The Journal of Rheumatology 2024;51 Suppl 2:74–6
doi:10.3899/jrheum.2024-0260
First Release July 15 2024

The Journal of Rheumatology

Biomarkers in Psoriasis and Psoriatic Arthritis: Where Are We Now?

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ABSTRACT. At the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual conference and trainee symposium, the status of psoriatic disease (PsD) biomarkers was discussed in a workshop. The significant heterogeneity of PsD causes disease management to be very challenging, but biomarkers can prove helpful in disease diagnosis, stratification, and precision medicine. Although a few potential biomarkers have been discovered, none have been fully validated. Recent studies have used omic technologies that show promise but need further verification and validation. Many challenges remain, but the anticipated results of studies being conducted by recently established large consortia may lead to the identification of clinically actionable biomarkers.

Key Indexing Terms: biomarkers, GRAPPA, precision medicine, psoriasis, psoriatic arthritis

At the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual conference and trainee symposium, a workshop discussed the status of biomarkers for psoriatic disease (PsD). Dr. Vinod Chandran presented why biomarkers are needed for management of PsD. He also discussed general concepts about biomarkers as well as the current status and future hopes of biomarkers for psoriasis (PsO) and psoriatic arthritis (PsA).

PsD is a heterogeneous inflammatory disease that primarily affects cutaneous and musculoskeletal structures.[1] The heterogeneity is reflected in the diverse clinical, imaging, and histopathological manifestations of the disease.[1-3] The disease course is also varied and unpredictable, with some patients having mild disease and others having more severe disease with periods of disease exacerbations and remission leading to joint damage, cardiovascular disease, mental health challenges, difficulty with day-to-day functions, and poor quality of life.[4,5] Response to treatment is unpredictable. Hence, biomarkers may help in the diagnosis, prognosis, and management of PsD.[6] Biomarkers would be essential for personalized medicine, especially given the heterogeneity of PsD.

A biomarker is a factor that can be objectively measured and evaluated as an indicator of normal biological or pathogenic processes or of pharmacologic responses to a therapeutic intervention.[7] Biomarkers can be useful for the prediction of disease state or progression. Molecular biomarkers are measurable or detectable based on their molecular characteristics and any modified versions of their analytes.[8] Biomarker use can be grouped into many categories including disease susceptibility, prognosis, diagnosis, monitoring, treatment choice and response, and safety, all of which are relevant for the management of PsD.[9,10]

There are at least 3 levels of medically related predictive factors: demographic, anatomic/cellular, and molecular. Medical predictions are necessary for 3 types of evaluations: risk (where the probability is much less than 100%), diagnosis predicting that the patient currently has the disease (where the probability would be close to 100%), and prognosis/outcome (where the probability is variable).[11] Biomarker-based prediction models should be thoroughly evaluated using measures for performance assessment such as sensitivity, specificity, false positive and negative rates, positive and negative predictive values, receiver-operating characteristic curves (ROCs), net reclassification improvement, and integrated discrimination improvement.[12] When using complex or artificial intelligence–generated models, transparency, explainability, generalizability, and ease of deployment are also important considerations. The biomarker pipeline of discovery is long and involves defining clinical endpoints, finding an appropriate biological factor to use as the

VC is supported by a salary award from the Department of Medicine, University of Toronto. As part of the supplement series GRAPPA 2023, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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VC has received research grants from AbbVie, Amgen, and Eli Lilly; has received honoraria for advisory board member roles from AbbVie, Amgen, BMS, Eli Lilly, Janssen, Novartis, and UCB; and his spouse is an employee of AstraZeneca. WL has received research grant funding from Amgen, Janssen, Leo, Novartis, Pfizer, Regeneron, and Trex Bio. KdV has received research grants from Amgen and has received honoraria for advisory board member roles from AbbVie, Amgen, BMS, Eli Lilly, Janssen, Novartis, and UCB.

This paper does not require institutional review board approval.

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Accepted for publication March 10, 2024.

biomarker, qualification, verification, validation, clinical assay development, regulatory approvals, and the assessment of clinical utility and economic analyses.[13]

Biomarker studies in PsD are in early stages, with no established markers for diagnosis, prognosis, or treatment response. In a recent systematic review, 124 candidate biomarker studies on PsA diagnosis and prognosis were reviewed.[14] They identified bone and cartilage turnover biomarkers, genetic markers, autoantibodies for diagnosis, acute-phase reactants, and bone and cartilage turnover biomarkers for disease activity or prognosis. These markers included cartilage oligomeric matrix protein (COMP/thrombospondin-5), matrix metalloproteinase 3 (MMP-3), and osteoprotegerin (OPG).[14]

Technologies are now available to obtain a large number of molecular measurements within a sample, tissue, or cell. These technologies, called "omic" technologies, allow us to obtain a snapshot of the underlying biology at a very high resolution. Genomics, transcriptomics, proteomics, epigenomics, and metabolomics are some examples. Omics-based approaches to discover biomarkers for PsD are ongoing. A genetic signature using 200 genetic markers was identified that provided an area under the ROC (AUROC) of 0.82 in distinguishing PsA from cutaneous PsO.[15] Studies have also identified proteins that distinguish PsA from rheumatoid arthritis (α2-HS glycoprotein, α1-antichymotrypsin, haptoglobin, haptoglobin-related protein, and RF C6 light chain [Vκ1]) as well as osteoarthritis (COMP, resistin, monocyte chemoattractant protein-1, and nerve growth factor).[16,17] Multiomic studies are currently being conducted, aided by machine learning methods that can combine cell type–specific gene and protein expression differences between PsA, cutaneous PsO, and healthy groups with 200 previously published genetic risk factors for PsA. Liu et al developed models achieving AUROC ≥ 0.87 when either classifying subjects among the 3 groups or specifically distinguishing PsA from cutaneous PsO.[18]

For biomarkers of treatment response, several studies examined the HLA-C*06:02 allele in PsO with conflicting results, though most indicate that HLA-C*06:02-positive patients respond better to ustekinumab, whereas HLA-C*06:02-negative patients respond better to adalimumab.[19,20] Interleukin (IL)-12 serum levels and IL-12B polymorphisms show promise as biomarkers of treatment response in PsO. Higher baseline C-reactive protein levels are associated with a better clinical response in PsA.[6] Treating patients with PsA using biologics selected according to phenotypic differences in peripheral helper T cells has been demonstrated to provide higher response rates compared to usual care.[21] Rho GTPase signaling pathway factors and beta-defensin 2 are associated with response to treatment with IL-17 inhibitors.[22,23]

Many challenges need to be overcome before biomarkers are available for use in clinical practice. Omic studies are beginning to identify markers for diagnosis, prognosis, and treatment response. Such studies require a better definition of clinical outcome as well as appropriate biospecimens such as synovial biopsies, synovial fluid, peripheral blood, and urine. There must be harmonizing of protocols between sites for consistency, reproducibility, deep phenotyping, biobanking, high-throughput platforms, data portals, integration, and analytics to develop precision medicine for improving PsD outcomes. Early health technology assessment and regulatory approvals will be required. Economic considerations may present barriers to using biomarkers for routine care in resource-poor settings. These challenges are now being addressed by large consortia such as the Health Initiatives in Psoriasis and Psoriatic Arthritis Consortium European States (HIPPOCRATES) and Accelerating Medicines Partnership Autoimmune and Immune-Mediated Diseases (AMP AIM) program.[24,25]

To summarize, biomarkers for defined clinical outcomes have the potential to improve clinical outcomes in patients with a heterogeneous condition like PsD. Although challenges exist, there is a concerted effort by multinational collaborations to overcome them. Members of GRAPPA are leading much of these efforts. It is likely that robust predictive and diagnostic markers for PsA, treatment response, disease activity, joint damage, and cardiovascular disease will be identified. This will hopefully lead to better short- and long-term outcomes for millions of people with PsD.

ACKNOWLEDGMENT

We thank DerMEDit (www.dermedit.com) for editing services in preparation of this manuscript.

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