Current Rheumatology Reports (2019) 21:72
https://doi.org/10.1007/s11926-019-0876-z

PSORIATIC ARTHRITIS (JU SCHER, SECTION EDITOR)

Strategies to Improve Outcomes in Psoriatic Arthritis

Christopher Ritchlin[1] · Jose U. Scher[2]

Abstract

Purpose of Review The therapeutic response to biologic agents in psoriasis is significantly higher than observed in psoriatic arthritis (PsA). In this review, specific actions to improve treatment outcomes in PsA are discussed.

Recent Findings Increased understanding of disease pathogenesis derived from improved preclinical models and advances in cell-based and molecular technologies provide new tools to identify therapeutic targets. In addition to the important contributions of metabolic comorbidities, chronic pain and the lack of a diagnostic biomarker signal the need for new strategies to improve outcomes. Potential strategies include the following: (1) discover a novel pathway or cellular subset, (2) apply stratification biomarkers to individualize therapy, (3) preclinical intervention, (4) combination therapy, (5) lifestyle modification, (6) address chronic pain and fatigue, and (7) multidisciplinary care.

Summary The future holds great promise for enhanced treatment responses in PsA based on improved understanding of individual variation in disease pathophysiology coupled with comprehensive and integrated treatment programs.

Keywords Strategies, · Psoriatic arthritis, · Challenges, · Transition, · Therapy, · Precision

Introduction

As recently as 50 years ago, psoriatic arthritis (PsA) was considered a variant of RA and treatment regimens were derived from the experience in rheumatoid disease. The publication of Moll and Wright's manuscript in 1973 established PsA as a distinct entity with a number of unique features that set it apart from RA [1]. The following year, these same authors described the family of spondyloarthritis (SpA), where PsA was considered a central member of that family [2]. Over the following 25 years, the realization that PsA was a different form of inflammatory arthritis took root, although this understanding did not initially translate into treatment advances.

The emergence of anti-tumor necrosis factor agents (TNFi) in the late 1990s for the treatment of RA went on to transform the therapeutic landscape for psoriasis and PsA in a most dramatic fashion. The expansion of the number of anti-TNF agents was followed by the discovery of several novel pathways including IL-23, IL-17, PDE4, and Jak-STAT resulting in the approval of a wide range of treatments for both psoriasis and PsA that have markedly expanded the pharmacologic toolbox for these diseases [3, 4]. Most strikingly, agents that inhibit IL-17 and/or IL-23 proved to be markedly effective for psoriasis. Intriguingly, however, a parallel magnitude of response has not been observed in PsA. In this review, we will discuss the reasons for why the current therapeutic outcomes in PsA are well below those in psoriasis. We will also identify strategies that can be undertaken to improve therapeutic response with the goal of inducing lasting disease remission in PsA and perhaps even prevent it altogether.

To meet the challenge of improving PsA outcomes can match those in psoriasis, we must understand the barriers that foster both primary and secondary non-response to oral DMARDs, small molecules, and biologic agents. The first major barrier is *heterogeneity*, a concept that is an essential element of PsA. This heterogeneity is present at many levels including the various domains of involvement (peripheral arthritis, axial disease, dactylitis, skin and nails, enthesitis) [4] along with the wide range of comorbidities that are so prevalent in patients with this disorder. Heterogeneity is also observed in the degree and extent of tissue involvement and undoubtedly a wide range

✉ Christopher Ritchlin
christopher_ritchlin@urmc.rochester.edu

[1] Allergy, Immunology and Rheumatology Division, Center for Musculoskeletal Research, University of Rochester Medical Center, Box 695, Rochester, NY 14642, USA

[2] Department of Medicine, Division of Rheumatology and Psoriatic Arthritis Center, New York University School of Medicine, New York, NY, USA

Published online: 07 December 2019

of genetic, epigenetic, transcriptional, and metabolic pathways that lead to onset and persistence of disease.

The other major barrier is *complexity*. Patients with psoriasis struggle with an inflammatory skin disease coupled with a number of comorbidities. In PsA, tissue involvement is varied involving a wide range of structures and cellular interactions between immune cells and bone, cartilage, entheses, synovium, and tendons. It is highly likely that molecular and cellular events in these different tissues are distinct but converge to foster ongoing inflammation and pathologic bone remodeling. In addition, the origins of pain in PsA are incredibly multifaceted and may arise from synovitis, osteitis, tendonitis, enthesitis, osteoarthritis, centralized pain, and chronic damage related to joint destruction and altered joint mechanics.

Many approaches to address the complexity and heterogeneity of PsA have been addressed and adopted into clinical practice. These include the incorporation of the domain approach for treatment recommendations [5]; tools to improve early recognition and diagnosis [6]; development of more robust outcome measures such as the minimal disease activity (MDA), low disease activity (LDA), and disease activity in psoriatic arthritis (DAPSA); [7•] and the recognition that certain agents work better for some domains than others. For example, methotrexate and IL-23 blocking agents are not effective for axial disease [8•, 9] while anti-IL-23 agents may be more effective than TNFi for treatment of enthesitis, while both IL-17 and IL-23 inhibition are extraordinarily effective for psoriasis [10]. Despite these advances, we are left with treatment responses in PsA [11••] that are of similar magnitude to those observed with TNFi over 15 years ago. In order to move forward, the field must think and act creatively to improve outcomes, quality of life, and function for our patients with PsA.

What actions can be taken to improve treatment response in PsA? Fortunately, we now have powerful tools at our disposal that allow us to interrogate the immune system to discover new cell subsets and pathways. Moreover, we have techniques in preclinical models that provide detailed views of the cellular topology and interactions in diseased tissues. However, to fully address the multiple dimensions of this disease, a reappraisal of our strategies will be required on multiple fronts. A number of approaches are envisioned as outlined in Box 1.

Discover a Novel Pathway or Cellular Subset

The discovery of the IL-23/IL-17 pathway in 2005 catalyzed the growth of a new therapeutic space that greatly expanded treatment options for PsA patients [12]. The challenging goal of unveiling new pathways or cells is ever more realistic and achievable with the availability of advanced analytic techniques for transcriptomic profiling of target tissues at the single-cell level [13]. These types of analyses are critical because cells that express the same cell surface markers often express distinct mRNA profiles and these may differ dramatically in target tissues from patient to patient [14]. Most importantly, the cost of mRNA profiling is dropping considerably given the development of more affordable alternatives [15••].

An array of technologies are now available that couple transcriptomic profiling with expression of cell surface molecules and parallel technologies that allow analysis of mRNA expression in tissues along with platforms for epigenetic studies (Table 1) [16]. Several recent publications applying single-cell RNA sequencing (scRNA-seq) to study of human rheumatoid synovium revealed that Thy1+ and Thy1− fibroblastic cells are situated at different locations in the synovial membrane and are characterized by discrete effector functions (tissue degradation and release of inflammatory cytokines) [17••]. Additional cellular subsets are now being identified in synovial tissues and blood using these technologies. Subsets of particular interest in PsA include CD8+ T resident memory cells [18], γδ T cells [19], and monocytes with discrete markers that are linked to particular functions [20].

The close relationship between obesity, metabolic syndrome, diabetes, and PsA is another area that may yield new therapeutic pathways. It is well established that signaling in immune and metabolic pathways converge at multiple levels (receptor, organelle, kinase pathways, and gene expression) such that altered metabolism can trigger an inflammatory response while cytokines can act as nutrient hormones [21]. Technologies such as metabolomics [22, 23] and analysis of mitochondrial function [24] are beginning to shed light on these most important interactions which are likely promoting ongoing systemic and target tissue inflammation in PsA.

Lastly, the application of big data analysis coupled with machine learning is already having a major impact on discoveries

Table 1 New technologies for analysis of cell subsets and tissue samples

Technology	Focus of analysis
scRNA-seq	Transcriptome
ATAC-seq	Epigenome
CyTOF	Cell sub-subsets
Cite-seq	Transcriptome and cell subsets
Slide-seq	Spatial transcriptome
Laser capture	Spatial transcriptome
Whole genome sequencing	Genome

scRNA-seq single-cell RNA sequencing, *ATAC-seq* assay for transposase-accessible chromatin using sequencing, *CyTOF* cytometry by time of flight, *CITE-seq* cellular indexing of transcriptomes and epitopes by sequencing, *Slide-seq* slide sequencing

and targeted therapies for individual PsA patients. In order to differentiate cell subsets and pathways in individual tissues, these technologies must have the capacity to analyze a large number of variables that may impact disease severity, identify potential therapies, and assist in outcome predictions. A major goal is to apply these data to select therapies based on the target tissue microenvironment (skin, blood, synovium, bone marrow). In a recent study, application of machine learning algorithms to synovial tissue samples from RA patients coupled with integrative analysis of clinical, histologic, and gene expression data allowed investigators to divide these tissues according to inflammatory, mixed, and non-inflammatory subtypes [25]. The non-inflammatory tissues were characterized by activation of fibroid and neuronal genes associated with fibrosis and pain with a paucity of inflammation. In contrast, the inflammatory subsets demonstrated an assortment of myeloid and lymphoid cells in the synovium. This type of strategy may permit individualization of therapy based on the integration of transcriptomics and histopathologic findings in synovial tissue. Machine learning strategies are particularly appealing because they are scientifically rigorous, intra- and inter-reader bias is lessened, a number of variables are rapidly analyzed, and they are scalable.

Apply Stratification Biomarkers to Individualize Therapy

The application of biomarkers to choose appropriate therapies for individual patients has been an ongoing quest in both rheumatoid and psoriatic arthritis. Serum biomarkers are the most available and feasible choice but they have not proven to accurately and reliably differentiate patients for specific therapies. In one recent study, flow cytometric analysis carried out on peripheral blood samples to identify cells with activated Th1, Th17, or combined Th1/Th17 profiles with a flow panel of eight monoclonal antibodies [26]. The treatment selection of secukinumab, a TNFi or ustekinumab was based on the flow cytometric pattern in one group while the other group received a biological agent based on the judgment of the treating physician. Patients treated with the flow cytometry-based strategy showed significantly better joint outcomes than those patients who received usual care while the change in the psoriasis scores was not different. This study demonstrates the potential advantage of cell subset analysis in improving treatment response but additional confirmatory studies are required [27]. Another technology that represents a major advance in single-cell analysis is cytometry by time-of-flight (CyTOF) or mass cytometry [28]. CyTOF is a flow cytometric approach that employs heavy metal isotopes to analyze cell populations and it can query over 50 separate markers per sample, a major advantage over conventional cytometry which is limited to about 20 fluorophores.

Preclinical Intervention

Longitudinal studies have demonstrated that about 20–30% of psoriasis patients develop PsA. Most importantly, psoriasis precedes the onset of PsA by an average of 6–8 years which provides a unique opportunity to intervene with treatment for psoriasis with the potential to mitigate the severity or even prevent the onset of arthritis [29]. Indeed, psoriasis is a biomarker of PsA and one that is readily accessible. In the Toronto cohort, the rate of annual conversion to PsA in the general psoriasis population (i.e., not enriched with factors of progression) was 3% annually and the onset of arthritis was preceded by a period of fatigue and arthralgias [30•]. Identification of risk factors for PsA holds the possibility that patients with increased likelihood of developing PsA may be selected for earlier and more targeted systemic therapy, even prior to the presence of synovio-enthesial inflammation. Candidate risk factors include obesity, duration of psoriasis, positive family history or psoriatic disease, nail disease, and scalp psoriasis [31]. In addition, screening psoriasis patients with imaging for subclinical musculoskeletal inflammation may help identify patients at risk for arthritis. It is now apparent that psoriasis patients without musculoskeletal symptoms demonstrate a wide array of imaging abnormalities on scintigraphy, high-resolution CT, MRI, and ultrasound [32–36]. Ultrasound imaging is a feasible screening modality that can be applied at point of care to identify patients with subclinical enthesitis, tendonitis, or arthritis. Currently, it is unclear whether these imaging findings can predict subsequent development of PsA. However, the report that treatment of psoriasis using ustekinumab in patients with positive ultrasound signals in the absence of joint symptoms resulted in suppression of these imaging findings is encouraging. Moreover, such an approach is not only feasible and valid but particularly attractive when combined with phenotypic risk factors identified above [37]. An interventional, preventive trial in psoriasis patients at elevated risk for arthritis would provide vital input into the validity and feasibility of such approaches and provide insights into the mechanisms underlying this transition [38••].

Combination Therapy

Preclinical intervention is an exciting approach but for the majority of patients, clinicians struggle with primary or secondary non-response to different therapies. Due to the complexity and heterogeneity of tissue involvement in the setting of varied comorbidities, more than one pathway is likely to require targeting to induce deep, long-lasting clinical responses or even cure. Regrettably, the addition of methotrexate to etanercept in the recent SEAM trial did not increase treatment response to any of the key musculoskeletal domains

[39••]. This outcome is in contrast to RA where combination of these two agents was more effective than etanercept monotherapy [40]. Many clinicians speak to the increased efficacy of apremilast plus a biologic over biologic monotherapy but controlled studies examining this combination have not been carried out. Enthusiasm for combined biologic approaches was greatly dampened by a trial that combined IL-1 and TNF inhibition for RA based on positive results in murine models. In contrast to the findings in mice, RA patients experienced more side effects and lower treatment efficacy raising deep concern for the effect of dual cytokine inhibition on host defense [41]. Moreover, the decreased efficacy with the combination was unexpected and in direct contrast to the results in preclinical studies. An alternative approach to combination therapy was undertaken using the bitypical antibody ABT 122, which combined anti-TNF and anti-IL-17 antibody construct in both RA and PsA trials [42, 43•]. The treatment response was not higher for the bitypical mAb when compared to adalimumab alone in either trial, but most importantly, adverse events were not higher in the ABT122 arms compared to adalimumab monotherapy. These studies show that combination therapy can be safe but additional work is required to improve efficacy and avoiding adverse events. Potential future strategies include administering two different biologics with separate but complementary mechanisms of action at lower doses than monotherapies, combining small molecules with biologic agents, or administering two different biologic agents at different treatment intervals to improve outcomes. This approach is already being explored in inflammatory bowel disease in the Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis (VEGA) trial (:dito_existshttps://clinicaltrials.gov/ct2/show/NCT03662542).

Lifestyle Modification

Patients often ask how they can take steps to improve their response to treatment and in many cases, lifestyle modifications can be undertaken with the potential to lessen pain and improve function. Most notably, obesity, metabolic syndrome, type II DM, and hypertension are prevalent comorbidities in PsA patients and these disorders are amenable to patient interventions [44]. It is important to stress to patients that elevated BMI is associated with an inadequate response to TNFi in PsA patients [45]. This lower response can be addressed however, since several studies demonstrated that weight loss is associated with increased response to TNFi as evidenced by improvement of a broad range of outcome measures [46, 47••]. The improved response is not surprising given the overlap of immune and metabolic pathways outlined above.

Other factors that may relate to the link between obesity and psoriatic disease are the microbiome which is altered in overweight patients. Studies have demonstrated that dietary intake may also have beneficial effects on the gut microbiome [48]. The bacteria *Akkermansia muciniphila* present at lower abundance in the gut of PsA patients [49] is negatively correlated with the presence of obesity, type 2 diabetes, and hypertension and may modulate the host immune response [50•]. In a recent pilot study, supplementation with *A. muciniphila* in overweight and obese human volunteers was associated with improved metabolic parameters and weight loss not seen in controls [51]. This is relevant, since Akkermansia was also found to be significantly decreased in the gut microbiome of patients with new-onset PsA [49]. Additional studies examining the effects of microbiome perturbations on psoriatic disease outcomes, obesity, and metabolic function are in progress.

Exercise cannot only assist with weight control but has also been shown to lessen chronic inflammation and indirectly improve multiple comorbidities including obesity, metabolic syndrome and depression, and lower cardiovascular risk [52]. Moreover, the benefit of exercise for centralized pain has been well documented although the magnitude of improvement is variable from person to person [53]. More emphasis should be placed on these lifestyle modifications with help from nutritionists, physical therapists, and psychologists with formal programs to help patients address and change habits that foster ongoing inflammation in the setting of psoriatic disease.

Address Chronic Pain and Fatigue

Unresolved chronic pain is a persistent feature in PsA that can lead to depression, impaired physical function, sleep disturbance, reduced work productivity, and disability [54•]. The pain may arise from ongoing synovitis, osteitis, enthesitis, osteoarthritis, and chronic damage with mechanical alterations in the joint. Many patients with PsA suffer from centralized pain that is often correlated with the significant psychosocial burdens that plague patients with psoriatic disease. In a large Danish Arthritis Cohort (DANBIO) administered the painDETECT (PDQ) questionnaire, a measure of centralized pain, PsA patients demonstrated significantly higher scores than RA subjects [55]. Persistent and unrecognized centralized pain is a major factor in non-response to targeted therapies in RA and it is not likely that altering biologic therapies will improve outcomes in this patient subgroup [56]. Current trials exclude patients with fibromyalgia in clinical trials although this decision is left to the investigators' discretion. One approach would be to identify fibromyalgia at screening in PsA patients and treat both the centralized pain and PsA together to determine if outcomes would improve.

One study that supports this approach found that PsA patients with high centralized pain scores on the Widespread Pain Questionnaire scale were significantly less likely to achieve the MDA outcome measure [57].

Fatigue is also a major challenge for PsA patients and may arise from depression, disease duration chronic pain, poor sleep, and ongoing inflammation [58]. Efforts to diagnose fatigue are essential to facilitate prompt intervention. Addressing the underlying cause and introducing therapies such as high-intensity interval training may be helpful for many patients [59•].

Multidisciplinary Care

The main theme of this review is that complexity and heterogeneity in PsA greatly complicate early diagnosis and effective therapy for many patients. Nowhere is this more evident than in the treatment decisions faced by clinicians when PsA patients present with multiple domain involvement, often dominated by psoriasis lesions and inflammatory arthritis in the setting of multiple comorbidities.

Therapeutic decisions are often required that take into account therapies for concomitant psoriasis and metabolic disorders such as obesity, metabolic syndrome, and elevated risk for cardiovascular disease. These types of decisions and patient interactions can be most effectively carried out in a team-based environment (Fig. 1).

A working relationship between dermatology and rheumatology and primary care provides numerous advantages to patients and trainees and offers a robust educational and research environment [60]. Cooperative care can facilitate prompt access and provide an opportunity for early diagnosis of arthritis in psoriasis patients. The relationships and coordinated efforts foster collaborative treatment decisions between rheumatology and dermatology for treatment of musculoskeletal disease in the setting of psoriasis and facilitate the recognition and incorporation of comorbidities into the treatment algorithm [61•].

The combined clinics also engage other members to participate in the team including advanced practice providers (APPs), students, medical and dermatology residents, and rheumatology fellows. The educational environment is enriched by the cross-collaborative interactions. These centers also engage other subspecialists to assist in treatment of

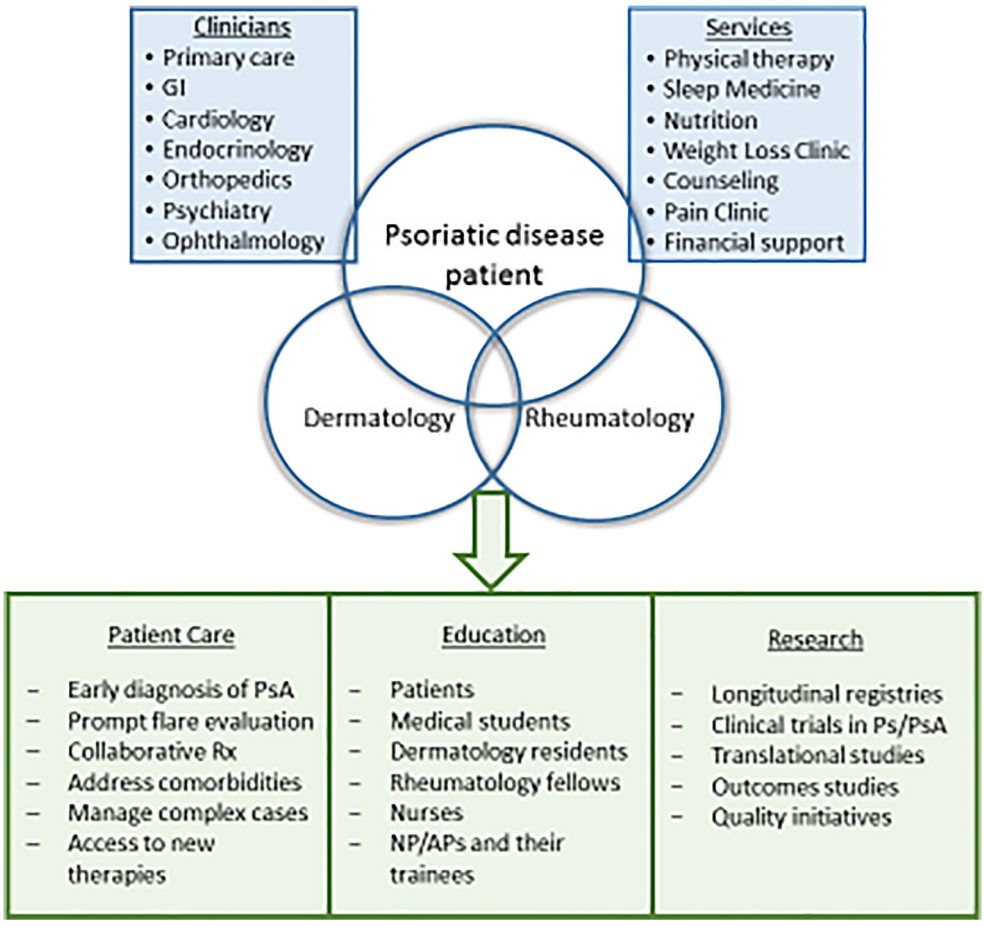

Fig. 1 Multidisciplinary care in psoriatic disease

comorbidities including GI, cardiology, hepatology, endocrinology, and psychiatry. Finally, the centers enhance and enable ongoing research through clinical trials, investigator-initiated studies, and longitudinal registries.

Multiple operational models have been adopted to provide multidisciplinary care in patients with psoriatic disease [62]. These include face-to-face, parallel, and preferential circuit efforts. In the face-to-face model, the dermatologist and rheumatologist see patients together in a combined clinic. In the parallel model, the rheumatology and dermatology visits are separate but the offices are physically close so that the patient transitions between offices asynchronously and the providers communicate regarding diagnosis and therapy. In the preferential circuit model, the two subspecialists schedule prompt appointments and discuss care in order to harmonize therapies but the visits are not necessarily tightly coordinated. The face-to-face model is more feasible in an academic environment while the other two models are more appropriate for practitioners who do not practice in the same center. Efforts to establish multidisciplinary clinics for patients with psoriatic disease are currently underway spearheaded by Psoriasis & Psoriatic Arthritis Clinics Multicenter Advancement Network (PPACMAN) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [60].

Conclusion

Advances in technology provide a unique opportunity to tailor individual therapies based on the assessment of tissue pathways of inflammation and injury and the presence of key comorbidities. It is anticipated that combinations of domain involvement are triggered by environmental and genetic interactions and orchestrated downstream by unique cell subsets and cytokine interactions that will ultimately guide treatment selection. To increase the effectiveness of our strategies, addressing the psychosocial burden of disease along with the sources of acute and chronic pain will be required. Multidisciplinary care models that are spearheaded by dermatology and rheumatology in collaboration with primary care and relevant subspecialists hold great promise for facilitating early diagnosis, integrating treatment regimens, and fostering the research and education of the next generation of caregivers, an essential element for improving care for patients with psoriatic disease. The diagnosis and treatment of PsA have undergone incredible transformation since the case descriptions of Moll and Wright in 1973, but the near future holds great promise for improved treatment response based on a better understanding of individual variation in disease pathophysiology coupled with comprehensive and integrated treatment programs.

Box 1 Strategies to improve outcomes in psoriatic arthritis

1. Discover a novel inflammatory pathway or cell subset
2. Apply stratification biomarkers to individualize therapy
3. Preclinical intervention
4. Combination therapy
5. Lifestyle modification
6. Address chronic pain and fatigue
7. Multidisciplinary care

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Moll JM, Wright V. Psoriatic arthritis. Seminars in Arthritis and Rheumatism. 1973;3(1):55–78.
2. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. Medicine. 1974;53(5):343–64.
3. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med. 2017;376(10):957–70.
4. Kavanaugh AF, Ritchlin CT, Committee GTG. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. The Journal of Rheumatology. 2006;33(7):1417–21.
5. Coates LC, FitzGerald O, Merola JF, Smolen J, van Mens LJJ, Bertheussen H, et al. Group for research and assessment of psoriasis and psoriatic arthritis/outcome measures in rheumatology consensus-based recommendations and research agenda for use of composite measures and treatment targets in psoriatic arthritis. Arthritis & Rheumatology. 2018;70(3):345–55.
6. Raychaudhuri SP, Wilken R, Sukhov AC, Raychaudhuri SK, Maverakis E. Management of psoriatic arthritis: early diagnosis, monitoring of disease severity and cutting edge therapies. J Autoimmun. 2017;76:21–37.
7•. Mease PJ, Coates LC. Considerations for the definition of remission criteria in psoriatic arthritis. Seminars in arthritis and rheumatism. 2018;47(6):786–96 **Thoughtful discussion on the application of composiite measures to define remission in PsA**.
8.• Baeten D, Ostergaard M, Wei JC, Sieper J, Jarvinen P, Tam LS, et al. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. Annals of the Rheumatic Diseases. 2018;77(9):1295–302 **The antibody to IL-23 was ineffective in treating ankylosing spondylitis. This finding was**

unexpected based on the preclinical reports that demonstrated an etiologic role of IL-23 in axial inflammation.

9. Araujo EG, Englbrech M, Hoepken S, Finzel S, Hueber AJ, Rech J, et al. Ustekinumab is superior to TNF inhibitor treatment in resolving enthesitis in Psa patients with active enthesitis- results from the enthesial clearance in psoriatic arthritis study [abstract]. Arthritis Rheumatol. 2017;69(suppl 10).
10. Conrad C, Gilliet M. Psoriasis: from pathogenesis to targeted therapies. Clinical Reviews in Allergy & immunology. 2018;54(1): 102–13.
11.•• McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 family of cytokines in health and disease. Immunity. 2019;50(4):892–906 **Comprehensive and timely review of the structure and function of the IL-17 molecules and the central importance of this family in immune-mediated disorders including psoriasis and PsA**.
12. Donlin LT, Rao DA, Wei K, Slowikowski K, McGeachy MJ, Turner JD, et al. Methods for high-dimensonal analysis of cells dissociated from cyropreserved synovial tissue. Arthritis Research & Therapy. 2018;20(1):139.
13. Tang F, Barbacioru C, Nordman E, Li B, Xu N, Bashkirov VI, et al. RNA-Seq analysis to capture the transcriptome landscape of a single cell. Nat Protoc. 2010;5(3):516–35.
14. Stadhouders R, Lubberts E, Hendriks RW. A cellular and molecular view of T helper 17 cell plasticity in autoimmunity. J Autoimmun. 2018;87:1–15.
15.•• Stephenson W, Donlin LT, Butler A, Rozo C, Bracken B, Rashidfarrokhi A, et al. Single-cell RNA-seq of rheumatoid arthritis synovial tissue using low-cost microfluidic instrumentation. Nat Commun. 2018;9(1):791 **This report demonstrated that scRNA-seq can be performed with a low-cost microfluidic instrument which was applied to the analysis of cell populations in rheumatoid synovium**.
16. Mimitou EP, Cheng A, Montalbano A, Hao S, Stoeckius M, Legut M, et al. Multiplexed detection of proteins, transcriptomes, clonotypes and CRISPR perturbations in single cells. Nat Methods. 2019;16(5):409–12.
17.•• Croft AP, Campos J, Jansen K, Turner JD, Marshall J, Attar M, et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. Nature. 2019;570(7760):246–51 **This scRNA-seq analysis of rheumatoid synovium identified 5 fibroblastoid populations located in different regions of the synovial membrane. Specific subsets expressed genes associated with inflammation or tissue degradation.**
18. Matos TR, O'Malley JT, Lowry EL, Hamm D, Kirsch IR, Robins HS, et al. Clinically resolved psoriatic lesions contain psoriasis-specific IL-17-producing alphabeta T cell clones. The Journal of Clinical Investigation. 2017;127(11):4031–41.
19. Nguyen CT, Maverakis E, Eberl M, Adamopoulos IE. gammadelta T cells in rheumatic diseases: from fundamental mechanisms to autoimmunity. Semin Immunopathol. 2019.
20. Culemann S, Gruneboom A, Nicolas-Avila JA, Weidner D, Lammle KF, Rothe T, et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. Nature. 2019;572(7771):670–5.
21.• Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177–85 **Elegant discussion of the interaction between metabolic and inflammatory pathways that is of particular relevance in PsA.**
22. Aterido A, Canete JD, Tornero J, Ferrandiz C, Pinto JA, Gratacos J, et al. Genetic variation at the glycosaminoglycan metabolism pathway contributes to the risk of psoriatic arthritis but not psoriasis. Annals of the Rheumatic diseases. 2019;78(3).
23. Pietrzak A, Chabros P, Grywalska E, Kicinski P, Pietrzak-Franciszkiewicz K, Krasowska D, et al. Serum lipid metabolism in psoriasis and psoriatic arthritis - an update. Arch Med Sci. 2019;15(2):369–75.
24. McGarry T, Orr C, Wade S, Biniecka M, Wade S, Gallagher L, et al. JAK/STAT Blockade alters synovial bioenergetics, mitochondrial function, and proinflammatory mediators in rheumatoid arthritis. Arthritis & Rheumatology. 2018;70(12):1959–70.
25. Orange DE, Agius P, DiCarlo EF, Robine N, Geiger H, Szymonifka J, et al. Identification of three rheumatoid arthritis disease subtypes by machine learning integration of synovial histologic features and rna sequencing data. Arthritis & Rheumatology. 2018;70(5):690–701.
26. Miyagawa I, Nakayamada S, Nakano K, Kubo S, Iwata S, Miyazaki Y, et al. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. Rheumatology. 2019;58(2):336–44.
27. Al-Mossawi H, Coates LC. Personalized medicine - a new reality in psoriatic arthritis? Nature Reviews Rheumatology. 2018;14(8): 449–51.
28. Palit S, Heuser C, de Almeida GP, Theis FJ, Zielinski CE. Meeting the challenges of high-dimensional single-cell data analysis in immunology. Front Immunol. 2019;10:1515.
29. Tillett W, Charlton R, Nightingale A, Snowball J, Green A, Smith C, et al. Interval between onset of psoriasis and psoriatic arthritis comparing the UK Clinical Practice Research Datalink with a hospital-based cohort. Rheumatology. 2017;56(12):2109–13.
30.• Eder L, Polachek A, Rosen CF, Chandran V, Cook R, Gladman DD. The development of psoriatic arthritis in patients with psoriasis is preceded by a period of nonspecific musculoskeletal symptoms: a prospective cohort study. Arthritis & Eheumatology. 2017;69(3, 622):–9 **Important report that documented early clinical symptoms of PsA in a large longitudinal psoriasis cohort**.
31. Ogdie A, Gelfand JM. Clinical risk factors for the development of psoriatic arthritis among patients with psoriasis: a review of available evidence. Current Rheumatology Reports. 2015;17(10):64.
32. Faustini F, Simon D, Oliveira I, Kleyer A, Haschka J, Englbrecht M, et al. Subclinical joint inflammation in patients with psoriasis without concomitant psoriatic arthritis: a cross-sectional and longitudinal analysis. Annals of the Rheumatic Diseases. 2016.
33. Finzel S, Ohrndorf S, Englbrecht M, Stach C, Messerschmidt J, Schett G, et al. A detailed comparative study of high-resolution ultrasound and micro-computed tomography for detection of arthritic bone erosions. Arthritis and Rheumatism. 2011;63(5): 1231–6.
34. Gisondi P, Tinazzi I, El-Dalati G, Gallo M, Biasi D, Barbara LM, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. Annals of the Rheumatic Diseases. 2008;67(1):26–30.
35. Namey TC, Rosenthall L. Periarticular uptake of 99mtechnetium diphosphonate in psoriatics: correlation with cutaneous activity. Arthritis and Rheumatism. 1976;19(3):607–12.
36. Simon D, Faustini F, Kleyer A, Haschka J, Englbrecht M, Kraus S, et al. Analysis of periarticular bone changes in patients with cutaneous psoriasis without associated psoriatic arthritis. Annals of the Rheumatic Diseases. 2016;75(4):660–6.
37. Savage L, Goodfield M, Horton L, Watad A, Hensor E, Emery P, et al. Regression of peripheral subclinical enthesopathy in therapy-naive patients treated with ustekinumab for moderate-to-severe chronic plaque psoriasis: a fifty-two-week, prospective, open-label feasibility study. Arthritis & Rheumatology. 2019;71(4):626–31.
38.•• Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nature reviews Rheumatology. 2019;15(3):153–66 **Comprehensive review of the risk factors and pathophysiologic events associated with the transition from psoriasis to PsA**.
39.•• Mease PJ, Gladman DD, Coller DH, Ritchlin CT, Helliwell PS, Kricorian G, et al. Monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis & rheumatology. 2019;71(7):1112-24. **First clinical**

trial to document that combination therapy with etanercept and methotrexate was not more effective than etanercept alone for treatment of PsA. Methotrexate monotherapy, however, was shown to be effective for all domains.

40. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis and Rheumatism. 2006;54(4):1063–74.
41. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis and Rheumatism. 2004;50(5):1412–9.
42. Genovese MC, Weinblatt ME, Aelion JA, Mansikka HT, Peloso PM, Chen K, et al. ABT-122, a bispecific dual variable domain immunoglobulin targeting tumor necrosis factor and interleukin-17A, in patients with rheumatoid arthritis with an inadequate response to methotrexate: a randomized, double-blind study. Arthritis & Rheumatology. 2018;70(11):1710–20.
43.• Mease PJ, Genovese MC, Weinblatt ME, Peloso PM, Chen K, Othman AA, et al. Phase II study of ABT-122, a tumor necrosis factor- and interleukin-17A-targeted dual variable domain immunoglobulin, in patients with psoriatic arthritis with an inadequate response to methotrexate. Arthritis & Rheumatology. 2018;70(11):1778–89 **The dual variable domain immunoglobulin (anti-IL-17 and anti-TNF) was not more effective than adalimumab alone but adverse events were not higher in the patients treated with the antibody construct**.
44. Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. Current opinion in Rheumatology. 2015;27(2):118–26.
45. Hojgaard P, Glintborg B, Kristensen LE, Gudbjornsson B, Love TJ, Dreyer L. The influence of obesity on response to tumour necrosis factor-alpha inhibitors in psoriatic arthritis: results from the DANBIO and ICEBIO registries. Rheumatology. 2016;55(12):2191–9.
46. Di Minno MN, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R, et al. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor alpha blockers. Annals of the Rheumatic Diseases. 2014;73(6):1157–62.
47.•• Klingberg E, Bilberg A, Bjorkman S, Hedberg M, Jacobsson L, Forsblad-d'Elia H, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: an interventional study. Arthritis research & therapy. 2019;21(1):17 **Marked caloric restriction followed by a supportive dietary counseling was associated with a high degree of weight loss and significant improvement in a wide range of clinical parameters in PsA**.
48. Liu R, Hong J, Xu X, Feng Q, Zhang D, Gu Y, et al. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nature Medicine. 2017;23(7):859–68.
49. Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis & Rheumatology. 2015;67(1):128–39.
50.• Ansaldo E, Slayden LC, Ching KL, Koch MA, Wolf NK, Plichta DR, et al. Akkermansia muciniphila induces intestinal adaptive immune responses during homeostasis. Science. 2019;364(6446):1179–84 **Interesting report that discusses the impact of this bacterial species on the gut immune reponse**.
51. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nature Medicine. 2019;25(7):1096–103.
52. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. Nature reviews. Rheumatology. 2015;11(2):86–97.
53. Bidonde J, Busch AJ, Schachter CL, Webber SC, Musselman KE, Overend TJ, et al. Mixed exercise training for adults with fibromyalgia. Cochrane Database Syst Rev. 2019;5:CD013340.
54.• Husni ME, Merola JF, Davin S. The psychosocial burden of psoriatic arthritis. Seminars in Arthritis and Rheumatism. 2017;47(3):351–60 **Comprehensive and thoughtful discussion of the psychosocial challenges prevalent in PsA**.
55. Rifbjerg-Madsen S, Christensen AW, Christensen R, Hetland ML, Bliddal H, Kristensen LE, et al. Pain and pain mechanisms in patients with inflammatory arthritis: a Danish nationwide cross-sectional DANBIO registry survey. PloS one. 2017;12(7):e0180014.
56. Lage-Hansen PR, Chrysidis S, Lage-Hansen M, Hougaard A, Ejstrup L, Amris K. Concomitant fibromyalgia in rheumatoid arthritis is associated with the more frequent use of biological therapy: a cross-sectional study. Scandinavian Journal of Rheumatology. 2016;45(1):45–8.
57. Hojgaard P, Ellegaard K, Nielsen SM, Christensen R, Guldberg-Moller J, Ballegaard C, et al. Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: a prospective cohort study. Arthritis Care & Research. 2019;71(6):798–810.
58. Skougaard M, Jorgensen TS, Rifbjerg-Madsen S, Coates LC, Egeberg A, Amris K, et al. In psoriatic arthritis fatigue is driven by inflammation, disease duration, and chronic pain: an observational DANBIO registry study. The Journal of Rheumatology. 2019.
59.• Thomsen RS, Nilsen TIL, Haugeberg G, Bye A, Kavanaugh A, Hoff M. Impact of high-intensity interval training on disease activity and disease in patients with psoriatic arthritis: a randomized controlled trial. Arthritis Care & Research. 2019;71(4):530–7 **High-intensity interval training was associated with decreased level of fatigue in PsA**.
60. Okhovat JP, Ogdie A, Reddy SM, Rosen CF, Scher JU, Merola JF. Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network Consortium (PPACMAN) Survey: benefits and challenges of combined rheumatology-dermatology clinics. The Journal of Rheumatology. 2017;44(5):693–4.
61.• Soleymani T, Reddy SM, Cohen JM, Neimann AL. Early recognition and treatment heralds optimal outcomes: the benefits of combined rheumatology-dermatology clinics and integrative care of psoriasis and psoriatic arthritis patients. Current rheumatology reports. 2017;20(1):1 **Excellent discussion of multidisciplinary care in psoriatic disease and potential impact on patient outcomes.**
62. Queiro R, Coto P, Rodriguez J, Notario J, Navio Marco T, de la Cueva P, et al. Multidisciplinary care models for patients with psoriatic arthritis. Reumatol Clin. 2017;13(2):85–90.