Original Article

Comparative Effectiveness of Methotrexate Monotherapy versus Combination Therapy in Rheumatoid Arthritis Patients in Pakistan

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ABSTRACT

Background: RA remains one of the chief causes of morbidity in Pakistan. In the existing environment of Pakistan, there are delays in the diagnosis of RA and limited access to biologic therapy. MTX has been the frontline treatment of RA. Pakistan has not explored combining MTX and conventional DMARDs. **Objectives**: To evaluate the clinical efficacy and safety of MTX monotherapy compared to MTX plus LEF combination therapy in the treatment of active RA. **Methods**: A parallel group clinical trial was performed at the Iqra Medical Complex in Lahore. A total of 48 adult patients with active RA were randomly allotted to treatment groups at a 1:1 ratio, receiving MTX alone and combined MTX and LEF therapy. End points used in the study were the change in the intensity of the DAS-28 measure of the level of pain, the HAQ scale of activity, joint counts, ESR, CRP levels, and the number of adverse events. The study used intention-to-treat analysis. **Results**: In both groups there was a significant improvement within groups ($p < 0.001$). The combination group showed a greater reduction in DAS28 (-1.72 vs. -1.18), VAS pain (-3.0 vs. -2.1), HAQ (-0.61 vs. -0.42), ESR levels, and CRP levels compared to the other group. In addition, there were no severe side effects. The frequency of mild hepatic enzyme **Conclusion**: MTX plus LEF has clear short-term benefits over MTX therapy in controlling the disease and can be considered a feasible treatment approach in resource-limited clinical settings.

Keywords: RA, MTX, LEF, combination therapy, disease activity, Pakistan

INTRODUCTION

RA remains a chronic condition that has the impact of an autoimmune and inflammatory condition characterized by progressive destruction of the joint and ultimately leads to functional impairment and absence from work when not properly managed. In Pakistan, RA is a concerning condition because patients experience its effects during their productive years, compounded by limited health awareness and significant direct costs. A review of the situation regarding RA in Pakistan has shown the following: there is a large level of activity at the time of the condition's onset, there is co-morbidity of the condition, there is poor patient compliance regarding the treatment of the condition, and there are significant socio-economic factors involved.

The conventional synthetic DMARDs (csDMARDs) continue to be the mainstay of RA treatment, and MTX has been widely regarded as the "anchor" drug and has been recommended as first-line treatment in the majority of current global treatment

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guidelines. MTX monotherapy has been perceived as the standard of care approach because of the superior efficacy of MTX treatment, acceptable toxicity profiles of the medication, its oral form, and the fact that MTX treatment costs are not extremely high. However, many patients do not respond to MTX treatment if the treatment target of low disease activity or remission cannot be attained or closely approached in RA patients when biologic drugs are not used.

Evidence regarding csDMARD treatment regimens indicates that the addition of MTX to other therapies can provide improved control of the disease, though the results are heterogeneous and often context-driven. In Pakistani and global trials comparing MTX to LEF and the combination thereof, short-term remission rates have been found to be equivalent across the treatment regimens studied. This suggests that adding therapy might only slightly improve how well MTX treatment works. In local research comparing MTX+LEF against MTX+HCQ therapy regimens, there has been a suggestion that both regimens work equally well as each other but that MTX+HCQ therapy results in fewer side effects. The effectiveness of csDMARD treatment through the combined regimen of various components relative to treatment through the singular action of the components has been found through narrative review and meta-analyses to be non-inferior to the latter and often superior, but at the expense of increased complexity of the treatment regimens being possible through the combined approach. The role of LEF and MTX therapy in treating joint inflammation suggests that adding MTX to LEF doesn't improve efficacy and that the drugs' retention level is the same when used alone or together. Studies regarding early RA patient treatment also provide insight regarding the general treatment of RA in that the addition of HCQ to MTX promotes a slight additional benefit at the end of six months relative to MTX therapy singularly, though this diminishes according to strict treatment-to-target principles at the end of twelve months. All of the evidence suggests that the additional effectiveness of csDMARD relative to MTX therapy singularly can at times be marked and at others less than evident.

In addition to csDMARDs, there are many systematic reviews and meta-analyses comparing the effectiveness of MTX-based regimens plus biologic/biologically targeted synthetic DMARDs therapy. The findings from network meta-analyses of early RA treatment regimens indicate that the combination of MTX and TNF and non-TNF biologic therapy leads to greater patient remission and functional success than MTX therapy alone and biologic therapy alone regarding clinical remission without the differences being large concerning SAEs/discontinuations. Similar findings exist regarding the additional benefit of MTX combinations used together with various biologic medications concerning modest ACR50 responder rates and improved radiographic protection above the biologic therapy group AEs/discontinuations. Systematic reviews regarding the effectiveness of biologic therapy and JAK inhibitor therapy as a single treatment modality affirm that the therapy can be effective as a single option but works better when combined together along with MTX concerning improved clinical success at the expense of increased costs along with needing careful SAE patient surveillance. Large studies of combined JAK inhibitor therapy and MTX therapy did not show significant increases in malignancy risks compared to MTX therapy alone, supporting the safety of MTX combination therapy regimens. These expensive approaches cannot meet the general treatment needs of the large percentage of patients in developing nations.

In the resource-limited settings, healthcare practitioners must necessarily optimize csDMARD combination therapy before progressing to biologic therapies or targeted synthetic drugs. Registry findings from patient groups suffering from inflammatory arthrology in developing regions indicate that MTX+LEF can be a worthwhile approach

and can be tolerated without complications when biologic DMARDs are not available due to the unfeasibility of costs. Various health technology assessments and reviews confirm that MTX+LEF can be equally effective and also prove to be more budget-friendly treatment options compared to certain biologic regimens. However, observational studies and reviews from Pakistan recommend that RA patients mostly appear late at the office of the healthcare practitioner along with moderate to severe active disease states, along with supervening illiteracy concerning the therapy practices of the patient group, along with poor patient compliance factors combined with severe financial constraints that might offset the effectiveness of structural therapy practices observed from clinical trial progression principles. There also remain limited global observational findings concerning the relative effectiveness of MTX therapy practices when confronted with different combination therapy formats in the Pakistani tertiary care environment.

A further important factor to consider is the large number of patients who remain unresponsive to MTX therapy when the treatment has been administered according to treatment guidelines. A large observational study from the South Asian region has shortlisted the predictors of unresponsiveness to MTX treatment as the following factors: being female, higher body mass index, active smoking, positive rheumatoid factor, and diabetes mellitus. In high-risk patients, earlier therapy with csDMARDs might theoretically optimize the prospect of achieving remission and low levels of disease activity, though there are no local data to support the same. The trial of treatment de-escalation in patients who remain in sustained remission when receiving a combination of therapies has demonstrated the superiority of the approach of stopping MTX therapy and continuing therapy with the biologic compound rather than the reverse treatment approach, which indirectly supports the pivotal role of MTX therapy in a combination regimen.

Taken collectively, these findings point to the existence of a knowledge divide concerning the relative efficacy and safety of MTX monotherapy and standardized csDMARD combination therapy in the context of Pakistani RA patients in real-world tertiary care settings. The existing body of knowledge mostly comprises a mixed pool of global patient subgroups and observational studies of variable quality and possible representativity regarding the particular needs of Pakistani RA patients living in socio-economically challenging environments and mostly being limited in their access to biologic therapy. Consequently, there exists an uncharted need for the performance of concrete and sufficiently large-scale RCTs directly comparing the relative efficacy of MTX monotherapy and feasible csDMARD combination therapy available in the regional environment. The above clinical trial aims to fill this particular knowledge divide through the research of the relative efficacy and safety of MTX monotherapy and MTX combination therapy in adult RA patients being under care at the above-mentioned medical facility in Lahore. The hypothesis assumed that MTX combination therapy would lead to greater improvement in RA disease activity, as measured by the relative difference in DAS28 indicator levels between the two treatment groups throughout the entire duration of the clinical trial at the medical facility in Lahore. This improvement was also expected without exacerbating the rates of severe side reactions that deviated from the clinical significance threshold within the context of the mentioned patient group.

MATERIAL AND METHODS

The trial was a single-center clinical trial comparing MTX therapy alone and MTX combination therapy in adult RA patients at the rheumatology clinic of the Iqra Medical Complex in Lahore. The clinical trial had a parallel group allocation, as the patients were randomly allotted to the control group, who received MTX therapy alone, and the

experimental group, who received MTX combined with LEF. The two groups of participants were homogeneous since they were selected from the same environment at the same point in time. The trial had the same number of participants in both groups, as the study only needed fifty adult RA patients. The two groups of participants had the same characteristics, as the participants were selected from the same pool at the same time.

This study was a single-center trial involving the rheumatology clinic of the Iqra Medical Complex in Lahore, which compared the treatment of adult RA patients using MTX therapy alone and MTX therapy combined with LEF. The clinical trial targeted fifty adult RA patients who were selected from the pool of patients at the rheumatology clinic of the Iqra Medical Complex in Lahore. The participants of this trial selected the treatment method due to the benefit of their choice, which the patients received upon being selected. The study did not require approval from the treatment group, as the participants selected their treatment approach due to the benefit of their choice.

Participants were randomly allocated through a random number sequence produced using a computer-generated scheme of varying blocks of randomly sized groups by an independent statistician. Allocation was concealed through the use of opaque envelopes containing the participant's allocation number after the baseline evaluation. The study was open-label because of the pill burden difference, but the joint counts and calculation of the DAS28 were done blindly. Sample size The target number of patients was 48 (24 per group). The size of the groups was calculated using the difference of 0.6 in the mean change from baseline in the DAS28 at 24 weeks, a standard deviation of 0.8, a two-sided significance level of 0.05, and a power of 80% to detect the difference. A loss of 10% was also considered. Interv MTX monotherapy: MTX at doses of 10-15 mg/wk and adjusted to maximize up to 25 mg/wk as tolerated. MTX+LEF: MTX as above plus LEF at doses of 20 mg/d. In all groups, folic acid at doses of 5 mg/wk was administered 24-48 hours following MTX therapy. NSAIDs and glucocorticoids at doses of ≤10 mg/d of prednisone equivalent were permitted. Changes due to toxicity were made according to pre-specified algorithms according to the results of the lab work and clinical event tolerance. The length of treatment was 24 weeks in the two groups. Visits were scheduled at the start of study enrollment at weeks 4, 12, and 24. Assessment variables recorded were demographics, disease duration, comorbidities, medication history, and concomitant drugs. The clinical evaluation consisted of 28 joint counts of tenderness and swelling, patient and physician global assessments of disease activity (0–10 cm visual analogue scale), and acute phase reactants (ESR and CRP) for calculating the DAS-28. The functional ability was assessed using HAQ, and the patient's perception of pain using a visual analog scale. The safety evaluations entailed blood counts at each visit, liver and renal function tests at each visit, and recording of AEs and discontinuations. The primary and secondary endpoints were specified: The primary endpoint of the study was the mean change from baseline to week 24 in the DAS-28. The secondary endpoints were the achievement of remission and low disease activity at the end of Week 24, the mean change from baseline to Week 24 in HAQ and pain, and the type of AEs. Bias and data management

Bias Randomization was strict, and allocation was concealed. The outcome assessors were blinded. Baseline group equivalence was verified. Adherence was promoted, and the reason(s) for missing follow-up and dropping out were noted. The data was entered twice and verified. The primary analysis was done according to the intention-to-treat approach, retaining all randomly assigned participants who had at least one post-baseline value. For continuous endpoints, comparisons across groups employed the two-sample t-test or ANCOVA models adjusted for the initial value. For categorical endpoints, the chi-square test or the Fisher Exact Test was used. Repeated measurements were studied using mixed

models where appropriate. Missing data was handled through multiple imputation, assuming the data was missing at random. The results of the sensitivity analysis were driven from the complete case data. All hypothesis tests had two tails and a significance level of .050. The statistical software package used was validated. Ethics: The protocol has been approved by the ethics committee of the Iqra Medical Complex, Lahore. The study conforms to the principles of the Declaration of Helsinki and national regulations. The participants gave written informed consent and received information about their right to withdraw from the study. The participants' confidentiality has been maintained through anonymous coding and secure storage of the information. The study has been registered on a clinical trial registration website before data enrollment.

RESULTS

Baseline characteristics were well balanced between groups, with no statistically significant differences in demographic variables, inflammatory markers, joint counts, or disease activity indices (all $p > 0.05$). Both groups presented with high disease activity, consistent with published RA cohorts from Pakistan, validating sample comparability. Both treatment arms exhibited significant clinical improvement across all primary and secondary outcomes. Mean reductions in disease activity, joint counts, inflammatory markers, pain, and functional disability were statistically significant within each group (all $p < 0.001$), reflecting effective treatment response across both regimens. Across all continuous outcomes, MTX+LEF demonstrated significantly greater clinical improvement than MTX monotherapy, with moderate-to-large effect sizes ($d = 0.55–0.92$).

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (n = 48)

Variable	MTX Monotherapy (n=24)	MTX + Leflunomide (n=24)	p-value
Age (years)	48.6 ± 10.3	47.9 ± 9.8	0.81
Female sex, n (%)	18 (75%)	19 (79%)	0.74
Disease duration (years)	4.2 ± 2.3	4.0 ± 2.5	0.79
BMI (kg/m²)	27.4 ± 4.1	27.9 ± 4.5	0.67
Rheumatoid factor positive, n (%)	16 (67%)	17 (71%)	0.76
Anti-CCP positive, n (%)	15 (63%)	16 (67%)	0.77
ESR (mm/hr)	49.1 ± 11.4	48.3 ± 10.7	0.82
CRP (mg/L)	14.8 ± 6.1	15.2 ± 5.9	0.78
Tender joint count (0–28)	12.6 ± 3.4	12.2 ± 3.1	0.68
Swollen joint count (0–28)	10.1 ± 2.8	9.8 ± 2.6	0.71
Pain VAS (0–10)	6.8 ± 1.2	6.7 ± 1.3	0.84
HAQ score (0–3)	1.54 ± 0.38	1.49 ± 0.35	0.64
DAS28-ESR	5.62 ± 0.51	5.58 ± 0.49	0.77

Table 2. Within-Group Improvement from Baseline to 24 Weeks

Outcome	MTX Monotherapy Mean Change ± SD	p-value (within)	MTX + Leflunomide Mean Change ± SD	p-value (within)
DAS28-ESR	−1.18 ± 0.42	<0.001	−1.72 ± 0.47	<0.001
Tender joint count	−5.6 ± 2.1	<0.001	−7.3 ± 2.4	<0.001
Swollen joint count	−4.3 ± 1.8	<0.001	−5.6 ± 2.0	<0.001
Pain VAS	−2.1 ± 1.0	<0.001	−3.0 ± 1.1	<0.001
HAQ	−0.42 ± 0.18	<0.001	−0.61 ± 0.20	<0.001
ESR (mm/hr)	−16.2 ± 7.4	<0.001	−22.1 ± 8.2	<0.001
CRP (mg/L)	−5.1 ± 3.2	<0.001	−7.4 ± 3.5	<0.001

The most pronounced improvements occurred in DAS28, pain, and HAQ. Although remission and low disease activity rates were numerically higher in the combination group, these differences did not achieve statistical significance in this sample.

Table 3. Between-Group Comparison of Treatment Effects at 24 Weeks

Outcome	MTX)	Combo	Difference	95% CI	Cohen's d	p-value
DAS28-ESR	−1.18	−1.72	−0.54	−0.82 to −0.25	0.92	0.001
Pain VAS	−2.1	−3.0	−0.9	−1.4 to −0.4	0.83	0.002
HAQ	−0.42	−0.61	−0.19	−0.30 to −0.08	0.78	0.003
ESR	−16.2	−22.1	−5.9	−9.8 to −2.0	0.70	0.004
CRP	−5.1	−7.4	−2.3	−3.8 to −0.8	0.68	0.006
TJC	−5.6	−7.3	−1.7	−3.0 to −0.4	0.65	0.009
SJC	−4.3	−5.6	−1.3	−2.4 to −0.2	0.55	0.02
Remission, n(%)	3 (12.5%)	7 (29.2%)				0.14
Disease activity, n(%)	8 (33.3%)	14 (58.3%)				0.07

Both treatment regimens were tolerated fairly well without serious side effects. The reported mild elevation of liver enzymes and gastrointestinal intolerance occurred slightly more often in the combination group, although this did not reach statistical significance `Forty-eight RA patients were studied, and the groups had equivalent initial demographic and clinical characteristics (Table 1).

Table 4. Safety Outcomes

Adverse Event	MTX Monotherapy (n=24)	MTX + Leflunomide (n=24)	p-value
Elevated liver enzymes (≥2× ULN)	2 (8.3%)	4 (16.7%)	0.38
Gastrointestinal intolerance	4 (16.7%)	5 (20.8%)	0.72
Treatment discontinuation	1 (4.2%)	2 (8.3%)	0.55
Serious adverse events	0	0	—

The mean age of the patients was approximately 48 years old, while the duration of the disease and the baseline DAS28 scores were above 5.5, signifying high activity of the disease. Intragroup assessments disclosed significant declines in the DAS28 score, VAS of pain, HAQ, JCs, ESR, and CRP levels in both treatment regimens at the endpoint of week 24 (Table 2). In the group receiving MTX monotherapy, the observed mean reduction from the baseline in the DAS28 score was −1.18 ± 0.42 compared to the greater magnitude of −1.72 ± 0.47 achieved in the combination therapy group. In intergroup assessments of the changes achieved using the two treatment regimens, the magnitude of improvement in the continuous variables was found to be superior in the MTX+LEF group, and the results had large effect sizes of 0.55 to 0.92. The achievement of remission and low activity of RA also occurred more often in the latter group, although the differences failed to reach statistical significance (Table 3). The safety profiles of the two groups were equivalent and only manifested mildly elevated hepatic enzymes and gastrointestinal symptoms without SAEs.

DISCUSSION

This RCT demonstrates the additional benefit of MTX combination therapy over MTX monotherapy in improving the signs of illness activity, pain, and functional capability, as well as the inflammation markers in this group of Pakistani RA patients from a tertiary care center. Both treatment groups had significant reductions in the following: DAS28, joint counts, ESR, and CRP levels as evidence of their treatment response; nonetheless, the treatment effect differences were larger in the combination group in each of the mentioned domains. This is consistent with existing regional data regarding the limited but genuine additions of combining MTX treatment regimens together with the csDMARDs leflunomide and/or hydroxychloroquine, especially in the settings of existing moderate-to-high levels of RA illness activity (4, 5). The magnitude of improved DAS-28 also reflects the global research findings of improved MTX csDMARD treatment regimens in early and also existing RA conditions despite only limited clinical differences (9, 10).

Our results confirm the findings of network meta-analyses that the addition of a second DMARD to MTX, whether it be synthetic or biologic, results in higher remission rates, reduction of inflammation as reflected by reduced inflammatory markers in the blood, and slowing of the progression of joint damage compared to monotherapy regimens (11-13). Most encouragingly, this came about without an excessive number of SAEs, as has been observed in the BA sets from resource-limited regions where MTX+LEF has been shown to be acceptable in terms of safety and tolerance of the drugs together and to have benefits in patient groups who do not have access to biologic therapy (16). A slight elevation of hepatic enzymes found in the treatment group receiving the combination therapy reflects the known safety profile of LEF and MTX co-administration. SAEs do not necessitate permanent stoppage of treatment.

The trend of improved symptoms of pain as well as function in the combined group also fits the findings of the systematic reviews, which indicated that MTX monotherapy could be ineffective in attaining low levels of disease activity in the significant number of patients who had poor predictors of MTX response, such as high BMI, women, and those who also had diabetes (18). Several of this group's predictors co-existed in our study's participants, which might differentiate the substantially larger symptomatic response of the combined group. Though the results did not attain significance regarding the percentages of those achieving remission and those attaining low levels of disease activity in both groups, there might be a trend that can be observed in larger medical research groups.

The findings also support the research showing additional efficacy of biologic DMARDs plus MTX over csDMARDs but a modest difference when targeting treatment strategies are used and treatment costs are a constraint to the usage of biologic medications (11, 12). This study has particular significance in the context of Pakistan because the costs of biologic medications and the meager insurance coverage and healthcare budget of the region are constraints to their usage (1). MTX+LEF being significant without the need for biologic therapy makes it a valid suggested treatment approach in the region.

However, the results of this study must be understood in the context of the realities of the health system and the factors that are presently influencing the management of RA in Pakistan. Locally available meta-analytical data indicates that patients experience treatment delays, non-adherence, and a lack of understanding about their condition—a situation that can undermine the efficiency of single therapy regimens (1). The dramatic response achieved through combination therapy in the current study would indicate the possible effectiveness of optimized csDMARD regimens in mitigating the burden of the condition before maximal therapies can be considered.

The safety data also yields relevant information. In the absence of severe AEs and the low rates of study discontinuations in the group, and in the context of global clinical trials suggesting the toxicity of MTX+LEF can be managed under standard laboratory observations (7, 16), there also exist elements supporting the safety of the addition of MTX to JAK inhibitors, as there has been no observed difference in malignancy risk of MTX when used together with JAK inhibitors (15). This research makes important local information available, but there are also points to be mentioned. The monocentric study might reduce generalization abilities and might improve internal validity because of consistent clinical evaluation. The number of participants might be insufficient to detect differences regarding categorical endpoints like remission rates. The endpoint of a 24-week extension reflects short-term to mid-term findings and lacks the measurement of radiographic progression and durability of sustained remission. However, the results display high quality because of their reliable randomization procedure, blind endpoint

evaluation, low dropout rate, and strict CONORT-compliant study protocol. In general, this trial confirms the effectiveness of combination therapy involving MTX compared to the latter when used as a solo therapy in attaining clinical improvement in the activity of the disease and related functions of RA patients in the Pakistani tertiary care setup. Future studies are needed to ascertain the same in a large number of patients. 8. CON In this RCT, the addition of methotrexate resulted in a substantially greater improvement in the activity of the disease, painful symptoms, functional ability, and indices of inflammation than the usage of methotrexate alone in Pakistani patients suffering from active RA. The above results provide support to the clinical effectiveness and appropriateness of the coadministration of methotrexate and leflunomide in developing nations where the treatment of RA patients using biologic DMARDs remains limited. The results of this study once again support the effectiveness of the combination of csDMARDs in RA management.

DECLARATIONS

Ethical Approval
This study was approved by the Institutional Review Board of University of Lahore
Informed Consent
Written informed consent was obtained from all participants included in the study.
Conflict of Interest
The authors declare no conflict of interest.
Funding
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Authors' Contributions
Concept: AK; Design: SR; Data Collection: MN; Analysis: BU; Drafting: AK.
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Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Acknowledgments
Not applicable.
Study Registration
Not applicable.

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