Biomarker Development in Psoriatic Arthritis

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ABSTRACT. Biomarkers can provide insights into disease pathogenesis and assist clinicians in screening patients with psoriasis for arthritis. They can also help to stratify patients who are at risk for progression to bone destruction or ankylosis. Biomarkers in psoriatic disease are still in the discovery phase, but the field is advancing at a rapid pace. This review discusses definitions of the different types of biomarkers and the development of markers that reflect preclinical and early psoriatic arthritis along with those that may be able to predict disease severity and response to anti-tumor necrosis factor agents. (J Rheumatol 2012;39 Suppl 89:57–60; doi:10.3899/jrheum.120245)

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Interest in biological markers has surged in the last few years as evidenced by the dramatic increase in US federal government funding for biomarker research and the plethora of medical literature devoted to this topic[1]. Despite this great interest, only a limited number of the several identified candidate biomarkers have undergone the extensive validation required for adoption into clinical practice or to be included as endpoints in clinical trials[2]. Indeed, uptake of biomarkers for inflammatory arthritis has been frustratingly slow; anticitrullinated protein antibodies (ACPA), a seminal marker in rheumatoid arthritis (RA), were first described more than 2 decades ago[3]. The slow pace of biomarker development can be partially explained by the inability to validate and replicate initial findings. Fortunately, in the case of soluble biomarkers in RA, a formal process of biomarker validation has been developed, which will serve as a model for studies in psoriatic arthritis (PsA)[4].

PsA is an inflammatory joint disease with marked phenotypic diversity and varied clinical course. Diversity is present not only in the musculoskeletal features but also in the cutaneous, gastrointestinal, and ocular manifestations that range considerably among patients[5]. Moreover, the bone pathology (erosion and ankylosis) and sites of involvement (peripheral and axial disease) provide additional heterogeneity and it is now appreciated that a wide range of comorbidities including obesity, type 2 diabetes, cardiovascular disease, and hypertension can significantly affect function and quality of life and are associated with increased mortality[6,7]. The wide array of clinical characteristics and outcomes offers unique opportunities for application of biomarkers that can identify preclinical and early disease and assist in the stratification of patients at risk for subsequent bone damage. Another important hurdle is the validation of a biomarker that can predict clinical response to specific therapeutic agents.

Unfortunately, biomarker development in PSA is still in the early discovery phase and markers that will require validation have not been revealed. Nevertheless, studies published in the last 5 years yielded a number of candidate markers that deserve close scrutiny. This review describes the types of biomarkers that may be of interest in PsA and discusses development of markers that reflect the likelihood of preclinical or early disease, or predict disease severity and have the potential to act as surrogates of disease response. Another topic is the development of markers that may predict disease flare and response to biologic agents.

THE BIOMARKER CONTINUUM

A biomarker can be defined as a disease-centered variable that provides insights into the underlying disease process[8]. Biomarkers can be viewed in a continuum that ranges from disease-centered to patient-centered variables[4]. Disease-centered variables, which can be derived from biochemical, cellular, serum, genetic, or imaging sources, may have no inherent significance to the patient or clinician, but the importance of these variables may become apparent as data are collected over time or after their link to pathologic processes or disease mechanisms is revealed. Examples include blood pressure, laboratory values, and imaging data. Because biomarkers may not have direct relevance to the patient, validation is required. At the other end of the continuum are patient-centered variables that reflect how a patient feels, functions, and survives and they do not require validation. A surrogate marker is a biomarker that can substitute for a clinical endpoint and that can predict clinical benefit or harm or lack of clinical benefit or harm. One

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example is a T score on a dual-energy x-ray absorptiometry scan, which can serve as a partial surrogate of the risk for bone fracture. Two other common terms are risk factor and prognostic factor; these may or may not be biomarkers. These factors are predictive over time, and patients without disease have risk factors while patients with disease have prognostic factors. Prognostic factors are important for therapeutic stratification because they can identify patient subgroups with characteristics that favor response to specific treatments.

EARLY DIAGNOSIS OF PsA

A major advantage in the assessment of risk factors for PsA is that the majority of patients with this disease develop psoriasis on average about 10 years before the diagnosis of joint disease[9]. This temporal sequence provides a unique opportunity to identify arthritis risk factors in a psoriasis population. Clinical factors associated with increased risk of PsA in patients with psoriasis include nail disease, obesity, extensive psoriasis, and scalp disease[10,11]. Unfortunately, these data are derived from relatively small case series, and high-quality population data are not yet available. Recent efforts have centered on the development of patient questionnaires that can be administered in dermatology or general practice settings[12]. Several instruments have been developed and validated and efforts to improve the sensitivity and specificity in different patient populations are in progress. Our group has identified cellular markers on osteoclast precursors that are upregulated in patients with PsA. These molecules include CD16[13] and dendritic cell specific membrane protein (DC-STAMP)[14], and studies are in progress to determine whether these monocyte markers, measured by flow cytometry on peripheral blood mononuclear cells (PBMC), are predictive of arthritis in patients with psoriasis. Preliminary data have demonstrated that patients with psoriasis who subsequently developed arthritis show increased DC-STAMP expression on PBMC[15]. Interestingly, a subset of CD4-positive T cells also express DC-STAMP and are elevated in patients with PsA but not psoriasis[14].

Over the last 30 years, imaging studies [scintigraphy, magnetic resonance imaging (MRI), and most recently Doppler ultrasound (US)] have demonstrated that patients with psoriasis and no musculoskeletal disease have abnormal findings suggestive of subclinical inflammation in bone, entheses, and synovium not observed in patients with other inflammatory skin disorders or in healthy controls[5]. Prospective studies that capture imaging data in patients with psoriasis followed by longitudinal followup for musculoskeletal disease will address the predictive value of these abnormal signals for the development of arthritis. It is also anticipated that Doppler US will become the instrument of choice for screening patients with psoriasis, given its increasing presence in rheumatology offices, ease of use, and relatively low cost.

A major unmet need is the development of markers to assist in the identification and diagnosis of patients with early PsA. In contrast to RA, where ACPA show high specificity, and systemic lupus erythematosus, in which the antinuclear antibody titer is highly sensitive and other autoantibody profiles are associated with specific organ involvement, PsA lacks diagnostic markers, and confirmation of disease is based extensively on history, clinical features, and imaging findings. Imaging studies such as MRI can reveal erosions, bone marrow edema, and enthesial inflammation, while Doppler US changes in early PsA include bone erosion, cartilage abnormalities, thickening of tendons and ligaments, and increased vascularity. Recently, Mehta, *et al* reported that fluorodeoxyglucose positron emission tomography/computed tomography can detect abnormal signals in the liver, blood vessels, entheses, and joints of patients with psoriasis without musculoskeletal signs and symptoms[16]. Thus, this instrument may be able to provide a comprehensive assessment of not only joint inflammation but information regarding the risk of peripheral vascular disease and fatty liver. Drawbacks include the high cost and radiation dose, but studies using this instrument should provide compelling insights into the burden of disease in patients with psoriasis who are asymptomatic.

PROGNOSTIC CHALLENGES IN PsA

A major challenge in PsA therapeutics is stratification of patients at risk for progression to erosive joint disease and/or bony ankylosis. Clinical risk factors for radiographic progression include age, duration of disease, initial erythrocyte sedimentation rate, number of tender and swollen joints at previous visit, and number of deformed joints[17]. Identification of rapid progressors is essential given that almost half of patients demonstrate erosions in the first 2 years of disease[18]. Efforts are under way for an observational study to develop serum markers to act as surrogates to date for radiographic damage[19]. Candidate surrogates include metalloproteinase-3, C telopeptide of type 1 collagen (CTX-1), CTX-2, receptor activator of nuclear factor-κB (RANK)/osteoprotegerin ratio, sclerostin, and Dickkopf-related protein-1; however, this list will be modified as new data become available. Patients naive to medications or on disease-modifying antirheumatic drugs will be enrolled in an observational study and evaluated every 3 months. The treatment goal at each visit will be the achievement of minimal disease activity[20], and therapy will be adjusted to reach this target. Serum will be collected at each visit and radiographs performed every 6 months for 2 years. This study, modeled after the Assessment of Structural Damage in Rheumatoid Arthritis Using Biomarkers and Radiography study currently under way, is still in the planning stages and funding has not been secured, but it has the potential to provide valuable information that will profoundly affect clinical practice and improve patient outcomes.

Another challenge faced by clinicians is the absence of prognostic factors to determine which patients are most likely to respond to anti-tumor necrosis factor (TNF) agents. The variables to predict response could be serum, genetic, cellular, or imaging. The TNF-α-induced protein 3 (*TNFAIP3*) gene is associated with psoriasis. In a recent study, Tejasvi, *et al* showed that a specific allele of *TNFAIP3* was associated with improved response to anti-TNF agents in patients with psoriasis or PsA[21]. In other studies, intracellular signals in the nuclear factor-κB (NF-kB) and RANK signaling pathways were upregulated when TNF levels were elevated[22,23]. These findings support the concept that these molecules could serve as biomarkers to predict anti-TNF therapy response; those with elevated levels of TNF-induced molecules may show more favorable response to TNF blockade. These exciting developments provide new avenues of investigation that could pave the way for new prognostic markers of treatment response.

A third challenge that remains to be addressed is detection of prognostic biomarkers to predict flare in PsA. The fluctuating course of joint disease is a great source of stress to patients and often brings pain and decreased function. In gadolinium MRI studies of TNF transgenic mice, we observed enlarged popliteal lymph nodes draining joints with inflammatory synovitis[24]. Parallel studies from our group revealed that these mice produce high levels of vascular endothelial growth factor-C, a factor that can induce lymphangiogenesis[25]. The popliteal lymph nodes increased in size after 2.5 months in these mice, a time when TNF serum levels rise, which coincides with release of CD11b+ macrophages. We observed that just before the onset of arthritis, the draining lymph node collapses, as evidenced by markedly diminished volume and increased contrast enhancement. In addition, flow through the draining lymphatics declined dramatically[24]. Histopathology of the collapsed but not expanded node showed migration of B cells from the periphery to the central region of the node but the number of B lymphocytes was not increased. Treatment of the mice with a B cell-depleting agent prevented the node collapse and onset of arthritis[26,27].

Current studies are under way to examine the mechanisms that lead to the collapse of the node and the subsequent synovitis. One potential explanation is that cells, chemokines, and cytokines that sustain joint inflammation cannot exit from the joint because of the obstruction in the node resulting in persistent synovial inflammation. We have performed technetium sulfur colloid scans in patients with inflammatory arthritis and found that lymphatic flow in the affected extremity is significantly diminished compared to the contralateral extremity in a patient who is in the midst of a flare (Figure 1). Additional studies are under way to determine whether treatment of patients with anti-TNF agents or rituximab is associated with expansion of the node and resumption of lymphatic flow in treatment responders. These studies provide a novel pathway to explain joint flare and provide opportunities to examine agents that affect lymph function and flow.

Biomarker discovery and validation has been frustratingly slow in the field of inflammatory arthritis, but the research environment is changing rapidly in 4 major areas that will facilitate biomarker development for psoriasis and PsA in the near future. The first area is the ability to perform

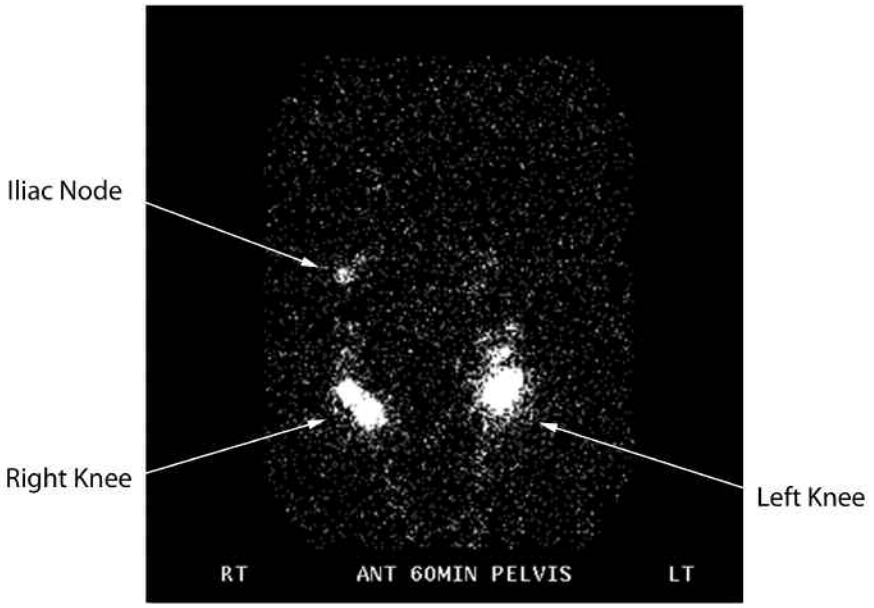

Figure 1. Technetium sulfur colloid scan in a 57-year-old man with rheumatoid arthritis. He had a severe flare in his left knee while on methotrexate. Note the delayed uptake of technetium to the left inguinal node compared to the right.

genetic (genome-wide scans) and genomic studies (microarray, RNA-seq) on large patient populations. The second area is improvements in proteomic and metabolomics technologies, which will provide additional sources for biomarkers. The third area is the development of well-phenotyped patients with data stored in medical record databases that can be linked to the genetic, genomic, proteomic, and metabolomic data. These databases also contain large numbers of controls without the disease, an essential resource for unbiased biomarker development[28]. The last area central to the success of biomarker discovery is the growth of bioinformatics. Analysis of these large datasets requires new statistical and mathematical approaches to identify 1 or a combination of markers (e.g., genetic combined with serum biomarkers) that may serve as risk or prognostic factors or as surrogates in patients with psoriatic disease.

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