3-1-2020

Preface to the psoriatic arthritis supplement.

Philip Mease
Rheumatology Division, Swedish Medical Center/Providence St. Joseph Health, Seattle, WA, USA

RHEUMATOLOGY

Rheumatology 2020;59:1–3
doi:10.1093/rheumatology/keaa041

Preface to the psoriatic arthritis supplement

Philip Mease [1,2]

Introduction

This supplement of Rheumatology is devoted to the 'many faces' of PsA. Highlighted is the point that PsA is a heterogeneous disease regardless of viewpoint, from genetics, pathophysiology, clinical features, assessment of disease activity or treatment. PsA can be likened to an orchestra performance. At times, the full orchestra—strings, brass, woodwinds, percussion—is playing, including arthritis (synovitis), enthesitis, dactylitis, spine inflammation, skin and nail disease, along with key comorbidities such as metabolic syndrome and associated conditions such as uveitis and inflammatory bowel disease. But at other times, or based on individual presentation, only certain sections or even a single section is playing, such as the patient who is presenting predominantly with back pain, arthritis, skin disease or enthesitis. On X-ray we can observe different forms of pathology from digit to digit, with osteolysis in one and osteoproliferation in the adjacent one. Different immunologic mechanisms may be operative in the spine and peripheral joints and entheses, or the skin and musculoskeletal domains, leading to differences in treatment response to targeted therapies in these different parts of the body. Independent of treatment, the dynamics of the various orchestra sections may change, at times forte, at times pianissimo, or not at all. When I am educating patients at their first presentation, I am able to advise them about what to expect in broad brush strokes, but I also advise them that their specific manifestations and disease course will be unique and unlike that of any other patient, simply due to the heterogeneity of PsA. The authors in this supplement provide an up-to-date review of our current understanding of PsA in genetics, clinical assessment and treatment recommendations.

PsA genetics

Winchester and FitzGerald review recent studies on the genetic underpinning of PsA. First, by comparing patients who have psoriasis with no musculoskeletal manifestations and those with PsA, it is clear there are distinctive HLA patterns in one population *vs* the other. Within the PsA phenotype, there are subphenotypes that are also associated with certain HLA patterns. The individual patient's susceptibility alleles determine the T cell repertoire, which determines what disease phenotype will become manifest as well as the timing of disease appearance and also disease severity. For example, the presence of HLA-B*40:01 and HLA-B*44:01 in psoriasis patients appears to be protective against the development of PsA. Patients with PsA spondylitis who have HLA-B*08:01 are more likely to present with asymmetric sacroiliitis, whereas those with HLA-B*27:05:02 are more likely to have symmetric sacroiliitis, enthesitis and dactylitis. The authors illustrate a number of such subphenotypes that appear to be directed by genetic specificity. This work points toward a future when we will be better able to predict disease evolution, which may aid us in patient education as well as targeting treatment.

PsA enthesitis (parts 1–3)

The clinical domain of enthesitis has recently become a special focus of translational and clinical research. Thus in this supplement, we have devoted three separate but coordinated articles to the subject: clinical description and pathophysiology (Araujo and Schett), imaging assessment (Kaeley) and clinical assessment and treatment (Mease). Enthesitis is characterized by inflammation at the site of tendon, ligament and joint capsule fiber attachment to bone. The anatomy is complex, involving the morphologic transition from pure tendon or ligament fibers to mineralized fibrocartilage to bone anchoring well below the bone cortex, thus providing the strength to withstand strong force while still providing some elasticity of movement. Vascularization comes from the bone marrow as well as from the extraosseous space, which is the source of immune cells and cytokines that migrate to this anatomic location and, in addition to resident immune cell reactivity, set up an inflammatory response to mechanotrauma, infectious antigens or a distant response to microbiome dysregulation. Key molecular mediators and cells include PGE2, IL-17, IL-23, IL-22, TNF and a number of different cell types, including dendritic cells, TH17 cells, innate lymphoid cells, $\gamma\delta$ T cells and others. Animal models suggest that the enthesium may be one of the first sites of inflammation noted in SpA pathogenesis. McGonagle has utilized the term 'enthesis organ' to denote the complex

[1]University of Washington School of Medicine and [2]Rheumatology Division, Swedish Medical Center/Providence St. Joseph Health, Seattle, WA, USA

Submitted 24 October 2019; accepted 23 January 2020

Correspondence to: Philip Mease, Seattle Rheumatology Associates, 601 Broadway Suite 600, Seattle WA 98122, USA. E-mail: pmease@philipmease.com

EDITORIAL

anatomy and immunology of this site. Postinflammatory changes can include ossification or enthesophyte formation.

Kaeley reviews the imaging approaches to enthesitis evaluation. Because of the limitations of radiography to evaluate soft tissue and inflammation, the utility of X-ray is limited. Thus the focus is more on advanced imaging techniques such as ultrasound and MRI. Advances in ultrasound technology now allow us to evaluate enthesitis in a granular way, with both anatomic characterization, e.g. tendon width, as well as the presence of active inflammation through the use of power Doppler. The number of rheumatologists trained in ultrasound has increased significantly in recent years, allowing the technique to be utilized readily in the clinic. Multiple enthesial sites can easily be evaluated in a brief encounter, thus increasing the feasibility of the technique. A limitation is that ultrasound cannot visualize beyond the bone cortex and thus is not reliable to evaluate osteitis associated with enthesitis. On the other hand, MRI is capable of evaluating both the tendon–ligament as well as the bone aspects of enthesitis, for a more comprehensive view. Both standard MRI and newer technologies such as dynamic contrast-enhanced MRI can provide exquisite tissue detail about both inflammation and structural changes. A disadvantage of standard MRI is that it stages one body area at a time, which is partially corrected by improving the quality of whole body MRI.

Mease reviews the performance characteristics of various enthesitis indices used to measure enthesitis by physical examination in clinical trials and registries. These include the Leeds Enthesitis Index (LEI), the Spondyloarthritis Research Consortium of Canada (SPARCC) Index and the Maastricht Enthesitis Index (MASES) that are currently being used. A limitation of these measures is that they may not always measure 'itis' but may instead simply measure 'algia', i.e. pain sensitivity rather than true inflammation. Despite this limitation, they have generally performed well in discriminating treatment from placebo in clinical trials. Mease then proceeds to describe the enthesitis results for each of the PsA treatments. It is on the basis of these results, coupled with the presence and impact of enthesitis in the patient we are working with, that helps guide the choice and monitoring of therapy. Also reviewed is the significant impact of enthesitis on function and quality of life as illuminated in clinical registries. The ability of targeted therapies such as those that inhibit TNF and IL-17 to effect enthesitis remission is one of the striking success stories of currently available and emerging therapies.

PsA assessments

McGagh and Coates review the evolving field of clinical measurement of PsA, particularly in clinical trials. Prior to this century there were essentially no validated measures for the variety of clinical domains that constitute PsA since there were few therapeutic trials in the disease. Clinicians typically assumed that medications that showed efficacy in RA trials would be efficacious in PsA and medicines benefiting psoriasis would work in treating PsA skin disease. Similarly, measures for RA, such as ACR response, an arthritis measure, and the Psoriasis Area and Severity Index (PASI) were used to measure those specific domains with reasonable success. Indeed, the ACR20 response has generally been the primary outcome measure for most PsA clinical trials to date. However, it has been appreciated that these measures, not designed specifically for PsA, may not accurately reflect disease in patient's with an oligoarticular presentation, as well as not measuring other clinical domains such as enthesitis, which may respond differently than arthritis or skin disease. Thus a number of measures have been developed, many of them through the work of members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), involving both clinical investigators and patients. These include specific measures of enthesitis, dactylitis, nail disease and spine symptoms, in addition to more PsA-specific measures of arthritis. An example of a more PsA-specific arthritis measure is the Disease Activity for Psoriatic Arthritis (DAPSA) score. In addition, a number of patient-reported outcome measures to measure function, quality of life and fatigue, for example, have been either brought in to be used in PsA, such as the HAQ and 36-item Short Form (SF-36), or developed specifically for PsA, such as the Psoriatic Arthritis Impact of Disease (PSAID) questionnaire. Several composite measures that more holistically take into account several PsA disease domains, such as arthritis, skin disease and enthesitis, have been developed. Examples include the Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA) indices, which are used as targets of therapy, as well as the Psoriatic Disease Activity Score (PASDAS) and Composite Psoriatic Disease Activity Index (CPDAI). In conjunction with OMERACT, the GRAPPA group is currently methodologically evaluating these measures.

PsA treatment recommendations

Ogdie, Coates and Gladman review the PsA treatment guidelines published to date, including those from the GRAPPA and EULAR organizations and the recently published ACR–National Psoriasis Foundation guideline. Thoroughly discussed are the differences and similarities of each organization's guideline development process and the similarities and differences of overarching principles of treatment and treatment recommendations. Examples of similarities of overarching principles include shared decision making with the patient; the importance of shared management with various medical disciplines depending on the patient's disease presentation, associated conditions and comorbidities, including rheumatology, dermatology, primary care, orthopedics, ophthalmology, gastroenterology, physical therapy, and so forth; and the principle of treating to a target of low disease activity or

remission. The authors describe the process of evaluating evidence for therapeutic efficacy and safety for a variety of drugs that have been studied in PsA and then make recommendations for treatment in various contexts, for example, in a patient who is just beginning treatment *vs* a patient who has experienced various previous treatments, patients with specific associated conditions or comorbidities that may influence treatment choice, and so on. A particular challenge in PsA is the multiplicity of clinical domains that are involved, including arthritis, enthesitis, dactylitis, spondylitis and skin and nail disease. Depending on which domains are involved and their relative severity, treatment recommendations may differ depending on the efficacy of a medicine in those particular domains. Patient preference for mode of administration and safety features will play a role in treatment choice as well. A truism about treatment guidelines, especially for a disease such as PsA in which the pace of discovery is rapid and new treatments are being introduced apace, is that the guidelines are outdated by the time they are published, necessitating relatively frequent updates.

PsA patient research partners

Goel reviews a topic that has had historically inadequate awareness among clinical researchers, the role of patients not only as subjects of research, or token contributors via focus groups, to qualitative research, but as completely equal colleagues in the design and conduct of research projects, as well as being coauthors on publications and active disseminators of research findings. The term coined for individuals fulfilling this role is 'patient research partner' (PRP). These are individuals who may have the disease, or a similar disease, being researched, but as well the agency to be engaged with all aspects of research, and in some cases may have a background of scientific or medical training that can facilitate their involvement and contribution. Additionally, an effective PRP will not just represent their own personal experience with the disease in question, but will try to represent more broadly the patient experience, taking into account the ethnic, geographic, gender, age and sociocultural diversity of the patient population. Within the rheumatology sphere, PRP engagement began with the OMERACT 2002 meeting. Since then, PRPs have become a required fixture of all OMERACT working groups. An example of the essential role of the PRP was their ability to highlight the importance of fatigue as a clinical domain of rheumatologic disease, leading to the inclusion of fatigue as a core item in core domain sets to be assessed in studies. In addition, numerous research, educational and advocacy organizations have included PRPs in their framework, exemplified by the GRAPPA. In addition to a learned review of the evolution of the PRP role in research, Goel also points out challenges, including 'tokenism', i.e. paying lip service to PRP involvement in order to satisfy grant requirements, as well as the additional cost involved in engaging PRPs in research projects.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article. This paper was published as part of a supplement funded by an educational grant from Novartis.

Disclosures statement: P.M. has served as a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Galapagos, Gilead, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Pfizer, Sun and UCB; received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Sun and UCB and received speaker fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Lilly, Novartis, Pfizer and UCB.