Soluble Biomarkers May Differentiate Psoriasis from Psoriatic Arthritis

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ABSTRACT. Patients with psoriatic arthritis (PsA) have a higher inflammatory burden and poorer quality of life compared to patients with psoriasis without PsA. Early identification of PsA may prevent joint damage progression and improve quality of life. Soluble biomarkers have the potential to be useful for screening patients with psoriasis for underlying PsA so that appropriate referral to a rheumatologist is made. Pilot studies have shown that C-reactive protein, interleukin 6, cartilage oligomeric matrix protein (COMP), Dickkopf-1, and macrophage-colony stimulating factor may differentiate PsA from psoriasis without PsA. Compared with controls, increased serum levels of receptor activator of nuclear factor-κB ligand, tumor necrosis factor superfamily member 14, matrix metalloproteinase-3 (MMP-3), and COMP are independently associated with psoriatic disease. Increased levels of high-sensitivity CRP (hsCRP), osteoprotegerin (OPG), MMP-3, and the ratio of C-propeptide of type II collagen (CPII) to collagen fragment neoepitopes Col2–3/4 $C_{long\ mono}$ (C2C) are independently associated with PsA. A combination of hsCRP, OPG, MMP-3, and the ratio CPII of C2C was able to distinguish patients with PsA from those with psoriasis alone in a receiver-operating characteristic curve analysis, with area under the curve 0.904. Therefore, a combination of the above biomarkers may at least have a role in screening patients with psoriasis for PsA. These findings need to be validated in prospective studies. (J Rheumatol 2012;39 Suppl 89:65–66; doi:10.3899/ jrheum.120247)

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Patients with psoriasis have a number of comorbidities. These include inflammatory arthritis involving peripheral and/or axial joints and entheses, eye and mucosal inflammation, nonalcoholic steatohepatitis as well as metabolic syndrome and associated cardiovascular disease[1]. Psoriatic arthritis (PsA), defined as an inflammatory arthritis associated with psoriasis usually seronegative for rheumatoid factor, is one of the most common comorbidities associated with psoriasis[2]. Compared to patients having psoriasis without PsA (PsC), patients with PsA have a higher inflammatory burden, more functional disability, and poorer quality of life[3]. Early diagnosis of PsA reduces the rate of peripheral joint damage progression. Patients seen within 2 years of diagnosis at a rheumatology clinic have less joint damage progression compared to those with greater disease duration at first clinic visit[4]. Thus, early diagnosis and treatment of PsA will lead to better longterm outcome.

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About 30% of patients seen in psoriasis clinics have PsA. Moreover, most patients with PsA develop PsA concomitantly or after psoriasis onset. Therefore, psoriasis may be considered a prearthritic condition. Studies have shown high prevalence of undiagnosed PsA in patients with psoriasis seen in dermatology clinics[5]. Identifying PsA in patients with psoriasis is the key to identifying PsA early. Because it is practically impossible for all patients with psoriasis to be evaluated by a rheumatologist, screening patients with PsC for PsA will result in appropriate referral to a rheumatologist. Toward this goal, screening questionnaires have been developed. Biomarkers may also be useful and are a subject of considerable research interest.

BIOMARKERS ASSOCIATED WITH PsA

A number of studies have recently investigated biomarkers for PsA. C-reactive protein (CRP) is a marker of inflammation as well as of cardiovascular risk. Reanalysis of data from a large clinical trial of etanercept in psoriasis showed that CRP levels are elevated in patients with psoriasis[6]. Patients with PsA and those with higher body mass index (BMI) had higher baseline CRP. Higher baseline CRP was shown to be associated with higher PASI scores independent of BMI[7]. CRP levels decreased significantly with etanercept treatment in patients with psoriasis as well as PsA[7]. Thus, high-sensitivity CRP (hsCRP) may be a marker for PsA, especially in nonobese patients with psoriasis. Serum cartilage oligomeric matrix protein (COMP) was found to be ele-

vated in patients with PsA as well as in those with psoriasis vulgaris, with no difference between the 2 patient groups[8]. Serum COMP values correlated with disease activity because the levels correlated with CRP levels as well as with swollen joints. Serum interleukin 6 (IL-6) has also been investigated. In a study with 219 patients, 134 of whom had PsA, IL-6 levels were significantly higher in PsA regardless of erythrocyte sedimentation rate (ESR)/CRP levels[9]. Serum IL-6 correlated with the joint counts, ESR, CRP, and IL-2Rα[9]. Bone biomarkers such as Dickkopf-1 (DKK-1), macrophage-colony stimulating factor (M-CSF), osteoprotegerin (OPG), and receptor activator of nuclear factor-κB ligand (RANKL) were also recently investigated in a small study[10]. DKK-1 and M-CSF levels were higher in PsA compared to PsC. In PsA, M-CSF and RANKL, but not DKK-1, correlated with radiographic erosion, joint-space narrowing, and osteolysis scores. These studies provide preliminary evidence for association between some soluble markers and PsA. However, to identify biomarkers for screening PsA, it will be necessary to establish cohorts of carefully phenotyped patients with PsC, PsA, and controls. Biological samples will need to be collected at appropriate timepoints. After selecting a set of candidate biomarkers, cross-sectional studies will have to be done to identify promising candidates that will then have to be validated in longitudinal studies. Randomized trials may then have to be done to determine the effect of screening on longterm outcomes.

SOLUBLE BIOMARKERS THAT DISTINGUISH PsA FROM PsC

Using a small number of carefully phenotyped subjects with PsA, PsC, and controls matched for age, sex, and ethnicity, and not treated with biologic agents, Chandran, *et al* recently evaluated biomarkers related to inflammation (hsCRP), bone (RANKL, OPG) and cartilage damage [Col2-3/4C $_{long}$ $_{mono}$(C2C), Col2-3/4C$_{short}$ (C1-2C), C-propeptide of type II collagen (CPII), COMP], tissue destruction [matrix metalloproteinase 3 (MMP-3)], and cytokines [IL-12, IL-12p40, IL-17, tumor necrosis factor (TNF) Super Family 14 (TNFSF14)] to identify the ones useful for PsA[11]. RANKL, TNFSF14, MMP-3, and COMP were associated with psoriatic disease (PsA and PsC) compared to controls. Higher serum levels of hsCRP, OPG, MMP-3, and the ratio of CPII to C2C (CPII/C2C) were independently associated with PsA. A combination of hsCRP, OPG, MMP-3, and CPII/C2C in the serum was able to distinguish patients with PsA from those with PsC in a receiver-operating characteristic curve analysis (area under the curve 0.904)[11]. A similar study investigated serum kallikrein related peptidases (KLK). KLK regulate skin desquamation, remodeling of extracellular matrix, and innate immunity. Serum levels of KLK-5, -6, -7, -8, -10, -11, and -13 were determined using ELISA. KLK-8 was associated with psoriatic disease, but did not discriminate between PsA and PsC[12]. Thus, RANKL, TNFSF14, MMP-3, COMP, and KLK-8 are candidate biomarkers for psoriatic disease, whereas hsCRP, OPG, MMP-3, and CPII/C2C are candidate biomarkers that may distinguish patients with PsA from those with PsC.

There is now evidence that early diagnosis of PsA will lead to better longterm outcomes. Identifying patients with PsA in dermatology clinics is the key to early diagnosis of PsA. There is a high prevalence of undiagnosed PsA in patients with psoriasis seen in dermatology clinics. Screening these patients using biomarkers may help facilitate appropriate referral to rheumatologists. A number of biomarkers have been investigated. OPG, hsCRP, MMP-3, and CPII/C2C have promise but need further replication and validation. Novel biomarkers await discovery. In future, biomarkers for disease activity, response to therapy, and joint damage progression need to be identified so that management of patients with PsA is optimized.

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