Exploring Care for Psoriatic Arthritis: Bridging Dermatology and Rheumatology
Dr. Leonard Calabrese: I want to welcome the faculty to this discussion where we will explore aspects related to the care of patients with psoriatic arthritis. In the past, issues associated with psoriasis and arthritis have been somewhat controversial and there has been a lack of understanding, particularly with regard to how the disease should be viewed nosologically. Recently our vision of psoriatic arthritis has become far clearer. It now appears that psoriatic arthritis represents a distinct form of musculoskeletal inflammatory disease, classified as a subtype of spondyloarthropathy on strong clinical, immunopathologic, and genetic evidence.1,2

As we look at this disorder, we see psoriasis, a formidable skin disorder affecting approximately 2% of the population; and, depending on the study population and study design, we see reports of psoriatic arthritis occurring in as few as 6% to as high as 39% of patients with psoriasis. It is a formidable problem. Advances in our understanding of psoriatic arthritis relative to its natural history, pathogenesis, along with some of the sequelae and treatment1,2 have mandated that physicians interested in these problems and those who participate in the care of these patients should enhance their learning and attempt to refine clinical pathways of care.

With this in mind, I’ve gathered two experts to discuss issues surrounding psoriatic arthritis. I am joined by Dr. Philip Mease, who is a Clinical Professor of Medicine at the University of Washington and the Chief of Rheumatology Research at Swedish Medical Center, both in Seattle, Washington. Also joining me is Dr. Mark Lebwohl, who is a Professor of Medicine and the Chair of the Department of Dermatology at Mt. Sinai School of Medicine in New York City. We will be discussing the clinical manifestations of psoriatic arthritis, its impact on patients, and some selected aspects of diagnosis and treatment.

Psoriatic Arthritis: A Historical Perspective
Dr. Calabrese: To start the discussion I will ask Dr. Mease—when we say psoriatic arthritis, what do we mean, how do we classify it, and how should we view it?

Dr. Philip Mease: Thank you. One of the interesting points about psoriatic arthritis is we believe it has been present much longer than rheumatoid arthritis. We know that psoriatic arthritis was present around the time of Christ based on archeological findings in the ruins of monasteries in the Sinai Desert. Patients with skin diseases were outcasts from society and they would go to these monasteries. Despite its antiquity, in the 1800s and for a good part of the 1900s, psoriatic arthritis was simply viewed as a variant of rheumatoid arthritis. It wasn’t until Professor Verna Wright in Leeds and his Fellow, John Moll, characterized the important distinctive clinical features of psoriatic arthritis, characterizing well over 100 patients, that we really began to appreciate it was a distinct entity. Now we have a genetic understanding and a much clearer idea of the distinctive features of psoriatic arthritis.
Figure 1c. Ankle: PsA synovitis, bone edema, enthesitis

Thick arrow: enthesitis; long thin arrow: synovitis; short arrow: bone marrow edema
McQueen et al. *Arthritis Res Ther*. 2006;8:207. Published by BioMed Central, open access.

Figure 1d. Fingers: PsA and dactylitis

Small arrow: synovitis; large arrow: flexor tenosynovitis with enhancement and thickening of tendon sheath
McQueen et al. *Arthritis Res Ther*. 2006;8:207. Published by BioMed Central, open access.

Figure 1e. PsA: sacroiliitis

McQueen et al. *Arthritis Res Ther*. 2006;8:207. Published by BioMed Central, open access.

Figure 1f. PsA: spondylitis

Arrows: inflammation
McQueen et al. *Arthritis Res Ther*. 2006;8:207. Published by BioMed Central, open access.

**CASPAR Criteria**

So these are the hallmark features leading to our understanding that psoriatic arthritis is distinct from rheumatoid arthritis. Then in 2001, Phillip Helliwell, also from Leeds, brought together a group of rheumatologists from around the world to develop a new classification criteria known as the CASPAR Criteria [Table 1]. This was published in *Arthritis and Rheumatism*, identifying the characteristic features which indicate a patient has psoriatic arthritis. These features include some form of inflammatory arthritis, enthesitis, or spine disease. If the patient has psoriasis, then two out of three points total are assigned confirming the diagnosis. CASPAR also assigns points when a patient has either a history of psoriasis or a family history of psoriasis, evidence of nail disease, absence of rheumatoid factor antibody, presence of dactylitis, or characteristic changes of periostitis seen in x-rays of the extremities. CASPAR established the distinct classification system for psoriatic arthritis.

Table 1. CASPAR* Criteria for the Diagnosis of Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Points</th>
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<tr>
<td><strong>PsA is diagnosed when ≥3 points are assigned in the presence of inflammatory articular disease (joint, spine, or enthesial)</strong></td>
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<tr>
<td>Current psoriasis, or, personal or family history of psoriasis</td>
<td>Current psoriasis=psoriatic skin or scalp disease confirmed by dermatologist or rheumatologist</td>
<td>2</td>
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<tr>
<td>Personal history=history of psoriasis from patient, family physician, dermatologist, rheumatologist, or other qualified practitioner</td>
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<tr>
<td>Family history=patient-reported history of psoriasis in first- or second-degree relative</td>
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<td></td>
</tr>
<tr>
<td>Psoriatic nail dystrophy on current physical exam</td>
<td>Includes onycholysis, pitting, and hyperkeratosis</td>
<td>1</td>
</tr>
<tr>
<td>Negative for rheumatoid factor (RF)</td>
<td>Measured by any method except latex. Enzyme-linked immunosorbent assay or nephelometry preferred using local laboratory reference range</td>
<td>1</td>
</tr>
<tr>
<td>Current dactylitis or history of dactylitis documented by a rheumatologist</td>
<td>Defined as swelling of entire digit</td>
<td>1</td>
</tr>
<tr>
<td>Radiographic evidence of juxtaarticular new bone formation</td>
<td>Appears as ill-defined ossification near joint margins excluding osteophyte formation, on plain radiographs of hand or foot</td>
<td>1</td>
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*CASPAR=ClASsification Criteria for Psoriatic ARthritis

Most rheumatologists now understand psoriatic arthritis and how it’s characterized, although historically many rheumatologists may not have understood these points. What’s more important is that many in the general public as well as other clinicians may not fully appreciate that psoriatic arthritis is its own disease entity and, in particular, do not realize that up to one-third of patients with psoriasis may develop...
psoriatic arthritis. This is a perfect situation for dermatologists and general practitioners to be asking patients if they have characteristic features of inflammation such as morning stiffness or multiple swollen and tender joints. These queries would identify the presence of psoriatic arthritis, allowing clinicians to intervene early to triage patients to appropriate therapy—especially if a patient has a more aggressive form of psoriatic arthritis that may progress to joint destruction.

**Questionnaires**
There are several questionnaires under development by members of GRAPPA (Group for the Research and Assessment of Psoriasis and Psoriatic Arthritis). These include one from the Harvard group known as the PASE (Psoriatic Arthritis Screening and Evaluation), another from the Toronto group (Toronto Psoriatic Arthritis Screening, ToPAS), and another from the Leeds Group (Psoriasis Epidemiology Project Questionnaire, PEST). These questionnaires are being tested now for use in dermatology and general physician offices to help clinicians identify patients with psoriatic arthritis within their practice.

**Dr. Calabrese:** Excellent. I see that Professor Gladman’s paper just came out recently in *Annals of Rheumatic Disease*. It shows that the sensitivity and specificity of their questionnaire (ToPAS) approaches 90%.

**Cutaneous Aspects of Psoriatic Arthritis**
**Dr. Calabrese:** Dr. Lebwohl, psoriatic arthritis generally has two components. Rheumatologists are very comfortable looking at arthritis but skin disease is a formidable component. How should clinicians who care for patients with psoriatic arthritis review the cutaneous component, and what is the relationship between the cutaneous component and arthritis?

**Dr. Mark Lebwohl:** The skin manifestations often precede psoriatic arthritis. About one out of six patients, around 15%, might develop joint pain first and subsequently develop skin lesions. When initially present, skin lesions are helpful in making the diagnosis. Of course, it becomes harder to diagnose psoriatic arthritis when skin lesions are absent—I would say the diagnosis is often missed when skin lesions are absent.

**Dr. Calabrese:** Focusing on the cutaneous aspect of psoriatic arthritis, if a rheumatologist sees someone with a suspicious pattern of psoriatic arthritis, what are the subtle to severe findings that they would look for in the skin?

**Dr. Lebwohl:** In some circumstances skin disease will be obvious—sharply demarcated red plaques. I often tell my residents if you can say the words “sharply demarcated, erythematous, scaling plaque,” you have the diagnosis of psoriasis and it doesn’t matter where the lesions are located. Psoriasis occurs in obvious locations like the elbows or knees, the intergluteal cleft, or the scalp. But what about a patient who comes in with a scaling patch on the penis? It turns out that it’s not rare for psoriasis to present only on the genitals. What about a patient who comes in with something that looks like athlete’s foot but doesn’t respond to anti-fungal therapy? If you look at those feet and you can say the words “sharply demarcated, red, and scaling,” more than likely it is psoriasis, not tinea pedis. Other clues include, first, to search in obvious places like the scalp or the intergluteal cleft, places where you wouldn’t necessarily look. Second, you need to look at the fingernails. Pitting is a subtle finding of nail psoriasis. Some more obvious findings of nail psoriasis might be misdiagnosed as onychomycosis, a fungal infection of the nails. If you see what looks like onychomycosis in the setting of arthritis, it could be psoriatic arthritis. Just confirm whether there is fungus in what you’re calling fungally infected nails. There is a good chance you are looking at psoriasis of the nails.

**Dr. Calabrese:** What other nail lesions present aside from pitting—onycholysis or onychohypertrophy?
Psoriasis of the nails.

**Dr. Lebwohl:** Subungual hyperkeratosis is the term for the nail bed thickening and the skin thickens under the nail. Onycholysis is separation of the nail plate from the nail bed; there are many things that cause onycholysis. Again, when there are skin lesions which are consistent with psoriasis, more often than not the onycholysis would be caused by the psoriasis. In the setting of arthritis where you’re searching for the skin disease and you see onycholysis, it should certainly at least cross your mind that this nail change could be a presentation of psoriasis.

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**The Relationship Between Skin and Joint Disease**

**Dr. Calabrese:** Dr. Mease, knowing that much has been written in the past, what is the relationship between articular activity and articular damage, and the extent and severity of skin disease?

**Dr. Mease:** Various investigators have looked for but not found a correlation between skin and joint disease. Severe skin and nail disease may present with very little musculoskeletal inflammation and vice versa. It appears that patients with more severe psoriasis tend to have a greater chance of developing psoriatic arthritis, but the relative severity of the skin and joint disease do not necessarily correlate. Also, some patients may start with flaring skin and nail disease but no articular disease, and then later it changes so they have more prominent articular disease. Parallels between the skin and joints can be unclear, making the optimal treatment paradigm more difficult to determine—this underlines the importance of good teamwork between the rheumatologist and the dermatologist. In my practice, I practically have a hotline to the handful of dermatologists who are interested in caring for psoriasis patients. We frequently speak by phone about nuances with patients who we are both seeing. It is unusual for a patient to see both a rheumatologist and a dermatologist at the same time. There are only a few academic centers where this occurs.

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**Distinguishing Immunopathologic and Genetic Features**

**Dr. Calabrese:** I would like to ask Dr. Mease to briefly provide an overview of the signature findings which distinguish psoriatic arthritis on an immunopathologic and/or genetic basis—how does this translate into clinical or radiographic findings?

**Dr. Mease:** We know there are key distinctions between psoriatic arthritis and the other major inflammatory arthritis condition, rheumatoid arthritis. For example, there tends to be less cellular infiltrate in the synovium. There are subtle differences in the cellular population with more macrophages and more neutrophils. Interestingly, we also see much greater vascularity in the synovium of psoriatic arthritis partly due to the overexpression of two key cytokines: VEGF, also known as vascular endothelial growth factor, and Ang-2 (angiopoietin-2).

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**Figure 4. Histology**

*Synovial histology in RA, PsA, and non-psoriatic SpA*


There are also subtle differences in the genetic profiling of these patients. For example, HLA-Cw6 is a prominent genetic marker in psoriatic arthritis patients, distinctive from HLA-DR4 in patients with rheumatoid arthritis. Differences in the expression of Toll-like receptors suggest there may be more activity of the innate rather than the adaptive immune system. All of these subtle differences in the immunology between psoriatic and rheumatoid arthritis suggest that there is a difference in the signature. What does bring them together is the fundamental aberration in immunologic regulation leading to overexpression of a variety of different inflammatory cytokines including TNF, IL-1, IL-6, and others—this occurs not only in the joints but also the enthesis and, as Dr. Lebwohl will share with us, the skin as well. There is a great deal of similarity between these diseases,
leading to the use of drugs that modulate the expression of these inflammatory cytokines and the proliferation of cells that have an inflammatory signature.

**Dr. Calabrese:** Dr. Lebwohl, can you briefly summarize any parallels or discordance between what Dr. Mease has been describing at the level of the joint and what key elements of the integrated immune system are important in skin disease?

**Dr. Lebwohl:** I will echo much of what Dr. Mease said—in addition to HLA-Cw6, there are many gene loci that have been linked to psoriasis. There are a number of SNPs, single-nucleotide polymorphisms, that have been specifically tied to psoriasis like RUNX1; however, none of these SNPs are sensitive or specific because the disease is multi-factorial. For that reason they’re not clinically useful though they are interesting. Some are associated with psoriatic arthritis but others are not. In terms of the pathogenesis, until recently we thought psoriasis was just a $T_{H}1$ disease and certainly the cytokine profile that we find in the skin is a $T_{H}1$ profile: interferon-gamma and TNF-alpha unequivocally play roles. Our understanding of the profile is undergoing some changes; it is now thought that with the discovery of drugs which block IL-12 and IL-23 that there are $T_{H}17$ cells which play a role in the pathogenesis of psoriasis. I would note that most everything Dr. Mease said about the joints also holds true for the skin.

**Dr. Mease:** I will add a couple of points. I concur that very recent work has shown that the $T_{H}17$ pathway in addition to the $T_{H}1$ pathway is important in psoriatic synovitis. This adds IL-23 as a prominent cytokine to the other cytokines I mentioned before. Also, some of the predominant inflammatory cells that are active in both the synovium as well as the skin include $T$-cells, dendritic cells, and macrophages. In the skin the macrophages have unique names like Langerhans cells. Additionally, a key type of cell in the skin that’s not present in the synovium is the keratinocyte, which is in the skin and part of the pathology of psoriasis. Keratinocytes are immunologically active cells with significant proliferation and lack of apoptosis or delay of normal apoptosis.

**The Natural History of Psoriatic Arthritis**

**Dr. Calabrese:** Now, we will look at psoriatic arthritis as a clinical entity and ask a question similar to what has been asked about rheumatoid arthritis. Can you summarize the natural history of psoriatic arthritis with respect to its lack of erosions, progression, and whether patients spontaneously go into remission?

**Dr. Mease:** Historically, psoriatic arthritis has been considered the milder cousin of rheumatoid arthritis. This is partly due to the fact that psoriatic arthritis often begins in an oligoarticular manner, meaning that patients have fewer involved joints than a typical rheumatoid will have early in the course of the disease. However, over time patients accumulate more and more inflamed joints as well as inflamed enthesal insertions and spinal involvement. When you look at a cohort of patients with long-standing, mature psoriatic arthritis, the burden for the patient is very similar to that of patients with rheumatoid arthritis considering physical function, degree of radiographic change, and overall impact on quality of life. We are beginning to dispel the idea that it’s a more benign disease than rheumatoid arthritis. Patients also tend to have a shortened life span. We believe this is largely due to earlier cardiovascular complications resulting from inflammation-induced atherogenesis. Many of the features that are characteristic of rheumatoid arthritis, including prominent comorbidities, are also present in patients with psoriatic arthritis. We do see some patients achieving remission either naturally, although this is unusual, or with effective therapies. Remission is now a treatment goal for patients with psoriatic arthritis.

**Quality of Life**

**Dr. Calabrese:** Since we are talking about the metrics of disease—rheumatologists are somewhat naive as to the effects of psoriasis on this patient population because they are more focused on the articular manifestations. Dr. Lebwohl, what can you say about psoriasis and quality of life in general?

**Dr. Lebwohl:** Dramatic differences are reported between surveys of quality of life measures in patients with psoriasis and patients with other diseases. The SF-36 (short form 36) has questions related to both the physical impact of the psoriasis on one’s life as well as the psychological impact. When the impact of psoriasis was compared to diseases like diabetes, cancer, congestive heart failure, or stroke, the only disease that had a greater negative impact on the psychological score component of the SF-36 was depression. Psoriasis had a greater impact than conditions like heart disease, diabetes, or cancer. The only condition that had a greater impact than psoriasis on the physical components of the SF-36 score was congestive heart failure. So, psoriasis affects quality of life measures related to both psychological and physical aspects in a dramatic way.

**Dr. Calabrese:** Dr. Mease, what about adding the component of psoriatic arthritis on top of this? How does it affect quality of life?

**Dr. Mease:** It is an exceptional burden. Dr. Lebwohl clearly suggested the skin aspects of psoriatic arthritis greatly impact quality of life. Patients are embarrassed to go out in public. They feel compromised at work, especially if they have cosmetically visible psoriasis. Add to this the physical dysfunction and pain that results from the arthritis and enthesitis component and you’ve got a considerable burden. When both aspects of the disease are very active, patients are greatly impacted and there is a ripple effect through their family, their social network, and their place of work.

**Multidisciplinary Approach to Treatment and the Influence of Disease Severity**

**Dr. Calabrese:** Thank you. I would now like to discuss the approach to treatment. We noted earlier that in an ideal world there is a need for increased communication between those with expertise and experience in treating skin disease and those with expertise and experience in treating joint disease. If you view a patient with both significant skin and significant joint disease versus a person with significant joint disease but minimal skin disease, how does this difference affect the way that you go about crafting therapy?

**Dr. Lebwohl:** It really depends on the patient’s initial presentation—there is not a single cookbook answer. If a patient has severe joint disease and the rheumatologist starts with a drug like methotrexate or a TNF blocker, either may also improve many of the patient’s skin complaints. Often, it is useful to have the patient see both a rheumatologist and a dermatologist. Even with overwhelming joint disease there’s often some residual skin disease that needs topical therapy and dermatologists may have more expertise in that area. The reverse holds true—if the
patient has severe skin disease and some joint complaints, using methotrexate or a TNF blocker to treat skin disease may also improve some of the psoriatic arthritis. I would say that on the whole patients generally benefit from seeing both physicians. There are some aspects of care for which dermatologists are not trained. For example, physical therapy modalities—do you use heat or cold, what kind of exercises are useful or should be avoided. This includes questions patients might ask about morning stiffness, questions that dermatologists should be asking but haven’t been asking, I believe patients do benefit by seeing both a dermatologist and a rheumatologist.

**Dr. Mease:** I would reinforce a couple of those points. The use of oral or biologic agents can greatly improve both the skin and joints but there are nuances. For example, let us look at a patient with one particularly troublesome joint even though multiple joints have improved with therapy. An intra-articular injection with steroid medication may be helpful, and this injection would typically be administered by the rheumatologist rather than the dermatologist. Also, as Dr. Lebwohl noted, we have a team approach often using physical therapists, occupational therapists, orthopedic surgeons, and others when it’s appropriate, to deal with aspects of the musculoskeletal disease. Rheumatologists typically have a list of these specialists who are local to the patient; they know how to facilitate that kind of triage and referral. This is one of the hallmark diseases where close teamwork between the dermatologist and rheumatologist really makes a difference.

**Dr. Calabrese:** Clearly this is a recurrent theme in this discussion. We have heard that not only are there different sensitivities of the practitioners towards varying elements of the patient’s disease, but there are varying components within the armamentarium that may favor therapeutic effect on the skin or joints, as well as many therapies that may affect both.

**Therapeutic Choices for Skin and Joint Disease**

**Dr. Calabrese:** For the treatment-naive patient presenting with formidable arthritis, at least symptomatic arthritis evidenced by three to five involved joints, along with mild-to-modest skin disease, there are numerous available therapies for both joint and skin disease [Table 2]. As an overview, drugs such as the non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, but we need to recognize that these are not remitve for any form of destructive inflammatory arthritis. We also have the non-biologic disease-modifying antirheumatic drugs (DMARDs), which include a cornerstone of therapy, methotrexate. Other non-biologic DMARDs are shown to have activity against psoriatic arthritis including leflunomide, cyclosporine, and sulfasalazine, with different levels of activity against skin disease. Non-biologic DMARDs have some advantages in cost and access and we have a long experience with them, but there is a lack of hard data on how effective they are at altering the natural history of psoriatic arthritis, particularly bone destruction. There are other considerations for use of non-biologic DMARDs in these patients, including whether the patient uses alcohol or has comorbidity such as fatty liver. These considerations may affect the choice of therapy.

Finally, there is also a growing class of biologic therapies. We have four approved anti-TNF agents that are effective for treatment of both skin and joint disease in psoriatic arthritis. There are also several new investigational TNF blockers and we have no reason to think their activity will be any different. It is a complex decision matrix for the clinician.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Psoriatic Arthritis Manifestation</th>
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<tr>
<td>NSAIDs</td>
<td>×</td>
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<tr>
<td>Intra-articular steroids</td>
<td>×</td>
</tr>
<tr>
<td>Topical therapies</td>
<td>×</td>
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<tr>
<td>Physiotherapy</td>
<td>×</td>
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<tr>
<td>Psoralen UVA/UVB</td>
<td>×</td>
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<tr>
<td>DMARDs (MTX, CsA, SSZ, LEF)</td>
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<tr>
<td>Biologic DMARDs (TNF inhibitors)</td>
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*NSAIDs = non-steroidal anti-inflammatory drugs, UV = ultraviolet, DMARDs = disease-modifying anti-rheumatic drugs, MTX = methotrexate, CsA = cyclosporine, SSZ = sulfasalazine, LEF = leflunomide, TNF = tumor necrosis factor

**Dr. Lebwohl:** I would confirm that skin manifestations share many of the same treatments with joint manifestations; there are certainly treatments that will address both. These treatments are often used for more advanced disease. For example, TNF blockers, which are associated with dramatic results for psoriatic arthritis, result in dramatic improvements for skin lesions as well. When skin disease is limited, the skin and joint disease have to be treated separately—we usually use topical therapy for limited skin disease. As psoriasis of the skin becomes worse, patients will often progress to a variety of oral agents or phototherapy. Phototherapy is of limited benefit for joint disease. There is certainly some evidence that treatments like PUVA, for example, help some manifestations of psoriatic arthritis, but it’s not as dramatic as TNF blockers or some of the oral agents that we use.

**Case Vignette**

**Patient with Mild Skin Disease and Worsening Joint Disease**

**Dr. Calabrese:** I will describe a patient and ask each of you how you might proceed. We’ll start with a patient who has mild psoriasis on the elbows and knees, which is not medically disfiguring but has waxed and waned for a number of years. Over the past year or so, he’s had increasing pain in his knees, wrists, and several fingers. He’s seen his family doctor and has been put on several non-steroidal anti-inflammatory drugs and is now coming to see the rheumatologist today. He is limping in. He has a job where he works with his hands and he’s having trouble with his activities of daily living. On physical examination he has dactylitis of a single digit. He’s got synovitis of four other joints, has an elevated ESR and normal x-rays of his hands. He has no other comorbidities. Dr. Mease, what is important to consider about this patient?

**Dr. Mease:** You have summarized many of the important features that suggest this patient will have a progressive and somewhat aggressive disease course. For example, he has several involved joints. He has dactylitis. He has an elevated ESR and his ability to perform work and activities of daily living are impacted. These are factors identified by Professor Gladman in her cohort of PsA patients in Toronto that suggest this patient should be on a systemic disease-modifying therapy. In this case, I would most
likely start with methotrexate rather than sulfasalazine because I would like to have some impact on—even though it’s mild and not too troublesome to the patient—the patient’s skin disease as well. Sulfasalazine doesn’t appear to have an effect on skin disease. The fact that the patient has no evidence of erosive change on initial x-rays is good, but it doesn’t mean that later he won’t have some structural damage. The one caveat about methotrexate along with background NSAID use in psoriatic arthritis is that unlike rheumatoid arthritis, there is no good evidence that methotrexate can have a meaningful effect on inhibiting structural damage. It hasn’t been as carefully studied in psoriatic arthritis. Even if the patient did get some benefit from methotrexate initially, we’d want to be carefully monitoring whether any structural damage was occurring by checking for persistence of synovitis. Later we can consider serial x-rays, and, if these showed signs of progressive damage, then we’d move to institute a biologic therapy as well.

**Dr. Calabrese:** In your practice would you be working with a dermatologist on this patient, or do you think the methotrexate may address his psoriatic arthritis?

**Dr. Mease:** That’s a good question. If methotrexate did improve his skin lesions then it may be a moot point. On the other hand, active co-management with a dermatologist may be warranted if methotrexate does not improve the skin lesions and the patient needs topical steroid cream or vitamin D cream, or in the case of slightly more severe skin disease some UV light therapy.

**Dr. Lebwohl:** I will echo what Dr. Mease has said. If a patient is treated for psoriatic arthritis and the skin lesions have cleared, and they are well managed on either methotrexate or a TNF blocker and some other therapy that also addresses the skin lesions, then the dermatologist wouldn’t expect to see the patient. The same holds true if the patient has severe skin disease and joint symptoms disappear when the dermatologist treats them. If the patient comes to me and I put them on methotrexate or a TNF blocker, I’ll give them the name and phone number of a rheumatologist at the same visit. Often I’ll see them at their follow-up visit, which may be weeks to three months later depending on what treatment I use, and the patient will tell me that their joint pains are gone. I’m not going to insist that they go to the rheumatologist.

**Patient with Severe Skin Disease and Debilitating Arthritis**

**Dr. Calabrese:** Now, let me give two twists to this case. The first twist is if this patient now comes to see you, Dr. Lebwohl, as the dermatologist, and instead of having mild psoriasis of the skin and knees he has severe psoriasis covering 25% of his body. He has been seeing only his family physician who has tried some mild topical therapy which has not improved his skin disease. He has the same debilitating arthritis; he’s limping in; he has difficulty with activities of daily living. What would your thoughts and approach be?

**Dr. Lebwohl:** The presence of arthritis makes me move fairly quickly. First of all, topical therapy is probably not going to be enough with 25% of the body surface area involved. If the patient didn’t have arthritis, I would have a discussion about phototherapy with that patient. Before paying for a biologic agent, many insurers actually require that a patient either not be a candidate for phototherapy or have failed phototherapy. Since the patient has arthritis, I’d move beyond phototherapy and go right to methotrexate, as insurers would have it. Insurers usually insist on patients failing methotrexate before they’ll consider biologic therapy, unless the patient simply is not a candidate for methotrexate or has failed methotrexate previously. So methotrexate would be the next step. A substantial proportion of patients for one reason or another are not candidates for methotrexate, and often that reason has to do with alcohol use. Another scenario is that patients will start methotrexate and then not tolerate it—then the next step would be biologic therapy, and the data right now supports the TNF blockers overwhelmingly as improving skin and joint disease.

**Dr. Calabrese:** You place this patient on methotrexate and the dose is increased up to 25 milligrams per week along with folic acid, and the patient is being monitored appropriately according to guidelines. He is tolerating this medication. Dr. Mease, what does it take, when you see this patient who was referred by Dr. Lebwohl, to call him a methotrexate failure?

**Dr. Mease:** There would be evidence of an inadequate response, meaning that he or she continues to have active synovitis with swelling, has elevation of the acute phase reactants, or persistence of morning stiffness, the markers which indicate the patient will progress and develop structural damage. In our practice we perform a DAS28 (Disease Activity Score) measure in these patients because the patients are part of long-term registries and the DAS28 is a composite measure of disease activity. So if the patient does not exhibit DAS28 low disease activity state or remission state, then I view the patient as an inadequate responder and I consider an anti-TNF therapy.

**Dr. Calabrese:** How long a trial on methotrexate do you give the patient?

**Dr. Mease:** Although many will say that three months is an adequate trial, in reality we should give the patient a good four to six months of therapy before we judge the quality of effect. We need to factor in that we are adding therapy and the patient is getting used to the therapy. In the meantime, we may have to address safety issues that can arise with methotrexate, possibly lowering or discontinuing the dose, or moving to a therapy with a different mechanism of action. Examples of safety concerns include a rise in liver enzymes by a factor of three despite having held alcohol consumption, or if the patient has significant nausea, mouth sores, or something like rare methotrexate lung toxicity.

**Inadequate-Responder to Methotrexate**

**Dr. Calabrese:** So now we have this patient who you determine to be a methotrexate failure. He has had a partial but not a dramatic response of the skin disease; however, he’s still far more bothered by his arthritis and he has been dealing with that for four to six months. There is a new class of drugs offering a good therapeutic option for patients with psoriasis. The TNF inhibitors are a unique class of biologic drugs which are highly effective for both skin and joint disease. All of the drugs within this class have been shown to be effective at improving signs and symptoms, quality of life measures, effects on the skin, and effects on progression of joint damage. They’re relatively rapid in their onset, yet as with all good things there are counterbalancing factors. The expense is significant. There are unique toxicities associated with the use of these drugs including the risk of opportunistic infection— toxicities which can be rare but significant.

If you both conclude that this patient may be a candidate for a TNF inhibitor, what is your view on the necessity or the advantage of add-on therapy versus monotherapy? In other words, do we continue or discontinue methotrexate?

**Dr. Lebwohl:** To begin, historically the guidelines for methotrexate use have differed substantially between
rheumatologists and dermatologists. With the latest set of dermatology guidelines\(^1\) we have come a little bit closer, in that we do not require liver biopsies in everyone at baseline and the period over which we require a liver biopsy has been lengthened. In the new guidelines, we now focus on patients who have risk factors for hepatic fibrosis like obese patients. Having said that, dermatologists are fairly cautious with methotrexate; and if our patients get a great response without it, we prefer to just use a biologic therapy. The main problem with methotrexate and the main cause of deaths with methotrexate has not been hepatic fibrosis but bone marrow toxicity. It often occurs when something was done incorrectly, something that could’ve been avoided. For example, it may be the patient who started methotrexate was then given sulfamethoxazole/trimethoprim, or a patient who has poor renal function was given excessive doses of methotrexate which their kidneys cannot handle. So having said that, the vast majority of dermatologists prefer to use monotherapy and not add methotrexate. However, if a patient is failing a TNF blocker, it would be reasonable and not so rare for a dermatologist to add methotrexate at that time.

**Dr. Calabrese:** Dr. Mease, let’s extrapolate from the rheumatoid experience where methotrexate and TNF blockers are clearly synergistic, where methotrexate has shown beneficial effects on the pharmacokinetics of the biologic. We’ll contrast that with psoriatic arthritis studies in which methotrexate was optional going in to these trials. One interpretation might be that methotrexate has not clearly added to the effects of TNF blockers in a significant way. How do you interpret these data?

**Dr. Mease:** I agree—the study design of the psoriatic arthritis trials allowed patients to enroll and remain on background methotrexate. These patients were then stratified in the randomization to receive the study drug versus placebo, so that there were four study arms—patients were either on methotrexate or not, and then received placebo or the study drug—so we’ve got a lot of information. The problem in interpreting these studies is that these were patients who were inadequate responders to methotrexate, so it’s not really a good analysis for methotrexate. What we are lacking is a study in which we take patients who are methotrexate-naïve, and then randomize patients to methotrexate alone, the study drug alone, or the combination, following patients over time to see if there is a difference in the quality of clinical improvement and the ability to inhibit radiographic progression. As you note, in rheumatoid arthritis there’s clear evidence that there is a superior effect in all of these domains when you use methotrexate combined with TNF blockers, but we don’t know if that is the case with psoriatic arthritis.

**Dr. Calabrese:** So what do you do?

**Dr. Mease:** We bridge and we keep the patient on methotrexate if they’re having a partial response, then add in the biologic agent. Then in three or four months, depending upon the patient’s response, we may gradually taper the methotrexate dose. In some cases, we’ll take patients off methotrexate altogether to simplify their regimen, and, if they remain good responders, we do not add methotrexate back in. If the patient starts to lose response for the skin or the musculoskeletal aspects, then we’ll add methotrexate back in, more often at a lower dose than previously used. Then we monitor patients over time and take serial x-rays to determine whether or not there is progressive structural damage. Structural damage may lead us to push more for combination therapy. Unfortunately, there are no good data confirming this is clearly the superior way to manage patients. We are also influenced by the background concern of dermatologists about methotrexate toxicity, especially because many patients are a bit more obese and may have an underlying fatty liver or hepatic sclerosis leading to a greater proclivity for developing hepatic fibrosis related to the use of methotrexate. Some rheumatologists I speak to are not as influenced by that concern and they will carry the rheumatoid management paradigm over to the management of their PsA patients. So in many rheumatology practices, you will see a high use of methotrexate combined with a biologic; in other practices, you may see that combination being used less often than in rheumatoid arthritis.

**Dr. Calabrese:** I suspect that many rheumatologists are using methotrexate at lower doses with pharmacokinetic enhancement in mind over the full doses used in psoriasis.

**Dr. Mease:** Yes, I agree. We also consider the possibility that a small amount of background methotrexate reduces antibody formation to a biologic which is structurally a chimeric antibody.

**Spondylitis**

**Dr. Calabrese:** Let me outline three other vignettes that briefly illustrate how our treatment approach would change. Dr. Mease, what about the patient who has some peripheral arthritis but has clear spondylitis. How does that change the treatment algorithm?

**Dr. Mease:** We know from multiple studies of methotrexate that it doesn’t work well for the spine disease seen in ankylosing spondylitis. We have then extrapolated that evidence to the psoriatic spondylitis patient, so we tend to start with an anti-TNF agent if the spine is prominently involved, sometimes even bypassing methotrexate. If the patient has almost purely spine disease and has not responded to methotrexate or sulfasalazine, then it’s more likely we’ll use an anti-TNF agent as monotherapy compared with the patient who has more predominant peripheral disease.

**Dr. Lebwohl:** I agree completely with that approach.

**Dactylitis**

**Dr. Calabrese:** What about the next vignette where you see a patient whose only musculoskeletal symptom is severe dactylitis of two or three digits, fingers and toes—does that affect the way you approach this from a treatment perspective?

**Dr. Mease:** That’s a very interesting situation as well. We have some evidence that the anti-TNF agents are effective in improving dactylitis. There are data with infliximab and data with etanercept from the new PRESTA (Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis) trial.\(^14\) Certainly, in practice we have seen improvement of dactylitis with all of the anti-TNF agents. Although it hasn’t been studied, there is generally an impression that methotrexate is not as effective in treating enthesitis and dactylitis. So, if dactylitis is a prominent feature and impairs function, we more readily start the patient on an anti-TNF agent. Whether or not we keep them on background methotrexate really depends upon their clinical course.

**Dr. Lebwohl:** I will say that most insurers require patients to fail methotrexate in that setting even though everything that Dr. Mease said was true. The patient usually has to have tried methotrexate for us to be able to prescribe a TNF blocker.

**Refractory Disease**

**Dr. Calabrese:** The final vignette is the same patient who still has severe joint and skin disease after a year on a TNF blocker and background methotrexate. He still has persistent synovitis and now has some early erosive disease. What are some options for salvage therapy at present in this type of patient?
Dr. Mease: We typically move to a second anti-TNF agent at this point, partly because we don’t have many other options in this therapeutic arena. We may have more options in the near future with drugs that have different mechanisms of action, but it’s very common for us to move to a second anti-TNF agent. We often see a response even if the patient has failed an initial anti-TNF agent. Sometimes we even move to a third anti-TNF agent; there are a couple of additional anti-TNF agents coming to the market so we will have more options within that drug class.

Dr. Calabrese: Can you address dose response to anti-TNF agents?

Dr. Mease: That is a good point. One thing we’ll consider is whether the patient had a great initial response to etanercept but then loses response. At that point we will try adalimumab or infliximab. If a good initial response to an anti-TNF agent diminishes, then we’ll increase the dose of those therapies. This means the dosing frequency of adalimumab might be increased to weekly or we might slightly increase the mg/kg dose of infliximab before we would try moving on to a different agent.

The choices become more difficult if a trial with a third anti-TNF agent fails. For physicians with access to ongoing clinical trials, you might consider enrolling the patient in a trial for a new investigational therapy for psoriatic arthritis such as abatacept. In the near future, we will have trials with one of the anti-IL6 medications or one of the various IL-12/IL-23 inhibitors. I suspect we will try the IL-12/IL-23 inhibitor ustekinumab when it becomes available (it is close to approval) because it shows efficacy in psoriatic arthritis.

Dr. Calabrese: Dr. Lebwohl, any thoughts on additional therapeutic options?

Dr. Lebwohl: Yes, just to comment about ustekinumab that is almost available to us. The regimen that was studied involved more frequent injections than what will likely be approved, but it certainly may be worth a try. We haven’t said much about alefacept. It is always worth a try when there are contraindications to the TNF blockers or perhaps when the TNF blockers are not working well enough. A paper just came out where repeated courses of alefacept showed some efficacy when given to patients on methotrexate. I wouldn’t discard alefacept as an option although alefacept doesn’t preserve the Sharp Score or the joint like the TNF blockers. Alefacept has been shown to be beneficial in terms of improved ACR scores.

Dr. Calabrese: Will ustekinumab be used intermittently or continuously?

Dr. Lebwohl: The pivotal trials in psoriasis looked at dosing as infrequently as every three months and no more frequently than every two months. If you call that continuous therapy, it’s continuous and certainly the approach is to give it on a regular basis—at least once every three months amounting to four injections a year. Having said that, there will probably be plenty of patients who don’t come in four times a year but come in less often to get injections because the drug’s effects are long-lasting and the psoriasis doesn’t come back for a long time.

Dr. Calabrese: A few thoughts in closing. Dr. Mease, you already talked about using DAS to follow disease activity; I think we’ve noted with all of these therapies that we need to be objectively monitoring response.

Managing Care with Allied Health Professionals

Dr. Calabrese: Moving forward, do either of you work with allied health professionals in managing patients with psoriatic arthritis, and if so, how?

Dr. Mease: Yes, we work actively and collegially with nurse practitioners and I know in dermatology practice that it is increasingly common, working with both nurse practitioners and physician assistants. We also work with physical therapists, occupational therapists, psychologists, and other types of counselors, including massage therapists and acupuncturists. In addition to dermatologists, we also work with orthopedists who can be extremely helpful with improving structural damage.

Dr. Lebwohl: The main allied health professionals we work with in dermatology are nurses, and we rely on them mostly for teaching patients how to self-inject and issues related to biologic use in general. There are a few dermatology practices with infusion centers which are run by nurse practitioners. That said, we certainly have the same type of contact lists and phone numbers that Dr. Mease mentioned. The dermatology practices that don’t have infusion centers will often have a contact with a dermatologist or a rheumatologist who uses infliximab infusions to take care of psoriasis and psoriatic arthritis.

Closing Comments

Dr. Calabrese: Thank you. We have heard several important themes here [Table 3]. Thinking of overall diagnostic awareness, we see that musculoskeletal inflammatory disease is common in patients with psoriasis. Dermatologists need to be attentive and alert to the articular phase and rheumatologists need to understand the serious impact that psoriasis has on patients who have concomitant arthritis. Second, there is a great need for interdisciplinary cooperation, and this is a perfect example of a disease where comanagement offers the patient important benefits related to quality of management with each practitioner bringing complementary expertise to care. Third, there is an interesting and impressive array of therapies available for both psoriasis and psoriatic arthritis. Some are more effective for skin or joint disease and others are effective for both. There are numerous decisions that go into the selection of these drugs, including the severity and activity of skin disease, the severity and activity of joint disease, and the type of musculoskeletal inflammatory disease, whether it is spondylitis, dactylitis, enthesitis, or arthritis. Finally, it is important to consider comorbidities when selecting therapy, whether it is liver disease, lifestyle, or metabolic syndrome, or others. Thank you to our two experts who shared their views about possible clinical approaches to what are common clinical vignettes often faced by clinicians in their practice.

Table 3. Key Points in the Care of Psoriatic Arthritis

- Dermatologists should be watchful for signs of musculoskeletal disease in patients with psoriasis.
- Conversely, rheumatologists should be watchful for signs of cutaneous disease in patients with arthritis.
- The complementary expertise of dermatologists and rheumatologists benefits patient care.
- In choosing therapy, physicians must consider multiple factors related to the presentation, severity, and activity of both cutaneous and musculoskeletal manifestations.
- Comorbidity is an important consideration when selecting therapy.
References


