

A Comparative Drug Study of Dexamethasone, Leflunomide and Methotrexate on Rheumatoid Arthritis at JLN Hospital Ajmer

Dr Dharmendra Garg¹, Dr. Sunil Kumar Mathur²

¹Department of Pharmacology, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan state, India
E-mail: dr.dharmendragarg[at]gmail.com

Abstract: *Background:* New studies focused on modern therapeutic methods which decrease the incidence of inflammation of joints and stimulate cartilage healing and repair the damage, including the use of Dexamethasone, Leflunomide and Methotrexate drug. This study has the purpose to present the use of these drugs in management of rheumatoid arthritis and its outcomes up to 6 month follow up

Keywords: RHUMATOID ARTHRITIS, dexamethasone, leflunomide

1. Rheumatoid Arthritis

Rheumatoid arthritis is a chronic multisystem disease of unknown cause. Although there are a variety of systemic manifestations, the characteristic Feature of Rheumatoid arthritis is persistent, progressive, inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of the synovial inflammation to cause cartilage destruction and bone erosions and subsequent changes in joint integrity is the hallmark of the disease. Despite of its destructive potential, the course of rheumatoid arthritis can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, whereas others will have a progressive polyarthritis with marked functional impairment (Lipsky, 2001).

2. Material and Methods

The present study was conducted in 108 patients of active rheumatoid arthritis at J.L.N. Medical College and Associated Group of Hospitals, Ajmer rajasthan. The subjects for study were taken from patients attending medical outdoors and admitted in various wards. The study design was open, Dexamethasone controlled, randomized, prospective 24 weeks trial. The subjects selected for study were grouped as follows viz.

GROUP I (Dexamethasone group; n=36)

This group consisted of age, sex, BMI matched patients of active RA in age range 18 to 70 years who were treated with Dexamethasone with or without stable doses of NSAIDs .

GROUP II. (Leflunomide group; n=36)

This group consisted of age, sex, BMI matched patients of active RA in age range 18 to 70 years who were treated with loading dose of leflunomide 100mg once a day for 3 days and then 20mg once a day for 12 weeks with or without stable doses of NSAIDs and low dose Dexamethasone.

GROUP III. (Methotrexate group; n=36)

This group consisted of age, sex, BMI matched patients of

active RA age range 18 to 70 years who were treated with A Dose of 7.5 mg weekly.

Inclusion Criteria

Patients of either sex, with age range 18 to 70 years with active RA based on American College of Rheumatology Criteria (ACR) and ACR functional class I, II, III were included. The stable doses of NSAIDs and low dose Dexamethasone were allowed and treatment with other DMARDs was discontinued 4 weeks prior to enrolment.

ACR Criteria for the Classification of RA

1. Morning stiffness: stiffness in an around the joints lasting 1 hour before maximal improvement.
2. Arthritis of three or more joint areas : at least three joint areas, observed by a physician simultaneously, having soft tissue swelling or joint effusions, not just bony over growth. The 14 possible joint areas involved are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints.
3. Arthritis of hand joints : arthritis of wrist, MCP, PIP joints.
4. Symmetric arthritis : simultaneous involvement of same joint areas on both sides of the body.
5. Rheumatoid nodules : Subcutaneous nodules over bony prominences, extensor surfaces or juxtaarticular lesions observed by a physician.
6. Serum Rheumatoid factor : Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.
7. Radiographic changes: Typical changes of RA on posteroanterior hand and wrist radiographs which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

Four of seven criteria are required to classify a patient as having rheumatoid arthritis. Patients with two or more clinical diagnosis are not excluded. Criteria 1-4 must be present for at least 6 week; criteria 2-5 must be observed by physician.

Criteria for active rheumatoid arthritis (Arnet et al., 1988).

1. Tender and swollen joint count 6.
2. Physician and patient global assessments of RA activity as fair, poor or very poor.
3. C-reactive protein (CRP) > 20mg/L or ESR > 28 mm 1st hr.

ACR Classification criteria of functional status in RA (Hochberg et al. 1992):

Class 1: Completely able to perform usual activities of daily living (Self care, vocational and avocational).

Class 2: Able to perform usual self-care and vocational activities, but limited in a vocational activities.

Class 3:-Able to perform usual self care activities, but limited in vocational and a vocational activities.

Class 4:-Limited ability to perform usual self care, vocational and a vocational activities.

Exclusion Criteria

Following patients were excluded from the study viz.:

1. Infective, gouty or traumatic arthritis.
2. Patients who were unwilling to give informed consent.
3. Pregnant and lactating women.
4. Patients (including men) planning a family.
5. Active GI tract, renal, hepatic or coagulation disorders.
6. Uncontrolled diabetes or hypertension.
7. Recent serious cardiovascular event.
8. Any condition that may interfere with patients self-assessment ability.

Evaluation Criteria

Efficacy and safety was assessed at baseline and 4 weekly interval for 12 weeks.

A. Efficacy outcome

1. Tender and swollen joint count (max. 28 joints) (Smolen et al., 1995).
2. Patient and physician global assessment of RA activity (visual analogue scale).
3. Pain intensity assessment (VAS).
4. Duration of morning stiffness (minutes).
5. Acute phase reactants ESR and CRP levels.
6. Functional disability (health assessment questionnaire score).

The primary efficacy variable was the rate at which the intention to treat achieved 20% improvement in ACR criteria (ACR 20) at the end of the study. To be classified as having achieved ACR 20, patients were required to complete 12 weeks of treatment and meet ACR 20 response criteria at end of the study (Felson et al., 1993).

The ACR criteria for 20 % clinical improvement :

The ACR 20 require:-20% improvement in tender and swollen joint counts and 20% improvement in 3 of the following 5 parameters.

1. Patient global assessment.
2. Physician global assessment
3. Patient's assessment of pain.
4. Degree of disability.
5. Levels of acute phase reactants (ESR & CRP).

These criteria have been extended to include criteria for 50% and 70% improvement measure (ACR 50, ACR70).

B. Safety Outcome

Monitored by physical examination, haematological and biochemical tests, and analysis of adverse events. The various investigations were done 4 weekly for safety profile e.g. Hb, TLC, platelet counts, serum creatinine, S. bilirubin, SGOT, SGPT.

Study Plan: Detailed history, physical examination and all routine and special investigations were done in each patient before the beginning of study.

3. Epidemiology: Incidence & Prevalence

The prevalence of rheumatoid arthritis is approximately 0.8% of the population (range 0.3 to 2.1%) (Lipsky, 2001). In India the prevalence is 0.75% and a rough calculation indicates that over seventy lac people are affected with this disorder (Malaviya et al., 1993, Chopara et al, 1997). The women are affected approximately three times more often than men. The prevalence increases with age and sex differences diminish in the older age group. It is seen throughout the world and affects all races. It has a lower prevalence and milder course in developing countries. Epidemiological studies from different regions show that varying prevalence is possibly related to urbanization (Kall and Tikly, 2003). The onset is most frequent during the fourth and fifth decades of life, with 80% of all patients developing the disease between the ages of 35 and 50. (Lipsky, 2001).

4. Etiology of Rheumatoid Arthritis

The cause of rheumatoid arthritis is unknown. It has been suggested that rheumatoid arthritis might be a manifestation of the. Response to an infectious agent in a genetically susceptible host. A number of possible causative agents have been suggested, including mycoplasma, Epstein Barr Virus (EBV), cytomegalovirus (CMV), parvovirus and rubella virus but convincing evidence that these or other infectious agents cause rheumatoid arthritis has not emerged (Lipsky, 2001).

Immunogenetic and Heritable Predisposing Factors in RA

Peter Stasny in 1976 first recognized an association between HLA class II antigen DR4 and rheumatoid arthritis. Later different groups studying different ethnic groups reported an association with HLA DR4, DR1 and DR10. The highest risk for concordance of rheumatoid arthritis is noted in twins who have two HLA – DRB 1 alleles known to be associated with rheumatoid arthritis. The class II major histocompatibility complex allele HLA-DR4. (DRB 1) and related alleles are known to be approximately four times the expected rate in first degree relatives of individuals with rheumatoid disease associated with the presence of the autoantibody. The monozygotic twins are at least four times more likely to be concordant for rheumatoid arthritis than dizygotic twins. Only 15 to 20% of monozygotic twins are concordant for

rheumatoid arthritis, implying that factors other than genetics play an important etiopathogenic role. These include genes controlling the expression of the antigen receptor on T cells and both immunoglobulin heavy and light chains. Polymorphism in the TNF α and the interleukin (IL) 10 genes are also associated with rheumatoid arthritis, as is a region on chromosome 3 (3913) (Lipsky, 2001).

5. Pathogenesis of Rheumatoid Arthritis

The pathogenesis of rheumatoid arthritis is characterized by the concerted action of different cell types that, through numerous signaling cascade and cytokines interact with each other and finally result in synovitis, and cartilage and bone destruction. Rheumatoid arthritis pathogenesis can be divided into different phases which can correlate with a clinical picture.

Clinicopathological correlation in rheumatoid arthritis (Aggarwal, 2001)

Phase	Pathological Changes	Clinical Feature
I	Interaction of genetic and environmental agents	None
II	Antigen presentation	None
III	Inflammatory cascade	Polyarthritis, juxta-articular osteopenia
IV	Cartilage and bone destruction	Severe arthritis, erosions, deformities
v	Vasculitis etc	Extra articular feature

The propagation of rheumatoid arthritis is an immunologically mediated event. The inflammatory process in the tissue is driven by the CD4⁺ T cells infiltrating the synovium. (Lipsky and Davis, 1998).

Within the rheumatoid synovium the CD4⁺ T cells differentiate predominantly into Th1-like effector cells producing the proinflammatory cytokine IFN- γ and appear to be deficient in differentiation into Th2-like effector cells capable of producing the anti-inflammatory cytokine IL-4. As a result of the ongoing secretion of IFN- γ without the regulatory influences of IL-4, macrophages are activated to produce the proinflammatory cytokine IL-1 and TNF- α and also increase expression of HLA molecules. The T lymphocytes express surface molecules such as CD 154 and also produce a variety of cytokines that promote p cell proliferation and differentiation into antibody forming cells and therefore also may promote local p cell stimulation. The resultant production of the immunoglobulin and rheumatoid factor can lead to immune complex formation with consequent complement activation and exacerbation of the inflammatory process by the production of the anaphylatoxins C3a and C5a and the chemotactic factor C5a. The rheumatoid inflammation could reflect persistent stimulation of T cells by synovial – derived antigens that cross react with determinants introduced during antecedent exposure to foreign antigens or infectious microorganisms. The local production of chemokines and cytokines by a variety of cells with chemotactic activity as well as inflammatory mediators such

as leukotriene and product of complement activation can attract neutrophils. The many of these same agents can also stimulate the endothelial cells of post capillary venules to become more efficient at binding circulating cells. The net result is the enhanced migration of polymorphonuclear leukocytes into the synovial site. The vasoactive mediators such as histamine produced by the mast cells that infiltrate the rheumatoid synovium may also facilitate the exudation of inflammatory cells into the synovial fluid. The vasodilatory effects of locally produced prostaglandin E₂ may also facilitate entry of inflammatory cells into the inflammatory site.

The polymorphonuclear leukocytes can ingest immune complexes in synovial fluid with the resultant production of reactive oxygen metabolites and other inflammatory mediators, further adding to the inflammatory milieu.

The production of large amounts of cyclooxygenase and lipoxygenase pathway production of arachidonic acid metabolism by cells in the synovial fluid and tissue further accentuates the signs and symptoms of inflammation.

The precise mechanism by which bone and cartilage destruction occurs has not been completely resolved. The synovial fluid contains a number of enzymes potentially able to degrade cartilage, the majority of destruction occurs in juxtaposition to the inflamed synovium or pannus that spread to cover the articular cartilage. The angiogenesis occurs under influence of vascular endothelial growth factor and other angiogenic stimuli. This is essential to support the new cells being formed and this finally results in formation of invasive pannus.

This vascular granulation tissue is composed of proliferating fibroblasts, small blood vessels, and a variable number of mono nuclear cells and produces a large amount of degradative enzymes, including collagenase, stromelysin, and matrix metalloproteinases. The cytokines IL-1 and TNF- α play an important role by stimulating the cells of the pannus to produce collagenase and other neutral proteases. These same two cytokines also activate chondrocytes to produce proteolytic enzymes that can degrade cartilage locally and also inhibiting synthesis of new matrix molecules. The cytokines IL-1 and TNF- α may contribute to the local demineralization of bone by activating osteoclasts that accumulate at the site of local bone resorption. The prostaglandin E₂ produced by fibroblasts and macrophages also contribute to bone demineralization (Koch 1998, Feldmann and Maini 1999, Fristein 2001, Lipsky 2001, Aggarwal, 2001).

The systemic manifestations of rheumatoid arthritis can be accounted for by release of inflammatory effector molecules from the synovium. These include IL-1, TNF- α and IL-6 which account for many of the manifestations of active rheumatoid arthritis, including malaise, fatigue and elevated levels of serum acute phase reactants. The immune complexes produced within the synovium and entering the circulation may account for other feature of the disease such as systemic vasculitis (Lipsky, 2001). The immune complexes containing rheumatoid factor and other antibodies get deposited in the small blood vessels and

cause complement activation. The chemoattractant and other inflammatory mediators cause neutrophilic infiltration and vascular damage. Rheumatoid vasculitis is associated

with high titre rheumatoid factor and hyocomplementemia (Aggarwal, 2001).

1. Age & Sex Distribution of Subjects Studied

Group	Age range in years				Total no. of pt's pt.subjects		
	20<40		41-70		Male	Female	Total
	M	F	M	F			
Dexamethasone (n=36)	0	4	15	17	15	21	36
Leflunomide (n=36)	0	3	6	27	6	30	36
Methotrexate (n=36)	1	2	11	22	12	24	36

2. Mean Age of Subjects Studied

Group	Age (Mean \pm S.D.) in years		
	Male	Female	Total
Dexamethasone	58.35 \pm 12.83	53.22 \pm 11.97	59.2 \pm 7.47
Leflunomide	53.66667 \pm 8.50098	53.7 \pm 8.994826	66.02 \pm 9.02
Methotrexate	56.58333 \pm 8.073057	54.5 \pm 9.026531	62.36 \pm 6.56
P value	> 0.1 NS	> 0.1 NS	> 0.1 NS

3. Mean Duration of Rheumatoid Arthritis, ACR Functional Class and Rheumatoid Factor of Subjects Studied

Variable		Dexamethasone Group (n=36)		Leflunomide Group (n=36)		Methotrexate Group (n=36)		P value
Duration of RA (Mean \pm SD) years Number with duration 10 years		12.93 \pm 5.58 10	(36%)	16.61 \pm 5.88 (11%)		15.94 \pm 4.92 (11%)		> 0.1
ACR Functional class number (%)	I	3	(8%)	3	(8%)	2	(5.55%)	N.S.
	II	11	(30.55%)	7 (19.44%)		8	(22.22%)	> 0.05
	III	22	(61.11%)	26 (72.22%)		26 (72.22%)	(72.22%)	> 0.05
Rheumatoid factor positive no. (%)		32	(88.88%)	31	(86.11%)	29	(80.56%)	> 0.05

4. Prior Use of DMARDs, Concomitant Stable Doses of NSAIDs and Steroids in Subjects Studied

Variables	Dexamethasone Group (n=36)		Leflunomide Group (n=36)		Methotrexate Group (n=36)		P value Group
Prior DMARDs use numbers (%)	23	(63.88%)	24	(66.66%)	24	(66.66%)	> 0.05 N.S.
Concomitant NSAIDs numbers (%)	20	(55.56%)	13	(36.11%)	12	(33.33%)	> 0.05 N.S.
Concomitant steroid numbers (%)	24	(66.66%)	15	(41.66%)	12	(33.33%)	> 0.05 N.S.

5. Tender Joint Counts of Subjects Studied

Group	Tender Joint Count (Mean±S.D.)				Mean Change	P value baseline v/s end point
	Time in weeks					
	0 Baseline	4	8	12 endpoint		
Dexamethasone	19.67±5.32	20.54±5.04	20.54±4.82	21.13±4.82	1.46±0.50	> 0.05 N.S.
Leflunomide	20.05±4.34	20.94±5.20	20.28±5.04	21.22±5.45	1.17±1.11	< 0.001 H.S.
Methotrexate	19.62± 5.77	19.02± 5.60	19.72± 5.25	20.97± 5.59	1.35±0.18	> 0.05 N.S.

6. Swollen Joint Counts of Subjects Studied

Group	Swollen Joint Count (Mea n±S.D.)				Mean changes	P value baseline vis end point
	Time in weeks					
	0 baseline	4	8	12 end point		
Dexamethasone	21.24±5.76	20.70±5.44	19.94±4.88	21.67±4.79	0.43±0.97	<0.05
Leflunomide	21.33±4.22	21.16±4.41	20.5±4.28	20.55±4.23	-0.78±0.01	< 0.001 H.S.
Methotrexate	20.75±5.44	20.70±5.19	20.16 ±4.69	20.32±4.40	-0.43±1.04	< 0.05

7. Patient Global Assessment (PGA) of Disease Activity in Subjects Studied

Grou p	PGA in mm (VAS) (Mea n± S.D.)				Mean Change	P value baseline v/s endpoint
	Time in weeks					
	0 baseline	4	8	12end point		
Dexamethasone	48.91±14.20	50.89±13.03	50.27±13.09	45.18±14.11	-3.73±0.09	> 0.05 N.S
Leflunomide	53.61± 10.53	53.33±11.51	53.72± 10.24	48.91±11.29	-4.70±0.76	< 0.001 H.S
Methotrexate	52.16±13.62	52±13.95	52.48±12.58	47.91±12.68	-4.25±0.94	< 0.001

8. Physician Global Assessment of Disease Activity in Subjects Studied

Group	Physician Assessment (VAS) (Mean ±S.D.)				Mean Change	P value base line vis end point
	Time in weeks					
	0 baseline	4	8	12 end point		
Dexamethasone	45.40± 13.45	45.83±14.08	44.37±13.06	44.91±12.78	0.49±0.67	> 0.05 N.S.
Leflunomide	47.66±11.78	50.11±11.78	51.11±11.72	49.44±11.96	1.78 ±0.18	< 0:001 H.S.
Methotrexate	46.37±14.01	48.86±13.87	49.94±13.55	48.43±13.30	2.06±0.69	< 0:001

9. Pain Intensity in Subjects Studied

Group	Pain intensity in mm (VAS) (Mean±S.D.)				Mean Change	P value baseline v/s end point
	Time in weeks					
	0 baseline	4	8	12 End point		
Dexamethasone	42.02±12.94	44±13.31	41.64± 11.64	43.18±12.47	1.16±0.47	> 0.05 N.S.
Leflunomide	45.63±10.84	47.47±11.53	43.80±12.18	42.22±10.72	-3.41±0.12	< 0.001 H.S.
Methotrexate	44.40±13.06	43.86±15.16	37.45±12.86	39.94±13.32	-4.46±0.26	< 0.001 H.S.

10. Morning Stiffness in Subjects Studied

Group	Morning stiffness (Mean±S.D) in min utes				Mean Change	P val ue baseline vis end point
	Time in weeks					
	0 Baseline	4	8	12 end point		
Dexamethasone	88.27±38.95	79.64±43.22	88.43±44.34	80.40±42.32	-7.87±3.37	> 0.1 N.S.
Leflunomide	96.91±40.98	84.05±40.42	81.27±41.84	61.41±32.34	-35.5±8.64	< 0.00 1 H.S.
Methotrexate	73.97±35.08	59.64±30.01	57.18±30.91	65.86±30.40	8.11±4.68	<0.1

11. Health Assessment Questionnaire (HAQ) Score in Subjects Studied

Group	HAQ score (Mean±S.D.)				Mean Change	P value base line v/s end point
	Time in weeks					
	0 baseline	4	8	12 end point		
Dexamethasone	1.54±0.63	1.20±0.60	1.28±1.21	1.50±1.86	-0.04±1.23	< 0.01
Leflunomide	1.16±0.46	1.10±0.44	1.09±0.46	1.10±0.50	-0.06±0.04	< 0.001 H.S.
methotrexate	0.80±0.28	0.87±0.55	1.01±1.20	1.14±1.84	0.03±1.56	>0.1

12. Erythrocyte Sedimentation Rate in Subjects Studied

Time	ESR mm 1st hr (Mean ± S.D.)		
	Dexamethasone	Leflunomide	Methotrexate
Baseline (B.L.) (0 week)	67.18±23.49	64.75±9.66	61.27±14.17
Endpoint (E.P.) (12 week)	65.16±18.16	67.83±9.51	64.86±13.27
Mean Change	(-)2.2±5.33	3.08±0.15	3.59±0.9
P value B.L. v/s E.P.	< 0.01	< 0.001 H.S.	< 0.001 H.S.

Rate in Subjects Studied

Group	ACR Response Rate Number (%)					
	ACR 20%				ACR 50%	ACR 70%
	Time in weeks					
	0 baseline	4	8	12end point		
Dexamethasone	0 (0)	2 (5.55%)	3 (8.33%)	7 (19.44%)	0 (0)	0 (0)
Leflunomide	0 (0)	5 (13.88%)	9 (25%)	16 (44.44%)	11 (55)	4 (20)
Methotrexate	0(0)	5 (13.88%)	10 (27.77%)	15 (41.66%)		

13. C-Reactive Protein In Subjects Studied

Time	CRP mg/L (Mean ± S.D.)		
	Dexamethasone Group	Leflunomide Group	Methotrexate group
Baseline (B.L.) (0week)	19.81±7.01	23.02±5.21	23.02±6.63
Endpoint (E.P.) (12 week)	23.62±6.05	26.08±3.66	26.67±3.95
Mean Change	3.81±0.96	2.88±1.55	3.65±2.68
P value B.L. v/s E.P.	> 0.1 N.S.	< 0.001 H.S.	> 0.1 N.S.

14. American College of Rheumatology (ACR) Response

15. Haemoglobin Levels in Subjects Studied

Time	Haemoglobin gm/dl (Mean ± S.D.)		
	dexamethasone	Leflunomide Group	Methotrexate group
Baseline (B.L.) (0 week)	11.58±2.37	12.03±1.36	11.42±2.33
Endpoint (E.P.) (12 week)	11.83±1.49	11.78±1.37	11.73±1.39
Mean Change	0.25±0.88	(-) 0.25±0.01	0.31±0.94
P value B.L. v/s E.P	> 0.05 N.S.	< 0.01	

16. Total Leucocytes Counts in Subjects Studied

Time	TLC / cm (Mean±S.D.)		
	Dexamethasone Group	Leflunomide Group	Methotrexate Group
Baseline (0 week)	8035±1628	8155±531	8195±418
Endpoint (12 week)	8150±1441	8038±550	8189±413
Mean Change	115±187	(-) 117±19	6±5
P value B.L. v/s E.P.	> 0.1 N.S.	<0.05	<0.05

17. Platelet Counts in Subjects Studied

Time	Platelet Counts lac/cm m Mean ± SD		
	Dexamethasone Group	Leflunomide group	Methotrexate Group
Baseline (B.L.) (0 week)	2.48±0.64	1.75±0.86	1.76±0.84
Endpoint (E.P.) (12 week)	2.73±1.62	1.76±0.84	1.68±0.96
Mean Change	0.25±0.98	0.01±0.02	(-)0.08±0.12
P value B.L. v/s E.P.	> 0.05	< 0.05	< 0.05

18. Serum Creatinine in Subjects Studied

Time	Serum Creatinine mg/dL (Mean±S.D.)		
	Dexamethasone Group	Leflunomide Group	Methotrexate Group
Baseline (0 week)	0.88±0.19	0.86±0.04	0.86±0.04
Endpoint (12 week)	1.19±1.82	0.86±0.05	0.88±0.03
Mean Change	0.31±1.63	0.0±0.01	0.02±0.01
P value B.L. v/s E.P.	> 0.1	> 0.1	> 0.1

19. Serum Bilirubin in Subjects Studied

Time	Serum Bilirubin mg/dL (Mean±S.D.)		
	Dexamethasone Group	Leflunomide Group	Methotrexate Group
Baseline(B.L.) (0 week)	0.85±0.24	1.00±0.21	1.05±0.21
Endpoint(E.P) (12 week)	1.22±1.83	0.94±0.22	0.98±0.24
Mean Change	0.37±1.59	(-)0.06±0.01	(-)0.07±0.03
P value B.L. v/s E.P.	> 0.1 N.S.	> 0.1 N.S.	

20. SGOT in Subjects Studied

Time	SGOT IU/L (Mean±S.D.)		
	Dexamethasone Group	Leflunomide Group	Methotrexate Group
Baseline (0 week)	25.02±5.38	24.41±2.69	23.83±4.94
Endpoint (12 week)	24.48±3.16	24.97±2.70	25.05±3.46
Mean Change	(-)0.54±2.22	0.56±0.01	1.22±1.48
P value B.L. v/s E.P.	> 0.1 N.S.	> 0.1 N.S.	> 0.1 N.S.

21. SGPT in Subjects Studied

Time	SGPT IU/L (Mean±S.D.)		
	Dexamethasone Group	Leflunomide Group	Methotrexate group
Baseline (B.L.)(0 week)	24.51±5.20	24.25±2.54	23.29±4.56
Endpoint (E.P.) (12 week)	23.45±3.16	24.47±2.32	25.02±2.88
Mean Change	(-)1.0.6±2.04	0.22±0.22	1.73±1.68
P value B.L. v/s E.P.	> 0.05 N.S.	> 0.1 N.S.	> 0.1 N.S.

22. Adverse Events in Subjects Studied

Adverse event	Dexamethasone group	Leflunomide group	Methotrexate group
Diarrhoea	2 (5.55%)	3 (8.33%)	2 (5.55%)
Respiratory infection	4 (11.11%)	2 (5.55%)	3 (8.33%)
Nausea	1 (2.75%)	2 (5.55%)	1 (2.75%)
Headache	2 (5.55%)	5 (13.88%)	3 (8.33%)
Abnormal hepatic enzyme levels	0 (0)	1 (2.75%)	0 (0)
Rash	0 (0)	1 (2.75%)	0 (0)
GI Pain	1 (2.75%)	3 (8.33%)	2 (5.55%)

Mechanism of action of Leflunomide

Two modes of action of leflunomide have been documented:

1. Inhibition of dihydro-orotate dehydrogenase (DHODH), by which leflunomide influences the de novo pyrimidine biosynthesis, and interaction with primary and secondary signaling events.

The main target of leflunomide seems to be pyrimidine biosynthesis, because leflunomide shows high affinity binding to DHODH, and, even at low concentrations, inhibits the enzyme. (DHODH is essential for the de novo synthesis of uridine monophosphate (UMP), a precursor of pyrimidine nucleotides.). Resting lymphocytes have low levels of DHODH and mainly use a salvage pathway for UMP to sustain survival. Activation of lymphocytes gives a seven- to eightfold increased demand for UMP, which makes these cells susceptible to DHODH inhibition by leflunomide in the absence of a salvage pathway. DHODH inhibition decreases UMP levels, decreases DNA and RNA synthesis and, consequently, inhibits cell proliferation and G1 phase cell cycle arrest. Other cells are less affected by DHODH because of the use of a salvage pathway. Another argument supporting the proposed inhibitory effects of leflunomide on T cells by DHODH inhibition is the reversal of the observed effects by exogenous uridine in vitro. Further support is found in the observation that the inhibition of de novo pyrimidine biosynthesis by leflunomide is 100-fold stronger than its effects on tyrosine kinases. Leflunomide also affects signal transduction, interferes with cell-cell contact, and inhibits tumour necrosis factor α (TNF α) induced activation of NF- κ B. Moreover, studies of leflunomide have shown that it affects neutrophil chemotaxis, which cannot directly be explained by effects on purine nucleotides. Therefore, it has been suggested that the effects on pyrimidine biosynthesis are associated with low doses of leflunomide, whereas other mechanisms might be operative at higher concentrations.

The mechanism of action of methotrexate in RA is currently not completely understood but seems to be more than an effect on purine biosynthesis, and appears to be not cell type specific.

Leflunomide group inhibition of IFN-alpha but not of IL6	Methotrexate group inhibition of IFN-alpha and IL6
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Serum IL6 levels of patients with RA have been associated with disease outcome. The T cell derived cytokine IFN-alpha is also produced by natural killer cells (NK cells) and is involved in nearly all phases of inflammation and in the regulation of inflammatory responses. It has effects on macrophage, B cell, and neutrophil function. The inhibition of IFN-alpha, as seen in this study, might be the result of inhibition of DHODH, which impairs T cell function with, as secondary effect, inhibition of monocyte/macrophage function. This is supported by the inhibition which occurs at concentrations of active metabolite present in patients with RA.

2. Leflunomide has also been shown to interfere with IFN-alpha induced inducible nitric oxide synthase activation and nitric oxide production in fibroblast. T cells are inhibited by leflunomide in the G1-S phase. The inhibitory effects of leflunomide are due to a combination of both inhibition of pyrimidine biosynthesis and interference with signalling events.

This observation supports the hypothesis that leflunomide preferentially affects activated T cells. It also supports the clinical observation of different pharmacodynamic profiles for methotrexate and leflunomide.

Both leflunomide and methotrexate drugs displayed equal clinical efficacy, with 8 leflunomide-treated patients (50%) and 10 methotrexate-treated patients (53%) fulfilling the American College of Rheumatology 20% response criteria. Both compounds showed similar effects on synovial tissue: reduced numbers of macrophages and reduced ICAM-1 and VCAM-1 expression were noted after 4 months of treatment. Both leflunomide- and methotrexate-treated patients exhibited a decreased MMP-1:TIMP-1 ratio in the synovial tissue. In the subset of patients fulfilling the 20% response criteria of the American College of Rheumatology, a more pronounced reduction in the expression of ICAM-1, VCAM-1, IL-1b, and MMP-1 was found compared with the nonresponders.

Leflunomide group (interference with pyrimidine biosynthesis)	Methotrexate group (interference with purine biosynthesis)
Nonresponders - increase expression of ICAM-1, TNF α , and IL-1b. - a decrease in VCAM-1 expression in the nonresponders Responders - reduction in expression of all markers, with the exception of IL-1b, which remained unchanged - a more pronounced reduction of VCAM-1 expression in the responders	Nonresponders in the methotrexate group showed an increase in ICAM-1, VCAM-1, and TNF α expression, - IL-1b expression decreased slightly.

Leflunomide reduced the total cellularity in synovial tissue. more pronounced reduction in the MMP-1:TIMP-1 ratio.	moderate decrease in total cellularity after treatment with methotrexate
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clinical response following addition of leflunomide to methotrexate treatment in patients with RA that had failed to respond adequately to methotrexate alone. This combination was chosen based on the complementary mechanisms of action of these 2 drugs. The primary action of leflunomide is to inhibit de novo pyrimidine biosynthesis and thus limit proliferation of activated T lymphocytes.

Methotrexate, on the other hand, appears to act through multiple mechanisms, including inhibition of purine biosynthesis, inhibition of cellular synthesis of polyamines, modulation of cytokine activity, promotion of adenosine release, and promotion of apoptosis of activated T cells.

7. Summary & Conclusion

This study was carried out in 108 patients of classical or definite R.A. proved by A.R.A. criteria (1987).

- All the patients in group A (Dexamethasone), B (Leflunomide) and C (Methotrexate) are identical in all the aspects like age, sex.
- In group A 36 patients treated with high dose IV pulse dexamethasone alone showed initial clinical response with decrease in their functional capacity class, decrease in duration of morning stiffness and decrease in Ritchie joint score and rheumatoid antibody titre for about 1-2 months only. After 6 months of therapy, the functional capacity class increased, and duration of morning stiffness decreased.
- In group B (Leflunomide group) 36 patients who had Leflunomide drug therapy showed sustained effect up to 6 months. Their functional capacity class was improved, and the duration of morning stiffness Ritchie's joint score and rheumatoid antibody titre were decreased.
- In group C (Methotrexate group) (36 patients, more effective and can be given for longer duration, and is well tolerated by the patients without any serious side effects.) Their functional capacity class was improved, and the duration of morning stiffness Ritchie's joint score and rheumatoid antibody titre were decreased.
- It is concluded from the study that dexamethasone is effective in patient's global assessment and physician's global assessment.
- Leflunomide drug therapy was highly effective in improves remission, improves functional capacity class and joint score and it reduced the rheumatoid antibody titre in all the cases. Leflunomide is highly effective in swollen joint count reduction, pain intensity reduction, decrease in ESR, low C-Reactive protein, Good ACR response rate, lower risk of anemia, no increase of Total leucocyte count, platelet count was unchanged, lowest elevation or unchanged S. creatinin, S. bilirubin, SGOT, SGPT and low risk of adverse reaction. No serious side effects were observed with dexamethasone, Leflunomide and methotrexate.
- While methotrexate is highly effective in low tender joint count and lowering the incidence of morning stiffness.
- Hence the routine use of Leflunomide therapy is

recommended for the management of rheumatoid arthritis, as it was found to be more effective and well treated by the patient in our study.

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