Biomarkers in Psoriasis and Psoriatic Arthritis: GRAPPA 2008

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ABSTRACT. Biomarkers can provide valuable insights into disease susceptibility and natural history and may serve as surrogate endpoints for a variety of different outcomes. At the 2008 annual meeting of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis), members were updated on the development of biomarkers in psoriatic arthritis (PsA). Plenary presentations included a translational approach to biomarker development (Christopher Ritchlin, University of Rochester, NY, USA), biomarkers for psoriasis (Abrar Qureshi, Harvard Medical School, MA, USA), new data on biomarkers for damage in PsA (Kurt de Vlam, University Hospitals Leuven, Belgium), and design considerations for a longitudinal study of joint damage being undertaken under the OMERACT umbrella with colleagues working on rheumatoid arthritis and ankylosing spondylitis (Costantino Pitzalis, Barts and the London School of Medicine, London, UK; Oliver FitzGerald, St. Vincent's Hospital, Dublin, Ireland). At the conclusion of this session, the meeting attendees discussed specific design issues of the proposed longitudinal study, including study duration, disease process core domains, and the instruments to be used in recording enthesitis, dactylitis, nail involvement, quality of life and structural damage. The appearance of new therapeutic options in PsA raises the need for sensitive biomarkers for both disease activity and outcome. (J Rheumatol 2010;37:462–7; doi:10.3899/jrheum.090957)

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The revolution in genomics has provided pharmaceutical companies with genetic biomarkers that have the potential to markedly improve the efficacy of drug discovery[1]. Biomarkers can also provide valuable insights into disease susceptibility and natural history and may serve as surrogate endpoints for a variety of different outcomes. Psoriatic arthritis (PsA) is an inflammatory joint disorder marked by heterogeneity in tissue involvement and disease course[2]. Moreover, diagnostic biomarkers such as anti-cyclic citrullinated protein (CCP) antibodies, which have been integral for early identification of rheumatoid arthritis (RA), are rarely present in PsA so disease recognition is often delayed. Thus, investigators in GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) have started to formally address an approach to biomarker development in psoriatic disease. Progress was discussed at the 2008 international meeting that took place in Leeds, UK.

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A translational approach to biomarker development in psoriatic disease: Christopher Ritchlin

The terminology related to biomarkers in the literature is often imprecise; however, clarity regarding the definitions and applications of the various measures has been published by the OMERACT 9 Soluble Biomarkers Working Group[3,4]. The nomenclature and definitions are shown in Table 1. A biomarker is a disease-centered variable that provides information about the underlying disease process or pathophysiological mechanisms. In the case of PsA, biomarkers may reflect a variety of different processes including genetic (Cw6 alleles), cellular (circulating osteoclast precursors), cytokines [tumor necrosis factor (TNF) expression in synovium], imaging (bone marrow edema on mag-

Table 1. Term definitions related to biomarkers of joint damage in psoriatic arthritis.

Biomarker	Disease-centered variable of biologic and pathological processes
Patient outcome	Patient-centered variable of how a patient "feels, functions, survives"
Risk factor	A variable that increases a person's chance of developing a disease
Prognostic factor	Patient variable, such as age, family history, lifestyle, or stage of presentation, that is weighed in determining a prognosis
Surrogate outcome	Disease-centered variable that meets validation criteria

netic resonance imaging), or physiologic [C-reactive protein (CRP) levels]. In addition to those outlined above, other disease-centered variables such as blood pressure, laboratory values, and imaging data have no intrinsic meaning to the patient, and the relevance of these variables to the patient can only be determined over time. As such, disease-centered variables must be validated; this process will be discussed below. In contrast, patient-centered variables that reflect how a patient "feels, functions, and survives" have face validity and do not require further validation.

Disease and patient-centered variables can be viewed as a continuum. Surrogate outcomes are disease-centered variables that have been validated; therefore, these measures can assist in clinical decisions or as an endpoint in a clinical trial. An example of a surrogate outcome in PsA would be a soluble biomarker that accurately reflects radiographic damage and can replace radiographs as an outcome measure. It is important that a change in the biomarker predicts change in the damage endpoint independently of known predictors such as baseline damage or elevated CRP level. In addition, the biomarker should be responsive to treatment, and the magnitude of change should parallel the change in the outcome of interest. A recent study with Vytorin® (ezetimibe and simvastatin) in which a drop in cholesterol was not associated with a change in the primary endpoint of mean change in the carotid intima-media thickness — a surrogate marker of atherosclerosis — illustrates the perils of choosing surrogate measures that do not predict intended patient outcomes[5]. In the case of PsA, surrogates of radiographic damage are challenging because potential confounders are less well defined than in RA; radiographic progression in patients receiving disease-modifying antirheumatic agents is not well studied, thus making it difficult to choose an appropriate comparator in randomized controlled trials.

Risk factors are present in patients who have not developed the disease of interest, and prognostic factors are present in those with a specific disease and are predictive of a specific outcome. Risk factors and prognostic factors may or may not be biomarkers, are longitudinally predictive, and require validation.

Biomarkers for cardiovascular comorbidities in psoriasis: Abrar Qureshi

Cutaneous psoriasis is a disease of immune dysregulation (predominantly T cells) and aberrant keratinocyte differentiation. The diagnosis of psoriasis is easily made clinically, with little need for diagnostic biomarkers. The discussion of genetic biomarkers is extensive and beyond the scope of this article; therefore, we have chosen to focus on soluble biomarkers in psoriasis that are relevant to associated risk of comorbidities such as diabetes and cardiovascular disease.

CRP is an acute-phase reactant, a biomarker for inflammation that has been associated with cardiovascular risk, and has been found to be elevated in individuals with psoriasis. A recent study found that baseline CRP levels were elevated in psoriasis patients with and without PsA. CRP was significantly reduced in both groups after 12 weeks of etanercept therapy[6]. Patients with PsA and patients with higher body mass index (BMI) had higher median baseline CRP values and greater reduction of CRP values compared with patients with psoriasis without arthritis and those with lower BMI. In another study of patients with psoriasis, RA, ankylosing spondylitis (AS), or with PsA, their CRP levels predicted all-cause mortality after adjusting for traditional risk factors, as did change in CRP status < 10 mg/l to > 10 mg/l[7].

Leptin, a 16-kDa adipocyte-derived hormone associated with the metabolic syndrome, has been implicated in the development of metabolic dysregulation in psoriasis. In one study, high serum leptin levels (≥ 7397.43 pg/ml) were found in female subjects (OR 6.05; $p < 0.001$) and in subjects with obesity (OR 3.45; $p = 0.01$), hypertension (OR 2.19; $p = 0.04$), metabolic syndrome (OR 3.58; $p = 0.008$), and psoriasis (OR 2.25; $p = 0.02$). On multivariate analysis, psoriasis (OR 4.57; $p = 0.009$) was significantly associated with hyperleptinemia independent of female sex, metabolic syndrome, and obesity[8]. Hence, hyperleptinemia has been associated with psoriasis independently of obesity and metabolic syndrome. Skin leptin and leptin receptor expression in both psoriasis patients and controls have previously been investigated by immunohistochemistry. Tissue leptin and leptin receptor expression were significantly higher in individuals with severe psoriasis compared with mild-moderate psoriasis and non-psoriatics[9].

Another adipokine shown to reflect psoriasis severity is resistin, which was found to correlate with the Psoriasis Area and Severity Index, but not with BMI[10].

S100 proteins regulate intracellular processes such as cell growth and motility, cell cycle regulation, transcription, and differentiation. Altogether, S100 proteins represent the largest subgroup in the EF-hand Ca^{2+}-binding protein family[11], and several members have been identified. Psoriasin (S100A7) is a member of the S100 family that is located

within the S100 gene cluster on chromosome 1q21 and shares the typical calcium-binding domains that define this family of proteins[12]. It was first identified as an 11.4-kDa cytoplasmic and secreted protein isolated from skin involved by psoriasis, which can be induced in cultured squamous epithelial cells. It is now known to be expressed by normal cultured keratinocytes and in psoriatic skin, suggesting an association with abnormal pathways of differentiation. Current evidence supports a role in the pathogenesis of inflammatory skin disease and as a chemotactic factor for hematopoietic cells. Psoriatic keratinocytes express high levels of psoriasin (S100A7). Psoriasin antigen levels can be detected with a sandwich enzyme-linked immunosorbent assay, and psoriasin autoantibody titers can be measured by using recombinant purified psoriasin and overlapping peptides. Systemic psoriasin antigen levels tend to be lower in individuals with psoriasis compared with non-psoriatics. Psoriasin levels also drop with increasing psoriasis severity. Therefore, psoriasin measured in the blood is not an appropriate biomarker for psoriasis severity. In the heart, S100A1 modulates Ca^{2+} homeostasis, contractile inotropy, and energy production by interaction with the elements involved in these functions. Further work is under way to explore the role of S100A and S100B proteins as biomarkers for cardiovascular risk in psoriasis.

New data on biomarkers for damage in psoriatic arthritis: Kurt de Vlam

The identification of relevant tools to evaluate the natural course, disease activity, treatment response, and outcome of PsA is of increasing relevance following raised awareness and the development of new therapeutic options. Until now these different aspects have been monitored by artificial patient-centered or physician-centered constructs. Very often the approach is indirect and is open to influences unrelated to disease.

The development of such tools is time-consuming and laborious but has been shown to be very useful in the assessment of patients with various rheumatic diseases. The major drawback with these tools is that they do not reflect directly the biological and pathological processes. Biological biomarkers measure objectively different aspects of the biological and pathological process and may contribute a major advance in the assessments of patients. The appearance of new therapeutic options in PsA raises the need for sensitive biomarkers for both disease activity and outcome. The underlying goal is to develop biomarkers that can provide guidance for individual patients in clinical practice.

For a long time, a "copy-paste" approach from RA was applied for the selection of biomarkers in PsA. Since RA and PsA have fundamentally different disease processes, this approach is now recognized to lead to inappropriate choices of biomarkers and subsequently to incorrect conclusions. The available data about biomarkers in psoriatic disease have recently been reviewed[13]. New potential biomarkers for diagnosis, disease activity, and tissue response were reported during the GRAPPA symposium in Leeds, UK.

The ideal biomarkers for diagnosis must be both specific and sensitive. Analysis of the primary involved tissue, such as synovial tissue and enthesis, is critical to differentiating PsA from other rheumatic inflammatory diseases. In a recent semiquantitative analysis of PsA synovial tissue, increases in vascularity and in the number of neutrophils were demonstrated, compared with RA synovial tissue. RA synovium demonstrated more staining for anti-CCP and the major histocompatibility complex/gp39 complex. Differences were observed only at the group level[14]. These differences found among the inflammatory rheumatic diseases appear to be quantitative and not qualitative, with no diagnostic feature emerging to date. Thus, the use of semiquantitative methods such as histopathology may be less appropriate, while flow-cytometric evaluation of the target tissue may be a valuable option. After digestion, the different cell populations of the synovial tissue can be measured by multichannel flow cytometry[15].

Differential gene expression in PsA compared to normal persons and other inflammatory arthritides was recently reported. Gene expression in peripheral blood mononuclear cells for nucleoporin 63-kDa distinguished PsA patients from controls. Overexpression of MAP3K3 followed by CACNA1S can discriminate PsA from RA[16]. Specific pathway polymerase chain reaction screening may be an alternative approach. Comparing specific pathways for inflammation and tissue response in fibroblast-like synoviocytes between normals and PsA surprisingly showed downregulation or silencing of specific genes in affected persons compared with normals (K. de Vlam, personal communication).

Biomarkers useful in monitoring disease activity must fulfill 3 conditions: (1) they must increase in active disease, (2) must show correlation with disease activity, and (3) must be sensitive to change. Most of the biomarkers studied for disease activity in PsA have not met these criteria. Synovial biomarkers have been the most extensively studied and include analyses of cellular infiltration such as the number of T cells, B cells, macrophages, blood vessels, adhesion molecule expression, and effector enzymes. Evaluation before and after treatment mostly demonstrates quantitative changes in different cell populations, but normalization of the target tissue is not yet attained. A closer look at activated signaling pathways reveals that some of these pathways are downregulated, but others, such as the p38 MAP kinase pathway, are still active and are even upregulated[17]. Although the joint seems clinically quiescent, determining presence or absence of biological disease activity is still a major challenge for the future.

Joint damage in PsA results from cartilage loss, bone destruction, and bone formation. Bone destruction and bone

formation are usually assessed by radiographs. Radiographic damage is a rather late phenomenon and quite insensitive for early detection. Most radiological scoring methods for PsA ignore bone formation features, with the exception of the Psoriatic Arthritis Ratingen Score (Wassenberg score)[18]. In addition, cartilage loss is generally not assessed. The use of biomarkers could enable early detection of all aspects of joint damage.

Cross-linked telopeptide of collagen-I, urinary deoxypyridinoline, osteoprotegerin, and alkaline phosphatase are increased, reflecting both increased bone resorption and bone formation. Soluble interleukin 2 receptor and circulating osteoclasts are independent biomarkers for erosive disease. TNF-α blockade reduces progression of damage but also decreases the number of circulating osteoclasts. Evaluation of specific pathways in tissue response, such as the bone morphogenetic protein (BMP) pathways, may be an alternative approach. Supervised clustering of genes involved in the BMP pathways have been shown to be upregulated in PsA, with these changes reversed by anti-TNF-α therapy (K. de Vlam, personal communication). Finally, DKK1 (Dickkopf family) was recently suggested as a biomarker for the absence of bone formation in RA compared with AS, but this remains to be confirmed in other cohorts of AS and PsA patients[19].

Biomarkers of outcome in early inflammatory arthritis: Costantino Pitzalis

The critical issue in PsA remains the poor sensitivity of prognostic indicators in early disease capable of predicting diverse disease evolution (different clinical phenotypes), disease severity, and disability. The main reason for this, in addition to the points discussed above, is a lack of systematic, prospective biomarker analysis using a comprehensive, unbiased approach. The majority of published studies are either cross-sectional or retrospective, while the few prospective studies include only a selective range of biomarkers. Further, there are no synovial biopsy-based prospective studies to assess whether diverse pathobiology ("pathotype") can predict disease outcome. Finally, early arthritis can present with undifferentiated phenotype that does not allow a precise diagnosis differentiating early PsA from early RA.

For this reason the UK Medical Research Council (MRC; http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC004616) and the National Institute for Health Research (NIHR) have invested in the Patient Research Cohorts Initiative to develop well characterized cohorts including, specifically for arthritis, the Pathobiology of Early Arthritis Cohort (PEAC).

The goal of PEAC is to create a unique resource with high-density prospective data (2-point analysis 6 months apart, patients followed up for 3 years) including genomic and transcriptomic analysis, biologic tissue characterization, and state of the art 3D/4D ultrasound imaging coupled with detailed clinical phenotyping, to enable an unbiased comprehensive analysis of blood, urine, and synovial tissue.

This resource will enable us to examine the role of multiple cellular and molecular pathways in various anatomical compartments to maximize the chances of identifying biomarkers involved in disease susceptibility, heterogeneous outcome, and treatment response. In addition, this cohort will represent an ideal platform for development and validation of clinical assessment tools, innovative clinical trials driven by imaging and biological variables, as well as clinical outcomes that will be of major interest to academia, industry, and government bodies.

Extending this approach specifically to collect data for patients with early PsA under the GRAPPA umbrella will bring together a large number of specialist centers in a major international effort.

Biomarkers for joint damage in psoriatic arthritis — design considerations for a longitudinal study: Oliver FitzGerald

GRAPPA has previously identified 2 key areas for biomarker development in psoriasis and PsA: (1) biomarkers of articular disease in patients presenting with psoriasis; and (2) biomarkers of joint damage in PsA. Shortly following this identification, GRAPPA was contacted by the OMERACT biomarker group (Walter Maksymowych, chair) to provide some members who might work with the OMERACT group to develop a longitudinal study design for biomarkers of joint damage in PsA. A similar initiative is also under way in RA and AS. The interaction between GRAPPA and the OMERACT biomarker group has indeed been synergistic. The initial focus has been on testing of the OMERACT 2008 validation criteria, issues related to statistical analysis, and longitudinal study design. Several Web-based surveys were conducted of GRAPPA members seeking agreement on aspects of study design. For consensus, ≥ 70% of respondents voting "Yes" was required for inclusion or ≥ 30% voting "No" for exclusion. As several items still required consideration (having between 30% and 70% respondents), considerable time was spent at the GRAPPA meeting discussing and voting on the outstanding issues. The resulting longitudinal study design for biomarkers of joint damage in PsA is summarized in Tables 2–6.

Note that several issues in the tables were debated in detail and, where consensus has not been achieved, a majority view will likely apply. The first such issue related to study duration (Table 2). The rate of development of new erosions in PsA is slower than in RA, with 47% of patients with recent-onset PsA having erosive disease within 2 years of presentation and the mean number (range) of erosions increasing from 1.2 (0–19) to 3 (0–25)[20]. Therefore, it was argued that on the one hand a 4-year followup would be appropriate; on the other, 4- or 3-year followup could prove

Table 2. Longitudinal study design for biomarkers of joint damage in psoriatic arthritis. Core methodological items.

	Psoriatic Arthritis
Inclusion criteria	Classification Criteria for Psoriatic Arthritis (CASPAR)
Treatment strategy	All treatments
Selection of patient cohort	Consecutive cases
Study duration	4 yrs (per 69.8% of members). Agreed study would be 2 years initially. Preferably, funding for a 4-yr study will be forthcoming; if not, GRAPPA will undertake to complete the study
Frequency of assessment	Every 6 months
Analysis of radiographic endpoint	Blinded to timepoint
Allow steroid	Yes, but should be recorded
Rules for changes in treatment	As directed by the treating physician

Table 3. Longitudinal study design for biomarkers of joint damage in psoriatic arthritis. Health status core domain.

	Psoriatic Arthritis	Instrument
Symptoms	Pain	Visual analog scale
	Skin global	Physician's global assessment
	Patient global	Patient's global assessment
Physical function	Patient self-reported function	Health Assessment Questionnaire
Psychosocial function	Quality of life	Dermatology Life Quality Index Short-Form 36
Other	Work status	Employment status

Table 4. Longitudinal study design for biomarkers of joint damage in psoriatic arthritis. Disease process core domain.

Disease Activity	Instrument
Joint inflammation	66/68 joint counts
Global disease activity (patient/physician assessments)	Visual analog scale
Clinical enthesitis	Leeds Enthesitis Index
Dactylitis	Simple count of tender digits (49%); Leeds Dactylitis Index (51%)
Spinal	Bath Ankylosing Spondylitis Disease Activity Score
Skin	Psoriasis Activity and Severity Index/body surface area
General laboratory results	Erythrocyte sedimentation rate/ C-reactive protein
Nail	Modified Nail Psoriasis Severity Index; 51%, 57%, respectively

more difficult to fund, and dropout rates could be significant. A compromise decision was that the study would be 2 years initially. Preferably, funding for a 4-year study will be forthcoming; if not, GRAPPA will undertake to complete the study.

The next major discussion items related to the disease process core domains, in particular the instruments to be used in recording enthesitis, dactylitis, and nail involvement (Table 4). Based on the evidence presented by Philip Helliwell, it was agreed that the recently described Leeds Enthesitis Instrument[21] would be the instrument employed. Nonetheless, there remained considerable support for collecting data on a more extended entheseal set so as to verify the Leeds findings. A demonstration of the appropriate entheseal sites was provided by Philip Mease. Discussion on the appropriate dactylitis instrument to be used proved more controversial. The Leeds Dactylitis Instrument[22] was thought by many to be the best instrument available and not too difficult to apply. However, in the setting of a multicen-

Table 5. Longitudinal study design for biomarkers of joint damage in psoriatic arthritis. Damage core domain.

	Psoriatic Arthritis	Instrument
Radiographic damage endpoint	Modified Sharp scale	Modified Sharp scale
Additional damage domains*	Spinal imaging	Modified Stoke Ankylosing Spondylitis Spinal Score

* Other imaging modalities could be undertaken in selected centers where facilities permit.

Table 6. Longitudinal study design for biomarkers of joint damage in psoriatic arthritis. Essential demographic data plus covariates.

Psoriatic Arthritis
Age
Sex
Symptom duration (years)
Age at onset
Disease phenotype: Not considered or discussed at the 2008 meeting
Psoriasis phenotype: Type 1 or 2; plaque/guttate/pustular/erythrodermic/flexural
PsA comorbidity (cardiac/cholesterol/depression/other)
Medication history (NSAID, DMARD, anti-TNF)
HLA-B27 status
Baseline radiographic damage
Smoking
Menopause
Body mass index
Ethnicity
Occupation
Non-arthritis comorbidity
Non-arthritis-related treatment
Socioeconomic status
Alcohol consumption

NSAID: nonsteroidal antiinflammatory drug; DMARD: disease modifying antirheumatic drug; TNF: tumor necrosis factor.

ter longitudinal study over 2–4 years, it was argued that a simpler approach, counting the number of swollen and tender digits, might be best. In the recorded decision, the opposing sides were irreconcilable. Finally, in relation to nail involvement, the modified Nail Psoriasis Severity Index score was thought best by a majority, but there was considerable voice for the concern that the instrument would prove too cumbersome and that a better instrument for nail disease was required[23].

Having largely agreed on the longitudinal study design, the next step is to seek appropriate funding support together with OMERACT partners in the other disease areas for these multicenter studies. The appropriate approach to the handling and assessment of biological samples also requires discussion. In the setting of PsA, it has been agreed that the collection of a DNA sample would be appropriate. The assessment of samples might include, for example, assays of candidate biomarkers of cartilage breakdown, but an approach more conducive to discovery using newer technologies such as proteomics might also be considered. It is hoped that these final issues can be resolved and that the study will be under way by 2010.

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