Biomarkers for Comorbidities in Psoriasis: A Report from the Grappa 2011 Annual Meeting

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ABSTRACT. Biomarkers are being recognized that will help identify patients with psoriasis who may be destined to develop psoriatic arthritis (PsA). Recent genome-wide association studies have identified genes that are common to both psoriasis and PsA, as well as differentially expressed in the 2 conditions. Further, biomarkers of inflammation and cartilage can differentiate between patients with PsA and those with psoriasis without arthritis. An overview of these biomarkers was presented at the 2011 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis. Additionally, a report was presented from the current database of the International Psoriasis and Psoriatic Arthritis Research Team, a group of dermatologists and rheumatologists with the objective to improve the lives of patients with psoriasis and PsA. (J Rheumatol 2012;39:2193–5; doi:10.3899/jrheum.120821)

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Psoriasis is an inflammatory immune-mediated skin disease that affects 2%–3% of the population[1,2]. Psoriasis presents with red, elevated, scaly skin, often over the elbows and knees, but may occur anywhere on the body. Whether restricted to the scalp, genital, or intergluteal areas, or whether widespread, it may also affect the nails with pits and onycholysis[3]. Patients with psoriasis have reduced quality of life and function due to pain and itchiness often associated with the disease[4,5]. Psoriasis that affects the face or hands or causes significant nail involvement may interfere with social interactions[5].

About 30% of patients with psoriasis may develop psoriatic arthritis (PsA)[6]. PsA is an inflammatory musculoskeletal disease that affects the peripheral joints, spine, and entheses, and may be associated with swollen digits due to inflammation of tendons, joints, and soft tissues (dactylitis)[7]. PsA may lead to joint deformities and damage, in turn leading to a reduced quality of life. PsA is also associated with significant morbidity and disability, as well as an increased mortality risk[8,9]. It was recently demonstrated that patients with PsA who present early in the course of their disease fare better than those who present later, suggesting that early diagnosis and treatment may prevent progression of damage[10].

PsA may be considered a disease within a disease. Because the majority of patients with PsA present with psoriasis first, it is important to identify clinical features and biomarkers that may distinguish patients destined to develop PsA and thus diagnose and treat these patients early to prevent untoward outcomes such as early mortality, progression of joint damage, and disability. The causes of psoriasis and PsA are not known, but genetic, environmental, and immunological factors are thought to be important in the pathogenesis of both diseases. Whether the same factors lead to skin and joint manifestations remains unclear.

Recent genome-wide association studies (GWAS) identified genes that are common to both psoriasis and PsA, as well as some genes that are differentially expressed in the 2 conditions[11]. *HLA-C* and *IL-23* were associated more strongly with psoriasis than PsA, and *IL-12B* was more strongly associated with PsA. In a recent metaanalysis, a genome-wide significant association was detected at 2p16 near the REL locus encoding c-Rel[12]. It is hypothesized that c-Rel, as a member of the Rel/nuclear factor-κB family, is associated with PsA in the context of disease pathways that involve other identified psoriasis and PsA susceptibility genes including *TNIP1*, *TNFAIP3*, *and NFκBIA*.

The strongest association with psoriasis and PsA is within the HLA region. A recent investigation revealed that HLA-B*27, HLA-B*08, and HLA-B*39 are increased among patients with PsA compared to those with psoriasis without arthritis, whereas HLA-C*06 is increased among patients with psoriasis without arthritis compared to PsA[13]. Further, biomarkers of inflammation and cartilage were shown to differentiate between patients with psoriasis without arthritis and those with PsA[14]. High sensitivity C-reactive protein (hsCRP), osteoprotegerin (OPG), matrix metalloprotein-3 (MMP-3), and the ratio of C-propeptide of Type II collagen (CPII) to collagen fragment neoepitopes Col2-3/4long mono (C2C) (CPII: C2C) are biomarkers for PsA in patients with psoriasis.

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Both psoriasis and PsA are associated with comorbidities. In addition to specific comorbidities that are associated with seronegative disease including iritis and inflammatory bowel disease, patients with psoriatic disease suffer from cardiovascular disease, obesity, diabetes, depression, and anxiety. The International Psoriasis and Psoriatic Arthritis Research Team (IPART) is a group of dermatologists and rheumatologists who assembled for a new emerging team grant provided by the Canadian Institutes of Health Research. IPART has a number of objectives, all of which aim to improve the lives of patients with psoriasis and PsA[15]. One of their first goals was to recruit and carefully phenotype patients with psoriasis without arthritis, as well as patients with PsA, according to a standard protocol. In all patients, psoriasis is diagnosed by a dermatologist, and all patients with psoriasis-without-arthritis are reviewed by a trained observer to assure absence of PsA. Patients are then followed at yearly intervals, and information is recorded on their disease characteristics, comorbidities, medications, and adverse events. Patients also provide blood for DNA and RNA extraction, as well as serum for biomarker studies. This database provides a unique opportunity to address the issue of biomarkers for comorbidities in patients with psoriasis without arthritis and those with PsA.

At the 2011 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), a presentation of the IPART database included 2400 patients (Table 1). The demographic features of these patients resemble other cohorts of patients with psoriasis and PsA[16]. A comparison between psoriasis patients with and those without arthritis registered in the IPART database revealed that patients with PsA tend to have higher Psoriasis Area and Severity Index scores and more frequent nail involvement than patients with psoriasis without arthritis. In terms of comorbidities, while patients with psoriasis without arthritis are more likely to have hyperlipidemia, patients with PsA are more likely to have hypertension, angina, and myocardial infarction (Table 2). Members of IPART have now completed a GWAS in PsA. Preliminary results confirm genetic associations previously noted for psoriasis.

Table 1. Demographic features in patients with psoriatic arthritis versus psoriasis without arthritis.

Feature	Psoriatic Arthritis	Psoriasis
No. patients	1747	653
Mean age, yrs	46.0	46.3
Disease duration since diagnosis, yrs		
Psoriasis	15.6	16.3
Psoriatic arthritis	7.3	NA
Average body mass index, %	31.4	28.8
Normal, % (range 18.5–24.9)	21.5	28.8
Overweight, % (range 25.0–29.9)	36.5	36.7
Obese (> 30)	40.6%	32.8%
Average waist circumference, cm		
Female	98.9	89.4
Male	98.6	96.6

Table 2. Comorbidities in patients with psoriatic arthritis versus psoriasis without arthritis.

Comorbidity	Psoriatic Arthritis n (%)	Psoriasis n (%)
Hypertension	265 (16)	124 (20)
Diabetes	121 (8.2)	49 (7.8)
Hyperlipidemia	77 (5.8)	90 (15)
Cancer	58 (6.2)	27 (4.8)
Depression	50 (4)	36 (6.2)
Myocardial infarction	40 (2.5)	12 (1.9)
Angina	34 (2.1)	9 (1.5)
Liver disease	30 (2.3)	13 (2.2)

Another area of investigation has been the role of osteoclast precursors (OCP) in distinguishing patients with PsA from those with psoriasis without arthritis. An increased frequency of circulating OCP was noted in one-third of patients with psoriasis without arthritis[17]. A dendritic-cell specific transmembrane protein (DC-STAMP) is a transmembrane protein required for the fusion of monocytes during osteoclast formation. It has been hypothesized that DC-STAMP may serve as an arthritis susceptibility biomarker in psoriasis without arthritis. In a longitudinal cohort of 24 psoriasis-without-arthritis patients from the IPART cohort with an average followup of 3 years, DC-STAMP expression patterns were analyzed by flow cytometry. OCP frequency in cultured monocytes was also analyzed. The data suggest that DC-STAMP is a potential marker to predict development of PsA in patients with psoriasis without arthritis. Three patients who developed PsA have the DC-STAMP pattern III and IV, the most common patterns seen in patients with PsA[18]. Whether these biomarkers can also identify the presence of comorbidities remains to be determined.

In conclusion, although clinical differences may readily identify patients with psoriasis who develop PsA, the questions that need more exploration concern the identification of biomarkers associated with development of PsA and development of comorbidities. Members of IPART will continue to explore these questions through their participation in GWAS in both psoriasis and PsA.

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