www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i7.169

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Research Article

Use of Non Biologic DMARD in Rheumatoid Arthritis with Emphasis on Leflunomide

Authors
Jacob Antony[1], Ajith S.N[2]
[1]Additional Professor, [2]Assistant Professor
Department of Medicine, Government Medical College, Thiruvananthapuram, Kerala, India
*Corresponding Author
Ajith S.N
Department of Medicine, Government Medical College, Thiruvananthapuram, Kerala, India
Phone (Mobile) No.: +919446551478, Email: *drajithsn@gmail.com*

ABSTRACT
Background: *Being the commonest rheumatoligical disease the treatment of rheumatoid arthritis requires optimisation. The use of disease modifying medications in rheumatoid arthritis needs particular emphasis. Many patients presents late with deformities resulting in significant morbidity.*
Methods: *We conducted a prospective study involving 60 patients with active rheumatoid arthritis and a double blind comparison sub study in which outcome of treatment of 35 patients were analysed between methotrexate and leflunomide.*
Results: *The 60 patients studied were predominantly women (mean age, 52 years; mean disease duration, 4.5 years) The ACR response for patients receiving leflunomide treatment was 52% and that of methotrexate treatment was 48%. They were statistically equivalent, with mean time to initial response at 8.2 weeks for patients receiving leflunomide vs 9.1 weeks for patients receiving methotrexate therapy. X-ray analyses demonstrated less disease progression with both arms of the study. Common adverse events for patients receiving leflunomide treatment included gastrointestinal complaints, skin rash, and reversible alopecia.*
Conclusions: *Current treatments for rheumatoid arthritis (RA) include nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose steroids, and disease-modifying antirheumatic drugs (DMARDs). No currently available medication is uniformly effective, and all may cause significant adverse effects. The active control drug for this study, methotrexate, is considered to be the "gold standard" DMARD for the treatment of RA. Clinical responses following administration of leflunomide, a relatively new therapeutic agent for the treatment of RA, were statistically equivalent to those with methotrexate treatment. Both treatments improved signs and symptoms of active RA, delayed disease progression as demonstrated by x-ray films, and improved function and health-related quality of life.*
Keywords: *Rheumatoid arthritis, DMRD, Leflunomide, Methotrexate.*

INTRODUCTION

Rheumatoid arthritis is the commonest of the systemic connective tissue diseases in all population groups all over the world. Even though formerly it was generally thought that the disease is less common, less severe & less crippling in India, compared to what is seen in the western world, recent studies have definitely shown that

rheumatoid arthritis is a major cause of morbidity, disability and suffering in India also.

The proper scientific management of rheumatoid arthritis involves a properly planned multisystem comprehensive approach involving:

- Drugs
- Physical modalities
- Education & Counseling
- Surgery including joint replacement in advanced cases

Drug therapy itself involves the following group of medications:

- NSAID
- Steroids in selected indications
- DMARDs (Disease Modifying Anti-Rheumatic Drugs)

Adjuvants:

- Analgesics
- Hematinics
- Antidepressants

Other drug to control different incidental or complicating problems as and when they arise.

Even though for a long time the concept was to have a pyramid approach to drug therapy, reserving the use of DMARDs to quite advanced stage of disease, it is now proven beyond doubt that DMARDs to be started early and aggressively, even in combination, to induce a remission as early as possible and also to prevent irreversible joint & periarticular destruction and damage.

DMARDs are readily available in the Indian market but often they are used incorrectly, so that our patients often do not get the full benefit out of it

The different nonbiologic DMARDs currently in use are:

- ❖ Chloroquine & Hydroxy Chloroquine
- ❖ Sulphasalazine
- ❖ Methotrexate
- ❖ Leflunomide
- ❖ D-Penicillamine
- ❖ Cytotoxics
- ➢ Cyclophosphamide
- ➢ Azathioprine

The present study was undertaken to evaluate the use and abuse of different DMARDs in the treatment of patients of rheumatoid arthritis as observed among patients attending the Rheumatology Clinic of Medical College, Thiruvananthapuram.

REVIEW OF LITERATURE

Rheumatoid arthritis is a chronic multi-system disease of unknown aetiology affecting men & women at the prime of their lives. It is a chronic symmetrical inflammatory polyarthritis of the synovial joints of the body. A persistent inflammatory polyarthritis of at least 6 weeks duration with objective manifestation of joint inflammation, morning stiffness of greater than 1hr essential for its diagnosis.

The term systemic rheumatoid disease refers to patients with rheumatoid arthritis who have clinical or histological evidence of vasculitis or serositis or both. Vasculitis develop in almost any organ. Rheumatoid nodules, joint deformities & erosions are often present even though the arthritis may be inactive. The condition is associated with high titre of IgG Rheumatoid factor.

RA has a prevalence of about 0.68 - 0.75% in our population. About 75% of them are having mild non-persistent disease. Only 5-7% achieves remission on NSAIDs alone. The rest have progressive disease. At 10yrs from the onset of disease over 90% have some functional disability with 50% not able to continue in employment and 15% unable to carry out activities of daily living, life expectancy shortened by 3 - 15 years and patients with active rheumatoid arthritis likely to develop substantial damage in first 2 years after onset.

NSAIDs & Steroids only control the symptoms of the disease without any effect on the progressive destructive disease process. Therefore NSAIDs & steroids do not form the mainstay of treatment for RA. Treatment with DMARDs has shown significant benefits in treated patients as compared to those who not treated with it. It is thought that RA causes the most significant joint damage with

in the first two years after onset another reason why early diagnosis & appropriate treatment are critical. Untreated, RA can irreversibly damage joints leading to pain, stiffness, deformity, loss of function & long-term disability. It is therefore important to receive appropriate treatment as early as possible to try to prevent this.

Common DMARDs includes gold salts, methotrexate, Chloroquine, hydroxychloroquine, d-penicillamine, cyclophosphamide, chlorambucil, Azathioprine, sulphasalazine, cyclosporine, Levamisole, Dapsone, minocycline, leflunomide, mycophenolate mofetil & anti TNF therapies infliximab & Etanercept cyclosporine is now well established as an effective second line drug to treat RA.

Methotrexate has replaced gold as the front line drug for the management of RA. The drug is effective, safe & affordable. However, patient receiving MTX need close monitoring. Methotrexate affects both inflammatory and immunosuppressive aspects of response in Rheumatoid arthritis. It is clearly effective in the treatment of RA & may be able to decrease the rate of formation of new bony erosions and it is also effective in psoriatic arthritis. "Poor man's Gold" i.e., Chloroquine and slightly expensive sibling hydroxychloroquine are now available for wide use as DMARD.

Despite these advances and changed approaches to the drug treatment of RA, it must be understood that in the long term, the response to DMARD therapy in RA is far from optimum. This makes it mandatory to continue the search for the newer modalities for the optimum treatment for RA. The newer drugs includes leflunomide, mycophenolate mofetil, minocycline, TNF α antagonist namely Etanercept & infliximab. Stem cell transplants & Gene therapies as treatment modalities are in experimental stage.

A multidisciplinary approach is required for the management of patients with RA. Physical therapy & rehabilitation measures are must do not replace medical therapy. Deformity may require surgical correction. The only early surgical therapy of RA is synovectomy others including arthroplasty arthrodesis & joint replacement.

Since DMARDs and newer therapies are expensive and have higher potential of side effects it would be prudent to identify patients with higher risk of development of progressive destructive joint disease. A severe disease at onset, a higher and persistent Rheumatoid Factor positivity, a higher CRP & ESR, low Hb, presence of erosion at the time of the first diagnosis are important markers of poor prognosis. Patient with aggressive disease can be managed more optimally with combination of DMARDs.

RA is a systemic immune- inflammatory disease of unknown etiology with natural remission & relapses. In the absence of known etiological factors its cure remains elusive. Its present day treatment therefore is aimed at

1) Symptomatic control mainly of pain and stiffness.
2) Physical Measures to prevent deformities & disabilities to preserve joint junction.
3) Control / suppression of inflammation for arresting progressive joint damage.
4) Prevention of complication.
5) Surgical intervention for correcting the joint deformities, including arthroplasty.

As a first step, NSAIDs & Steroids are used for symptomatic relief simultaneously the immuno inflammation is suppressed using drugs that are slow acting compounds of diverse origin with immuno modulating & anti inflammatory properties (so called DMARDs / SAARDs - Slow Acting Anti Rheumatic Drugs).

Glucocorticoids (GC) are the best and the most powerful anti inflammatory drug known to human beings used judiciously and intermittently only for the period of acute inflammatory activity they can provide quick and dramatic relief of symptoms however if used for chronic inflammation over prolonged periods they can have devastating ill effects in almost all organ systems in the body.

Present day Rheumatologist use steroids for

1) A/c inflammatory flares (usually as IM or IV "pulse therapy")

2) As "bridge therapy" till the action of other DMARDs set in
3) Low dose prolonged therapy in combination with other DMARD especially Methotrexate.

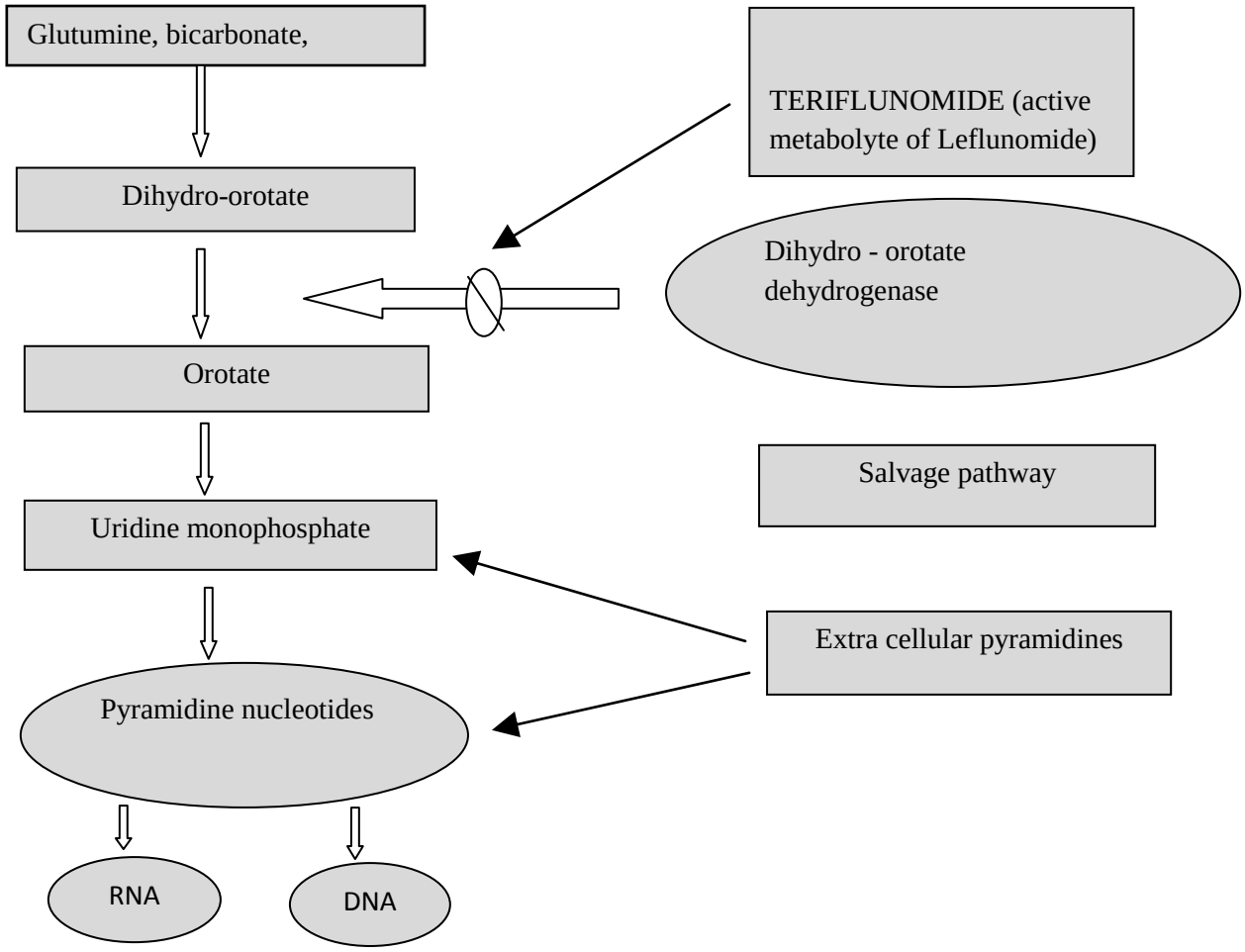
DMARD in RA

RA has traditionally been treated using the pyramid approach, in which NSAIDs first and DMARD relatively last in the disease. However this tenet is not valid any more. Timing is critical. The initiation of DMARD therapy should not be delayed beyond 3 months for any patients with an established diagnosis, who in spite of adequate treatment with NSAIDs has ongoing joint pain, significant morning stiffness. The goal of treatment is to intervene in the disease before joints are damaged. In RA joint damage occurs early in its course. This realization has led to a change in the therapeutic strategy from go slow and go low to aggressive early treatment aimed both at symptomatic relief & preventing joint destruction & loss of function. Among the class of classical DMARDs a recent addition has been that of an inhibitor of pyramidine biosynthesis leflunomide.

Leflunomide

Leflunomide is a new DMARD that acts principally as a denovo inhibitor of pyramidine synthesis thus prevents proliferation of activated T-lymphocytes and has antiproliferative activity. Following oral administration, it is rapidly metabolized to Teriflunomide - the active metabolite. Due to the long plasma half - life, 15 - 18 days, loading dose are required to achieve steady state concentration.

Mechanism of Action



Leflunomide - loading dose - 100mg/day for 3 days
Maintenance dose - 20mg once daily
Since teriflunomide is extensively protein bound & cleared via metabolic pathway through biliary secretion it should be administrated very cautiously in patients with hepatic dysfunction.
Side effects - Abdominal pain, anorexia, oral ulcers.
Hypertension, transient thrombocytopenia and elevated liver enzyme.
Contraindicated in pregnancy and lactation.

2015 Guidelines for the Management of RA - (American College of Rheumatology)

Goal of RA Management

- Control of joint damage
- Decrease pain
- Prevent loss of function
- Complete remission - absence of following

1) Symptoms of active inflammatory joint pain
2) Morning stiffness
3) Fatigue
4) Synovitis on joint examination
5) Progression of radiographic damage on sequential X-ray
6) Elevation of ESR or CRP level.

Guidelines for DMARD use in RA

It is strongly recommended to use a treat-to-target strategy rather than a nontargeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices.

Recommendations for Early RA Patients

For disease-modifying antirheumatic drug (DMARD)-naïve patients with early, symptomatic RA, it is strongly recommended to use DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity and DMARD monotherapy is conditionally recommended over double or triple DMARD therapy in patients with moderate or high disease activity. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease.

For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), treatment with a combination of DMARDs or a TNFi or a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, is recommended rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to superior efficacy.

For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, adding low-dose glucocorticoids (defined as ≤10 mg/day of prednisone or equivalent) is conditionally recommended. Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favourable as long as the dose is low and the duration of therapy is short.

For patients experiencing a flare of RA, we conditionally recommend adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient.

Recommendations for Established RA Patients

For DMARD-naïve patients with low disease activity, DMARD monotherapy over a TNFi is strongly recommended. For DMARD-naïve patients with moderate or high disease activity, DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib is conditionally recommended. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease.

For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, combination DMARDs or adding a

TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate) in no particular order of preference is strongly recommended, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy.

For moderate or high disease activity despite TNFi therapy in patients currently• not on a DMARD, adding one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone is strongly recommended.

2010 ACR/EULAR Classification Criteria for RA

To be classified as 'definite RA' requires the confirmed presence of synovitis in at least one joint, the absence of an alternative diagnosis for the observed arthritis, and a total score of at least 6 from the individual scores in four domains:

Number and site of involved joints (range 0–5),

Serological abnormalities (range 0–3),

Elevated acute-phase response (range 0–1), and

Symptom duration (two levels; range 0–1).

The classification criteria are summarized in Table 1.

Table 1. The 2010 ACR/EULAR classification criteria for rheumatoid arthritis

Score	
Target population (who should be tested?): patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)	
2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2−10 large joints	1
1−3 small joints (with or without involvement of large joints)	2
4−10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1

D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

ACPA, anticitrullinated protein antibodies; CRP, c-reactive protein; ESR, erthytrocyte sedimentation rate; RF, rheumatoid factor.

AIMS OF STUDY

1) To evaluate the pattern of use by different segments of medical practitioners with respect to the already available DMARD in RA.
2) Double blind prospective comparison study of the new DMARD - Leflunomide.

MATERIALS AND METHODS

Study Population & Design

Hospital based prospective study of 60 patients meeting the inclusion criteria. Who attended the Rheumatology OPD. Medical College, TVPM.

Inclusion Criteria

Male & female aged 18 to 75 years with active RA.

Exclusion Criteria

1. Pregnancy and lactating mothers
2. American College of Rheumatology functional class IV
3. Uncontrolled DM / CAD / IBS; active pepatientic ulcer, malignancy, terminal illness major traumatic injury.
4. H/o other inflammatory joint disease eg: MCTD, SSA, Psoriatic arthropathy Reiter's Syndrome. SLE, Sarcoidosis.
5. HIV+ve / immuno deficiency state.

Methods

Data Collection

The study was conducted over a period of 18 months during 2009 - 2010.

Age, sex, occupation, a detailed history, duration of illness, h/o DM / HTN / CAD / tuberculosis, h/o alcoholism & detailed drug history with duration of treatment were assessed.

Family h/o arthritis, a through physical examination including ht / wt, joint examination & other system examination were done.

Laboratory parameters which include hematology, biochemistry, urine analysis, serology, Rheumatoid factor urine pregnancy test, ECG, X-ray were done.

Rheumatoid evaluation includes

- Tender joint count (TJC) by 28 joints
- Swollen joint count by 28 joints
- Patients general health assessment using visual analog scale(S)
- Duration of morning stiffness
- Pain intensify assessment using VAS
- Patient global assessment using VAS

Comparison Study of Leflunomide

Study design for Leflunomide

Double blind prospective comparison study of 35 patients with active RA.

The duration of active treatment phase is 16 weeks followed by a post treatment observation of 6 weeks.

Two treatment groups

Leflunomide, oral tablets

Loading dose - 100mg / day x 3days

Maintenance dose - 20mg OD

Methotrexate oral tab - 7.5mg/wk

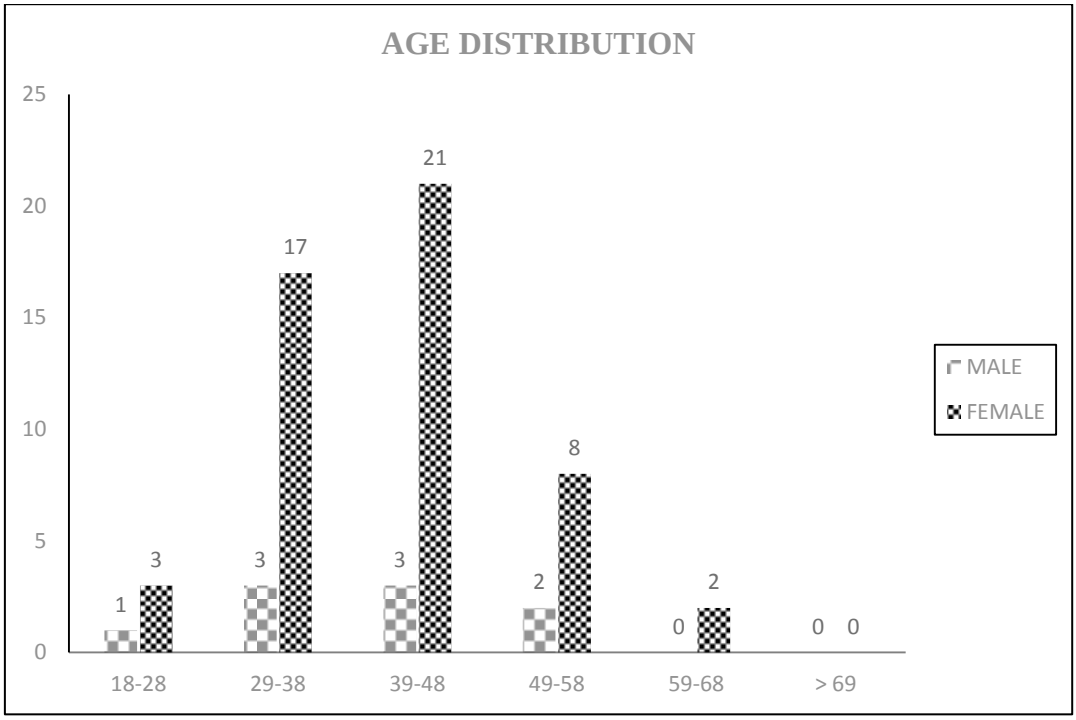
In addition all patient will receive oral folate supplementation 1mg / day.

RESULTS AND OBSERVATION

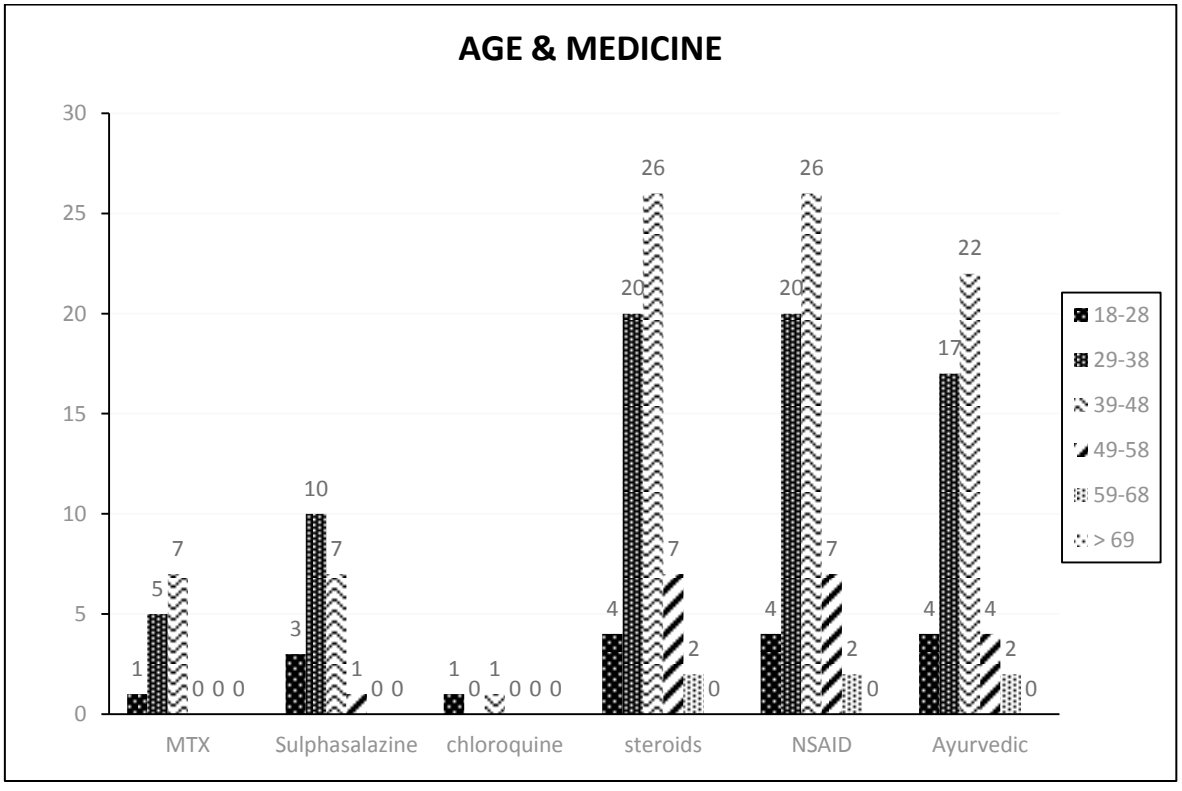
60 patients of RA, meeting the inclusion criteria were included in the study.

Personal Data

Age



Age and Medications



SEX

Male female ratio of cases

	No. Of cases	
Total	60	Percentage
Male	9	15
Female	51	85

Response to treatment

Rheumatological evaluation done on each visit:

1) Tender joint count (28)
2) Swollen joint count
3) Patients general health assessment using VAS
4) ESR
5) Patients global assessment using VAS
6) Pain intensity assessment using VAS
7) Duration of morning stiffness

Disease activity is assessed according to the above parameters

GOOD RESPONSE	
MODERATE RESPONSE	
	NO RESPONSE

Analysis of baseline data

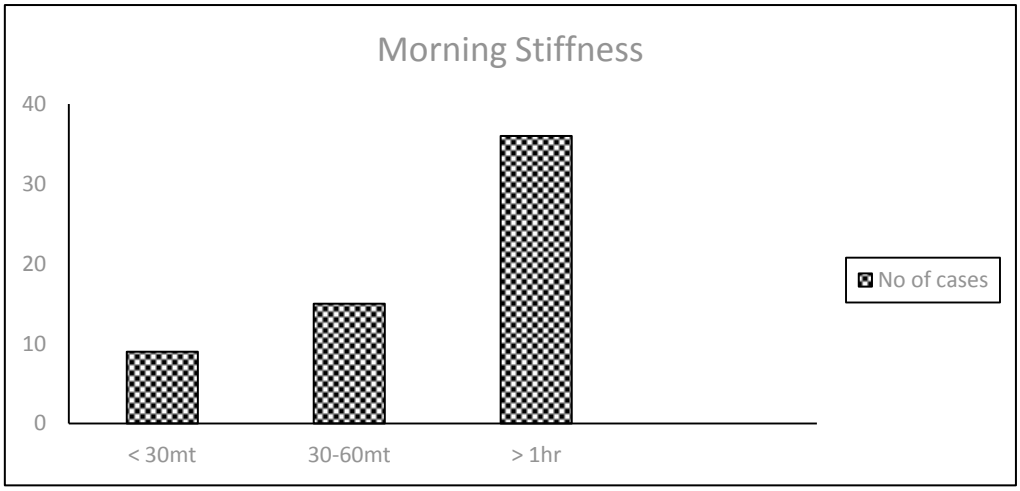
Age / sex / disease duration, morning stiffness.

No: of patient on MTX, SLZ / chl / steroids / NSAID, Leflunomide

Symptoms

Joint pain present in all patients (100%)

Morning stiffness



Swelling & tenderness of joint present in almost all joints in the body - PIP / MCP / wrist / elbow/ knee / ankle / MTP.

Other symptoms

	No. Of cases	Percentage
Fever	32	53
Alopecia	36	60
Wt loss	12	20
Anorexia	12	20
Fatigue	15	25

Lab Investigations

	NO. Of cases	%
Rheumatoid Factor	32	53
CRP	36	60

Change in Clinical / Laboratory Outcome Parameters

Characters		Leflunomide Group	Methotrexate Group
1.Joint Count (Range,0-28) Definite Arthritis (Tender and swollen)	Baseline	13,7 ± 5.8	13.0 ± 5.7
	Mean Change	-5.7 ± 6.5	-5.2 ± 5
2.Global Assessment of Disease Activity (VAS)	Baseline	5.6 ± 2.3	5.9 ± 1.7
	Mean Change	-2.8 ± 2.7	-2.4 ± 2.5
3. ESR, mm/hr	Baseline	38.0 ± 26.8	32.6 ± 25.4
	Mean change	-5.2 ± 20.7	-5.5 ± 21.6
4.CRP, mg/dL	baseline	2.03 ± 2.50	1.58 ± 1.78
	Mean change	-0.52 ± 2.45	-0.70 ± 1.78

DISCUSSION

This study is based on analysis of 60 patients with clinical features of rheumatoid arthritis belonging to the age of 18 - 70 yrs who were treated with different types of DMARDs. The study incorporated information related to personal date, symptoms & signs drugs used in the treatment of RA, response to treatment & laboratory parameters in these patients.

Personal Data

Of the 60 patients, 51 (81%) were females & 9 (15%) were males, maximum number of cases were between the age group of 39 - 48 yrs. i.e 24 patients (40%) & next age group is 29 - 38 yrs 20 patients (33%). The disease is very rare age of 60, between the age group of 49 - 58 it is 16.6%, between the age group of 18 - 28 yrs it is 6.6% & between the age group of 59 - 68 yrs it is 3.3%.

Symptoms / Signs

All patients were joint pain. The common joint involved are Proximal Interphalangeal joint, Metacarpophalangeal joint, Wrist, Knee joints. 60% of these patients have alopecia as an associated symptoms 53% of these patients were associated with fever. 25% having fatigue & 20% have anorexia & weight loss. Majority of the patients 36 (60%) having morning stiffness of > 1hr and with joint swelling & tenderness, 25% patients has morning stiffness between 30 - 60 mnts & 15% has < 30mnt.

Laboratory Investigation

60% of these patient has C-reactive protein +ve & 53% rheumatoid factor +ve.

Treatment

Of the 60 patients, 59 patients (98%) were using prednisolone 20mg OD along with NSAID indomethacin 25mg tds; 49 patients (81%) were using Ayurvedic medicines, 21 patients (35%) were using NSAID & sulphasalazine. 13 patients (21%) were using NSAID daily & methotrexate 7.5mg per week. 2 patients (3%) were using Chloroquine + NSAID.

Almost all patients were having pain & swelling of PIP, MCP & wrist joint involvement before treatment and after treatment with prednisolone, sulphasalazine, methotrexate, indomethacin, 80% of joint inflammation subsided maximum subsidence rate is seen in PIP, elbow, MCP joints. Joints which shows some resistance to DMARDs / steroids are knee joints & wrist joints.

Fever, weight loss, anorexia & fatigue improved after treatment

SUMMARY & CONCLUSION

- Sulphasalazine, Methotrexate and Chloroquine were the most commonly used DMARD in the treatment of RA.
- Leflunomide is a new DMARD, found to be effective among the patient population studied in the treatment of rheumatoid arthritis.

- Initiation of DMARDs early in the course of RA slows disease progression more effectively than their initiation late in the disease course, unfortunately 80% patient studied have received DMARD after established deformities had settled.
- Complete remission was observed with 25 - 35% of the study population.
- The side effects of leflunomide observed in this study are Aphthous ulcer, Nausea, Vomiting, Abdominal discomfort, Diarrhea, Alopecia, Headache.
- Side effects of other DMARD observed were as follows:

■ Chloroquine - nausea & skin ulcers
■ Sulphasalazine - allergy in three patients
■ D-penicillamine - albuminuria in one patient
■ Methotrexate - elevation of liver enzyme in 5 patients

The following were the mistakes in the use of DMARDs observed among the patients included in the study

1) In sufficient dosage - often under dosage.
2) Sufficient time interval is not given for these essentially slow acting drugs to produce an identifiable effect upon the disease.
3) Proper monitoring for potential toxic effects is not done.
4) As DMARDs cannot produce immediate symptoms relief, during the initial period while waiting for the DMARDs to start acting, sufficient suppression of inflammation by NSAID is needed. Many a time this aspect is neglected.

REFERENCES

1. Silva HTMorris RE Leflunomide and the malanonitriloamides. Am J Med Sci. 1997;313289- 301.
2. Ward MMFries JF Trends in antirheumatic medication use among patients with rheumatoid arthritis, 1981-1996. J Rheumatol. 1998;25408- 416.
3. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356-361
4. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-1588
5. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359:1173-1177.
6. O'Dell JR. Treatment of rheumatoid arthritis. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, eds. Kelley's textbook of rheumatology. 9th ed. Philadelphia: Elsevier, 2013:1137-60..
7. Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken)2012;64:625-639.
8. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-975[Erratum, Ann Rheum Dis 2011;70:1519.]
9. Lipsky PE, van der Heijde DMFM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-1602.
10. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-324
11. Felson DT, Anderson JJ, Boers M, et al. Preliminary definition of improvement in

rheumatoid arthritis. Arthritis Rheum 1995;38:727-735

12. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med 2004;350:2167-2179
13. Krishnan E, Fries JF. Reduction in long-term functional disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. Am J Med 2003;115:371-376
14. Tsakonas E, Fitzgerald AA, Fitzcharles MA, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the Hydroxychloroquine in Early Rheumatoid Arthritis (HERA) study. J Rheumatol 2000;27:623-629
15. Moreland LW, O'Dell JR. Glucocorticoids and rheumatoid arthritis: back to the future? Arthritis Rheum 2002;46:2553-2563.