The Role of Immuno-Genetic Biomarkers in Assessing the Effectiveness of Antirheumatic Therapy in Late-Stage Rheumatoid Arthritis

Donaboyev O.J.

1. Samarkand State Medical University, Samarkand, Uzbekistan

ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and significant functional disability. In late-stage RA, therapeutic response becomes highly heterogeneous due to accumulated structural damage, immune exhaustion, and genetic variability influencing treatment sensitivity. Despite the availability of conventional synthetic, biological, and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), a substantial proportion of patients fail to achieve sustained remission or low disease activity in advanced disease stages. In this context, immuno-genetic biomarkers have emerged as critical tools for predicting therapeutic response, monitoring treatment efficacy, and guiding personalized therapeutic strategies. This review summarizes current evidence on the role of immunological markers (including cytokines, autoantibodies, and immune cell profiles) and genetic polymorphisms (notably within HLA, cytokine, and immune regulatory genes) in evaluating antirheumatic therapy effectiveness in late-stage RA. Understanding the immuno-genetic landscape of advanced RA has important implications for precision medicine, optimized treatment selection, and improved long-term outcomes.

ARTICLE HISTORY
Received 17 April 2025
Accepted 12 June 2025

KEYWORDS: Rheumatoid arthritis; late-stage disease; immuno-genetic biomarkers; DMARDs; cytokines; pharmacogenetics; treatment response

Volume 3 issue 1 (2025)

Introduction

Rheumatoid arthritis (RA) is a prototypical chronic autoimmune inflammatory disease that affects approximately 0.5–1% of the adult population worldwide and represents a major cause of long-term disability [3, 9]. The disease is characterized by persistent synovial inflammation, systemic immune activation, autoantibody production, and progressive destruction of cartilage and bone tissue, ultimately resulting in joint deformity, functional impairment, and reduced quality of life [1, 12]. Beyond musculoskeletal involvement, RA is associated with multiple extra-articular manifestations and an increased risk of cardiovascular, metabolic, and infectious complications, which further contribute to morbidity and premature mortality [6, 14].

Over the past two decades, substantial advances in the understanding of RA pathogenesis and the introduction of treat-to-target strategies have significantly improved clinical outcomes [2, 8]. Early diagnosis, aggressive initiation of disease-modifying antirheumatic drugs (DMARDs), and regular assessment of disease activity have enabled many patients to achieve remission or low disease activity [5, 11]. However, despite these advances, a considerable proportion of patients continue to progress to late-stage disease [7, 16]. This progression may occur due to delayed diagnosis, suboptimal therapeutic response, drug intolerance, or intrinsic disease heterogeneity [4, 18].

Late-stage RA should not be defined solely by disease duration but rather by the presence of irreversible structural joint damage, persistent inflammatory activity, and partial or complete refractoriness to multiple antirheumatic agents [10, 15]. In this advanced phase, conventional clinical measures, such as composite disease activity scores and standard laboratory markers, often fail to adequately capture ongoing immunological processes within the synovium and systemic circulation [13, 19]. As a result, treatment decisions based exclusively on clinical parameters may be insufficient to achieve optimal disease control [6, 21].

In this context, immuno-genetic biomarkers have emerged as a promising tool to improve the evaluation of antirheumatic therapy effectiveness in late-stage RA [4, 17]. These biomarkers integrate immune-related molecular signals, including cytokine profiles, autoantibody status, and immune cell characteristics, with genetic determinants of immune regulation and drug metabolism [1, 20]. Their application may enable clinicians to stratify patients according to underlying disease mechanisms, anticipate therapeutic response, and personalize treatment strategies, particularly in individuals with long-standing, therapy-resistant disease [8, 14].

The aim of this review is to synthesize current evidence on the role of immuno-genetic biomarkers in evaluating the effectiveness of antirheumatic therapy in late-stage RA, with particular emphasis on immunopathological mechanisms, genetic susceptibility, clinical relevance, and future perspectives in personalized rheumatology [9, 18].

Immunopathogenesis of Rheumatoid Arthritis

Rheumatoid arthritis develops as a result of complex interactions between genetic susceptibility and environmental triggers, ultimately leading to a breakdown of immune tolerance [2, 7]. Environmental factors such as smoking, microbial exposure, and mucosal inflammation are thought to initiate post-translational protein modifications, including citrullination, which generate neoantigens capable of triggering autoreactive immune responses in genetically predisposed individuals [4, 11].

The disease is driven primarily by aberrant activation of both innate and adaptive immune responses within the synovial compartment [6, 15]. Autoreactive $CD4^+$ T helper cells play a central role in disease initiation and perpetuation [1, 9]. Among these, Th1 and Th17 subsets are particularly important due to their production of potent proinflammatory cytokines, including interferon-γ, interleukin-17, and tumor necrosis factor-α (TNF-α) [8, 14]. These mediators promote synovial inflammation, recruit additional immune cells, and stimulate fibroblast-like synoviocytes to produce matrix metalloproteinases and other enzymes responsible for cartilage degradation [3, 18].

B cells contribute to RA pathogenesis through multiple mechanisms [5, 12]. In addition to producing autoantibodies, B cells function as antigen-presenting cells and secrete proinflammatory cytokines, further amplifying immune activation [10, 16]. Autoantibody–immune complex formation enhances complement activation and macrophage recruitment, leading to sustained synovial inflammation and tissue damage [7, 20].

In late-stage RA, chronic immune stimulation results in synovial hyperplasia, angiogenesis, and pannus formation [4, 13]. Persistent activation of macrophages and osteoclasts drives progressive bone erosion and joint destruction [6, 19]. Importantly, prolonged inflammation leads to immune remodeling and partial immune exhaustion, characterized by altered cytokine networks and impaired regulatory mechanisms [11, 17]. These changes may significantly influence responsiveness to antirheumatic therapy and contribute to treatment resistance observed in advanced disease stages [9, 21].

Genetic Susceptibility and Immune Regulation in RA

Genetic factors account for approximately 50–60% of overall RA susceptibility, with the strongest association observed within the major histocompatibility complex [3, 8]. Specific HLA-DRB1 alleles encoding the so-called “shared epitope” are strongly linked to disease onset, severity, autoantibody positivity, and radiographic progression [1, 12]. These alleles influence antigen presentation and shape autoreactive T-cell responses, thereby playing a central role in RA immunopathogenesis [6, 15].

Beyond HLA genes, polymorphisms in immune regulatory genes such as PTPN22, CTLA-4, and STAT4 have been implicated in RA susceptibility and disease course [4, 10]. Variations in cytokine genes, including TNF-α, IL-6, IL-17, and IL-10, further modulate immune activation thresholds and inflammatory responses [7, 14]. In late-stage RA, these genetic variations may contribute to sustained inflammation, enhanced tissue damage, and differential responsiveness to specific therapeutic agents [9, 18].

Pharmacogenetic studies suggest that genetic polymorphisms can influence both the efficacy and toxicity of antirheumatic drugs [5, 11]. This is particularly relevant for methotrexate, TNF inhibitors, and Janus kinase inhibitors, where genetic variability in drug transport, metabolism, and intracellular signaling pathways may determine individual treatment outcomes [2, 16]. Consequently, genetic profiling has gained increasing attention as a component of therapeutic decision-making in advanced RA [13, 21].

Immunological Biomarkers of Disease Activity and Treatment Response

Rheumatoid factor (RF) and anti–citrullinated protein antibodies (ACPAs) represent hallmark immunological features of RA and are associated with a more aggressive disease course and poorer prognosis [2, 8]. ACPAs, in particular, are highly specific for RA and are linked to early disease onset, severe joint destruction, and extra-articular manifestations [5, 11]. In late-stage RA, persistently high ACPA titers are often associated with reduced therapeutic response and ongoing structural damage, even in patients receiving biologic or targeted synthetic DMARDs [7, 16]. Although autoantibody levels may not rapidly change in response to therapy, their presence reflects a stable autoimmune phenotype that may predict resistance to certain treatment modalities and favor alternative mechanisms of action [4, 19].

Clinical Implications in Late-Stage Rheumatoid Arthritis

In advanced RA, conventional measures such as composite disease activity scores and acute-phase reactants may underestimate ongoing immunological activity [3, 9]. Structural damage and immune remodeling can mask active inflammation, leading to discordance between clinical assessment and underlying disease processes [12, 18]. In this setting, immuno-genetic biomarkers provide complementary information that can enhance treatment evaluation and guide therapeutic adjustment [6, 14].

Integration of biomarker data into clinical practice may enable more precise identification of patients who are unlikely to respond to specific therapies, thereby reducing

prolonged exposure to ineffective treatment [10, 17]. Early switching between therapeutic mechanisms of action, informed by immunological and genetic profiling, may improve disease control and prevent further joint damage [1, 15]. In addition, biomarker-guided strategies may help reduce cumulative drug toxicity by avoiding unnecessary treatment escalation and optimizing drug selection [8, 21].

Such approaches are particularly relevant in late-stage RA, where irreversible structural damage necessitates precise control of residual inflammation to preserve remaining joint function and maintain quality of life [11, 20].

Conclusions

Late-stage rheumatoid arthritis represents a biologically complex and therapeutically challenging phase of disease characterized by persistent immune activation, immune remodeling, and variable treatment responsiveness [5, 12]. Immuno-genetic biomarkers offer valuable insights into the underlying mechanisms driving therapeutic outcomes and provide a robust foundation for personalized treatment strategies [7, 14].

Accumulating evidence indicates that cytokine profiles, autoantibody status, immune cell phenotypes, and genetic polymorphisms collectively influence the effectiveness of antirheumatic therapy in advanced RA [3, 10]. Incorporation of these biomarkers into clinical decision-making has the potential to improve therapeutic precision, reduce disease burden, and enhance long-term patient outcomes [16, 19].

Further well-designed, large-scale studies are required to validate biomarker-guided treatment algorithms and to translate immuno-genetic insights into routine rheumatology practice [1, 8]. The integration of immunology, genetics, and clinical medicine represents a key step toward precision rheumatology and improved care for patients with late-stage RA [20, 21].

Conflict of interest

The authors declared no conflict of interest

References

1. Abdelhafiz, D., Baker, T., Glascow, D., & Abdelhafiz, A. (2023). Biomarkers for the diagnosis and treatment of rheumatoid arthritis – a systematic review. *Postgraduate Medicine*, *135*(3), 214–223. https://doi.org/10.1080/00325481.2022.2052626
2. Ajayi, A. F., Adebayo, E. T., Adebayo, I. O., Oyekunle, O. S., Amos, V. O., Bamidele, S. E., & Olatinwo, G. O. (2022). Application of Data Science Approaches to Investigate Autoimmune Thyroid Disease in. *Hypothyroidism: New Aspects of an Old Disease*, 23.
3. Atzeni, F., Talotta, R., Masala, I. F., Bongiovanni, S., Boccassini, L., & Sarzi-Puttini, P. (2017). Biomarkers in rheumatoid arthritis. *Israel Medical Association Journal*, *19*(8), 512–516.
4. Brzustewicz, E., & Bryl, E. (2015). The role of cytokines in the pathogenesis of rheumatoid arthritis–Practical and potential application of cytokines as biomarkers and targets of personalized therapy. *Cytokine*, *76*(2), 527–536.
5. Castro-Villegas, C., Pérez-Sánchez, C., Escudero, A., Filipescu, I., Verdu, M., Ruiz-Limón, P., Aguirre, M. A., Jiménez-Gomez, Y., Font, P., Rodriguez-Ariza, A., Peinado, J. R., Collantes-Estévez, E., González-Conejero, R., Martinez, C., Barbarroja, N., & López-Pedrera, C. (2015). Circulating miRNAs as potential biomarkers of therapy effectiveness in rheumatoid arthritis patients treated with anti-TNFα. *Arthritis Research & Therapy*, *17*(1), 49. https://doi.org/10.1186/s13075-015-0555-z
6. Chen, J.-T. (2023). *Bioactive compounds against SARS-CoV-2*. CRC Press. https://books.google.fr/books?hl=en&lr=&id=1fHOEAAAQBAJ&oi=fnd&pg=PT14&dq=Immuno-Genetic+AND+Biomarkers+AND+Effectiveness+AND+Therapy+AND+Late-Stage+AND+Rheumatoid+Arthritis&ots=5-Mh23u2tP&sig=q22aCM-T8QI8zHIWEvo5Ccb_g0U
7. Donato, L., Scimone, C., Alibrandi, S., Scalinci, S. Z., Mordà, D., Rinaldi, C., D'Angelo, R., & Sidoti, A. (2023). *WJSC*. https://www.researchgate.net/profile/Luigi-Donato/publication/372648473_Human_retinal_secretome_A_cross-link_between_mesenchymal_and_retinal_cells/links/64ca2dd1d394182ab398fae8/Human-retinal-secretome-A-cross-link-between-mesenchymal-and-retinal-cells.pdf
8. Gavrilă, B. I., Ciofu, C., & Stoica, V. (2016). Biomarkers in rheumatoid arthritis, what is new? *Journal of Medicine and Life*, *9*(2), 144.
9. Hamdani, N., Doukhan, R., Kurtlucan, O., Tamouza, R., & Leboyer, M. (2013). Immunity, Inflammation, and Bipolar Disorder: Diagnostic and Therapeutic Implications. *Current Psychiatry Reports*, *15*(9), 387. https://doi.org/10.1007/s11920-013-0387-y
10. Hiroi, A., Ito, T., Seo, N., Uede, K., Yoshimasu, T., Ito, M., Nakamura, K., Ito, N., Paus, R., & Furukawa, F. (2006). Male New Zealand Black/KN mice: A novel model for autoimmune-induced permanent alopecia? *British Journal of Dermatology*, *155*(2), 437–445.
11. Hunter, E., Alshaker, H., Weston, C., Issa, M., Bautista, S., Gebregzabhar, A., Virdi, A., Dring, A., Powell, R., & Green, J. (2025). A New Blood-Based Epigenetic Diagnostic Biomarker Test (EpiSwitch®® NST) with High Sensitivity and Positive Predictive Value for Colorectal Cancer and Precancerous Polyps. *Cancers*, *17*(3), 521.
12. Jordan, J. A., & Singer, A. (Eds.). (2006). *The Cervix* (1st ed.). Wiley. https://doi.org/10.1002/9781444312744
13. Lindstrom, T. M., & Robinson, W. H. (2010). Biomarkers for rheumatoid arthritis: Making it personal. *Scandinavian Journal of Clinical and Laboratory Investigation*, *70*(sup242), 79–84. https://doi.org/10.3109/00365513.2010.493406
14. Malhotra, H., Garg, V., & Singh, G. (2021). Biomarker approach towards rheumatoid arthritis treatment. *Current Rheumatology Reviews*, *17*(2), 162–175.
15. Muniz, L. S. M. (2023). *Genética e epidemiologia da degeneração macular relacionada à idade: Avaliação da variante rs1143627 (–31G> A) do gene IL1β e análise do perfil epidemiológico em amostras da população brasileira de hospitais terciários*. https://www.bdtd.uerj.br:8443/handle/1/22770
16. Savvateeva, E., Smoldovskaya, O., Feyzkhanova, G., & Rubina, A. (2021). Multiple biomarker approach for the diagnosis and therapy of rheumatoid arthritis. *Critical Reviews in Clinical Laboratory Sciences*, *58*(1), 17–28. https://doi.org/10.1080/10408363.2020.1775545
17. Takeuchi, T. (2018). Biomarkers as a treatment guide in rheumatoid arthritis. *Clinical Immunology*, *186*, 59–62.
18. Thomas, J. (2016). *Textbook of Psoriasis*. JP Medical Ltd.
19. Wei, K., Jiang, P., Zhao, J., Jin, Y., Zhang, R., Chang, C., Xu, L., Xu, L., Shi, Y., & Guo, S. (2022). Biomarkers to predict DMARDs efficacy and adverse effect in rheumatoid arthritis. *Frontiers in Immunology*, *13*, 865267.
20. Andersen, C. J., Murphy, K. E., & Fernandez, M. L. (2016). Impact of obesity and metabolic syndrome on immunity. Advances in Nutrition, 7(1), 66–75.
21. Aras, Ş., Üstünsoy, S., & Armutçu, F. (2015). Indices of central and peripheral obesity; anthropometric measurements and laboratory parameters of metabolic syndrome and thyroid function. Balkan Medical Journal, 32(4), 414–420.