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ORIGINAL ARTICLE

Risk of Hepatotoxicity in Leflunomide Vs Methotrexate in Treatment of Rheumatoid Arthritis

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ABSTRACT

Objective: To compare the hepatotoxicity in Leflunomide vs Methotrexate in rheumatoid arthritis patients.
Study design: Cross sectional study.
Place and duration of study: Study was conducted from Jun 2021 to Mar 2022 at Department of Rheumatology and immunology Sheikh Zayed Hospital Lahore.
Methodology: Inclusion criteria were any patient aged between 18-70 years males and females. Patients who were diagnosed with RA according to ACR criteria 2010. Exclusion criteria were pregnancy, Known case of hepatitis B or C, patients having known hypersensitivity to DMARDS. Group A (MTX) of 150 patients received 20 mg/week of MTX and Group B (LEF) of 150 patients received 20mg/day of LEF. The collected data was analyzed on (SPSS) version 24.0.
Results: 40 patients were excluded from study. Mean age of patients in Group A (MTX) was 52.73±9.34 years and in Group B (LEF) it was 51.15 + 9.79 years. 44 patients (33.8%) of group A which were given MTX developed GI symptoms while 22 patients (16.9%) of group B who were given LEF developed GI symptoms. Similarly hepatotoxicity was seen in 15 patients (11.5%) of MTX group while 27 patients (20.8%) of LEF group developed hepatotoxicity which was statistically significant (p = 0.04). 5 patients (3.8%) of LEF developed liver fibrosis.
Conclusion: We conclude that most LEF with rapid onset of action is quicker in reducing symptoms of RA patients and is associated with high degree of hepatotoxicity with low liver fibrosis when compared with MTX.
Keywords: Hepatotoxicity, LEF, MTX, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis is a chronic systemic inflammatory disease of joints which if untreated leads to irreversible joint destruction[1]. Its prevalence varies in different populations. Globally 0.5 – 1 % world population is affected by rheumatoid arthritis and rheumatoid arthritis affects women three times more than men[2]. As reported in literature its prevalence is about 0.142% in the southern to 5.5% in the northern regions of Pakistan. Although there is no known cure for rheumatoid arthritis but use of disease modifying antirheumatic drugs(DMARDS) is recommended to be started early by American college of rheumatology that will prevent further joint damage[3]. Methotrexate(MTX) is considered first line drug among DMARDS to be used as recommended by European league against rheumatism(EULAR). MTX is structural analogue of folic acid and was first used in 1951.

Leflunomide (LEF) a pyrimidine synthesis inhibitor is currently recommended by European league against rheumatism (EULAR) as first line drug which can be used for treatment of rheumatoid arthritis[4]. It inhibits proliferation of T lymphocytes and slows joint damage process as effectively as MTX[5].

Previously randomized control trials have proved that MTX and LEF monotherapy is associated with liver hepatotoxicity and leads to elevated ALT/AST levels[6]. Study by P Bird et al showed that 12% patients of the MTX group, 16% patients of the LEF group developed liver enzymes abnormalities[7].

In our hospital we use MTX and LEF in patients but there is little published data on the hepatotoxicity of these drugs in Pakistan. In this study we will evaluate and compare the hepatotoxic effect of MTX and LEF to that which drug is less hepatotoxic and can be used with less monitoring.

MATERIAL AND METHODS

This cross sectional Study was conducted from Jun 2021 to Mar 2022 at Department of Rheumatology and immunology Sheikh Zayed Hospital Lahore after approval from Institutional Review Board committee. A sample size of 300 patients was calculated by using WHO sample size calculator level of significance was set at 5%, Power of study was 80% and elevation in liver enzymes level i-e 5.4% with LEF and 16.2% with MTX5. Inclusion criteria were any patient aged between 18-70 years males and females. Patients diagnosed with RA according to ACR criteria 20108. Patients who had raised ESR and CRP levels and patients previously using DMARDS not more than 1 month and on monotherapy. Hypertensive and diabetic patients were included who haven't developed end organ damage. Patients using NSAIDS and corticosteroids were included provided their dosage should remain stable throughout study. Exclusion criteria was pregnancy, Known case of hepatitis B or C, patients having known hypersensitivity to DMARDS, patients who had intrarticular steroid injections in past 2 months, patients with comorbids who had already developed end organ damage and alcohol abusers. Non-probability consecutive sampling technique was used to include the patients. Informed consent was obtained from those fulfilling the eligibility criteria. The patients were divided into two groups. Group A (Methotrexate) of 150 patients received 20 mg/week of MTX and Group B (Leflunomide) of 150 patients received 20mg/day of LEF. A detailed history, examination, and all base lines investigations and USG abdomen were carried out before commencing treatment. All included patients were called for follow up after every 8 weeks. At every follow up visit complete history and examination was carried out with LFTs and USG Abdomen to see for any liver structural or functional abnormality i-e any significant change in size or shape of liver, any change in texture, any fibrosis or significant scarring and any change in fat ratio in liver. So by end of six months every patient had 3 follow up visits with complete history, examination and LFTs data along with liver structural evidence by USG Abdomen. If at any stage patient developed hepatotoxicity (Hepatotoxicity was labeled if serum AST/ALT levels rise more than 2 times of normal and if they rise to 3 times of normal range treatment will be stopped at this stage9) treatment was reduced and if they had risen to 3 times of normal then treatment was stopped and Liver function tests were monitored after 2 weeks of suspension of treatment. If Liver function tests remain at same level even after suspension of treatment subject was removed from study. If serum AST/ALT levels rose to 1.5 times of normal it is a red flag sign. (Treatment dosage was reduced at this stage)[10].

The collected data was analyzed in in the statistical package for social science (SPSS) version 24.0. Descriptive statistics were

calculated for qualitative and quantitative variables. Qualitative variables like gender were measured as frequency and percentage. Quantitative variables like age and liver enzymes values were measured as mean and standard deviation. Statistical analysis of means was done by independent sample test between two groups. P value ≤ 0.05 was taken as significant.

RESULTS

Total 300 patients were included in study. 25 patients lost the follow up and were removed from study. 6 patients of group A and 9 patients of group B have shown raised LFTs in start of treatment. They were also removed from study as their LFTs did not come to normal levels despite cessation of treatment. Out of 260 patients, 130 patients were present in each group. Mean age of patients in Group A (MTX) was 52.73±9.34 years and in Group B (LEF) it was 51.15 + 9.79 years. Mean duration of symptoms in Group A (MTX) was 3.92 ± 1.51 months and in Group B (LEF) it was 3.35 + 1.42 months. There were 70 (53.8%) males and 60 (46.2%) females in group A and 55 males (42.3%) and 75 (57.7%) females in group B.

Table 1: Demographics of patients

	Study Group	
	Group A(MTX)	Group B (LEF)
No of patients	130	130
Age (years)	52.73±9.34	51.15 + 9.79
Gender		
Male	70 (53.8%)	55 (42.3%)
Female	60 (46.2%)	75 (57.7%)
Mean duration of symptoms(months)	3.92 ± 1.51	3.35 + 1.42

52 patients (40%) were of group A were given steroids along with methotrexate while 46 patients (35.4%) of group B were given steroids along with leflunomide. Similarly 35 patients (26.9%) of group A were started NSAIDS along with methotrexate while 41 patients (31.5%) were given NSAIDS with leflunomide. CRP levels and ESR Values of both groups were done initially for diagnosis and are mentioned in table II.

Table 2: concomitant treatment and lab values at start of treatment

Variable	Study Group	
	Group A (MTX)	Group B (LEF)
Concomitant steroids	52 (40%)	46 (35.4%)
Concomitant NSAIDS	35 (26.9%)	41 (31.5%)
Mean CRP levels	5.1 + 3.33	6.02 + 3.79
Mean ESR levels	49.42 + 9.23	47.82 + 9.6

When adverse effects are seen over a period of 6 months it was seen that 44 patients (33.8%) of group A which were given MTX developed GI symptoms frequently like nausea, vomiting and pain abdomen while 22 patients (16.9%) of group B who were given LEF developed GI symptoms. Similarly hepatotoxicity was seen in 15 patients (11.5%) of MTX group while 27 patients (20.8%) of LEF group developed hepatotoxicity which was statistically significant (p = 0.04). 5 patients (3.8%) of LEF developed liver fibrosis on Ultrasound over a period of 6 months.

Table 3: Adverse effects of MTX vs LEF

Variable	Study Group		P value
	Group A (MTX)	Group B (LEF)	
GI symptoms(Nausea, Vomiting, Pain Abdomen)	44 (33.8%)	22 (16.9%)	0.002
Raised LFTs	15 (11.5%)	27 (20.8%)	0.04
Ultrasound abdomen(fibrosis)	6 (4.6%)	5 (3.8%)	0.7

DISCUSSION

Since last 2-3 decades DMARDS are in active use for treatment of RA[11]. They are in wide use as they reportedly decrease the progression of disease by decreasing joint destruction, but their long use is associated with a number of adverse effects like Nausea, vomiting, abdominal pain, dyspepsia, mouth ulceration, generalized body rash, alopecia hypertension, headache and hepatotoxicity as reported in different studies[12,13]. MTX which is an analogue of folic acid affects the metabolism within the cells by decreasing amount of folinic acid (FH4)[14]. LEF inhibits the pyramidine synthesis pathway by blocking the rate limiting enzyme dihydroorotate dehydrogenase. So it inhibits production of T cells as T cells are dependent on pyramidine for expansion which leads to reduce joint inflammation[15]. DMARDS are slow acting antirheumatic drugs which require months to put in their action, but LEF is found to be very quicker in action in relieving symptoms of RA patients as compared to other drugs available. LEF reduces the functional disability of RA patients and reduces the further progression of disease.

In our study patients in LEF group had reported quick relieve of symptoms in early months of commencement of treatment as compared to MTX group which has taken a long time in alleviation of symptoms. These results are similar to study by JS Somlen et al that LEF is quicker in action in symptomatic relief when compared with MTX[16]. Similarly study by Ishaq M et al also reported quick response in LEF patients when compared with MTX[5]. LEF is quicker in action in symptomatic relief and it has got GI complaints like Nausea, vomiting, gastritis and pain abdomen. In our study 22 patients (16.9%) of LEF group reported GI complaints while 44 patients (33.8%) of MTX reported similar complaints. These results are similar to results reported by JS Somlen and Dayer Jm et al in two different studies that MTX is associated with increased GI symptoms when compared with LEF[16,17]. Regarding hepatotoxicity 15 (11.5%) patients of MTX group developed elevated liver enzymes and 27 (20.8%) patients of LEF group developed elevated liver enzymes which was statistically significant. These results are similar to a meta-analysis by Alfaro-Lara R et al who showed the LEF is associated with greater hepatotoxicity and few GI complaints[18]. Similarly Choi SR also reported that MTX is associated with low hepatotoxicity[19]. 5 patients (3.8%) of LEF group developed mild liver stiffness in 6 monthly follow up period. These results are comparable to those stated by Bafna P et al that LEF is associated with less degree of liver fibrosis as compared to MTX in 6 monthly follow up[20,21].

The limitation of this study is that we have compared MTX and LEF alone but nowadays combination of DMARDS are used with other drugs to reduce adverse effects. A study need to be done to evaluate adverse effects in combination therapies.

CONCLUSION

We conclude that most LEF with rapid onset of action is quicker in reducing symptoms of RA patients but it is associated with high degree of hepatotoxicity with low liver fibrosis when compared with MTX.

Conflict of Interest: This study has no conflict of interest be declared by any author.

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