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

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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 m age range 18 to 70 years who were treated with loading dose of leflunomide l OOmg 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 7Q 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 fun ctional 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 m 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 stl!dy viz.:

1. Infective, go.uty 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 quationnarie score).

The primary efficacy variable was the rate at which the intension 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 criteia 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 DRl0. 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 atleast 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 TNFa 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 signalingcascade 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 bonedestruction	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 Th l -like efector cells producing the proinflammatory cytokine IFN-y and appear to be deficient in differentiation into Th2-like effectors cells capable of producing the anti inflammatory cytokine IL-4. As a result of the ongoing secretion of INF-y without the regulatory influences of IL-4, macrophages are activated to produce the proinflammatory cytokine IL-1 and TNF-a 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 immunoglbulin 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 C_3a and C_5a and the chemotactic factor C_5a · The rheumatoid inflammation could reflect persistent stimulation of T cells by synovial – derived antigens that cross react with determinants introducedduring 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 E_2 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-alpha 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. Thecytokines IL-1 and TNF-a may contribute to the local demineralization of bone by activating osteoclasts that accumulate at the site of local bone resorption. The prostaglandin E_2 produced by fibroblasts and macrophages also contri bute to bone demineralization (Koch 199&, .Feldmann and Maini 1999, Friestein 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-a and IL-6 which account for many of the manifestationsof 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 andother inflammatory mediators cause neutrophilic infiltration and vascular · damage. Rheumatoid vasculitis is associated with high titre rheumatoid factor and hyocomplementemia (Aggarwal, 200 l).

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) (n=36)	1	2	11	22	12	24	36

2. Mean Age of Subjects Studied

Group	Age (Mean ± S.D.) in years		
	Male	Female	Total
Dexamethasone	58.35±12.83	53.22± 11.97	59.2 ±7.47
Leflunomide	53.66667 ±8.50098	53.7 ±8.994826	66.02±9.02
Methotrexate	56.58333±8.073057	54.5±9.026531	62.36 ±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±SD) years Number with duration 10 years		12.93±5.58 10	(36%)	16.61±5.88	(11%)	15.94± 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
Rheu matoid factor positive no. (%)		32	(88.88%)	31	(86.11%)	29	(80.56%)	> 0.05

4. Prior Use of DMARDS, Concomittant Stable Doses of Nsaids and Steroids in Subjects Studied

Varia bles	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.) Time in weeks				Mean Change	P value baseline v/s end point
	0 Baseline	4	8	12 end point		
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.) Time in weeks				Mean changes	P value baseline vis end point
	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) (Mea n±S.D.)				Mean Cha nge	P val ue 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 base line 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 Tudied

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.)		
	Dexamthasone	Leflunomide group	Methotrexate Group
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 N u m ber (%)					
	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 Grou p	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 Grou p	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 iIn 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	Lefluomide 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
Basel ine (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 a (TNFa) induced activation of NF-kB. 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	Methotrexate group
inhibition of IFN-alpha but not of IL6	inhibition of IFN-alpha and IL6

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, TNFa, and IL-1b . -a decrease in VCAM-1expression 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-1expression in the responders	**Nonresponders** in the methotrexate group showed an increase in ICAM-1,VCAM-1, and TNFa 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

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 therepy, the:·ir functional capacity class increased, and duration of morning stiffness decreased ,
- In group B (Leflunomide group) 36patients who had Leflunomide drug therepy showed sustained effect up to 6 months. Their functional capacity class was improved , and the duration of morning stiffness Richie' s joint score and rheumatoid antibody titre were decresed.
- In group C (Methotrexate group) (36patients,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 in duration of morning stiffness Richie' s joint score and rheumatoid antibody titre were decresed.
- 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, platlet 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.

References

[1] Aggarwal A : Pathogenesis of rheumatoid arthritis. 1n Sidharath Kumar Das editor. Rheumatoid arthritis Indian College of Physicians. Technical series lSt edition 2001:15-16.
[2] Aggarwal A, Kulshreshtha A, Charturvedi v, Misra R: Cervical spine involvement in rheumatoid arthritis: JAPI 1996; 44: 468-71.
[3] Ahem MJ, Chandran G: Category III symptom-modifying antirheumatic drugs: Clin Immunother 1995 Mar. 3 : 196-217. ‘ '
[4] Ahmed SA, Penhale WJ, and Talal N : Sex hormones, immune responses, and autoimmune diseases. Am J Pathol 1985; 121: 431.
[5] Alldred A, Emery P : Leflunomide : a novel DMARD for the treatment of RA. Expert Opin Pharmacother 2001 ; 2 :125-37.
[6] American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 1996 May; 39: 713-22 '
[7] American College of Rheumatology Ad Hoc Committee on clinical guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996 May: 39: 723-31.
[8] American College of Rheumatology subcommittee on rheumatoid arthritis guidelines. Guidelines for the management of rheumatoid arthritis. 2002 update. Arthritis and Rheum 2002; 46(2): 328-346.
[9] Amett FC, Edworthy SM, Bloch DA, et al : The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315-24. /
[10] Ballou SP and Kushner 1 : Laboratory evaluation of inflammation. In Kelly‘s Textbook of Rheumatology. Eds. Ruddy s, Harris ED Jr, Sledge CB, 4“ Ed, Philadelphia, Saunders, 1993 ;671-79.
[11] Bambery P: Extra articular manifestations of rheumatoid arthritis. In SK Das, editor. Rheumatoid arthritis Indian College of Physicians. Technical series:l“ edition 2001 :21-22.
[12] Bao C, et al : Leflunomide, a new disease modifying drug for treating active RA in methotrexate controlled phase II clinical trial. Chin Med J (Engl) 2003: 116 (8) : 122834.
[13] Bienenstock H : Rheumatoid plantar synovial cysts. Ann Rheum Dis 1975 34:98-99.
[14] Bombardier C,et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with RA. N Engl J Med 2000; 343 : 1520 8.
[15] Borigini MJ, Paulus HE : Rheumatoid arthritis. In Treatment of the rheumatic diseases. Eds. Weisman MH, Weinblatt ME, Louie JS. 2"‘1 ed., Philadelphia, Saunders, 2001; 2l7-35.
[16] Breedveldt FC, Dayer JM : Letlunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis 2000;59:841-849
[17] Brook A, Corbett M : Radiographic Changes in early rheumatoid arthritis. Ann Rheum Dis 1977; 36: 71-3.
[18] Cao WW, et al. Mechanism of the antiproliferative action of letlunomide. J Heart Lung Transplant 1995;14(Pt I) : 1016-30.
[19] Caplan A: Certain unusual radiographic appearances in the chest of coal miners suffering from RA. Thorax 1953;8:29.
[20] Cary GR : Methods for determining the presence of subtle knee joint effusion. J Louisiana State Med Soc I966; l 18:147.
[21] Chan KA, et al. The lag time between the oriset of symptoms and diagnosis of RA. Arthritis Rheum.l994; 37: 814
[22] Chandrasekarn AN and Radhakrishna B: Clinical significance of rheumatoid factor and other marker antibodies in rheumatoid arthritis. Mediquest (Medical information seriesRanbaxy) 1995; 13(2): 14
[23] Chandrasekaran AN, et a1 : Spectrum of clinical and immnogenetic features of systemic rheumatic disorders in a referral hospital in South Indiarheumatoid arthritis. J Ind Rheum Assoc. 1994; 2: 18-26.
[24] Chopra A, Patil J, Billanpelly V, Relwami .I, Tandale HS : The Bhigwan (India) COPCORD: Methodology and first information report. APLAR J. Rheumatol 1997; 1: 145-151.
[25] Cohen S, Canon GW, Schiff M, et a1 : Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Arthritis Rheum 2001 ;44(9):1984-92.
[26] Das SK : Rheumatoid arthritis Present status. In: SK Das editor, Rheumatoid arthritis, Indian College of Physicians. Technical series; 1" edition 2001; 9-10.
[27] Das SK and Ramakrishnan S : Rheumatoid factor. In: SK Das editor. Rheumatoid arthritis, Indian College of physicians. Technical series: 1“ edition 2001: 23-24.
[28] DeSmet AA, Ting YM and Weiss 1] : Shoulder arthrography in rheumatoid arthritis. Diagn Radio] 1975; 1162601.
[29] Dev1in, et a1 : Clinical associations of dual energy X-ray absorptiometry measurement of hand bone mass in Rheumatoid Artritis. Br Rheumatol 1996; 35(12): 1256-62.
[30] Dodson WH and Hollingsworth JW : Pleural effusion in rheumatoid arthritis . Impaired transport of glucose. N Engl j Med 1966; 275: 1337-42.
[31] Drugs facts and comparisons 55m edition 2001 : 1649-51.
[32] Dubost JJ, Soubrier M, Sauvezie B : Treatment of rheumatoid polyarthritis : evolution of concepts and strategies. Rev Med Inteme 1999 Feb; 20(2) :l71-8
[33] Edeiken J, Hodes PJ : Roentgen diagnosis of disease of bone. 2"d edn. Baltimore, Williams and Wilkins 1978; 690-709.
[34] Emery P : Disease modification in rheumatoid arthritis with let1unomide. Scand J Rheumatol Suppl 1999; 115: 9-14.
[35] Emery P : Leflunomide: a new DMARD for rheumatoid arthritis. Hosp Med 2000 May; 61(5) : 344-7.
[36] Emery P : Therapeutic approaches for early RA. How early? How aggressive? Br. J Rheumatol 1995; (Suppl.

2): 87-90.
[37] Emery P, Breedveld FC, Lemmel EM, et al :_A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. J Rheumatol 2000; 39: 655-65.
[38] Emery P,'Salmon M : Early rheumatoid arthritis : Time to aim for remission. Ann Rheum Dis 1995; 54: 944-7.
[39] Emery P. The optimal management of early rheumatoid arthritis: The key to preventing disability. Br J Rheumatol 1994; 38: 765-8.
[40] Ericson S and Lundberg M : Alterations in the temporomandibularjoints at various stages of RA. Acta Rheum Scand.l967; 13: 257.
[41] Feldmann M, Maini RN : The role of cytokincs in the pathogenesis of I rheumatoid arthritis. Rheumatology 1999; 38 (supp 2): 3-7.
[42] Felson DT, Anderson JJ, Boers M, et al : The American College of Rheumatology preliminary core set of disease activity measures for RA clinical trials. Arthritis Rheum 1993; 36: 729-40.
[43] Felson DT, Anderson J]. Boers M, et al : American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 38: 727-35.
[44] Felson DT, et al 2 Use of short-term efficacy/toxicity tradeoffs to select second line drugs in RA : a metaanalysis of published clinical trials. Arthritis Rheum 1992; 35: 1117-25
[45] Firestein GS : Etiology and pathogenesis of rheumatoid arthritis. In Kelly's textbook of rheumatology Eds. Ruddy S, Harris ED Jr, Sledge CB, 6'" Ed. Philadelphia, Saunders, 2001: 921-66. '
[46] Fleming A, Benn RT, Carbett M et al: Early rheumatoid disease: patterns of joint involvement. Ann Rheum Dis.l976; 35: 361.
[47] Forslind K, Larsson EM, Johansson A, Svensson B : Detection of joint pathology by magnetic resonance imaging in patients with early rheumatoid arthritis. BrJ Rheumatol 1997; 36: 683-8.
[48] Fox RI : Mechanism of action of leflunomide in rheumatoid arthritis. J Rheumatol 1998 Jul: 25 Suppl. 53: 20-6.
[49] Fox RI, et al : Mechanism of action for letlunomide in rheumatoid arthritis. Clin Immunol 1999 Dec; 93(3) :198-208.
[50] Frank ST, Weg JG, Harkleroad LE, et a] : Pulmonary dysfunction in rheumatoid disease. Chest 1973; 63: 27-34.
[51] Friedman BA and Rice DH : Rheumatoid nodules of the larynx. Arch Otolaryngol 1975; 1011361.
[52] Fries JF : Current treatment paradigms in rheumatoid arthritis. Rheumatology (Oxford) 2000; 39 Suppl 1: 30-5. 53.Furst DE : Are there differences among nonsteroidal anti-inflammatory drugs? Comparing acetylated salicylates, non-acetylated salicylates, and non-acetylated nonsteroidal anti-inflammatory drugs. Arthritis Rheum 1994; 37(1): 1-9.
[53] Gay S: Rheumatoid arthritis. Editorial overview. Curr Opin Rheumatol 2000; 12: 179-80.
[54] Georgescu L, Paget SA. Lymphoma in patients with RA: What is the evidence of a link with methotrexate. Drug Saf 1999;20:475-87.
[55] Ginsberg MH, et al : Rheumatoid nodulosis: An unusual variant of rheumatoid disease. Arthritis Rheum. 1975; 18:49-58.
[56] Gordon DA, Hastings DE: RAfeatures of early, progressive and late disease. In: Rheumatology. Eds. Klippel JH and Dieppe PA. Mosby International, London, 2"d edition, 1998: 5.3.1-5.3.4.
[57] Hall AP, Scott 11' : Synovial cysts and rupture of the knee joint in rheumatoid arthritis. Ann Rheum Dis 1966; 25: 32-4.
[58] Handa R and Kumar U : Early rheumatoid arthritis. In: SK Das editor. Rheumatoid arthritis Indian College of Physicians. Technical series: 1" edition 2001; 39-42.
[59] Hanis ED : Clinical feature of rheumatoid arthritis. In : Textbook of rheumatology Eds. WN Kelly, s Rubby, ED Harris, CB Sledge, 4'" ed. WB Saunders Co. Philadelphia 1993: 874-91 1.
[60] Harris ED : Etiology and pathogenesis of rheumatoid arthritis. In : Text book of rheumatology Eds. WN Kelly, S Rubby, ED Harris, CB Sledge, 4'h edn. PhiladelphiaWB Saunders co. 1993; 833-73.
[61] Harris ED Jr : Clinical features of rheumatoid arthritis. In Kelly's Textbook of Rheumatology. Eds. Ruddy S, Harris ED Jr., Sledge CB. 6th Ed., PhiladelphiaWB Saunders co. 2001; 967-1000.
[62] Hastings DE and Parker SM : Protrusio acetabuli in rheumatoid arthritis. .. Clin Orthop 1975; 108276-83.
[63] Hazes JMW : Pregnancy and its effect on the risk of developing rheumatoid arthritis. Ann Rheum Dis 1991; 50:71.
[64] Hickling P, et a1 : Joint destruction after glucooorticoids withdrawn in early rheumatoid arthritis. Br J Rheumatol 1998; 37: 930-6.
[65] Hochberg MC. et al : ACR classification criteria of functional status in RA. Arthritis Rheum. 1992; 35: 498.
[66] Hu Y, Tu S, Liu P : A randomized, controlled, single-blind trial of leflunomide in the treatment of rheumatoid arthritis. J Tongji Med Univ 2001;21(1):72-4.
[67] Hutchinson D,et al : Heavy cigarette smoking is strongly associated with rheumatoid arthritis. particularly in patients without a family history of RA. Ann Rheum Dis 2001; 60: 223-227.
[68] Indian core committee : Indian Guidelines for the management of rheumatoid arthritis. JAPI 2002 (Sept); 50: 1201 ~1218.
[69] lntemational committee for standardization in hematology: Recommendation for measurement of eyrthrocyte sedimentation rate of human blood. Am J Clin Pathol 1977; 68: 505.
[70] Jackson CG, Chess R1. and Ward JR : A case of rheumatoid nodule formation within the central nervous system and review of the literature. J Rheumatol 1984; 11: 237-40.
[71] Jayson MIV and Dixon A St J : Valvular mechanisms in juxtaarticular cysts. Ann Rheum Dis 1970; 29: 415-20.
[72] Kalden JR, et a1 : The emcacy and safety of lcflunomide in patients with active rheumatoid arthritis: a five year follow up study. Arthritis Rheum 2003; 48(6): 1513-20.
[73] Kalden JR. et al : Improved functional ability in

patients with rheumatoid arthritis -longterm treatment with leflunomide versus sulfasalazine. J Rheumatol2001 Sep;28(9):1983-91.
[74] Kalla AA and Tikly M : Rhematoid arthritis in the developing world. Best Pract Res Clin Rheumatol 2003 Oct; 17(5): 863-75.
[75] Karlson EW, et al : Coffee consumption and risk of rheumatoid arthritis. k' :krthritis Rheum. 2003; 48(11):3045-60.
[76] Karvonen RL, Negendank WG, Fraser SM et al : Articular cartilage defects of the knee: correlation between MR] and gross pathology. Ann Rheum Dis 1990; 49: 672-5.
[77] khare N, Das SK : Clinical features of rheumatoid arthritis. 1n Sidharath Kumar Das, editor. Rheumatoid arthritis Indian College of Physicians. Technical series : 1" edition 2001; 17-18.
[78] Kirwan JR and the Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group : The effect of glucocorticoids on joint destruction in rheumatoid arthritis. Engl J Med 1995', 333: 142-6.
[79] Klarlund M, et al and the TIRA group. MRI, radiography, and scintigraphy of the fingerjoints: one-year followup of patients with early arthritis. Ann Rheum Dis 2000; 59: 521-8.
[80] Koch AE : Angiogenesis implications for rheumatoid arthritis. Arthritis Rheum 1998;41: 951-62. M
[81] Kozer E, Moretti ME, Koren G : Leilunomide : new antirheumatic drug. Effect on pregnancy outcomes. Can Fam Physician 2001 Apr ; 47:721-2.
[82] Kraag G. et al : The hemorrhage crescent sign of acute synovial rupture. Ann lntem Med 1976; 85: 477-78.
[83] Kraan MC : Inhibition of neutrophil migration soon after initiation of treatment with leflunomide or methotrexate in patients with RA: Anhritis rheum 2000;43: 1488-1495.
[84] Kremer .IM : Methotrexate and letlunomide: biochemical basis for combination therapy in the treatment of rheumatoid arthritis. Semin Arthritis Rheum 1999; 29: 14-26.
[85] Kremer JM, Genovese MC, Cannon GW et al : Concomitant leflunomide therapy in patients with active RA despite stable doses of methotrexate. Ann Intern Med 2002; 137: 726-733.
[86] Krishnan E, Sokka T and Hannonen P: Smoking gender interaction and risk for RA . Arthritis Res Ther 2003, 5: R 158-R162.
[87] Kumar A: DMARDs : Current status. In: SK Das editor, Rheumatoid arthritis, Indian College of Physicians. Technical series; 1'? edition 2001; 59-61.
[88] Lard LR, et al : Early versus delayed treatment in patients with recent onset RA: Comparsion of two Cohorts who received different treatment strategies. Am J Med 2001 ; 111: 446-45].
[89] Larsen A : How to apply Larsen score in evaluating mdiographs of rheumatoid arthritis in longterm studies? J Rheumatol. 1995;22:1974-5.
[90] Levy RN, Hermann G, Haimov M, et a1 : Rheumatoid synovial cyst of the hip. Arthritis Rheum 1933;; 25: 1382-4.
[91] Lipsky PE : Rheumatoid arthritis. In: Fauci AS, Braunwald E, et al, editors. Harrison's -rinci -1es of inWim. McGrawHill, International Edition.2001; 1928-37.
[92] Lipsky PE and Davis LS : The centrol involvement of T cells in rheumatoid arthritis. Immunologist 1998; 6: 121.
[93] Lofgren RH and Montgomery WW : Incidence of laryngeal involvement in rheumatoid arthritis. N Engl J Med 1962; 267:193.
[94] Walaviya AN, Kapoor SK, Singh RR,et a1 : Epidemiology Rheumatoid arthritis predominantly affects women between age groups of 20 to 40 years. Rheumatology Int 1993; 13: 1314.
[95] Malaviya AN, Mehra NK, Dasgupta B. et al : Clinical and lmmunogenetic studies in Rheumatoid Arthritis from North India. Rheumatol Int 1983; 3: 105-8.
[96] Matsuda Y : Disease modifying anti-rheumatic drugs (DMARDs). Nippon Rinsho 1999 Feb; 57(2) :43944.
[97] Mladenovic V, Domljan Z, Rozman B, et al : Safety and effectiveness of Icflunomide in the treatment of patients with active rheumatoid arthritis: Arthritis Rheum 1995; 38 : 1595-603.
[98] Mody GM and Meyers 0L : Resorptive arthropathy in rheumatoid arthritis. J Rheumatol 1988; 15: 1075.
[99] Moreland LW, Bridges SL : Early rheumatoid arthritis: A medical emergency? Am J Med 2001; 111 : 498 500.
[100] Mortonen T, Hannonen P, Leirisalo-Repo M. et al : Comparison of combination therapy with single agent therapy in early rheumatoid arthritis, a randomized trial. Lancet 1999; 353: 1568-73.
[101] O'Dell J, Rheumatoid Arthritis lnvestigational Network (RAlNS) : Combination DMARD therapy for rheumatoid arthritis; apparent universal acceptance. Arthritis Rheum 1997; 40 Suppl. : $50.
[102] Pearson ME, et a1 : Rheumatoid nodules of the spine: Case report and review of the literature. Arthritis Rheum 1987; 30:709.
[103] Persellin RH : The effect of pregnancy on rheumatoid arthritis. Bull Rheum Dis 1977; 27: 922.
[104] Pincus '1', Ferraccioli G, Sokka T, et a1 : Evidence from clinical trials and long term observational studies that disease modifying antirheumatic drugs slow radiographic progression in RA. Updating a 1983 review. Rheumatology 2002: 41: 1346-1356.
[105] Pincus T. O'Deli IR. Kremer JM : Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. Ann Intern Med 1999; 131: 768-74.
[106] Pispati PK: Rheumatoid arthritis. In Shah SN editor, API textbook of medicine, 7 edition 2001; 1160-64.
[107] Portner MM and Gracie WA : Rheumatoid lung disease with cavitary nodules, pneumothorax and eosinophilia. 'n 1 J Med 1966; 275: 697.
[108] Prakash A, Jarvis B. : Leflunomide : a review of its use in active rheumatoid arthritis. Drugs 1999 Dec; 58(6) :1137-64.
[109] Rains CP, Noble S, Faulds D : Sulfasalazine: a review of its pharmacological properties and therapeutic efficacy in the treatment of rheumatoid arthritis. Drugs 1995 Jul; 50: 137-56.
[110] Ramakrishnan S : Imaging in Rheumatoid arthritis. ln Sidharath Kumar Das editor. Rheumatoid arthritis 1ndian College of Physicians. Technical series : 1" edition 2001 : 25-27.

[111] Rask MR : Achilles tendon rupture owing to rheumatoid disease. JAMA.1978; 239:435-36.
[112] Ringertz B, Petersson 1 : Leflunomide -the first specific diseasemodifying drug against rheumatoid arthritis. Lakanidningen 2001 Feb 7; 98(6):566-7.
[113] Rubbins pathologic basis of disease. 5"' edition, W.B. Saunders company, Philadelphia, 1994: 1249.
[114] Salisburry MD and Nottage WM : A new evaluation of gross pathologic changes and concepts of rheumatoid articular cartilage degeneration. Clin Orthop Rel Res 1985; 199: 243.
[115] Schattenkirchner M : The use of leflunomide in the treatment of rheumatoid arthritis : an experimental and clinical review. Immunopharmacology 2000 May ; 47(2-3):291-8.
[116] Schiff MH, Strand V, Oed C and Loew Friedrich 1 : Leflunomide:Efficacy and safety in clinical trials for the treatment of rheumatoid arthritis. Drugs of today 2000; 36(6) ; 383-394.
[117] Schumacher HR. Palindromic onset of rheumatoid arthritis. Arthritis Rheum_1982; 25: 361.
[118] Scott DL : Leflunomide improves quality of life in rheumatoid arthritis. Scand J Rheumatol Suppl 1999; 112:23-9.
[119] Scott DL and Strand V : The effects of disease modifying antirheumatic drugs on the health assessment questionnaire score. Lessons from the leflunomide clinical trails database. Rheumatology (oxford) 2002: 41 (8) : 899-909.
[120] Scott D1,, Smolem IS, Kalden IR, et a1 : Treatment of active rheumatoid arthritis with leflunomide : two year follow up of a double blind, placebo controlled trial versus sulfasalazine,for .the European Leflunomide Studys group . Ann Rheum Dis 2001 Oct; 60(10): 913-23.
[121] Sharp IT, Strand V, Leung H, et al : Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trails of leflunomide in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 2000;43:495-505.
[122] Sheam MA, and Kang IY: Effect of age and sex on the erythrocyte sedimentation rate. I Rhem 1986; 13: 297.
[123] Shimoyama M, Ohtahara A, Fukui H, et a1 : Acute secondary gastrointestinal amyloidosis in a patient with rheumatoid arthritis. Am J Med Sci 2003', 326(3) '. 145.
[124] Silverstein FE, et a1 : Gastrointestinal toxicity with celecoxib vs NSAiDs for osteoarthritis and rheumatoid arthritis: the CLASS Study: a randomized controlled trial. JAMA 2000; 284 : 1247 55
[125] Silverstein FE, et al : Misoprostol reduces serious gastrointestinal complications in patients with RA receiving NSAle: Ann lntem Med 1995; 123:241-9.
[126] Simon LS and Yocum D : New and Future drugtherapies for rheumatoid arthritis. Rheumatology 2000; 39 (Suppl.l) : 36-42.
[127] Smolen JS : Efficacy and safety of the new DMARD leflunomide:comparison to placebo and sulfasalazine in active rheumatoid arthritis. Scand J Rheumatol Suppl 1999; 112: 15-21.
[128] Smolen JS, Breedveld FC, Eberl G, et a1 : Validity and reliability of the twenty eight joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995; 38: 38-43.
[129] Smolen JS, Emery P : Efficacy and safety of leflunomide in active rheumatoid arthiritis. Rheumatology 2000 Jun; 39 Suppl 1:48-56.
[130] Smolen JS, Kalden JR, Scott DL. et al : Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind, randomized, multicentre trial. European leflunomide study group. Lancet. 1999; 353: 259-66.
[131] Strand V, Cohen S, SchifT M, et al : Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch I Intern Med 1999 ; 159: 2542-50.
[132] Strand V, Tugwell P, Bombardier C, et al 1 Function and healthrelated quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Arthritis Rheum 1999; 42 : 1870-8.
[133] Stucki G, Langenegger T : Management of rheumatoid arthritis. Curr Opin Rheumatol 1997 May; 9(3) 2 229-35.
[134] Sturrock RD, et a1 : The forgotten nodule: Complications of sacral nodules in rheumatoid arthritis. Br Med J 1975; 2:92.
[135] Sugimoto H, Takeda A, Masuyama J, Furusc M : Radiology 1996; 198: 185-92.
[136] Taha AS, Hudson N, Hawkey C], et a1 : Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal anti-inflammatory drugs. N Engl J Med 1996; 334: 1435 9.
[137] Tigbe H and Carson DA: Rheumatoid factor. In : Textbook of Rheumatology, Eds. WN Kelly, S Rubby, ED Harris, CB Sledge, 6'" ed. 2001; 151-60.
[138] Turesson C, O' Fallon WM, Crowson CS, et a1 : Extra articular disease manifestations in rheumatoid arthritis incidence trends and risk factors over 46 years. Ann Rheum Dis 2003; 62: 722-27.
[139] Van der Heide A. et al : The effectiveness of early treatment with "second-line" antirheumatic drugs: a randomized, controlled trial. Ann Intern Med 1996; 124: 699-707.
[140] Vidigal E, Jacoby R, Dixon A St J,et al : The foot in chronic rheumatoid arthritis. Ann Rheum Dis.l975 34: 292-97.
[141] Wanchu A : Joint involvement in rheumatoid arthritis. 1n Sidharath Kumar Das editor. Rheumatoid arthritis Indian College of Physicians. Technical series : 1" edition 2001 : pp 19-20.
[142] Wanchu A, Suri L, Deodhar SD, et a1 : Extra articular Manifestations among North Indian Patients with Rheumatoid Arthritis. JIRA 1997; 5:75-77.
[143] Weaver A, Caldwell .1, Olsen N, et al : Treatment of active rheumatoid arthritis with Ietlunomide compared to placebo for methotrexate. Arthritis Rheum 1998 Sep; 41 Suppl: 8131.
[144] Weinblatt ME, Kremer IM. Coblyn JS, et al : Pharmacokinetics, safety and efficacy of combination treatment with methotrexate and letlunomide in patients with active rheumatoid arthritis. Arthritis Rheum 1999; 42: 1322-8.

[145] Whelton A : Nephrotoxicity of NSAIDs : Physiologic foundations and clinical implications. Am J Med 1999; 106 suppl Sle3S-24S.
[146] Wingrave SJ and Kay CR : Reduction in incidence of rheumatoid arthritis associated with oral contraceptives. Lancet 1: 569, 1978.
[147] Wolfe P, Vander Heijde DM, Larson A : Assessing radiographic status of rheumatoid arthritis: Introduction of a short erosion scale. J Rheumatol 2000; 27(9); 2090-9.
[148] Wolfe MM, Lichtenstein DR, Singh G : Gastrointestinal toxicity of NSAIDs . N Engl J Med 1999; 340: 1888 99.
[149] Wood J : Rheumatoid Arthritis: Management with DMARDs. Pharmaceutical J. 1999; 263:162-167.
[150] Kraan MC, Smeets TJ, van Loon MJ, Breedveld FC, Dijkmans BA, Tak PP. Differential effects of leflunomide and methotrexate on cytokine production in rheumatoid arthritis. Annals of the rheumatic diseases. 2004 Sep 1;63(9):1056-61.
[151] Kraan MC, Reece RJ, Barg EC, Smeets TJ, Farnell J, Rosenburg R, Veale DJ, Breedveld FC, Emery P, Tak PP. Modulation of inflammation and metalloproteinase expression in synovial tissue by leflunomide and methotrexate in patients with active rheumatoid arthritis: Findings in a prospective, randomized, double-blind, parallel-design clinical trial in thirty-nine patients at two centers. Arthritis & Rheumatism. 2000 Aug 1;43(8):1820-30.
[152] Weinblatt ME, Kremer JM, Coblyn JS, Maier AL, Helfgott SM, Morrell M, Byrne VM, Kaymakcian MV, Strand V. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis & Rheumatism. 1999 Jul 1;42(7):1322-8.