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ВЫПУСК 8 (№ 13)
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RHEUMATOID ARTHRITIS: NEW TREATMENT APPROACHES - A COMPARATIVE EVIDENCE REVIEW

Abstract: *Rheumatoid arthritis (RA) is a systemic autoimmune disease that has undergone a therapeutic revolution over the past two decades. Conventional synthetic DMARDs remain foundational, but the introduction of biologic and targeted synthetic DMARDs has transformed outcomes. This article reviews pivotal randomized controlled trials, comparative efficacy and safety data, and evolving treatment algorithms. Quantitative comparisons including absolute risk reduction (ARR), relative risk (RR), and number needed to treat (NNT) are provided for head-to-head studies, alongside safety analyses from ORAL Surveillance and regulatory guidance. A treat-to-target approach, precision medicine, and risk stratification remain essential for optimizing outcomes in 2025 and beyond.*
Key words: *Upadacitinib, bDMARDs, tofacitinib, baricitinib*

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РЕВМАТОИДНЫЙ АРТРИТ: НОВЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ - СРАВНИТЕЛЬНЫЙ ОБЗОР ДОКАЗАТЕЛЬСТВ

Аннотация: *Ревматоидный артрит (РА) - это системное аутоиммунное заболевание, которое претерпело терапевтическую революцию за последние два десятилетия. Конвенциональные синтетические базисные противоревматические препараты (csDMARDs) остаются основой терапии, однако внедрение биологических (bDMARDs) и таргетных синтетических препаратов (tsDMARDs) значительно изменило прогноз заболевания. В данной статье рассматриваются ключевые рандомизированные контролируемые исследования, сравнительная эффективность и профиль безопасности препаратов, а также эволюция терапевтических алгоритмов. Приводятся количественные показатели, включая абсолютное снижение риска (ARR), относительный риск (RR) и число пациентов, которых необходимо лечить (NNT), для прямых сравнительных исследований, а также анализ безопасности по результатам исследования ORAL Surveillance и регуляторные рекомендации. Подход «лечение до достижения цели» (treat-to-target), принципы прецизионной медицины и стратификация риска остаются ключевыми элементами оптимизации исходов терапии в 2025 году и далее.*
Ключевые слова: *Упадацитиниб, bDMARDs, тофацитиниб, барицитиниб*

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REVMATOID ARTRIT: DAVOLASHDA YANGI USULLAR - QIYOSIY DALILLARNI KO'RIB CHIQISH

Annotatsiya: *Revmatoid artrit (RA) – bu so'nggi ikki o'n yillikda davolashda inqilobiy o'zgarishlarga uchragan tizimli autoimmun kasallikdir. An'anaviy sintetik DMARDlar (csDMARD) asosiy davolash vositasi bo'lib qolmoqda, biroq biologik (bDMARD) va nishonli sintetik preparatlarning (tsDMARD) joriy etilishi natijalarni tubdan o'zgartirdi. Ushbu maqolada asosiy randomizatsiyalangan nazoratli tadqiqotlar, dorilarning solishtirma samaradorligi va xavfsizlik profili, shuningdek rivojlanayotgan davolash algoritmlari ko'rib chiqiladi. To'g'ridan-to'g'ri taqqoslovchi tadqiqotlar uchun mutlaq xavf kamayishi (ARR), nisbiy xavf (RR) va bitta natijaga erishish uchun davolanishi zarur bo'lgan bemorlar soni (NNT) kabi miqdoriy ko'rsatkichlar keltirilgan. Shuningdek, ORAL Surveillance tadqiqoti natijalaridan kelib chiqib xavfsizlik tahlili va regulyator ko'rsatmalar beriladi. "Maqsadga yo'naltirilgan davolash" (treat-to-target) yondashuvi, aniq tibbiyot tamoyillari va xavfni stratifikatsiya qilish 2025-yilda va undan keyin ham davolash natijalarini optimallashtirishda muhim ahamiyatga ega bo'lib qolmoqda.*
Kalit so'zlar: *Upadacitinib, bDMARD, Tofacitinib, Baricitinib*

Introduction: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovitis, progressive structural joint damage, functional impairment, and substantial extra-articular morbidity. With a global prevalence estimated at 0.5–1% of the adult population, RA represents a major contributor to disability-adjusted life years (DALYs) and imposes a considerable socioeconomic burden on patients and healthcare systems alike [1,2,3] Despite advances in early diagnosis and treat-to-target (T2T) strategies, RA remains a disease with significant heterogeneity in clinical course, treatment response, and long-term outcomes. The therapeutic landscape of RA has undergone a paradigm shift over the past two decades. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), particularly methotrexate, remain the cornerstone of therapy; however, limitations in efficacy and intolerance necessitated the development of biologic DMARDs (bDMARDs) targeting pivotal cytokines and immune pathways, such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and T-cell co-stimulation [4,6,7] More recently, targeted synthetic DMARDs (tsDMARDs), including Janus kinase (JAK) inhibitors, have provided potent oral alternatives with broad immunomodulatory activity. Collectively, these agents have transformed the management of RA, achieving unprecedented rates of remission and low disease activity. Nevertheless, critical challenges persist [5,8,9] Optimal sequencing of therapies following csDMARD failure, comparative efficacy of newer agents against established biologics, and the balance between therapeutic benefit and long-term safety—particularly cardiovascular and oncologic risks associated with JAK inhibitors—remain subjects of intense investigation [10,11,12] Moreover, questions regarding cost-effectiveness, sustainability of remission, and the feasibility of tapering or drug-free strategies are increasingly relevant in contemporary clinical practice. This review synthesizes evidence from landmark randomized controlled trials, comparative head-to-head studies, and long-term extension data, integrating statistical analyses such as absolute risk reduction (ARR), relative risk (RR), and number needed to treat (NNT). In addition, evolving safety data and international guideline recommendations are considered, with the objective of providing a critical appraisal of new treatment approaches and their implications for precision medicine in RA.

Material and Methods.

A targeted literature search was conducted to identify pivotal randomized controlled trials (RCTs), long-term extension studies, and safety investigations relevant to novel therapeutic approaches in rheumatoid arthritis (RA). Electronic databases (PubMed, MEDLINE, Embase, and the Cochrane Library) were searched from January 2000 to June 2025, using combinations of keywords and MeSH terms including *rheumatoid arthritis*, *biologic DMARDs*, *targeted synthetic DMARDs*, *JAK inhibitors*, *RA-BEAM*, *SELECT-COMPARE*, *ADACTA*, *FINCH-1*, and *ORAL Surveillance*. Additional sources included reference lists of retrieved articles, conference abstracts (EULAR, ACR, APLAR), and regulatory communications from the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA). Studies were included if they met the following criteria: (1) randomized controlled trial or prespecified extension study evaluating biologic or targeted synthetic DMARDs in adults with RA; (2) sample size ≥200 participants; (3) primary or key secondary outcomes reported in terms of American College of Rheumatology (ACR20/50/70) responses, Disease Activity Score in 28 joints (DAS28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), or radiographic progression measured by modified total Sharp score (mTSS); and (4) safety endpoints, including major adverse cardiovascular events (MACE), malignancy, and venous thromboembolism, where available. Trials were excluded if they were non-comparative, had inadequate reporting of outcomes, or involved non-RA populations.

Results: This review identified four pivotal randomized controlled trials—RA-BEAM, SELECT-COMPARE, ADACTA, and FINCH-1—as well as the large safety study ORAL Surveillance, supported by long-term extension data and international guidelines. Together, these provide robust evidence for the comparative efficacy and safety of biologic and targeted synthetic DMARDs in rheumatoid arthritis. In RA-BEAM (NEJM 2017, n = 1307, MTX-IR), baricitinib 4 mg daily achieved ACR20 responses in 70% of patients at week 12 compared with 61% with adalimumab and 40% with placebo, all on background methotrexate. Radiographic progression at week 24 was lower with baricitinib (mTSS 0.41) versus placebo (0.90). Compared with adalimumab, the absolute risk reduction (ARR) for ACR20 was 9%, the relative risk (RR) was 1.15, and the number needed to treat (NNT) was approximately 12, confirming a clinically meaningful advantage. In SELECT-COMPARE (Arthritis Rheumatol 2019, n = 1629, MTX-IR), upadacitinib 15 mg daily demonstrated superiority over adalimumab 40 mg q2w. At week 12, ACR50 responses were 45.2% versus 29.1%, corresponding to an ARR of 16.1%, RR of 1.55, and NNT of ∼7. Upadacitinib also achieved higher DAS28-CRP remission rates and maintained structural benefit in the 5-year extension study, with a consistent safety profile. The ADACTA trial (Lancet 2013, n = 325, MTX-intolerant) established tocilizumab 8 mg/kg IV q4w as superior to adalimumab 40 mg q2w in the monotherapy setting. At week 24, mean change in DAS28 was −3.3 with tocilizumab compared to −1.8 with adalimumab, yielding a between-group difference of −1.5 (95% CI −1.8 to −1.1; $p < 0.0001$). These findings highlight IL-6 receptor blockade as a preferred monotherapy strategy when methotrexate is contraindicated. In FINCH-1 (Ann Rheum Dis 2021, n ≈ 1755, MTX-IR), filgotinib 200 mg daily significantly improved ACR20 responses versus placebo and inhibited radiographic progression at week 24. While not designed for superiority against adalimumab, filgo-

tinib demonstrated non-inferior efficacy and a favorable tolerability profile, supporting its role as an alternative JAK1-selective inhibitor. Safety outcomes were critically informed by the ORAL Surveillance trial (NEJM 2022), which compared tofacitinib (5/10 mg bid) with TNF inhibitors in RA patients aged ≥50 years with cardiovascular risk factors. Hazard ratios indicated numerically higher risks for major adverse cardiovascular events (MACE; HR 1.33, 95% CI 0.91–1.94) and cancer (HR 1.48, 95% CI 1.04–2.09) with tofacitinib. Venous thromboembolism was increased at the higher 10 mg dose. These findings led to regulatory action: the FDA (2021) applied boxed warnings to all approved JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib), recommending their use only in patients with inadequate response to TNF inhibitors. The EMA issued similar guidance, mandating caution in older patients and those with cardiovascular or malignancy risk. Integration of EULAR 2023 recommendations places JAK inhibitors as effective targeted options but emphasizes risk stratification and shared decision-making, particularly in high-risk populations. TNF inhibitors remain first-line targeted biologics following methotrexate failure, while tocilizumab is endorsed as the most effective monotherapy option. Across trials, treat-to-target strategies focusing on remission or low disease activity consistently yielded superior long-term outcomes, including reduced radiographic damage and improved functional status.

Table 1.

Pivotal Head-to-Head Efficacy Trials Safety of JAK Inhibitors

Study	Population	Interventions	Primary Outcome	Key Results
RA-BEAM (2017)	MTX-IR RA (n=1307)	Baricitinib vs Adalimumab vs Placebo (all + MTX)	ACR20 at wk12	70% vs 61% vs 40%; mTSS lower with Baricitinib
SELECT-COMPARE (2019)	MTX-IR RA (n=1629)	Upadacitinib vs Adalimumab vs Placebo (all + MTX)	ACR20/50 at wk12	Upa 45% vs ADA 29% ACR50; sustained to 5y
ADACTA (2013)	MTX-intolerant (n=325)	Tocilizumab vs Adalimumab (monotherapy)	ΔDAS28 at wk24	−3.3 vs −1.8; diff −1.5 (95% CI −1.8 to −1.1)

ORAL Surveillance (NEJM 2022) examined tofacitinib (5/10 mg bid) vs TNFi in RA patients ≥50 years with cardiovascular risk. Hazard ratios were elevated for MACE (HR 1.33; 95% CI 0.91–1.94) and cancer (HR 1.48; 95% CI 1.04–2.09). The FDA consequently updated class boxed warnings across JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib). Guidelines recommend reserving JAK inhibitors for patients with inadequate TNFi response, with shared decision-making in high-risk populations.

Table 2.

Key Safety Findings for JAK Inhibitors

Study/Agency	Endpoint	Effect	Implication
ORAL Surveillance	MACE (HR)	1.33 (95% CI 0.91–1.94)	↑ risk vs TNFi
ORAL Surveillance	Cancer excl. NMSC (HR)	1.48 (95% CI 1.04–2.09)	↑ risk vs TNFi
FDA 2021	Class Boxed Warning	All approved JAK inhibitors	Reserve after TNFi failure

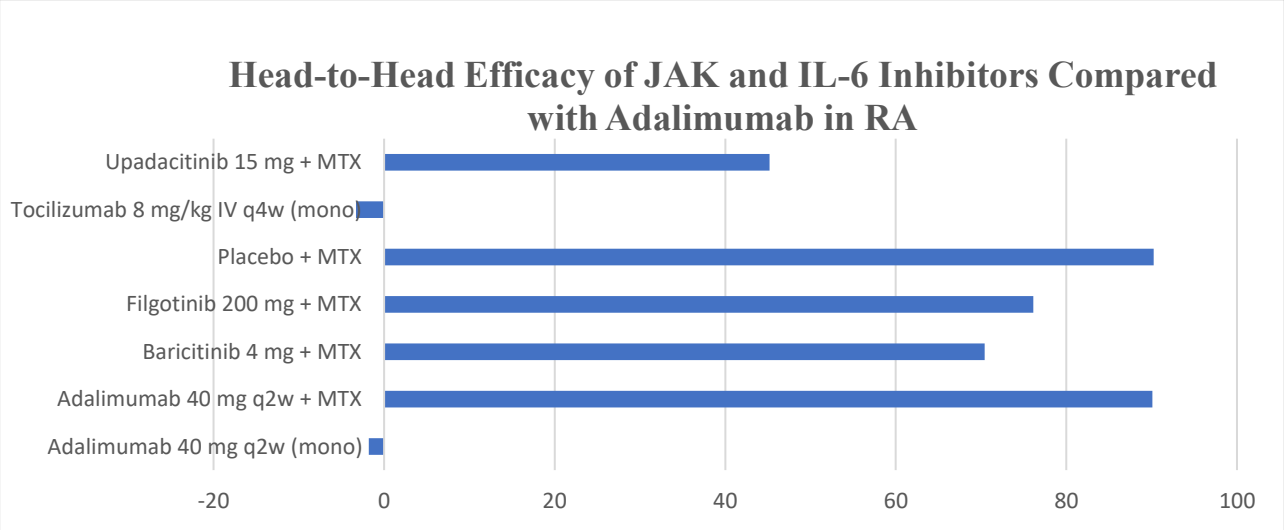

Figure 1. **Head-to-Head Efficacy of JAK and IL-6 Inhibitors Compared with Adalimumab in RA**

Discussion: The therapeutic landscape of rheumatoid arthritis (RA) has evolved substantially with the introduction of biologic and targeted synthetic DMARDs, allowing remission and low disease activity to become achievable treatment goals for many patients. Comparative analyses from pivotal randomized trials provide clear evidence that targeted synthetic DMARDs, particularly the JAK inhibitors upadacitinib and baricitinib, deliver superior short-term efficacy compared with adalimumab when combined with methotrexate. The calculated number needed to treat values, ranging from approximately 7 to 12, underscore the clinical relevance of these advantages. Similarly, in the monotherapy setting, tocilizumab has demonstrated superiority over adalimumab, highlighting IL-6 receptor blockade as a preferred option for patients who are unable to tolerate or continue methotrexate. Filgotinib, while not directly superior to adalimumab in head-to-head comparisons, has shown non-inferior efficacy with favorable tolerability, further expanding the therapeutic armamentarium. Despite these advances, safety considerations remain central to treatment decisions, particularly for JAK inhibitors. The ORAL Surveillance trial identified increased risks of major adverse cardiovascular events and malignancy with tofacitinib compared to TNF inhibitors in older patients with pre-existing cardiovascular risk factors. Although the generalizability of these findings across all JAK inhibitors is debated, the subsequent regulatory response by the FDA and EMA—issuing boxed warnings and recommending restriction of use to patients with inadequate TNF inhibitor response—reflects the importance of cautious, risk-stratified prescribing. This has shifted clinical practice towards shared decision-making, especially in patients over 65 years of age or those with cardiovascular and oncologic comorbidities**.** Looking forward, the integration of precision medicine strategies is expected to further refine therapy selection in RA. Biomarkers such as calprotectin, MMP-3, and cytokine signatures, together with advances in genomics and artificial intelligence, may allow for early identification of responders and non-responders, reducing reliance on sequential trial-and-error prescribing. Real-world registries and post-marketing surveillance provide complementary data to randomized trials, particularly in assessing long-term safety, adherence, and persistence. Cost-effectiveness analyses also remain crucial: in high-income countries the adoption of JAK inhibitors is expanding, whereas in resource-constrained regions biosimilars and optimized csDMARD combinations may remain the most pragmatic strategies. Collectively, these findings suggest that while JAK inhibitors and IL-6 blockade offer meaningful advantages over TNF inhibition in specific patient populations, their optimal use must balance efficacy with individual safety profiles and health-system constraints. Future research should focus on refining sequencing strategies, exploring tapering and de-escalation in sustained remission, and evaluating emerging classes such as TYK2 and BTK inhibitors, cell-based therapies, and microbiome-directed approaches. Ultimately, the integration of comparative trial evidence, safety monitoring, biomarker development, and economic evaluation will guide a more personalized and sustainable approach to RA management, with the overarching goal of achieving durable remission, preserving function, and improving quality of life for patients worldwide.

Conclusion: Rheumatoid arthritis management has progressed from symptom control to an era defined by precision, targeted therapies, and the realistic goal of sustained remission. Landmark comparative trials demonstrate that JAK inhibitors, particularly upadacitinib and baricitinib, achieve superior short-term efficacy compared with adalimumab in methotrexate-inadequate responders, while tocilizumab provides the most effective monotherapy option. Filgotinib adds to the therapeutic armamentarium with non-inferior efficacy and a favorable tolerability profile. Nevertheless, efficacy must be weighed against safety. The cardiovascular and malignancy risks identified in ORAL Surveillance and subsequent regulatory warnings underscore the need for careful patient selection and shared decision-making when prescribing JAK inhibitors, particularly in individuals with established comorbidities. These safety considerations have reshaped therapeutic algorithms, positioning TNF inhibitors as the standard first targeted option and reserving JAK inhibitors for selected patient populations.Moving forward, the integration of biomarkers, real-world registry data, and cost-effectiveness analyses will be essential for guiding individualized treatment strategies. Emerging therapeutic targets—including TYK2 and BTK inhibitors, cell-based interventions, and microbiome-directed therapies—hold promise for expanding options further. Ultimately, optimal care in RA requires balancing efficacy, safety, accessibility, and patient preference within a treat-to-target framework, with the overarching aim of achieving durable remission, preventing disability, and enhancing quality of life.

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