Strategies for Biomarker Development in Psoriatic Disease: A Report from the GRAPPA 2010 Annual Meeting

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ABSTRACT. Psoriatic disease includes psoriasis and associated comorbidities (arthritis, uveitis, inflammatory bowel disease, cardiovascular disease, metabolic syndrome, and anxiety/depression) and is remarkably diverse in disease presentation and course. The marked heterogeneity of musculoskeletal involvement in psoriatic arthritis (PsA) presents major challenges to clinicians regarding diagnosis, risk stratification, and management. Members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have begun collaborative efforts to develop biomarkers that can assist in the diagnosis and management of patients with psoriasis and related comorbidities. This brief review provides a rationale for biomarker research in PsA, consideration of types and sources of biomarkers, and examples of important biomarker studies in PsA, followed by a review of trial designs for biomarker research and a discussion of potential funding sources. (J Rheumatol 2012;39:423–6; doi:10.3899/jrheum.111240)

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The marked heterogeneity of musculoskeletal involvement in psoriatic arthritis (PsA) was first noted by Moll and Wright[1]. Recent studies have highlighted the association between psoriasis and increased risk of major metabolic and vascular disorders[2,3], which can lead to increased morbidity and mortality[4]; as well, similar associations have been noted in PsA[5]. This brief review, along with accompanying articles by FitzGerald and Chandran[6], Rahman and Elder[7], and Gladman, *et al*[8], summarizes recent discussions of biomarker development by members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). The short-term objective of these articles is to generate consensus on an approach to biomarker discovery and validation in PsA; a longterm goal is to develop disease biomarkers and surrogate measures that will lessen morbidity and mortality in patients with psoriatic disease.

Challenges and Opportunities of Biomarker Discovery in Psoriatic Disease

The multiplicity of clinical phenotypes in PsA (oligoarticular and polyarthritis, axial inflammation, enthesopathy, dactylitis, and mutilans) provides many obstacles for biomarker development; however, the availability of validated diagnostic criteria, a well defined source population, and the emergence of well characterized patient populations in clinical trials and registries provide unique opportunities for biomarker discovery and validation. In rheumatoid arthritis (RA), a majority of patients have anti-cyclic citrullinated peptide antibodies, a marker that is central to diagnosis and that also reflects severity. In addition, the presence of the shared epitope, HLA-DRB*1 0401, 0404, 0101, provides a genetic marker with a high relative risk that may regulate protein citrullination, especially in the presence of smoking[9]. We have no diagnostic test for PsA, and the genetic risk factors are not as well delineated as in RA. Moreover, it is very difficult to determine which genetic factors are related to psoriasis versus PsA since most patients with PsA also have psoriasis. Nevertheless, we know that most patients with PsA develop psoriasis first; thus, psoriasis patients with subclinical or mild disease may be targeted for early intervention. Gene-environmental interactions are undoubtedly a factor in psoriasis and PsA based on epidemiologic data[10], but environmental effects on skin and joints may diverge, as recently reported by Daniel Zaghi, *et al* with regard to smoking[11]. Also, the Classification Criteria for PsA (CASPAR)[12] allow accurate diagnosis in the absence of a defined serum marker, and we have a growing data source from clinical trials to analyze candidate molecules. Finally, the presence of large registries [Consortium of Rheumatology Researchers of North America (CORRONA), International Psoriatic Arthritis Research Team (IPART), and others] with high quality phenotypic data and/or banked specimens provides unique opportunities for biomarker discovery and validation.

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Types of Biomarkers in PsA

Potential utility for biomarkers in PsA (Table 1) centers around 3 major timepoints in the disease process[13]. In the preclinical phase, we can focus on a target population with psoriasis, an advantage in PsA over RA. Several studies have shown that a significant subset of psoriasis patients without musculoskeletal symptoms or signs have evidence of subclinical inflammation using scintigraphy, magnetic resonance imaging (MRI), and ultrasonography (reviewed by Anandarajah and Ritchlin[14]); however, a longitudinal study is required to determine if patients with abnormal imaging findings subsequently develop PsA. In patients with early disease, biomarkers can assist in determining both activity and severity. In RA, for example, patients with high bone marrow signals are more likely to develop joint erosions at the site of these signals at later timepoints[15]. In patients with established disease, biomarkers can screen for response to therapy and disease progression. A soluble marker that predicts subsequent radiographic progression would be an important surrogate marker for joint damage, but would have to act independently of other markers and be sensitive to change. Another important marker is one that could predict likelihood of response to a targeted biologic therapy such as anti-tumor necrosis factor (TNF) agents or predict which patients would benefit most from combination therapies.

Sources of Biomarkers

Assays for several sources of biomarkers are shown in Table 2. Analyses for genetic markers have been performed using association studies and genome-wide association scans[16,17]. Several genes have been identified in PsA; however, the odds ratios are relatively low, and it is challenging to determine which factors are related to skin versus joint involvement in patients with both disorders. Microarray studies have been performed on psoriatic skin and on peripheral blood mononuclear cells in PsA patients, but inter-individual variation is high, and the sample sizes relatively small, precluding development of definitive biomarkers[18,19]. Soluble markers may act as surrogates of joint damage and help distinguish specific targets, as discussed in the accompanying report by FitzGerald and Chandran[6]. Cellular biomarkers such as osteoclast precursors (OCP) are elevated in PsA patients and correlate with disease severity[20], but the assays are technically demanding and expensive. Two OCP biomarkers, CD16[21] and dendritic cell-specific transmembrane protein[22], are under investigation to simplify identification of these cells through antibody staining followed by flow cytometric analysis.

Imaging, particularly MRI, has provided important insights into the role of enthesis and bone marrow edema in disease pathogenesis[23]. The edema signal declines following anti-TNF therapy[24]; however, while increased bone marrow edema predicts subsequent erosion risk in RA, this relationship has not been demonstrated in PsA. The combination of MRI and cellular studies can provide additional insights into the relationship between cellular markers and target inflammation and damage, but more studies are needed to determine the validity of this approach[25]. Whole-body MRI has been used in ankylosing spondylitis[26] and may be a potential marker of total disease burden and severity at disease onset. Ultrasound studies have provided evidence of subclinical soft tissue changes by grayscale and Doppler imaging in the musculoskeletal structures of psoriasis patients[27]; however, additional studies are required in a well defined healthy population matched for age, sex, and body mass index, given that obesity, prevalent in patients with psoriatic disease, could influence tendon, bone, and vascular structures independent of joint inflammation. Ultrasound imaging has also provided insights into carotid artery intimal-medial thickening in cross-sectional studies of patients with PsA[28], which has the potential to identify patients with asymptomatic vascular disease. The ability of functional MRI to assess pain and mood disorders is in its infancy; however, it has potential as evidenced by recent studies demonstrating altered cortical and subcortical pain signals in preclinical models and patients with RA that significantly improved following treatment with TNF antagonists[29]. Proteomics also has potential in the study of inflammation and possibly atherosclerosis in psoriatic disease, but definitive studies in these areas have not been published.

Methods to Study Biomarkers

Biomarkers may be studied via clinical trials, observational studies, patient registries, or investigator-initiated pilot studies. Clinical trial data can provide a valuable sample source from a well defined population. Moreover, the effect of targeted interventions on biomarkers of interest, such as the decline of OCP following etanercept therapy[25] or normalization of C-reactive protein in patients who showed less

Table 1. Potential utility of biomarkers[13].

As markers for:	Example
Susceptibility (risk factor)	Cw6 allele and psoriasis
Treatment response	Resolution of bone edema on magnetic resonance imaging in ankylosing spondylitis spine
Severity	Anti-citrullinated protein antibodies in rheumatoid arthritis
Activity	C-reactive protein level
Surrogate	T score on dual-energy X-ray absorptiometry scan as surrogate for fracture risk

Table 2. Types of biomarkers in psoriatic disease.

Type of Biomarker	Assay	Example
Genetic	Association studies, GWAS	GWAS studies in PsA patients
Gene expression	Microarray, RNA sequence	Gene expression in PBMC
Cellular	OCP or Th17 frequency	Frequency of Th17 cells in blood and synovial fluid
Soluble	Cytokines, cartilage/bone markers	Expression of CTX-1 and MMP-3 in peripheral blood
Imaging	Radiograph, MRI, Doppler ultrasound	Radiographic erosions, bone edema in PsA joints, increased Doppler ultrasound signal
Proteomics	High-resolution mass spectrometry	Serum proteomic analysis in psoriasis patients vs another inflammatory skin disease and controls
Tissue	H & E staining and IHC	Expression of RANKL in synovium

CTX-1: collagen 1 degradation product; GWAS: genome-wide association scan; H & E: hematoxylin and eosin; MMP: metalloproteinase; MRI: magnetic resonance imaging; OCP: osteoclast precursors; PBMC: peripheral blood mononuclear cells; PsA: psoriatic arthritis; RANKL: receptor activator of nuclear factor kappa-B ligand; RNA-seq: whole transcriptome shotgun sequencing.

radiographic damage following treatment with adalimumab[30], can provide important insights for biomarker development. Observational studies that include patients with a wide spectrum of PsA symptoms (duration, activity, severity) more accurately reflect disease in the clinic and are particularly effective for the development and validation of surrogate markers (e.g., soluble markers of radiographic damage). Patient registries such as IPART, CORRONA, Psoriasis Longitudinal Assessment and Registry, and others provide critical longitudinal data that can be applied to the evaluation of arthritis susceptibility markers, safety signals, treatment response variables, and pharmacogenetics in psoriatic disease. Investigator-initiated studies can provide novel opportunities for hypothesis generation and biomarker development and validation using samples obtained from sources as varied as small clinical trials, large observational cohorts, and existing datasets (e.g., military serum banks or population-based studies).

Funding of Biomarker Studies in Psoriatic Disease

Financial support for biomarker discovery, development, and validation can be obtained from a variety of sources. Government agencies such as the National Institutes of Health and the Canadian Institutes of Health Research can provide funds for biomarker discovery that is coupled with existing trials or in some cases through an existing registry. Small investigator-initiated proposals are also funded by nonprofit organizations such as the National Psoriasis Foundation and the National Arthritis Foundation. However, costs of an observational study typically exceed the amount supplied by governmental agencies and nonprofit organizations, so pharmaceutical support is required and could be funded within the setting of an existing trial or as a separate biomarker study. An example of this latter approach is the RA BIODAM trial, an international biomarker observational study that is funded by Abbott Pharmaceuticals. Pharmaceutical companies that specialize in the development and validation of biomarkers are another potential funding source. The challenges of financial support for collections, intellectual property rights, and safety issues surrounding sample collections in the early phase of drug marketing were recently addressed by Miossec, *et al*[13].

Next Steps for GRAPPA in Biomarker Development

GRAPPA is an ideal group to study biomarkers in psoriatic disease for several reasons. First, GRAPPA members comprise an international team of rheumatologists and dermatologists who can work together to identify relevant biomarkers for psoriatic disease. Second, members have large well characterized patient databases that will facilitate biomarker research. Third, a number of physician scientists, epidemiologists, and clinical investigators in GRAPPA have experience in the procurement of funding from governmental agencies, nonprofit organizations, and pharmaceutical companies. Finally, GRAPPA has a large number of trainees, many of whom are interested in biomarker studies and will assist in protocol development and patient recruitment. The first trial planned by GRAPPA will be an observational study that is focused on soluble surrogate markers for radiographic damage. Another study will analyze risk factors for arthritis and cardiovascular disease in psoriasis patients using data from IPART and possibly other longitudinal registries. A number of investigator-initiated studies are also planned to examine a spectrum of different biomarkers in the synovium, skin, and peripheral blood of patients with psoriatic disease.

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