GRAPPA 2013 Annual Meeting, Rheumatology Updates: Psoriatic Arthritis (PsA) Biomarker Project, Arthritis Mutilans, PsA-Peripheral Spondyloarthritis Epidemiology Project

Oliver FitzGerald, Philip J. Mease, Philip S. Helliwell, and Vinod Chandran

ABSTRACT. At the 2013 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), several key GRAPPA projects on musculoskeletal aspects of psoriatic disease were reviewed. In this article, lead investigators summarize the progress made in a multicenter study, the PsA BioDam (Psoriatic Arthritis Biomarkers for Joint Damage), to identify soluble biomarkers for joint damage, as well as developing classification criteria for arthritis mutilans. Also reviewed are concepts and rationale behind a proposal to study classification criteria for peripheral spondyloarthritis, including PsA, reactive arthritis, inflammatory bowel disease-associated arthritis, and undifferentiated arthritis. (J Rheumatol 2014;41:1244–8; doi:10.3899/jrheum.140181)

Key Indexing Terms:
PSORIATIC ARTHRITIS | PSA BIODAM | BIOMARKERS
OSTEOLYSIS | ANKYLOSIS | SPONDYLOARTHRITIS

At the 2013 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), members reviewed the progress in key research endeavors related to musculoskeletal aspects of psoriatic disease and considered a new proposal on criteria for peripheral and axial spondyloarthritis. The 3 projects were presented to the general GRAPPA audience by the lead investigators.

Psoriatic Arthritis Biomarkers for Joint Damage (PsA BioDam) Study *(Oliver FitzGerald)*

For some time, GRAPPA and the Outcome Measures in Rheumatology (OMERACT) Biomarker subgroup led by Walter Maksymowych have been working on a study to prospectively validate soluble biomarkers as predictors of structural damage in psoriatic arthritis (PsA). The patient population would have active disease and be about to start either a disease-modifying antirheumatic drug or their first course of anti-tumor necrosis factor therapy. The primary radiographic outcome measure would be the number of new erosions assessed on radiographs of hands and feet, according to the modified Sharp/van der Heijde score, with radiographs obtained at baseline and after 24 months of followup. It is expected that the study will identify prognostic biomarkers to help stratify treatment.

The proposed study will assess candidate markers likely related to joint damage progression, as well as explore novel techniques such as proteomics or transcriptomics to identify biomarkers of interest. Candidate biomarkers include markers of inflammation such as C-reactive protein or serum amyloid A; markers of collagen breakdown such as C2C, C1-2C, and CPII levels; proteolytic enzymes such as matrix metalloprotease 3 (MMP3); and markers of bone turnover such as Dickkopf-1, sclerostin, bone alkaline phosphatase, C-telopeptide fragments of type II collagen (CTX-II), CTX-1, receptor activator of nuclear factor-κB ligand, and osteoprotegerin. It is possible that a combination of biomarkers or a biomarker panel may function better than a single biomarker level. Investigators would also like to collect DNA to explore genetic associations with radiographic change.

The study will include 1000 patients with PsA, with 6 visits over a 2-year period: at baseline and at months 3, 6, 12, 18, and 24. Investigators at up to 40 study sites will collect patient phenotypic data, patient-reported question-

From the Department of Rheumatology, St. Vincent's University Hospital and Conway Institute for Biomolecular Research, University College, Dublin, Ireland; Rheumatology Research, Swedish Medical Center, University of Washington School of Medicine, Seattle, Washington, USA; Academic Unit of Musculoskeletal Disease, Chapel Allerton Hospital, Leeds, UK; Division of Rheumatology, Department of Medicine, University of Toronto; Centre for Prognostic Studies in the Rheumatic Diseases, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada.

O. FitzGerald, MD, Department of Rheumatology, St. Vincent's University Hospital and Conway Institute for Biomolecular Research, University College; P.J. Mease, MD, Rheumatology Research, Swedish Medical Center and Clinical Professor, University of Washington School of Medicine; P.S. Helliwell, DM, PhD, Academic Unit of Musculoskeletal Disease, Chapel Allerton Hospital; V. Chandran, MBBS, MD, DM, PhD, Division of Rheumatology, Department of Medicine, University of Toronto, and Centre for Prognostic Studies in the Rheumatic Diseases, Toronto Western Hospital, University Health Network.

Address correspondence to Dr. Chandran, Centre for Prognostic Studies in the Rheumatic Diseases, Toronto Western Hospital, University Health Network, Room 1E 416, 399 Bathurst St., Toronto, Ontario M5T 2S8, Canada. E-mail vchandra@uhnresearch.ca

naires, blood and urine samples, and radiographs. The preliminary budget estimate is $6.9 million CDN.

Two organizations answered a call for declarations of interest to act as the contract research organization to manage this project and were sent a set of criteria. Responses were judged by senior GRAPPA members: the International Psoriasis and Arthritis Research team (IPART) based in Toronto was awarded the contract in January 2013. Since then, IPART members have been preparing for the study. The protocol was finalized in August 2013, along with patient informed consent documents and case report forms.

Funding the study is the remaining major issue. A number of possibilities exist including funding from industry or through national agencies, such as the US Foundation for the National Institutes of Health (FNIH). GRAPPA members presented the study at the FNIH Biomarker Consortium meeting in June 2013, following which FNIH indicated they were interested in PsA BioDam but were more likely to get involved at a later stage of biomarker validation. FNIH further suggested that GRAPPA should consider collaboration with industry, in particular within the area of early treatment protocols, such as a comparison between methotrexate, a tumor necrosis factor inhibitor, and a combination of both. To further prepare for this study, the IPART team was awarded a grant for a 1-day planning meeting by the Canadian Institutes of Health Research. This planning meeting took place early in 2014 and included members of GRAPPA, industry partners, and others involved in biomarker science. Thus, the GRAPPA PsA BioDam study is at an advanced stage of planning.

Psoriatic Arthritis Mutilans (*Vinod Chandran)*

Arthritis mutilans is recognized by rheumatologists as a severe destructive form of PsA; however, a precise definition has not yet been universally accepted. At the 2012 annual meeting, GRAPPA members initiated an exercise to develop a precise definition of arthritis mutilans so that clinical, epidemiological, genomic, and biomarker research into this disease may be conducted. It is hoped that early identification of psoriasis patients at risk for development of arthritis mutilans will lead to suitable intervention and prevent severe outcomes.

At the 2013 meeting, the definitions used by various research groups were reviewed, including those used by Moll and Wright; McGonagle, *et al;* Marsal, *et al*; McQueen, *et al*; and Chandran, *et al*[1,2,3,4,5]. Key terminologies used by these experts include telescoping, severe osteolysis, bone destruction, diffuse involvement, involvement of small joints of the hands, involvement of distal interphalangeal joints, and digital shortening. Pencil-in-cup deformities, complete erosion of both sides of a joint of the hands or feet, subluxation, and ankylosis were also important features. During breakout group discussions, GRAPPA members agreed that the definition of PsA mutilans should involve peripheral joints especially of the hands and feet, but not axial joints. Involvement of 1 joint was considered to be sufficient. Both radiographic and clinical features were important in defining the condition, although radiographic features were likely to be more sensitive. The groups agreed that osteolysis is the defining feature, and that ankylosis is a category distinct from arthritis mutilans. The post-discussion voting was consistent with these discussions[6].

Results were presented of a systematic review of the literature to identify clinical and radiographic features associated with the definition and manifestations of PsA. The review suggested that the most commonly used definition was that by Moll and Wright (78%)[1]. The clinical features that were mentioned in the definitions included shortening of digits (38%), presence of digital telescoping (36%), and flail joints (15%). Only 21% of the articles specified the type of joints affected, and few commented on time to joint destruction. Radiographic items included were the presence of bone resorption (45%), pencil-in-cup change (17%), ankylosis (21%), total joint erosion (13%), and subluxation (9%). Based on data availability of a total of 244 patients in the studies, 49% were males, with a mean age of 44.7 ± 14.7 years. Most patients had psoriasis before the diagnosis of arthritis. The mean (SD) age of psoriasis diagnosis was 25.6 (6) years and of PsA was 30.9 (6.7) years. Invariably, patients had one or more of the aforementioned clinical and radiographic features that affected one or more of the small joints in hands and feet within different time intervals. Thus, the systematic review showed a lack of consensus on the clinical and radiographic items used to define and characterize patients with arthritis mutilans and advocates for a formal definition of PsA mutilans. GRAPPA will use the data from the systematic review and from the survey of its members to propose a formal definition that must then be validated.

Characterizing the Spectrum of Spondyloarthritis Patients with Current and Evolving Classification Criteria: A Study Proposal *(Philip Mease)*

Currently, several classification criteria may be applied in clinical trials to patients with SpA, including PsA. The most commonly used are the ClASsification for Psoriatic ARthritis criteria (CASPAR), yielding high specificity and sensitivity, 99% and 92%, respectively (Table 1)[7]. Historically, patients entering trials for ankylosing spondylitis (AS) had to fulfill the modified New York criteria, which included convincing evidence of damage of the sacroiliac joints on plain radiography. Partly to address the problem that radiographic damage was a late finding and to encourage earlier diagnosis and intervention, the Assessment of Spondyloarthritis (ASAS) group developed criteria defining a broader spectrum of predominantly axial and

Table 1. Classification criteria for PsA (CASPAR*), after Taylor *et al*[7].

Established inflammatory musculoskeletal disease (joint, spine, or entheseal) with 3 or more of the following†.		
1. Psoriasis	(a) Current	Psoriatic skin or scalp disease present today as judged by a qualified health professional
	(b) History	A history of psoriasis that may be obtained from patient or qualified health professional
	(c) Family history	A history of psoriasis in a first or second degree relative according to patient report
2. Nail changes		Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination
3. A negative test for RF		By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range
4. Dactylitis	(a) Current	Swelling of an entire digit
	(b) History	History of dactylitis recorded by a qualified health professional
5. Radiological evidence of juxtaarticular new bone formation		Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of hand and foot

*The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%. †Patient must accrue ≥ 3 points total: Only one of the 3 subcriteria in criterion 1 may be applied, with 2 points accrued with fulfillment of criterion 1a, and 1 point for fulfillment of either 1b or 1c. Only one of the 2 subcriteria in criterion 4 may be applied, with 1 point for either 4a or 4b. The remaining points may be scored using criteria 2, 3, and 5, each of which may be assigned a score of 1. CASPAR: ClASsification of Psoriatic ARthritis; RF: rheumatoid factor: PsA: psoriatic arthritis.

peripheral forms of SpA (Table 2)[8,9,10]. The ASAS effort was to simplify the criteria, which evolved from older modes of subtyping patients into subsets of PsA, AS, arthritis related to inflammatory bowel disease (IBD), reactive arthritis (ReA), and forms that do not fit any of these categories, i.e., undifferentiated SpA. In the axial criteria, patients can be included if they present either sacroiliac change by radiographic or magnetic resonance imaging or with the presence of a positive HLA-B27, plus at least 1 or 2 characteristic SpA feature(s), respectively[8,9]. The axial criteria are valuable because they allow broader, more sensitive, and earlier diagnosis by including patients who do not display radiographic sacroiliitis, which is inclusive of more women and younger individuals. Indeed, whereas the estimated prevalence of AS in the United States is 0.5%, a recent National Health and Nutrition Examination Survey showed that prevalence of axial SpA lay between 0.9% and 1.4% of the US population[11]. The converse is that some patients, particularly in the non-imaging arm without true inflammatory disease, may be improperly classified as having SpA. Currently, these broadened criteria for axial disease have been accepted for approval of drug therapy in much of the world, except for the United States. The more recently adopted peripheral SpA criteria[9] are an attempt to bring these forms of SpA (peripheral arthritis, enthesitis, and dactylitis) under 1 umbrella with the aim of improving recognition. This is particularly important for forms of SpA that are less well-recognized or do not have approved therapies (e.g., arthritis related to IBD, ReA, and undifferentiated forms), whereas PsA is better recognized and has approved therapies.

Both criteria sets include psoriasis as one SpA feature that may define either axial or peripheral classification. Indeed, some patients with PsA would not be defined as having predominantly axial or peripheral SpA by these criteria. But is it appropriate to combine those few PsA patients with predominantly axial manifestations under the same classification as the majority of cases with peripheral SpA? Do genetics, clinical manifestations, natural history, assessment approaches, and treatment effects overlap sufficiently to warrant such combining? Or are there enough distinctive features or circumstances to warrant applying separate criteria?

A study by Stafford, *et al*[12] sheds light on this issue. Patients presenting to an early arthritis clinic in Dublin, 82 with PsA, 16 with ReA, and 59 with undifferentiated SpA, with < 2 years of symptoms, were prospectively followed over 2 years. Although patients with ReA presented with severe and often disabling symptoms, by 1 year over 55% and by 2 years 60% were in remission, none were in Steinbrocker's class III or IV disability, and 80% did not have radiographic erosions at either timepoint. In contrast, patients with PsA tended to have a more insidious onset; however, by 2 years, only 15% were in remission, over 10% were in Steinbrocker's class III or IV, and over 40% had erosions. Undifferentiated patients scored between patients with ReA and patients with PsA. These results suggest distinct courses of natural history and outcomes for patients with 2 different forms of peripheral SpA.

Van den Berg, *et al*[13] studied the performance characteristics of the CASPAR and ASAS peripheral SpA criteria in the Leiden early arthritis cohort. In patients with PsA, the

Table 2. ASAS classification criteria for axial and peripheral SpA, after Rudwaleit, *et al*[8,9,10].

Axial SpA Criteria[8,9]			Peripheral SpA Criteria[10]
In patients with ≥ 3 months back pain and age at onset < 45 yrs			In patients with peripheral symptoms ONLY
Sacroiliitis on imaging plus ≥ 1 SpA feature	*OR*	HLA-B27 plus ≥ 2 other SpA features	Arthritis or enthesitis or dactylitis plus
SpA features:			≥ 1 SpA feature:
· Inflammatory back pain (IBP)			· Uveitis
· Arthritis			· Psoriasis
· Enthesitis (heel)			· Crohn disease/colitis
· Uveitis			· Preceding infection
· Dactylitis			· HLA-B27
· Psoriasis			· Sacroiliitis on imaging
· Crohn disease/colitis			*OR*
· Good response to NSAID			≥ 2 other SpA features:
· Family history for SpA			· Arthritis
· HLA-B27			· Enthesitis
· Elevated CRP			· Dactylitis
			· IBP ever
			· Family history for SpA

The Axial SpA criteria have sensitivity of 79.5% and specificity of 83.3% (n = 975). ASAS: Assessment of Spondyloarthritis Society; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drugs; SpA: spondyloarthritis; IBP: inflammatory back pain.

CASPAR criteria had a sensitivity of 88.7% and specificity of 95.6%, whereas the ASAS peripheral SpA criteria had a sensitivity of 52% and specificity of 89.8%, suggesting a better sensitivity for CASPAR to identify patients with PsA. In patients with peripheral SpA other than PsA, the sensitivity and specificity of CASPAR were 5.3% and 95.6%, suggesting a low likelihood of misidentifying these patients as non-PsA SpA. The ASAS peripheral SpA criteria yield a 48.7% sensitivity and 89.8% specificity in patients with PsA. These results support the value of CASPAR in its ability to identify and correctly classify the population of patients with PsA.

GRAPPA members, working collaboratively with ASAS and the Spondyloarthritis Research and Treatment Network, will explore the value of a study to catalogue the clinical phenotype, natural history, and genetic markers of a large group of patients with SpA, especially those presenting with more peripheral disease, to evaluate current classification methods and determine whether they should be refined. This study can help determine whether it is appropriate to combine potentially heterogeneous disease characteristics, historically used in AS or PsA studies, to determine their use across the range of SpA presentations, and to address questions about potential duration of therapy, i.e., whether disease is likely to persist or naturally remit. Data could be gathered from a standalone study if sufficient funding can be obtained, or through data mining of existing SpA registries that are studying similar outcome measures. Further discussion is being pursued among those involved with SpA outcomes research.

Thus, although progress has been made in these GRAPPA rheumatology studies, execution of these projects would require a significant resource commitment. It is hoped that upon completion of these studies, clinically useful tools for diagnosis, classification, and prognostication of PsA will be developed, ultimately benefitting patients with psoriasis and PsA.

REFERENCES

1. Wright V, Moll JMH. Seronegative polyarthritis. Amsterdam: North Holland Publishing Co; 1976.
2. McGonagle D, Conaghan PG, Emery P. Psoriatic arthritis: a unified concept twenty years on. Arthritis Rheum 1999;42:1080-6. Erratum in: Arthritis Rheum 1999;42:1997.
3. Marsal S, Armadans-Gil L, Martinez M, Gallardo D, Ribera A, Lience E. Clinical, radiographic and HLA associations as markers for different patterns of psoriatic arthritis. Rheumatology 1999;38:332-7.
4. McQueen F, Lloyd R, Doyle A, Robinson E, Lobo M, Exeter M, et al. Zoledronic acid does not reduce MRI erosive progression in PsA but may suppress bone oedema: the Zoledronic Acid in Psoriatic Arthritis (ZAPA) Study. Ann Rheum Dis 2011;70:1091-4.
5. Chandran V, Thavaneswaran A, Pellett FJ, Gladman DD. The association between human leukocyte antigen and killer-cell immunoglobulin-like receptor gene variants and the development of arthritis mutilans in patients with psoriatic arthritis [abstract]. Arthritis Rheum 2011;63 Suppl:S532.
6. Chandran V, Gladman DD, Helliwell PS, Gudbjornsson B. Arthritis mutilans: a report from the GRAPPA 2012 annual meeting. J Rheumatol 2013;40:1419-22.
7. 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.
8. Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by

expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770-6.
9. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777-83.
10. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25-31.
11. Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey. Arthritis Care Res 2012;64:905-10.
12. Stafford L, Kane D, Murphy E, Duffy T, Lassere M, Youssef PP, et al. Psoriasis predicts a poor short-term outcome in patients with spondylarthropathy. Arthritis Rheum 2001;45:485-93.
13. van den Berg R, van Gaalen F, van der Helm-van Mil A, Huizinga T, van der Heijde D. Performance of classification criteria for peripheral spondyloarthritis and psoriatic arthritis in the Leiden Early Arthritis Cohort. Ann Rheum Dis 2012;71:1366-9.