ISSN 2664-4169 (Print) & ISSN 2664-7923 (Online)
South Asian Research Journal of Biology and Applied Biosciences
Abbreviated Key Title: South Asian Res J Bio Appl Biosci

| Volume-8 | Issue-1 | Jan-Feb -2026 | **DOI: https://doi.org/10.36346/sarjbab.2026.v08i01.011**

Review Article

A Review on the Role of IL-12 and IL-17 Levels in the Incidence of Rheumatoid Arthritis (RA)

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Article History
Received: 20.12.2025
Accepted: 16.02.2026
Published: 20.02.2026

Abstract: Rheumatoid arthritis (RA) is chronic systemic autoimmune inflammatory disorder, characterized with progressive synovitis, cartilage damage and bone resorption. Inflammation is a complex immune response and cytokines play an important role. Interleukin-12 (IL-12 and interleukin 17(A IL-17) are now known to be key players of the pathogenesis in RA. IL-12 promotes differentiation of T helper type 1 (Th1) cells and IFNγ production, whereas Th17-induced IL-17 coordinates inflammatory cascades leading to articular destruction. In this review we detail the data from 2015 to 2026 supporting roles for IL-12 and IL-17 in the pathogenesis of RA, serum and synovial levels, association with disease activity, and therapeutic efficacy. Understanding these cytokines is helpful for establishing new- agents and personalized therapies.

Keywords: Rheumatoid Arthritis, IL-12, IL-17, Th17 Cells, Cytokines, Therapeutic Targets.

INTRODUCTION

Rheumatoid arthritis (RA) is a symmetric polyarthritis involving 0.5-1% of the population worldwide, and leads to persistent synovial inflammation resulting in cartilage damage as well as bone resorption (Smolen *et al*., 2016). Along with joint phenotypes, extra-articular co-morbidities and complications associated with RA, such as cardiovascular disease and pulmonary fibrosis significantly impact QoL (Gao *et al*., 2024).

RA pathogenesis is a result of complex interaction between genetic susceptibility and environment factors that trigger immune dysregulation and loss of self-tolerance. Approximately 80% of all patients are seropositive for autoantibodies such as rheumatoid factors (RF) and ACPA (Picerno *et al.,* 2015). The disease starts with a preclinical phase of autoantibody formation and extends to clinical onset as symptomatic synovitis (McInnes *et al*., 2017).

Cytokines are key players in the inflammatory process of RA. Cytokines such as Tumor Necrosis Factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) have been targeted with therapeutic success, but the inadequate response in many patients indicates that alternative pathways involving cytokines are likely to be involved in disease pathogenesis (Furst & Emery, 2014). Mechanisms of the regulation of the immune response have been invoked in this context, leading to focus on IL-12 and IL-17 pathways.

Being incomparable in autoimmune pathogenesis, the identification of T helper 17 (Th17) cells has changed knowledge completely. Th17 cells secrete IL-17A, IL-17F, IL-21 and IL-22, with IL-17A being a signature cytokine (Furst & Emery, 2014). IL-23 sequesters Th17 and IL-12 determines Th1. This review summarizes recent advances in understanding of the role of IL-12 and IL-17 in RA from 2015 to 2026 with regard to their levels, clinical correlations, pathogenic mechanisms, and potential therapeutics.

1. IMMUNOBIOLOGY OF IL-12 AND IL-17

IL-12 is a p35/p40 heterodimeric cytokine (IL-12p70). IL-12 is produced by dendritic cells and macrophages. It binds the IL-12 receptor complexes on T cellsand natural killer (NK) cells, inducing JAK-STAT signaling (Gao *et al.*, 2024). IL-12 promotes Th1 differentiation and IFN-γ expression, enhancing macrophage activation and cell-mediated immunity. p40 is also part of IL-23 and thus generating the network pathways of cytokines.

The best-characterised IL-17 family member is IL-17A, which is made by Th17 cells matured in the presence of TGF-β, IL-6, IL-21 and/or IL-23. Other include sources γδ T cells, ILC3 and synovial mast cells (Furst & Emery, 2014). IL-17RA on fibroblasts, chondrocytes and osteoblasts by IL-17A ligation activates NF-κB and MAP kinases pathways. This in turn leads to chemokines (CXCL8, CXCL1), cytokines (IL-6, G-CSF) and matrix metalloproteinases (MMPs) release as well as recruitment of neutrophils and amplification of inflammation and tissue destruction (Samaan *et al*., 2024).

Th1 response is a process stimulated by IL-12 and Th17 cells are kept alive by IL-23. Both pathways are involved in RA pathogenesis and Th1 and Th17 responses coexist in inflamed synovium due to partially non-redundant shared mechanisms (Kunwar *et al*., 2016).

2. IL-12 AND IL-17 IN RA

2.1 Levels of Serum IL-12 in RA Patients

Serum IL-12 level could be higher in RA patients than that in healthy controls. Paradowska-Gorycka *et al*., (2017) detected serum IL-12p70 among 634 RA patients compared to 341 healthy controls ($P < 0.0001$), where it was associated with tender/swollen joint, extra-articular manifestations, CRP and platelets levels. An analysis of seropositive arthralgia patients that progressed to RA showed trends towards higher baseline IL-12, implicating IL-12 in disease transition (Lubbers *et al*., 2016).

Polymorphisms of the IL12B gene (rs3212227, rs17860508) correlate with the susceptibility to RA and IL-12 production. These SNPs are associated with an elevated risk of RA and higher serum IL-12 levels, indicating the genetic factors that contribute to individual variability in disease (Paradowska-Gorycka *et al*., 2017).

2.2 Concentrations of IL-17 in Serum and Synovial Fluid

IL-17A is greatly increased in the serum and synovial fluid of RA. Mahmoud *et al*., (2020) reported serum IL-17 11.25 ± 9.67 pg/mL in RA vs 0.6 ± 1.4 pg/mL controls ($p = 0.0002$). There was a positive correlation between synovial fluid and serum concentrations of C1, 2C ($r = 0.5$, $p = 0.005$), indicating local joint production and extra-articular release.

The relationship between IL-17 and disease activity was extensively investigated. There were some studies showing a positive correlation between serum IL-17 and DAS28 (Clinical Disease Activity Score), CRP, ESR (Samaan *et al*., 2024). Interestingly, Disclosure of the mechanism driving the decline in IL-17 levels with disease severity remains elusive, a alone some studies reported an association between increased production of cellular exhaustion or feedback inhibition explain this phenomenon (Andonova *et al*., 2017).

2.3 Links with Disease Activity and Severity

IL-12 has not consistently correlated with disease activity parameters in contrast to IL-17, which have been reported to strongly correlate with DAS28 and HAQ disability (Elhewala *et al*., 2015; Pradhan *et al*., 2024). Consistent with a role of IL-17 in driving inflammation, but not structural damage is the fact that recent musculoskeletal ultrasound studies have reported an association between IL-17 and active synovitis, but not established erosions (Al-Bogami *et al*., 2025).

Severity on radiograph has inconsistent association with any cytokines between the studies. Some studies describe positive relations of IL-17 with radiographic damage (Mahmoud *et al*., 2020) or stronger correlations with the presence of inflammatory parameters. These variations may be due to diversities in duration of disease, use of treatment and study population (Al-Bogami *et al*., 2025).

3. PATHOGENIC MECHANISMS IN RA

3.1 Cellular Sources and Targets

Various immune cells such as T, B, and macrophages, dendritic cells (DCs), and fibroblast-like synoviocytes (FLS) are present in the rheumatoid synovium. Dendritic cells and macrophages generate IL-12, Th1 differentiation and IFN-γ production, induce positive feedback of inflammatory loops (Gao *et al*., 2024). IL-12 also drives T follicular helper cell differentiation in preclinical RA that promotes B cell activation and autoantibody production (Nakayama *et al*., 2025).

IL-17 is produced by Th17 cells and mast cells, and regulates FLS, chondrocytes and osteoblasts. FLS react to this challenge by secreting IL-6, IL-8 and MMPs, which induce synovial hyperplasia and cartilage degradation. Chondrocytes are stimulated to enhance MMP production and suppress proteoglycan synthesis, which amplifies the degradation of cartilage. IL-17 induces osteoclastogenesis through upregulation of RANKL and downregulation of OPG, accounting for bone destruction in RA (Furst & Emery, 2014).

3.2 Synergistic Interactions

IL-17 collaborates with TNF-α very effectively for the production of pro-inflammatory mediators. Co-stimulation generates additive IL-6, IL-8, and MMP levels than alone, thereby single pathway blockade is not so effective (Furst& Emery, 2014). IL-12 can act together with IL-18 to enhance IFN-γ production in T cells and NK cells,achieveing an effective inflammatory response in rheumatoid synovium (Yamamura *et al*., 2003).

Although IL-12-induced IFN-γ is theoretically capable of inhibiting Th17 differentiation, however, established Th17 cells in RA joints may be refractory to this regulation, thus permitting both Th1 and Th17 responses to coexist and synergistically contribute to inflammation (Furst & Emery, 2014).

3.3 Joint Destruction Mechanisms

IL-17 stimulates MMP release (MMP-1, MMP-3, and MMP-13) leading to cartilage degradation as well as suppresses matrix secretion by chondrocytes. In animal studies, cartilage destruction is severe when IL-17 is overexpressed, and joint destruction is inhibited by IL-17 neutralization (Furst & Emery, 2014).

MDB with bISE-IL-17 promotes RANKL expression on osteoblast cell and FLS, but also decreases the OPG, resulting in a promotion of the ratio of RANKL/OPG for exertion on osteoclastogenesis and bone resorption. Radiographic studies relate to increased IL-17 levels with erosion progression, and current ultrasound data show an even stronger association with active synovitis than osteophytes (Al-Bogami *et al.,* 2025).

IL-12 is indirectly involved in joint destruction via IFN-γ production and macrophage activation. Furthermore, upon activation TNF-α and IL-1β are modified that is able to increase other proinflammatory cytokines in addition with chemokines (Richeldi *et al*., 2004) this creates a net production of produced pro-inflammatory cytokine arised by activated macrophages (Gao *et al*., 2024).

4. THERAPEUTIC INTERVENTIONS IN IL-12 AND IIL-17

Inversely, IL-17 Blockade in Clinical Trials 4.1 Reasons for the Development of New Treatment Options A-Based Treatments Squalene acetyltransferase-Inhibitors.

IL-17 pathway targeting for RA has been tried with variable findings in a number of clinical trials. Secukinumab (anti-IL-17A) has demonstrated effectiveness in Phase II where a high ACR20 had been observed, particularly in biologic-naïve patients (Burmester *et al*., 2016). But that is not what we saw with the Phase III trials in TNF-inhibitor failures. Although some were statistically better than placebo, the effects size was small and no other drug was inferior to comparators such as abatacept (Blanco *et al*., 2017; Tahir *et al*., 2017). One Phase III trial did not reach superiority over placebo (Dokoupilová *et al*., 2018).

Phase II efficacy was also demonstrated for ixekizumab but RA development was abandoned in favor of psoriasis and psoriatic arthritis where the response profile was superior (Genovese *et al*., 2014). The modest success of RA, despite biological plausibility is a reflection of the redundancy and complexity of the cytokine network with various pathways filling in for IL-17 inhibition and heterogeneity of patients (only sub-groups are IL-17 driven) along with TNF-α/IL-6 domination in diagnosed RA (McInnes, 2020).

Of particular interest, IL-17 blockade has demonstrated impressive efficacy in psoriatic arthritis and ankylosing spondylitis; this suggests a diversity of pathogenic drivers across inflammatory arthritides and RA's relative complexity (McInnes, 2020).

4.2 Combination and Dual-Targeting Strategies

Due to the limitation of single-cytokine blockade, dual-targeting strategies have been developed. ABT-122, dual TNF-α and IL-17A blockade showed Phase I safety with reduced inflammatory chemokines (CXCL9, CXCL10 and CCL23) (Fleischmann *et al.,* 2017). However, additional RA development was not continued due to what were probably efficacy discrepancies in these larger studies.

Targeting IL-12 and IL-23 via the shared p40 subunit (ustekinumab) or selective IL-23 blockade (guselkumab) demonstrated psoriasis/psoriatic arthritis efficacy but modest RA effects. In selective IL-23 inhibitor trial, there was no

improvement in RA symptom, indicating that IL-23 is likely more essential as a disease initiator than a sustainer of the establish disease (Smolen *et al*., 2017).

4.3 The Next Frontier and Individualized Strategies

The responses to IL-17 inhibition are diverse, and patient stratification is needed. Approaches range from the stratification based on genetic findings in HLA-DR2 alleles having some secukinumab response correlation (Blanco *et al*., 2017), and profiling of synovial tissue generated pathotypes (lymphoid, myeloid) that may show different degrees of IL-17 pathway dependence (Gao *et al*., 2024).

Biomarker-informed treatment algorithms, which include baseline cytokine fingerprints, frequencies of circulating Th17 cells and genetic markers are a promising next step. Machine learning integrated multi-omic data can eventually predict response for each patient, in order to choose the most effective treatment and avoid unnecessary exposure to ineffective therapy. Similar to melanoma, therapy could be matched to synovial phenotype using needle biopsy with immunohistochemistry or gene expression profiling. 25 High IL-17 expressors could potentially benefit the most (Gao *et al*., 2024).

CONCLUSION

IL-12 and IL-17: the yin and yang of arthritis. Available data (2015-2026) report the significant increase of both cytokines in serum and synovial fluid from RA patients, with variable associations with activity and structural damages. IL-12 promotes Th1 differentiation and IFN-a production, which results in macrophage activation and chronic inflammation. IL-17 initiates a cascade of inflammation via synovial fibroblasts, chondrocytes and osteoclasts which directly result in cartilage destruction and bone erosions.

In contrast, IL-17 inhibitors were not successful in RA clinical trials despite biologicals advancement of the therapeutic approach and while being effective for psoriatic arthritis and axial spondyloarthritis. This disparity highlights heterogeneous RA and suggests that the pathogenesis of this disease occurs via multicircular redundant cytokine networks rather than single-pathway blockade. Partial successes do not question the pathogenic relevance of IL-17, but underscore the need for patient stratification and combination strategies.

This review will further dissect RA subpopulations highly dependent on IL-17 pathway there through synovial phenotyping, genetic and complete biomarker analysis. The use of multi-omics integration may enable precision medicine based on individual pathology aimed at optimizing treatment. Dual-targeting schemes and their combination with DMARDs should be studied. An understanding of the kinetics of cytokines throughout disease stages may identify windows for beneficial intervention.

While IL-12 and IL-17 have not yet become established target therapies in RA, new research work is helping to refine the pathological pathways. Best in the 10 Supporting Information Figure S1RA). Recent breakthroughs in imaging, single-cell profiling and longitudinal observation have revealed how cytokines are regulated and mediate their activity in human RA. The above efforts combined with work in clinical trials, would enable the field to construct rational personalized approaches for manipulation of the IL-12/IL-23/Th17 axis resulting in matching of interventions to appropriate patients and disease stages based on comprehensive pathobiologic profiling.

REFERENCES

- Al-Bogami, S. H., Abo-Elghar, M., & El-Shafey, A. M. (2025). Serum interleukin-17 and its association with inflammation and bone remodeling in rheumatoid arthritis and hand osteoarthritis: Insights from musculoskeletal ultrasound. *Diagnostics*, *15*(11), 1335. https://doi.org/10.3390/diagnostics15111335
- Andonova, S., Apostolova, I., Stanilova, S., Rashkov, R., & Rashkova, M. (2017). Serum and synovial concentration of IL-17A in rheumatoid arthritis patients. *Annals of the Rheumatic Diseases*, *76*(Suppl 2), 1130-1136.
- Blanco, F. J., Möricke, R., Dokoupilová, E., Codding, C., Neal, J., Andersson, M., Rohrer, S., & Richards, H. (2017). Secukinumab in active rheumatoid arthritis: A phase III randomized, double-blind, active comparator- and placebo-controlled study. *Arthritis & Rheumatology*, *69*(6), 1144-1153. https://doi.org/10.1002/art.40070
- Burmester, G. R., Durez, P., Shestakov, A., Genovese, M. C., Schulze-Koops, H., Klopsch, T., Fonseca, J. E., Luo, Z., Pappu, R., & Patel, A. M. (2016). Efficacy and safety of secukinumab in patients with rheumatoid arthritis: Primary results of a randomized, double-blind, placebo-controlled phase II study. *Arthritis & Rheumatology*, *68*(Suppl 10).
- Dokoupilová, E., Aelion, J., Takeuchi, T., Goez, J., Meaux-Ruault, N., & Mistry, N. (2018). Secukinumab treatment in patients with active rheumatoid arthritis and inadequate response to anti-TNF therapy: Phase 3 study results. *Arthritis & Rheumatology*, *70*(Suppl 10).

- Elhewala, A. E. I., Soliman, S. G., Labeeb, A. A., Mousa, W. A., & Salah, D. (2015). Interleukin-17 level in rheumatoid arthritis patients and its relation to disease activity: A clinical and ultrasound study. *Egyptian Rheumatologist and Rehabilitation*, *42*(4), 183-187. https://doi.org/10.4103/1110-161X.171912
- Fleischmann, R. M., Wagner, F., Kivitz, A. J., Mansikka, H. T., Shah, M. H., Kanik, K. S., & Connolly, S. E. (2017). Safety, tolerability, and pharmacodynamics of ABT-122, a tumor necrosis factor- and interleukin-17A-targeted dual variable domain immunoglobulin, in patients with rheumatoid arthritis. *Arthritis & Rheumatology*, *69*(12), 2283-2291. https://doi.org/10.1002/art.40319
- Furst, D. E., & Emery, P. (2014). Rheumatoid arthritis pathophysiology: Update on emerging cytokine and cytokine-associated cell targets. *Rheumatology*, *53*(9), 1560-1569. https://doi.org/10.1093/rheumatology/ket414
- Gao, Y., Xiao, F., Wang, C., Wang, C., Cui, P., Zhang, X., Chen, X., & Liu, J. (2024). Rheumatoid arthritis: Pathogenesis and therapeutic advances. *MedComm*, *5*(3), e509. https://doi.org/10.1002/mco2.509
- Genovese, M. C., Durez, P., Richards, H. B., Supronik, J., Dokoupilová, E., Mazurov, V., Aelion, J. A., Lee, S. H., Codding, C. E., Kellner, H., Ikawa, T., Hugot, S., & Mpofu, S. (2014). Efficacy and safety of secukinumab in patients with rheumatoid arthritis: A phase II, dose-finding, double-blind, randomised, placebo controlled study. *Annals of the Rheumatic Diseases*, *73*(1), 207-213. https://doi.org/10.1136/annrheumdis-2013-203334
- Kunwar, S., Dahal, K., & Sharma, S. (2016). Anti-IL-17 therapy in treatment of rheumatoid arthritis: A systematic literature review. *Immunotherapy*, *8*(8), 1113-1124. https://doi.org/10.2217/imt-2016-0018
- Lubbers, J., Brink, M., van de Stadt, L. A., Vosslamber, S., Wesseling, J. G., van Schaardenburg, D., Rantapää-Dahlqvist, S., & Verweij, C. L. (2016). Analysis of serum immune markers in seropositive and seronegative rheumatoid arthritis and in high-risk seropositive arthralgia patients. *Scientific Reports*, *6*, 26021. https://doi.org/10.1038/srep26021
- Mahmoud, G. A., Sayed, S. K., Farag, Y. M. K., & El-Amawy, H. S. (2020). Serum and synovial fluid interleukin-17 concentrations in rheumatoid arthritis patients: Relation to disease activity, radiographic severity and power Doppler ultrasound. *Egyptian Rheumatology and Rehabilitation*, *47*(1), 14. https://doi.org/10.1186/s43166-020-00014-0
- McInnes, I. B. (2020). Interleukin-17 in rheumatoid arthritis: Trials and tribulations. *Journal of Experimental Medicine*, *217*(3), e20192048. https://doi.org/10.1084/jem.20192048
- McInnes, I. B., Schett, G., Ulfgren, A. K., Zhou, W., Schulze-Koops, H., & Emery, P. (2017). Immunopathogenesis of rheumatoid arthritis. *Immunity*, *46*(2), 183-196. https://doi.org/10.1016/j.immuni.2017.02.006
- Nakayama, T., Yoshimura, M., Higashioka, K., Miyawaki, K., Ota, Y., Ayano, M., Kimoto, Y., Mitoma, H., Ono, N., Arinobu, Y., Tsukamoto, H., Horiuchi, T., & Akashi, K. (2025). Pathogenic role of cytokines in rheumatoid arthritis. *Journal of Clinical Medicine*, *14*(18), 6409. https://doi.org/10.3390/jcm14186409
- Paradowska-Gorycka, A., Wajda, A., Romanowska-Próchnicka, K., Walczuk, E., Kuca-Warnawin, E., Kmiolek, T., Stypinska, B., Rzeszotarska, E., Majewski, D., Jagodzinski, P. P., & Pawlik, A. (2017). IL-12B gene polymorphisms and IL-12 p70 serum levels among patients with rheumatoid arthritis. *Scandinavian Journal of Immunology*, *85*(3), 212-220. https://doi.org/10.1111/sji.12514
- Picerno, V., Ferro, F., Adinolfi, A., Valentini, E., Tani, C., & Alunno, A. (2015). One year in review: The pathogenesis of rheumatoid arthritis. *Clinical and Experimental Rheumatology*, *33*(4), 551-558.
- Pradhan, R., Jain, P., Paria, A., Saha, A., Sahoo, J., Pattnaik, K., Beg, M. A., Meher, P., & Dubashi, B. (2024). Association of serum IL-17 and IL-23 cytokines with disease activity and various parameters of rheumatoid arthritis in Indian patients. *Cureus*, *16*(12), e75251. https://doi.org/10.7759/cureus.75251
- Samaan, S. F., Taha, S. I., Mahmoud, F. A., Elsaadawy, Y., Khalil, S. A., & Gamal, D. M. (2024). Role of interleukin-17 in predicting activity of rheumatoid arthritis and systemic lupus erythematosus. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, *17*, 11795441241276880. https://doi.org/10.1177/11795441241276880
- Smolen, J. S., Agarwal, S. K., Ilivanova, E., Xu, X. L., Miao, Y., Zhuang, Y., Nnane, I., Radziszewski, W., Greenspan, A., Beutler, A., & Baker, D. (2017). A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. *Annals of the Rheumatic Diseases*, *76*(5), 831-839. https://doi.org/10.1136/annrheumdis-2016-209831
- Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. *Lancet*, *388*(10055), 2023-2038. https://doi.org/10.1016/S0140-6736(16)30173-8
- Tahir, H., Deodhar, A., Genovese, M., Takeuchi, T., Aelion, J., Van den Bosch, F., Vakili, P. M., Parenti, D., & Levin, R. (2017). Secukinumab in active rheumatoid arthritis after anti-TNFα therapy: A randomized, double-blind placebo-controlled phase 3 study. *Rheumatology and Therapy*, *4*(2), 475-488. https://doi.org/10.1007/s40744-017-0074-2
- Yamamura, M., Kawashima, M., Taniai, M., Yamauchi, H., Tanimoto, T., Kurimoto, M., Morita, Y., Ohmoto, Y., & Makino, H. (2003). Decreased response to IL-12 and IL-18 of peripheral blood cells in rheumatoid arthritis. *Arthritis Research & Therapy*, *5*(6), R320-R329. https://doi.org/10.1186/ar1020.