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Discovery and Clinical Validation of C1M and C4M as Soluble Biomarkers for Diagnosis, Prognosis, and Symptom Prediction in Psoriatic Disease and Other Inflammatory Arthropathies

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ABSTRACT. Psoriatic disease (PsD) is a complex, heterogeneous disease with unmet medical needs in terms of its diagnosis, management, and prognosis. The identification of biomarkers could improve the implementation of precision medicine in PsD, but to date, none of these biomarkers have been clinically validated. Biomarkers can support clinical trials in several ways, including (1) diagnostics, (2) drug pharmacodynamics, (3) prognostics for patient selection and monitoring of drug efficacy, and (4) predictive models for clinical outcomes. Biomarkers can sometimes be used for both diagnosis and prognosis. Benefits of biomarkers use may include shorter duration of clinical trials, faster access to new treatments, and a personalized approach to disease management. Several potential biomarkers have recently demonstrated promise for use in PsD, including C1M, a serum biomarker reflecting collagen type I collagen degradation, and C4M, a type IV collagen metabolite, but clinical validation has not yet been completed. Here, and as presented at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2024 annual meeting, we summarize the status of biomarker discovery for PsD and their overlap with other musculoskeletal diseases such as rheumatoid arthritis and axial spondyloarthritis.

Key Indexing Terms: axial spondyloarthritis, biomarkers, GRAPPA, psoriasis, psoriatic arthritis, rheumatoid arthritis

Introduction

Psoriatic disease (PsD) is heterogeneous and, despite advances over the last several decades, unmet needs in terms of diagnosis, disease progression, response to treatment, and precision medicine persist.[1,2] Personalized medicine allows for a tailored approach to disease management, catalyzed by the integration of biomarkers, which are objective, quantifiable measures of a physiological or pathological process or response to treatment.[3,4]

Basics of biomarkers

Biomarker use extends beyond diagnostics to pharmacodynamics, prognostics, and development of predictive models.[3] Benefits of biomarkers, apart from routine clinical practice, may include increased drug development efficiency, shorter clinical trial duration—which may lead to faster access to a new treatment—and an individualized, stratified approach to symptom management.[5]

Key criteria for developing a successful biomarker include specificity, sensitivity, cost, feasibility, environmental stability, prompt detection, and reproducibility.[3,4] Biomarkers are classified by their origin as genetic, tissue-associated, or soluble.[6] Although a few potential biomarkers have been investigated in PsD, further verification and validation are required.[1,7-10]

There is growing interest in soluble biomarkers that reflect joint tissue remodeling and may therefore serve as potential biomarkers of joint damage. Soluble biomarkers can be detected from bodily fluids, such as peripheral blood or synovial fluid.[11] For example, collagen degradation products such as C1M and C4M may be useful as biomarkers of joint and skin damage in PsD.[12]

Soluble collagen biomarkers in chronic inflammatory musculoskeletal diseases

The extracellular matrix (ECM) is integral to the integrity of all tissues and organs. It is composed of 3 main classes of molecules: proteoglycans, adhesive glycoproteins, and fibrous proteins; the most abundant ECM protein is collagen, a fibrous protein.[11] Constituting 30% of all tissues, collagens are the supporting pillars of biological structures; 28 different types of collagens and 46 side chains exist, with type I collagen as the most abundant.[13]

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ECM remodeling is necessary for tissue homeostasis. Under inflammatory and profibrotic stimuli, abnormal ECM remodeling can lead to either fibrosis or fibrolysis (Figure).[11] Imbalanced ECM remodeling, such as during degradation of damaged tissues as a consequence of organ damage and disease activity, can generate protein fragments (neoepitopes) that can be released into the circulation that may serve as quantitative biomarkers. For instance, type I collagen can be degraded by several metalloproteinases, resulting in C1M, whereas other biomarkers are processed by cathepsin K (CTX-I [C-terminal telopeptide]) or internal fragments of type I collagen propeptides (ICTP [type I collagen degradation product] and PINP [procollagen type I N-propeptide]).[7] Similarly, type IV collagen degradation results in the production of C4M. Patients with psoriatic arthritis (PsA) and joint damage present with C1M and C4M release, signifying their potential relevance as biomarkers of PsA.[12,14]

Serological biomarker C1M in PsD

Approximately 30% of patients diagnosed with psoriasis (PsO) will develop PsA, but the prediction of which patients and the monitoring of disease progression remains challenging.[15,16] Holm Nielsen et al[14] investigated the potential use of collagen biomarkers in patients with PsD (PsO: n = 30; PsA: n = 30) compared with healthy donors (n = 41). C1M was significantly higher in PsA compared to healthy controls ($P < 0.001$). In addition, C1M was able to separate between patients with cutaneous PsO and those with PsA with an AUROC of 0.66, indicating that C1M may be a biomarker of joint involvement.[14]

In the phase III clinical trial DISCOVER-2, serum concentrations of ECM biomarkers C1M, C3M, C4M, C6M, PRO-C3, and PRO-C6 were evaluated at baseline and following treatment with the interleukin 23 inhibitor guselkumab in patients with active PsA. The aim with regard to biomarker development was to test C1M in patients with PsA at baseline and in response to guselkumab treatment. Results showed suppression of C1M in patients with PsA who responded to guselkumab treatment beginning at week 4. Moreover, C1M was significantly decreased in those who achieved the American College of Rheumatology (ACR) 20 response at week 24, suggesting that C1M could be related to improvement of joint symptoms and signs.[12]

Serological biomarker C4M in PsD

C4M, the serologic marker of type IV collagen metabolism, has been investigated as a biomarker of basement membrane turnover in patients with PsD.[12,17]

In a phase II clinical trial where patients with PsA were treated with the tyrosine kinase 2 inhibitor deucravacitinib, higher C4M levels were correlated with joint disease activity scores at baseline. Moreover, C4M levels were significantly reduced at week 16 vs baseline ($P < 0.01$) in patients responding to treatment, suggesting that C4M could serve as a biomarker for response to treatment with deucravacitinib in patients with joint involvement.[18]

Soluble collagen biomarkers in rheumatoid arthritis

Investigation of biomarkers in different chronic inflammatory musculoskeletal diseases has uncovered significant overlap between these conditions. Since there are similarities clinically and in imaging findings between PsA and rheumatoid arthritis (RA), including the presence of synovitis and bone erosions, biomarkers associated with RA may also have relevance for PsA.[19]

Although the CTX-I neoepitope measuring cathepsin K–mediated destruction of type I collagen is the standard measure for bone resorption, other biomarkers for tissue destruction have also been investigated for RA. The phase III, double-blind placebo-controlled, parallel group study LITHE (Tocilizumab Safety and the Prevention of Structural Joint Damage) assessed the efficacy of tocilizumab 4 mg/kg or 8 mg/kg

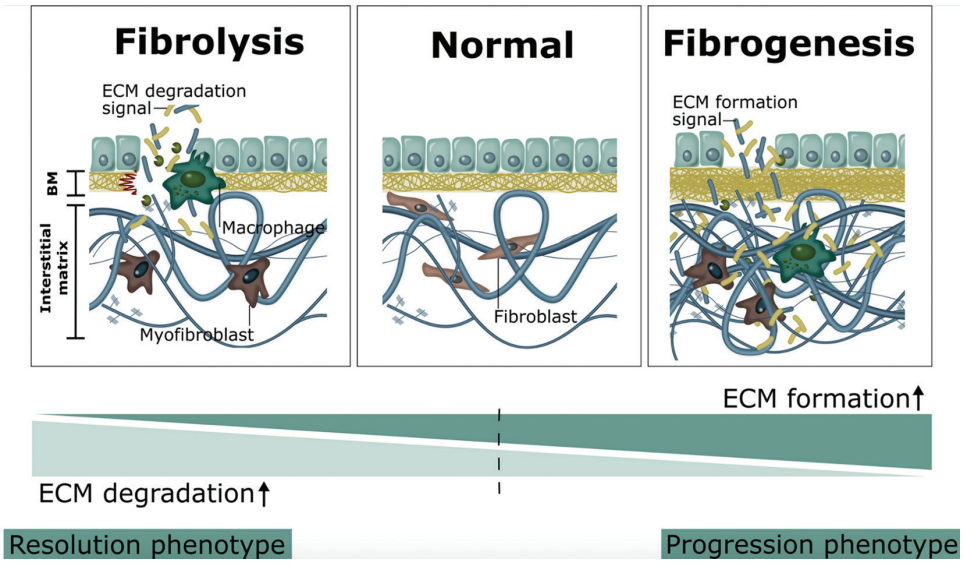

Figure. Imbalances in ECM remodeling. Reprinted with permission from Karsdal et al.[11] BM: basement membrane; ECM: extracellular matrix.

every 4 weeks in patients with RA on a stable dose of methotrexate. Several biomarkers were measured to assess their potential predictive value toward response to tocilizumab. Biomarkers with predictive value for tocilizumab response included baseline CTX-I/osteocalcin (OC; AUC 0.66, $P < 0.001$) and changes in C1M (AUC 0.67, $P = 0.007$), C2M (AUC 0.72, $P < 0.001$), C3M (AUC 0.63, $P = 0.02$), and the combination of the above biomarkers (AUC 0.81, $P = 0.002$). Early response to tocilizumab was most likely in patients with high bone turnover (CTX-I/OC) and low C2M were 6.8-fold ($P = 0.003$) more likely to have an early response to tocilizumab.[20]

C1M levels were also assessed as a biomarker of structural progression. At baseline, C1M was significantly correlated to C-reactive protein ($P < 0.001$), visual analog scale for pain ($P < 0.001$), Disease Activity Score in 28 joints (DAS28) based on erythrocyte sedimentation rate (ESR; $P < 0.001$), joint space narrowing (JSN; $P = 0.006$), and modified total Sharp score (mTSS; $P < 0.001$). In the placebo group, baseline C1M was also significantly correlated with ΔJSN at week 24 (R^2 0.09, $P < 0.001$) and at week 52 (R^2 0.27, $P < 0.001$), and with ΔmTSS at 24 weeks (R^2 0.01, $P = 0.002$) and strongly at 52 weeks (R^2 0.01, $P < 0.001$). Baseline C1M levels also correlated with worsening joint structure at the 12-month timepoint. The study concluded that serum C1M levels could potentially serve as a useful biomarker for patients with RA who need earlier and more aggressive treatment.[21]

In the OSKIRA-1 (Oral Syk Inhibition in Rheumatoid Arthritis 1) phase III trial, the potential use of soluble biomarkers of bone turnover, such as CTX-I and C1M, was assessed in patients with RA treated with fostamatinib, a small molecule Syk inhibitor. A decrease in serum levels of CTX-I was found after fostamatinib treatment, indicating a positive effect on bone resorption. However, there were no statistically significant differences in C1M levels in the fostamatinib treatment groups vs the placebo group. Overall, in the study, patients failed to reach the primary endpoint of preventing structural damage. Later experiments in ex vivo models of human synovial membranes to determine the cause of primary endpoint failure with fostamatinib in the clinical trial suggested that the dosage was too low to affect synovial membranes. This could have possibly been determined using CTX-1 as a biomarker of dose response in preclinical models, thus improving the OSKIRA-1 trial design through use of biomarkers. Biomarkers may be useful as a decision-making tool to aid drug development for RA and other diseases.[22]

Serological biomarkers C1M and C4M in axial spondyloarthritis

Axial involvement in patients with arthritis can be challenging to manage. In the TORTUGA trial, the Janus kinase 1 inhibitor filgotinib was assessed in patients with active axial spondyloarthritis (axSpA). C1M levels were significantly decreased by 45% as early as 1 week with filgotinib treatment compared to the placebo group. The decrease in C1M levels was maintained at weeks 4 and 12, supporting the potential use of C1M as a biomarker in the context of axial involvement and not only in peripheral arthritis.[23,24]

ECM blood-based biomarkers were also useful to assess response to the tumor necrosis factor inhibitor adalimumab in patients with axSpA. In 2 randomized, double-blind, placebo-controlled trials of patients with axSpA, the ASIM (Adalimumab in Axial Spondyloarthritis) and DANISH (Danish Multicenter Study of Adalimumab in Spondyloarthritis) cohorts, C1M and C4M levels declined after 6 or 12 weeks in some patients receiving adalimumab compared to placebo (all $P < 0.05$). Patients with clinically important improvement and/or major improvement in the Axial Spondyloarthritis Disease Activity Score (ASDAS) based on C-reactive protein had significantly higher C1M and C4M levels than patients with no to low improvement at baseline (all $P < 0.05$). The authors concluded that C1M and C4M were associated with response to treatment with adalimumab and may therefore be useful biomarkers for monitoring axSpA treatment responses.[25]

Conclusions

Although multiple biomarkers have been investigated in PsD, none have been clinically validated for use in clinical practice. Serum collagen biomarkers correlate with joint damage and response to various treatments, making them promising biomarkers for PsD. Further studies are needed to assess their potential use in patients with PsD and other similar diseases.

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ETHICS AND PATIENT CONSENT

Institutional review board approval and patient consent were not required.

PEER REVIEW

As part of the supplement series GRAPPA 2024, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

REFERENCES

1. Chandran V, Liao W, de Vlam K. Biomarkers in psoriasis and psoriatic arthritis: where are we now? J Rheumatol 2024;51 Suppl 2:74-6.

2. Winthrop KL, Mease P, Kerschbaumer A, et al. Unmet need in rheumatology: reports from the Advances in Targeted Therapies meeting, 2023. Ann Rheum Dis 2024;83:409-16.
3. Tan IJ, Podwojniak A, Parikh A, Cohen BA. Precision dermatology: a review of molecular biomarkers and personalized therapies. Curr Issues Mol Biol 2024;46:2975-90.
4. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95.
5. Mohamed L, Manjrekar S, Ng DP, Walsh A, Lopes G, Parker JL. The effect of biomarker use on the speed and duration of clinical trials for cancer drugs. Oncologist 2022;27:849-56.
6. Maksymowych WP, Landewe R, Boers M, et al. Development of draft validation criteria for a soluble biomarker to be regarded as a valid biomarker reflecting structural damage endpoints in rheumatoid arthritis and spondyloarthritis clinical trials. J Rheumatol 2007;34:634-40. Erratum in: J Rheumatol 2007;34:2506.
7. de Vlam K, Gottlieb AB, Fitzgerald O. Biological biomarkers in psoriatic disease. A review. J Rheumatol 2008;35:1443-8.
8. Corbett M, Ramessur R, Marshall D, et al. Biomarkers of systemic treatment response in people with psoriasis: a scoping review. Br J Dermatol 2022;187:494-506.
9. Ramessur R, Corbett M, Marshall D, et al. Biomarkers of disease progression in people with psoriasis: a scoping review. Br J Dermatol 2022;187:481-93.
10. Kar BR, Sathishkumar D, Tahiliani S, et al. Biomarkers in psoriasis: the future of personalised treatment. Indian J Dermatol 2024;69:256-63.
11. Karsdal MA, Daniels SJ, Holm Nielsen S, et al. Collagen biology and non-invasive biomarkers of liver fibrosis. Liver Int 2020; 40:736-50.
12. Schett G, Loza MJ, Palanichamy A, et al. Collagen turnover biomarkers associate with active psoriatic arthritis and decrease with guselkumab treatment in a phase 3 clinical trial (DISCOVER-2). Rheumatol Ther 2022;9:1017-30.
13. Karsdal MA, ed. Biochemistry of collagens, laminins and elastin: structure, function and biomarkers. Cambridge: Academic Press; 2016.
14. Holm Nielsen S, Magee C, Groen SS, et al. Differentiating patients with psoriasis from psoriatic arthritis using collagen biomarkers. Clin Exp Rheumatol 2023;41:574-80.
15. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957-70.
16. Pennington SR, FitzGerald O. Early origins of psoriatic arthritis: clinical, genetic and molecular biomarkers of progression from psoriasis to psoriatic arthritis. Front Med 2021;8:723944.
17. Gudmann NS, Junker P, Juhl P, et al. Type IV collagen metabolism is associated with disease activity, radiographic progression and response to tocilizumab in rheumatoid arthritis. Clin Exp Rheumatol 2018;36:829-35.
18. FitzGerald O, Gladman DD, Mease PJ, et al. Phase 2 trial of deucravacitinib in psoriatic arthritis: biomarkers associated with disease activity, pharmacodynamics, and clinical responses. Arthritis Rheumatol 2024;76:1397-407.
19. Gladman DD. Clinical features and diagnostic considerations in psoriatic arthritis. Rheum Dis Clin North Am 2015;41:569-79.
20. Bay-Jensen AC, Platt A, Siebuhr AS, Christiansen C, Byrjalsen I, Karsdal MA. Early changes in blood-based joint tissue destruction biomarkers are predictive of response to tocilizumab in the LITHE study. Arthritis Res Ther 2016;18:13.
21. Siebuhr AS, Bay-Jensen AC, Leeming DJ, et al. Serological identification of fast progressors of structural damage with rheumatoid arthritis. Arthritis Res Ther 2013;15:R86.
22. Kjelgaard-Petersen CF, Platt A, Braddock M, et al. Translational biomarkers and ex vivo models of joint tissues as a tool for drug development in rheumatoid arthritis. Arthritis Rheumatol 2018;70:1419-28.
23. Maksymowych WP, Østergaard M, Landewé R, et al. Filgotinib decreases both vertebral body and posterolateral spine inflammation in ankylosing spondylitis: results from the TORTUGA trial. Rheumatology 2022;61:2388-97.
24. Maksymowych W, Tian Y, Xu J, et al. Filgotinib treatment results in reduction of inflammatory and matrix remodeling biomarkers associated with disease in patients with ankylosing spondylitis [abstract]. Arthritis Rheumatol 2021;73 Suppl 9.
25. Port H, Holm Nielsen S, Frederiksen P, et al. Extracellular matrix turnover biomarkers reflect pharmacodynamic effects and treatment response of adalimumab in patients with axial spondyloarthritis-results from two randomized controlled trials. Arthritis Res Ther 2023;25:157.