ORIGINAL ARTICLE

Comparative Effects of Combination Therapies; Methotrexate with Leflunomide & Sulfasalazine in the Treatment of Rheumatoid Arthritis

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ABSTRACT:

Objective: To study the role of combination therapies in the treatment of rheumatoid arthritis.

Methodology: This open-label, randomized 180-day clinical trial was conducted in the Department of Pharmacology and Therapeutics, BMSI and Medical unit ward 6, after approval of JPMC ethical committee, in which enrolled patients were 89. Patients were divided into two groups, A and B. 44 patients of group A received methotrexate (MTX) 7.5-20 mg/ week orally and Leflunomide (LEF) 10-20 mg/ day orally as maximally tolerated. 45 patients of group B were given MTX 7.5-20 mg/ week orally and Sulfasalazine (SSZ) 500 mg to 1 gm daily orally as maximally tolerated.

Result: Comparing the combination of group A with group B, group B showed highly significant improvement in mean swollen joint count (1.9±0.9) and morning stiffness (46.0=19.06) as compared to group A (2.9=1.71, 54.4=10.14). The drugs of group A showed significant improvement in mean pain (2.9= 1.71), physician's global assessment (2.80±0.97) and patient's global assessment (1.4=0.66) as compared to group B (1.9= 1.45, 3.8±1.22, 2.0=0.99). Therefore, our study revealed that patients receiving combination of MTX and LEF responded slightly better than MTX and SSZ. Both the combination treatments were well tolerated.

Conclusion: Both combinations of MTX & SSZ and MTX & LEF were well tolerated but the efficacy of MTX and LEF was marginally superior to combination of MTX and SSZ.

Key words: Rheumatoid Arthritis, Methotrexate, Leflunomide, Sulfasalazine, Disease Modifying Anti-rheumatic Drugs.

INTRODUCTION:

Rheumatoid arthritis is a chronic, systemic inflammatory disease that affects many tissues and organs, but mainly attacks synovial joints. The cause of rheumatoid arthritis is unknown; autoimmunity plays an important role in both its chronicity and progression. Rheumatoid arthritis is considered as a systemic autoimmune disease.[1] It affects 0.5-1% of population all over the world[2]. Studies from Nigeria, Indonesia and Africa showed lower prevalence than that reported from the western countries. The prevalence of rheumatoid arthritis in India is 0.75%. In the urban populatio of southern Pakistan, Karachi, its prevalence is 0.14%, whereas in northern Pakistan the estimated prevalence is 0.55%.[3] Women are three times more commonly affected than men. Onset is most frequent between ages of 40- 50 years, but people of any age can be affected.[4] If rheumatoid arthritis remain untreated, patients will become permanently disable.[5] Therefore, various treatments for rheumatoid arthritis are available. Analgesics and anti-inflammatory drugs, including steroids, are used to suppress the symptoms, while disease-modifying antirheumatic drugs (DMARDs) are required to inhibit the underlying immune process and prevent long-term damage.[6]

One of the new approaches has been the combinations of DMARDs. The increase in the use of combination therapies is due to the fact that monotherapy with DMARDs is often ineffective. Although, the use of combination therapies has increased, but it is not known that which combination therapy is most useful.[7] To address this question, we compared two combinations of DMARDS; methotrexate with leflunomide, and methotrexate with sulfasalazine. Methotrexate is on the World Health Organization List of Essential Medicine.[8]

Leflunomide is an immunosuppressive disease-modifying anti-rheumatic drug (DMARD).[9] Its uses include active, moderate to severe rheumatoid arthritis and psoriatic arthritis. Mechanism of action of leflunomide is inhibition of pyrimidine synthesis.[10] Sulfasalazine is a sulfa drug and a derivative of mesalazine, formed by combining sulfapyridine and salicylate with an azo bond. It is used in the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease, rheumatoid arthritis and other types of inflammatory arthritis (e.g. psoriatic arthritis). It is often well tolerated compared to other DMARDs.[11] It has also been used in the treatment of liver cirrhosis in chronic alcoholics, where it reversed scarring of tissue in clinical trials.[12] It is also used in idiopathic urtricaria not responding to antihistamines.[13] With this background, the purpose of this study was to compare the effects of combination therapies, methotrexate with leflunomide and sulfasalazine in patients of rheumatoid arthritis.

METHODOLOGY:

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This randomized, open-label, clinical trial was conducted in the Department of Pharmacology and Therapeutics, BMSI and Medical unit ward 6, with the approval of JPMC ethical committee for six months .

Patients of Rheumatoid arthritis of either sex, 30-60 years old, with 6-month history of active disease, and at least 3 of the following 4 features: erythrocyte sedimentation rate (ESR)>28 mm/hour, duration of morning stiffness ≥ 45 minutes, ≥ 8 tender joints, and ≥ 3 swollen joints, despite monotherapy with methotrexate since 6 months were included in the study. Written informed consent was taken from enrolled patients.

110 patients were enrolled, divided into two groups, A and B, with 55 patients in each group. Randomization was done by allocation ratio 1:1 and it was blocked at every sixth patient i.e. first three patients were given methotrexate and leflunomide; next three patients were given methotrexate and sulfasalazine[14]. Out of these, 89 patients completed the study, 44 patients in group A and 45 patients in group B. Group A (n=44) was treated by methotrexate 7.5-20 mg/ week orally and leflunomide 10-20 mg/ day orally as maximally tolerated. Group B (n=45) were treated by methotrexate 7.5-20 mg/week orally and sulfasalazine 500 mg to 1 gm daily orally as maximally tolerated.

The enrolled patients were evaluated every 7th day until 30th day, then every 30th day. If there was no improvement in symptoms at the 60th day of evaluation, it was considered as an ineffective treatment. If they improved, they were evaluated every 30th day for the duration of next 90 days and then after 90 days. Efficacy was assessed by patient's global assessment, physician's global assessmrnt, erythrocyte sedimentation rate, morning stiffness, Numeric pain scale scoring, number of tender joint count and number of swollen joint count. The pain of the patients was assessed by patient's global assessment. It was measured by visual analogue scale (VAS) from 0cm (no pain) to 10cm (severe pain) which was marked by the patient. VAS was horizontally placed on which patient was asked to mark from 0 cm to 10 cm[15] (Figure-1).

Figure-1: Visual Analogue Scale

0 cm	5 cm	10cm
No Pain		Worst possible pain

Pain assessed by physician's global assessment[16].

Physicians scored pain on a six-point scale of global assessment of arthritis. This scale consists of:

- 0= None- No pain.
- 1= Mild- slight, tolerable pain.
- 2= Moderate- pain causing discomfort.
- 3= Severe- unbearable pain.
- 4= Very severe pain.
- 5= Worst possible pain

ESR determines degree of non-specific inflammation in the body. It is governed by balance between pro-sedimentation factors, mainly , and factors resisting sedimentation, namely negative charge of erythrocytes (zeta potential). When an inflammatory process is present, the high proportion of fibrinogen in the blood causes red blood cells to stick to each other. The red cells form stacks called 'rouleaux,' which settle faster, due to their increased density.

The patients of rheumatoid arthritis who had morning stiffness,[17] of ≥ 45 minutes were included and evaluated. In baseline, most of the patients gave history of morning stiffness which persisted for two hours. Sometimes it lasted throughout the day. It was observed noticeably in the joints of fingers and hand; wrist, elbow, knee, ankles, feet, shoulder, hip, and jaw were also affected in different enrolled patients.

Tenderness and swelling were assessed as present or absent. Shoulder, elbow, wrist, metacarpophalangeal, proximal and distal interphalangeal joints and knee were examined.[18]

Numeric Pain Scale determined pain according to following score: 0-none, 1-3-mild, 4-6-moderate, 7-10-severe.[19]

Monitoring of toxicity: Before enrolment for the study, following investigations were done for all the patients: ECG, X-ray of chest and hands, liver function test, complete blood cell counts, ESR, urine D/R (Detailed Report) and at every follow-up visit. Patients were excluded from the study if their laboratory results were deranged.

Concurrent therapy with systemic corticosteroids was continued if dosage remained stable throughout the study period and patient took no more than 10 mg of prednisone (or its equivalent) per day. We also permitted non-steroidal anti-inflammatory drugs.

The data analysis was done by SPSS version 16.0.The results were given as Mean and Standard deviation (SD) for quantitative variables (age, duration of diseases, pain score, ESR, laboratory investigations etc.) and percentage/proportion for categorical qualitative variables (gender, complaints, ECG and x-ray findings, efficacy and side effects etc.). Efficacy and side effects were compared among treatment groups by Chi- square test. An analysis of variance (ANOVA) was used to compare the average change (mean ± SD) in outcome over treatment period among the two groups.

RESULTS:

Group A was randomly dispensed MTX and LEF, and B was treated by MTX and SSZ for six-month duration. At baseline, the difference in the age of the patients, disease duration, rheumatoid factor positivity, percentage

of females, and percentage of steroid usage in two treated groups were non-significant. The mean MTX dosage ranged from 16.0 to 17.0 mg/week. The mean SSZ dosage ranged from 1.5 to 1.6 gm/day. The mean LEF dosage ranged from 16.0 to 17.0 mg/day.

At the end of study period, that is 6 months, there was insignificant decrease in mean tender joint count in group B as compared to group A. However, there was highly significant decrease in mean swollen joint count in group B, when compared to group A. When mean patient's global assessment scale and mean physician's global assessment scale (for pain and quality of life) in group A were compared with group B, the decrease in both parameters was highly significant in group A. At the same time, there was non-significant decrease in mean erythrocyte sedimentation rate in both groups A

Table: 1
Comparative effects of Group A (MTX & LEF) and Group B (MTX & SSZ) in rheumatoid arthritis

PARAMETERS	MTX & LEF Vs MTX & SSZ	p-value
Tender joint count (maximum 38)		
Baseline (day 0)	14.5±7.22 13.7±7.08	>0.05
6 months	5.8 ± 3.71 4.0 ± 3.63	>0.05
Swollen joint count (maximum 38)		
Baseline (day 0)	11.3±4.59 8.6±4.37	
6 months	2.9± 1.71 ** 1.9 ± 0.9	**<0.01
Global assessment – Patient's (0-10 scale)		
Baseline (day 0)	5.2±0.76 5.6±1.64	>0.05
6 months	** 1.4 ± 0.66 2.0± 0.99	**<0.01
Global assessment – Physician's (0-10 scale)		
Baseline (day 0)	4.6±1.23 5.6±1.46	>0.05
6 months	** 2.8 ± 0.97 3.8 ± 1.22	**<0.01
ESR (mm/ hour)		
Baseline (day 0)	87.2±13.10 86.2±18.87	>0.05
6 months	56.5 ± 8.15 56.1 ± 10.41	>0.05
Morning stiffness (minutes)		
Baseline (day 0)	82.8±15.89 71.6±19.06	>0.05
6 months	54.4 ± 10.14 ** 46.0 ± 19.06	**<0.01
Pain (0-10 scale)		
Baseline (day 0)	5.4±1.26 6.0±1.65	>0.05
6 months	* 1.3±1.11 1.9±1.45	*<0.05

Significant p-value *<0.05, highly significant**<0.01
MTX=methotrexate, LEF=leflunomide, SSZ=sulfasalazine

Figure: 2
Comparison of group A (Methotrexate & Leflunomide) and Group B (Methotrexate & Sulfasalazine) after 6 months

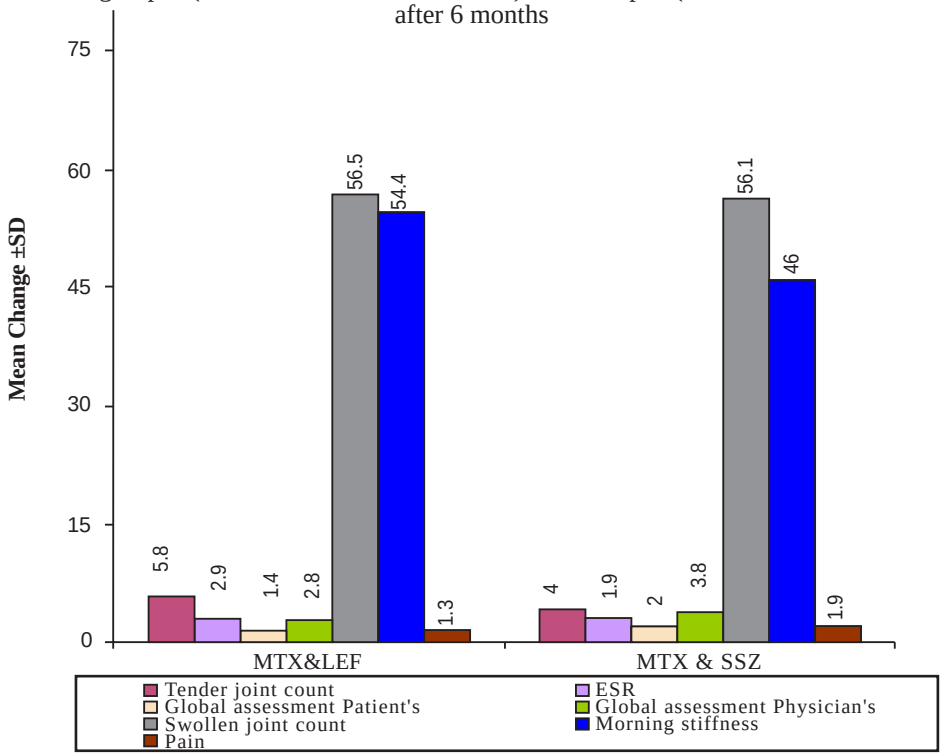

Table: 2
Observed side effects of combination therapies in rheumatoid arthritis patients

	Group A (MTX & LEF)	Group B (MTX & SSZ)
No. of patients	44	45
Headache	2(4.5%)	1 (2.3%)
Rash	1 (2.3%)	2 (4.4%)
Pneumonia	-	-
GIT distress	2 (4.5%)	2 (4.4%)
Weight loss	-	-
Total	5	5
Percentage of side effects	11.4%	11.1%

and B. A highly significant decrease was seen in the mean morning stiffness in group B when compared to group A. A significant decrease in mean joint pain in group A was observed when compared to group B (Table-1, Figure-2).

DISCUSSION:

Due to the advancement in pathophysiology of rheumatoid arthritis, its management is continuously evolving. Traditional DMARDs will undoubtedly remain the chosen initial treatment. Recent guidelines promote early and continued use of DMARDs.[20] Various studies demonstrate the effectiveness of combination therapy over monotherapy in the treatment of rheumatoid arthritis.[14] Most of DMARD therapies have a weakness that their comparison with active therapy have not been done.

The treatment of rheumatoid arthritis with MTX and LEF, and MTX and SSZ had already been established[21]. In the present trial, we compared the efficacies of these combination therapies. The results of the present trial proved the effectiveness, improvement in symptoms and slowing of progression of disease.

The study conducted by Dougados et al.[9] showed that the mean changes in the DAS during one-year-follow up of the study was -1.15, -0.87, -1.26 in the SSZ, MTX, and SSZ + MTX group respectively, in accordance with our study. This study showed the minimum advantage of combination of MTX and SSZ over other therapies, as it was indicated in our study that combination of MTX and LEF showed marginal benefit over combination of MTX and SSZ.

In another study,[22] combination therapy of DMARDs was prescribed. 199 patients with early and active rheumatoid arthritis were enrolled in this cohort study. The patients were initially randomized to receive the treatment with a combination of methotrexate, sulfasalazine and leflunomide with prednisolone or

treatment with single DMARD with or without prednisolone. The results of this study were also in accordance with our study by proving that combination of MTX and LEF was marginally benefited over combination of MTX and SSZ.

In contrast, Haagsma et al.[23] indicated that combination of methotrexate and sulfasalazine had no significant difference in comparison with monotherapy with either of the drug alone.

A randomized, double-blind, placebo-controlled trial[24] was also in accordance with our study, indicating the effectiveness of methotrexate and leflunomide therapy in the patients of rheumatoid arthritis. Adverse effects were mild or moderate similar to our study but the percentage was more i.e. 89.25%. In our study, adverse effects were only 11.4% (Table-2), this means our study showed better result both in terms of adverse effects and response of the patients.

CONCLUSION:

The patients of rheumatoid arthritis responded slightly well to the combination of methotrexate and leflunomide in terms of efficacy and safety.

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