

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

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ABSTRACT

Objective: To determine the efficacy of Methotrexate versus Leflunomide versus combination of both among patients managed at Pak Emirates Military Hospital with active rheumatoid arthritis.

Study Design: Prospective comparative study.

Place and Duration of Study: Rheumatology/General Medicine Department, Pak Emirates Military Hospital Rawalpindi, from May 2019 to June 2020.

Methodology: Patient of active rheumatoid arthritis who fulfilled American college of rheumatology criteria of 1997 were included in the study. They were randomly divided into three groups with group A receiving Methotrexate, group B receiving Leflunomide while group C received the combination of both Methotrexate and Leflunomide. Disease activity was assessed by using the Disease Activity Score-28 in all the three groups after three months of treatment.

Results: Mean age of the study participants was 36.919 ± 6.85 years. One hundred and fifty (83.3%) patients were female while 30 (16.7%) were male. Out of 160 (88.9%) patients achieved remission according to Disease Activity Score-28 score at the end of three months while 20 (11.1%) did not achieve remission. Pearson chi-square test revealed that none of the factors studied including the treatment option had any statistically significant relationship with presence of remission among the target population (p -value 0.386, 0.815, 0.194 and 0.145 for age, gender, duration of symptoms and type of treatment respectively).

Conclusion: Remission rate among the rheumatoid arthritis patients in response to treatment was overall good in the study. In terms of efficacy for symptoms of rheumatoid arthritis and achieving remission, after three months of treatment all the three options i.e., Methotrexate, Leflunomide and combination were equal in our study.

Keywords: Efficacy, Leflunomide, Methotrexate, Rheumatoid arthritis.

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INTRODUCTION

Immune mediated disorders have gained a lot of attention of clinicians and researchers in last few decades due to more understanding of the etiopathogenesis of these disorders. Rheumatoid arthritis has been one of the most commonly diagnosed immune based disorder around the globe.¹ Situation has been same in our part of the world and due to diagnostic facilities more people have been diagnosed with this disorder in last few years.² Various symptomatic and definitive treatments have been available to cater for the patients suffering from this disorder in which pain has usually been the primary complain.^{3,4} Choice of treatment usually depends upon local availability of medications, patients and physician's choice, relative efficacy and adverse effects of the medications.^{4,5}

Methotrexate has been one of the preferred options by the rheumatologist all around the world for managing rheumatoid arthritis.⁵ Other options

include biological disease modifying drugs and conventional disease modifying drugs. They all have certain adverse effects which may be troublesome for the patients in short and long term.⁶ Therefore best choice for the patients of rheumatoid arthritis is still questionable and sometimes combination drugs may be offered to the patients.

Multiple trials and reviews have been conducted in past few years to look for the best treatment option for the patients of rheumatoid arthritis. Hunag *et al.*, compared combination therapy with Methotrexate and Sinomenineor Leflunomide for active Rheumatoid Arthritis. They concluded that after twenty-four weeks of therapy Methotrexate and Sinomenine, combination therapy is probably one of the choices for treating patients with active rheumatoid arthritis in addition to Methotrexate and Leflunomide combination therapy.⁷ A local study published by Ishaq *et al* compared the efficacy and toxicity of Methotrexate and Leflunomide for the treatment of rheumatoid arthritis in a double-blind randomized clinical trial. Conclusion of their trial was that both the medications have been efficacious in

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managing the symptoms of rheumatoid arthritis, but they put Methotrexate above Leflunomide because of cost effectiveness and better tolerability.⁸ SMILE study by Bird *et al.*, has been interesting in this regard as well. They studied the adverse effects or tolerability of individual Methotrexate and Leflunomide and then the combination of both drugs. They came up with the findings that combination has been as safe as the individual drugs contrary to the belief that combination may be more toxic as compared to the individual drugs.⁹

Recent data show that rheumatoid arthritis has been one of the most common immunological disorders among patients reporting in rheumatological and medical outpatient departments.¹⁰ Multiple treatment options have been available to manage this chronic condition, but all have certain merits and demerits. Methotrexate has been a commonly used and studied disease modifying agent in our setup with limited studies reporting the side effects experienced by the patients put on this agent. We therefore planned this study to determine the efficacy of Methotrexate versus Leflunomide versus combination of both among patients managed at Pak Emirates Military Hospital (PEMH) with active rheumatoid arthritis.

METHODOLOGY

This prospective comparative study was conducted from May 2019 to March 2020 on patients presenting at General Medicine/Rheumatology Outpatient Department of PEMH, Rawalpindi.

Inclusion Criteria: Patients fulfilling the American college of rheumatology classification criteria of active rheumatoid arthritis with ages between 15-60 years and Disease activity score >3.2.

Exclusion Criteria: Patients who without a clear diagnosis of Rheumatoid Arthritis or with comorbid other autoimmune disease or those who were pregnant were excluded from the study.

Sample size was calculated by using the WHO sample size calculator and keeping the population prevalence proportion of response to treatment in Rheumatoid Arthritis at 8.1%.⁹ Non-probability consecutive sampling technique was used to gather the required sample size for this study and then lottery method was used to randomly divide the patients into three groups. 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. Any patient not agreeing to the above mentioned terms and conditions regarding safety were not included in the study. These points were highlighted in all the assessment clinics during the 3 months study and anytime patients disagreed to these terms were excluded from the study.

Permission from hospital ethics committee via letter number A/28/EC/141/20 was sought prior to commencement of study. All the patients signed the informed consent form after full description regarding erotogenic and mutagenic side effects of the medications under study before getting enrolled into the study. Patients were divided into three groups randomly via lottery method. Group A received the Methotrexate, group B received the Leflunomide while group C received the combination of both drugs.

Methotrexate was given in standard dose (Single dose: 7.5 mg orally or subcutaneously once a week, divided dose: 2.5mg orally every 12 hours for 3 doses once a week 11 with a maximum weekly dose: 20 mg) and started as per the protocol with regular monitoring of the liver function tests and blood counts.¹² Leflunomide was given at a dose of 20 mg once daily with a clear description of adverse effects and precautions needed to be taken.¹³

Response of the patients and remission was decided on the basis of Disease activity score- 28 score. It includes number of tender and swollen joints, self-assessment of health using the visual analog scale (VAS), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). It predicts the activity and severity of underlying rheumatoid arthritis. Due to its complex calculation and variable contribution of each parameter a set formula has been used to incorporate all the clinical and laboratory parameters and calculate the final score.¹⁴ Remission was considered if at the end of three months of the treatment disease activity score-28 score assessed by an independent blind assessor was <2.6.

Statistical analysis was performed by using the Statistical Package for the social sciences (SPSS) version 23. Frequency and percentage were calculated for the qualitative variables in the study. Mean and standard deviation was calculated for the age of the patients and duration of illness. Pearson chi-square test was used to see the association between the age, gender, duration of symptoms and type of treatment used with the remission. The *p*-value ≤ 0.05 was considered as significant for this study.

RESULTS

After excluding the patients which could not fulfill the criteria 180 patients of rheumatoid arthritis were randomized into three groups via lottery method. Mean age of the study participants was 36.919 ± 6.85 years. Table-I shows that 150 (83.3%) patients were female while 30 (16.7%) were male. Out of 160 (88.9%) patients achieved remission according to Disease activity score-28 score at the end of three months while 20 (11.1%) did not achieve remission. Out of 62 (34.4%) patients were in group-A taking Methotrexate, 64 (34.6%) in group-B taking Leflunomide and 54 (30%) in group C taking combination of both the drugs). Table-II revealed that efficacy of Methotrexate versus Leflunomide versus combination of both among patients managed at Pak Emirates Military Hospital with active rheumatoid arthritis was not statistically different (*p*-value=0.145). Other factors studied including the age, gender and duration of treatment also had no statistically significant relationship with presence of

Table-I: Characteristics of patients with Rheumatoid arthritis included in the study (n=180).

Variables	n (%)
Age (years)	
Mean ± SD	36.919 ± 6.85
Range (min-max)	18-57 years
Mean duration of symptoms	11.4 ± 3.212 months
Gender	
Male	50 (83.3%)
Female	130 (16.7%)
Treatment Response	
Remission	160 (88.9%)
No remission	20 (11.1%)
Treatment Options	
Methotrexate	62 (34.4%)
Leflunomide	64 (35.6%)
Combination	54 (30%)

Table-II: Efficacy of treatment options and relationship of other factors with the presence of remission of symptoms among the target population.

Factors	Remission of Symptoms	No Remission of Symptoms	<i>p</i> -value
Age			
<40 years	104 (65%)	11 (55%)	0.386
>40 years	56 (35%)	09 (45%)	
Gender			
Female	116 (72.5%)	14 (70%)	0.815
Male	44 (27.5%)	06 (30%)	
Duration of Symptoms			
<12 months	78 (48.7%)	06 (30%)	0.194
>12 months	88 (51.3%)	14 (70%)	
Treatment Option			
Methotrexate	58 (36.2%)	04 (20%)	0.145
Leflunomide	53 (33.1%)	11 (55%)	
Combination	49 (30.7%)	05 (25%)	

remission among the target population (*p*-value=0.386, 0.815 and 0.194 respectively).

DISCUSSION

Limited number of experts in rheumatology have been in practice in our part of the world. Most of the burden of rheumatological diseases has been catered by the medical specialists and general physicians.¹⁴ Methotrexate has been the commonly used drug for rheumatoid arthritis in our setup but other drugs have also been used with limited data on their efficacy and adverse effects in our own population.^{15,16} Due to this gap in literature regarding efficacy of various treatment options for rheumatoid arthritis in our population we planned this study with the rationale to determine the efficacy of Methotrexate versus Leflunomide versus combination of both among patients managed at Pak Emirates Military Hospital with active rheumatoid arthritis. Nisar *et al*,¹⁶ conducted a very similar study, in a large public sector hospital in Islamabad and concluded that Methotrexate, Leflunomide and combination; all three options have been equally effective in controlling the symptoms of rheumatoid arthritis and no statistically significant difference could be found in efficacy and adverse effects of the three options.¹⁶ Our study design was similar to them except the fact that we looked for the adverse effects in each assessment session but did not include in the analysis. Our results were also comparable to them as we could also not establish any statistically significant difference among the efficacy of three options for treatment of rheumatoid arthritis.

Lee *et al*,¹⁷ conducted a study with the objective to evaluate the efficacy of Leflunomide and Methotrexate combination among the patients of rheumatoid arthritis at various centers. They came up with the conclusion that combination treatment was an effective option for controlling the symptoms of rheumatoid arthritis and they recommended that combination should be tried before thinking of stating the new biological disease modifying agents for these patients,¹⁷ our results showed that though combination treatment was effective option but it was as effective as the monotherapy with either of Methotrexate or Leflunomide. Therefore, this combination can give any added benefit or not in terms of efficacy is still unsure from our results.

Emery *et al*,¹⁸ published an interesting double blinded multi-center trial involving 999 patients and comparing Methotrexate and Leflunomide. It was a long term follow up trial and they evaluated patients

with regular intervals. At the end of trial there was not much difference between the efficacy of two drugs but at the end of first year Methotrexate was found more efficacious. They recommended to weigh risks versus benefits and use of folate with Methotrexate before generalizing their results.¹⁸ We though concluded that all treatment options we studied have been equal in efficacy but again we did not include the adverse effects in our study so after efficacy, adverse effects and cost are two major issues which need to be looked after before starting any medication especially the long term medications.

Ishaq *et al*,⁸ published a study with holistic approach comparing Methotrexate and Leflunomide in terms of efficacy, safety and effectiveness. They concluded that both medications have been equally effective, but Methotrexate may be used in routine because of being cost effective for the patients of a developing nation like ours.⁸ Our results are similar to their findings in terms of no difference in efficacy of both the medications.

LIMITATION OF STUDY

Limited number of patients from a single center were recruited in the study which has been the main limitation of this study. Use of Disease activity score-28 score may also pose some methodological issues as it may not be a true reflection for remission. Future studies with better methods of outcome or ascertaining of remission and large sample size may generate better results. Moreover, tolerability or adverse effects may also be recorded and studied along with the efficacy in order to paint a holistic picture.

CONCLUSION

Remission rate among the rheumatoid arthritis patients in response to treatment was overall good in the study. In terms of efficacy for symptoms of rheumatoid arthritis and achieving remission, after three months of treatment all the three options i.e Methotrexate, Leflunomide and combination were equal in our study.

Conflict of Interest: None.

Authors' Contribution

SHT: Main author, data collection, AF: Proof reading, data collection, AA: Data collection, KS: Data collection, KHN: Data collection, AS: Data collection.

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