ORIGINAL ARTICLE

Safety Profile Of Methotrexate And Leflunomide In Rheumatoid Arthritis

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ABSTRACT

Objective: To compare the safety profile of Methotrexate and Leflunomide in patients of rheumatoid arthritis.

Material and Methods: A 24-week, single-blind, interventional, study was carried out on 274 patients of either sex, aged 29-69 years, diagnosed to have rheumatoid arthritis. One group was given tablet Methotrexate, 10 mg (four 2.5 mg tablets), once weekly and the other was put on tablet Leflunomide, 20 mg, once daily, orally. At each follow up laboratory parameters (Hb%, TLC, ESR, PC, SGPT,S Creatinine) and adverse effects were evaluated.

Results: Of the 274 patients, 126 were on Methotrexate (70.63 % females, 61.11% RF positive, mean age 45.57 + 10.32 years) and 148 on Leflunomide (79.72 % females, 73.64 % RF positive, mean age 46.35 + 9.68 years). Laboratory parameters (TLC, SGPT, creatinine) between the two groups showed statistically significant results at the end of the study. Nausea was seen in 30.2% & 10.8% patients at 6 weeks and 5.6% and 0% at 24 weeks in the Methotrexate and Leflunomide groups respectively while alopecia was seen in 0% & 19.6% patients at 6 weeks and 1.6% & 24.3% at 24 weeks in the Methotrexate and Leflunomide groups respectively. All values were significant statistically.

Conclusion: Leflunomide was found to have a better safety profile than Methotrexate as it produced greater improvement in laboratory parameters with lesser adverse effects in comparison to the traditionally used, first-choice, drug Methotrexate.

Keywords: Rheumatoid arthritis, Methotrexate, Leflunomide, Laboratory parameters, Adverse effects.

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic, progressive, systemic, autoimmune disease in which joint destruction and loss of function is followed by deterioration in life quality [1]. It has a worldwide prevalence of 1%, the highest incidence being in the fifth decade, and a female preponderance, affecting women three to five times as often as men[2]. India and Pakistan have prevalence rates of 0.5% and 0.2-1% respectively [3]. Genetic association with (HLA-DR4), cigarette smoking, use of decaffeinated coffee, presence of Herpes virus, Epstein-Barr virus and Human Herpes Virus- 6 infections are all risk factors that make a person susceptible to RA [4,5]. Patients present with joint inflammation and constitutional symptoms like fever, malaise, anorexia, weight loss, pain, local edema, synovial thickening and joint erosion. They have painful, mostly symmetrical small joint involvement, initially of the hands, feet and cervical spine with subsequent involvement of the large joints. Morning stiffness is present whereas, the presence of rheumatoid nodules, usually seen in 20-30% of patients, is indicative of a poor prognosis. Extra-articular manifestations are seen in about 15% of individuals 6. Eventually, synovitis and resultant joint erosion leads to deformity and loss of function.

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Diagnosis is based upon a combination of physical examination, laboratory tests, x-rays and the American College of Rheumatology (ACR) criteria (1987) [7]. The latter are:

- Stiffness of joints lasting for more than 1 hour in the morning Inflammation and swelling of more than 3 of 14 joints or groups of joints
- Inflammation of joints of the hands
- Arthritis of the same joints on both sides of the body.

The above given points must be present for a minimum of six weeks ,while other features are the presence of subcutaneous nodules, rheumatoid factor and changes involving erosion of joints seen on radiography. A person fulfilling four of seven given criteria can be said to be suffering from RA.

Disease-modifying anti-rheumatic drugs (DMARDs) are the mainstay in the current treatment of RA. Of these Methotrexate, Leflunomide, Penicillamine, Cyclosporine, the newer biologics along with NSAIDs and Corticosteroids (where and when needed) are the common choices. However, the traditionally used first- choice drug is Methotrexate. Present study was designed to evaluate the safety profile of the first-choice drug, Methotrexate, and Leflunomide; two commonly prescribed drugs in our population.

MATERIALS AND METHODS:

This twenty-four week, interventional, prospective, single-blind study was conducted from October, 2009 to March, 2011 after being approved by the Institutional Review Board (IRB) and Board of Advanced Studies and Research (BASR), Dow University of Health Sciences (DUHS). It was carried out on patients visiting the out-patients department of a private teaching hospital and a private consultant's clinic in Karachi. 317 patients, fulfilling the ACR criteria, were included after an informed, written consent. Each patient was asked to pick a chit from a box which had previously been filled with chits labeled with alphabets 'A' and 'B'. The Principal Investigator was the only one aware that 'A' stood for Methotrexate and ''B' for Leflunomide. In this way two groups of patients were obtained, one taking tablet Methotrexate (159) and the other taking tablet Leflunomide.

(158). 33 patients in group A and 10 patients in group B were lost to follow-up. Remaining 274 patients who completed the study consisted of 126 patients on tablet Methotrexate, 10 mg weekly (4 tablets of 2.5 mg, orally) and 148 patients on tablet Leflunomide, 20 mg, orally daily. They were advised to continue with (or were prescribed) NSAIDs or corticosteroids which they had been taking when included into the study and were told to return for follow up at 6, 14 and 24 weeks. Laboratory parameters as hemoglobin (Hb), total leucocyte count (TLC), erythrocyte sedimentation rate (ESR), platelet count (PC), C-reactive protein (CRP), serum creatinine and serum glutamic pyruvic transaminase (SGPT) were evaluated at baseline and at each follow up till 24 weeks. Statistical analysis was done on SPSS version 18.0. Independent t-test was used for continuous variables. Chi-square test was used for categorical variables. P value of < 0.05 was taken as significant.

RESULTS:

The Methotrexate group (126) consisted of 89 (70.63 %) females with 77 (61.11%) patients positive for Rheumatoid factor while Leflunomide (148) group consisted of 118 (79.72 %) females with 109 (73.64 %) patients positive for Rheumatoid factor.(Table 1)

In methotrexate group mean age was 45.57 + 10.32 years whereas in leflunomide group mean age was 46.35 + 9.68 years. Baseline laboratory parameters did not show statistical difference between the groups.(Table 2). Comparison of laboratory parameters of total leucocyte count, SGPT and serum creatinine showed statistically significant results at 24 weeks between the two drugs with more decrease being produced numerically by leflunomide.(Table 3) Comparing the adverse effects in the two groups nausea was seen in 38 (30.2%) patients using Methotrexate and 16 (10.8%) patients using Leflunomide at 6 weeks which fell to only 7 (5.6%) patients in the Methotrexate group at 24 weeks; all being very highly significant (p = 0.004). Mouth ulcers were seen in 14 (11.1%) patients taking Methotrexate and 10 (6.8%) patients taking Leflunomide at 6 weeks (p = 0.204) but were absent at 24 weeks. Diarrhea was seen in 10 (7.9%) patients taking Methotrexate and 14 (9.5%) patients taking Leflunomide at 6 weeks only and had subsided by the next follow-ups, being statistically insignificant (p= 0.657). Rash was similarly seen only at 6 weeks in 3 (2.4%) patients taking Methotrexate and 4 (2.7%) patients taking Leflunomide, both values being statistically insignificant (0.866). Alopecia was seen in 29 (19.6%) patients using Leflunomide at 6 weeks which increased to 36 (24.3%) patients at 24 weeks whereas it was seen in only 2 (1.6%) patients at 24 weeks who were on Methotrexate; all values being very highly significant (p< 0.001) (Table 4).

Table: 1
Gender and Rheumatoid factor

	METHOTREXATE N=126	LEFLUNOMIDFE N=148
	No of paticnts (%)	No of paticnts (%)
Sex:		
Females	89 (70.63)	118 (79.72)
Males	37 (29.36)	30 (20.27)
Rheumatoid factor:		
Present	77 (61.11)	109 (73.64)
Absent	49 (38.88)	39 (26.35)

Table: 2
Age and Baseline laboratory parameter

PARAMETERS	METHOTREXATE N = 126 Mean ± S.D.	LEFLUNOMIDFE N = 148 Mean ± S.D.	P Value
Age	45.57±10.32	46.35±9.68	0.520^{NS}
Hemoglobin (g/dl)	10.76±1.12	10.81±1.07	0.651^{NS}
Total leucocyte count (per cubic mm)	8572.1±1445.1	8318.1±1,716.8	0.185^{NS}
Erythrocyte Sedimentation Rate (per cubic mm)	81.03±17.98	82.10±14.36	0.591^{NS}
Platelet count (per cubic mm)	2,90,277.8± 688,813.7	2,96,165.5± 63,475.8	0.462^{NS}
C-Reactive Protein (microgram/dl)	2.33±0.69	2.39±0.75	0.540^{NS}
Serum glutamic pyruvic transaminase (SGPT, IU/l)	31.67±7.37	31.84±6.38	0.711^{NS}
Serum creatinine (mg/dl)	0.95±0.16	0.94 0.18	0.838^{NS}

S.D = Standard deviation, NS= non-significant statistically, Independent T-test utilized

Table : 3
Methotrexate v/s leflunomide laboratory parameters at 24 weeks
N=274

	METHOTREXATE Mean ± S.D N=126	LEFLUNOMIDE Mean ± S.D. N= 148	P Value
Hemoglobin (g/dl)	12.43±0.92	12.63±0.89	0.078^{NS}
Total leucocyte count (per cubic mm)	7,142.46± 1,332.23	6,727.70± 1,171.65	0.007**
Erythrocyte Sedimentation Rate (per cubic mm)	40.14±15.79	39.01±12.88	0.522^{NS}
Platelet count (per cubic mm)	2,33,738.10± 59,769.58	2,37,418.92± 60,968.27	0.616^{NS}
Liver enzyme (SGPT, IU/l)	55.29 ± 21.97	38.01±17.32	<0.001***
Serum creatinine (mg/dl)	1.106 ± 0.14	0.936±0.13	<0.001***

** = highly significant statistically *** = very highly significant statistically, NS= non-significant
Statistically, S.D. = standard deviation, Independent T-test utilized

DISCUSSION:

DMARDs have been the drugs of choice as, besides relieving the symptoms, they have demonstrated the potential to retard joint destruction; a hallmark of disease progression. Permanent joint damage begins relatively early in subjects having active, polyarticular RA; initiating early therapy with an effective DMARD improves prognosis whereas delaying therapy, for as little as a few months after the onset of symptoms, worsens it. Though drugs resulting in a cure or leading to permanent remission would be the ideal solution the ground reality is that treatment options currently available, though aiming for remission, should adequately control the acute symptoms with a minimum of adverse effects and lead towards a good prognosis in the long run [8].

Methotrexate acts by inhibiting amino-imidazole- carboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase. AICAR produces accumulation of adenosine monophosphate (AMP) which in turn is converted to adenosine and inhibits inflammation. Whereas Leflunomide inhibits dihydroorotate dehydrogenase leading to arrest of stimulated cells in the G1 phase of the cell growth. Comparing the effect of Methotrexate and Leflunomide on laboratory parameters at baseline was non-significant indicating equally matched patients in both groups whereas at 24 weeks both drugs revealed suppressant effects on the bone marrow; more so

Table: 4
Adverse effects
Methotrexate / Leflunomide
N=126/148

At 6 weeks Drug	Nausea Present	Absent	P-value
Methotrexate	38	88	0.001***
Leflunomide	16	132	
	Mouth Ulcer		
	Present	Absent	
Methotrexate	14	112	0.204^{NS}
Leflunomide	10	138	
	Diarrhoea		
	Present	Absent	
Methotrexate	14	116	0.657^{NS}
Leflunomide	10	134	
	Rash		
	Present	Absent	
Methotrexate	3	123	0.866^{NS}
Leflunomide	4	144	
	Alopecia		
	Present	Absent	
Methotrexate	0	126	0.001***
Leflunomide	29	119	
At 24 Weeks Drug	Nausea		P-value
	Present	Absent	
Methotrexate	7	119	0.004**
Leflunomide	0	148	
	Mouth Ulcer		
	Present	Absent	
Methotrexate	0	126	N/A
Leflunomide	0	148	
	Diarrhoea		
	Present	Absent	
Methotrexate	0	126	N/A
Leflunomide	0	148	
	Rash		
	Present	Absent	
Methotrexate	0	126	N/A
Leflunomide	0	148	
	Alopecia		
	Present	Absent	
Methotrexate	2	124	0.001***
Leflunomide	36	112	

*** = very highly significant statistically, NS = non-significant statistically, NA= not applicable Chi square test utilized by leflunomide.

An increase in, hemoglobin level was seen with both drugs. In a comparative study carried out by Emery et al it was seen that treatment with these drugs showed an improvement in the hemoglobin level accompanied with a fall in the leucocyte and platelet counts[9]. Smolen et al found a significant increase (p= 0.01) in hemoglobin levels with Leflunomide i.e 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) [10].

Upon comparing the levels seen between the drugs at 24 weeks the decline was numerically greater in the Leflunomide group indicating a more potent control of the disease process than Methotrexate. Changes in the platelet count were not significant when comparing the 24-week values for the two drugs in our study. These features indicate that our patients had tolerated the drugs well and the blood indices had not deteriorated to the extent that any dose alteration was needed. This may have been due to the fact that they belonged to a younger age group (mean ~ 46 years) in comparison to the studies mentioned above.

Researchers, using Methotrexate and Leflunomide have found a significant reduction (p=0.001) in the ESR values viz. 52.5 to 34.3 mm of Hg in patients using Methotrexate and 51.2 to 36.8 mm of Hg in patients using Leflunomide 11. Hansen et al, using Leflunomide, showed a fall of ESR values from 52 mm of Hg to 32 mm of Hg [12]. Our study also showed similar results with ESR values falling from 81.03 to 40.14 mm of Hg in patients put on Methotrexate and from 82.10 to 39.01 mm of Hg in patients using Leflunomide. Rau and Herborn studying the benefits and risks of Methotrexate in RA found elevated serum creatinine levels in their patients which subsided on stopping therapy. Serum creatinine in our patients too rose from a baseline level of 0.95 mg/dl to 1.11 mg/dl[13].

Several studies have shown that both Methotrexate and Leflunomide are hepatotoxic (with the former causing fibrosis), the degree of damage being judged by an increase in the SGPT levels, the cut-off point being a greater than two-fold increase. These changes are reversible if the dose of the drugs is reduced or they are stopped where severe damage has resulted. An Indian study, in which Leflunomide was used as monotherapy, reported a figure of just 3% patients who had raised transaminase levels [14]. Attar studying the adverse effects of Methotrexate in RA demonstrated elevated SGPT levels in 14.1% of her patients [15]. Curtis et al using Leflunomide and Methotrexate in RA patients found 14-22% incidence of SGPT elevation[16]. Similarly, elevations in liver enzymes were also seen in several Western studies [17,18,19].

Changes in the SGPT levels in our study were statistically very highly significant (p<0.001) regarding comparison of drugs at 24-week.. In our study a total of 27 (9.9%) patients showed alteration in SGPT levels with 19 (15.1%) patients on Methotrexate and 8 (5.4%) patients on Leflunomide, the ratio between the two being 2.7 in favor of Methotrexate. The difference seen in the number of patients affected is most probably due to the fact that our patients were younger and our values were obtained at the end of 24 weeks as opposed to the other studies which were of a longer duration (52 weeks). Furthermore, the incidence of liver toxicity seen in our patients with Methotrexate treatment may have been due to the lack of folate supplementation which is known to ameliorate this effect of Methotrexate [20, 21].

An incidence rate of 34% mild to moderate adverse effects was seen in a trial conducted by Hoekstra et al who studied the efficacy and safety of Methotrexate in patients with RA[22]. Ahmed et al in a study carried out in Lahore, Pakistan, obtained an overall figure of 20% in their patients given Leflunomide [23]. In our study 119 (43.43%) patients complained of adverse effects with 89 (32.5%) patients suffering from at least one adverse effect, a figure which is in accordance with that obtained by Hoekstra et al.

Gastrointestinal adverse events (nausea, diarrhea, mouth ulcers) and rash were reported at a rate of 14.5% and 12% respectively in a study by Kalden et al where they compared different treatment strategies in early RA [24]. Silverman et al in their patients on Leflunomide found nausea in 28% with diarrhea and alopecia each in 15% of patients as compared to nausea (34%), diarrhea (17%) and alopecia (6%) in patients given Methotrexate [25]. Similarly Buhroo and Baba studying the effects of low dose Methotrexate demonstrated 21% GIT side effects [26].

In our study gastrointestinal adverse events (nausea, diarrhea, mouth ulcers) and rash were found at an average of 32.1% and 2.6 % respectively. The difference in values in our patients may be due to different demographics between the two patient groups as well as the fact that we did not use folic acid which was used in the above studies. It can be seen that Methotrexate showed a lesser number of patients complaining of diarrhea, rash and alopecia while Leflunomide showed better numerical improvement in blood parameters like hemoglobin, leucocyte count, ESR, platelet count and a lesser increase in the SGPT levels. It also had fewer numbers of patients complaining of nausea and mouth ulcers. It is thus evident that Leflunomide, although not a drug of first choice in RA, is superior to Methotrexate, the traditionally considered drug of first choice in context of effects and safety profile in patients having rheumatoid arthritis in our local setting.

CONCLUSION:

Leflunomide has a better safety profile than Methotrexate. It produced greater improvement in laboratory parameters with less adverse effects and better control of the disease in comparison to the traditionally used, first-choice, drug Methotrexate. Large, multi-centric studies are needed to further ascertain the effects and safety profile of Methotrexate and Leflunomide in our population.

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