic arthritis, but it may be that even across the whole population there's an increased risk for cardiovascular events, in particular myocardial infarction. Patients with psoriatic arthritis and patients with severe psoriasis both have about a 30% or so increase in the risk for myocardial infarction or cardiovascular outcomes, in general.

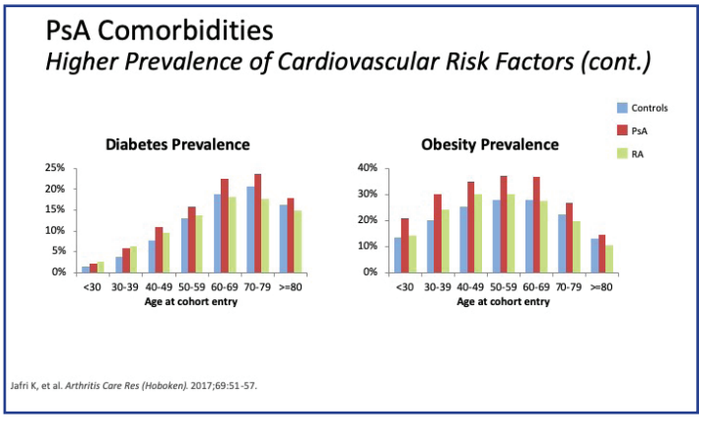
Patients with rheumatoid arthritis have about 2 times the risk of the general population. It is somewhere in between the general population and rheumatoid arthritis, and, certainly, it's something that needs to be addressed. Why do patients with psoriatic arthritis have increased risk for cardiovascular disease? Is it the systemic inflammation that's driving the development of atherosclerotic plaques?

Cardiovascular Risk Factors

That is one theory, and it probably is part of the problem. But it also turns out the patients with psoriatic arthritis tend to be more obese than the general population, and they also tend to have more cardiovascular risk factors. This includes an increased risk for hypertension, or increased prevalence of hypertension, compared to the general population and compared to patients with rheumatoid arthritis.



Jafri K, et al. *Arthritis Care Res (Hoboken)*. 2017;69:51-57.



Jafri K, et al. *Arthritis Care Res (Hoboken)*. 2017;69:51-57.

Also, an increased risk for hyperlipidemia, and increased prevalence as well, compared to the general population. But one of the most stunning aspects is the increased risk for diabetes. Patients with psoriatic arthritis have about a 45% increase in the risk for diabetes compared to the general population, and they also have an increased risk for diabetes compared to patients with rheumatoid arthritis. There certainly is some difference in metabolic disease in patients with psoriatic arthritis compared to rheumatoid arthritis, or compared to the general population, that we need to be aware of.

PsA and Obesity

I mentioned that obesity is certainly part of this, and we think that having more obesity or fat mass can drive some of the inflammation. That fat mass itself is an inflammatory organ and it does probably stimulate TNF and inflammatory cascade. In addition, patients who have systemic inflammation do have more conversion of their plaques to unstable plaques that could rupture and cause myocardial infarction.

I find this overlap with metabolic disease really interesting and also important. As I mentioned, patients with psoriatic arthritis tend to be more obese than the general population. They're also more obese than patients with psoriasis and more obese than patients with rheumatoid arthritis, and they also have more fatty liver disease. Both fatty liver disease and obesity are significantly associated with decreased likelihood of responding to a TNF inhibitor. This is probably true across therapies, but it's been best studied in patients who are initiating a TNF inhibitor.

PsA – Effects of Weight Reduction

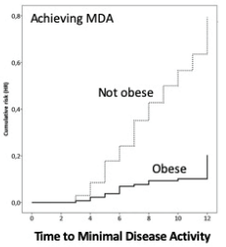
What happens if we address the specific problem? What if we addressed the obesity? Well first, how big of a problem is it? It turns out that patients who are obese or have a BMI greater than 30 are about half as likely to have a response to therapy, really achieve remission, and that may be measured by minimal disease activity or by a CDAI, for example.

PsA Comorbidities
Obesity Affects MDA Achievement

Odds of achieving MDA

Body Weight	OR
Normal	Ref
Overweight	0.66 (0.50-0.87)
Obese	0.53 (0.41-0.69)

*Adjusted for age, sex, duration, DMARD use, NSAIDs



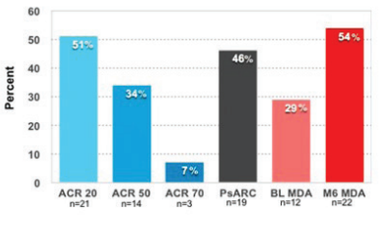
Eder L, et al. *Ann Rheum Dis*. 2015;74:813-817;
di Minno MN, et al. *Arthritis Care Res (Hoboken)*. 2013;65:141-147.

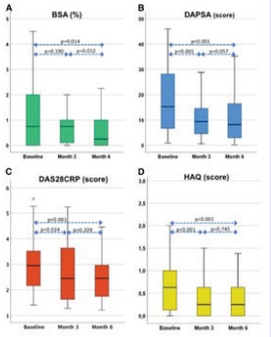
Similarly, patients with fatty liver disease have a similar likelihood of achieving remission. But what's really interesting is what happens if you get patients to lose weight. di Minno and colleagues published a report of a study in which they randomized patients who are initiating a TNF inhibitor, and happened to be obese, to 1 of 2 diets. They either received a Mediterranean diet or they were on a freely managed diet.

It turned out that the Mediterranean diet was significantly better in terms of getting patients to minimal disease activity compared to the freely managed diet. What was most striking is that regardless of what diet arm you were on, if you lost weight, you did better. If you lost 5% to 10% of your body weight, you were 3.75 times as likely to reach minimal disease activity as someone who didn't lose weight or lost less than 5% of their weight.

If you lost more than 10% of your body weight, you were 6.67 times more likely to reach minimal disease activity. That's a substantial effect, a bigger effect than we see with most of our therapies; so, weight loss is really important for our patients. In addition, there are newer studies now that have demonstrated that even a very low-calorie diet in patients who are in reasonably low disease activity can continue to improve their disease activity.

Very Low Calorie Diet in PsA





Klingberg E, et al. *Arthritis Res Ther*. 2019;21:17.

Klinberg et al gave patients with psoriatic arthritis, with at least some activity and obesity, a diet, which was a very low-calorie diet. So, it was restricted to about 600 calories per day made up of shakes. They basically had 4 shakes a day, which is a tough diet, for 16 weeks. What they found at the end of 16 weeks is that most patients lost weight and those patients also felt significantly better in terms of patient-reported outcomes; but also in objective measures of disease activity.

Most interesting to me is that even at 12 months, most of them maintain some of that weight reduction and maintain the benefits of the weight reduction even after converting back to a regular diet after 16 weeks. Weight reduction is really important. Achieving weight reduction is very difficult, but it's something that we should always counsel our patients about, particularly those who are obese.

PsA Comorbidities
Increased Risk for Suicide

	Unexposed	PsA	RA
Suicide	40	12	31
Deaths (%)	0.61	1.41	0.20
Incidence	0.93	2.44	1.29
Age- and Sex-Adjusted HR	REF	3.03 (1.56-5.90)	2.47 (1.51-4.04)

Ogdie A, et al. *Rheumatology (Oxford)*. 2017;56:907-911.

Depression and Anxiety

Now let's move on to some other comorbidities. We have talked about depression and anxiety. Patients with psoriatic arthritis are much more likely to be depressed than patients in the general population or even patients with psoriasis. If you have psoriatic arthritis, the probability of having depression is around 22%, compared to about 9.6% in patients with psoriasis, according to one study studying the Toronto cohort.

In addition, anxiety was common. Around 36% of patients had anxiety, and then around 17% of patients or 18% of patients had both depression and anxiety.

Not only are depression and anxiety important for therapy outcomes, but they're also important because suicide is more common in patients with psoriatic arthritis. Patients with psoriatic arthritis have a hazard ratio of 3 for attempting suicide compared to the general population. This is a significant elevation compared to other people without psoriatic arthritis. It is really important that we screen for depression and consider this and ask about suicidal ideation in patients who are severely depressed.

Crohn's Disease and Eye Disease

Inflammatory bowel disease and uveitis are known to be associated with spondyloarthropathies. Crohn's disease is actually more commonly associated than ulcerative colitis. Among patients with psoriatic arthritis and psoriasis, they have a hazard ratio of about 6.5 for developing Crohn's

PsA Comorbidities
Crohn's Disease

Nurses Health Study I and II

	Person-years	Cases	Age-Adjusted RR	Multivariable-Adjusted RR
No psoriasis	2,401,946	174	REF	REF
Psoriasis	41960	11	3.74 (2.03-6.89)	3.49 (1.89-6.44)
Psoriasis/PsA	5661	3	7.99 (2.55-25.08)	6.54 (2.07-20.65)

Li WQ, et al. *Ann Rheum Dis*. 2013;72:1200-1205.

disease compared to patients without psoriasis or psoriatic arthritis; among patients with psoriasis, their hazard ratio is about 3.5. There is a significant elevation in the risk of Crohn's disease.

On the other hand, Crohn's disease is generally rare in the population and it affects about up to 10% of patients with psoriatic arthritis. It is important to consider, particularly as something that we screen for. When I'm doing the review systems for patients with psoriatic arthritis, I commonly ask about bowel movements, for example, and if they're having normal bowel movements or if they're having any diarrhea.

If they are having diarrhea, then I would consider referring back to primary care or to a gastroenterologist. I also mentioned uveitis, which is more common in patients with psoriatic arthritis and psoriasis compared to the general population. It affects up to 10%, depending on the study that you've looked at. Both uveitis and inflammatory bowel disease may help you differentiate therapy. It is important to know about not only do they have it, but how active are those conditions.

While we think about uveitis often as the most common eye disease, it's actually not the most common. It might be the most differential from the general population. But among patients with psoriatic arthritis, the most common eye complaint is actually dry eye. We don't exactly know why that is. They tended not to fit Sjogren's criteria as if they would in rheumatoid arthritis, but it is something that you can refer patients to ophthalmology to manage if they're having issues with dry eye.

Comorbidity Screening – GRAPPA Recommendations

As is a part of the GRAPPA treatment recommendations published in 2015, we developed a set of recommendations for comorbidity screening. These include all of the things that I've already discussed, but to summarize, among patients with obesity, it's important to discuss the impact of obesity on a treatment response and to recommend weight loss. Diabetes, it's important to screen for diabetes using general recommendations. In the United States, the recommendation is that adults should have hemoglobin A1c at some point or a fasting glucose.

Inflammatory bowel disease screen by asking questions about gastrointestinal symptoms. For ophthalmic disease, ask about eye disease, in particular, red painful eyes.

What we do know about malignancies is that patients with psoriatic arthritis who are on TNF inhibitors or other biologic agents, or even methotrexate, have an increased risk for nonmelanoma skin cancer. They should have a skin check annually, especially if they're on one of those therapies, and particularly if they've had phototherapy in the past.

Liver and kidney disease, we're often the ones checking all the labs. It is important to pick up on fatty liver disease because that may steer you in one or another direction in terms of therapy. Finally, depression and anxiety are important to screen for as a part of your review of symptoms as well.

PsA Comorbidities
Screening Considerations

Cardiovascular Disease	**Check blood pressure, lipid panel Encourage smoking cessation**
Obesity	Council patients on the benefits of weight loss
Diabetes	Check fasting glucose or hemoglobin A1c
Inflammatory Bowel Disease	Ask about gastrointestinal symptoms in the ROS
Ophthalmic Disease	Ask about ophthalmic symptoms in the ROS
Malignancy	Consider yearly or periodic skin check for patients with a history of UV light therapy
Liver and Kidney Disease	Check LFTs, Cr, HBV/HCV serologies before starting therapy
Depression and Anxiety	Ask about symptoms of depression and anxiety

Ogdie A, et al. *Curr Opin Rheumatol*. 2015;27:118-126.

GRAPPA Treatment Recommendations vis-a-vis Comorbidities

I mentioned that comorbidities often also influence treatment selection. Within the GRAPPA treatment recommendations, we also included a table that has each comorbidity, as well as all available therapies at the time the treatment recommendations were republished, and kind of some notes about that. Avoid certain therapies. For example, avoid secukinumab in a patient with inflammatory bowel disease or avoid TNF inhibitors in patients with New York Heart Association class III or IV heart failure. There is a nice grid there that is an easy reference if you are interested in which comorbidities your patient has and what therapies they may not do best with.

Comorbidities Influence Treatment Selection

Comorbidity	NSAIDs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast	Secukinumab
Cardiovascular Disease	C	?											?		
Congestive Heart Failure								?	?	?	?	?			
Obesity					C										
Metabolic Syndrome		C			C										
Diabetes		C			C										
Inflammatory Bowel Disease	?														C
Uveitis		P						?	P	P					
Osteoporosis		C													
Malignancy								C	C	C	C	C	?		
Fatty Liver Disease	C			C	C	C									
Chronic HBV or HCV	C				C	C		SM/P	SM	SM	SM	SM	?		
HIV								SM	SM	SM	SM	SM	?		
Chronic Kidney Disease	C				C	?	SM								
Depression														C	

C	Caution
?	Data insufficient, concerns raised
P	Preferred therapy
SM	Requires special monitoring

Coates LC, et al. *Arthritis Rheumatol*. 2016;68:1060-1071; Ogdie A, et al. *J Rheumatol*. 2014;41:2315-2322.

Summary

In summary, comorbidities are a really important part of psoriatic arthritis management. This is important because we are the ones who often know these relationships and it's important for us to screen for them, and to alert primary care physicians, and to educate patients about the existence of these comorbidities and the need for management in order to improve overall outcomes. In addition, knowing about comorbidities is really important for our understanding of treatment selection for that individual patient and for how we're going to monitor the therapy or what we might consider in the future as we're continuing to follow the patient forward in time. In order to optimize overall outcomes, it's really important to screen for these comorbidities, and to address them as we treat the patient, to improve their overall disease.

Case: Addressing Obesity

Alexis R. Ogdie-Beatty, MD, MSCE

Initial Presentation

This is a 40-year-old patient of mine who came in as a new patient with psoriasis and a new inflammatory arthritis. She is treatment-naive, newly diagnosed.

She came in because she had been having toe pain and swelling intermittently in the last 3 months or so. Then over the last 6 weeks, in particular, she developed knee swelling and a swollen finger and then, today, her toes are fine, but she still has the knee and finger swelling. Clearly there's inflammatory arthritis there. She has active psoriasis that's been getting worse lately as well, and she has morning stiffness that is lasting for about an hour.

Her past therapies for her psoriasis had been primarily topicals, although she did do prior phototherapy on her legs and for her joints. She's been mainly self-treating with Naproxen. She did have Naproxen 500 mg twice daily prescribed by her physician as well. She's been finding benefit with it, but certainly continues to have swelling, disability and morning stiffness, and she needs something more.

Exam & Labs

On a full review of her past medical history, she has high blood pressure. Her blood pressure today is 145/95. She's also obese; her BMI is around 32. She has a normal heart rate and respiratory rate and temperature. On exam, her psoriasis body surface area is around 5%, so pretty significant. It's mostly on her lower extremities, scalp, and behind her ears. She also has some nail pitting.

Case: 40-Year-Old Woman with Psoriasis
Exam & Labs

- She has mild hypertension (BP 145/95), she is obese (BMI 32), and has normal HR, RR, and temperature
- She has psoriasis with ~5% BSA, mostly on her lower extremities and scalp
- She has nail pitting with some onycholysis of 1 nail
- She has 3 swollen joints, 3 tender joints, 1 tender lateral epicondyle and right troch bursa tenderness (2 entheses on SPARCC index), and dactylitis of the right second finger
- No spine or SI joint tenderness or pain on ROM of the spine
- Labs are remarkable for elevated CRP 5 mg/dl (<3 normal), and her fasting glucose is 110

Doesn't really bother her, but she does get her nails painted frequently because she doesn't really want anyone to see the pitting or the onycholysis of 1 of her nails. On a joint exam, we did a 66/68 joint exam and she has 3 swollen joints and 3 tender joints. She also has 2 tender entheses, 1 in the lateral epicondyle and 1 at the right trochanteric bursa, and she has dactylitis of her second finger.

She doesn't have any spine tenderness, no pain on range of motion of her lumbar or cervical spine, and no history of back pain really being all that bothersome to her. Labs are remarkable for an elevated C-reactive protein of 5 mg/dL where less than 3 is normal on that particular scale, and her fasting glucose is 110.

Initial Treatment Options

The first question is, which therapy will you begin? We discussed all the different therapy options for her. But let's think about some of her key comorbidities. One is obesity and the other one is hypertension. The NSAIDs aren't really helping with her hypertension because we know that they can increase blood pressure. She can still take them for symptomatic relief, but we have to be a little bit careful with that.

As far as the obesity, how does that interact with other therapies? Well, first of all, it does make her less likely to respond to any particular therapy well, but the other thing that I worry about with obesity is fatty liver disease. There are a lot of patients, particularly those that have central obesity, who may have more organ obesity as well, or visceral obesity, and that's associated with fatty liver disease.

Sometimes when you start methotrexate or leflunomide, you often see that liver function test bump and I generally would prefer to use something else in that particular scenario. Additionally, she has a pretty aggressive inflammatory arthritis, particularly for someone who just developed inflammatory arthritis. Some of her poor predictors of inflammatory arthritis or poor prognostic predictors are elevated C-reactive protein.

She has dactylitis and she has a polyarticular arthritis. I forgot to mention that some of the joints that are swollen are not tender or vice versa. She has more than 5 joints involved total. This puts her in a more aggressive phenotype and what adds to the severity definition per the PsA guidelines from the NPF and ACR published in January 2019, are that she's having a significant burden from her arthritis.

We ask her more details about how this is affecting her, is that causing her to have problems carrying her baby around, her toddler, and causing trouble and getting everybody ready for school in the morning? She has felt an impact on her life that's been negative from the disease. So, those would be more in a severe category then, or moderate-to-severe category. According to the ACR/NPF guidelines, you would then choose a TNF inhibitor as a first line agent for this particular patient.

That's particularly true since she has more psoriasis as well. That might drive you more toward a biologic first rather than oral systemic therapy. To summarize that whole thought process, obesity might steer me away from methotrexate or leflunomide. The fact that she has psoriasis and pretty significant amount of psoriasis, as well as kind of a more moderate-to-severe active PsA would, according to the ACR/NPF guidelines, steer you more toward a TNF inhibitor as a first line agent.

There are a lot of conditions in those guidelines about why you would choose another biologic. For example, first, such as patient preference for dosing interval, or the psoriasis being particularly severe, might lead you to choose interleukin-17, for example, but, in general, the first therapy might be a TNF inhibitor. Beyond just getting the therapy, though, giving her a prescription for one of the TNF inhibitors, we need to think about a few other things.

Screening Prior to Starting Therapy

One is, we have to do all the screening prior to starting the TNF inhibitor. That would be a hepatitis serologies and potentially an HIV. Then we have to deal with the fasting glucose. She has a fasting glucose of 110, which would be in the insulin resistant range, but by some definitions it does constitute diabetes.

You could either send the hemoglobin A1c with your next set of labs, which would be typically my practice, or refer back to primary care to note the

Case: 40-Year-Old Woman with Psoriasis
Further Workup Before Initiating Therapy

- Diabetes
- Lipids
- Consider full cardiovascular risk assessment
- Depression, anxiety

elevated glucose. As a rheumatologist or someone who gets labs frequently, we are often the ones picking up the diabetes. It is really important to keep your eye out for those abnormal glucose levels and ask [if] the patient wasn't fasting before they got the blood test done. We sent a note about diabetes.

In addition, she probably had elevated risk for cardiovascular disease and there's a few things that suggest this. One is she's obese; number 2, she has hypertension; number 3, she either has prediabetes or diabetes and she has an elevated C-reactive protein, which may be making her more likely to have elevated risk for cardiovascular disease.

As a part of your cardiovascular risk assessment, you may then send a lipid panel as well. Or again, direct the primary care doctor to perform a full cardiovascular risk assessment, for example, such as Framingham score and then to direct care appropriately. Of note, there are new guidelines from the ACA and AHA that are for primary prevention of cardiovascular disease and they now list psoriasis as well as rheumatoid arthritis and lupus as risk factors for cardiovascular disease.

That's a new addition to these guidelines. She already has an elevated risk for that. Her primary care doctor may be considering a statin. Now we've talked about the bundle of her metabolic comorbidities. We didn't ask her about depression in the very beginning, but that would be really important for screening for depression and anxiety in this woman who's got a new diagnosis of inflammatory arthritis that's clearly impacted by her disease in the way that she's leading her life.

Talking about depression, anxiety, normalizing that this is very common, particularly when people are first diagnosed. But throughout the course of the illness people may have depression, anxiety, and it's really important to address that in order to improve overall outcomes.

Importance of Physical Activity

Putting together this patient's full plan, there's one piece missing, which is the physical activity piece. So regular physical activity is recommended by EULAR guidelines now for all patients with inflammatory arthritis or osteoarthritis. In fact, not only is physical activity recommended, it's recommended at the same level as a patient without inflammatory or arthritis or joint disease.

Patients are supposed to be exercising about 30 minutes a day, 5 days a week. That's a lot to jump into, and I wouldn't recommend my patients jump right into 30 minutes a day, 5 days a week. What I would suggest is slowly increasing exercise capacity. Would you do that while her disease is still active? Probably not. You might tell her when she's feeling a little bit better, but it's certainly okay to get started on some light exercise and in particular, for example, water exercise or even light stretching, for example.

It's never too early to start doing something, and if it hurts too much, do something different. I also tell patients that when they first start exercising, they're going to have to ease into it a little bit because they may get a little bit sore afterwards because they haven't done that for a while. Some patients also feel like they have flares after starting exercise.

That makes it even more important to go gradually. Prescribing physical therapy or aquatic therapy to help patients get started can be really helpful in this particular scenario.

Communicating Treatment Plan

We have just addressed that our patient's plan now would have: start a TNF inhibitor, get blood work prior to the TNF inhibitor prescription being approved or started, screening for diabetes and screening for lipids, cardiovascular risk, and screening for depression and anxiety; and then increasing physical activity, whether that be with physical therapy or on their own at first.

It is a lot for a patient to digest, but it's nice to have a nice written plan and sometimes you can create a template where you can kind of just check off the pieces of the plan. I also have a general handout that has kind of all these pieces of the puzzle that can be helpful for patients to kind of digest all the pieces and just start with one piece at a time.

A 3-Month Follow-Up

We sent our patient off with a treatment plan and it was a lot all for the first visit. We started the TNF inhibitor, and she returns 3 months later. She's feeling much better, but she continues to have some joint pain. So, we go through the whole review systems and ask her about morning stiffness and all the typical questions that we ask as part of the assessment and other review symptoms. She does ascribe to have some depression this time.

Case: 40-Year-Old Woman with Psoriasis
3-Month Follow-Up

- She returns 3 months after starting a TNFi
- She's feeling better, but she continues to have some joint pain
- On ROS, she ascribes to some depression
- Not exercising much due to fear of worsening arthritis
- RAPID3 declines from 12 to 7, suggesting she's had a good improvement
- On exam, no significant swelling although the dactylitis is still not completely resolved
- Knee pain intermittent as well, but no significant swelling on exam

She's also not exercising because she's really nervous about how that's going to affect her joints and she fears that it's going to worsen arthritis. On a patient-reported outcome, her RAPID3 declines from a 12 at her first visit to 7 at this visit. So, we know that suggests that there's really good improvement overall on the TNF inhibitor. On exam, there is no significant swelling. The dactylitis isn't completely resolved yet. It's still present, but it is better and not as tender anymore. Finally, there's knee pain but intermittently on range of motion, but there's no specific tenderness and no swelling on examination.

Follow-Up Management Plan

She continues to have a BMI of 32 and we didn't discuss this at the last visit. So that brings us to our management plan now and that might be one of the

Case: 40-Year-Old Woman with Psoriasis
Follow-Up Management Plan

- Obese patients likely to have inadequate response (but she's done OK)
  - Weight loss is an important discussion here
  - Consider referring her to the nutritionist
- Also important to discuss management of depression
- Physical activity important as well
- Physical therapy may be a good place to start!

things we're going to discuss first. In summary, she's done very well on a TNF inhibitor initially, but she continues to have some symptoms of joint pain and there's a lot more we could optimize about her overall care.

Let's start with the obesity. During the comorbidity section I mentioned that patients who were obese and who lost weight were able to achieve minimal disease activity more readily than patients who did not lose weight. So, now's the time to bring that up with this patient. At the first visit, it's kind of difficult to bring that up as a first thing. I often just hint at it and then now is the time we might be able to have a more in-depth discussion about weight loss.

How do you recommend weight loss to a patient? You can kind of feel this best out with a patient and mention just a matter-of-factly that today I see on your bioscience it calculates the body mass index, and your body mass index is 32. We know that patients with a BMI of greater than 30 have a harder time achieving low disease activity on a therapy.

This is partly because fat may produce some inflammation and there's also a mechanical component to the fat as well. So, we know that from this particular study that if you reduce your body weight by 5% or more that can lead to a significant improvement in your overall outcomes. Patients will naturally have a variety of different responses to that. You may consider referring them back to primary care to talk about more in depth ways of managing this.

You might also consider referring to nutritionist, depending on where you are, that may or may not be easily accessible or there's a variety of weight loss programs online you can suggest. So, for example, Weight Watchers or there's a couple of different apps like a Lose It app for example, where the patient can track their physical activity as well as their calories and shoot for a goal for weight loss.

You don't have to be the primary one driving that. That could again be referred back to primary care, but it's really important to mention to the patient so that they're aware of the fact that there is something that they can do to improve outcomes as well. Next, for the joint pain, sometimes I find the patients continue to have joint pain after the swelling is gone, and that may be because there's still inflammation that we can't see or maybe it's because of differences in the muscle quality around the joints, if they haven't been using them as much, but regardless, some of this can get better with physical therapy. Physical therapy prescription would be very important now to help her dealing with this residual pain and talking more about how to increase exercise, and kind of thinking through with the patient how might they increase physical activity.

Finally, it's really important to discuss the depression with her and also talk about how improving depression might also improve her overall sense of well-being and the way she's feeling. Depression can certainly worsen pain. It can also worsen sleep, and poor sleep leads to worse pain. Depression is also a form of stress and we know that higher stress in the autoimmune disease can lead to disease flares.

There is a cycle there and if we can help break the cycle by talking about the depression, treating the depression, then we might get better outcomes as well. That, again, could be referred back to primary care, directly to therapy, or to psychiatry as well, depending on what the patient feels most comfortable with.

Case: Holistic Management

Alexis R. Ogdie-Beatty, MD

Initial Presentation

I'm going to talk about Tina. She is a 46-year-old business owner. She came to me with multiple different inflamed joints, but particularly dactylitis. Her main problem was dactylitis of her fingers.

Case: Tina
46-Year-Old Business Owner

SJC	5
TJC	4
Enthesitis	0
Dactylitis	2
Psoriasis	<1%
Spine	no
Impact	Can't use fingers, trouble typing, severe pain in dactylitic fingers, pain causes her to be grumpy, affects relationship with husband

Because of the dactylitis of her finger, she was having trouble typing. Her business is an online business and she's always on the computer, and she was actually having trouble typing and trouble working. She also had substantial amounts of pain and so some of that was in the joints where she clearly had swelling. Some of it wasn't as clearly related to swelling; it was in some entheseal spots, for example, or some spots, we kind of call fibromyalgia spots or tender points sometimes. She may have had some overlay of fibromyalgia or more now known as central sensitization.

Follow-Up Management Plan

As we treated her for her inflammatory arthritis, we did bring down her level of pain overall. So, she was able to function better. When she was having high levels of pain that really interfered with her life in a variety of different ways.

For example, it affected her relationship with her husband. When she was in pain, she said she would be cranky and really sharp with him and grumpy and, if you're grumpy and sharp, it's really hard to have a good conversation, and it does hurt the relationship over time. In addition, it was hard to manage her business. She was just so distracted by the pain and fatigue and because of that she'd become more depressed.

She also had interrupted sleep, she was sleeping only a couple hours a night, and then the pain continued to worsen. So, this began a cycle that we

Case: Tina
Follow-Up Management Plan

- Treatment of inflammatory arthritis reduced her overall level of pain
- We adopted personalized/holistic approach
  - To improve her sleep, she enrolled into a sleep study (it turned out, she had sleep apnea)
    - Improved sleep helped with depression
  - Addressed fatigue and sarcopenia with exercise
  - Physical therapy may be a good place to start!

commonly see in rheumatology and particularly in psoriatic arthritis, axial spondyloarthritis, and RA as well. We see this kind of a cycle where you had depression or poor sleep, fatigue, worsening pain, and it just kind of keeps cycling. Then because people don't feel well, they don't exercise. So, they're having less and less movement all the time as well.

I commonly draw out that circle for patients and say I can give you any therapy for psoriatic arthritis, but it's only going to make you feel so much better because we have to address all these other things that are contributing to the pain. So, we decided to kind of target each one a little bit, and that's usually what I suggest, ie, doing little pieces for each so they can kind of lift up some of the pain.

For example, for sleep, we got her plugged in with a sleep study and she in fact had sleep apnea. Addressing the sleep apnea was helpful in terms of getting better sleep. You're getting better sleep, your depression gets a little bit better anyway, but we also got her into therapy so that they could help her kind of work through her depression, but also how her relationship with her husband is going and how she's managing her business.

Then we also talked about fatigue and exercise. Exercise is incredibly important for addressing fatigue, and, if anything, addresses fatigue better than any other aspect of the disease. It can also help with sleep as well. It can also help with pain and it can help with sarcopenia that can happen in patients with inflammatory arthritis who aren't active on a regular basis.

Sarcopenia can maybe cause some joint immobility or kind of differential joint function that could cause more pain as well. By addressing all of these things, people can start to feel better. Unfortunately, over time her business kind of fell apart and she ended up losing her business. You can imagine that caused a severe flare of her arthritis and her psoriasis, but also her pain. These flares can be very stress-related.

Unfortunately, that also means we have to kind of put that into the context now of dealing with her disease as well. Therapy is very helpful in that particular point but now we ended up adding on amitriptyline, for example, at night, so that can help her sleep a little bit better, but also can help with pain. There's a variety of other methods of addressing pain. Not opiate medications because those are generally not recommended, particularly for patients with fibromyalgia.

While they're bad overall, they're really bad for fibromyalgia because there's no ceiling, just keep going up. There are other therapies like duloxetine for example, or even venlafaxine that can help, or other TCAs or tricyclic antidepressants such as nortriptyline may be helpful as well. A variety of other ways of managing central sensitization or fibromyalgia.

This gets very complicated when you're assessing patients and especially when flares happen. Sometimes it's both, sometimes it's one or the other, but it's important to go back to that circle. The disease is part of the circle, but also there's the depression, the stress, the anxiety, the sleep and fatigue and exercise as well, and make sure that we're kind of addressing the whole circle.

Summary

I hope that over the course of these short segments I conveyed that psoriatic arthritis is a complex disease that is more than just the disease of peripheral joints. It impacts patients in very different ways and is different from patient to patient. Not only is it heterogeneous in terms of the physical manifestations that we see as physicians, but also in the way that it impacts patients' lives.

In order to really give patients the overall best outcomes possible, we really do have to think about the whole patient and all the different aspects of, not only the disease, but also the aspects of the impact in order to improve long-term outcomes, and also to improve how the patient feels and how they're able to live their lives.

Case: Treating-to-Target

Philip J. Mease, MD

Musculoskeletal Manifestations

This is a case of a 45-year-old female with an 8-year history of psoriasis and 6-month history of musculoskeletal symptoms. She's been referred in by her primary care physician. The musculoskeletal manifestations include 1 knee, 3 metatarsophalangeal joints that are tender and swollen, as she falls in to an oligoarticular class of less than 5 involved joints. She has enthesitis, as evidenced by pain with palpation of the insertion side of the Achilles tendon, the plantar fascia and the inferior patella on the left side. She has dactylitis of the left fourth toe. She mentions that she has low back pain. Her skin involvement includes psoriasis in the scalp on the promontory of the left elbow and the left leg, and she has a total of 2% body surface area (BSA) involvement. Her CRP is slightly elevated at 3.2 and her patient-reported outcome measures show pain 40 out of 100, patient global 40 out of 100, and a HAQ score of 1.0.

PsA Clinical Trials
Outcome Measures

Domains	Instruments
Joint assessment	68/66 T/S joint count, ACR, DAS, PsARC, PsAJAI, DAPSA, cDAPSA
Axial assessment	BASDAI, BASFI, BASMI
Skin assessment	PASI, target lesion, global, PSI, PSD
Composite (holistic)	MDA, VLDA, PASDAS, CPDAI, AMDF
Pain	VAS, NRS
Patient global	VAS (joint global, skin + joints global)
Physician global	VAS (joint global, skin + joints global)
Function	HAQ, HAQ-S, PSAID
HRQoL	SF-36, PsAQoL, DLQI, PSAID
Fatigue	FACIT, Krupp, MFI, VAS
Enthesitis assessment	Leeds, SPARCC, MASES, 4-point
Dactylitis assessment	Leeds, present/absent, acute/chronic
Acute phase reactant	ESR, CRP
Imaging	X-ray (modified Sharp or van der Heijde–Sharp), MRI, US
Work/home productivity	WPAI, WPS

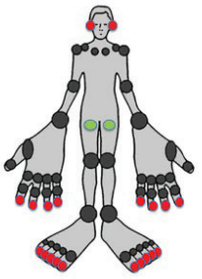
Mease P. *Arthritis Care Res.* 2011;63 Suppl 11:S64-85;
Mease P, et al. *Ann Rheum Dis.* 2005;64:ii49 -ii54;
Mease P, van der Heijde D. *Int J Adv Rheum.* 2006;4:38 -48.

Clinical Measures

There are a number of different clinical measures that are used in psoriatic arthritis clinical trials. There are several that are used in the tight control trial, which we'll refer to including joint assessment, a skin assessment with various measures, patient pain, patient global function, etc.

Rheumatic Diseases
Joint Counts

- AS: 46/44
- PsA: 68/66
- RA: 28



Sieper J, et al. *Ann Rheum Dis.* 2009 Jun;68 Suppl 2:ii1 -44.
Chandran V, et al. *Arthritis Rheum.* 2009;61:1235 -1242.

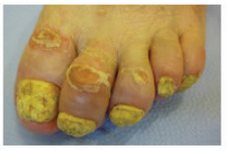
First of all, joint counts in psoriatic arthritis; we like to measure 68 joints for tenderness and 66 for swelling–we don't try to assess the hips for swelling–and the reason for this, and this patient exemplifies this very well, is that there can be quite a bit of disease in the feet, especially earlier on in the musculoskeletal disease progression. And so, we'd be missing a lot, if we didn't evaluate the feet.

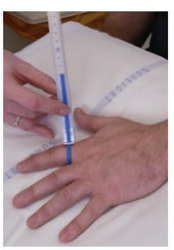
Palpating the proximal interphalangeal joint of a patient's finger with a standardized amount of pressure, enough to blanch the fingernail from the fingernail tip down in the examiner's finger about a fifth of the way down. You can see the whitening or blanching there and so that's the standard amount of pressure, which is 4 kg/cm^2 and we're trying to assess the joint line here for tenderness and swelling. For enthesitis assessment there are a number of different indices that have been used on the left-hand side, the Leeds Enthesitis Index in which there are red dots at the 6 sites that we palpate, including the lateral epicondyle, the medial condyle of the femur, and the Achilles tendon insertion. We also use the SPARCC index in which there are 18 sites that we palpate and those are depicted here including at the elbow, the shoulder, the tracheal versa on either side of the patella and the Achilles implant or fascial insertions.

The Maastricht is a measure that's primarily used in axial spondyloarthritis trials. Dactylitis is assessed either by visualizing the fingers and toes, and we can see clearly here that the toes are diffusely swollen, looking like sausages. And in clinical trials we may use an instrument known as the dactylometer, which we measure the circumference of the digit, as well as assessing for tenderness of the digit. And, of course, skin disease, where we're looking at the amount of erythema, an induration and plaque, and also assessing a surface area where the patient's handprint represents 1% of body surface area. In psoriasis, in clinical trials, we'll often use a PASI score, but also in practice, we'll use the BSA (body surface area). And this depicts the fact that the handprint represents 1% of the body surface area.

Dactylitis
LDI

- Assessed for a total score (0-3)
  - Circumference
    - Affected fingers
    - Contralateral fingers
  - Tenderness
    - Affected fingers





Mease P. *Arthritis Care Res.* 2011;63 Suppl 11:S64-85.

Initial Treatment and Further Workup

Let's come back to our case. And we've assessed the different clinical domains after the patient was initially treated with methotrexate up to 20 mg per week.

Case: 45-Year-Old Female
Initially treated with MTX to 20 mg/wk

- Symptoms lessened in most domains
  - Oligoarticular arthritis: now 2 swollen and tender joints
  - Enthesitis: 2 sites
  - Dactylitis: persistent
  - Complains of low back pain
  - Skin: 2% BSA
  - PROs: Pain 30/100, Pt Global 25/100, HAQ 0.8

She now has just 2 swollen and tender joints. She has 2 enthesitis sites. There's persistent, unfortunately, not changed dactylitis. She still complains of low back pain. Her body surface area is 2%, and pain, and patient global, and HAQ have diminished somewhat, but not a lot. So, this is what we see with methotrexate. We see some impact, but not a tremendous amount of impact. We are still left with the patient with different clinical domains being affected.

We ask ourselves, have we achieved a state of minimal disease activity, or not? And we'll address that in a moment. CRP is down to 2.1, still a bit elevated. Ultrasound could be considered to assess for smoldering synovitis, or enthesitis, by looking at power Doppler results. And she's complained of some back pain, but we don't know whether that's just standard issue degenerative spine disease, or does she actually have some psoriatic spondylitis?

Let's first address, has she achieved minimal disease activity criteria? Here are the 7 items that are part of that criteria set developed by GRAPPA. And as you can see, she hasn't achieved 5 of the 7. She's only achieved 1 of the 7, and that is her body surface area is 2% of psoriasis. Everything else is slightly above the threshold for what we consider minimal disease activity in terms of tender and swollen joint count, patient pain, patient global, HAQ score and tender entheseal sites. We also might do some ultrasound, and if the patient has evidence of smoldering synovitis or enthesitis, as reflected by light-up on power Doppler, then we haven't really stamped out the inflammation activity.

MDA Criteria
GRAPPA

- A patient is classified as in MDA when they meet 5 of 7 of the following criteria:
  - Tender joint count ≤1 No
  - Swollen joint count ≤1 No
  - PASI ≤1 or BSA ≤3 Yes
  - Patient pain VAS ≤15 No
  - Patient global activity VAS ≤20 No
  - HAQ ≤0.5 No
  - Tender entheseal points ≤1 No

Coates L, et al. *Ann Rheum Dis.* 2010;69:48-53.

Now in terms of the back workup, we start with the set of questions, which we call the inflammatory back pain (IBP) criteria. And the most recent IBP criteria include the following 5 items: age of onset of the back pain less than 40 years of age, insidious rather than acute onset, improvement with exercise, no improvement with rest, and pain that awakens the person in the middle of the night. These are classic manifestations of an immunologic inflammatory spine condition, as opposed to a mechanical spine condition, where we might not see these items being present. And if 4 of the 5 are present, then they fulfilled IBP criteria.

We know that a spine disease occurs in about 40% of patients with psoriatic arthritis. This is data we know from Dr. Gladman's cohort and other cohorts. And to assess the spine disease, the ideal ways of approaching [this], are to do imaging of the sacroiliac joints and spine. And if we see classic changes for spondyloarthritis, such as MRI light-up in the bone adjacent to the sacroiliac joint, then that may highlight the presence then of PsA spondylitis. I have to acknowledge though, that frequently we do this assessment, and find that the patient mainly has degenerative arthritis contributing to their back pain. Plain x-rays of the sacroiliac joints are helpful if they are either completely normal, or completely abnormal. But oftentimes we find something in between, where we can't quite tell. And that's why MRI scanning is so important. Notice I've focused on the sacroiliac joints. Of course, the spine is important, but we get many false positives in the spine, including degenerative spine disease showing light-up on MRI scan.

In this patient, we'll want to assess the spine with some of these strategies. Now, if we wanted to try to get the patient into a state of minimal disease activity, first of all, do we think that this is an appropriate target? And I would say, yes. Over the years that we've been using this instrument, we found a significant correlation with improvements in function, quality of life, inhibition of radiographic progression. So, getting the patient to a state of MDA, or even better, a state of very low disease activity, where all 7 items are fulfilled is one where the patient is quite satisfied, and we, as physicians, should be satisfied with the achievement of that state.

Aiming at MDA

Back to our patient. We did strive to achieve an MDA state. We suggested using either a TNF inhibitor or an IL-17 inhibitor, either could be chosen from my perspective, as well as from the GRAPPA treatment guidelines perspective. And what occurred, at the 6-month mark of treatment, with, admittedly, it could be with either of these medications. The patient's joint count had diminished to 1 tender, their enthesitis count to 1 tender. Their psoriasis had further improved to 1% of body surface area. Their HAQ score was 0.6, which was still above the 0.5 that is the threshold for improvement. Patient global and patient pain had both improved significantly. And the back pain when worked-up was considered to be related to degenerative disease, so she still had some of that.

Case: 45-Year-Old Female
Encouraged to Strive for a Target of MDA

- Biologic or tsDMARD are possible options (a TNFi or IL-17i could be chosen here)
- Six-month evaluation demonstrated improvements in clinical domains
  - Left knee tender at joint line (1 T, 0 S)
  - Left distal patella tender (1/6 Leeds enthesitis index)
  - Psoriasis BSA 1% - elbow, knees
  - HAQ 0.6
  - Patient global – 10, patient pain – 10
  - Back pain considered to be due to degenerative spine disease and not PsA spondylitis

The answers to the MDA criteria were, yes, she had achieved this now, because she only had the HAQ score, which hadn't quite achieved the threshold of less than or equal to 0.5. This case illustrates the potential value of using a quantitative measure of outcome, ie, the minimal disease activity criteria, while we're trying to achieve a state of low disease activity or remission for our patients, with treatment.

Case: Managing Treatment Challenges

Philip J. Mease, MD

Initial Presentation and Treatment

Here we have a case of a 42-year-old woman, who has 1-year history of psoriatic arthritis, and a 10-year history of psoriasis. In her initial presentation of psoriatic arthritis, she had a 28 tender and 3 swollen joint count. Five out of 6 enthesitis sites that were tender using the Leeds Enthesitis Index. She had 2 dactylitic digits, her toes. She had lumbar and cervical pain. Her skin body surface area involvement was 4%. When examining her nails, she had evidence of pitting. And she had elevated patient-reported outcome measures, including pain of 60 out of 100, patient global of 60 out of 100, fatigue of 50 out of 100. We initially treated her with methotrexate up to 20 mg per week.

Case: 42-Year-Old White Female
1 yr hx PsA + 10 yr hx PsO

- Initial presentation of PsA:
  - Joint count: 28 T/3S (out of 68/66)
  - Enthesial assessment: 5/6 (Leeds index)
  - Dactylitis: 2 toes swollen and tender mid-shaft
  - Lumbar and cervical pain present
  - Skin: 4% BSA
  - Nails: Nail pitting present
  - PROs: Pain 60/100, Pt Global 60/100, fatigue 50/100
- Initial treatment: MTX titrated to 20 mg/wk

After 6 Months of Methotrexate

After 6 months of methotrexate therapy, her joint count had slightly diminished to 24 tender, 2 swollen but still very active. Her entheseal assessment did not diminish. Her dactylitic count had diminished to 1, but not resolved. She still had lumbar and cervical pain. Skin disease had gone to 2% of body surface area. She still had nail pitting, and her patient-reported outcomes had diminished somewhat, but still not acceptable.

What happened was, then, adalimumab was added to methotrexate.

After 6 Months of Adalimumab and Methotrexate

We are seeing a slightly better response after 6 months of his combination treatment, with 16 tender, 0 swollen joints. Entheseal assessment was 4 out of 6, interesting, not much budge there at all. Dactylitis had resolved. She

still had lumbar and cervical pain. Skin disease had diminished to 1%. Nail pitting had resolved, so no more nail findings. And her pain–patient global and fatigue had diminished a bit, but they were still reasonably high at 30, 30, and 20, respectively.

Case: 42-Year-Old White Female
After 6 mos of MTX Therapy

- Joint count: 24 T/2 S (out of 68/66)
- Enthesial assessment: 5/6 (Leeds index)
- Dactylitis: 1 toes swollen and tender mid-shaft
- Lumbar and cervical pain present
- Skin: 2% BSA
- Nails: Nail pitting present
- PROs: Pain 40/100, Pt Global 40/100, fatigue 30/100

- Patient does not feel that she has had an adequate response, and you note that she has not achieved target of MDA.
- Adalimumab added to MTX.

There are some clues here, there are some problems. The joint count, 0 swollen, yet 16 tender ones. So, lots of pain, but objective evidence for inflammation had gone away. Entheseal assessment, what we're doing is we're palpating the entheseal assessment site and asking the patient if they have pain. We have an objective evidence of dactylitis, which is a swollen digit that had clearly completely resolved, and nail pitting had completely resolved. And, then, there were several patient-reported outcome measures that were still elevated.

We switched the patient to secukinumab, choosing a different mechanism of action. The TNF inhibitor, and instead using an IL-17 inhibitor.

After 6 Months of Secukinumab and Methotrexate

But, still, very little change of several of these important measures. The joint counts still were 16 tender and 0 swollen. So fortunately, there had not been any recurrence of swelling of the joint. She still had 3 out of 6 tender entheses. Dactylitis remained resolved. Lumbar and cervical pain was still present. There was no change of body surface area or nail pitting. And she still had elevation of the patient global measures. So, a titch better, but not that much. And she's still not quite happy.

Case: 42-Year-Old White Female
After 6 mos of Adalimumab + MTX Therapy

- Joint count: 16 T/0 S (out of 68/66)
- Enthesial assessment: 4/6 (Leeds index)
- Dactylitis: resolved
- Lumbar and cervical pain present
- Skin: 1% BSA
- Nails: Nail pitting resolved
- PROs: Pain 30/100, Pt Global 30/100, fatigue 20/100

- Patient states she is better but does not feel that she has had an adequate response, and you note that she has not achieved target of MDA.
- Switch from adalimumab to secukinumab and continue MTX.

Next Treatment Options

We have 2 different very effective biologic inhibitors that have been used so far. What would you do next? Switch to a JAK inhibitor? Switch to ustekinumab? These are 2 different medicines that are approved for psoriatic arthritis, but we haven't yet tried. A third . . . do we do a tender point assessment for fibromyalgia? Okay, that's interesting. Or would we apply the widespread pain index and symptoms severity scale to assess for fibro, or central sensitization? You may not know these instruments, but they've been validated and used in assessing fibromyalgia. Suggest treatment with duloxetine or pregabalin? These are drugs that are approved for the treatment of fibromyalgia. Suggest multidisciplinary treatment for central sensitization, which we're using as a synonymous term for fibromyalgia?

Case: 42-Year-Old White Female
Next Treatment Options?

- Switch to a JAK inhibitor
- Switch to ustekinumab
- Do tender point assessment for fibromyalgia
- Apply Widespread Pain Index and Symptom Severity Scale to assess for central sensitization
- Suggest treatment with duloxetine
- Suggest treatment with pregabalin
- Suggest multidisciplinary treatment for central sensitization

Possible Fibromyalgia

By asking these questions and giving these as options, I'm sure you're clearly thinking along the same lines as I am. That perhaps this patient has concomitant fibromyalgia, or central sensitization, that is inhibiting us [from] getting to a state of minimal disease activity, despite objective measures showing evidence of abrogation of inflammation with both adalimumab and secukinumab. But although we had been tempted to do the switch, and we did, from adalimumab to secukinumab, maybe this time around we'll be a little bit less tempted to do so, if we think that the key issue is fibromyalgia that's contributing to her symptoms. So, first, some terminology: fibromyalgia is a term that is frequently used for a patient who has extensive pain response, maybe fatigue, maybe sleep disturbance. There's also, especially in Europe, the phrase "chronic widespread pain syndrome" that's been used. And an overarching term that I tend to use is "central sensitization syndrome." We know that there is a lot of biological underpinning to this, with certain genetic profiles that make patients more prone to having central sensitization. We also know that there are alterations in central nervous system neurotransmitters, including increases in nociceptive neurotransmitters, or diminishment of inhibitory neurotransmitters, such as norepinephrine or serotonin, that contribute to central sensitization. And then, of course, sociological factors, psychological factors that can contribute as well.

A classic study, which demonstrates the underlying biologic factors that influence fibromyalgia, was conducted by Rick Gracely at the University of Michigan and published in 2002. In the experimental paradigm, subjects are administered a stimulus intensity using a little device, which I call the thumb smasher, in which you put a certain amount of pressure on the patient thumb.

If you put a low amount of stimulus intensity on a normal subject, they will not subjectively describe much pain intensity, and in a correlated fMRI scan, there will not be light-up in the pain centers in the brain. If you double the stimulus intensity on that normal individual, to more than 4 kg/cm^2 of pressure, then the patient will say, "Yes, that is painful," and they will light up on the fMRI scan in the characteristic areas where pain reception is occurring.

If you take a fibromyalgia subject, and give them the low stimulus intensity, they will symptomatically describe a high amount of pain intensity, even with that low stimulus intensity. And the way that we know that they are really experiencing that level of pain, is by looking at the fMRI scan and seeing that, indeed, they are lighting up in the places of the brain where a high pain intensity is being experienced. So, this is kind of a lie detector test to teach us that the fibromyalgia patients are really experiencing a high amount of pain intensity, even with a low amount of stimulus intensity. We also know from studies that have been done at the University of North Carolina and other institutions, that there are a number of important genetic factors that contribute to this phenomenon of central sensitization, including, for example, the catecholamine, O-methyltransferase gene. And depending on the alleles that you have of that gene, then you're either going to be a high pain sensitive person, or low pain sensitive person. And then if you layer on top of that, alterations of various neurotransmitters, and then layer on top of that high psychological distress, then you get the perfect storm, which is the state of fibromyalgia or increased central sensitization.

Chronic Inflammation and Fibromyalgia

We know that in states of chronic inflammation or chronic pain, there is an increased prevalence of fibromyalgia compared to the normal population, which is typically depicted as being present in 2% to 4% of the general population. If we study different disease states, like rheumatoid arthritis, Lupus, Sjogren's, osteoarthritis, spondyloarthritis, psoriatic arthritis, a common denominator is that somewhere around 15% to 20% of patients, with some differences in studies showing higher levels, will have concomitant fibromyalgia, along with their underlying immunologic inflammatory disease.

Rheumatic Diseases
Comorbid "Central Sensitization"

Comorbid Condition	Author	Prevalence of FM (%)
SLE	Valencia-Flores Grafe Neumann, Buskila	10 30 65
RA	Wolfe, Michaud	17
Sjogren's	Bonafede	50
OA	Wolfe, Cathey	6.7
SpA	Wallis D Aloush V Azevedo V	6 (AS) 14 (nr-axSpA) 50 (Fem AS) 15 (AS)
PsA	Husted, Gladman Brikman Salaffi Graceffa	22 17.8 17.2 (axPsA) 16

Weir PT, et al. *J Clin Rheumatol*. 2006;12:124-128.
Wallis D, et al. *J Rheum*. 2013. 40:2038-2041.
Aloush V, et al. *Rheumatol Int*. 2007; 27:865-8.
Azevedo V, et al. *Bras J Rheumatol*. 2010;50(6):646-54.
Mease PJ. *Curr Opin Rheumatol*. 2017;29:304-310.
Brikman S, et al. *J Rheum*. 2016; doi:10.3899/jrheum.151491.
Salaffi F, et al. *Rheumatol Int*. 2014;34:1103-10.
Graceffa D, et al. *Clin Exp Dermatol*. 2015;40:136 -41.
Husted JA, et al. *J Rheumatol* 2013; 40;1349 -1356.

The ways we assess for this include various patient-administered questionnaires, including the chronic widespread pain index and symptoms severity scale, the pain DETECT questionnaire, the fibromyalgia rapid screening tool, as well as more objective measures, including the tender point exam, quantitative sensory testing, and fMRI scanning.

Why does this matter? The reason it matters, is that what we have found is that if you take a cohort, for example psoriatic arthritis patients, as was done in a study in Tel Aviv, with 60 patients who have had psoriatic arthritis without concomitant fibromyalgia, and 13 patients, or 18%, that have psoriatic arthritis and at the same time constantly have fibromyalgia, when we administer various outcome measures that include a subjective element to them, including the MDA criteria for example, or the DAS28, the DAPSA, the enthesitis index, the PASDAS score, all of them show that in the patients with PsA and fibromyalgia, they have much higher scores, and, indeed, almost twice as high severity scores as the patients without fibromyalgia.

CSS
Assessment

- Chronic Widespread Pain Index (CWI) + Symptom Severity Scale (SSS)
  - 19 body areas assessed for pain
  - Also assesses fatigue, sleep quality, dyscognition, other sxs
- painDETECT Questionnaire (PDQ)
  - Graded 12 item questionnaire
- Fibromyalgia Rapid Screening Tool (FIRST) questionnaire
  - 6 questions
- Tender point exam
- Quantitative sensory testing
- Neuroimaging, eg, fMRI

Mease PJ. *Curr Opin Rheumatol*. 2017;29:304-310; Mease P. Neurobiology of Pain. Oxford Textbook of Osteoarthritis. 2018

And in the case of minimal disease activity, it was found that whereas 26% of the psoriatic arthritis alone patients had the ability to achieve that with treatment, 0% of the PsA and fibromyalgia patients could achieve a state of minimal disease activity.

This is going to influence our assessment of patients, and our determination of whether or not we're appropriately getting to the target of minimal disease activity, or remission, in our patient group. And it's important to know this, so that if we're assessing the effectiveness of say, a biologic agent, we don't inappropriately say, "Oh, this patient has not achieved the state of MDA," and then keep moving on, switching from one biologic to another, if we don't take into account the possibility that they have underlying fibromyalgia.

I'm particularly interested in this in relation to our assessment of enthesitis in which we think of enthesitis as an active immunologic inflammation at the entheseal insertion sites, such as the Achilles tendon or plantar fascia.

PsA
Enthesitis or "Enthesalgia"?

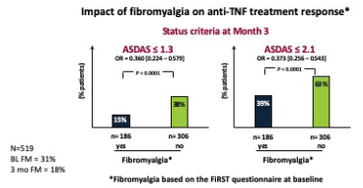
- Enthesitis: active immunologic inflammation at enthesial insertion site
- "Enthesalgia" (Mease definition): tenderness at enthesial insertion site on physical exam and the examiner has no way of knowing how much of the tenderness is due to an "it is," how much "mechanical-degenerative," or how much may be contributed to by central sensitization (aka FM)

Brikman S, et al. *J Rheumatol*. 2016;43:1749-1754.

But what if the patient has fibromyalgia, and what if when we're palpating that site, we're eliciting tenderness, but instead of actual immunologic inflammation, we're getting a central sensitization response from the patient? And they're tender, but not actively inflamed, ie, having an enthesalgia, rather than an enthesitis. So, we need to be aware of this as we are taking an evaluation of our patients and thinking about whether to maintain current therapies or switch.

This is further illustrated in a very interesting study conducted by Pil Højgaard, a young Danish rheumatology researcher based in Copenhagen. In this study, she evaluated 69 psoriatic arthritis patients, who were initiating either a csDMARD or biologic DMARD. And then she did clinical and ultrasound evaluations, at baseline, as well as at 4 months. And then she also applied 2 of these indices, the widespread pain index, and the pain detect questionnaire, and looked at different outcomes. What was fascinating was

Anti-TNF Treatment Response in axSpA
Predisposing Factors



Moltó A, et al. *Ann Rheum Dis.* 2018;77:533-540.

that she found that 35% of the patients at baseline responded positively on the widespread pain index, in other words, had some element of central sensitization or fibromyalgia. At 4 months, none of these patients, this 35%, were able to achieve minimal disease activity vs 20% of the patients who did not have evidence of central sensitization. This was statistically separated discrimination. Furthermore, in the patients that answered positively on the widespread pain index, there was a complete lack of correlation between tender joints, and entheseal tenderness, and ultrasound findings of synovitis or entheseal inflammation. So, in other words, these patients were tender, but they were not having active inflammation.

I think that this is an important lesson for us to think about. The possibility that a concomitant fibromyalgia, or central sensitization, is confounding our ability to really assess outcomes in our patients, and we need to take this into account and use more objective measures for determining response. And I'd like to show one other study that I think is quite fascinating with a different disease state than psoriatic arthritis, ie, axial spondyloarthritis. In this particular study, conducted in France, there were 519 patients. They had the fibromyalgia questionnaire applied at baseline, and interestingly, 31% answered positively on this questionnaire. And then if you looked at outcomes, there were many fewer patients in the fibromyalgia-positive group that could achieve ASDAS remission, or low disease activity state. And another interesting finding is that at the 3-month mark of treatment, after more effective treatment of inflammation and pain, the number that responded, or the percentage that responded positively on the questionnaire had gone down to 18% from 31%, suggesting that there could be some potential modulation of central sensitization by effective treatment.

Concomitant Fibromyalgia Treatment Options

If we return to our patient, and look at the treatment options available to us, you can predict what I'm going to recommend. I'm not going to recommend switching to a JAK inhibitor or ustekinumab, because I don't think that those are going to necessarily treat the underlying problem that's leading to persistent pain response and to persistent, not completely improved, patient-reported outcomes. And that's that the patient has concomitant fibromyalgia, or central sensitization. So, instead, I will probably be working with her to suggest multidisciplinary treatment, and possibly using one of the drugs approved in the United States for treatment of fibromyalgia, ie, duloxetine or pregabalin.

Case: 42-Year-Old White Female
Next Treatment Options

- Switch to a JAK inhibitor
- Switch to ustekinumab
- Do tender point assessment for fibromyalgia
- Apply Widespread Pain Index and Symptom Severity Scale to assess for central sensitization
- Suggest treatment with duloxetine
- Suggest treatment with pregabalin
- Suggest multidisciplinary treatment for central sensitization

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