Development of Criteria to Distinguish Inflammatory from Noninflammatory Arthritis, Enthesitis, Dactylitis, and Spondylitis: A Report from the GRAPPA 2013 Annual Meeting

Philip J. Mease, Amit Garg, Philip S. Helliwell, Jane J. Park, and Dafna D. Gladman

ABSTRACT. ***Objective.*** To describe a research project to develop simple clinical criteria to aid in the identification of inflammatory arthritis, enthesitis, dactylitis, and spondylitis and distinguish these from non-inflammatory conditions. The criteria are particularly intended to aid non-rheumatologists, e.g., dermatologists, who need assistance identifying psoriatic arthritis in patients with psoriasis, but may be useful to all clinicians in properly diagnosing rheumatologic conditions.

Methods. The proposed research methodology includes the use of a nominal group exercise among expert clinicians and patient focus groups, Delphi exercises among clinicians and patients, application of criteria test sets to a small group of representative patients with inflammatory and non-inflammatory musculoskeletal conditions, and validation by application of optimal criteria sets to large groups of patients with inflammatory and noninflammatory conditions.

Results. Examples of elements to describe inflammatory conditions derived from a nominal group exercise conducted at the 2013 GRAPPA annual meeting are described, along with planned project activities.

Conclusion. This project will lead to the development of practical criteria to aid in the diagnosis and appropriate clinical care of patients with chronic inflammatory musculoskeletal conditions. (J Rheumatol 2014;41:1249–51; doi:10.3899/jrheum.140182)

Key Indexing Terms:
PSORIATIC ARTHRITIS INFLAMMATORY ARTHRITIS ENTHESITIS
DACTYLITIS SPONDYLITIS

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has initiated a research project with a goal of creating criteria to aid the identification of inflammatory arthritis, enthesitis, dactylitis, and spondylitis. The purpose of this project has been summarized[1]. The problem that this project addresses was brought to light with the application of the ClASsification of Psoriatic Arthritis (CASPAR) criteria for the classification of psoriatic arthritis (PsA)[2]. In using the CASPAR criteria, the clinician must first be satisfied that the subject being evaluated has an inflammatory arthritis, enthesitis, or spondylitis; then the other elements of the criteria can be applied (e.g., presence of psoriasis, nail disease, dactylitis, etc.; for details, see Table 1 in accompanying article by FitzGerald, *et al*)[3].

Rheumatologists are trained to distinguish inflammatory arthritis conditions based on patient history, physical examination, and laboratory and imaging studies. Patient history (e.g., age of onset of condition), prolonged morning stiffness, number and distribution of joints affected, detection of a "spongy" feel of the joint suggesting synovitis, laboratory evidence of elevated inflammation markers (erythrocyte sedimentation rate and C-reactive protein), and characteristic radiographic, ultrasound, or magnetic resonance imaging evidence of synovitis and joint damage all help rheumatologists identify inflammatory, as opposed to degenerative, arthritis. However, non-rheumatologists may not know which key questions to ask the patient; or be able to reliably distinguish the spongy enlargement of an inflamed joint from the hard enlargement of an osteo-

From Seattle Rheumatology Associates, Swedish Medical Center, University of Washington School of Medicine, Seattle, Washington; Department of Dermatology, Hofstra North Shore LIJ School of Medicine, Hempstead, New York, USA; University of Leeds, Leeds, UK, and Bradford Hospitals National Health Service (NHS) Foundation Trust, Bradford, UK; University of Toronto; Toronto Western Research Institute; Psoriatic Arthritis Program, University Health Network, Toronto, Ontario, Canada.

P.J. Mease, MD, Seattle Rheumatology Associates, director, Rheumatology Research, Swedish Medical Center, and clinical professor, University of Washington School of Medicine; A. Garg, MD, Department of Dermatology, Hofstra North Shore LIJ School of Medicine; P.S. Helliwell, DM, PhD, FRCP, Senior Lecturer in Rheumatology, University of Leeds; and Bradford Hospitals NHS Foundation Trust; J.J. Park, MD, Seattle Rheumatology Associates, and University of Washington School of Medicine; D.D. Gladman, MD, FRCPC, professor of medicine, University of Toronto, senior scientist, Toronto Western Research Institute, and director, Psoriatic Arthritis Program, University Health Network.

Address correspondence to Dr. Mease, Seattle Rheumatology Associates, 601 Broadway, Suite 600, Seattle, Washington 98122, USA. E-mail: pmease@philipmease.com

Table 1. Descriptive elements derived from nominal group exercise.

Disease	Descriptors
Inflammatory arthritis	Morning stiffness ≥ 30 min, joint swelling, joint tenderness, pain that improves with activity and worsens with rest, NSAID/steroid-responsive, limited motion, insidious onset, chronic duration, fatigue, proximal distribution, joint deformity, boggy/spongy joint, joint erythema or warmth, presence of extraarticular manifestations
Spondylitis	Morning stiffness ≥ 30 min, chronic back pain > 3 mos, hip/buttock pain, younger age, pain that improves with activity and worsens with rest, night pain, insidious onset, no prior history of trauma or surgery at site of pain, NSAID-responsive, limited motion, sacroiliac joint tenderness
Enthesitis	Pain near the joint, swelling at site of pain, functional limitations, history of plantar fasciitis, younger age, bilateral involvement, tenderness at entheseal insertion sites (Achilles, plantar fascia, quadriceps tendon, patellar ligament, iliac crest)
Dactylitis	Digital swelling, digital warmth, digital erythema, focal or diffuse swelling, tenderness at site of swelling, decreased mobility, "sausage"-like appearance

NSAID: nonsteroidal antiinflammatory drug.

arthritic joint; or be aware of key laboratory or imaging studies to confidently interpret the results. Specifically, in evaluating patients with PsA the non-rheumatologist may not know how to examine for nonarticular clinical domains such as enthesitis, dactylitis, or spondylitis.

This latter criterion was illustrated in the results of the PREPARE study, which was designed to identify PsA in patients being evaluated for psoriasis in dermatology clinics in North America and Europe[4], where psoriasis patients were subsequently seen by rheumatologists. Of 949 psoriasis patients, 30% were considered to have PsA, and of those, 41% had not previously known they had this diagnosis; these results highlight the need for improved identification of inflammatory arthritis, enthesitis, dactylitis, and spondylitis, which characterize PsA in psoriasis patients with musculoskeletal symptoms. On the other hand, 5% of the patients, previously diagnosed with PsA, were considered not to have PsA with more authoritative consultation, thus highlighting the need to distinguish inflammatory from noninflammatory etiologies of musculoskeletal (MSK) symptoms such as osteoarthritis (OA) or fibromyalgia.

In an earlier study of patients with psoriasis referred for further diagnosis of MSK symptoms to a combined dermatology-rheumatology clinic at Harvard, 41% were diagnosed with PsA alone, 15% with a combination of PsA and OA, 27% with OA alone, and 4% with gout, either alone or in combination with PsA or OA, thus again highlighting the importance of distinguishing inflammatory from noninflammatory conditions to avoid misdiagnosis and inappropriate treatment[5].

These problems can be partly addressed by using screening questionnaires to identify patients with possible inflammatory arthritis such as PsA[6]. However, questionnaires are not widely used. To address this problem, rheumatologists and dermatologists from GRAPPA are jointly developing criteria that can be used by clinicians to help with the identification of inflammatory disease distinct from noninflammatory disease, with the intent of devising simple criteria comprising elements from the patient's history and physical examination, for practical application in the clinic.

One model for this exercise is from the Assessment of SpondyloArthritis international Society (ASAS), which developed simple clinical criteria for the identification of inflammatory back pain (IBP)[7]. Through nominal group exercises, the testing of element sets in a small group of patients with chronic back pain with suspected axial spondyloarthritis, and a validation step in 686 patients with chronic back pain, an optimal criteria set was determined, in which there was high sensitivity and specificity for IBP if 4 of these 5 elements were present: (1) age at onset < 40 years; (2) insidious onset; (3) improvement with exercise; (4) no improvement with rest; and (5) pain at night (with improvement upon getting up). Of note, the GRAPPA exercise would involve key physical signs as well as key features in the patient's history.

GRAPPA Project to Develop Simple Criteria for Identification of Inflammatory Arthritis, Enthesitis, Dactylitis, and Spondylitis

Step 1. In a nominal group exercise, expert clinicians, patient researchers, and patient focus groups, facilitated by experts in qualitative research, will generate a list of key words, phrases, and concepts that define the features of inflammatory disease in each clinical domain and distinguish inflammation from noninflammatory causes of disease, such as OA, mechanical or degenerative tendonitis and back pain, or fibromyalgia. The elements that emerge from these exercises will be prioritized by a Delphi process conducted among the participating experts, patient researchers, and patients. Because the elements suggested by experts and patients during the Delphi process may be expressed differently, a further exercise to harmonize the language will be conducted by a representative panel of expert clinicians and patient researchers.

As part of Step 1, a nominal group exercise was conducted at the GRAPPA 2013 annual meeting. In 4 groups, which included patient researchers, participants brainstormed clinical descriptors of inflammatory arthritis, spondylitis, enthesitis, and dactylitis, and shared their initial thoughts within their respective groups. The groups' ideas

were then reported back to all meeting participants. The following is a brief summary of the elements that could distinguish inflammatory arthritis, enthesitis, dactylitis, and spondylitis (Table 1).

The inflammatory arthritis group agreed that morning stiffness was a predominant feature. Duration of morning stiffness of ≥ 30 min was the general consensus, although some suggested longer or shorter cutoff periods. Other notable features included pain that improves with activity and worsens with rest, insidious onset, proximal and distal distribution, joint swelling, and joint tenderness. Chronicity was also discussed, although the duration was uncertain. Enthesitis descriptors included pain or tenderness at various entheseal sites, including a history of plantar fasciitis, swelling at periarticular sites, and bilateral involvement. Dactylitis, although difficult to diagnose by physical examination given the often variable nature of normal toes, was characterized by digital swelling, warmth, tenderness, and erythema — a "sausage-like" appearance. Spondylitis descriptors were similar to those for inflammatory arthritis: significant characteristics were morning stiffness and pain that improves with activity and worsens with rest; additional characteristics were insidious onset, younger age, and limited range of motion. Some questioned the need for a spondylitis definition because ASAS has already defined IBP. Laboratory and radiographic characteristics were avoided as the goal is to make the definitions simple and easy to use in daily clinical practice.

This nominal group exercise is considered a starting point. Full involvement of GRAPPA members, including those who could not attend the annual meeting, will include an online survey. Patient focus groups have yet to be convened and are essential to gain a more complete perspective.

Step 2. In this step, test sets (e.g., with 5 elements apiece) of key elements chosen by the above-described process in patients with different disease conditions (e.g., inflammatory arthritis vs OA) will be evaluated. One approach is to have expert clinicians meet with patients with various types of MSK diseases and apply the test sets to them to evaluate which elements and groups of elements provide the greatest sensitivity and specificity for correctly identifying inflammatory disease and distinguishing from noninflammatory disease. One methodological approach for this step could be Latin square design, as exemplified by the IMPART study[8], in which a set number of expert clinicians (e.g., 20) interview and examine ≥ 20 patients to apply the test sets. It will be important to include a mixture of patients, both those with inflammatory arthritis, enthesitis, dactylitis, and spondylitis as well as those with noninflammatory conditions that are potentially difficult to distinguish from inflammatory disease (e.g., OA and/or mechanical or degenerative tendonitis). Statistical evaluation of the accuracy of test sets will determine which are preferred for further research in each clinical domain. Other methodological approaches may also be considered depending on the quality of outcome, funding, and logistical feasibility of this process.

Step 3. In a validation step, test sets that show the greatest sensitivity and specificity in Step 2 will be advanced to testing in larger numbers of patients being observed in GRAPPA investigative centers globally, again involving patients with inflammatory conditions and those with noninflammatory arthritis, tendonitis, and back pain. It is anticipated that the final criteria sets will be independently assessed and further validated in other patient cohorts and settings, but that is beyond the scope of this project.

GRAPPA has initiated a project to develop simple, practical criteria for the identification of inflammatory arthritis, enthesitis, dactylitis, and spondylitis to aid non-rheumatologists in the diagnosis and treatment of PsA. It is hoped that these criteria will eventually lead to earlier diagnosis and thus more appropriate clinical care of patients with chronic inflammatory MSK conditions.

REFERENCES

1. Mease PJ, Garg A, Gladman DD, Helliwell PS. Development of simple clinical criteria for the definition of inflammatory arthritis, enthesitis, dactylitis, and spondylitis: a report from the GRAPPA 2012 annual meeting. J Rheumatol 2013;40:1442-5.
2. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
3. FitzGerald O, Mease PJ, Helliwell PS, Chandran V. GRAPPA 2013 Annual Meeting, rheumatology updates: PsA Biomarker Project, arthritis mutilans, PsA-Peripheral SpA Epidemiology Project. J Rheumatol 2014;41:1244-8.
4. Mease PJ, Gladman DD, Papp KA, Khraishi MM, Thaci D, Behrens F, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. J Am Acad Dermatol 2013;69:729-35.
5. Mody E, Husni ME, Schur P, Qureshi AA. Multidisciplinary evaluation of patients with psoriasis presenting with musculoskeletal pain: a dermatology: rheumatology clinic experience. Br J Dermatol 2007;157:1050-1.
6. Dominguez P, Gladman DD, Helliwell P, Mease PJ, Husni ME, Qureshi AA. Development of screening tools to identify psoriatic arthritis. Curr Rheumatol Rep 2010;12:295-9.
7. Sieper J, van der Heijde D, Landewe R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009;68:784-8.
8. Chandran V, Gottlieb A, Cook RJ, Duffin KC, Garg A, Helliwell P, et al. International multicenter psoriasis and psoriatic arthritis reliability trial for the assessment of skin, joints, nails, and dactylitis. Arthritis Rheum 2009;61:1235-42.