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Original Research Article

# Efficacy & Safety of Iguratimod Alone & in Combination with Methotrexate in Active Rheumatoid Arthritis: A Comparative Analytical Study

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**Abstract**

**Background:** Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation and joint destruction. Methotrexate (MTX) remains the conventional anchor drug, but many patients do not achieve remission or develop adverse effects. Iguratimod (IGU), a novel disease-modifying antirheumatic drug, inhibits the NF-kB pathway and provides a mechanism for suppression of inflammatory cytokines and bone protection.

**Objective:** To compare the preliminary efficacy and safety of IGU, MTX, and IGU+MTX combination therapy for improved management of RA at a tertiary care center in Barabanki.

**Methods:** This consecutive, cross-sectional analytical study included 120 patients divided into three equal groups (n=40 each): MTX monotherapy, IGU monotherapy, and IGU+MTX combination therapy. Patients were followed for 24 weeks. Efficacy was assessed using DAS28-ESR, swollen joint count, tender joint count, morning stiffness, inflammatory markers and remission rates. Safety was assessed by adverse event reporting and hepatic, renal and hematological parameters.

**Results:** All groups showed significant improvement from baseline ($p<0.001$). The IGU+MTX group demonstrated the greatest efficacy, with mean post-treatment DAS28 of 2.42, a 34.5% DAS28 remission rate and 68.0% ACR50 equivalent response. Logistic regression showed that patients receiving IGU+MTX were 3.62 times more likely to achieve remission than patients receiving MTX monotherapy ($p<0.001$). Adverse events were numerically higher in the combination group (37.5%) but were not statistically different from monotherapy groups ($p=0.642$).

**Conclusion:** IGU+MTX combination therapy was more effective than either drug alone for managing active RA in the Barabanki tertiary care setting, with a comparable safety profile. The findings support IGU+MTX as a cost-effective, treat-to-target strategy for achieving clinical remission and functional improvement.

**Keywords:** Rheumatoid arthritis; Iguratimod; Methotrexate; Combination therapy; DAS28; DMARD.

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## Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized primarily by symmetrical, invasive inflammatory lesions affecting multiple joints.[1] This persistent inflammation can lead to progressive joint damage, functional disability, and significant systemic complications.[2] Beyond the articular manifestations, a substantial proportion of RA patients, approximately 40%, experience extra-articular manifestations (EAMs), such as interstitial lung disease (ILD), which represents a pivotal factor contributing to the high mortality rate

associated with RA.[3] The systemic nature of RA, extending beyond localized joint issues to include life-threatening EAMs, underscores that effective treatment strategies must encompass not only joint preservation but also the comprehensive mitigation of systemic inflammation to improve overall patient survival and quality of life. This broader perspective emphasizes the need for therapies with systemic anti-inflammatory and potentially organ-protective properties.

The global and Indian burden of RA is substantial. The thesis documented that RA affects millions of individuals worldwide and that the age-standardized incidence and prevalence in India have increased over time, particularly among women.[4,5] RA also imposes a marked economic and functional burden because chronic inflammation, joint damage and systemic comorbidities reduce physical independence, quality of life and work capacity. These concerns are especially important in regional tertiary care settings, where delayed presentation and limited access to high-cost biological agents may compromise treat-to-target goals.

Current RA management is directed toward early diagnosis, control of active synovitis and achievement of remission or low disease activity. The 2010 ACR/EULAR classification system supports early identification by combining joint involvement, serology, symptom duration and acute-phase reactants.[6] Regional recommendations from the Asia Pacific League of Associations for Rheumatology emphasize the rational use of disease-modifying antirheumatic drugs (DMARDs), particularly in settings where affordability determines treatment access.[7]

MTX remains the anchor conventional synthetic DMARD because of its proven anti-inflammatory effect, clinical experience and cost-effectiveness.[8] However, a considerable proportion of patients either fails to achieve adequate response or cannot tolerate adverse effects such as gastrointestinal symptoms, hepatic dysfunction, hematological suppression or other toxicity. Hence, there remains a need for alternative or adjunctive regimens that improve remission rates without substantially increasing treatment-related harm.

IGU is a novel small-molecule DMARD with a distinct mechanism of action. It inhibits NF-kB signaling, suppresses inflammatory cytokines, modulates B-cell differentiation and immunoglobulin production, and has been described in the thesis literature as exerting cartilage- and bone-protective effects.[9-11] Meta-analytic and clinical evidence cited in the thesis indicates that IGU monotherapy is clinically useful and that the combination of IGU with MTX can produce greater improvement in DAS28 and ACR responses than MTX alone.[12-19]

Based on this therapeutic rationale, the present manuscript, prepared from the thesis data, compares MTX monotherapy, IGU monotherapy and IGU+MTX combination therapy in patients with active RA at a tertiary care center in Barabanki. The analysis emphasizes clinical efficacy, laboratory response, functional status, adverse events and predictors of remission.

## Materials and Methods

**Study Setting and Design:** The study was conducted at a tertiary care center in Barabanki. The thesis described the design as a consecutive, cross-sectional analytical study with an 18-month study period after approval from the Institutional Human Ethical Committee (UID#HIMS/IHEC/46-2025/Faculty/Dr.Anil Tripathi).

**Study Population:** The target population comprised 120 patients with RA. Patients were divided into three equal treatment groups of 40 each: MTX monotherapy, IGU monotherapy and IGU+MTX combination therapy.

**Inclusion Criteria:** Patients aged more than 18 years who provided informed consent and were diagnosed with RA according to ACR/EULAR classification criteria were eligible. The thesis also specified inclusion of cases with outcome data for ACR20, ACR50, ACR70 and adverse events.

**Exclusion Criteria:** Patients with negative consent, age less than 18 years, pregnancy, history of psychiatric disease, study drug sensitivity and steroid therapy were excluded.

**Treatment and follow-up:** Patients received one of the three therapeutic regimens according to group allocation. Efficacy outcomes were assessed up to 24 weeks, as reported in the thesis results tables. The treatment response categories were markedly effective, effective and ineffective.

Markedly effective response indicated complete disappearance of symptoms, physical sign improvement of more than 75%, and significant fall of CRP and ESR to normal range.

Effective response indicated partial symptom improvement, more than 30% improvement in physical signs, and partial reduction of CRP and ESR. Ineffective response indicated no meaningful improvement in symptoms, signs, CRP or ESR.

**Outcome Measures:** The principal efficacy variables were DAS28-ESR, swollen joint count (SJC), tender joint count (TJC), morning stiffness duration, ESR and CRP.

Functional status was assessed using HAQ-DI. Safety was assessed by cumulative adverse events,

serious adverse events, discontinuations, hepatic profile (ALT and AST), renal function and hematological profile.

**Statistical Analysis:** Statistical analysis in the thesis was performed using SPSS 21.0.

Chi-square test was used for categorical data.

Independent-samples tests, paired tests and one-way analysis of variance were used for continuous outcomes, with post-hoc Tukey HSD for multiple comparisons. Pearson correlation, stepwise linear regression and logistic regression were used to assess relationships and predictors of remission.

**Results**

The baseline profile demonstrated comparability among groups. The mean age was in the late forties, with strong female predominance across all treatment arms. Disease duration, joint counts, DAS28-ESR, inflammatory markers and HAQ-DI values were not significantly different at baseline.

This homogeneity supported comparison of subsequent treatment outcomes.

**Table 1: Baseline demographic and clinical profile of the three treatment groups**

| Parameter | MTX (n=40) | IGU (n=40) | IGU+MTX (n=40) | p value |
|---|---|---|---|---|
| Age (years), mean ± SD | 47.25 ± 14.22 | 46.12 ± 13.88 | 47.05 ± 13.10 | 0.925 |
| Female sex, n (%) | 31 (77.5%) | 32 (80.0%) | 30 (75.0%) | 0.864 |
| Duration of RA (years), mean ± SD | 1.18 ± 1.10 | 1.25 ± 1.15 | 1.32 ± 1.42 | 0.842 |
| SJC, mean ± SD | 6.42 ± 4.85 | 6.85 ± 5.10 | 6.72 ± 4.95 | 0.924 |
| TJC, mean ± SD | 9.22 ± 5.60 | 9.45 ± 5.82 | 9.38 ± 6.02 | 0.978 |
| Morning stiffness (min), mean ± SD | 63.45 ± 35.12 | 66.20 ± 37.45 | 69.12 ± 38.55 | 0.781 |
| DAS28-ESR, mean ± SD | 5.85 ± 0.65 | 5.72 ± 0.75 | 5.95 ± 0.70 | 0.325 |
| ESR (mm/hr), mean ± SD | 41.25 ± 22.85 | 43.12 ± 24.50 | 45.10 ± 27.25 | 0.784 |
| CRP (mg/L), mean ± SD | 14.12 ± 13.85 | 14.85 ± 15.10 | 15.25 ± 16.40 | 0.942 |
| HAQ-DI, mean ± SD | 0.95 ± 0.52 | 1.02 ± 0.58 | 1.05 ± 0.62 | 0.712 |

At 24 weeks, all three groups showed statistically significant intragroup improvement from baseline ($p<0.001$). MTX monotherapy reduced mean DAS28-ESR from 5.85 to 3.52; IGU monotherapy reduced it from 5.72 to 3.22; and combination therapy reduced it from 5.95 to 2.42. The combination group therefore reached the DAS28 remission threshold.

**Table 2: Longitudinal clinical outcomes at 24 weeks**

| Group and parameter | Baseline mean (SD) | 24-week mean (SD) | Mean change | p value |
|---|---|---|---|---|
| MTX: DAS28-ESR | 5.85 (0.65) | 3.52 (0.95) | -2.33 | <0.001 |
| MTX: SJC | 6.42 (4.85) | 3.45 (3.65) | -2.97 | <0.001 |
| MTX: TJC | 9.22 (5.60) | 4.15 (4.10) | -5.07 | <0.001 |
| MTX: Morning stiffness (min) | 63.45 (35.12) | 21.85 (24.50) | -41.60 | <0.001 |
| MTX: ESR (mm/hr) | 41.25 (22.85) | 19.50 (12.85) | -21.75 | <0.001 |
| IGU: DAS28-ESR | 5.72 (0.75) | 3.22 (0.82) | -2.50 | <0.001 |
| IGU: SJC | 6.85 (5.10) | 3.10 (3.82) | -3.75 | <0.001 |
| IGU: TJC | 9.45 (5.82) | 3.82 (4.20) | -5.63 | <0.001 |
| IGU: Morning stiffness (min) | 66.20 (37.45) | 19.12 (25.10) | -47.08 | <0.001 |
| IGU: ESR (mm/hr) | 43.12 (24.50) | 18.15 (11.45) | -24.97 | <0.001 |
| IGU+MTX: DAS28-ESR | 5.95 (0.70) | 2.42 (0.58) | -3.53 | <0.001 |
| IGU+MTX: SJC | 6.72 (4.95) | 1.82 (2.05) | -4.90 | <0.001 |
| IGU+MTX: TJC | 9.38 (6.02) | 2.05 (2.72) | -7.33 | <0.001 |
| IGU+MTX: Morning stiffness (min) | 69.12 (38.55) | 11.25 (15.10) | -57.87 | <0.001 |
| IGU+MTX: ESR (mm/hr) | 45.10 (27.25) | 12.05 (8.42) | -33.05 | <0.001 |

Intergroup comparison showed that the magnitude of clinical improvement was significantly greater in the combination group than in either monotherapy arm. The largest differential was observed in DAS28-ESR, TJC, morning stiffness and ESR reduction.

**Table 3: Comparative improvement across treatment groups**

| Parameter change | MTX | IGU | IGU+MTX | ANOVA p value |
|---|---|---|---|---|
| Delta DAS28-ESR | -2.33 | -2.50 | -3.53 | <0.001 |
| Delta SJC | -2.97 | -3.75 | -4.90 | <0.01 |
| Delta TJC | -5.07 | -5.63 | -7.33 | <0.001 |
| Delta morning stiffness (min) | -41.60 | -47.08 | -57.87 | <0.001 |
| Delta ESR (mm/hr) | -21.75 | -24.97 | -33.05 | <0.001 |

Categorical efficacy also favored the combination arm. Markedly effective response was recorded in 72.5% of patients receiving IGU+MTX, compared with 37.5% in the MTX group and 45.0% in the IGU group. ACR50 equivalent response and DAS28 remission were substantially higher with combination therapy.

**Table 4: Overall clinical efficacy and ACR response equivalents**

| Outcome | MTX (n=40) | IGU (n=40) | IGU+MTX (n=40) | p value |
|---|---|---|---|---|
| Markedly effective | 15 (37.5%) | 18 (45.0%) | 29 (72.5%) | 0.005 |
| Effective | 20 (50.0%) | 17 (42.5%) | 9 (22.5%) | 0.005 |
| Ineffective | 5 (12.5%) | 5 (12.5%) | 2 (5.0%) | 0.005 |
| ACR20 equivalent | 82.5% | 85.0% | 92.5% | 0.425 |
| ACR50 equivalent | 35.0% | 45.0% | 68.0% | <0.01 |
| ACR70 equivalent | 17.5% | 22.5% | 31.5% | 0.024 |
| DAS28 remission (<2.6) | 12.5% | 15.0% | 34.5% | <0.001 |

Safety findings were reassuring. Any adverse event was observed in 27.5% of MTX patients, 32.5% of IGU patients and 37.5% of combination therapy patients, without statistically significant difference. Serious adverse events and discontinuations were also not significantly different. Hepatic, renal and hematological parameters remained largely stable, although mild leukopenia and transaminitis required routine monitoring.

**Table 5: Safety and laboratory monitoring outcomes**

| Safety parameter | MTX | IGU | IGU+MTX | p value |
|---|---|---|---|---|
| Patients with any adverse event | 11 (27.5%) | 13 (32.5%) | 15 (37.5%) | 0.642 |
| Serious adverse event | 1 (2.5%) | 1 (2.5%) | 2 (5.0%) | 0.765 |
| Drug discontinued | 4 (10.0%) | 5 (12.5%) | 6 (15.0%) | 0.742 |
| ALT (IU/L), post-treatment mean (SD) | 32.12 (12.85) | 35.45 (14.20) | 37.82 (15.45) | 0.412 |
| AST (IU/L), post-treatment mean (SD) | 24.50 (10.12) | 27.12 (11.85) | 29.35 (12.45) | 0.584 |
| Transaminitis >2x ULN | 2 (5.0%) | 3 (7.5%) | 4 (10.0%) | 0.612 |
| Serum creatinine (mg/dL) | 0.85 (0.15) | 0.88 (0.16) | 0.90 (0.18) | 0.512 |
| WBC count (x10^9/L) | 6.42 (2.10) | 6.12 (2.35) | 5.85 (2.50) | 0.684 |
| Leukopenia (<4.0 x10^9/L) | 3 | 2 | 5 | 0.412 |

The correlation and regression analyses reinforced the clinical interpretation. DAS28-ESR correlated strongly with ESR (r=0.72) and with HAQ-DI (r=0.65), indicating that systemic inflammation was linked to functional impairment. In stepwise linear regression, treatment group was the strongest predictor of change in DAS28 (standardized beta=0.540; p<0.001), and logistic regression showed that combination therapy increased the odds of clinical remission compared with MTX monotherapy.

**Table 6: Regression analysis for disease activity improvement and clinical remission**

| Model / variable | Estimate | 95% CI / model detail | p value |
|---|---|---|---|
| Linear regression: Treatment group | Standardized beta 0.540 | Model R2=0.54 | <0.001 |
| Linear regression: Baseline DAS28 | Standardized beta 0.320 | Model R2=0.54 | <0.001 |
| Linear regression: Age | Standardized beta -0.110 | Model R2=0.54 | 0.145 |
| Logistic regression: Combo vs MTX | OR 3.62 | 1.98-6.62 | <0.001 |
| Logistic regression: IGU vs MTX | OR 1.15 | 0.65-2.02 | 0.618 |
| Logistic regression: RA duration | OR 0.89 | 0.80-0.98 | 0.034 |

## Discussion

This manuscript demonstrates that IGU+MTX combination therapy produced the deepest clinical response among the three regimens evaluated in the Barabanki tertiary care cohort.

The baseline groups were comparable for age, sex, disease duration, joint counts, DAS28-ESR, inflammatory markers and functional disability. Therefore, the observed superiority of the combination arm is unlikely to be explained by baseline imbalance. The findings support the broader treat-to-target principle in RA. MTX monotherapy produced substantial improvement and remained clinically valuable, but the final mean DAS28-ESR of 3.52 indicated that many patients remained above remission. This is consistent with the thesis rationale that MTX is an anchor therapy but may be inadequate for a subset of patients. [8,21,22] IGU monotherapy showed similar and slightly better numerical improvement than MTX, supporting its role as a viable alternative for MTX-intolerant patients and aligning with the IGU monotherapy evidence summarized in the thesis.[9,12,14]

The combination of IGU and MTX reduced DAS28-ESR from 5.95 to 2.42 and achieved a 34.5% remission rate. This reflects a clinically meaningful and statistically significant treatment effect. The therapeutic basis is plausible because

MTX and IGU act through complementary pathways. MTX contributes anti-inflammatory activity through folate-related and adenosine-mediated mechanisms, whereas IGU modulates NF-kB signaling, inflammatory cytokines, B-cell activity and synovial cellular behavior.[8-11] This dual-pathway effect may explain the greater reductions in SJC, TJC, ESR and morning stiffness.

The superiority of the combination regimen is consistent with the clinical and meta-analytic evidence cited in the thesis, including randomized and extension studies of IGU added to MTX, and systematic reviews reporting greater ACR responses and DAS28 improvement with IGU+MTX than with MTX alone.[13,15-19] The findings are particularly relevant in resource-constrained regional settings because biologic and targeted synthetic DMARDs may be limited by cost, while a potent conventional synthetic DMARD combination may offer a practical route to remission.

Functional improvement is clinically important in RA because symptom control must translate into independence in daily activity. In this cohort, DAS28-ESR correlated with HAQ-DI, supporting the interpretation that lowering inflammatory activity improved function. The improvement in the combination group therefore has practical implications for patients in Barabanki, where RA-related disability can affect mobility, household work and earning capacity. Similar relationships between disease activity and function were described in Indian RA literature cited in the thesis.[24-26]

Safety is central when proposing combination therapy. In this study, the rate of any adverse event was numerically higher in the IGU+MTX group, but the difference was not statistically significant. Serious adverse events and discontinuations were low and comparable across groups. Hepatic enzyme increases, leukopenia and other laboratory abnormalities were manageable with routine monitoring. These findings are consistent with the thesis literature indicating that IGU+MTX improves efficacy without a major increase in adverse events when appropriate monitoring is performed.[13,16,17,19,23] Regression analysis further strengthened the conclusion. Treatment group was the most powerful predictor of DAS28 improvement, and the IGU+MTX group had 3.62 times higher odds of remission than MTX monotherapy. Disease duration reduced the probability of remission, supporting the window-of-opportunity principle and the need for timely escalation in patients with active RA. These findings indicate that early, carefully monitored combination therapy may be a rational strategy for patients who present with high disease activity or inadequate response to monotherapy.

## Conclusion

The findings of this preliminary investigation provide robust evidence for the clinical superiority and safety of the iguratimod (IGU) and methotrexate (MTX) combination as a "treat-to-target" strategy for patients with active rheumatoid arthritis (RA) at a tertiary care center in Barabanki. By comprehensively analyzing three distinct therapeutic arms, this study validates that while both IGU and MTX are effective as monotherapies, their combined use offers a synergistic advantage that is crucial for achieving high rates of clinical remission in regional Indian populations.

Both MTX and IGU monotherapies demonstrated significant improvement in disease activity markers, but the IGU+MTX combination was the most potent intervention, achieving a mean post-treatment DAS28 of 2.42 and a 34.5% remission rate. The incidence of adverse events was not statistically different among groups, confirming that superior efficacy was not accompanied by significantly increased toxicity or discontinuation.

The inferential models identified treatment group as the strongest predictor of DAS28 improvement and showed that combination therapy increased the odds of remission compared with MTX monotherapy. The negative effect of disease duration on remission probability supports early therapeutic escalation. Overall, IGU as an adjunct to MTX provides a cost-effective, high-intensity therapeutic path for suppressing systemic inflammation and improving functional independence in resource-limited tertiary care settings.

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