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CLINICAL AND LABORATORY EFFICACY OF CELECOXIB IN COMBINED THERAPY WITH METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Objective: To evaluate the clinical, functional, and laboratory efficacy, as well as the safety profile, of adding celecoxib to standard methotrexate therapy in patients with active rheumatoid arthritis.

Material and methods: A prospective, open-label comparative study was conducted enrolling 50 adult patients with confirmed rheumatoid arthritis (2010 ACR/EULAR criteria). Patients were randomized into two parallel treatment arms (n = 25 each). Group I received basic disease-modifying antirheumatic therapy with oral methotrexate (initiated at 10 mg/week with folic acid supplementation). Group II received celecoxib (200 mg twice daily orally) in combination with weekly methotrexate (10 mg/week). Paracetamol (up to 2 g/day) was permitted as rescue analgesia in Group I. Clinical parameters, tender (TJC) and swollen (SJC) joint counts, pain intensity (VAS 0–100 mm), disease activity score (DAS-28-ESR), functional disability index (HAQ-DI), acute-phase reactants (ESR, CRP), and cardiovascular/gastrointestinal tolerability were evaluated at baseline and after 6 months.

Results: Patients in Group II demonstrated statistically significant improvements compared to Group I across all evaluated metrics ($P < 0.001$). By month 6, the number of tender joints decreased to 11.1 ± 2.0 (vs. 17.2 ± 3.4 in Group I), swollen joints to 5.9 ± 2.6 (vs. 7.9 ± 2.4), ESR to 10.8 ± 4.9 mm/h (vs. 16.4 ± 5.9 mm/h), and serum CRP to 17.6 ± 5.2 mg/L (vs. 29.7 ± 5.1 mg/L). Pain scores on the VAS dropped to 26.8 ± 2.0 mm in Group II (vs. 32.4 ± 2.1 mm in Group I). DAS-28-ESR declined to 3.62 ± 1.1 in Group II (approaching the low disease activity threshold), compared to 4.08 ± 1.2 in Group I. Functional capacity substantially improved, with the HAQ-DI decreasing to 0.51 ± 0.07 in Group II (vs. 0.71 ± 0.08 in Group I). No serious gastrointestinal ulcerations or adverse cardiovascular events were recorded.

Conclusion: Co-administration of celecoxib with methotrexate provides superior control over articular inflammation, accelerates pain relief, suppresses systemic acute-phase reactants, and enhances functional independence compared to methotrexate monotherapy, while maintaining acceptable gastrointestinal and cardiovascular safety profiles over 6 months of treatment.

Keywords: rheumatoid arthritis, celecoxib, methotrexate, DAS-28, HAQ index, acute-phase reactants, COX-2 inhibitors.

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by persistent synovial inflammation, progressive cartilage degradation, and juxta-articular bone erosion [1, 2]. Symmetrical polyarthritis primarily targets diarthrodial joints of the hands, wrists, and feet. The global prevalence of RA ranges between 0.5% and 1.0%, showing a distinct female predominance with a female-to-male ratio of 3:1 to 4:1 [3]. Clinically, active flares manifest as severe articular pain, prolonged morning stiffness, and soft tissue tumefaction, which profoundly limit physical performance and quality of life.

Modern therapeutic guidelines emphasize the early implementation of disease-modifying antirheumatic drugs (DMARDs) to achieve remission or low disease activity, with methotrexate (MTX) established as the cornerstone anchor agent [4, 5]. However, oral DMARDs possess an inherent therapeutic latency period lasting 4 to 8 weeks before clinical benefits materialize. Symptomatic relief during this induction phase relies heavily on non-steroidal anti-inflammatory drugs (NSAIDs). Nevertheless, prolonged exposure to non-selective NSAIDs is constrained by severe gastrointestinal adverse effects, including peptic ulcerations, perforations, and life-threatening gastrointestinal hemorrhage caused by non-specific cyclooxygenase-1 (COX-1) inhibition [6, 7].

Celecoxib is a targeted, selective cyclooxygenase-2 (COX-2) inhibitor that delivers robust anti-inflammatory and analgesic properties without suppressing COX-1-mediated gastroprotective prostaglandins at therapeutic concentrations [8, 9]. Consequently, celecoxib preserves gastroduodenal mucosal integrity and does not impair platelet aggregation or bleeding time [9, 10]. Oral administration yields peak plasma concentrations within approximately 3 hours, with an elimination half-life of 11 hours, predominantly metabolized via hepatic CYP2C9 [9]. While providing gastrointestinal tolerability superior to classic non-selective NSAIDs, long-term celecoxib administration warrants vigilant monitoring of hemodynamic parameters and cardiovascular safety [8, 10]. This clinical investigation was designed to evaluate the clinical, functional, and laboratory outcomes of adding celecoxib to methotrexate therapy in patients with active RA.

The purpose of the study was to evaluate the clinical and laboratory efficacy, as well as the impact on functional status and disease activity indices (DAS-28, HAQ, VAS), of combined therapy with celecoxib (200 mg twice daily) and methotrexate compared to methotrexate monotherapy in patients with rheumatoid arthritis.

Materials and methods

A prospective, comparative clinical study was carried out between 2025 and 2026 across the specialized rheumatology, cardio-rheumatology, and rehabilitation divisions of the multidisciplinary clinic at Tashkent State Medical University.

The study enrolled 50 patients aged 18 to 55 years (mean age: 41.82 ± 4.75 years) who met the 2010 ACR/EULAR classification criteria for rheumatoid arthritis. Age stratification revealed that 4 patients (8.0%) were aged 18–19 years, 6 patients (12.0%) were aged 20–29 years, 18 patients (36.0%) were aged 30–39 years, and 22 patients (44.0%) were aged 40–55 years. The cohort consisted of 39 females (78.0%) and 11 males (22.0%), with a mean disease duration of 6.9 ± 1.4 years. At baseline, morning stiffness lasting longer than 30 minutes was observed in 41 patients (82.0%), periarticular swelling

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in 26 patients (52.0%), and persistent joint deformities in 9 patients (18.0%). Patients with uncontrolled arterial hypertension, a history of ischemic heart disease, heart failure, peptic ulcer exacerbation within the previous 6 months, or severe renal/hepatic impairment were excluded.

Patients were randomized into two parallel cohorts (n = 25 each):

• **Group I (Control):** Received standard DMARD monotherapy with oral methotrexate at 10 mg/week, accompanied by oral folic acid (5 mg/week administered 24 hours after MTX). Paracetamol (up to 2,000 mg/day as needed) was permitted as rescue analgesia for acute pain exacerbations, while other NSAIDs and systemic glucocorticoids were restricted.

• **Group II (Active Combination):** Received celecoxib (200 mg orally twice daily, total 400 mg/day) in combination with weekly oral methotrexate (10 mg/week) and folic acid.

Clinical and laboratory assessments were performed at baseline and after 6 months of continuous therapy. Physical assessment recorded the 28-joint counts for tenderness (TJC) and swelling (SJC). Laboratory assays included the erythrocyte sedimentation rate (ESR, Westergren method) and quantitative serum C-reactive protein (CRP, turbidimetric immunoassay). Subjective pain intensity was documented via a Visual Analog Scale (VAS, 0–100 mm). Disease activity was quantified using the DAS-28-ESR formula. Functional capacity was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). Blood pressure, electrocardiographic parameters, and hepatic/renal functions were monitored monthly.

Statistical analysis was conducted using SPSS version 26.0. Quantitative parameters were checked for normality via the Shapiro-Wilk test and are expressed as mean ± standard deviation (M ± SD). Pre- and post-treatment differences within groups were analyzed using paired Student's t-tests (or Wilcoxon signed-rank tests for non-normal distributions), whereas inter-group comparisons were evaluated using two-sample independent t-tests (or Mann-Whitney U tests). Significance was set at $P < 0.05$.

Table 1. Baseline demographic and clinical characteristics of the study cohort (n = 50)

Clinical / Demographic Parameter	Total RA Cohort (n = 50)
Gender: Female / Male, n (%)	39 (78.0%) / 11 (22.0%)
Mean age, M ± SD (years)	41.82 ± 4.75
Age distribution: 18–19 / 20–29 / 30–39 / 40–55 yrs, n (%)	4 (8.0%) / 6 (12.0%) / 18 (36.0%) / 22 (44.0%)
Disease duration, M ± SD (years)	6.9 ± 1.4
Morning stiffness (>30 min), n (%)	41 (82.0%)
Joint swelling / Periarticular edema, n (%)	26 (52.0%)
Joint deformities, n (%)	9 (18.0%)

Results and Discussion

Immunological screening confirmed that 41 patients (82.0%) were seropositive for Rheumatoid Factor (RF), and 37 patients (74.0%) tested positive for anti-cyclic citrullinated peptide (anti-CCP) antibodies. Baseline disease stratification according to DAS-28-ESR showed high disease activity (DAS-28 > 5.1) in 5 patients (10.0%), moderate disease activity ($3.2 \leq$ DAS-28 ≤ 5.1) in 36 patients

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(72.0%), and low disease activity (DAS-28 < 3.2) in 9 patients (18.0%). Both study groups presented comparable baseline demographic, clinical, and biochemical profiles (P > 0.05).

After 6 months of continuous intervention, patients receiving celecoxib adjunctive therapy (Group II) achieved distinctly superior clinical improvement relative to the methotrexate monotherapy cohort. Swollen joint counts in Group II decreased by 55.3%, falling from 13.2 ± 3.8 to 5.9 ± 2.6 (P < 0.001), compared to a 30.7% decrease in Group I (from 11.4 ± 2.9 to 7.9 ± 2.4). Similarly, tender joint counts exhibited a 61.2% reduction in Group II (from 28.6 ± 9.8 to 11.1 ± 2.0), whereas Group I achieved a 30.6% decline (from 24.8 ± 8.9 to 17.2 ± 3.4; P < 0.001).

Systemic inflammatory biomarkers showed parallel down-regulation. In Group II, ESR dropped by 72.4% (from 39.1 ± 6.8 mm/h to 10.8 ± 4.9 mm/h), compared to a 55.4% reduction in Group I (from 36.8 ± 6.2 mm/h to 16.4 ± 5.9 mm/h; P < 0.001). Serum CRP levels demonstrated a 59.8% suppression in Group II (from 43.8 ± 4.9 mg/L to 17.6 ± 5.2 mg/L), whereas Group I achieved a 29.8% reduction (from 42.3 ± 4.1 mg/L to 29.7 ± 5.1 mg/L).

Articular pain alleviation (VAS) was markedly pronounced in Group II, exhibiting a 63.9% reduction from 74.2 ± 2.5 mm to 26.8 ± 2.0 mm, compared to a 53.3% decline in Group I (from 69.4 ± 2.6 mm to 32.4 ± 2.1 mm; P < 0.001).

Comprehensive assessment using DAS-28-ESR demonstrated a marked decline in Group II from 5.04 ± 1.6 to 3.62 ± 1.1, representing a transition toward the borderline of low disease activity (3.2 < DAS-28 ≤ 3.6), with 8 patients (32.0%) achieving formal low disease activity (≤ 3.2). In contrast, Group I remained within the moderate disease activity range (4.08 ± 1.2). Functional rehabilitation, evaluated via the HAQ-DI, fell by more than 54% in Group II (from 1.12 ± 0.3 to 0.51 ± 0.07), indicating substantial restoration of daily functional autonomy, compared to 0.71 ± 0.08 in Group I (P < 0.001).

Both treatment protocols were well tolerated. Mild dyspeptic symptoms were documented in 2 patients (8.0%) in Group I and 1 patient (4.0%) in Group II; no endoscopic lesions or gastrointestinal hemorrhages occurred. Regular hemodynamic monitoring demonstrated stable blood pressure readings across Group II, with no de novo cases of secondary hypertension or thromboembolic cardiovascular events observed over the 6-month trial.

Table 2. Dynamics of clinical, laboratory, and functional parameters before and after 6 months of therapy (M ± SD)

Parameter	Group I: Baseline (n = 25)	Group I: 6 Months (n = 25)	Group II: Baseline (n = 25)	Group II: 6 Months (n = 25)
Swollen Joint Count (SJC)	11.4 ± 2.9	7.9 ± 2.4	13.2 ± 3.8	5.9 ± 2.6*
Tender Joint Count (TJC)	24.8 ± 8.9	17.2 ± 3.4	28.6 ± 9.8	11.1 ± 2.0*
ESR (mm/h)	36.8 ± 6.2	16.4 ± 5.9	39.1 ± 6.8	10.8 ± 4.9*
C-reactive protein, CRP (mg/L)	42.3 ± 4.1	29.7 ± 5.1	43.8 ± 4.9	17.6 ± 5.2*
VAS pain score (mm)	69.4 ± 2.6	32.4 ± 2.1	74.2 ± 2.5	26.8 ± 2.0*
DAS-28-ESR score	4.91 ± 1.4	4.08 ± 1.2	5.04 ± 1.6	3.62 ± 1.1*
HAQ Disability Index	1.02 ± 0.40	0.71 ± 0.08	1.12 ± 0.30	0.51 ± 0.07*

** P < 0.001 — statistically significant difference compared to pre-treatment baseline and between Group I and Group II at 6 months.*

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Conclusion

Adding the selective COX-2 inhibitor celecoxib (200 mg twice daily) to standard weekly methotrexate therapy yields significantly superior clinical, immunological, and functional outcomes compared to methotrexate alone in patients with active rheumatoid arthritis. Co-therapy accelerates articular symptom resolution, induces more pronounced suppression of systemic inflammatory reactants (ESR and CRP), and restores functional capacity without increasing gastrointestinal ulceration risk or adverse cardiovascular events over a 6-month treatment period.

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