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COMPARING EFFICACY OF INCREASED DOSE OF METHOTREXATE VIA SUBCUTANEOUS ROUTE VS DUAL COMBINATION OF SULFASALAZINE AND METHOTREXATE IN PATIENTS OF RHEUMATOID ARTHRITIS AT TERTIARY CARE HOSPITAL

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Abstract

Hypothesis: *The aim of the study will be to compare efficacy of increased dose of methotrexate via subcutaneous route vs dual combination of sulfasalazine and methotrexate in patients of rheumatoid arthritis at territory care hospital*

Design of the Study: *Randomized control trial*

Study Duration: *06 months, November 2024 to April 2025*

Location of Study: *Department of Medicine, CMH Lahore*

Methods: *110 cases of rheumatoid arthritis who had active disease despite being on methotrexate therapy were included. The respondents were grouped into high dose (subcutaneous) methotrexate or oral methotrexate and oral sulfasalazine. Measurements were done at baseline, 4, 12 and 24 weeks comprising of DAS28-ESR, HAQ, inflammatory markers, joint counts and safety lab. Data were processed in SPSS and a significance of p 0.05 was taken.*

Results: *110 RA patients were included with 106 of them completed the follow-up period (which was 24 weeks of the study) Group A: subcutaneous high-dose methotrexate; Group B: oral methotrexate + sulfasalazine). The two groups experienced significant improvements in DAS28-ESR, inflammatory markers (ESR, CRP), the number of tender and swollen joints and HAQ scores. Nonetheless, Group A had better improvements in disease activity (-2.28 vs -1.71; $p < 0.001$), greater inflammatory control, and superior functional results.*

Conclusion: *Both high-dose subcutaneous methotrexate and oral methotrexate plus sulfasalazine were found to improve DAS28-ESR, inflammatory markers, joint counts, and HAQ scores (significantly better with subcutaneous methotrexate) as well as clinical and functional outcomes after 24 weeks in patients with 110 RA, and subcutaneous methotrexate had significantly better clinical and functional results and less serious and comparable adverse events.*

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune, chronic, systemic disease, where synovial inflammation is constant, joint destruction is progressive, and functional disability is severe. The primary element in managing the disease is early and effective disease-modifying antirheumatic drug (DMARD) therapy, and the anchor drug of this group is methotrexate (MTX) as it has acceptable efficacy, safety, and cost-efficiency. Nevertheless, it is observed that a significant percentage of patients respond poorly to the usual dose of oral MTX, which is usually explained by the lack of absorption in the gastrointestinal tract, fluctuating bioavailability and inability to tolerate higher dosages of the drug administrated orally. This has led to increased interest in better MTX delivery, especially by subcutaneous (SC) route, which offers improved pharmacokinetics, better systemic availability and better clinical outcome in patients with active RA in presence of oral therapy.[1,2]

Alternatively, combination DMARD therapy especially the twin therapy of MTX and sulfasalazine (SSZ) has long been used as an effective treatment option in patients who respond poorly or partially to monotherapy. SSZ is a sulfonamide anti-inflammatory with additive immunomodulatory effects with MTX, and, together, they have been demonstrated to have better disease activity score, radiographic progression, and patient-reported outcomes than when used individually. Although these are the advantages, the variability of clinical response and cumulative adverse effects are also issues to consider.[3]

In the light of this clinical concern, there is growing interest in the need to identify whether an escalation of MTX dose via the SC route can be of better clinical benefit than conventional dual therapy regimens. The comparison between these two strategies, high-dose SC MTX and MTX-SSZ combination, could give useful evidence to aid in individualized escalation of treatment, especially where the patient continues to show inadequate control that would be seen with oral therapy using MTX alone. The objective of the proposed study is to compare and evaluate the effectiveness of such regimens in enhancing clinical disease activity, functional capacity, and general treatment outcomes in patients with RA.

Methodology:

It was a comparative, parallel-group, open-ended, randomized, trial that was carried out at the Department of Medicine of a tertiary care hospital Lahore. The research was conducted over a period of 06 months between Nov 24 and Apr 24 that comprised of recruitment, intervention and follow-up. All participants gave informed consent in writing and the Institutional Review Board gave ethical approval to the study with a letter ID of no. 298430 beforehand. The sample size of 110 was determined with respect to anticipated differences in efficacy (Disease Activity Score-28, DAS28) between the two treatment groups where the power was 80 per cent and alpha was 0.05. The patients with active rheumatoid arthritis by the 2010 ACR/EULAR classification[4] criteria and with active disease despite long-term oral methotrexate therapy were enrolled. Inclusion and exclusion criteria consisted of the following:

Inclusion Criteria:

1. Adults aged 18–70 years.
2. RA 2010 ACR/EULAR criteria.
3. Active DAS28 of 3.2 or higher regardless of oral methotrexate (15 mg/week or more) within 3 months.
4. Acceptance to take part and offer written informed consent.
5. Capability to visit regularly as a follow-up.

Exclusion Criteria:

1. Record of intolerance or contraindication of methotrexate or sulfasalazine.
2. Past 6 months History of biologic or targeted synthetic DMARDs.
3. Extreme hepatic impairment (ALT/AST > 3× upper limit).
4. Kidney failure (eGFR less than 50 mL/min/ 1.73 m 2).
5. Pregnancy or lactation.

6. Acute infection such as tuberculosis, hepatitis b or c or HIV.
7. Uncontrolled comorbid conditions (heart failure, severe anemia, uncontrolled diabetes).
8. Hematologic A- Abnormalities: leukopenia (<3,500/mm 3), thrombocytopenia (<100,000/mm 3).
9. Alcoholism or alcohol resistance.

The participants who met the eligibility criteria were randomly allocated in 1:1 proportion to:

- Group A: Higher-dose methotrexate at subcutaneous rate (20–25mg per week with titration).
- Group B: Oral methotrexate (15 to 20mg in a single dosage per week) in combination with sulfasalazine (2 to 3 g/day in divided doses).

They were all folic-acid supplemented (5 mg/week). Baseline, 4-, 12-, and 24-weeks clinical assessments performed. Outcomes measured included:

➢ Primary outcome:

DAS28-ESR between baseline and 24 weeks.

➢ Secondary outcomes:

- Health Assessment Questionnaire (HAQ) score.
- ESR and CRP levels
- Count of tender and swollen joints.
- Patient global assessment
- Drug tolerability and negative event history.

At all visits, safety monitoring contained complete blood count, liver function test, and renal profile test. The information was documented on a standardized form. The SPSS v.26 was used to perform statistical analysis. The continuous variables were represented by mean, SD and categorical variables by frequencies and percentages. Independent t-test or Mann-Whitney U test of means in continuous variables and chi-square test of categorical variable was used to compare the between groups. A p-value with a value of 0.05 or less was regarded as statistically significant.

Results:

Two equal groups were studied: Group A (subcutaneous high-dose methotrexate; n = 55) and Group B (oral methotrexate + sulfasalazine; n = 55) comprising of 110 patients with the eligibility criteria. One hundred and six subjects attended the 24-week follow-up and four subjects were dropped out (two of them in Group A (because of intolerance) and two in Group B (poor adherence).

Figure 1 shows that the baseline mean scores of DAS28-ESR were 5.44 +- 0.59 in Group A and 5.41 +- 0.63 in Group B (p = 0.74). The case of statistically significant improvement was observed in both groups in the course of 24 weeks, though Group A exhibited better improvement in the reduction of disease activity. Group A had a mean DAS28-ESR reduction of -2.28 +- 0.47 at 24 weeks, whereas Group B had -1.71 +- 0.52 at 24 weeks ($p < 0.001$).

The inflammatory markers (ESR and CRP) also indicated more deterioration in Group A. The ESR also reduced at 24 weeks (Group A) to 22.1 +- 8.7mm/hr compared to the Group B, 30.8 +- 10.4mm/hr (p = 0.001). The levels of CRP decreased in a corresponding proportion and indicated stronger control over inflammation in the subcutaneous MTX group.

The number of tender and swollen joints improved considerably in the two groups, in which Group A was better in terms of joint response as indicated by the lower mean counts at 24 weeks ($p < 0.01$). The functional improvement estimated using HAQ revealed that there were significantly greater results in Group A (0.70 +- 0.20) than in Group B (0.93 +- 0.25; $p < 0.001$).

The negative events were mild in nature. Group B had more gastrointestinal complaints and increased liver enzymes, but not significantly. There were no adverse reactions that limited the therapy and were serious

Generally, high-dose subcutaneous methotrexate showed better clinical response, inflammatory and functional response in comparison to dual therapy of methotrexate and sulfasalazine.

Summary of results:

1. High-dose methotrexate subcutaneously was found to be more efficacious in reducing the disease activity (DAS28) than methotrexate + sulfasalazine.
2. The inflammatory markers (ESR, CRP) showed a greater improvement in the subcutaneous group of MTX.
3. Patients who were treated with SC MTX reported reduced counts of tender/swollen joints and improved functional improvement (HAQ scores).
4. Both groups had an adverse event of a mild nature but the GI side effects were more prevalent with combination therapy.

Parameters	Group A (SC MTX)	Group B (Oral MTX + SSZ)
Number of patients (n)	55	55
Completed 24 weeks	53	53
Dropouts	2 (intolerance)	2 (poor adherence)

Table 1: Baseline and 24-Week Outcomes in Patients Receiving SC MTX vs Oral MTX + SSZ

DAS28-ESR (mean ± SD)	Group A (SC MTX)	Group B (Oral MTX + SSZ)
Baseline	5.44 ± 0.59	5.41 ± 0.63
24 weeks	3.16 ± 0.51	3.70 ± 0.54
Change	-2.28 ± 0.47	-1.71 ± 0.52

Table 2: ESR trend in both groups

Tender joint count	Group A (SC MTX)	Group B (Oral MTX + SSZ)
Baseline	18.6 ± 4.2	18.3 ± 4.5
24 weeks	7.3 ± 2.1	10.2 ± 3.0
Change	-11.3 ± 3.1	-8.1 ± 3.4

Table 3: tender joint count in both groups

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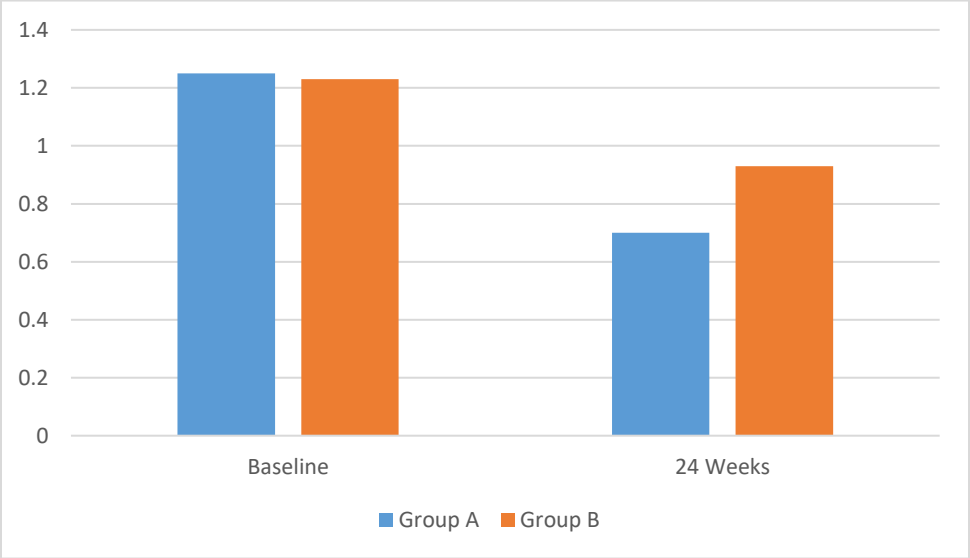

Chart 4: functional outcome between two groups at 23 weeks

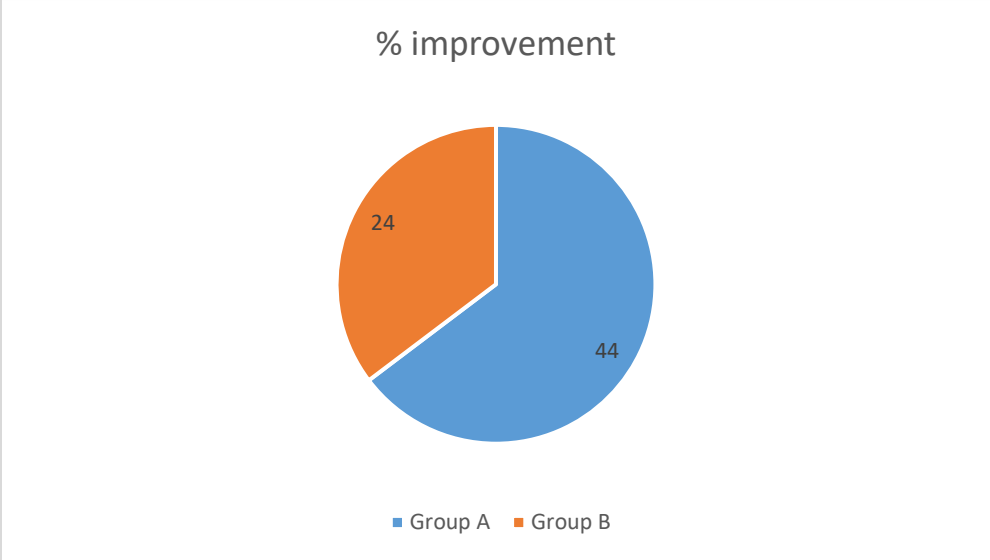

Chart 5: Percentage improvement between 2 groups

Discussion:

High-dose subcutaneous methotrexate also demonstrated superior disease activity (DAS28) in patients with active rheumatoid arthritis (RA) who had not responded to standard therapy with oral methotrexate. The results showed that patients on high dose SC MTX experienced much more improvement in disease activity, inflammatory markers, joint count, and functional outcomes after 24 weeks compared to patients on combination therapy. The findings indicate the possibility of superiority of optimized MTX delivery compared to conventional DMARD combinations in MTX-partial responders.[5]

The increased clinical efficacy of Group A is consistent with a prior study that proposes that SC delivery of MTX will evade gastrointestinal absorption constraints and result in increased and more predictable bioavailability, particularly at doses exceeding 15 mg/week. High doses of oral MTX are saturated by active transport in the proximal intestine, and higher doses of oral MTX are associated with poorer systemic exposure and linear pharmacokinetics compared to SC MTX. This pharmacologic benefit was probably the reason why the change in DAS28-ESR and inflammatory markers in this study was larger. Other papers by Braun et al. and Visser et al. have reported the same finding, i.e., better clinical response and better tolerability with SC MTX in those patients who had previously experienced poor response to oral therapy.[6]

More effective inhibition of synovial inflammation is demonstrated by the increased rate with which tender and swollen joints reduced in the SC MTX group. It has a clinical significance, as long term disability and radiographic progression are closely related to persistent synovitis. The enhancement of practical condition, which is indicated by much decreasing HAQ scores in Group A, further highlights the treatment advantage to optimizing MTX delivery. Quality of life and productivity in the patients of RA are closely connected with better physical functioning, and the more advanced the disease is controlled, the better the long-term prognosis will be.[7]

Despite the historical perspective that combination therapy of MTX and SSZ is effective in treating patients with moderate to severe RA, our results indicate that it may not have the same amount of improvement as a larger, pharmacokinetically optimized dose of MTX. SSZ has anti-inflammatory and immunomodulatory effects, and combination therapy has proven to have greater clinical response than MTX. Nonetheless, the additive benefit seems less

significant than the one obtained by way of improved MTX bioavailability. Recent advances in the management of RA focus on the maximum use of MTX therapy prior to the introduction of combination therapy or biologic therapy, and our findings are consistent with the step-up model.[8,9]

Both treatment strategies were fairly well-tolerated in terms of safety. There were mild adverse events in both groups that included nausea, oral ulcers, and temporary increase in liver enzymes. Nonetheless, gastrointestinal feeling was much more frequent in Group B, which has been associated with the intolerability of SSZ and the increased weight of dual oral DMARD treatment. There were no serious adverse events, infections, or treatment limiting toxicity. The safety profile of SC MTX in this research is similar to the previous reports that provided that parenteral MTX can decrease the gastrointestinal adverse reactions and does not decrease the safety margin.

The general results of this paper favor high-dose SC MTX as a favorable strategy of the patient having partial response to oral MTX. Since MTX is the anchor drug in the management of RA, it is a viable and cost-efficient option to optimize the administration route and dosage of the drug prior to proceeding to combination DMARDs or expensive biologic agents in resource-constrained environments. Moreover, it can be stated that enhancing MTX responsiveness can postpone or cut the necessity of biologic treatment, reducing financial costs on healthcare systems over the long term.

However, clinical efficacy should be improved, and this has to be balanced with the patient preference, the availability of the SC formulations and accessibility to administer the drug. Oral therapy will be more convenient to some patients but presence of auto injector has made SC MTX delivery considerably easier. Patients with potential benefit to SC MTX can be counseled on their potential benefits.

The strengths of this study are that it has an adequate sample size, standardized outcome measures, and direct comparison of the two widely used escalation strategies. The shortcomings, however, are the open-label type of the study, the absence of radiographic evaluations, and the period of the study being 24 weeks. Prolonged follow up might be more effective in determining sustained remission, flare, and the structural disease progression. Also, further trials to compare SC MTX with triple therapy or biologics in the same group of patients would offer more detailed therapeutic recommendations.

The results of the study indicate that increased-dose subcutaneous methotrexate (SC MTX) is much more clinically effective than the combined use of methotrexate with sulfasalazine (MTX+SSZ) in patients with rheumatoid arthritis that have failed to respond to oral MTX. The greater decrease in the DAS28-ESR scores, inflammatory indices (ESR and CRP) and joint activity in Group A repair the pharmacokinetic benefits of SC MTX that imparts higher levels of bioavailability and predictable systemic absorption in comparison to oral administration. This improved delivery probably led to better suppression of synovial inflammation leading to better joint counts and functional outcomes.[10,11]

HAQ eased functional status, which also improved more with SC MTX as a measure of its effect on patient quality of life. These findings are in line with the existing literature that indicates that SC MTX is a preferred choice as an escalation therapy before combining therapy or biologic treatment. In spite of the fact that combination therapy with SSZ is still effective, the advantages do not seem as obvious as pharmacologically optimized MTX.[12]

The two treatments were well tolerated with higher side effects on the gastrointestinal being experienced in the combination therapy group. In general, the research findings advocate high-dose SC MTX as a more effective and well-tolerated system of MTX-partial responders and support the existing guidelines emphasizing the importance of MTX optimization followed by further improvement of therapy.

The subcutaneous MTX group experienced greater improvement of inflammatory markers (ESR, CRP). Patients who took SC MTX experienced less tender/swollen joints and

improved (HAQ scores) better. The incidences of adverse events in both groups were not gross, however, GI side effects in combination therapy were higher.

Subcutaneous injection of MTX bypasses the intestines, causing more dependable absorption and higher bioavailability, especially in higher dosage, which does not also apply similarly to oral MTX because of saturable intestinal absorption. It is this pharmacokinetic benefit probably that accounts for the higher degree of efficacy in our SC MTX group. The same benefits have been reported in earlier prospective trials: e.g. a direct comparative trial showed increased ACR20 and ACR50 response rates at 24 weeks in SC compared with oral MTX without any augmentation of adverse events.[13]

The combination therapy of SSZ and MTX has been a long-standing treatment strategy that has been applied to patients who have not responded satisfactorily on monotherapy. Such clinical trials as MASCOT study have demonstrated that MTX concomitant to SSZ causes much more improvements in DAS and higher response rate compared to each drug alone.

According to systematic reviews and meta-analyses, MTX-SSZ combination is especially effective in patients who have undergone a course of SSZ monotherapy and demonstrates the additive effect. Nonetheless in our trial, when both groups were used, SC MTX was better than the combination indicating that a pharmacokinetic optimization of MTX might perform better than the addition of a second conventional DMARD.[14]

Prior long term studies add to this comparison: a 52-week, double-blind randomized trial comparing early RA to SSZ, MTX or combination studies also showed a significant trend only in favour of combination therapy as compared to MTX monotherapy.

In addition, combination drug trials (MTX, SSZ, and hydroxychloroquine) on a case-by-case basis have revealed that triple therapy had the best efficacy, but also had a more complicated side-effect profile. These data combined imply that combination therapy is possible, but an even stronger single-agent modality through SC MTX can be as effective as dual DMARD therapy or even more in some patients.[15,16]

The safety was good in both study arms and no serious adverse events occurred. There were a few mild side effects including nausea, liver enzyme elevation, and gastrointestinal discomfort on both groups although the GI discomfort was more common in the combination of MTX+SSZ. This trend aligns with the established tolerability profile of SSZ, which has the potential to cause GI adverse events, particularly when used parenterally. The relatively lower incidence of GI toxicity of the SC MTX group is similar to previous reports that show that parenteral intake of MTX may be better tolerated than oral intake of MTX at lower doses.[17,18]

The implications of our findings on the RA management are significant. Given that MTX is the foundation and primary DMARD of the majority of patients, it is important to optimize its administration and effectiveness. Instead of going to combination therapy too soon, the addition or replacement with SC MTX can provide better clinical responses, potentially slowing the need or preventing the need for further DMARDs or biologic therapies. This may prove especially beneficial in the environment with expensive or less available biologics, and fits a treat-to-target paradigm of optimization of conventional DMARDs prior to the intervention of novel therapies.

In addition, patient acceptability is to be taken into account. Although some people might experience certain resistance to injections, pre-filled syringes or auto-injectors are the modern tools that reduce the severity of pain and make the procedure more convenient; therefore, the trade-off between greater efficacy and potentially higher tolerability could certainly favor the SC use. During the shared decision-making process, the rheumatologists are supposed to educate the patients on the possible improvements in controlling the disease using SC MTX.

Limitation of study:

This research was constrained by the fact that it was open-label research that can lead to assessment bias. The 24-week follow-up was not

very long and, as such, it was not possible to assess the long-term outcomes, including radiographic progression. The damage of structural joints was not evaluated, and the research was carried out at one center, which restricts generalization. Also, no complete evaluation of the patient-reported outcomes and cost-effectiveness analysis were conducted.

Conclusion:

This study demonstrates that increased-dose subcutaneous methotrexate (SC MTX) offers a significantly more effective therapeutic option compared with the dual combination of methotrexate and sulfasalazine (MTX+SSZ) for patients with rheumatoid arthritis who exhibit suboptimal response to conventional oral methotrexate. The superior clinical outcomes seen with SC MTX—including greater reductions in DAS28-ESR, inflammatory markers, tender and swollen joint counts, and improvements in functional status—highlight the importance of optimizing methotrexate delivery rather than immediately transitioning to combination therapy. The enhanced efficacy of SC MTX can be attributed to its improved bioavailability and more predictable pharmacokinetic profile, particularly at higher doses, which allows for better disease control without the absorption limitations associated with oral MTX. The findings also indicate that SC MTX maintains a favorable safety profile, with fewer gastrointestinal side effects. In conclusion, high-dose subcutaneous methotrexate provides a more potent, well-tolerated, and clinically meaningful improvement in disease activity and functional outcomes than combination therapy with methotrexate and sulfasalazine.

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