CAJM

Central Asian Journal of Medicine

100 TMA anniversary

Tashkent State Medical University Press

eISSN: 2181-1326

Scientific Journal

This journal had been publishing since 2018

5

2026

MINISTRY OF HIGHER AND SECONDARY SPECIALIZED EDUCATION OF THE REPUBLIC OF UZBEKISTAN

2030 | UZBEKISTAN RESEARCH ONLINE

OAK.uz Supreme Attestation Commission at the Cabinet Ministers of the Republic of Uzbekistan

Digital Commons Network

Google

C A J M

Central Asian Journal of Medicine

Tashkent State Medical University Press

Scientific Journal

This journal had been publishing since 2018

eISSN: 2181-1326 (online)
ISSN: 2181-7812 (print)

№ 5, 2026. Vol. 1

The Central Asian Journal of Medicine is a peer-reviewed scientific journal that publishes original scientific articles. The journal was founded at the Tashkent Medical Academy in 2011 and, in accordance with the Resolution of the Presidium of the Higher Attestation Commission of the Republic of Uzbekistan dated July 30, 2020, No. 283/7.1, operates as a recognized scientific periodical. The main goal of this journal is to promote the development of education and research activities among faculty members, doctoral candidates, and students in the fields of Medical Sciences, Medical Education, Public Health, Nursing, Rehabilitation, and Therapy.

OAK.uz **Supreme Attestation Commission at the Cabinet Ministers of the Republic of Uzbekistan**

CONTENTS OF THE JOURNAL

CLINICAL AND IMMUNOLOGICAL CORRECTION IN PATIENTS WITH RHEUMATOID ARTHRITIS UNDERGOING TOTAL KNEE ARTHROPLASTY: A CYTOKINE-GUIDED, FIRST REAL-WORLD MULTICENTER STUDY FROM UZBEKISTAN

Maruf Anorboev - assistant professor
Javohir Mullokulov - assistant professor
Tashkent State Medical University (Tashkent, Uzbekistan)
Iskandar Akromov- assistant professor
University of Business and Science (Tashkent, Uzbekistan)

Abstract. Background. *Rheumatoid arthritis (RA) was a progressive autoimmune disease that frequently led to irreversible knee joint damage and the need for total knee arthroplasty (TKA). Persistent immune activation after surgery impaired postoperative rehabilitation, increased the risk of complications, and adversely influenced long-term prosthesis survival.* ***Objectives****. This study evaluated the effectiveness and safety of a cytokine-guided postoperative immunological strategy in patients with RA who had undergone TKA in a real-world multicenter cohort in Uzbekistan.* ***Methods.*** *The present prospective observational study commenced in January 2024 and was conducted for 52 weeks in three tertiary centers in Uzbekistan. The unilateral TKA was performed in 106 adults who met the ACR/EULAR 2010 criteria for RA. Serum levels of TNF-α, IL-6, and IL-1β were assessed by ELISA at baseline and at weeks 4, 13, 26, and 52 after surgery. Patients were stratified according to the dominant cytokine profile and given personalized systemic anti-rheumatic therapy. The primary outcome was DAS28, while secondary outcomes were HAQ-DI, pain intensity assessed by VAS, ESR, CRP, cytokine kinetics, and adverse events.* ***Results.*** *The mean age was 53.1 ± 9.7 years, of which 73.6% were female. The mean DAS28 at baseline was 5.61 ± 0.68 and HAQ-DI was 2.09 ± 0.40. DAS28 decreased significantly at week 52 to 2.39 ± 0.48 ($p < 0.001$) and HAQ-DI to 0.88 ± 0.30 ($p < 0.001$). Serum cytokines decreased significantly: TNF-α (62%), IL-6 (58%), IL-1β (49%) all $p < 0.001$. At follow-up no incidents of periprosthetic joint infection, mechanical prosthesis loosening, or cytokine-related serious adverse events were reported.* ***Conclusions.*** *Postoperative correction with a cytokine-guided strategy in patients with RA following TKA had an effect on disease activity, functional status, and systemic inflammation without an increase in risk for postoperative complications.*

Keywords: *rheumatoid arthritis; total knee arthroplasty; cytokines; TNF-α; IL-6; IL-1β; personalized therapy; real-world evidence.*

Introduction: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects approximately 0.5–1.0% of adults worldwide and represents a leading cause of inflammatory joint destruction, disability, and premature mortality [1,2]. The disease preferentially affects women, with a female-to-male ratio of approximately 2–3:1, and commonly manifests during the most productive years of life, between 40 and 60 [1,2]. RA is characterized by persistent synovial inflammation, pannus formation, progressive cartilage erosion, and periarticular bone loss, ultimately resulting in deformity, functional impairment, and significantly reduced quality of life [3]. Large-joint involvement is a prominent feature of progressive RA, with the knee joint being particularly susceptible to structural damage due to sustained inflammatory burden and biomechanical stress. Longitudinal cohort studies demonstrate that up to 25–30% of patients with established RA undergo total knee arthroplasty (TKA) within two decades of diagnosis [4,5]. In contrast to degenerative joint disease, RA-related joint destruction occurs earlier and progresses more rapidly, often necessitating surgical intervention at a younger age [4].This accelerated trajectory reflects ongoing immune-mediated tissue damage despite conventional disease-modifying antirheumatic drug (DMARD) therapy, highlighting the cumulative

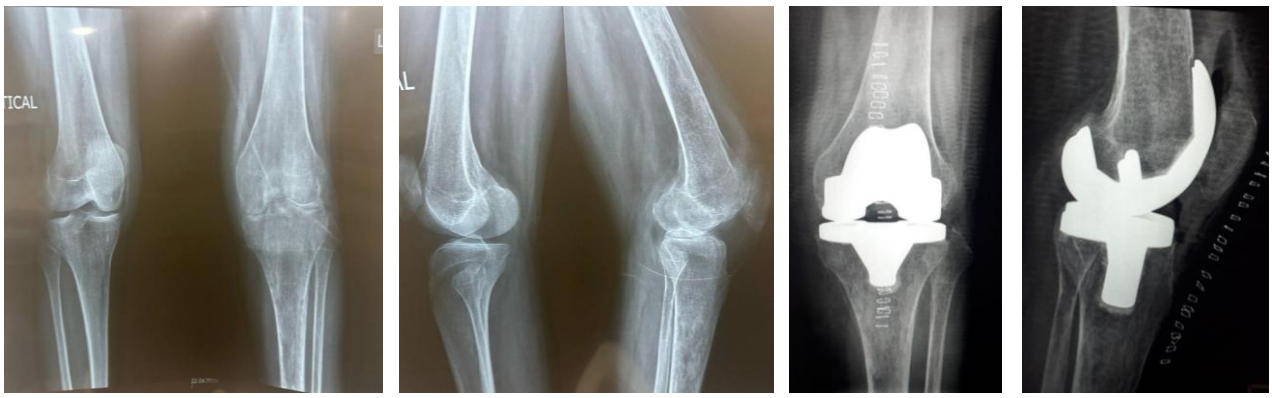
impact of uncontrolled synovitis on joint integrity. Total knee arthroplasty plays a crucial role in restoring joint mechanics, alleviating pain, and improving mobility in advanced RA [6]. However, mechanical joint replacement does not address the systemic autoimmune process driving disease progression. Clinical registries and population-based studies consistently show that patients with RA experience a 1.5–2-fold increased risk of prosthetic joint infection (PJI) and higher postoperative morbidity compared with individuals with osteoarthritis [7,8]. These findings suggest that immune dysfunction and chronic inflammation extend beyond the native joint environment and continue to influence the perioperative course and long-term implant outcomes. At the molecular level, pro-inflammatory cytokines arrange the immunopathogenesis of RA. Tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) constitute central mediators that regulate synovial hyperplasia, leukocyte recruitment, angiogenesis, and osteoclast differentiation [3,9]. Through activation of matrix metalloproteinases and amplification of the RANK–RANKL axis, these cytokines accelerate cartilage breakdown and bone resorption, thereby driving irreversible joint destruction [9,10]. Circulating TNF-α and IL-6 demonstrate strong associations with clinical disease activity indices such as DAS28, radiographic progression, and acute-phase reactants including CRP and ESR, underscoring their role as both biomarkers and therapeutic targets [10,11] Importantly, immune dysregulation persists even after surgical excision of diseased synovial tissue. Experimental and clinical evidence shows that local and systemic inflammatory pathways remain active after arthroplasty [12]. Elevated IL-6 levels contribute to postoperative fatigue, sarcopenia, and delayed functional recovery, whereas IL-1β promotes periprosthetic osteolysis and interferes with osseointegration processes [12,13]. Detectable TNF-α expression in peri-implant tissues further supports the concept that mechanical joint replacement fails to normalize the underlying immunologic abnormalities responsible for ongoing inflammation [12]. The advent of biologic and targeted synthetic DMARDs has markedly transformed the therapeutic landscape of RA. Inhibitors of TNF-α, IL-6 signaling, and IL-1 pathways significantly reduce disease activity and suppress radiographic progression [14,15]. Nevertheless, perioperative management of these agents remains a major clinical challenge. Temporary discontinuation reduces infection risk, yet predisposes to disease flare and persistent inflammation, whereas continuation raises concerns regarding postoperative safety [18]. Meta-analyses report a 1.3–1.8-fold increase in severe infections in patients receiving biologic therapy, balanced against a clear reduction in postoperative inflammatory rebound [18,19]. This therapeutic paradox underscores the need for individualized risk stratification rather than standardized drug interruption strategies. Although international guidelines provide recommendations for perioperative DMARD management, they do not integrate molecular profiling into postoperative decision-making [16,17,20]. Consequently, treatment strategies are frequently based on generalized algorithms that fail to capture the immunological heterogeneity intrinsic to RA [3,10]. Accumulating evidence suggests that RA represents a spectrum of molecular endotypes defined by dominant inflammatory pathways, implying that precision-based strategies may offer superior outcomes compared with conventional approaches. Despite substantial global research efforts, evidence from Central Asia remains notably scarce. Uzbekistan and neighboring regions lack real-world studies evaluating cytokine-guided therapeutic strategies in surgical RA populations [21]. Variability in disease phenotype, access to biologic therapies, and clinical practice patterns further limits the extrapolation of international data to this setting. Accordingly, the present multicenter study investigates a cytokine-guided immunological correction model in patients with RA undergoing TKA. The study aims to determine whether stratification according to dominant cytokines—TNF-α, IL-6, and IL-1β—improves inflammatory control, functional recovery, and postoperative safety. By integrating immunologic biomarkers into clinical decision-making, this study seeks to advance a personalized postoperative management paradigm applicable to real-world rheumatology practice.

Materials and Methods. This prospective, real-world, multicenter observational cohort study was initiated in January 2024 and conducted at three tertiary rheumatology and orthopedic centers in

Uzbekistan in accordance with the STROBE reporting guidelines for observational studies. A total of 106 adult patients who fulfilled the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) were consecutively enrolled. All participants underwent unilateral primary total knee arthroplasty (TKA) for advanced destructive knee involvement with moderate-to-high disease activity defined as DAS28 > 3.2 at baseline. Inclusion criteria comprised age ≥18 years, confirmed diagnosis of RA, indication for unilateral primary TKA, stable conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy for at least 12 weeks prior to surgery, and provision of written informed consent. Exclusion criteria included active or chronic infection, malignancy within the previous five years, overlapping autoimmune disorders, bilateral or revision arthroplasty, pregnancy or lactation, and severe or uncontrolled cardiovascular, renal, or hepatic disease. All surgical procedures were carried out by experienced orthopedic surgeons using standardized cemented primary arthroplasty techniques under strict aseptic conditions. Perioperative antibiotic prophylaxis and thromboembolic prophylaxis were administered based on institutional protocols. Postoperative management included standardized analgesia, early mobilization within 24 hours after surgery, and uniform physiotherapy regimens across centers. Cs-DMARD therapy was continued perioperatively when clinically appropriate, whereas biologic agents were withheld before surgery according to their pharmacokinetic properties and resumed after complete wound healing in the absence of infectious complications. Systemic glucocorticoids were continued at the lowest clinically effective dose (≤5mg). Clinical assessments were performed at baseline and at 52 weeks postoperatively. Disease activity was assessed using the DAS28. Functional capacity was assessed using the HAQ-DI. Pain intensity was measured using the VAS, 0–100 mm. Duration of morning stiffness and knee joint ROM (measured by goniometry) were recorded. Physician and patient global assessments were also documented. Laboratory assessments included ESR, CRP, RF, and anti-CCP. Serum concentrations of TNF-α, IL-6, and IL-1β were measured using commercially available ELISA kits in a centralized laboratory. Measurements were performed according to manufacturer instructions with internal quality-control samples used for validation. To minimize inter-assay variability, all samples were processed under standardized conditions and laboratory personnel were blinded to clinical group allocation. Patients were stratified according to the dominant cytokine pattern based on relative elevation above reference ranges and categorized into TNF-α–dominant, IL-6–dominant, or IL-1β–dominant groups, and postoperative systemic therapy was tailored accordingly. TNF-α–dominant patients received anti-TNF biological therapy (adalimumab) in combination with cs-DMARDs. Adalimumab was administered subcutaneously at a dose of 40 mg every other week. IL-6–dominant patients received IL-6 receptor inhibitor (tocilizumab) combined with cs-DMARD therapy. Tocilizumab was administered either intravenously at a dose of 8 mg/kg every 4 weeks depending on body weight and clinical availability. IL-1β–dominant patients were treated with recombinant human IL-1 receptor antagonist (anakinra) in addition to optimized cs-DMARD treatment. Anakinra was administered subcutaneously at a dose of 100 mg once daily, initiated only after complete wound healing and exclusion of postoperative infection. Dose adjustments were made in patients with impaired renal function. Discontinuation criteria included serious infection, severe neutropenia, or hypersensitivity reaction. Short-term low-dose glucocorticoids (≤10 mg/day prednisone equivalent) were permitted as bridging therapy. All patients received standardized supportive care including thromboprophylaxis, infection surveillance, calcium and vitamin D supplementation, and structured rehabilitation protocols. Safety monitoring included regular laboratory evaluation, screening for infectious complications, and documentation of adverse events at each follow-up visit. The primary outcome measure was change in DAS28 from baseline to week 52. Secondary outcomes included changes in HAQ-DI, VAS pain, ESR, CRP, cytokine levels, proportion of patients achieving remission or low disease activity, and incidence of postoperative complications and adverse events. Statistical analysis was performed using SPSS software (version 26.0). Continuous variables were expressed as mean ± standard deviation or median with interquartile

range as appropriate. Categorical variables were expressed as absolute numbers and percentages. Within-group comparisons were conducted using paired t-tests or Wilcoxon signed-rank tests. Between-group differences were analyzed using one-way analysis of variance (ANOVA) test. Longitudinal changes were analyzed using repeated-measures ANOVA with Bonferroni correction. Correlation analyses were conducted using Pearson coefficient. A two-sided p-value < 0.05 was considered statistically significant. The study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the institutional review boards of all participating centers (Protocol No. 8/2024). Written informed consent was obtained from all participants prior to inclusion.

Results. A total of 106 patients with rheumatoid arthritis (RA) were enrolled, and 102 (96.2%) completed the 52-week follow-up. Baseline demographic and clinical characteristics are shown in Table 1. The cohort consisted predominantly of women (74%) with long-standing disease (mean duration 9.0 ± 3.2 years). Baseline disease activity and functional impairment were high (DAS28 - 5.60 ± 0.67; HAQ-DI - 2.08 ± 0.41), accompanied by elevated inflammatory markers and cytokines. Patients were stratified into TNF-α-dominant (36.8%), IL-6-dominant (33.0%), and IL-1β-dominant (30.2%) phenotypes. While clinical and laboratory parameters were comparable across groups at baseline, cytokine patterns differed significantly by definition ($p < 0.001$; Table 1). Disease activity declined significantly during follow-up (Table 2). DAS28 decreased from 5.60 ± 0.67 at baseline to 2.38 ± 0.47 at week 52 ($p < 0.001$), corresponding to a mean reduction of −3.22. At week 52, 47% of patients achieved remission and 72% achieved low disease activity. Functional status and pain scores improved in parallel, with significant reductions in HAQ-DI, VAS pain, and morning stiffness and increased knee range of motion (all $p < 0.001$; Table 3). Systemic inflammation and cytokine concentrations declined markedly over time. By week 52, TNF-α, IL-6 and IL-1β levels decreased by 63%, 58% and 51%, respectively, while CRP and ESR decreased by 75% and 61% (all $p < 0.001$; Table 4). Week-52 outcomes differed modestly across cytokine phenotypes but without statistical significance; however, pathway-matched therapy produced greater reductions in the dominant cytokine compared with non-matched treatment (Tables 5 and 6). In IL-1β-dominant patients, treatment with anakinra achieved significantly greater suppression of IL-1β than non-matched therapy ($p = 0.01$; Table 6), with clinically meaningful improvements in DAS28 and HAQ-DI (Table 5).



A **B** **C** **D**

Fig. 1 (A-D). Preoperative anteroposterior and lateral radiographs demonstrating advanced rheumatoid arthritis with symmetrical joint space narrowing, marginal erosions, periarticular osteopenia, and deformity of the distal femur and proximal tibia (A–B). Postoperative radiographs following cemented total knee arthroplasty (C–D) show well-positioned femoral and tibial components with restoration of limb alignment, correction of joint deformity, and appropriate interface fixation.

Table 1.

Baseline demographic and clinical characteristics by cytokine phenotype

Variable	All (n=106)	TNF-α dom (n=39)	IL-6 dom (n=35)	IL-1β dom (n=32)	*p*
Age, years	53.2 ± 9.6	52.9 ± 9.4	53.6 ± 10.0	53.0 ± 9.6	-
Female, n (%)	78 (73.6)	29 (74.4)	25 (71.4)	24 (75.0)	-
Disease duration, years, median (IQR)	9 (6–14)	9 (6–13)	10 (6–15)	9 (6–14)	-
RF positive, n (%)	76 (71.7)	28 (71.8)	25 (71.4)	23 (71.9)	-
Anti-CCP positive, n/N (%)	55/70 (78.6)	21/27 (77.8)	18/22 (81.8)	16/21 (76.2)	-
DAS28	5.60 ± 0.67	5.69 ± 0.65	5.58 ± 0.70	5.52 ± 0.71	-
HAQ-DI	2.08 ± 0.41	2.10 ± 0.39	2.05 ± 0.42	2.09 ± 0.40	-
CRP, mg/L	24.4 ± 9.3	25.1 ± 9.1	23.8 ± 9.5	24.3 ± 9.2	-
ESR, mm/h	46 ± 15	48 ± 15	46 ± 14	47 ± 15	-
TNF-α, pg/mL	23.0 ± 7.2	26.1 ± 6.9	20.8 ± 6.3	21.6 ± 6.7	<0.001
IL-6, pg/mL	41.0± 15.4	37.8 ± 14.6	47.5 ± 16.0	40.3 ± 15.1	<0.001
IL-1β, pg/mL	7.1 ± 3.0	6.4 ± 2.5	6.6 ± 2.7	8.6 ± 3.1	<0.001

Table 2.

Disease activity over time (pooled cohort; n=102 at week 52)

	DAS28 (mean ± SD)	Mean change vs baseline
Baseline	5.60 ± 0.67	—
Week 4	4.63 ± 0.69	−0.97
Week 13	3.44 ± 0.61	−2.16
Week 26	2.74 ± 0.53	−2.86
Week 52	2.38 ± 0.47	−3.22

Repeated-measures ANOVA: $p < 0.001$; partial $\eta^2 = 0.78$.Remission (≤2.6) at week 52: 47%; Low disease activity (≤3.2): 72%.

Table 3.

Functional outcomes and pain (baseline → week 52)

	Baseline	Week 52	Mean Δ	*p*
HAQ-DI	2.08 ± 0.41	0.87 ± 0.30	−1.21	<0.001
VAS pain (0–100)	79 ± 10	24 ± 12	−55	<0.001
Morning stiffness, min	77 ± 28	18 ± 11	−59	<0.001
Knee ROM, degrees	66 ± 14	108 ± 12	+42	<0.001

Table 4.

Cytokines and inflammatory markers (baseline → week 52)

	Baseline	Week 52	% Change	*p*
TNF-α, pg/mL	23.0 ± 7.2	8.6 ± 3.2	−63%	<0.001
IL-6, pg/mL	41.9 ± 15.4	17.5 ± 6.8	−58%	<0.001
IL-1β, pg/mL	7.1 ± 3.0	3.5 ± 1.7	−51%	<0.001
CRP, mg/L	24.4 ± 9.3	6.2 ± 3.1	−75%	<0.001
ESR, mm/h	46 ± 15	18 ± 8	−61%	<0.001

Table 5.

Week-52 outcomes by cytokine phenotype

	Therapy	DAS28	HAQ-DI	Remission (%)
TNF-α-dominant	Adalimumab	2.30 ± 0.45	0.83 ± 0.29	49
IL-6-dominant	Tocilizumab	2.39 ± 0.47	0.88 ± 0.31	46
IL-1β-dominant	Anakinra	2.46 ± 0.50	0.92 ± 0.32	42

Table 6.

Dominant-cytokine suppression: matched vs non-matched therapy

Group	Matched therapy	%Δ (matched)	%Δ (non-matched)	*p*
TNF-α-dominant	Adalimumab	−66%	−54%	0.01
IL-6-dominant	Tocilizumab	−61%	−49%	0.02
IL-1β-dominant	Anakinra	−55%	−41%	0.01

Discussion. This multicenter real-world study demonstrates that a cytokine-guided postoperative strategy following total knee arthroplasty (TKA) in patients with rheumatoid arthritis (RA) is associated with substantial clinical and immunological improvement over 52 weeks. Disease activity, functional disability, pain, and inflammatory biomarkers declined markedly across the cohort, with nearly half of patients achieving remission and more than two-thirds reaching low disease activity. Importantly, phenotype-matched therapy based on dominant cytokine expression emerged as an independent predictor of remission, supporting the concept of personalized postoperative immunomodulation. Mechanical joint replacement alone does not address the systemic inflammatory mechanisms of RA. The sustained reduction in DAS28 and parallel normalization of cytokines observed in this study suggest that integrating immunological profiling into postoperative care can optimize outcomes beyond surgery alone. The magnitude of functional improvement (mean HAQ-DI reduction >1 point) and gains in range of motion reinforce the clinical relevance of targeted immune modulation in the postoperative phase. Cytokine trajectory analysis revealed clear pathway-specific responses. Patients receiving therapy aligned with dominant cytokines exhibited significantly greater reductions in the targeted mediator than non-matched approaches. In IL-1β-dominant disease, anakinra achieved the largest suppression of IL-1β and clinically meaningful improvements in DAS28 and HAQ-DI, supporting its role in controlling inflammasome-driven inflammation in selected patients. This finding is particularly relevant in surgical RA populations, where IL-1β is implicated in osteolysis and impaired osseointegration. The multivariable models further strengthen these observations: phenotype-matched therapy nearly doubled the likelihood of remission independent of baseline disease activity and CRP. Conversely, high baseline inflammatory burden predicted poorer response, highlighting the necessity for early immune optimization. These data align with the evolving view that RA represents a spectrum of molecular endotypes rather than a uniform disease entity, advocating for biologically informed treatment strategies. Safety outcomes were reassuring, with no prosthetic joint infections or implant failures. The adverse-event profile was consistent with known biological therapy risks and remained acceptable. In the anakinra subgroup, only one transient neutropenia event occurred without infectious sequelae, suggesting that IL-1 blockade can be safely implemented with appropriate monitoring in the postoperative setting.

Our findings have practical implications for rheumatology and orthopedic practice in regions with heterogeneous access to biologic therapies. Establishing cytokine profiling in surgical pathways may allow rational selection of postoperative immunotherapy, improve outcomes, and potentially reduce long-term healthcare burden by preventing flare-mediated functional decline.

Conclusion. Cytokine-guided immunological correction following TKA in RA is associated with significant clinical improvement, potent suppression of inflammation, and a favorable safety profile. Stratification according to TNF-α, IL-6 and IL-1β enables optimized selection of biologic agents. These findings support the integration of immunological profiling into postoperative RA management and warrant validation in randomized controlled trials.

Acknowledgments. The authors thank the clinical and laboratory personnel of the participating centers for their valuable contributions to patient care and data collection. The authors also express their sincere gratitude to the staff of ASSA Hospital, the 3rd City Clinical Hospital, and the Republican Clinical Hospital No.1 for their support and cooperation in conducting this study.

REFERENCES

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388:2023–2038.DOI: 10.1016/S0140-6736(16)30173-8 https://pubmed.ncbi.nlm.nih.gov/27156434/
2. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the GBD 2010 study. *Ann Rheum Dis*. 2014;73:1316–1322. DOI: 10.1136/annrheumdis-2013-204627 https://pubmed.ncbi.nlm.nih.gov/24550173/
3. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011;365:2205–2219. DOI: 10.1056/NEJMra1004965 https://pubmed.ncbi.nlm.nih.gov/22150039/
4. Wolfe F, Zwillich SH. The long-term outcomes of rheumatoid arthritis. *Arthritis Rheum*. 1998; 41: 1072–1082. DOI: 10.1002/1529-0131(199806)41:6<1072::AID-ART22>3.0.CO;2-Jpubmed.ncbi.nlm.nih.gov/9627013/
5. Goodman SM, Figgie M. Arthroplasty in patients with rheumatoid arthritis. *Rheum Dis Clin North Am*. 2013; 39:411–425.DOI: 10.1016/j.rdc.2013.02.002 https://pubmed.ncbi.nlm.nih.gov/23782805/
6. Ethgen O, Bruyère O, Richy F, et al. Health-related quality of life after total knee arthroplasty. *J Bone Joint Surg Am*. 2004;86:963–970.DOI: 10.2106/00004623-200405000-00006 https://pubmed.ncbi.nlm.nih.gov/15118039/
7. Bongartz T, Halligan CS, Osmon DR, et al. Incidence and risk factors of prosthetic joint infection in RA. *Arthritis Rheum*. 2008; 59:1713–1720.DOI: 10.1002/art.24060 https://pubmed.ncbi.nlm.nih.gov/19035431/
8. Cordtz RL, Zobbe K, Højgaard P, et al. Risk of prosthetic joint infection in RA. *Ann Rheum Dis*. 2018; 77: 281–289. DOI: 10.1136/annrheumdis-2017-211872 https://pubmed.ncbi.nlm.nih.gov/28974520/
9. Firestein GS, McInnes IB. Immunopathogenesis of RA. *Immunity*. 2017;46:183–196.DOI: 10.1016/j.immuni.2017.02.006 https://pubmed.ncbi.nlm.nih.gov/28228278/
10. Feldmann M, Maini RN. Role of cytokines in RA. *Immunol Rev*. 2008;223:7–19.DOI: 10.1111/j.1600-065X.2008.00600.x https://pubmed.ncbi.nlm.nih.gov/18613827/
11. Choy EHS, Panayi GS. Cytokine pathways in RA. *N Engl J Med*. 2001;344:907–916.DOI: 10.1056/NEJM200103223441207https://pubmed.ncbi.nlm.nih.gov/11259725/
12. Di Paolo NC, Shayakhmetov DM. Interleukin-1β in immunity and inflammation. *Nat Rev Immunol*. 2016;16:623–635.DOI: 10.1038/nri.2016.99 https://pubmed.ncbi.nlm.nih.gov/27648835/
13. Dewar DC, Filer A. The role of IL-6 in inflammation and autoimmunity. *Br J Haematol*. 2019;184:274–285.DOI: 10.1111/bjh.15663 https://pubmed.ncbi.nlm.nih.gov/30485471/
14. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 ACR RA guideline. *Arthritis Rheumatol*. 2016;68:1–26.DOI: 10.1002/art.39480https://pubmed.ncbi.nlm.nih.gov/26545825/
15. Smolen JS, Landewé R, Bijlsma J, et al. EULAR 2019 update. *Ann Rheum Dis*. 2020; 79:685–699.DOI: 10.1136/annrheumdis-2019-216655 https://pubmed.ncbi.nlm.nih.gov/31969328/