The Path Forward to Biomarker Discovery in Psoriatic Disease: A Report from the GRAPPA 2010 Annual Meeting

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ABSTRACT. At the 2010 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), wide-ranging discussions were held regarding biomarker research in psoriatic disease. Consensus was reached on 2 areas of priority: (1) the study of soluble biomarkers of radiographic progression in psoriatic arthritis (PsA); and (2) the analysis of comorbidity biomarkers, specifically cardiovascular and articular, in a psoriasis inception cohort. For each of these areas, rigorous definition of the clinical phenotype of PsA will be essential. To date, 2 instruments have been identified to define the phenotype: the CIASsification of Psoriatic Arthritis criteria and various screening questionnaires. In this overview, we discuss the challenges of the clinical phenotype of PsA and review GRAPPA plans for developing a research program for biomarker discovery.

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease associated with psoriasis. Moll and Wright1, who initially described it as an inflammatory arthritis associated with psoriasis and usually seronegative for rheumatoid factor, identified 5 clinical patterns of PsA: distal involvement, oligoarthritides, polyarthritides indistinguishable from rheumatoid arthritis (RA), spondyloarthritides, and arthritis mutilans. This definition has been used to identify cases of PsA during the past several decades. However, it has become clear that these patterns do not remain static over time and are not mutually exclusive. Although distal joint disease is common among patients with PsA, occurring in 53% of the patients, few have isolated distal involvement2. Some patients with oligoarthritides develop polyarticular disease, while others with initial polyarticular disease respond to therapy and then remain with oligoarthritides disease3,4. A certain number of patients present with axial disease, whereas an additional 15% will develop spinal disease after 10 years of disease5. Thus, several investigators have suggested that PsA could be defined by the presence of peripheral arthritis, with or without spinal disease, and spinal disease alone6. It is difficult to identify the phenotype of PsA when the features described vary over time. Moreover, some patients have more than one feature at a time. For example, patients may have distal joints involved and yet have polyarticular disease, while all patterns may be associated with spinal involvement.

Until the development of the CASPAR (CIASsification of Psoriatic Arthritis) criteria, consensus on the diagnosis of PsA has been challenging. The CASPAR criteria, developed by an international effort under the leadership of Philip Helliwell and William Taylor, have been proven to be 90% sensitive and 98% specific for PsA when compared to other forms of inflammatory arthritis7, and are extremely sensitive and specific even when tested in patients with early PsA8, patients in an early arthritis clinic9, or in a family medicine clinic10. Thus, these criteria should identify patients with PsA with a high degree of sensitivity and specificity regardless of disease duration.

However, the CASPAR criteria require a rheumatologist’s assessment because they can only be applied to patients with an inflammatory musculoskeletal condition, e.g., arthritis, spondylitis, or enthesitis. It is difficult for non-experts to fulfill this criterion. For that reason, several groups have concentrated on developing screening instruments that are completed by patients to identify the presence of PsA. Screening tools that can be applied to patients with psoriasis include the Psoriatic Arthritis Questionnaire (PAQ)11, the Psoriatic Arthritis Epidemiology Screening Tool (PEST)12, the Psoriatic Arthritis Screening Evaluation (PASE)13, and the Psoriatic Arthritis Screening Questionnaire (PASQ)14. Additionally, the Toronto Psoriatic Arthritis Screening (ToPAS) questionnaire was developed to identify...
PsA among patients with or without psoriasis\textsuperscript{15}. Presently, several of these tools are being compared in different studies. At the same time, rheumatologists and dermatologists within the Group for Research and Assessment of Psoriasis and PsA (GRAPPA) are working to define inflammatory musculoskeletal disease so that nonexpert physicians can apply the CASPAR criteria appropriately\textsuperscript{16}.

Some of the screening questionnaires can identify individuals with PsA with high sensitivity and specificity (about 90%); however, there is still a 10% margin of error in exact identification of the phenotype. How such potential error would affect genetic and biomarker studies remains to be determined. Another challenge is the diagnosis of patients with very early findings of musculoskeletal inflammation — tendonitis, plantar fasciitis, or focal enthesisitis — who may not meet the CASPAR criteria or have high scores on one of the screening tools but who clearly have new musculoskeletal manifestations that often precede development of straightforward PsA.

It is assumed that patients who complete these questionnaires have psoriasis, yet the diagnosis of psoriasis is largely based on clinical impression (and occasionally biopsy) since no validated classification or diagnostic criteria have been published. Most investigators accept psoriasis as diagnosed by a dermatologist as the basis for the phenotypic assignment of the disease. Consensus regarding the diagnosis of psoriasis can vary among dermatologists, however, and many mimics of psoriasis exist. Nonetheless, before accepting samples for biomarker or genetic studies, confirmation of psoriasis by a dermatologist is critical.

When studying biomarkers in patients with PsA, it is important to compare the presence of the biomarkers in a healthy control group and in a control group of patients with psoriasis but without arthritis. Thus, it is important to determine whether a patient with psoriasis has arthritis. Several investigators have shown that patients with psoriasis may have undiagnosed arthritis. In a German study of 2009 patients with psoriasis, 19% had inflammatory arthritis and many mimics of psoriasis exist. Nonetheless, before accepting samples for biomarker or genetic studies, confirmation of psoriasis by a dermatologist is critical.

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Accurately identifying the phenotype is the most important aspect of the path toward biomarker discovery in PsA, after which studies may begin. The next step is to determine what samples and what information to collect from patients for biomarker discovery.

GRAPPA has proposed 2 areas of priority for biomarker research in psoriatic disease: (1) the study of soluble biomarkers of radiographic progression in PsA; and (2) the analysis of comorbidity biomarkers (cardiovascular and articular) in a psoriasis inception cohort. For the first area, given concerns that erosions develop more slowly in PsA compared to RA, much discussion centered on the necessity of expanding the cohort to include patients who manifest baseline erosions or risk factors that may increase the likelihood of future erosive disease. While a pragmatic solution would be for inclusion criteria to require erosions at baseline, this approach would make it impossible to identify PsA in patients who have no baseline radiographic damage, a population of great clinical importance. A central question discussed by GRAPPA: Should we identify only those patients with progressive erosive disease, or are we also interested in patients likely to develop erosive change despite normal baseline radiographs? GRAPPA members agreed that unless power calculations indicate that non-enrichment for erosions is not feasible, the most appropriate analysis would be an observational study of an inception cohort of PsA patients (< 2 years since diagnosis; disease-modifying antirheumatic drug-naive) that excludes patients with isolated axial disease and patients with no foot or hand involvement.

The primary radiographic outcome measure was discussed extensively. Many GRAPPA members were enthusiastic about magnetic resonance imaging (MRI), given its ability to show early changes in the bone (bone marrow edema) and soft tissue inflammatory changes that are very sensitive to change following therapeutic interventions. While members expressed considerable support for the advantages provided by MRI as an outcome measure in PsA, it was agreed that since no scoring technique has yet been validated, the inclusion of MRI as the primary outcome imaging tool may be premature. Thus, plain radiographs of hands and feet were considered an essential primary radiologic outcome measure for progression of erosions, with an MRI substudy strongly recommended, where feasible and where funds permit. Discussions between GRAPPA and several pharmaceutical and biomarker companies have commenced regarding these critical funding considerations.

It is well known that about 20% of patients with psoriasis develop PsA\textsuperscript{18}. This fact provides a unique opportunity to identify risk factors for arthritis in a psoriasis population, with the goal of early diagnosis and intervention for PsA. A longitudinal observational registry, comprising a large population of carefully phenotyped patients with psoriasis monitored for development of arthritis, is ideal for the study of these biomarkers for arthritis susceptibility. The International Psoriasis and Arthritis Research Team (IPART) registry is a multicenter registry that has so far enrolled over 800 patients with psoriasis but without arthritis. These patients have all been evaluated clinically to exclude the presence of PsA and are tracked on a Web-based Oracle
REFERENCES


