Biological Biomarkers in Psoriatic Disease. A Review

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ABSTRACT. Biomarkers are important in clinical practice because they allow quantitative assessment of diagnosis, disease processes, and treatment response. However, because development of biomarkers lags significantly behind that of drug development, absence of new and appropriate markers may slow the development of patient-tailored targeted therapies. At the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), members of the biomarker committee discussed the possible use of biomarkers in psoriasis and psoriatic arthritis and reviewed the results of several studies of biomarkers in the pathogenesis, diagnosis, and treatment of both the inflammatory and dermatologic aspects of psoriatic disease. We review those discussions. (J Rheumatol 2008; 35:1443–8)

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PSORIATIC ARTHRITIS PSORIASIS BIOMARKERS

The US National Institutes of Health (NIH) Biomarkers and Surrogate Endpoint Working Group defines a biological biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention[1]. Biological biomarkers include markers for drug effect or response, as well as for diagnosis, prognosis, or physiologic status information, such as disease activity or damage not related to drug effect. The US Food and Drug Administration (FDA) distinguishes 3 context-specific types of biomarkers: known valid biomarker, probable valid biomarker, and possible valid biomarker, based on the available scientific data for the biomarker (available from http://www.fda.gov/cber/gdlns/pharmdtasub.htm).

The NIH Working Group developed a 3-class system for biomarkers:

- Type 0: Markers of the natural history of a disease that correlate longitudinally with known clinical indices, such as symptoms over the full range of disease states.
- Type I: Markers that capture the effects of an intervention in accordance with the mechanism of action of the drug, even though the mechanism might not be known to be associated with clinical outcome.
- Type II: Markers that are considered surrogate endpoints because change in that marker predicts clinical benefit. These biomarkers must be relevant to the mode of actions of the drug and the pathophysiology of the disease and are thus more difficult to develop compared with Type 0 or Type I[2]. Surrogate endpoints are intended to use clinical endpoints or hard outcome measures such as damage to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Biomarkers are important in clinical practice because they allow quantitative assessment of diagnosis, disease processes, and treatment response. They are used to select appropriate therapy and drug dosage to maximize effect, minimize toxicity, and monitor disease outcomes, and thus are the foundation of evidence-based medicine. However, because development of biomarkers lags significantly behind that of drug development, absence of new and appropriate markers may delay development of patient-tailored targeted therapies.

The development of new biomarkers is seriously hampered by conservative thinking, lack of quality control, and methodological issues such as inappropriate statistical analysis and validation. Within the rheumatology community under the umbrella of OMERACT (Outcome Measures in Rheumatology), a subcommittee is developing validation criteria for soluble biomarkers reflecting structural damage in rheumatoid arthritis (RA) and spondyloarthropathies (SpA)[3]. A special working group for the development of soluble biomarkers and synovial tissue biomarkers in psoriatic arthritis (PsA) is within the scope of the next OMERACT meeting 2008 (available from http://www.omeract.org/).

The techniques used to develop and measure biomarkers are diverse, e.g., *in vitro* analyses such as protein expression, gene patterns, or gene expression, and *in vivo* analyses such as those in functional imaging, which are still in early development in humans. Technologies available today may evaluate biochemical and chemical markers by proteomics and metabolomics; genetic markers using pharmacogenomics,

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gene expression profiles, systems biology, and single-nucleotide polymorphisms (SNP); and structural markers using classical molecular imaging techniques.

Possible Use of Biomarkers in Psoriatic Disease

Outcome or clinical endpoints in PsA include diagnosis, inflammation, prognosis, disease activity, disease severity, damage, disability, and quality of life (QOL). Recent specific instruments have been attributed to disease activity or damage, but for other domains the instruments are still under development or not yet validated. Moreover, some instruments assess more than one domain, and others include composite scores (e.g., QOL).

Fulfilling the OMERACT standards for validity (truth, feasibility, and discrimination) is a major concern. For some domains, no gold-standard instrument has been identified. Additionally, different studies have used different instruments, making cross-comparisons difficult. A better approach might be to define domains based on the biology of the disease and then to look for the outcome of different biological processes such as the inflammatory process or the tissue response including damage.

Biomarkers in PsA can be determined in different compartments of the human body such as blood (serum/cellular compartment), synovial fluid (plasma/cellular compartment), urine, and synovial tissue. The technological possibilities are expanding and include flow cytometry, reverse transcription-polymerase chain reaction (RT-PCR), ELISA, immunohistochemistry, *in situ* hybridization, and DNA microarray. Other technologies, such as proteomics, metabolomics, and microarray may help to identify novel candidate biomarkers.

Biomarkers in Psoriatic Arthritis

Most candidate biomarkers in PsA have been borrowed from RA, which implies similarities in outcome or disease process between RA and PsA; however, recent clinical and translational research questions this premise. Increasingly, data demonstrate the different disease processes in RA and PsA, including genetics, the inflammatory process, and disease outcome. Thus, this "copy-paste" approach may lead to inappropriate choices of biomarkers and subsequently to incorrect conclusions. Compared with other forms of rheumatic disease, only limited data are available about biomarkers in PsA. Serum markers and biomarkers in synovial tissue as surrogates for disease activity or damage are most frequently studied, but these studies are hampered by the use of RA as a control group.

Diagnosis. A few biomarkers associated with diagnosis have been studied in patients in clinical trials. Gene expression in peripheral blood mononuclear cells (PBMC) for nucleoporin 63 kDa distinguished PsA patients from controls. Overexpression of MAP3K3 followed by CACNA1S can discrimate PsA from RA[4]. Immunohistology of synovial tissue in PsA showed increased vascularity, CD3+ lymphocytes, and neutrophils compared with RA[5,6].

Disease activity. Biomarkers useful in monitoring disease activity must be increased in active disease, must correlate with disease activity, and must be sensitive to change. Most biomarkers of disease activity in PsA have not met these criteria.

Erythrocyte sedimentation rate (ESR), interleukin 6 (IL-6), IL-2R, IL-10, IL-1 receptor antagonist (IL-1RA), and hyaluronic acid have been studied in PsA, but only IL-1RA and ESR correlated with the number of swollen and tender joints, reflecting disease activity[7,8]. Hyaluronic acid correlated with the degree of skin involvement but not with the joint disease[9]. The proinflammatory protein S100A12 was increased in PsA serum but not in synovial fluid and was sensitive to change under treatment with methotrexate[10]. ESR and C-reactive protein correlated well with response to tumor necrosis factor-α (TNF-α) blockade at the group levels in patients with PsA[11], but not with cytokine levels[12]; matrix metalloproteinase-3 (MMP-3) was increased in PsA patients with active disease and correlated with increased inflammatory parameters[13]. A decrease of MMP2 and MMP9 correlated well with clinical improvement in PsA (Table 1)[14].

T lymphocyte subsets, which are increased in peripheral blood and synovial tissue in PsA, decreased with improvement in clinical signs following alefacept treatment[15].

More than 300 genes showed an altered expression in PBMC obtained from patients with active PsA. Genes associated with the suppression of the innate and acquired immune response had a reduced expression, while others such as thioreductin, S100A8, and S100A12 were increased. This latter finding corresponds with an increase in S100A12 previously demonstrated in the serum[4].

Most work for biomarkers of disease activity in PsA has been undertaken in synovial tissue. Histological and immunohistochemical features studied both before and after treatment intervention have included analyses of cellular infiltration such as number of T cells, B cells, macrophages, vessels, and adhe-

Table 1. Serum biomarkers for disease activity in psoriatic arthritis.

Biomarker	Increased	Correlated to Disease Activity	Sensitivity to Change
Soluble interleukin 2 receptor	+	—	—
Interleukin 10	+	—	—
Interleukin 6	+	—	—
Interleukin 1 receptor antagonist	+	+	—
Hyaluronic acid	+	—	—
S100A12 protein	+	ND	+
Matrix metalloproteinase-3	+	ND	ND
Erythrocyte sedimentation rate	+	?	+
C-reactive protein	+	?	+

sion molecule expression, effector enzymes, and signaling pathways. The results are summarized in Table 2[5,6,11,16-22].

Damage. Damage may occur in the cartilage or in the bone compartment, and may include change in bone mineral density (BMD), bone destruction, or new bone formation such as syndesmophyte formation or ankylosis. Studies of serum biomarkers in bone have shown no correlation between TNF-related apoptosis-inducing ligand (TRAIL) or osteoprotegerin (OPG) and low BMD in PsA. Increased levels of crosslinked telopeptide of collagen-I, urinary deoxypyridinoline (CTX-I), and OPG may reflect increased bone resorption but was countered by an increase in alkaline phosphatase, resulting in bone formation[23]. No longitudinal data are available.

Soluble IL-2 receptor correlates with the development of erosive disease in PsA[8]. Circulating osteoclasts are increased, may be a biomarker for erosive disease, and are sensitive to change following TNF-α blockade[24]. Polymorphisms in TNF-α and TNF-ß are significantly associated with joint erosions in PsA and progression of joint erosions in early PsA. TNF -α gene polymorphisms may be useful prognostic markers for damage[25]. Clinical improvement also correlates with reduction in serum cartilage oligomeric matrix protein levels, indicating reduction in cartilage loss[26].

Biomarkers in skin. Studies of the pathogenesis and treatment of psoriasis have greatly benefited from the fact that both psoriatic plaques and uninvolved skin are accessible to repeated biopsy. Several studies demonstrated important pathogenic roles of Th17 and Th1 T cells, plasmacytoid and myeloid dendritic cells, activated endothelial cells, and keratinocytes bearing the regenerative maturation phenotype[27-38]. Immunocytochemistry, flow cytometry, RT-PCR, and DNA array analyses have generated large lists of biomarkers, some of which have been validated in clinical trials with cyclosporin, phototherapy, calcipotriol, calcitriol, corticosteroids, retinoids, 6 thioguanine, alefacept, efalizumab, etanercept, and infliximab (Table 3)[30,31,33,39-52]. Biomarkers in skin have been instrumental for understanding the pathogenesis of psoriasis and mechanism of action of psoriasis therapies. Biomarkers have been used as surrogate treatment endpoints in early, short-term, proof of concept studies[38,45,53].

Immunocytochemical biomarkers include those identifying members of the inflammatory infiltrate (e.g., T cells, dendritic cells, neutrophils, macrophages), transcription factors [e.g., activated nuclear factor-κB (NF-κB)], and markers of keratinocyte activation or regenerative maturation (keratin K-16, Ki-67, filaggrin, involucrin, epidermal thickness, intercellular adhesion molecule-1, and HLA-DR expression). RT-PCR has demonstrated increased mRNA expression of multiple chemokines [e.g., IL-8, MIG (monokine inducible by interferon gamma), IP-10 (inducible protein-10), MIP3α (macrophage inflammatory protein3α)], cytokines (e.g., IL-12, IL-23, interferon-γ, IL-6, IL-1ß, IL-8, IL-22, IL-20),

Table 2. Changes in selected biomarkers in the synovial tissue of patients with psoriatic arthritis (PsA) treated with methotrexate or tumor necrosis factor-α blockade.

	Domain	Treatment	Controls	PsA
Kruithof 2005[5]	Diagnosis	—	RA	↑ Vascularity ↑ Neutrophils
Van Kuijk 2006[6]	Diagnosis	—	RA	↓ CD3 T cells
Kane 2004[16]	Active disease	MTX	Post R/	↓ T cells ↓ Macrophages ↓ Adhesion molecules ↓ IL8 gene expression
Goedkoop 2004[22]	Active disease	IFX/placebo 48 h	Post R/	↓ T cells ↓ Macrophages in sublining
Goedkoop 2004[21]	Active disease	IFX 4 wks	Post R/	↓ Cell infiltrate ↓ Blood vessels ↓ AlphaVbeta3 expression ↓ Adhesion molecules VEGF unchanged
Kruithof 2005[18]	Active disease SpA	ETC	Post R/	↓ Cell infiltrate (T cells and macrophages, not B cells) ↓↓ Macrophage subsets (CD68, CD163, MRP8, and MRP14) ↓ MMP3 and 9
Canete 2007[19]	Active disease	MTX	Post R/	↓ Lymphoid aggregates
Lories 2008[20]	Active disease	ETC	Post R/	↓ Composite histology score ↓pERK ↓pJUN ↓pp38

MTX: methotrexate; IFX: infliximab; ETC: etanercept; Post R: at the end of the treatment period; MRP8: migration inhibitory factor-rated protein 8; VEGF: subcutaneous vascular endothelial growth factor.

Table 3. Change in expression of selected biomarkers in clinical trials of biologics in psoriasis vulgaris.

Biomarker	Etanercept[27,55-57]	Infliximab[51,58]	Alefacept[30]	Efalizumab[31]
CD3	↓	↓	↓	↓
CD4	↓	↓	↓	↓
CD8	↓	↓	↓	↓
CD11c (myeloid dendritic cells)	↓	↓	↓	↓
CD83	↓	ND	↓	↓
Elastase (neutrophils)	↓	ND	ND	ND
Inducible nitric oxide synthase	↓	ND	↓	↓
Interleukin 12/23 p40	↓	ND	↓	ND
Interleukin 23 p19	↓	ND	↓	ND
Interleukin 22	↓	ND	ND	ND
Interleukin 17	↓	ND	ND	ND
Interferon-γ	↓	ND	↓	ND
Signal transducer and activator of transcription-1	↓	ND	↓	ND
Inducible protein 10	↓	ND	ND	ND
Monokine inducible by IFN-γ	↓	ND	↓	ND
Granzyme B	↓	ND	ND	ND
Keratinocyte (intercellular adhesion molecule-1 and/or HLA-DR)*	↓	↓	↓	↓
Interleukin 6	↓	ND	ND	ND
Interleukin 1ß	↓	ND	ND	ND
Interleukin 8	↓	ND	↓	ND
Macrophage inhibitory protein-3α	↓	ND	ND	ND
Activated nuclear factor-κB	↓	ND	ND	ND
Interleukin 20	↓	ND	ND	ND
Matrix metalloproteinase-12	↓	ND	ND	ND
Keratin K-16*	↓	↓	↓	↓
Epidermal thickness	↓	↓	↓	↓
Cleaved caspase-3	↑	↑	↑	ND

ND: not done; *↓ = ↓ or absent.

nuclear transcription factors (NF-κB, STAT-1), MMP-12, antimicrobial peptides, and keratin K-16. DNA array analysis identified over 1300 genes differentially expressed in psoriatic plaques versus nonlesional skin[54].

In conclusion, only limited data about biological biomarkers in psoriasis and psoriatic arthritis are available. There is an urgent need for a research agenda for development and validation of biomarkers in psoriatic disease.

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