

Update on Biomarkers in Psoriatic Arthritis: A Report from the GRAPPA 2010 Annual Meeting

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ABSTRACT. Biomarkers may be used to screen patients with psoriasis for psoriatic arthritis (PsA) and to assess disease activity and severity. Candidate biomarkers should fulfil the key features of the OMERACT (Outcome Measures in Rheumatology) filter, that is, truth, discrimination, and feasibility. A number of biomarkers are currently being investigated in psoriatic disease for important clinical outcomes. Serum high sensitivity C-reactive protein, cartilage oligomeric matrix protein, interleukin 6 (IL-6), osteoprotegerin, matrix metalloproteinase-3 (MMP-3), and the ratio of C-propeptide of type II collagen (CPII) to collagen fragment neoepitopes Col2-3/4 (long mono) (C2C) show promise as serum biomarkers that distinguish subjects with PsA from those with psoriasis alone. Serum MMP-3 and melanoma inhibitory activity, synovial fluid IL-1, IL-1 receptor- α , IL-6, IL-8, and chemokine CCL3 and synovial tissue CD3-positive T cells may prove useful as biomarkers of PsA activity. Circulating osteoclast precursors, Dickkopf-1, macrophage colony stimulating factor, receptor activator of nuclear factor- κ B ligand, and bone alkaline phosphatase are strong candidates as biomarkers of radiographic change. Prospective studies to identify biomarkers for psoriatic disease are high on the research agenda of the Group for Research and Assessment of Psoriasis and PsA. (J Rheumatol 2012;39:427–30; doi: 3899/jrheum.111241)

Key Indexing Terms:

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Assessing and predicting outcome of psoriatic disease is challenging. Patients with psoriasis are at increased risk of developing other inflammatory manifestations, especially psoriatic arthritis (PsA). Current tools to evaluate the natural course, disease activity, treatment response, and outcome of psoriatic disease are inadequate. Biomarkers, however, have valuable applications in detection of disease and monitoring of health status, including diagnosing, staging, or classifying the extent of disease; indicating disease prognosis; and predicting and monitoring the clinical response to an intervention¹. Biomarkers provide insights into the natural history and serve as surrogate endpoints for a variety of different outcomes. Members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have identified several biomarker studies as research priorities in psoriatic disease. These studies include biomarkers for detecting PsA in patients with psoriasis, biomarkers for joint damage in patients with PsA, and biomarkers of cardiovascular comorbidities. In preparation for these possible

GRAPPA-led studies, this review provides additional information that has emerged since last reviewed by de Vlam, *et al* in 2008².

Biomarker Development

Candidate biomarkers should fulfill the key features of the OMERACT (Outcome Measures in Rheumatology) filter³, that is, truth, discrimination, and feasibility. Biomarkers in PsA should reflect either joint or skin pathophysiology; the sensitivity and specificity of a proposed biomarker and in particular the inclusion of control material are critical in meeting the discrimination filter; and to be feasible, a synovial tissue biomarker might pass the truth and discrimination filters, but is unlikely to be generally acceptable unless it is measurable in more accessible samples, such as blood or urine.

Current Knowledge

Biomarkers that differentiate PsA from psoriasis without PsA (PsC). The prevalence of undiagnosed PsA is high in patients with psoriasis seen in dermatology clinics⁴. Identifying biomarkers for PsA may help screen patients with psoriasis for appropriate referral to a rheumatologist. Reanalysis of data from a large clinical trial of etanercept in psoriasis showed that patients with PsA and those with higher body mass index have higher median baseline high-sensitivity C-reactive protein (hsCRP) values than patients with psoriasis without PsA⁵. Thus, hsCRP may be used as a marker for PsA, especially in non-obese patients with psori-

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asis. Serum cartilage oligomeric matrix protein is elevated in patients with psoriatic disease and correlates with CRP and swollen joint count but does not distinguish PsA patients from those with psoriasis without PsA⁶. In a study comparing PsA patients to those with psoriasis without PsA, it was also shown that IL-6 levels are higher in PsA patients and correlate with joint counts, erythrocyte sedimentation rate (ESR), CRP, and serum interleukin 2 (IL-2) receptor- α ⁷. Chandran, *et al* recently evaluated biomarkers related to inflammation, bone, and cartilage damage to identify biomarkers for PsA⁸. A combination of hsCRP, osteoprotegerin, matrix metalloproteinase 3 (MMP-3), and the ratio of C-propeptide of type II collagen (CPII) to collagen fragment neopeptides Col2-3/4 (long mono) (C2C) in the serum was able to distinguish patients with PsA from those with psoriasis without PsA in a receiver-operating characteristic curve analysis (area under the curve 0.904). Although a combination of the above biomarkers may help screen psoriasis patients for PsA, these findings need validation in prospective studies.

Biomarkers of disease activity. In PsA, a number of processes can be evaluated by biomarkers, including diagnosis, early identification, disease activity or the inflammatory process, and severity or response to treatment. Van Kuijk and colleagues showed that serum levels of MMP-3 increase and melanoma inhibitory activity (MIA) decreases after 4 weeks in adalimumab-treated patients, with no change in either marker in placebo patients⁹. Synovial fluid cytokines including IL-1, IL-1-receptor antagonist (IL-1RA), IL-6, IL-8, and chemokine (C-C motif) ligand 3 (CCL3) appeared to correlate with systemic markers of inflammation (ESR and CRP) and decreased following intraarticular tumor necrosis factor (TNF) administration¹⁰.

Zaba, *et al* analyzed gene expression profiles in lesional and nonlesional skin of psoriasis patients at baseline and at 1, 2, 4, and 12 weeks after starting treatment with etanercept¹¹. Comparison of responders to nonresponders revealed rapid downregulation of innate IL-1 α and IL-8 sepsis cascade cytokines in both groups, but only responders downregulated IL-17 pathway genes to baseline levels. Therefore, at least in psoriasis, response to anti-TNF therapy is associated with downregulation of IL-17 pathway genes, suggesting a critical role for IL-17 in driving skin inflammation, a finding consistent with the beneficial effect of IL-17 inhibition shown in a recent study in mice¹².

Two studies have attempted to identify biomarkers associated with active treatment in PsA synovial tissue. Van Kuijk and colleagues conducted a prospective, randomized, placebo-controlled study in patients with active PsA using adalimumab⁹. Placebo patients switched to adalimumab after a second synovial biopsy at 4 weeks. After applying a ranked analysis of covariance model to correct for baseline imbalances, a significant effect of treatment was observed on CD3-positive cells: a median reduction of 248 cells/mm²

after adalimumab versus placebo ($p = 0.035$). These findings were confirmed by Pontifex, *et al*, who conducted synovial biopsies and magnetic resonance imaging (MRI) scans at baseline and after 12 weeks of treatment¹³, in 2 treatment cohorts, the first using etanercept and the second IL-1RA. Change in CD3-positive T cell infiltration in synovial tissue specimens correlated with the change in DAS28 (28-joint Disease Activity Score; $R = 0.49$, $p = 0.023$). No significant correlation was found between any clinical variables and changes in CD68 infiltration or with changes in factor VIII expression. Interestingly, a change in CD3 also correlated with a change in a semiquantitative MRI score of the same affected knee joint ($R = 0.58$, $p = 0.009$). Thus, a change in CD3 expression in the synovium of PsA correlated with both change in DAS28 and change in MRI following initiation of biologic treatment. These articles identify change in CD3 as a possible candidate biomarker of treatment response in PsA, which contrasts with rheumatoid arthritis (RA), where a change in CD68 infiltration has been identified as the most likely biomarker of treatment response.

Biomarkers of radiologic outcome. Damage in PsA is certainly slower to occur than in RA and is difficult to predict. In the CORRONA (Consortium of Rheumatology Researchers of North America) registry, a reduced prevalence of erosion was seen in PsA compared with RA (OR 0.609; $p < 0.001$)¹⁴. In an early PsA cohort, 27% of patients presenting within 2 years of symptom onset had erosions at baseline, which increased to 47% at 2 years. The mean baseline Sharp erosion score was low at 1.2 and increased to 3 after 2 years. Features such as periostitis, reflecting new bone formation, were found in 19% at baseline, increasing to 29% at 2 years.

A number of articles from Christopher Ritchlin's group have examined the questions of bone remodeling, osteoclastogenesis, and bone erosion in PsA. In an examination of the frequency of osteoclast precursors (OCP) in patients treated with etanercept, a decrease in OCP was observed after 3 and 6 months of therapy, but had no correlation with bone marrow edema volume on MRI scanning¹⁵. In a report by Dalbeth, *et al*, PsA patients had higher circulating concentrations of Dickkopf-related protein 1 and macrophage-colony stimulating factor (M-CSF), compared with psoriasis patients and controls¹⁶. Levels of M-CSF and receptor activator of nuclear factor kappa-B ligand also correlated with erosion, joint space narrowing, and osteolysis scores. Finally, in a study of patients with PsA and RA by Ng and colleagues, bone biomarkers were measured at baseline, 1 month, and 1 and 3 years after commencing treatment with anti-TNF therapy¹⁷. Of interest, both at baseline and following treatment, an increase in bone alkaline phosphatase was seen in PsA. Other markers of bone formation were also increased, although not significantly. These observations are consistent with the observation that patients with PsA, in contrast to RA, frequently show both erosive

destruction changes and new bone formation. In a recent study by Finzel, *et al* that examined the metacarpophalangeal (MCP) joints in patients with PsA and RA using microcomputerized tomography¹⁸, erosions occurred less frequently in PsA, whereas PsA was distinguished by prominent new bone formation over the MCP joint, with a crown of new bone or corona being observed in some patients. A summary of recently identified biomarkers for psoriatic disease is provided in Table 1.

Following discussion at the GRAPPA 2010 meeting, it was agreed that one critical area for future study is the identification of biomarkers of joint damage, including both erosive change and new bone formation, in patients with PsA. This would be consistent with the overall aims of the OMERACT biomarker subgroup, which plans to conduct studies of biomarkers of joint damage in RA, ankylosing spondylitis, and PsA. The RA biomarker study commenced mid-2011. A protocol for a PsA study was drafted and details of the protocol were to be discussed at the GRAPPA 2011 meeting in Naples, Italy.

REFERENCES

1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89-95.
2. de Vlam K, Gottlieb AB, FitzGerald O. Biological biomarkers in psoriatic disease. A review. *J Rheumatol* 2008;35:1443-8.
3. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. *J Rheumatol* 1998;25:198-9.
4. Radtke MA, Reich K, Blome C, Rustenbach S, Augustin M. Prevalence and clinical features of psoriatic arthritis and joint complaints in 2009 patients with psoriasis: Results of a German national survey. *J Eur Acad Dermatol Venereol* 2009;23:683-91.
5. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *Br J Dermatol* 2008;159:322-30.
6. Skoumal M, Haberhauer G, Fink A, Steiner A, Klingler A, Varga F, et al. Increased serum levels of cartilage oligomeric matrix protein in patients with psoriasis vulgaris: A marker for unknown peripheral joint involvement? *Clin Exp Rheumatol* 2008; 26:1087-90.
7. Alenius GM, Eriksson C, Rantapaa Dahlqvist S. Interleukin-6 and soluble interleukin-2 receptor alpha — Markers of inflammation in patients with psoriatic arthritis? *Clin Exp Rheumatol* 2009;27: 120-3.
8. Chandran V, Cook RJ, Edwin J, Shen H, Pellett FJ, Shanmugarajah S, et al. Soluble biomarkers differentiate patients with psoriatic arthritis from those with psoriasis without arthritis. *Rheumatology* 2010;49:1399-405.
9. van Kuijk AW, DeGroot J, Koeman RC, Sakkee N, Baeten DL, Gerlag DM, et al. Soluble biomarkers of cartilage and bone metabolism in early proof of concept trials in psoriatic arthritis: Effects of adalimumab versus placebo. *PLoS One* 2010;5(9) pii:e12556.
10. Fiocco U, Sfriso P, Oliviero F, Roux-Lombard P, Scagliori E, Cozzi

Table 1. Recently identified biomarkers for psoriatic disease.

Biomarker	Screening*	Disease Activity	Treatment Response	Radiographic Change†
Peripheral blood/serum/plasma				
Bone alkaline phosphatase				✓
C-reactive protein	✓	✓	✓	✓
Cartilage oligomeric matrix protein	✓	✓		
Ratio of C-propeptide of type II collagen to collagen fragment neopeptides Col2-3/4 (long mono)	✓			
Interleukin 6 (IL-6)	✓	✓		
Matrix metalloproteinase-3	✓	✓	✓	
Melanoma inhibitory activity		✓		
Macrophage-colony stimulating factor				✓
Osteoprotegerin	✓			
Circulating osteoclast precursors				✓
Receptor activator of nuclear factor kappa-B ligand				✓
Synovial fluid				
Chemokine (C-C motif) ligand 3		✓	✓	
IL-1		✓	✓	
IL-1 receptor antagonist		✓	✓	
IL-6		✓	✓	
IL-8		✓	✓	
Synovial tissue				
CD3-positive cells			✓	
Skin				
IL-17 pathway genes			✓	

* Screening indicates screening psoriasis patients for PsA. † Radiographic change indicates both erosions and new bone formation.

- L, et al. Synovial effusion and synovial fluid biomarkers in psoriatic arthritis to assess intraarticular tumor necrosis factor-alpha blockade in the knee joint. *Arthritis Res Ther* 2010;12:R148.
11. Zaba LC, Suarez-Farinas M, Fuentes-Duculan J, Nograles KE, Guttman-Yassky E, Cardinale I, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. *J Allergy Clin Immunol* 2009;124:1022-10.e1-395.
 12. Singh TP, Schon MP, Wallbrecht K, Michaelis K, Rinner B, Mayer G, et al. 8-methoxypsoralen plus ultraviolet A therapy acts via inhibition of the IL-23/Th17 axis and induction of Foxp3+ regulatory T cells involving CTLA4 signaling in a psoriasis-like skin disorder. *J Immunol* 2010;184:7257-67.
 13. Pontifex EK, Gerlag DM, Gogarty M, Vinkenoog M, Gibbs A, Burgman I, et al. Change in CD3 positive T-cell expression in psoriatic arthritis synovium correlates with change in DAS28 and magnetic resonance imaging synovitis scores following initiation of biologic therapy — A single centre, open-label study. *Arthritis Res Ther* 2011;13:R7.
 14. Reddy SM, Anandarajah AP, Fisher MC, Mease PJ, Greenberg JD, Kremer JM, et al. Comparative analysis of disease activity measures, use of biologic agents, body mass index, radiographic features, and bone density in psoriatic arthritis and rheumatoid arthritis patients followed in a large U.S. disease registry. *J Rheumatol* 2010;37:2566-72.
 15. Anandarajah AP, Schwarz EM, Totterman S, Monu J, Feng CY, Shao T, et al. The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. *Ann Rheum Dis* 2008;67:296-301.
 16. Dalbeth N, Pool B, Smith T, Callon KE, Lobo M, Taylor WJ, et al. Circulating mediators of bone remodeling in psoriatic arthritis: Implications for disordered osteoclastogenesis and bone erosion. *Arthritis Res Ther* 2010;12:R164.
 17. Ng CT, Gibbs A, Murray B, Brady JJ, Bresnihan B, Veale DJ, et al. Bone biomarkers and bone density measurements in patients with inflammatory arthritis prior to and following anti-TNF therapy [abstract]. *Arthritis Rheum* 2008;58 Suppl:S56.
 18. Finzel S, Englbrecht M, Engelke K, Stach C, Schett G. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. *Ann Rheum Dis* 2011;70:122-7.