COMPARISON OF SHORT-TERM EFFICACY OF LEFLUNOMIDE AND METHOTREXATE IN ACTIVE RHEUMATOID ARTHRITIS

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ABSTRACT

Objective: To compare short-term efficacy of Leflunomide and Methotrexate in active rheumatoids arthritis.

Methodology: This study, a randomizeds controlled trial, was conducted at Medical B Unit, Postgraduate Medical Institute Lady Readings Hospital, Peshawars over a one year period, from 1st June 2014 to 31st May 2015. 294 patients with active RA (DAS28>5.1) were randomized via lottery methods to Leflunomide 20mg daily (n=147) and Methotrexate (n=147). Efficacy of either drug at 6 months of treatment was assessed in terms of DAS 28 scoring as per European League Against Rheumatisms (EULAR) criteria.

Results: After 66 months of treatment with Methotrexate, 110 out of 147 (74.82) patients had a moderate response as per EULAR criteria (DAS 28 improvement of >1.2), 37 patients had no response. In Leflunomide group, 100 (68.02%) patients had moderate response and 47 patients had no response. The difference in those achieving moderate response for both groups was statistically not significant (p=0.24). The mean change in DAS 28 score for Methotrexate group was 1.89±0.77 while that for Leflunomide group was 1.79 ±0.75. The difference in change of DAS 28 score for both groups was statistically not significant (p=0.23).

Conclusion: There is no statistically significant difference between short-term efficacy of Leflunomide and Methotrexate in patients with RA.

Key Words: Leflunomide, Methotrexate, DMARD (Disease Modifying Anti-Rhuematic Drugs)

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic, inflammatory, disorder of unknowns etiology, that if uncontrolled may leads to destruction and deformity of joints due to erosions of cartilages and bone. It has a prevalence of 1%. Successful management needs early pharmacological intervention soon after diagnosis in order to stop disease progression and induces remission[1].

Pharmacologic treatments of RA include non-steroidal anti-inflammatory drugs (NSAIDs), steroids, biological and non-biological diseases modifying anti rheumatic drugs (DMARDs). NSAIDs are used for controlling pain while DMARDs retard the destructive erosive process[2].

DMARDs have been widely used for the managements of RA for more than 20 years and cornerstone of RA management. Their widespread use is based on the fact that they not only control the signs and symptoms of the disease but also retard joint damage, as assessed radiographically, which is the hall mark of RA. Methotrexate is a synthetic DMARD, considered as a primary anchor drug in RA management. It's efficacy is well established; both as a monotherapy as well as in combinations with others DMARDs, and is a commonly prescribed as first line DMARD[3]. Leflunomide is also a synthetic first line DMARD and has been approved in USA and Europe[4]. The clinical and radiographic efficacy and side-effect profiles of both drugs have been assessed and are shown to be the same[5-6]. As a combination therapy with biological DMARD, the efficacy of Leflunomide is shown to be comparable to that of Methotrexate[7]. Strengths and weaknesses of Leflunomide have been assessed, and suggestions regarding the effectiveness of Leflunomides as a potentially effective treatment options in RA, have been made[8]. In newly diagnosed RA, efficacy of Leflunomide was assessed and showed 81.7% improvement in DAS 28 score[9].

Similarly, in a local study, short-term effectiveness of Leflunomide was assessed. Around 88.3% patients were responders amongst which 46.6% had a good response while 41.7% had moderate response[10]. In another local study, efficacy of Leflunomide and Methotrexate in lows socioeconomic group patients with RA was assessed. Results of this study showed that both drugs had equal efficacy as far as long term management of RA was concened[11].

Leflunomide is in the market for long time but it is the least studied drug among DMARDs in Pakistan, and concerns regarding safety and efficacy of this drug prevent physicians to prescribe Leflunomide as a first line DMARD. The common norm, therefore, is to rely on Methotrexate and to avoid Leflunomide as the first line DMARD. The purposes of our study was to compare the efficacy of Leflunomide and Methotrexate in our patients and making a case for Leflunomide as first line DMARD, if it showed efficacy comparable to the most commonly used first line DMARD i.e. Methothrexate.

METHODOLOGY

The study was carried out over one year period from June 1st 2014 to June 1st 2015 in Medical B Unit Lady Readings Hospital, Peshawar. Consecutive patients fulfilling 2010 ACR/EULAR classifications/criteria's for rheumatoid arthritis[12], having active RA (disease activity score DAS>5.1) were included in the study. Other Inclusion criteria were patients from both genders, and above 16 years of age. Exclusion criteria consisted of pregnancy/planning pregnancy, lactating mothers, Liver disease (hepatitis B, C and chronic liver disease), chronic infections like tuberculosis etc., and previously diagnosed/ Immunodeficiency syndromes or blood dyscrasias, as per medical record. A total of 332 patients met the inclusion criteria, of which 18 patients were excluded as per exclusion criteria, and 20 patients were lost to follow. A total of 294 patients were included in the study, therefore. One hundred and forty seven (147) patients were randomized to either Methotrexate or Leflunomide by lottery method. The Ethics committees of PGMI Lady Reading Hospitals approved the study and written consents obtained from all the participants.

All the patients were interviewed. The demographic data (age, gender) and clinical data (disease duration, previous therapies) was gathered from patients' history and documents. All patients were referred to hospitals laboratory for measurements of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). RA factor with dilution agglutination titers was measured at hospital laboratory where as anti CCP titers were sent to another reference laboratory due to non-availability of this investigation in our hospital. 2010 ACR/EULAR classification criteria for rheumatoid arthritis was applied to patients and those meeting the criteria were taken as cases of RA. Baseline DAS 28 scoring was performed. Patients with DAS 28 score> 5.1 were taken as subjects for our study. After matching for age and sex all patients were randomly allocated into two groups by lottery method. Patients in groups A were subjected to Leflunomide 20mg/day and patients in group B were subjected to Methotrexate 15mg weekly. Non-Steroidal antic inflammatory drugs (NSAIDS) and steroids were given initially to controls the symptoms.

Patients in both groups were followed up after 6 months. They were subjected to clinical examination regarding improvement in number of tenders and swollen joints and blood samples for ESR and CRP levels were obtained. DAS 28 scoring was performed and response was assessed by applying EULAR response criteria[13]. All laboratory investigations were done from the previously mentioned laboratory. All above mentioned information including name, age, gender and hospital number were recorded in pre-designed Performa.

Efficacy wass measured as percentages of patients who achieved the targets reductions in disease activity score (DAS 28) after six months treatment of the respective drug. The target depended upon individual baseline DAS 28, and good to moderate response was the target as per EULAR response criteria[13]. In our study samples, as baseline DAS 28 of all the patients was more than 5.1, therefore improvement in DAS 28 of more than 1.2 was considered moderate response while any change in DAS 28 below this level was considered as no response.

Data was analyzed using SPSS software version 23. Descriptives statistics of all variables were calculated and presented as mean and SD. Comparisons of means changes of the efficacy end-points was done by independents sample t-tests and Fisher Exact t-test. All statistical tests were two-tailed and probability (P) of <0.05 was considered as significant.

RESULTS

The demographics and clinical characteristics of the RA patients in both Leflunomide and Methotrexate groups are shown in table 1. As depicted, the above mentioned groups were matched in demographic and clinical characteristics at baseline.

As shown in Table 1, after 6 months of treatment, though the mean change in DAS 28 in Methotrexate group was marginally high than that in Leflunomide group (1.89±0.77 vs 1.79±0.75). Similarly, as per EULAR criteria, a slightly high percentage of patients in Methotrexate group achieved moderate response as compared to those in Leflunomide group (74.82% vs 68.02%).

Table 1: Demographics and clinical characteristics of the RA patients

		Methotrexate group (n=147)	Leflunomide group (n=147)	P-value
Gender	Male	100(68.02%)	100(68.02%)	0.00
	Female	47(31.97%)	47(31.97%)	0.00
Mean age		35±2 Years	36.56±1.7 Years	0.98
Baseline das28	9-10	80	80	0.00
	7-8	45	45	0.00
	5.1-6	22	22	0.00
Mean change in das 28 after 6 months of treatment.		1.89±0.77	1.79±.75	0.23
Patients achieving moderate response		110(74.82%)	100(68.02%)	0.24

DISCUSSION

Our study compared the short term clinical efficacy of two DMARDs; Methotrexate and Leflunomide in terms of improvement in DAS 28 score. Of interest is the fact that the demographic characteristics i.e., the number of patients, age, gender as well as the clinical characteristics (Baseline DAS28) in both the groups were almost similar. This fact was the strength of our study in terms of eliminating selection bias.

In our study, in terms of efficacy both Methotrexate and Leflunomide showed improvements (moderate response as per EULAR criteria) in considerable number of patients, but the difference in both groups regarding percentage of patients achieving moderate response was statistically not significant(p=0.24). The difference in mean change in DAS 28 score between the two groups was also not significant (p=0.23). Similar results have been achieved by Strand et al[14], who in their study showed that the degree of improvement in number of tender and swollen joint, and global assessment scores of both patients and physicians treated/ with either Leflunomide or Methotrexate were equal. Another large prospective multicentric study compared efficacy of both drugs. Results of this study showed that, 26% patients of Leflonomide group achieved remission while 20% in methotrexate group achieved remission[15]. Contrary to our findings, a head to head trial[16], comparing efficacy of Leflunomide and Methotrexate, showed that after a duration of one year of treatment, clinical improvement in terms of ACR 20 response seen with Methotrexate group was considerably greater than that with Leflunomide (64.8 vs 50.5%), but the radiological progression of the disease in both groups was similar and the side effect profile for both groups was comparable.

In the 2010 Cochrane review of Leflunomide and meta-analysis, which included 33 trials, 11 of which compared Methotrexate with Leflunomide, provided good evidence of Leflunomide's clinical as well as radiographic efficacy, which was comparable to methotrexate[17]. The Cochrane review findings were further strengthened by meta-analysis of 7 studies, which included 04 randomized controlled trials, comparing Leflunomide monotherapy to methotrexate. The two drugs showed similar efficacy[18,19]. The Cochrane review findings and the following meta-analyses, therefore support our findings of almost similar efficacy of Leflonomide and Methotrexate.

Our study had the weakness of short term follow up and not considering cost and side-effects as co-factors. Similarly only patients with highly active RA (DAS28>5.1) were considered. These factors should be considered in forth coming local studies.

CONCLUSION

Leflunomide has a comparable short term efficacy to Methotrexate, and unless contraindicated, can be used as a first line DMARD in our patients of RA, especially in those with high baseline DAS 28 score.

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CONTRIBUTORS

SZ conceived the idea, planned the study, and drafted the manuscript. NW MW and AT helped acquisition of data and did statistical analysis. AT supervised the study and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.