International Journal of Science and Healthcare Research
[Indexed, Peer-Reviewed Journal]
Vol. 10; Issue: 4; Oct.-Dec. 2025
Website: ijshr.com
Original Research Article
ISSN: 2455-7587

Comparative Study of Efficacy and Safety of Iguratimod Plus Methotrexate versus Methotrexate Monotherapy in Patients with Rheumatoid Arthritis

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DOI: https://doi.org/10.52403/ijshr.20250409

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with progressive joint destruction, disability, and comorbidities. Methotrexate (MTX) is the cornerstone of RA therapy, but many patients exhibit inadequate response or intolerance. Iguratimod (IGU), a novel disease-modifying antirheumatic drug (DMARD), inhibits NF-κB signaling and complements MTX's mechanisms. Evidence from East Asia suggests that IGU combined with MTX improves disease control, but data from Indian populations remain limited.

Methods: This was a prospective, randomized, open-label, parallel-group clinical trial conducted over 18 months. A total of 120 RA patients fulfilling the 2010 ACR/EULAR criteria with active disease despite stable MTX therapy were randomized into two groups: MTX monotherapy (n=60) and MTX + IGU (n=60). Patients were followed for 24 weeks. The primary endpoint was the proportion achieving ACR20 at week 24. Secondary outcomes included ACR50/70, DAS28-ESR/CRP, HAQ-DI, ESR, CRP, and safety assessments. Statistical analysis was performed using intention-to-treat principles.

Results: Baseline characteristics were comparable between groups. At 24 weeks, the MTX+IGU group demonstrated significantly greater improvements in tender/swollen joint counts, ESR, CRP, DAS28, and HAQ-DI compared to MTX alone (all $p < 0.0001$). ACR20, ACR50, and ACR70 response rates were higher in the combination group (90%, 70%, and 26.7%) versus MTX monotherapy (83.3%, 33.3%, and 16.7%). Adverse events, including nausea, leukopenia, and elevated liver enzymes, were mild and comparable between groups, with no significant differences.

Conclusion: The combination of iguratimod and methotrexate was significantly more effective than methotrexate monotherapy in reducing disease activity and improving functional outcomes in Indian RA patients, without increasing adverse events. These findings support IGU + MTX as a safe, potent, and cost-effective therapeutic strategy for RA in resource-limited settings.

Keywords: Rheumatoid arthritis; Methotrexate; Iguratimod; Combination therapy; Disease Activity

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovitis, progressive joint

destruction, and significant disability. Affecting 0.5–1% of the global population, RA is associated with pain, functional impairment, and increased mortality. Its pathogenesis involves genetic susceptibility, environmental triggers, and immune dysregulation, with aberrant activation of T and B cells and overproduction of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17. [1-6]

Methotrexate (MTX) remains the cornerstone of RA therapy due to its efficacy, affordability, and long-term safety. However, many patients fail to achieve adequate disease control or develop intolerance, necessitating combination regimens. [7]

Iguratimod (IGU), a novel small-molecule DMARD, has shown promise as an adjunct to MTX. IGU inhibits NF-κB activation, reduces immunoglobulin production, and suppresses pro-inflammatory cytokines, thereby complementing MTX's mechanisms. [8]

In India, RA prevalence is estimated at 0.5–0.75%, translating into millions of affected individuals. Indian patients often present with more severe disease activity at diagnosis compared to Western cohorts, partly due to delayed recognition and limited access to rheumatology care. The disease disproportionately affects women, with a female-to-male ratio of about 3:1, and typically manifests during peak productive years, amplifying socioeconomic burden. [9]

Comorbidities such as anemia, cardiovascular disease, and osteoporosis are common in Indian RA patients, complicating management and increasing healthcare costs. Limited access to biologics due to financial constraints further underscores the need for effective, affordable oral DMARD combinations. [10]

RA pathophysiology is driven by immune dysregulation. Antigen-presenting cells activate autoreactive T cells, which stimulate B cells to produce autoantibodies such as RF and ACPA. These immune complexes perpetuate synovial inflammation, while cytokines like TNF-α and IL-6 drive synovial proliferation, angiogenesis, and osteoclast-mediated bone erosion. MTX exerts anti-inflammatory effects by inhibiting folate-dependent enzymes and increasing extracellular adenosine. However, it does not fully suppress all inflammatory pathways. IGU complements MTX by inhibiting NF-κB signaling, reducing cytokine transcription, and modulating B- and T-cell responses. This mechanistic synergy suggests that IGU plus MTX may achieve superior disease control compared to MTX alone. [7-11]

Clinical studies from East Asia have demonstrated that IGU, either as monotherapy or combined with MTX, improves ACR response rates, DAS28 scores, ESR, and CRP levels compared to MTX alone. Meta-analyses confirm that IGU plus MTX enhances efficacy without significantly increasing serious adverse events. Reported side effects are generally mild, including gastrointestinal discomfort and reversible liver enzyme elevations. [12]

Long-term safety data on IGU remain limited, especially regarding hepatotoxicity, hematological effects, and drug interactions in Indian populations. Moreover, head-to-head comparative studies of IGU plus MTX versus MTX monotherapy in India are scarce.

This study seeks to determine whether combination therapy with Iguratimod plus methotrexate provides superior efficacy and comparable safety to methotrexate monotherapy in Indian patients with rheumatoid arthritis. The null hypothesis is that there is no significant difference in efficacy or safety between the two regimens, while the alternative hypothesis is that Iguratimod plus methotrexate achieves greater disease control without compromising safety. The objectives are threefold: (1) to compare clinical efficacy between the two regimens using standardized disease activity measures; (2) to evaluate safety and tolerability profiles in Indian patients; and (3) to generate region-specific evidence that can inform cost-

effective, accessible treatment strategies for rheumatoid arthritis in India.

MATERIALS & METHODS

This study was designed as a prospective, randomized, open-label, parallel-group comparative clinical trial. The study was conducted over a period of 18 months, which included 3 months for patient recruitment, 12 months of treatment and follow-up, and 3 months for data analysis and reporting.

Inclusion Criteria: Patients were eligible for inclusion if they were between 18 and 65 years of age, fulfilled the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA),[13] had active disease defined as a DAS28-ESR score greater than 3.2 despite receiving stable methotrexate (MTX) therapy for at least 12 weeks, and were willing to provide informed consent and comply with all study procedures.

Exclusion Criteria: Patients were excluded if they had prior exposure to Iguratimod or biologic DMARDs, significant hepatic, renal, or hematological dysfunction, were pregnant, lactating, or planning pregnancy during the study period, had active infections such as tuberculosis, hepatitis B or C, or HIV, or had a history of malignancy or other autoimmune connective tissue diseases.

Sample Size

The sample size was calculated based on an expected difference of 20% in ACR20 response rates between the two groups, with 80% power and a 5% significance level. Accounting for a 10% dropout rate, a total of 120 patients were recruited, with 60 patients allocated to each treatment arm.

Outcome Parameters: The primary outcome was the proportion of patients achieving an ACR20 response at 24 weeks, while secondary outcomes included ACR50 and ACR70 response rates, changes in DAS28-ESR and DAS28-CRP scores, improvement in the Health Assessment Questionnaire Disability Index (HAQ-DI), evaluation of laboratory markers such as ESR, CRP, and RF/ACPA titers, as well as safety outcomes including the incidence of adverse events, liver function abnormalities, hematological changes, and gastrointestinal intolerance.

Data Collection: Baseline demographic and clinical data were collected at enrollment. Patients were evaluated at baseline, 4 weeks, 12 weeks, and 24 weeks. At each visit, disease activity scores, laboratory parameters, and adverse events were recorded. Compliance was assessed through pill counts and patient diaries.

Methodology: Patients in the MTX monotherapy group received oral methotrexate at a dose of 15–25 mg/week with folic acid supplementation. Patients in the combination group received the same MTX regimen plus oral Iguratimod 25 mg twice daily. Dose adjustments were permitted based on tolerability and laboratory monitoring.

All patients received standard supportive care, including non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose corticosteroids if clinically indicated. Concomitant use of other DMARDs or biologics was not permitted.

Adverse events were monitored through clinical evaluation and laboratory investigations, including complete blood counts, liver and renal function tests, performed at baseline and every 4–8 weeks.

STATISTICAL ANALYSIS

Data were analyzed using SPSS software (version XX). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Between-group comparisons were performed using the independent t-test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Efficacy outcomes were analyzed on an intention-to-treat basis. Repeated measures ANOVA was used to assess changes in disease activity scores over time. A p-value < 0.05 was considered statistically significant. Safety analyses included all patients who received at least one dose of study medication.

RESULTS

The results show that the groups were well-matched, with no statistically significant differences in age, gender distribution, duration of RA, or key disease activity measures like tender/swollen joint counts, ESR, and CRP (all p-values > 0.05) [Table 1].

Table 1: Comparison of Baseline Demographic and Clinical Characteristics

Parameters	Group MTX + IGU (N=60)	Group MTX (N=60)	P-Value
Age in Years, Mean ± SD	47.73 ± 11.15	48.04 ± 10.79	0.8773*
Female Gender, n (%)	43 (71.67)	39 (65)	0.5564**
Duration of RA in years, Mean ± SD	7.47 ± 2.58	7.32 ± 2.61	0.7521*
Tender Joint Count, Mean ± SD	5.06 ± 1.53	4.97 ± 1.32	0.7307*
Swollen Joint Count, Mean ± SD	2.39 ± 0.82	2.31 ± 1.10	0.6523*
ESR in mm/h, Mean ± SD	57.78 ± 26.56	57.91 ± 22.89	0.9771*
CRP in mg/L, Mean ± SD	33.49 ± 24.57	32.80 ± 17.61	0.8600*

***Unpaired t test; **Fisher's Exact Test**

MTX + IGU combination therapy was significantly more effective than MTX alone in reducing disease activity. The group receiving the combination showed markedly lower mean scores for tender joint count, swollen joint count, ESR, and CRP, with all differences being highly statistically significant (p < 0.0001), indicating a superior clinical response in reducing inflammation and joint symptoms [Table 2].

Table 2: Comparison of Clinical Features of RA after 24 Weeks

Parameters	Group MTX + IGU (N=60)	Group MTX (N=60)	P-Value (Unpaired t test)
Tender Joint Count, Mean ± SD	0.26 ± 0.07	0.79 ± 0.26	<0.0001
Swollen Joint Count, Mean ± SD	0.24 ± 0.11	0.68 ± 0.20	<0.0001
ESR in mm/h, Mean ± SD	14.35 ± 5.95	25.54 ± 12.08	<0.0001
CRP in mg/L, Mean ± SD	5.67 ± 2.31	10.83 ± 5.16	<0.0001

While both groups started with similar, high disease activity at baseline, the MTX + IGU group showed a more rapid and pronounced improvement. A statistically significant difference in favor of the combination therapy emerged by week 12 (p=0.0409) and became highly significant by week 24 (p<0.0001), with the combination group achieving a mean DAS-28 score of 2.03, indicating low disease activity, compared to 2.97 in the MTX group [Table 3].

Table 3: Comparison of DAS-28 score from Baseline to 24 Weeks

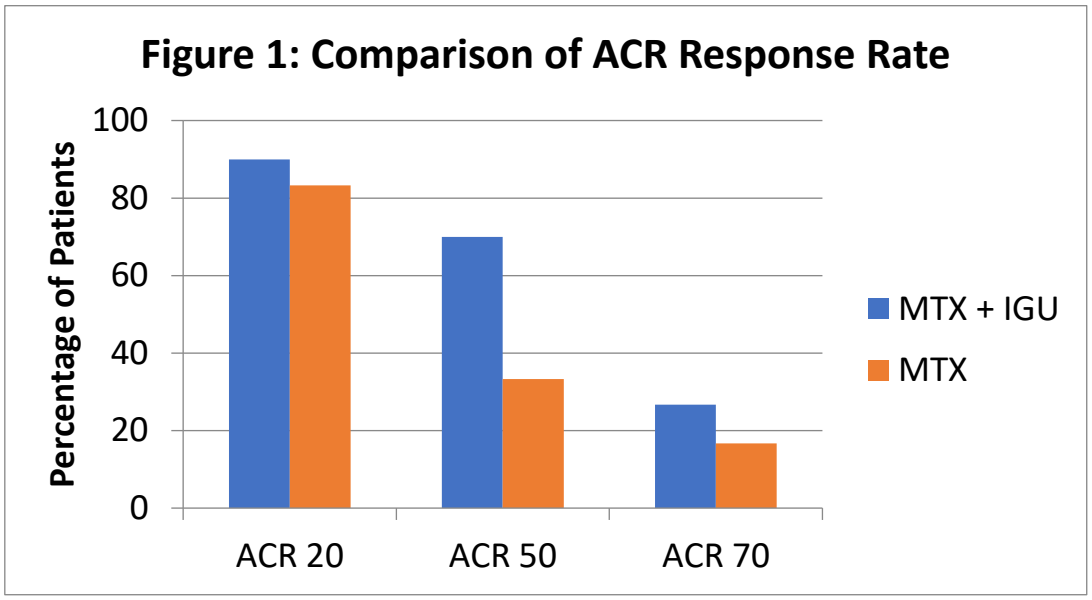
Time	Parameters in Mean ± SD		P-Value (Unpaired t test)
	Group MTX + IGU (N=60)	Group MTX (N=60)	
Baseline	5.26 ± 1.32	5.19 ± 1.07	0.7502
4 Weeks	4.63 ± 1.41	4.89 ± 1.17	0.2739
12 Weeks	3.09 ± 1.12	3.54 ± 1.26	0.0409
24 Weeks	2.03 ± 0.39	2.97 ± 0.65	<0.0001
P-Value (Repeated Measure ANOVA)	<0.0001	<0.0001	

The results show that both groups improved from baseline, but the MTX + IGU group experienced a significantly greater reduction in disability. The difference became highly

significant from week 12 onward ($p<0.0001$), culminating at 24 weeks with the combination group reporting a much lower mean disability score, suggesting a meaningful improvement in patients' physical function compared to the MTX-only group [Table 4].

Table 4: Comparison of HAQ-DI Score from Baseline to 24 Weeks

Time	Parameters in Mean ± SD		P-Value (Unpaired t test)
	Group MTX + IGU (N=60)	Group MTX (N=60)	
Baseline	1.74 ± 0.69	1.81 ± 0.54	0.5372
4 Weeks	1.47 ± 0.55	1.59 ± 0.62	0.2643
12 Weeks	0.98 ± 0.31	1.33 ± 0.47	<0.0001
24 Weeks	0.65 ± 0.14	1.12 ± 0.27	<0.0001
P-Value (Repeated Measure ANOVA)	<0.0001	<0.0001	



More patients in MTX + IGU achieved ACR20, ACR 50 and ACR 70 as compared to MTX group [Figure 1].

Table 5: Comparison of Adverse Events from Baseline to 24 Weeks

Adverse Event	Number of Patients		P-Value (Fisher's Exact Test)
	Group MTX + IGU (N=60)	Group MTX (N=60)	
Nausea/Vomiting	5	4	>0.9999
Leukopenia	3	2	>0.9999
Rise in Liver Transaminase	7	5	0.7623
Oral Ulcer	0	1	>0.9999

The incidence of common side effects such as nausea/vomiting, leukopenia, elevated liver enzymes, and oral ulcers was low and similar between the two treatment groups, with no statistically significant differences (all p-values > 0.05). This indicates that adding IGU to MTX did not lead to a significant increase in the measured adverse events, suggesting a comparable safety and tolerability profile to MTX monotherapy in this study [Table 5].

DISCUSSION

The scientific rationale for combining iguratimod (IGU) with methotrexate (MTX) in rheumatoid arthritis (RA) lies in their

complementary mechanisms of action. MTX, a conventional synthetic disease-modifying antirheumatic drug (csDMARD), primarily exerts anti-inflammatory and immunomodulatory effects by inhibiting folate metabolism and adenosine signaling. Iguratimod, a newer synthetic DMARD, specifically inhibits nuclear factor-kappa B (NF-κB) signaling, which is a master regulator of the pro-inflammatory cytokines that drive RA pathogenesis. Furthermore, IGU has been shown to directly suppress antibody production by B cells and inhibit osteoclastogenesis. Therefore, the combination theoretically provides a more comprehensive suppression of the inflammatory cascade and joint destruction than either drug alone. [7-11]

The results of our study demonstrate clear clinical significance. The data show that the MTX+IGU combination was significantly more effective than MTX monotherapy in reducing all measured parameters of disease activity, including tender/swollen joint counts, ESR, CRP, DAS-28, and HAQ-DI, with differences becoming highly statistically significant by the 24-week endpoint. Most notably, Result indicates a superior ACR response rate, particularly for the more stringent ACR50 and ACR70 criteria, signifying that the combination therapy not only improves symptoms but also delivers a deeper, more meaningful level of disease control and functional improvement for patients. Critically, safety profile confirms that this enhanced efficacy was not achieved at the cost of increased adverse events, underscoring the combination's favorable safety profile.

Our findings are strongly reinforced by and consistent with the broader body of previous research. The significant improvements in ACR responses and DAS-28 scores you observed align perfectly with the pooled results of the meta-analyses by Chen et al. (2021) and Zeng et al. (2022), which reported similar relative risks for ACR20/50/70 and reductions in DAS-28 for the IGU+MTX combination.[12, 14] The specific outcomes from our 24-week RCT closely mirror those of Duan et al. (2015) and the landmark Ishiguro et al. (2013) trial, both of which established the efficacy of adding IGU to MTX in inadequate responders. [15, 16] The real-world data from Mu et al. (2021) further validates that the high ACR response rates you observed are achievable in routine clinical practice. [17]

A pivotal comparative point arises from the recent SMILE study (Du et al., 2025), which expands the clinical application of IGU into MTX-naïve, early RA patients. [18,] While our study and others focused on MTX-inadequate responders, the SMILE study demonstrates that IGU monotherapy is non-inferior and even superior to MTX monotherapy as an initial treatment. [18] This positions IGU not just as an add-on therapy but as a viable first-line option. [19] Our results, showing the clear superiority of the combination, complement this by solidifying IGU+MTX as a potent initial combination strategy for achieving high disease control, as also seen in the SMILE study's combination arm. Finally, the long-term extension study by Hara et al. (2014) provides a reassuring outlook that the significant benefits you observed at 24 weeks can be maintained over a longer duration with a consistent safety profile. [20]

In summary, our study's results are a robust confirmation within a well-established scientific and clinical context. They contribute to the compelling evidence that the combination of iguratimod and methotrexate is an effective, safe, and valuable treatment strategy for RA, capable of providing superior disease control and improved patient outcomes compared to MTX alone.

A key limitation of this study is its single-center design and relatively small sample size (N=120), which may limit the generalizability of the findings to broader, more diverse RA populations. The 24-week duration is sufficient to establish efficacy but is too short to evaluate long-term safety, drug sustainability, and radiographic outcomes.

Future research should prioritize a large-scale, multicenter, double-blinded, randomized controlled trial with a longer follow-up period of at least 52 to 104 weeks to confirm these efficacy results and thoroughly evaluate long-term safety and the impact on radiographic progression. Subsequent studies should also investigate the effectiveness of the MTX+IGU combination in specific subpopulations, such as MTX-naïve patients or those with particular serological or genetic profiles, to enable more personalized treatment strategies. Furthermore, comparative effectiveness research pitting the MTX+IGU combination against other modern csDMARD and bDMARD combinations would be invaluable for determining its optimal position within the RA treatment algorithm.

CONCLUSION

In conclusion, this study robustly demonstrates that the combination of iguratimod and methotrexate is significantly more effective than methotrexate monotherapy in reducing disease activity and improving functional outcomes in patients with rheumatoid arthritis over a 24-week period, without a significant increase in adverse events. These findings align with and strengthen the existing body of evidence from both randomized trials and real-world studies, confirming the role of this combination as a potent and safe treatment strategy. Despite limitations such as sample size and study duration, the results provide compelling support for the use of iguratimod as a valuable therapeutic option, both in combination for enhanced efficacy and, as supported by newer research, as a potential first-line monotherapy.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: We are thankful to the healthcare workers of NMCH, Patna

Source of Funding: Nil

Conflict of Interest: Nil

Presentation at a meeting: Nil

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How to cite this article: Priyanka Kumari, Santosh Kumar, Kumar Gaurav, Arun Kumar, Asha Singh. Comparative study of efficacy and safety of Iguratimod plus methotrexate versus methotrexate monotherapy in patients with rheumatoid arthritis. *Int. J. Sci. Healthc. Res.* 2025; 10(4): 55-62. DOI: *https://doi.org/10.52403/ijshr.20250409*

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