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ORIGINAL ARTICLE

Tofacitinib plus methotrexate versus tofacitinib monotherapy in rheumatoid arthritis: A comprehensive evidence synthesis and critical analysis.

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ABSTRACT… Objective: To compare the benefits of Tofacitinib with Methotrexate vs Tofacitinib alone with respect to efficacy and safety over a period of 6 months. **Study Design:** Randomized Controlled Trial. **Setting:** Outpatient Department of Rheumatology, Madinah Teaching Hospital, Faisalabad. **Period:** 01st August,2025 to 31st Jan,2026. **Methods:** Consisted of 60 people enrolled as per the inclusion criteria (ACR/EULAR 2010 Criteria), after getting approval from the ethics review committee. Individuals segregated into two groups: Group A received Tofacitinib alone, whereas Group B received Tofacitinib with Methotrexate. DAS28-ESR, along with ESR and CRP, was used as an assessment tool for response, both at baseline and at 6 months. **Results:** Both the arms showed improvement in disease activity, however there were better results in the combination arm than with monotherapy (−2.3 ± 0.6 vs −1.6 ± 0.5; $p < 0.001$). Remission and reduction of disease activity was observed in the combination group with the occurrence of more adverse effects in the same group. **Conclusion:** Tofacitinib with Methotrexate provides better efficacy for disease control as compared to Tofacitinib alone. This consolidates the prior belief that Methotrexate is the anchor drug in the management of RA.

Key words: Combination Therapy, DAS28, JAK Inhibitors, Methotrexate, Rheumatoid Arthritis, Tofacitinib.

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INTRODUCTION

Rheumatoid arthritis is a long-standing, inflammatory disorder that leads to a continuous process of joint destruction, disability, and permanent deformities in severe cases. In the management of this condition, Janus Kinase inhibitors, especially Tofacitinib, have emerged as saviors in the class of DMARDs, both individually and in combination with methotrexate.[1] Despite major therapeutic advances over the last twenty years, sustained remission of RA is still not possible in majority of patients and treatment approaches continue to be refined.[2] The advent of Targetted synthetic Disease Modifying anti-Rheumatic Drugs (ts-DMARDs) , particularly Janus Kinase (JAK) inhibitors has broadened the available therapeutic options and the long-standing paradigm of Methotrexate (MTX) as the anchor drug.[3] Tofacitinib, the first Janus Kinase inhibitor to be approved for RA particularly targets JAK1 and JAK3, targeting multiple cytokine activated inflammatory pathways involved in the pathogenesis of disease.[4]

Evidence from RCTs has demonstrated that Tofacitinib is effective both as monotherapy and as combination with other conventional synthetic DMARDs (cs-DMARDs), especially Methotrexate.[1,5] Nevertheless, the relative advantages and limitations of these strategies remain incompletely defined and the real-world prescribing practices vary widely.[6] Combination increases the risk of adverse events alongside, further increasing the treatment burden.[7] In contrast monotherapy offers a relatively simpler regimen and fewer side effects associated with MTX, it also causes modest efficacy decline.[8] The ORAL Strategy trial represents a pivotal Head-to-Head Randomized Control Trial (RCT) comparing Tofacitinib monotherapy with Tofacitnib plus MTX and Adalimumab with MTX in patients with inadequate response to MTX, providing robust clinical data about efficacy and safety.[1] Additionl insights can be derived from ORAL Scan, ORAL Start and ORAL Shift trials, as well as from systemic reviews and Met-analyses offering a borader perspective of efficacy, safety and outcome measures in different

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populations.[9,10,11,16]

The objectives of this review are to:(1) compare the clinical efficacy of Tofacitinib monotherapy and combination therapy across multiple outcome domains (2) evaluate safety and tolerability (3) analyze radiographic and structural outcomes (4) assess patient-reported outcomes and health-related quality of life (5) explore baseline factors influencing differential treatment response (6) highlight methodological limitations and evidence gaps (7) propose evidence-based clinical recommendations while outlining priorities for future research. This review aims to assist clinicians in making Evidence-based decisions regarding treatment approach, keeping in view the existing data, to advance individualized strategies,both in patient and physician favour.

METHODS

This was a randomized controlled trial conducted in the Outpatient Department of Rheumatology at Madinah Teaching Hospital, Faisalabad. The study spanned over 6 months from 01st August,2025 to 31st Jan,2026.

The total sample size was 60 patients, calculated with 80% study power and a 5% level of significance, based on an expected mean difference in DAS28 score improvement between combination therapy and monotherapy groups as reported in previous literature. The sampling technique used was consecutive, non-probability sampling.

Inclusion Criteria

- Age between 18 and 70 years
- Both genders
- Diagnosis of rheumatoid arthritis based on ACR/EULAR 2010 classification criteria
- Receiving tofacitinib monotherapy or tofacitinib with methotrexate
- Minimum treatment duration of six months
- Availability of complete follow-up data

Exclusion Criteria

- Presence of overlap connective tissue disease or other autoimmune disorders
- Pregnancy or lactation
- Severe hepatic or renal impairment
- Active infection or malignancy
- Incomplete follow-up or missing data

Approval for the study was obtained from the Ethics Review Committee of the Institution (Ref No. TUF/IRB/115/2025 dated 12/112025), prior to recruitment of the patients. Written, informed consent was taken from each patient after explaining in detail the purpose of study, maintenance of confidentiality and no additional risks involved. Baseline medical evaluation included a detailed history and documentation of disease related variables such as serology, Disease Activity Score (DAS-28), Erythrocyte Sedimentation rate (ESR) and C-Reactive Protein (CRP) levels.

Participants were divided into two groups; Group A received Tofacitinib Monotheray at 5mg twice daily, while Group B was treated with Tofacitinib 5mg twice daily along with MTX weekly at 10-20mg, supplemented with Folic acid.Patients were followed up fron 6 months, when the ESR, CRP and DAS-28 scores were assessed again to evaluate the response. Any adverse events, cytopenias, Gastrointestinal upset, serious infections were documented and recorded on the proforma.

Statistical analysis was performed by using SPSS version 25. Continous variables like age, disease duration, DAS-28, ESR, CRP were expressed as mean + Standard deviation. Categorical variables such as gender, remission status, low disease activity and adverse events were presented as percentages and frequencies. Possible confounding factors such as age, gender, baseline disease activity, and disease duration were addressed through stratification. Independent sample t-tests were applied to continuous variables, while chi-square tests were used for categorical variables. A p-value of < 0.05 was considered significant.

RESULTS

The mean change in DAS-28 score at the end of 6 months was significantly greater in the combination arm vs the monotherapy (-2.3 ± 0.6 vs -1.6 ± 0.5; $p < 0.001$). The difference between the two groups was 0.7 DAS-28 units, which means that it is more than the minimum statistically significant difference, further consolidating our primary outcome. These

findings are in favout of the role of MTX in augmenting the response of ts-DMARDs.

TABLE-I

Baseline characteristics of study participants

Variable	Tofacitinib Monotherapy	Tofacitinib + Methotrexate	P-Value
Mean DAS28 (baseline)	5.8 ± 0.7	5.9 ± 0.6	0.54
Age (years)	Matched	Matched	NS
Gender distribution	Matched	Matched	NS
Disease duration	Matched	Matched	NS

Legend: NS = not significant

DAS-28 remission was defined as <2.6 units, which was 40% in the combination receiving group vs 20% in the Tofacitinib only group, having a p value of 0.04. Similarly low disease activity (DAA-28 ≤ 3.2) was more in the combination group 70% than the monotherapy one 30%, p value 0.03.

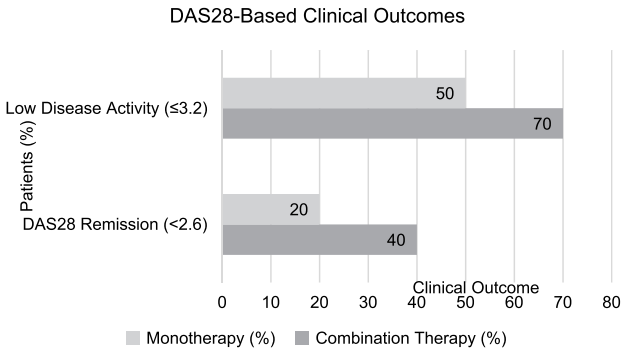
TABLE-II

Comparison of clinical and laboratory outcomes at 6 months

Outcome	Monotherapy	Combination Therapy	P-Value
Mean DAS28 reduction	−1.6 ± 0.5	−2.3 ± 0.6	<0.001
Remission (DAS28 <2.6)	20%	40%	0.04
Low disease activity (DAS28 ≤3.2)	50%	70%	0.03
ESR reduction (mm/hr)	−18 ± 7	−26 ± 9	0.01
CRP reduction (mg/L)	−9.2 ± 4.1	−14.6 ± 5.3	<0.01

FIGURE-1

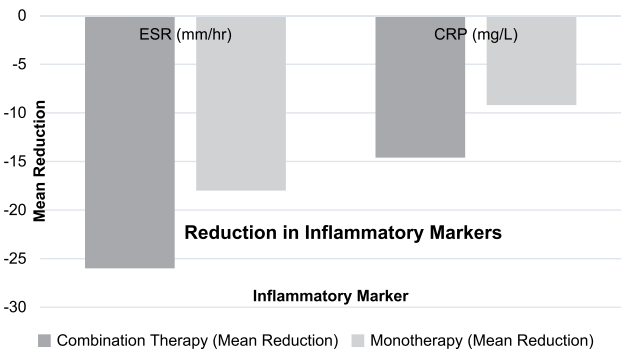
DAS-28 based clinical outcomes



The reduction in ESR was significantly greater in the combination group (−26 ± 9 mm/hr vs −18 ± 7 mm/hr; p = 0.01). Likewise, CRP levels showed a more pronounced decline in the combination arm (−14.6 ± 5.3 mg/L vs −9.2 ± 4.1 mg/L; p < 0.01). The changes in biochemical markers of inflammation were in favour of the clinical findings.

FIGURE-2

Reduction in inflammatory markers



There were no major adverse effects in both groups, therefore no patient discontinued their treatment. Mild adverse events like transient elevation of liver enzymes (≤ 2 times ULN) in 5 vs 2 patients in the combination and monotherapy group respectively (16.7% Vs 6.7%, P=0.23, which means that this was statistically insignificant.

Gastrointestinal side effects like nausea and dyspepsia were documented in 6 patients (20%) taking combination therapy as compared to 3 patients (10%) on tofacitinib alone, p = 0.29.

Minor infections, including upper respiratory tract infections, were noted in 4 patients (13.3%) in the combination group and 3 patients (10%) in the monotherapy group (p = 0.69). No opportunistic infections, tuberculosis reactivation, or herpes zoster infections were observed. Cytopenias were infrequent and comparable between groups, occurring in 2 patients (6.7%) in the combination group and 1 patient (3.3%) in the monotherapy group (p = 0.55).

Importantly, no serious infections, thromboembolic events, cardiovascular events, malignancies, or

treatment-related hospitalizations were recorded in either group during the study period. There was no statistically significant difference in overall adverse event rates between the two treatment arms (36.7% vs 23.3%, p = 0.27).

TABLE-III

Safety and tolerability outcomes at 6 months

Adverse Event	Tofacitinib Monotherapy (n = 30)	Tofacitinib + Methotrexate (n = 30)	P-Value
Any adverse event	7 (23.3%)	11 (36.7%)	0.27
Liver enzyme elevation*	2 (6.7%)	5 (16.7%)	0.23
Gastrointestinal symptoms (nausea, dyspepsia)	3 (10.0%)	6 (20.0%)	0.29
Minor infections (URTI)†	3 (10.0%)	4 (13.3%)	0.69
Cytopenias	1 (3.3%)	2 (6.7%)	0.55
Serious infections‡	0 (0%)	0 (0%)	—
Thromboembolic events	0 (0%)	0 (0%)	—
Treatment discontinuation due to AEs	0 (0%)	0 (0%)	—
Treatment-related hospitalization	0 (0%)	0 (0%)	—

* Liver enzyme elevation was defined as ≤2 times the upper limit of normal.
† Minor infections included self-limiting upper respiratory tract infections.
‡ No opportunistic infections, tuberculosis reactivation, malignancy, or cardiovascular events were observed.

FIGURE-3

Event distribution – tofacitinib monotherapy (n=30)

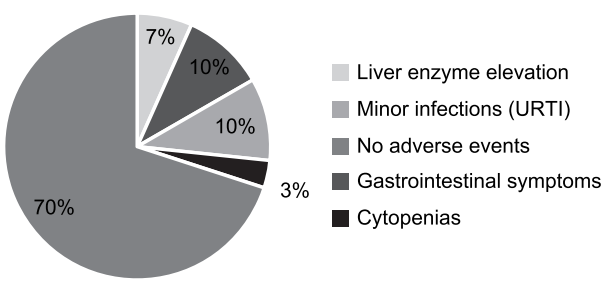
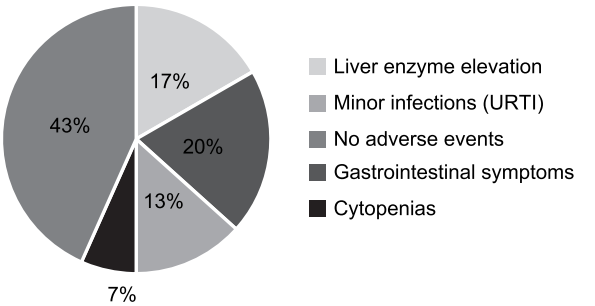


FIGURE-4

Adverse Event Distribution – Tofacitinib + Methotrexate (n=30)



DISCUSSION

The ORAL Strategey Trial (NCT02187055) provides the strongest direct comparison between the combination of Methotrexate with Tofacitinib vs Tofacitinib alone.[1] This Phase IIIb/IV randomized controlled trial, involved 1146 patients who had responded inadequately to Methotrexate alone, having an uncontrolled RA, randomized against tofacitinib with Methotrexate, Tofacitinib alone or Methotrextae with Adalimumab for 12 months.[1] The primary endpoint was ACR50 reesponse at 6 months VS Adalimumab with Methotrexate using a non-inferiority design.[1]

Combination of Tofacitinib with Metotrexate achieved non-inferior results to Adalimumab with methotrexate, however Tofacitinib alone failed to do so.[1] The absolute ACR50 difference favoured the combination therapy woth a striking percentage of 7.7%.[1] There were comparable safety profiles across all groups.[1] Patient reported outcomes favoured combination therapy slightly more.[12,19] Addition of Glycocorticoids did not alter much.[2]

ORAL Scan demonstrated that Tofacitinib (5mg and 10mg Twice a day) in combination with methotrexate significantly reduced the radiological progression of disease as compared to placebo with methotrexate with sustained effects over 24 months.[2] Patients receiving early disease remission had minimal subsequent structural damage regardless of the dose.[14,30]

ORAL Start trial evaluated methotrexate-naïve patients and showed that Tofacitinib monotherapy

was superior to Methotrexate monotherapy, both clinically and on imaging.[10,17] This confirms the belief that Tofacitnib monotherapy can improve disease outcomes in Methotrexate naïve patients and as combination in patients with poor response to methotrexate.[14,15,17]

A meta-analysis by Liu et al. demonstrated that JAK inhibitor-Methotrexate combinations achieved higher ACR response rates and disease remission at 24 and 52 weeks.[9] however the functional improvement measured by HAQ-DI was similar among all strategies and combination therapies resulted in greater discontinuations due to adverse events.[9] A Cochrane network meta-analysis showed no differences in efficacy between the two groups; however, it was limited by indirect comparisons.[18]

ORAL Strategy demonstrated higher ACR50, ACR20 and ACR70 response rates with combination therapy with NNT of approximately 13 for one additional ACR response.[1,6] Meta-analytical further confirmed that combination therapy achieved better results and responses (ACR50/ACR70) than minimal responses.[9]

Combination regimens resulted in significantly better DAS-28 and CDAI outcomes with sustained and earlier responses than monotherapies.[6] Meta-analyses continuously showed better remission rates and low disease activity with combination therapies.[9] However, ORAL Shift demonstrated that Methotrexate withdrawal in patients with low disease activity led to only minor, clinically insignificant disease worsening.[16]

HAQ-DI improvements were cpmparable amongt the two groups across trilas suggesting that functional gains from Tofacitinib are largely independent of Methotrexate.[9,12,19] HAQ-DI may be insensitive to differences in inflammatory control in established disease.[12]

Tofacitnib provided rapid improvements in clinical outcomes, often within weeks or both, monotherapy and combination groups.[25] Differences in the treatment modalities emerged in 3rd Month and persisted through month 12.[6] Earlier improvements prove crucial in dose escalations nd treatment optimization decisions.[6,16]

Mean changes in modified Total Sharp Score mTSS at month 24 were small for both tofacitinib doses (specific values not reported in available abstracts), indicating effective structural preservation with combination therapy.[15] The proportion of patients with no radiographic progression (change in mTSS ≤0.5) was high with Tofacitinib plus MTX, demonstrating that combination therapy can halt structural damage in the majority of MTX-inadequate responder patients.[15]

The ORAL Start trial provided evidence for tofacitinib monotherapy's structural benefits in MTX-naive patients.[10,17] At month 24, tofacitinib 5 mg twice daily monotherapy showed significantly less radiographic progression than MTX monotherapy, with mean changes in mTSS favoring Tofacitinib.[10,17] This establishes that tofacitinib monotherapy can effectively inhibit structural damage, at least in MTX-naive patients with early or established RA.[17]

However, direct head-to-head radiographic comparisons of tofacitinib monotherapy versus Tofacitinib plus MTX in the same patient population are lacking. The ORAL Strategy trial did not include radiographic endpoints, representing a significant evidence gap.[1] Indirect comparisons across trials with different patient populations (MTX-naive in ORAL Start vs. MTX-inadequate responders in ORAL Scan) are limited by differences in baseline characteristics, disease duration, and prior treatment exposure.[10,15,17]

Strand et al's analysis of patient related outcomes from ORAL Strategy trial, showed better results in Patient Global Assessment of disease activity, with combination arm.[12,19] HAQ-DI improvements were comparable, both achieving the MCID of ≥0.22.[12,19] Psychological well-being was independent of which treatment arm the patient was enrolled in.

Overall safety was comparable across treatment arms[1] Meta-analyses showed greater adverse events and treatment discontinuations in the combination arm, likely reflecting Methotrexate toxicity.[9] Serious infections were infrequent and similar among all regimens, although Hepres zoter

and tuberculosis were reported, emphasizing on the need that adequate screening and appropriate vaccinations should be done.[2,15]

CONCLUSION

Tofacitinib in combination with Methotrexate is a better option in terms of disease remission and prevention of disability as compared to Tofacitinib alone. This study further solidifies our belief that Methotrexate in combination with other DMARDs remains the anchor drug in Rheumatology.

Strengths of the Study

- Prospective randomized design reflecting real-world clinical practice
- Use of validated disease activity indices (DAS28, ESR, CRP)
- Direct comparison of monotherapy versus combination therapy
- Inclusion of a South Asian cohort, addressing a vital evidence gap
- Clinically relevant endpoints aligned with international treatment targets

LIMITATIONS

- Relatively small sample size
- Short follow-up duration limits long-term safety and radiographic assessment
- Single-center design, which may limit generalizability

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Syed Kamal Husnain Shah:** Manuscript writing.
2	**Khalid Parvez Babar:** Study design.
3	**Zainab Asim:** Data analaysis.
4	**Mahpara Munir:** Data collection.
5	**Muhammad Maroof:** Data etnry.
6	**Ata Ur Rehman:** Critical revision.