EFFICACY OF LEFLUNOMIDE IN PATIENTS PRESENTING WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Objective: To determine the efficacy of leflunomide in patients presenting with rheumatoid arthritis.

Methods: This descriptive case series was conducted in the Medicine Department, Lady reading Hospital, Peshawar, for a period of six months on 158 patients. Thorough history, detailed clinical examination and necessary investigations (Full blood count, ESR, Blood glucose, ALT, creatinine & RA Factor) were carried out and DAS28 score was calculated. All diagnosed patients meeting criteria were started on Leflunomide 20 mg daily. During the follow up appointments, DAS28 Score was recalculated; blood counts, creatinine and liver function tests were performed. Effectiveness assessment was done on the basis of DAS28 score. Confounding variables were controlled by strictly following exclusion criteria based on history, clinical examination and investigations.

Results: In this study mean age was 43 ± 9.38 years. Seventy eight percent patients were female while 22% patients were male. More over in 65% of the patients leflunomide was effective and in 35% patients it was not effective.

Conclusions: Our study concludes that leflunomide was 65% effective in patients presenting with rheumatoid arthritis

Keywords: Efficacy, Leflunomide, Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease that is characterized by articular as well as extra-articular manifestations. Rheumatoid arthritis is present all over the world. The prevalence of rheumatoid arthritis is 0.5 to 1% of the adult population, with females affected approximately three times more often than males, usually between 25 and 55 years of age.[1]

Rheumatoid arthritis is among the common causes of disability. Because of the disease, more than one third of patients eventually experience work disability.[2] Patients with preliminary, active rheumatoid arthritis, are at an increased danger of irreversible joint damage, especially those with having poor risk factors and fast radiological continuance, resulting in functional decline.

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Preliminary intervention with disease-modifying anti-rheumatic drugs (DMARDs) control disease activity preventing outcomes of long-term disease inflammation, radiological continuance and upcoming functional decline.[3]

The extended prognosis of RA is not good. After 20 years, 80% of affected patients are disabled. Life hope is decreased by an average of 3-18 years. So it is important to diagnose the disease early and manage promptly.[4] Leflunomide, an Isoxazole derivative, is a disease-modifying anti-rheumatic drug. Teriflunomide (A-77 1726), the active metabolite of leflunomide, is an immunomodulatory agent that inhibits pyrimidine synthesis, thereby reducing the proliferation of T-lymphocytes and resulting in down-regulation of autoimmune response.[5] The efficacy of leflunomide in the treatment of RA has been the subject of numerous studies. Some difficulties in comparing these studies are related to differences in the principles of patient selection. Significant decrease in DAS28 score after therapy was observed in 68% of the patients in one of the studies.[6]Another study shows that there were no demographically significant differences in the comparison of leflunomide and Methotrexate treated patients regarding ACR20 response 52% versus 46% respectively.[7]

The rationale of the study is that leflunomide is used commonly in our setup and no such study is available over its efficacy. It is clear from the

literature that this drug is efficacious in the treatment of rheumatoid arthritis, so we will recommend this drug in our setup if found to have high efficacy as in literature, which will not only be beneficial for the patients but also least the burden on our hospitals.

Materials and Methods

This descriptive case series was conducted in the Medicine Department, Lady reading Hospital, Peshawar, for a period of six months from 10/7/2018 to 10/01/2019. Sample size for the study was **158**, using 52% efficacy of leflunomide, 7.8% margin of error and 95% confidence level, under WHO formula for determination of sample size. Moreover Consecutive (non-probability) sampling was used for the study

All adult patients including both genders aged 18-65 years with Rheumatoid arthritis with DAS28 > 2.6 and normal baseline liver function tests i.e. if patient's ALT is less than two times of upper limit of normal (50 U/L) were included in the study. While patients with rheumatoid arthritis disease already on leflunomide therapy alone or on leflunomide in combination with another DMARD assessed on the basis of history, females of child bearing age (15-45 years) and patients with other comorbid conditions like liver disease, neuropathies or decreased blood cell lineage, not fit for leflunomide therapy based on history, clinical examination and investigations were excluded from the study.

After approval from the hospital ethical review committee, data for this study was collected from OPD patients visiting department of medicine, Lady Reading Hospital, Peshawar and fulfilling the inclusion criteria. Informed and written consent was taken from all patients.A thorough history was taken which was followed by detailed clinical examination in a respectful and comfortable manner, and necessary investigations (Full blood count, ESR, Blood glucose, ALT, creatinine & RA Factor) were carried out and DAS28 score was calculated. All diagnosed patients meeting criteria were started on Leflunomide 20 mg daily. During the follow up appointments, DAS28 Score was recalculated; blood counts, creatinine and liver function tests were performed. Attempts were made to minimise the lost follow up. Effectiveness assessment was done on the basis of DAS28 score. Safety assessment included monitoring of adverse events (like anaemia, petichiae/bruises, jaundice, alopecia, skin lesions, diarrhoea and neurological symptoms) and laboratory tests (full blood count, ALT and creatinine) results. Confounding variables were controlled by strictly following exclusion criteria based on history, clinical examination and investigations. The data so collected was used to fill up a specially designed proforma. The collected data was analyzed by SPSS statistical package version 20. Mean ± SD was calculated for age, BMI, initial DAS28 score and follow-up DAS28 score. Percentages and frequencies were calculated for categorical variables like efficacy, gender, RA Factor and smoking. Efficacy was stratified among gender, age, RA Factor, BMI and smoking to see the effect modifications. Chi square test was used for post stratification. P-value <0.05 was considered as significant. All collected data represented by using charts, graphs and tables.

In this study mean age was 43 ± 9.38 years. 24(15%) out of 158 patients were in age range of 18-30 years, 52(33%) patients having the age group 31-40 years, 55(35%) patients having the age group 41-50 years, with 27(17%) patients being between the ages of 51-65 years. 123(78%) patients out of 158 were female and 35(22%) were male.

RA Factor among 158 patients was analyzed as 98(62%) patients were RA factor Positive while 60(38%) patients were RA factor Negative. Mean BMI was 25 ± 4.271 Kg/m^2. 66(42%) patients out of 158 had BMI ≤ 25 Kg/m^2 while 92(58%) had BMI > 25 Kg/m^2. 24(15%) patients out of 158 were smokers while 134(85%) did not smoke. Efficacy of leflunomide among 158 patients was analyzed as leflunomide was effective in 103(65%) patients where as in 55(35%) patients it was not effective (table 1). Status of DAS28 Score among 158 patients was analyzed as mean initial DAS28 Score was 7 with SD ± 1.26 where as mean follow-up DAS28 Score was 5 with SD ± 1.47. (table 2)

Stratification of efficacy of leflunomide with respect to age, gender, BMI, RA Factor and smoking is given in table no 3,4,5,6 &7 respectively.

TABLE NO: 1. STATUS OF BMI, RA FACTOR, SMOKING AND EFFICACY OF LEFLUNOMIDE (n=158)

	BMI		RA FACTOR		SMOKING		LEFLUNOMIDE	
	≤25 Kg/m^2	>25 Kg/m^2	POSITIVE	NEGATIVE	YES	NO	EFFECTIVE	NOT EFFECTIVE
Frequency	66	92	98	60	24	134	103	55

Percentage	42%	58%	62%	38%	15%	85%	65%	35%

TABLE NO: 2. STATUS OF DAS28 SCORE (n=158)

DAS28 SCORE	MEAN	STANDARD DEVIATION
INITIAL	7	± 1.26
AFTER 12 WEEKS	5	± 1.47

TABLE NO: 3. EFFICACY OF LEFLUNOMIDE W.R.T AGE (n=158)

Efficacy	18-30 years	31-40 Years	41-50 Years	51-65 Years	Total
Effective	16	34	36	17	103
Not effective	8	18	19	10	55
Total	24	52	55	27	158

P value 0.9936 (Chi Square test)

TABLE NO: 4. EFFICACY OF LEFLUNOMIDE W.R.T GENDER (n=158)

Efficacy	Male	Female	Total
Effective	23	80	103
Not effective	12	43	55
Total	35	123	158

P value 0.9411(Chi Square test)

TABLE NO: 5. EFFICACY OF LEFLUNOMIDE W.R.T BMI (n=158)

Efficacy	≤ 25 Kg/m^2	> 25 Kg/m^2	Total
Effective	43	60	103
Not effective	23	32	55
Total	66	92	158

P value 0.9931(Chi Square test)

TABLE NO: 6. EFFICACY OF LEFLUNOMIDE W.R.T RA FACTOR (n=158)

Efficacy	Positive	Negative	Total
Effective	64	39	103
Not effective	34	21	55
Total	98	60	158

P value 0.9687(Chi Square test)

TABLE NO: 7. EFFICACY OF LEFLUNOMIDE W.R.T SMOKING (n=158)

Efficacy	Yes	No	Total
Effective	16	87	103
Not effective	8	47	55
Total	24	134	158

P value 0.8690 (Chi Square test).

Discussion

Rheumatoid arthritis (RA) is a persistent systemic disease that is characterized by articular as well as extra-articular abstracts. Rheumatoid arthritis is present all over the world. The commonness of rheumatoid arthritis is 0.5 to 1% of the adult population, with females affected approximately three times more often than males, usually between 25 and 55 years of age.[1] Rheumatoid arthritis is among the common causes of disability. Because of the disease, more than one third of patients eventually experience work disability.[2]

In our study mean age was 43 ± 9.38 years. Seventy eight percent patients were female while 22% patients were male. More over in 65% of the patients leflunomide was effective and in 35% patients it was not effective.

The efficacy of leflunomide in the therapy of rheumatoid arthritis has been the subject of numerous studies. Some difficulties in comparing these studies are related to differences in the principles of patient selection. Significant decrease in DAS28 score after therapy was observed in 68% of the patients in one of the studies.[6]

Another study shows that there were no statistically significant differences in the comparison of leflunomide and Methotrexate treated patients regarding ACR20 response; 52% versus 46% respectively.[7]

In another study conducted by Poór VG et al[8] in which in the intent-to-treat population, mean progress at the end-point in the 10 and 20 mg treatment groups respectively were: TJC, –7.57 and –8.89 (P = 0.061); SJC, –6.38 and –6.96 (P = 0.304); and HAQ DI, 0–0.37 and 0–0.49 (P = 0.095). Response rates were 49.8 and 56.6% respectively (P = 0.1724) by American College of Rheumatology (ACR) ≥20% criteria. Adverse effects resulting in withdrawal of treatment were higher in the 10 mg (15.3%) than in the 20 mg treatment group (12.0%), as were serious adverse events: 12.9 *vs* 10.0%.

In another study conducted by Ahmad NM et al[9] had reported that mean age was 46 years with SD ± 12.6. Fifty-four (85.7%) out of 63 patients were female. Mean disease duration was 5.1 years with SD ± 4.5. Fifty-two (86.6%) patients got ACR-20 response at 6 months. Thirty-two (53%) patients got ACR-50 response at 6 months. At least one unpleasant event was reported by 20% patients, which was resolved by reducing leflunomide dose. Only 7 (11%) patients had increased liver enzymes from the standard. They had concluded that this prospective study expresses that leflunomide is an effective as well as a safe DMARD in treatment of rheumatoid arthritis in patients from Pakistan. In another study Maddison Pet al[10] had reported that Leflunomide was well tolerated and at least as effective as methotrexate and sulphasalazine. Withdrawal rates due to adverse events were similar for the three drugs. Avoidance of the loading dose reduces 'nuisance' side-effects, but onset of action is probably delayed by avoidance of the loading dose. Adverse events could usually be managed by reducing dose and/or symptomatic therapy. Based on safety, efficacy and cost, leflunomide should be considered in those patients with who have failed first-line DMARD drug therapy. Leflunomide may be used in combination with, for example, methotrexate in refractory cases, before biological agents are introduced. Therapy should be initiated by a rheumatologist, but repeat prescription in general practice is acceptable using agreed protocols. Clear mechanisms are required to monitor toxicity, manage side-effects and avoid unnecessary discontinuation of leflunomide, with good communication between the rheumatologist and the patient.

Conclusion

Our study concludes that leflunomide was 65% effective in patients presenting with rheumatoid arthritis.

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