



EFFICACY OF METHOTREXATE VERSUS LEFLUNOMIDE VERSUS COMBINATION OF BOTH IN ACTIVE RHEUMATOID ARTHRITIS

Pharmacology

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ABSTRACT

OBJECTIVE: To compare the efficacy and safety of methotrexate (MTX) versus leflunomide (LEF) versus combination of both in patients with active rheumatoid arthritis (RA).

Place and duration: This prospective, interventional, open-label, randomized trial was carried out in Department of Pharmacology associated with Department of Orthopaedics, Jawaharlal Nehru Medical College, Bhagalpur, Bihar over 24 weeks.

MATERIALS AND METHODS: It included 100 adult patients with active RA. Patients were randomized to receive methotrexate, leflunomide or combination of both in a 1:1:1 ratio. Dose adjustment was done according to clinical response.

RESULTS: Seventy-three patients completed 24 weeks of the trial including 26, 24 and 23 patients in methotrexate, leflunomide and combination group respectively. DAS 28 remission was achieved in 30.8%, 37.5% and 26.1% patients at 24 weeks in methotrexate, leflunomide and combination group respectively. ACR 20 response was seen in 84.6%, 83.3%, 78.3%; ACR 50 response was seen in 53.8%, 45.8%, 43.5% and ACR 70 response was seen in 23.1%, 16.7% & 21.7% in methotrexate, leflunomide and combination groups respectively. However this difference in response between three groups was not statistically significant. Adverse effect profile was also comparable between 3 groups with anorexia, nausea, raised alanine transaminase (ALT) and infections being the commonest.

CONCLUSION: Both methotrexate and leflunomide are equally effective in patients with active RA. There is no added benefit of combination treatment in DMARD naïve patients. Combination of methotrexate and leflunomide is safe and well tolerated and can be used if regularly monitored for adverse effects.

KEYWORDS

Methotrexate, leflunomide, rheumatoid arthritis, DMARDs.

INTRODUCTION

RA is a chronic, systemic, inflammatory autoimmune disease that mainly targets the synovial tissue¹. It is an erosive arthropathy that has substantial personal, social and economic costs². It affects 1% of adults worldwide³.

If not treated adequately, it can lead to joint destruction and disability. The long term prognosis is not good; 80% of affected patients are disabled after 20 years and life expectancy is reduced by an average of 3-18 years⁴. So it is important to diagnose early and manage the disease promptly¹. Early aggressive treatment of RA is associated with better disease control, slower radiological progression and improved functional outcome⁵. The most important aspect in the treatment of RA is control of inflammation and prevention of joint damage⁵. Current treatment strategy includes the use of NSAIDs, low dose steroids, disease modifying antirheumatic drugs (DMARDs) and biologic agents. It is now recommended that DMARDs are used in early RA, before the radiographic evidence of disease sets in to prevent joint damage and disability⁶. Among the DMARDs, methotrexate is the most effective, with less toxicity, less cost and better tolerability^{1,6,7}. It is considered to be the primary anchor drug used in rheumatoid arthritis management and is commonly prescribed as first line DMARD⁸. Unfortunately methotrexate alone does not always fully control the disease and other DMARDs have to be added. These DMARDs include leflunomide, sulphasalazine, hydroxychloroquine etc. Leflunomide is the newest DMARD that has proven to be effective in control of RA and is found to be as efficacious as MTX⁹.

Various studies have been published comparing efficacy of methotrexate versus leflunomide and have shown that both are equally effective^{3,10-13}.

Combination DMARDs are increasingly being used nowadays¹. At least a third of RA patients in USA are receiving combination therapy¹⁴.

Methotrexate plus leflunomide is a popular combination that is very effective and well tolerated in the treatment of active RA¹⁵⁻¹⁷.

Contrasting modes of action of methotrexate and leflunomide make them very suitable for use in combination¹⁶. Both these drugs are hepatotoxic and have gastrointestinal (GI) adverse effects. There is a concern that the combination therapy can increase the risk of hepatotoxicity. However various studies have shown that combination therapy is very efficacious without increased incidence of

hepatotoxicity¹⁸. The aim of this study is to compare the efficacy and safety of methotrexate versus leflunomide versus the combination of both in newly diagnosed patients of RA.

MATERIAL AND METHODS

This prospective, interventional, open-label, randomized trial was carried out in the Department of Pharmacology associated with Department of Orthopaedics, of the Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar over a period of about 1.5 years between May 2020 to October 2021.

Inclusion criteria included active disease by ACR criteria with DAS $\geq$ 3.2 in males or females diagnosed to have RA, between ages of 18 and 75 years. Female subjects were of non-childbearing potential or agreed to practice a medically accepted contraceptive regimen. They agreed to not get pregnant for 12 months after discontinuation of treatment with study medication. Male subjects consented to practice contraception during the study. Concomitant therapy was permitted with NSAIDs and corticosteroids at a dose of less than or equal to 10 mg prednisolone daily. Informed consent was obtained for all subjects before enrollment in the study.

Exclusion criteria included patients who had previously used any DMARD within past 2 months; patients with liver disease, renal failure, active tuberculosis, evidence of pulmonary fibrosis, uncontrolled diabetes mellitus or hypertension. Patients with contraindication to any of the drug were also excluded.

Complete medical history and physical examination was done. RA was diagnosed according to ACR criteria and anti-CCP (anti cyclic citrullinated peptide) antibodies if needed. Baseline tests including full blood count, ESR, liver function tests, renal function tests, random blood glucose levels and chest x-ray were done. Clinical assessment included tender and swollen joint counts (28 joints), patient global assessments of disease activity on a visual analogue scale (VAS 0-100 cm), patient assessment of pain (VAS, 0-100 cm) and Modified Health Assessment Questionnaire-Disability Index (mHAQ-DI) score. Radiographs of the hands and feet were taken at baseline and at 24 weeks or at the time of early study exit.

Patients were assigned to 1 of 3 treatment groups in a 1:1:1 randomization; leflunomide (20 mg/day without loading dose), methotrexate (7.5 mg/wk) or the combination of both in same

doses. All patients on MTX also received 5mg of folic acid once weekly. If active disease was still present, methotrexate dose was increased to a maximum of 20mg at increment of 2.5-5mg per visit.

Patients were followed up monthly for first 4 months and then final analysis done at 24 weeks. Clinical and laboratory evidence of adverse effects was noted at each follow up. Dosage adjustments or discontinuation of treatment was done according to standard protocols.

The measures of efficacy were:

- Change in DAS score to ≤ 2.6
- Improvement in European league against rheumatism (EULAR) criteria for measuring RA disease activity.
- American College of Rheumatology criteria for level of improvement from base line (ACR 20, ACR 50 and ACR 70)

Statistical Analysis: All data was entered into SPSS version 16. To compare efficacy, chi square test was applied for categorical data. For numerical data as e.g. mean DAS score; independent sample t-test was applied for comparing two groups. For comparing 3 groups, ANOVA test was applied. Overall frequency of efficacy in all 3 groups was also compared.

RESULTS

One hundred patients were included in the trial. 36 patients received methotrexate; 33 patients received leflunomide and 31 patients were given combination of methotrexate and leflunomide. 27 patients dropped out from the trial due to various reasons. Finally 73 patients completed the study; 26 in methotrexate group; 24 in leflunomide group and 23 in the combination group.

Sixty-one i.e. 83.6% of the patients were females. 50.7% of the patients had disease duration of more than 2 year.

Patients in 3 groups were matched for age and gender.

Dose of leflunomide was 20mg/day in all patients. Mean dose of MTX was 13.75 ± 3.89 mg/ week in MTX only group and 11.08 ± 3.89 mg/week in combination group.

Baseline characteristics of patients are given in table I. All the patients were followed up for 24 weeks. At each follow-up visit, DAS scoring was done, ACR response was assessed, laboratory results were checked and patients were inquired about possible adverse effects.

Table I : Baseline Characteristics of Patients

Characteristic	MTX (n=26)	LEF (n=24)	MTX+LEF (n=23)	Total (n=73)
Age	38.69 $\pm$ 9.35	38.92 $\pm$ 10.78	35.56 $\pm$ 10.54	37.78 $\pm$ 10.19
Females	22(84.6%)	22(91.7%)	17(73.9%)	61(83.6%)
Males	4(15.4%)	2(8.3%)	6(26.1%)	12(16.4%)
Disease duration				
<6months	7(26.9%)	4(16.7%)	2(8.7%)	13(17.8%)
6-24 months	6(23.1%)	8(33.3%)	9(39.1%)	23(31.5%)
>24 months	13(50%)	12(50%)	12(52.2%)	37(50.7%)
RA Factor				
Positive	22(84.6%)	15(62.5%)	19(82.6%)	56(76.7%)
Negative	4(15.4%)	9(37.5%)	4(17.4%)	17(23.3%)
Erosions				
Positive	6(23.1%)	5(20.8%)	11(47.8%)	22(30.1%)
Negative	20(76.4%)	19(79.2%)	12(52.2%)	51(69.9%)
Mean DAS28	6.61 $\pm$ 1.14	6.83 $\pm$ 0.92	6.84 $\pm$ 1.14	6.75 $\pm$ 1.06
Mean Hb (g/dL)	11.12 $\pm$ 1.46	11.03 $\pm$ 1.63	11.54 $\pm$ 1.68	11.23 $\pm$ 1.58
Mean ALT	21.92 $\pm$ 1.36	23.25 $\pm$ 10.14	19.83 $\pm$ 7.29	21.7 $\pm$ 9.79
Mean ESR	53.11 $\pm$ 28.09	48.58 $\pm$ 25.95	42.83 $\pm$ 26.38	48.38 $\pm$ 26.83
Receiving steroids	21(80.8%)	18(75%)	21(91.3%)	60(82.2%)
mHAQ-DI	1.15 $\pm$ 0.57	0.98 $\pm$ 0.42	1.08 $\pm$ 0.59	1.07 $\pm$ 0.53
Mean VAS	76.54 $\pm$ 21.25	76.47 $\pm$ 20.3	79.13 $\pm$ 21.14	77.31 $\pm$ 20.65

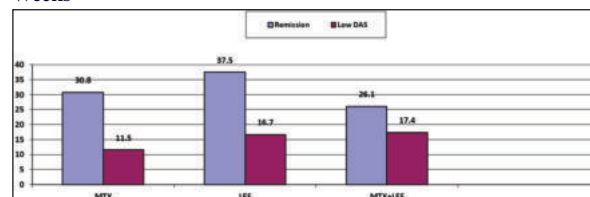
MTX- Methotrexate, LEF- leflunomide, DAS- disease activity score, VAS- Patient's visual analogue scale, mHAQ DI- health assessment questionnaire- disability index

Mean DAS was calculated at each visit and patients were also categorized into various disease categories according to their DAS score:

- ≤ 2.6 Remission
- 2.6-3.2 Low disease activity
- 3.2-5.1 Moderate disease activity
- > 5.1 High disease activity

At 24 weeks; 30.8%, 37.5% and 26.1% of the patients were in remission in MTX, LEF and combination groups respectively. 11.5%, 16.7% and 17.4% of the patients were in low disease activity in MTX, LEF and combination groups respectively as shown in figure 1.

Figure1. Patients In Remission And Low Disease Activity At 24 Weeks



MTX- Methotrexate, LEF- leflunomide, DAS- disease activity score
There are some differences in response rate but this difference is not significant statistically. Similarly mean DAS 28 at 24 weeks was lowest for leflunomide but statistically there was no difference in mean DAS in 3 groups. EULAR response and ACR response is shown in table II.

A high percentage of patients were ACR responders in all 3 groups but statistically there was no difference between MTX, LEF and MTX+LEF group. There was significant improvement in mHAQ-DI and patient's VAS but there was no difference in 3 groups statistically. Acute phase reactant (ESR) also dropped with treatment in all the groups.

60 patients (82.2%) were on steroids (5-10mg/d) at baseline. This number decreased to 47 patients (64.4%) at 24 weeks.

Table II : Outcome/Efficacy Measures

Efficacy Measure	MTX (n=26)	LEF (n=24)	MTX+LEF (n=23)
Mean DAS 28			
Baseline	6.6104 $\pm$ 1.4442	6.8339 $\pm$ 0.91831	6.8361 $\pm$ 1.14342
4 weeks	4.5846 $\pm$ 1.54928	4.5575 $\pm$ 1.11217	5.0843 $\pm$ 1.47616
12 weeks	3.886 $\pm$ 1.48671	3.4688 $\pm$ 1.25615	4.3122 $\pm$ 1.69838
24 weeks	3.4458 $\pm$ 1.33506	3.1446 $\pm$ 1.17011	3.8587 $\pm$ 1.47874
EULAR response at 24 weeks			
Good	12(46.2%)	15(62.5%)	11(47.8%)
Moderate	12(46.2%)	8(33.3%)	10(43.5%)
None	2(7.7%)	1(4.2%)	2(8.7%)
ACR response at 12 weeks			
Nil	38.5%	12.5%	26.1%
ACR 20	61.5%	87.5%	73.9%
ACR 50	34.6%	45.9%	39.1%
ACR 70	15.4%	16.7%	8.7%
ACR response at 24 weeks			
Nil	15.4%	16.7%	21.7%
ACR 20	84.6%	83.3%	78.3%
ACR 50	53.8%	45.8%	43.5%
ACR 70	23.1%	16.7%	21.7%
mHAQ-DI at 24 weeks	0.35 $\pm$ 0.32	0.29 $\pm$ 0.24	0.36 $\pm$ 0.31
Mean VAS at 24 weeks	28.00 $\pm$ 22.21	28.25 $\pm$ 21.1	30.96 $\pm$ 21.6
Mean ESR at 24 weeks	25.54 $\pm$ 17.2	23.12 $\pm$ 17.51	28.13 $\pm$ 18.59

MTX- Methotrexate, LEF- leflunomide, DAS- Disease Activity Score, ACR- American College of Rheumatology, EULAR- European League Against Rheumatism, VAS- Patient's Visual Analogue Scale, HAQHealthAssessment Questionnaire

On the matter of side-effects and tolerability, gastrointestinal adverse effects were the most common i.e. anorexia and nausea. Significantly more patients in combination group had these side effects. New-onset hypertension was seen in 2 patients taking leflunomide.

Infections were observed in 5 patients on MTX; 1 patient on LEF and 5 patients on combination treatment. Most of the infections were related to skin, followed by respiratory tract infections followed by UTI. However there was no serious infection. Overall 15 patients had derangement in transaminase levels however only 1 patient in combination group had a significant (>3 times the upper limit of normal) rise in ALT requiring drug discontinuation. Others had <2 times upper limit of normal elevation in ALT. Incidence of anaemia was also equal in all 3 groups. No serious adverse event was noted in any of the patient.

Reasons for discontinuation of drug therapy in 27 dropped out patients were similar including adverse effects, lack of efficacy, social reasons and unknown factors.

DISCUSSION

Many trials have been conducted to see the efficacy and safety of combination treatment of MTX and LEF. It has been observed that combination treatment is effective and well tolerated.^{15,16}

One hundred patients were initially recruited but 73 patients completed 24 weeks of study period. Patients are still being followed up and results at 1 year will be published later. One big reason for drop outs in this study was the socio-economic factor. PIMS has a large catchment area and it becomes difficult for the patients to come for regular frequent follow ups.

Our study results are comparable to the studies done in other parts of world. These have shown that MTX & LEF are equally effective and combination treatment does not offer any added benefits when initiated in DMARD naïve patients. Recent study by Saima Zeb and her colleagues showed that leflunomide and methotrexate are equally effective in management of RA with equal change in mean DAS 28 and equal incidence of adverse effects³.

Cohen S et al¹⁰ did a study to compare efficacy of MTX & LEF. They showed that both MTX & LEF are equally effective in terms of ACR 50 (43 vs 56%) and ACR 70 (20 vs 26%) response. However ACR 20 response was significantly more with LEF as compared to MTX (79 vs 67%). Our study has also shown insignificant difference of response between MTX & LEF and resembling values of ACR responses.

Paul Emery and his colleagues¹¹ in a similar study found out similar results with ACR 20 of 64.8% and 50.5% with MTX and LEF respectively. This difference was not significant statistically. Vibeke Strand et al¹² in their study found equivalent ACR response with both MTX & LEF. DAS 28 remission in our study is 30.8% with MTX and 37.5% with LEF. This is almost similar to results of other studies on MTX & LEF. PREMIER & COMET studies showed a DAS remission rate of 21% and 28% respectively with MTX^{20,21}. Remission rate of 25% was reported with use of LEF in a study done by Herbert Kellner²². Second important aspect of our study was to ascertain whether combination of MTX and LEF is superior to either monotherapy. Results of our study have rejected this hypothesis as all 3 treatment groups proved to have equal efficacy. Katchmart W⁷ and Donahue KE²³ also studied the efficacy and safety of MTX monotherapy versus its combination with LEF. Both studies concluded that in DMARD naïve patients, there is no significant advantage of MTX plus LEF combination versus monotherapy. There is significant improvement with combination therapy only in those patients who do not respond well to MTX monotherapy. Our study also did not show superiority of MTX combination therapy over monotherapy probably because the patients were not previously declared to be MTX non-responders.

Combe B et al⁶ reported that initial combination therapy yields better results than monotherapy only in the group of patients with severe disease. However they recommended using monotherapy initially.

Kremer JM and his colleagues¹⁸ also reported in their study that combination therapy is good in patients already on MTX who are non-responders to it. Singer O & Gibofsky A²⁴ in their review article mentioned that LEF is as safe and effective as MTX both as monotherapy and in combination with biologics. They also suggested that LEF is beneficial as an add-on agent to MTX in RA patients who fail monotherapy. Recent guidelines by ACR also recommend

monotherapy as initial treatment in new RA patients²⁵.

However few studies have also shown that initial combination therapy with MTX & LEF is more efficacious as well as safe.^{15,17}

MTX and LEF both have different modes of action but adverse effect profile is similar. Major side effects of both of these agents are gastrointestinal problems like anorexia, nausea, vomiting, diarrhoea and hepatotoxicity.

Blood dyscrasias have also been mentioned with both.

There is a concern that adding two agents together can increase these adverse effects. Our study showed that only anorexia and nausea are significantly more with combination treatment. However these are minor side effects that can be managed easily. Mild anaemia was seen equally in all three groups and no patient had neutropaenia in any of the group. Hypertension was only observed in 2 (8.3%) patients on LEF monotherapy.

Incidence of non-lethal infections was more in MTX monotherapy and combination group. One patient of age 65 years died after completing one year of treatment with LEF. However cause of death was not probably linked to use of LEF.

Most importantly, elevation of transaminase levels was seen equally in 3 groups. No patient had liver failure and only 1 patient in combination group left treatment due to deranged LFTs (>3 times upper limit of normal). Various other studies have also concluded that combination treatment with MTX & LEF is safe and well-tolerated^{15-18,26}.

Withdrawal rate is also similar to that seen with monotherapy⁷.

Data from the CORRONA registry²⁷ suggested a greater toxicity with LEF + MTX combination. Curtis JR and colleagues²⁷ showed a two to five-fold increased rate of LFT abnormalities depending on the MTX dose with combined MTX + LEF compared with MTX alone in patients with RA. Significantly greater number of patients on combination therapy had LFT abnormalities.

There are various limitations of this study. First; it has a small sample size. Secondly it is not double blinded.

Thirdly, follow-up period is not sufficiently long.

This limited data does not favour one monotherapy over other or superiority of combination treatment over monotherapy. More trials are needed with large population size for head to head comparison of these 3 popular treatment options in newly diagnosed patients of RA.

CONCLUSION

We can conclude that both methotrexate & leflunomide are equally effective in patients with active RA. There is no added benefit of combination treatment in DMARD naïve patients. Combination of methotrexate and leflunomide is well tolerated, not more toxic, and can be safely used with regular monitoring for adverse effects.

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