ORIGINAL ARTICLE

Leflunomide in Rheumatoid Arthritis: Effect on Laboratory Parameters

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ABSTRACT:

Objective: To evaluate the effect of leflunomide on laboratory parameters in patients of rheumatoid arthritis.

Materials and Methods: A 24-week, single-blind study was carried out on 158 consecutive patients, aged 29-70 years, diagnosed with rheumatoid arthritis. They received tablet leflunomide 20 mg daily, orally. Laboratory tests were recorded at the initial visit and follow-ups. Leflunomide has been known to bring about changes in various blood parameters like hemoglobin, total white cell and platelet counts, erythrocyte sedimentation rate, serum creatinine and serum glutamic pyruvic transaminase levels. All patients were subjected to these laboratory tests.

Results: At the end of the study at 24 weeks the hemoglobin was raised to 12.62 grams per deciliter (g/dl) from a baseline of 10.81 g/dl, white cell count fell to 6,728 per cubic mm (cmm) from 8,318 / cmm, the ESR fell to 39.01 millimeters of mercury (mm of Hg) in 1st hour from 82.10 mm of Hg, the platelet count fell to 2,37,419 / cmm from 2, 96,166 / cmm, the SGPT levels were raised to 38.01 international units per litre (IU/l) from 31.84 IU/l and the serum creatinine fell to 0.936 mg/dl from 0.937 mg/dl. All values, except serum creatinine, were found to be highly significant statistically ($p<0.001$).

Conclusion: Leflunomide showed significant effects on the laboratory parameters. These parameters may be utilized in patients follow up to monitor the drug response and as a marker of drug safety of leflunomide

Keywords: Rheumatoid arthritis, Leflunomide, Laboratory parameters, Drug response, Drug safety

INTRODUCTION:

Rheumatoid arthritis (RA) is a progressive, autoimmune disorder of long duration which involves the entire body and is manifested by symmetric, small joint synovitis. The inflammation so produced causes joint destruction that in turn leads to deformities in the joints. Altered joint structure renders them unable to perform their normal function. Persistent symptoms with varying intensity of pain and progressive joint damage thus results in joint deformities and disabilities.[1] The average annual incidence of RA is around 0.03% with a 1% worldwide prevalence rate.[2] Almost one-sixth of the world population lives in India and Pakistan with prevalence rates of 0.5% and 0.2-1% respectively.[3] A prevalence rate of 0.9 and 1.98 per thousand cases was seen in the poor and affluent districts of Karachi respectively.[4]

The disease shows a rising incidence until the age of 80 with hardly any cases seen below 15 years. It is a female-oriented condition, being 3-5 times more common in women as well as smokers. Onset in men is common after 45 years with the incidence approaching that of women in the over 65-years age group. Smoking has been seen to be associated with those who also show the presence of RF and antibodies to cyclic, citrullinated peptides (CCPs). Human leukocyte antigen (HLA) marker cluster, HLA-DR4/DR1,[5] Epstein-Barr virus (EBV) and Human Herpes virus 6 (HHV-6) have been linked with the etiology of rheumatoid arthritis.[6,7,8,9]

American College of Rheumatology (ACR) has classified RA and has framed the following criteria. A person fulfilling four of these criteria is regarded to be suffering from RA (Table 1).[10]

Table: 1
The classification criteria based on ACR

S. No.	Parameter	Features
1	Morning stiffness	>1 hour most mornings
2	Arthritis and soft-tissue swelling	of >3 of 14 joints
3	Arthritis of hand joints	
4	Symmetric arthritis	
5	Subcutaneous nodules	
6	Rheumatoid factor	
7	Radiological changes	suggestive of joint erosion

Criteria 1-4 should have been present for at least 6 weeks.
At least 4 criteria have to be met for classification as Rheumatoid arthritis

Permanent joint damage is an early feature in patients with active polyarticular disease.[11] The currently available treatment options are disease-modifying anti-rheumatic drugs (DMARDs), anti-inflammatory agents and analgesics.[12,13] DMARDs have been in use in patients with RA for the last several years.[14] Anti-inflammatory

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drugs and analgesics have no effect on joint damage or rate of disease progression though they may reduce the intensity of pain and joint stiffness.

In September 1998 the United States Food and Drug Administration gave approval for leflunomide to be used in the treatment of RA.[15] It acts via its active metabolite A77 1726, produced in the liver as a result of first-pass metabolism, to block pyrimidine (uridine and cytidine) synthesis by reversibly inhibiting the rate-limiting enzyme dihydro-orotate dehydrogenase[16]. Rapid proliferation of activated CD4+ T cells, essential in the initiation of RA, requires synthesis of new DNA, signalling the lymphocytes to increase their content of pyrimidines nucleotides.[17] A77 1726 intervenes here by not allowing the T-cells to produce the pyrimidines needed for the production of new DNA.

Diarrhea, rash, weight loss, reversible alopecia, changes in blood elements and an increase in liver enzyme levels are associated with the use of leflunomide. Occasionally fatal acute liver failure is seen within 6 months of starting therapy. The dose of leflunomide should be reduced if the serum alanine transaminase (ALT)/serum glutamic pyruvic transaminase (SGPT) levels increase to twice the upper limit of normal with discontinuation of drug if this increase persists. Some patients have been known to develop acute interstitial lung disease which has occasionally proven fatal. Patients prescribed leflunomide should have their platelet count, leucocyte count, hemoglobin and liver enzyme levels checked prior to initiating therapy then regularly at the time of follow up preferably at monthly interval for initial six months.[18] Changes in the above parameters can be utilized to monitor therapy response and determine level of safety of the drug in RA. Although methotrexate is the first line therapy for treating rheumatoid arthritis but leflunomide has been used commonly as an alternative. The present study was thus designed to evaluate the effect of leflunomide on blood, liver and renal laboratory parameters in patients having rheumatoid arthritis.

MATERIAL & METHODS:

This was a 24-week, prospective, single-blind, interventional study conducted between October 2009 to March 2011, on patients of either sex suffering from rheumatoid arthritis who visited the out-patient department of a private teaching hospital and a private consultant's clinic in Korangi, Karachi. Approval was obtained from and granted by the Institutional Review Board (IRB), Dow University of Health Sciences (DUHS). The hospital and clinic where the study was carried out catered patients from different strata of society. There were daily wage earners, roadside workers, students, office workers, housewives and business executives.

Of the selected 158 consecutive patients fulfilling the ACR criteria 6 patients dropped out due to personal reasons despite initially agreeing and 4 patients just did not report for follow up. The remaining 148 patients were put on leflunomide, 20 mg orally, daily. They were given drugs and directed to return for follow up with certain labs, at which time they were given drugs for further use. Follow ups were conducted at 6, 14 & 24 weeks.

Statistical analysis: Statistical analysis was done by SPSS version 18.0 with paired t-test. The results are shown as mean along with standard deviation. The cut off P -value was taken to be less than 0.05.

RESULTS:

Of the 148 patients that completed the study 118 (79.7 %) were female with 109 (73.6 %) positive for Rheumatoid Factor. They had a mean age of 46.35 ± 9.68 years, ranging between 29 to 70 years (Table 2). The mean baseline hemoglobin was 10.81 ± 1.04 grams per deciliter (g/dl), mean white cell count was 8,318 ± 1,717 per cubic mm (/cmm), ESR was 82.10 ± 14.36 mm of Hg in 1st hour, mean platelet count was 2, 96,166 ± 63,476 /cmm, mean SGPT value was 31.84 ± 6.38 international units per litre (IU/l) and mean serum creatinine was 0.937 + 0.19 mg/dl (Table 3). At the end of the study at 24 weeks the hemoglobin was raised to 12.62 ± 0.89 g/dl, white cell count fell to 6,727.70 ± 1171.65 /cmm, the ESR fell to 39.01 ± 12.88 mm of Hg, the platelet count fell to 2, 37,418.92 ± 60,968.27 /cmm, the SGPT levels was raised to 38.01 ± 17.32 IU/l and the serum creatinine fell to 0.936 ± 0.13 mg/dl, all values, except those of serum creatinine, being statistically significant (P <0.001, Table 4a). At 24 weeks there were 8 (5.4%) female patients with SGPT levels greater than twice the upper limit of normal (Table 4b).

Table: 2
Baseline characteristics
N = 148

		No of Patients	%	Mean ± Standard Deviation
Sex	Male	30	20.3	___
	Female	118	79.7	___
Rheumatoid Factor				___
	Present	109	73.6	___
	Absent	39	26.4	
Age (years)		___	___	46.35 ± 9.68

No of Patients = number of patients , _____ = Nil

Table: 3
Laboratory parameters: baseline and follow up visits
N = 148

Parameter	Baseline Mean ± SD	6 weeks Mean ± SD	14 weeks Mean ± SD	24 weeks Mean ± SD
Hemoglobin (g/dl)	10.81 ± 1.04	13.29 ± 11.41	12.31 ± 0.96	12.62 ± 0.89
Total leucocyte count (per cubic mm)	8,318.11 ± 1716.80	7,548.65 ± 1,407.92	7,120.95 ± 1,295.58	6,727.70 ± 1,171.65
Erythrocyte Sedimentation Rate (mm of Hg in 1st hour)	82.10 ± 14.36	65.46 ± 14.19	52.12 ± 13.51	39.01 ± 12.88
Platelet count (per cubic mm)	2,96,165.54 ± 63,475.8	267,094.59 ± 60,336.51	266,817.57 ± 201,574.79	2,37,418.92 ± 60,968.27
Serum glutamic pyruvic transaminase (SGPT, IU/l)	31.84 ± 6.38	31.03 ± 6.71	35.33 ± 11.84	38.01 ± 17 .32
Serum creatinine (mg/dl)	0.937 ± 0.19	0.912 ± 0 .135	0.924 ± 0.1221	0.936 ± 0.13

SD : Standard deviation, g/dl: grams per deciliter, mm of Hg: millimeters of mercury, IU/l: international units per litre mg/dl: milligrams per deciliter

Table: 4a
Baseline v/s 24 weeks
N = 148

	Mean ± Standard Deviation	P value
Hemoglobin (g/dl) Hemoglobin (g/dl) at 24 weeks	10.81 ± 1.04 12.62 ± 0.89	< 0.001 ***
White cell count (per cmm) White cell count (per cmm) at 24 weeks	8,318.11 ± 1716.80 6,727.70 ± 1,171.65	< 0.001 ***
Erythrocyte sedimentation rate (mm in 1st hour) Erythrocyte sedimentation rate (mm in 1st hour) at 24 weeks	82.10 ±14.36 39.01 ± 12.88	< 0.001 ***
Platelet count (per cubic mm) Platelet count (per cubic mm) at 24 weeks	2,96,165.54 ± 63,475.84 2,37,418.92 ± 60,968.27	< 0.001 ***
Serum glutamic pyruvic transaminase (IU/l) Serum glutamic pyruvic transaminase (IU/l) at 24 weeks	31.84 ± 6.38 38.01 ± 17 .32	< 0.001 ***
Serum creatinine (mg/dl) Serum creatinine (mg/dl) at 24 weeks	0.937 ± 0.19 0.936 ± 0.13	0.915 NS

*** = very highly significant statistically, Paired t-test utilized, NS = non-significant statistically

Table: 4b
Serum Glutamic Pyruvic Transaminase (SGPT)
N=148

	14 weeks		24 weeks	
Sex	No of Patients	%	No of Patients	%
Male	0	00	0	00
Female	3	2.5	8	6.8
Total	3	2.0	8	5.4

No of patients = Number of patients with > 2 x upper limit of normal [26] (> 68 IU/L in females & > 90 IU/L in males)

DISCUSSION:

DMARDs, having the ability to slow down joint destruction, are regarded as the drugs of first choice in treating RA. Since permanent joint damage starts early in patients with active, polyarticular RA initiating therapy with a DMARD shows promising results. The current treatment options can adequately control the acute symptoms and hold the promise of a good prognosis in the long run.[19]

Leflunomide acts via its active metabolite A77 1726 to block pyrimidine synthesis by reversibly inhibiting the rate-limiting enzyme dihydro-orotate dehydrogenase thereby reducing the intensity of the inflammatory response.[16] Effects on blood parameters along with changes in hepatic and renal function have been observed with its use. Smolen has found a significant increase in hemoglobin levels with leflunomide from a baseline of 12.15 g/dl to 12.55 g/dl along with a significant reduction in the leucocyte count ($p< 0.0001$).[20] In our study the hemoglobin rose to 12.62 ± 0.89 g/dl from a baseline of 10.81 ± 1.04 g/dl while the white cell count fell to 6,727.70 ± 1171.65 /cmm from a baseline of 8,318.11 ±1716.80 /cmm; values which were comparable to the above study. It has been documented that leflunomide caused a fall in ESR from 52.5 mm of Hg to 24.3 mm of Hg ($p = 0.0001$).[21] The ESR values in our study fell from a mean baseline level of 81.03 mm in 1st hour to 40.14 mm in 1st hour ($p<0.001$). A study conducted by Mehta and colleagues using leflunomide has demonstrated significant thrombocytopenia.[22] Similar to this patients in our study have also demonstrated a decrease which was statistically significant. Leflunomide-induced hepatotoxicity has been judged by the increase in the SGPT levels, with the cut-off point being greater than two-fold increase in levels.[23]These changes are said to be reversible if the dose of the drug is reduced or it is discontinued if severe damage has resulted. In a trial where leflunomide was used as monotherapy derranged SGPT levels were seen in 16% of patients.[24] An Indian study, which used Leflunomide as monotherapy, reported a figure of just 3% patients who had raised transaminase levels.[25] In our patients changes in SGPT levels were seen in 5.4% of patients which are comparable to the indian study whereas the large difference seen between the sub-continental studies and the one mentioned above could be due to the different demographics of the population as the first mentioned study was carried out on an Australian population. In above mentioned studies leflunomide has not shown significant change in serum creatinine levels whereas in our study the serum creatinine level fell to 0.936 ± 0.13 mg/dl from a baseline value of 0.937 ± 0.19 mg/dl, which was statistically insignificant.

CONCLUSION:

Leflunomide showed significant beneficial effects on the laboratory parameters in patients with rheumatoid arthritis.These parameters may be utilized in patients follow up to monitor the drug response and as a marker of drug safety.

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