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COMPARATIVE EFFECTIVENESS OF METHOTREXATE HYDROXYCHLOROQUINE LEFLUNOMIDE ALONE AND IN COMBINATION IN THE TREATMENT OF EARLY RHEUMATOID ARTHRITIS WITH CONCURRENT ADMINISTRATION OF LOW DOSE CORTICOSTEROID

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic disabling inflammatory arthritis, which is associated with significant morbidity and increased mortality. Disease severity is based on the number of joints involved and the extent of pain associated with it and how it affects the daily life activities. The disease severity can be assessed using different calculators like DAS28, CDAI, SDAI, and RAPID 3. Different DMARD'S are used in the treatment of Rheumatoid Arthritis alone or in combination. Biologic DMARD'S are efficacious but are too costly and hence most often synthetic DMARD'S are used. The present study seeks to analyze the efficacy of different DMARD'S used alone or in combination, with simultaneous administration of low dose corticosteroid. The efficacy is assessed based on the ability of DMARD(S) to reduce the disease severity. The disease severity was assessed at baseline and at follow up after two months of initiation of therapy using RAPID 3 calculator.

KEYWORDS: Rheumatoid Arthritis(RA), Routine Assessment of Patient Index Data 3(RAPID 3) score, Methotrexate (MTX), Leflunomide (LFM), Hydroxychloroquine (HCQ).

INTRODUCTION

Rheumatoid Arthritis is a chronic, systemic inflammatory autoimmune disease distinguished by joint swelling and tenderness and destruction of synovial joints, leading to disability and premature death. The exact cause of RA is not known. Research has found that there are many possible causes, including.

- Genetics: People with family members who have RA may be more likely to get it.
- Hormones: Female hormones may play a role in the disease.
- Viruses or bacteria: RA may be related to viruses or bacteria.

Signs And Symptoms Of RA: Painful joints, Swollen joints, Stiffness in joints particularly in the morning, Low fever, Fatigue, Loss of appetite, Feeling weak, Lumps under the skin especially on the hands or elbows, Weight loss, Over time, decreased range of motion, Dry eyes and mouth.

Diagnosis: The current diagnostic criteria for RA require at least **six points** on a classification scale, and one positive, confirmed blood test, according to the American College of Rheumatology.

- Symptoms affecting one or more joints(up to 5 points)
- elevated erythrocyte sedimentation rate (ESR) (1 point)
- C-reactive protein (CRP)- which may indicate the presence of an inflammatory process in the body.(1 point)
- anti-cyclic citrullinated peptide (anti-CCP) antibodies(up to 3 points)
- Rheumatoid factor(up to 3 points)

Treatment: Includes use of biological and synthetic DMARDS, NSAIDS and low dose corticosteroids.

METHODOLOGY

Study site: ASIAN RHEUMATOLOGY CENTER, WARANGAL, TELANGANA
SRI MEDILIFE HOSPITAL, WARANGAL, TELANGANA.

Study design: A prospective questionnaire based study. It is an questionnaire based study involving assessment and reassessment of disease activity at baseline and at two months of initiation of therapy respectively.

Study period: 6 months (November 2018 to April 2019).

Sample size: 270 patients suffering from RA were considered and patient information was collected.

Study population: All patients diagnosed with Rheumatoid Arthritis according to ACR criteria.

Study criteria: The outpatients who were diagnosed with RA were enrolled into the study by considering following inclusion and exclusion criteria.

Inclusion Criteria

- Patients of either sex
- All patients must fulfil ACR classification criteria for Rheumatoid Arthritis
- All patients must have been 16 years of age or older at time of diagnosis of Rheumatoid Arthritis

Exclusion Criteria

- Sensitivity to study medications.
- Patients with osteoarthritis and other bone disorders.
- Patients who are unable to comply with study criteria.

Study procedure

The study is aimed at finding the efficacy of different DMARD'S in treatment of Rheumatoid Arthritis based on their ability to reduce the disease severity. Patients who were diagnosed with Rheumatoid Arthritis by the physician were taken into study. Initial assessment of the disease severity was made using RAPID 3 questionnaire. Patient data was collected in a Data Collection Form and patient was reassessed after two months of using of medication and disease severity was again assessed using RAPID 3 questionnaire. The data was mainly focused at the parameters which include Age, Sex, DMARD(S) used, ESR levels, WBC count and Hb levels. The patients were divided to seven groups based on the DMARD(S) used. The groups included three Monotherapy groups of MTX, HCQ and LFM, three dual combination groups of MTX+HCQ, MTX+LFM and HCQ+LFM and one triple combination group of MTX+HCQ+LFM. After collection of data relative decrease in the disease severity from baseline to two months treatment was calculated and efficacy of different DMARD'S was assessed based on their disease severity reducing capacity.

Sources of the data

All the relevant and necessary data was collected from the following:

- Patient Medication Chart.
- Patient Profile Form.
- Patient and Attendant Interview.

RESULTS

During the study period, a total number of 270 patients were reviewed. The roles of several factors were assessed in the study.

DISTRIBUTION OF PATIENTS ACCORDING TO AGE

Out of 270 patients participated in our study, majority of patients belonged to age group 41-50years.The distribution is as follows.

Table1: Age Wise Assessment.

AGE GROUP (Years)	NO. OF PATIENTS	PERCENTAGE (%)
21-30	20	7.40
31-40	73	27.03
41-50	85	31.48
51-60	68	25.18
61-70	22	8.14
71-80	02	0.74

The mean age was found to be **46.4±11.22, 45.6±11.23, 50.5±11.2** in total population, female and male populations respectively

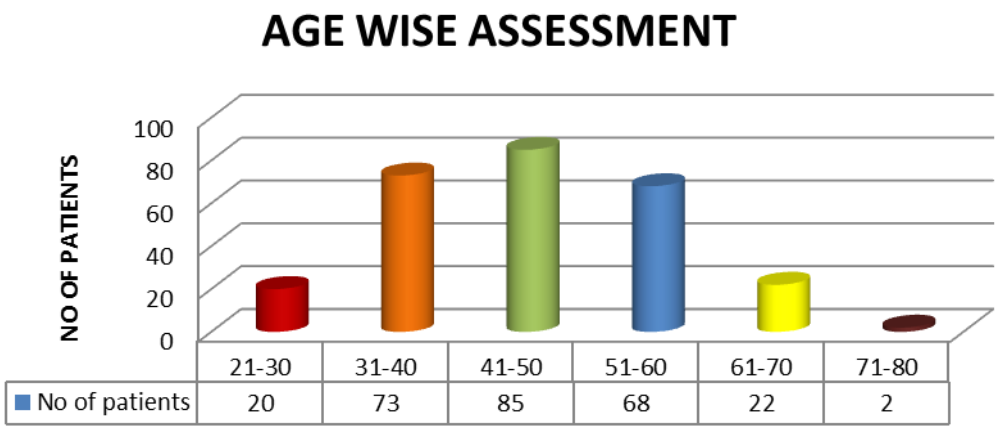


Fig 1: Age Wise Assessment Chart.

DISTRIBUTION OF PATIENTS ACCORDING TO GENDER

The prevalence of Rheumatoid Arthritis was considerable greater in women (82.2%) than in men (17.8) of total 270 patients participated in the study. The distribution is as follows:

Table 2: Gender Wise Assessment.

Gender	No.of patients	Percentage (%)
Male	48	17.8
Female	222	82.2

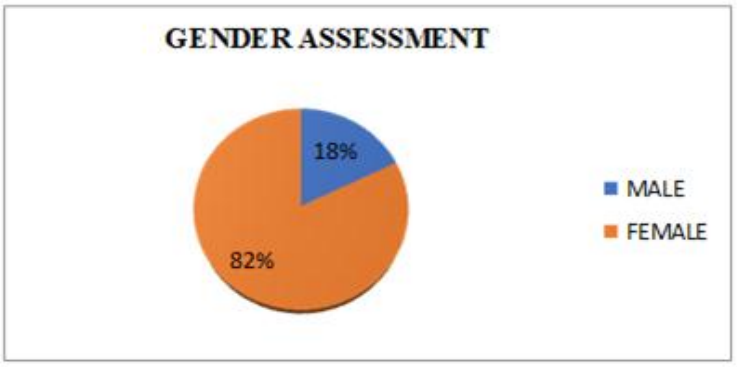


Fig 2: Gender Wise Assessment Chart.

POPULATION SEGGREGATION WITH REPSECT TO TREATMENT

Among 270 patients, 37 patients received Methotrexate monotherapy, 28 patients received Hydroxychloroquine monotherapy, 26 patients received Leflunomide monotherapy, 20 patients received a combination of Hydroxychloroquine + Leflunomide, 25 patients received a combination of methotrexate + Leflunomide, 78 patients received a combination of Hydroxychloroquine + Methotrexate and 56 patients received a triple combination of Methotrexate + Hydroxychloroquine + Leflunomide.

NOTE: All the patients received a low dose corticosteroid along with the above mentioned treatment plan.

Table 3: Treatment Seggregation.

DRUG	NO. OF PATIENTS	PERCENTAGE (%)
MTX	37	13.7
HCQ	28	10.37
LFM	26	9.62
MTX+HCQ	78	28.88
MTX+LFM	25	9.25
HCQ+LFM	20	7.40
MTX+HCQ+LFM	56	20.74

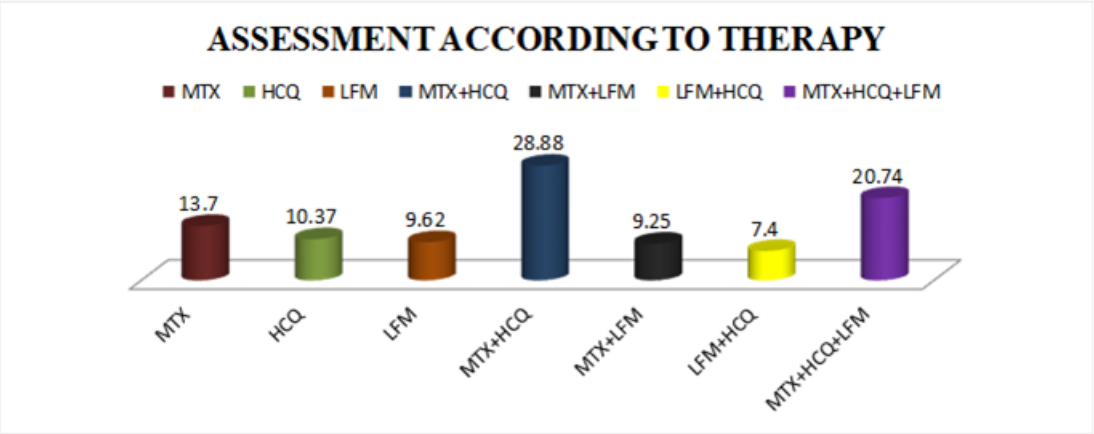


Fig 3: Population Seggregation Based On Therapy.

A. METHOTREXATE

- The reduction in RAPID-3 at the end of second month relative to the baseline is found to be 52.4%
- The percentage reduction in WBC relative to baseline is found to be 12.1%
- The percentage reduction in ESR relative to baseline is 9.31%
- The percentage improvement in HB relative to baseline is 27.79%
- The average of SGPT level at the end of second month is found to be 25.71 $\pm$ 4.402

Table 4: Assessment of Methotrexate Monotherapy.

PARAMETERS	MEAN	STANDARD DEVIATION
RAPID3 SCORE(I)	5.28	1.53
RAPID3 SCORE(F)	2.486	1.05
SGPT	25.721	4.4022
HB(I)	11.013	1.564
HB(F)	12.143	0.946
WBC(I)	10091.8	2718
WBC(F)	8871.6	2618.9
ESR(I)	74.51	24.03
ESR(F)	53.702	27.47
(I)=initial assessment i.e. at baseline (F) =final assessment i.e. at two months from baseline		

B. HYDROXYCHLOROQUINE

- The reduction in RAPID-3 at the end of second month relative to the baseline was found to be 51.4%
- The percentage reduction in WBC relative to baseline is found to be 13.86
- The percentage reduction in ESR relative to baseline is found to be 31.86%
- The percentage improvement in HB relative to baseline is found to be 8.59%

- The average of SGPT level at the end of second month is found to be 25.01±4.32

Table 5: Assessment of Hydroxychloroquine Monotherapy.

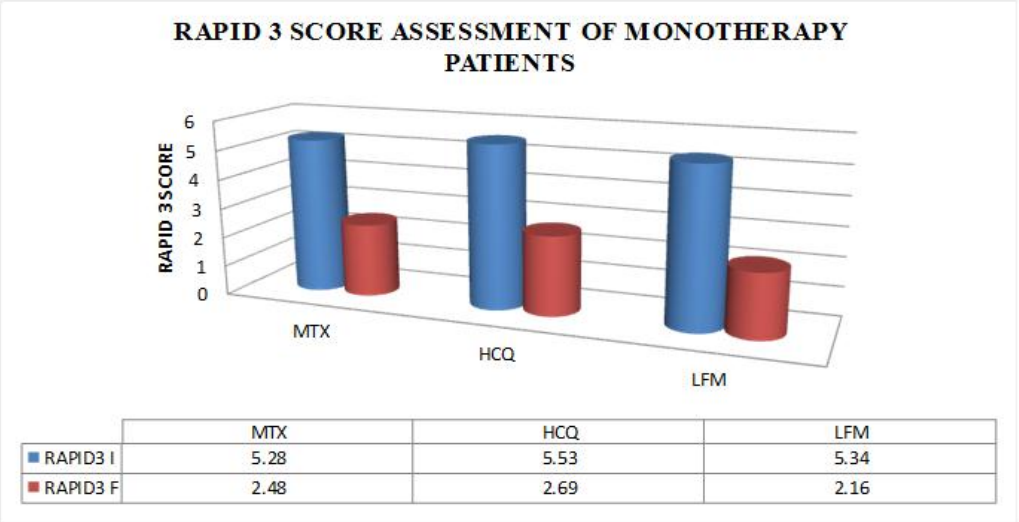
PARAMETERS	MEAN	STANDARD DEVIATION
RAPID3 SCORE(I)	5.53	1.53
RAPID3 SCORE(F)	2.69	1.04
SGPT	25.01	4.32
HB(I)	10.95	1.488
HB(F)	11.96	0.92
WBC(I)	10684.28	2741.4
WBC(F)	9203.5	2647
ESR(I)	78.42	24.19
ESR(F)	53.78	27.90
(I)=initial assessment i.e. at baseline (F) =final assessment i.e. at two months from baseline		

C. LEFLUNOMIDE

- The reduction in RAPID-3 at the end of second month relative to baseline is found to be 59.7%.
- The percentage reduction in WBC relative to baseline is found to be14.12%.
- The percentage improvement in ESR relative to baseline is found to be 12.68%.
- The percentage improvement in HB relative to baseline is found to be 11.39%. The average of SGPT level at the end of second month is found to be 25.76±3.51.

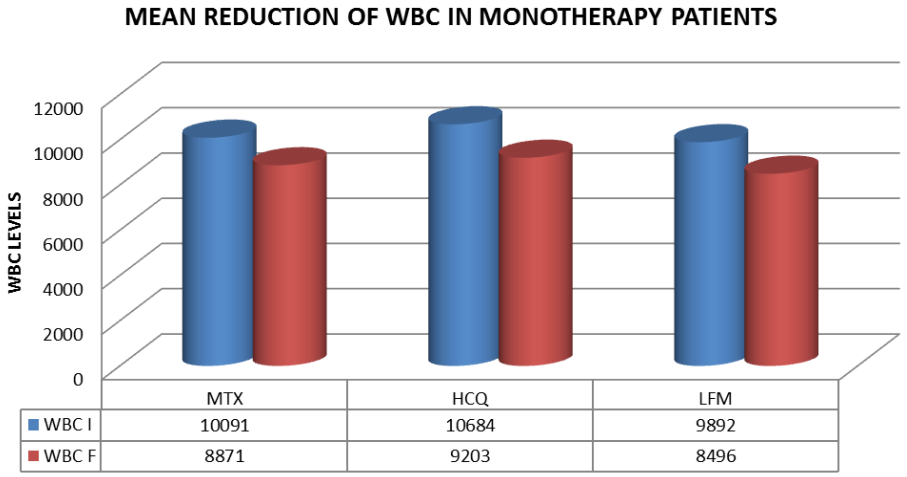
Table 6: Assessment of Leflunomide Monotherapy.

PARAMETERS	MEAN	STANDARD DEVIATION
RAPID3 SCORE(I)	5.348	1.18
RAPID3 SCORE(F)	2.16	0.869
SGPT	25.76	3.51
HB(I)	10.35	1.35
HB(F)	11.68	0.73
WBC(I)	9892	2193
WBC(F)	8496	2003.9
ESR(I)	81.44	19.79
ESR(F)	71.03	26.51
(I)=initial assessment i.e. at baseline (F) =final assessment i.e. at two months from baseline		



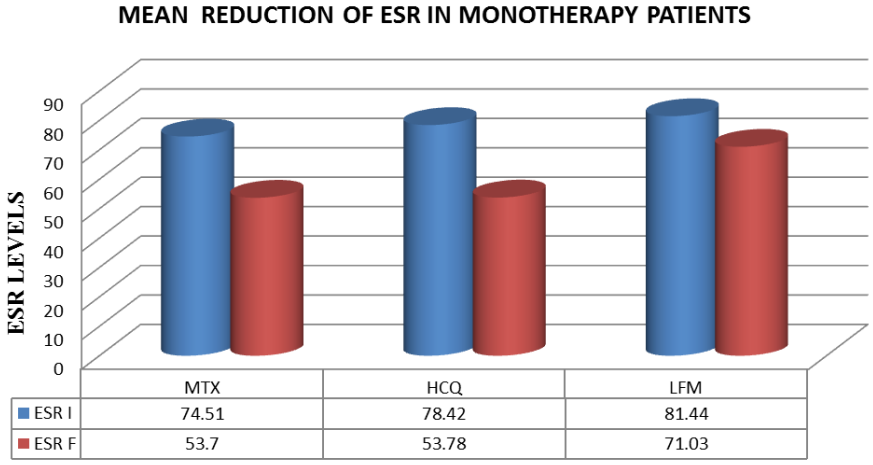
	MTX	HCQ	LFM
RAPID3 I	5.28	5.53	5.34
RAPID3 F	2.48	2.69	2.16

Fig 4: Assessment of Rapid 3 Scores In Monotherapy.



	MTX	HCQ	LFM
WBC I	10091	10684	9892
WBC F	8871	9203	8496

Fig 5: Assessment of Wbc Levels In Monotherapy.



	MTX	HCQ	LFM
ESR I	74.51	78.42	81.44
ESR F	53.7	53.78	71.03

Fig 6: Assessment Of Esr Levels In Monotherapy.

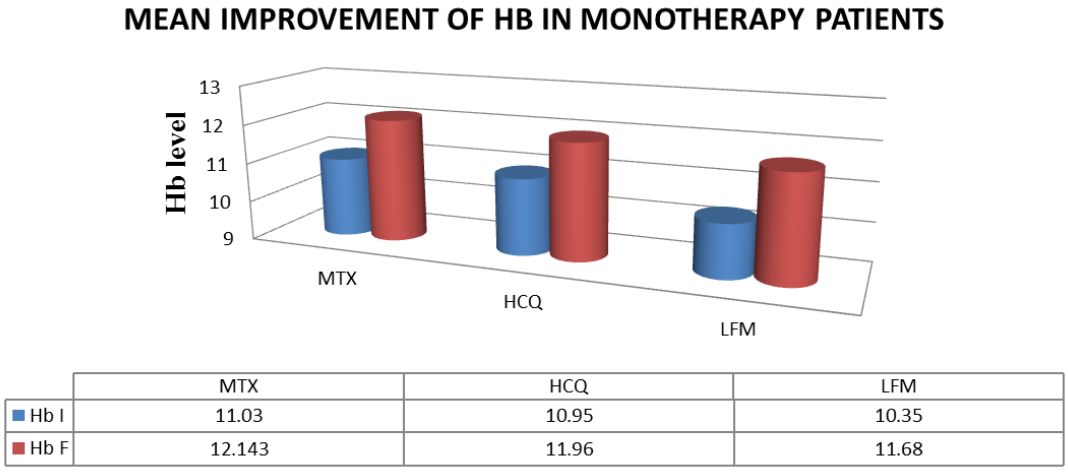


Fig 7: Assessment Of Hb Levels In Monotherapy

DUAL COMBINATION THERAPY

HCQ+MTX

- The reduction in RAPID-3 at the end of second month relative to baseline is found to be 49.65%
- The percentage reduction in WBC relative baseline is found to be13.3%
- The percentage improvement in ESR relative to baseline is found to be 31.8%
- The percentage improvement in HB relative baseline levels is 9.63%
- The average of SGPT levels were found to be 26.52±4.39

Table 7: Assessment of MTX + HCQ Therapy.

PARAMETERS	MEAN	STDEVIATION
RAPID3 SCORE(I)	5.5	1.55
RAPID3 SCORE(F)	2.769	1.060
SGPT	26.52	4.39
HB(I)	10.8	1.61
HB(F)	11.95	0.94
WBC(I)	10486.5	2722.2
WBC(F)	9084	2620.8
ESR(I)	95.8	23.9
ESR(F)	51.9	27.34
(I)=initial assessment i.e. at baseline (F) =final assessment i.e. at two months from baseline		

MTX+LFM

- The reduction in RAPID-3 at the end of second month relative to baseline is found to be 48.29%
- The percentage reduction in WBC relative to baseline is found to be 7.03%

- The percentage improvement in ESR relative to baseline is found to be 20.52%
- The percentage improvement in HB relative to baseline is 7.61%
- The average of SGPT levels were found to be 25.4±4.390.

Table 8: Assessment of MTX + LFM Therapy.

PARAMETERS	MEAN	STDEVIATION
RAPID3 SCORE(I)	5.244	1.524
RAPID3 SCORE(F)	2.712	1.00
SGPT	25.4	4.390
HB(I)	11.024	1.693
HB(F)	11.932	0.989
WBC(I)	9972	2751
WBC(F)	9271	2606
ESR(I)	73.88	23.97
ESR(F)	58.72	26.96
(I)=initial assessment i.e. at baseline **(F) =final assessment i.e. at two months from baseline**		

HCQ+LFM

- The reduction in RAPID-3 at the end of second month relative to baseline is found to be 45.92%.
- The percentage reduction in WBC relative to baseline is found to be 10.43%.
- The percentage improvement in ESR relative to baseline is found to be 24.84%.
- The percentage improvement in HB relative to baseline is 5.93%.
- The average of SGPT levels were found to be 26.2±4.15.

Table 9: Assessment of HCQ + LFM Therapy.

PARAMETERS	MEAN	STDEVIATION
RAPID3 SCORE(I)	4.16	1.55
RAPID3 SCORE(F)	2.25	1.055
SGPT	26.2	4.15
HB(I)	11.245	1.47
HB(F)	11.985	0.90
WBC(I)	10932	2755
WBC(F)	9792.7	2649.7
ESR(I)	76.5	23.89
ESR(F)	57.5	27.777
(I)=initial assessment i.e. at baseline **(F) =final assessment i.e. at two months from baseline**		

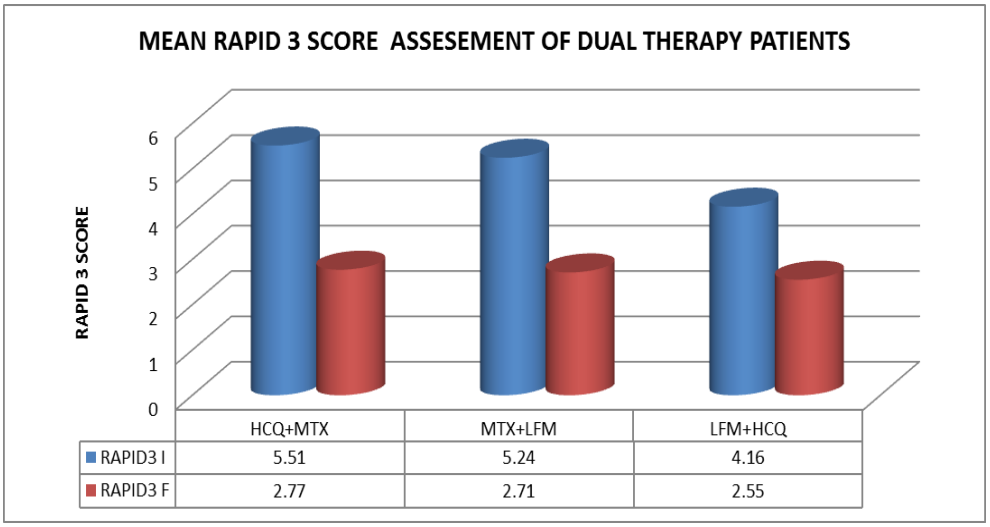


Fig 8: Assessment of Rapid 3 Scores In Dual Therapy.

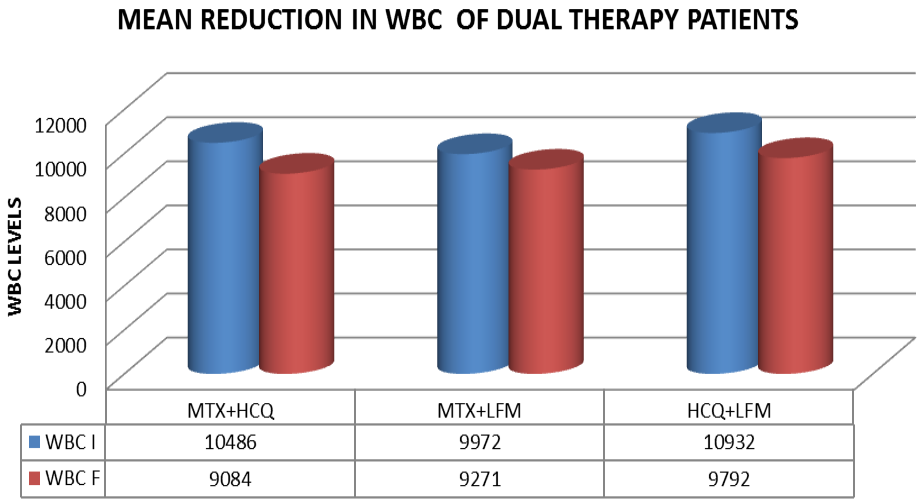


Fig 9: Assessment of Wbc Levels In Dual Therapy.

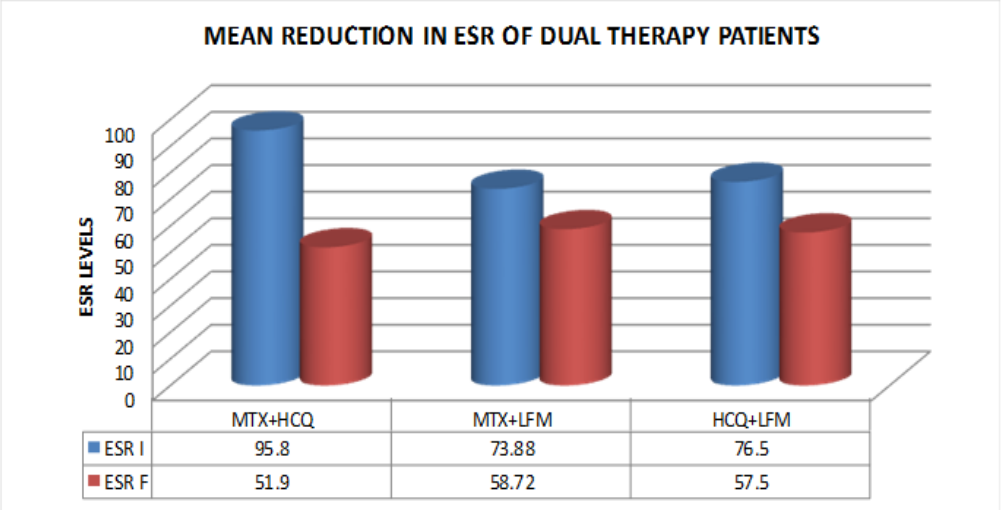


Fig 10: Assessment of Esr Levels In Dual Therapy.

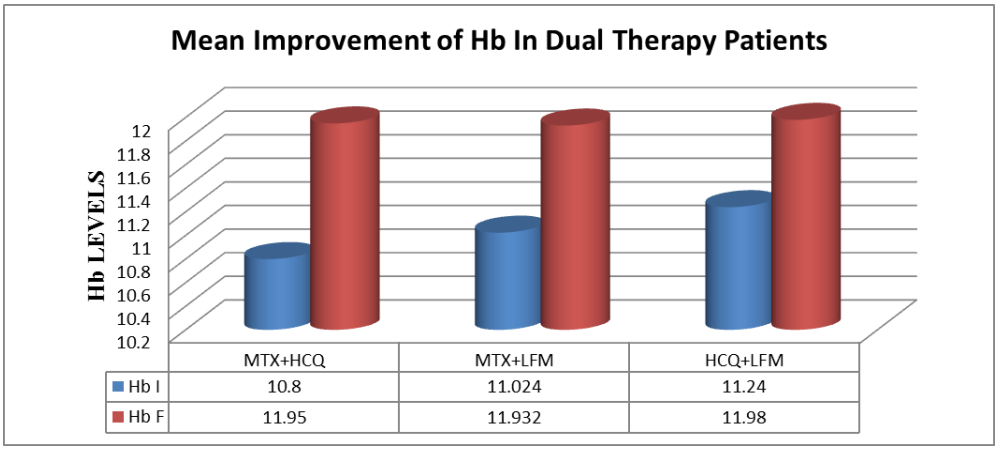


Fig 11: Assessment of Hb Levels In Dual Therapy.

TRIPLE COMBINATION THERAPY

HCQ+LFM+MTX

- The reduction in RAPID-3 at the end of second month relative to baseline is found to be 62.85%
- The percentage reduction in WBC relative to baseline levels is found to be 6.1%
- The percentage improvement in ESR relative to baseline level is 28.59%
- The percentage improvement in HB relative to baseline levels was 6.85%
- The average of SGPT levels were found to be 25.94±4.373.

Table 10: Assessment of LFM + HCQ + MTX Therapy.

PARAMETERS	MEAN	STDEVIATION
RAPID3 SCORE(I)	4.16	1.55
RAPID3 SCORE(F)	2.25	1.055
SGPT	26.2	4.15
HB(I)	11.245	1.47
HB(F)	11.985	0.90
WBC(I)	10932	2755
WBC(F)	9792.7	2649.7
ESR(I)	76.5	23.89
ESR(F)	57.5	27.777
(I)=initial assessment i.e. at baseline **(F) =final assessment i.e. at two months from baseline**		

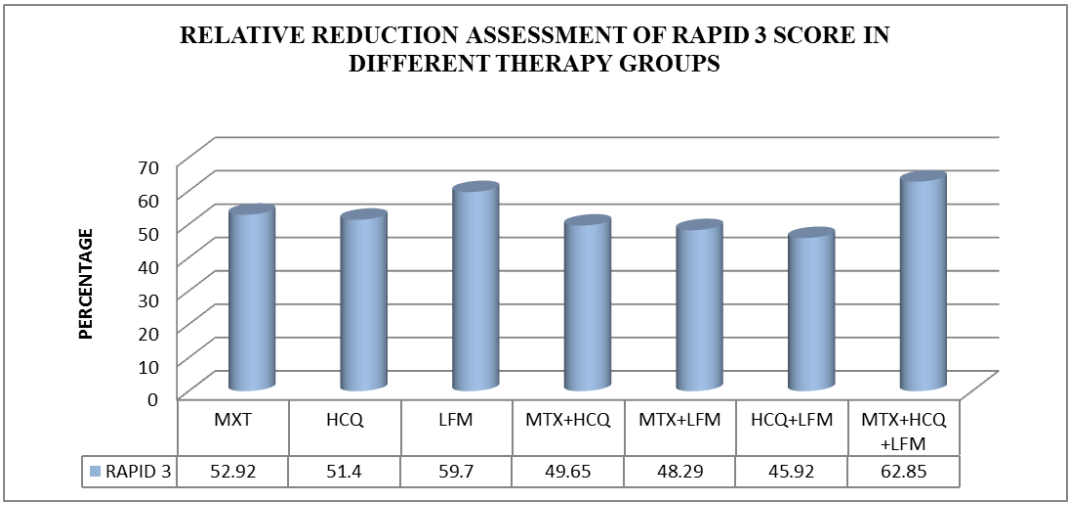


Fig 12: Assessment Of Rapid 3 Scores In Different Therapy Groups

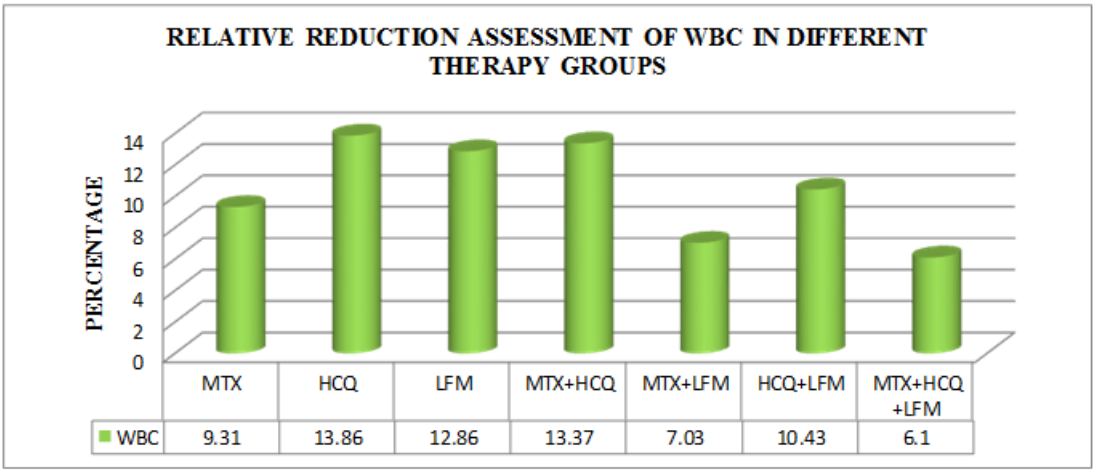


Fig 13: Assessment Of Wbc Levels In Different Therapy Groups

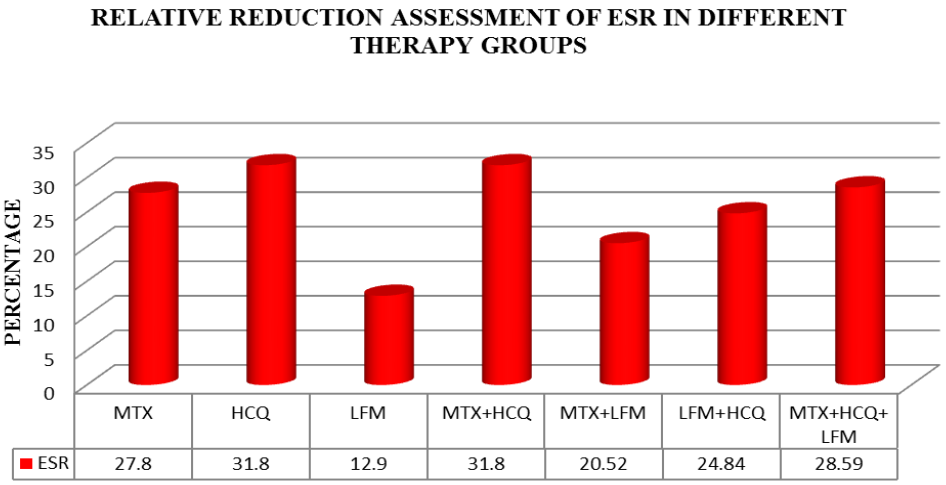


Figure 14: Assessment Of Esr In Different Therapy Groups

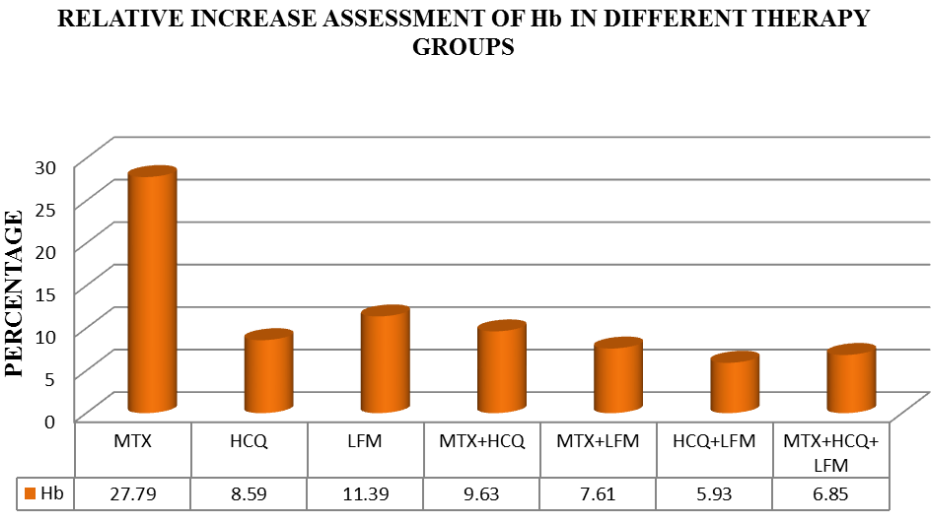


Fig 15: Assessment Of Hb In Different Therapy Groups

DISSCUSSION

Rheumatoid arthritis is an inflammatory pain associated with joint. Although till recently NSAIDS have been the choice of treatment for RA, with the increase in use of DMARDS has pushed back the use of NSAIDS. Moreover long term use of NSAIDS is not preferred due to their complications. Biologics though efficient are used relatively less because of their higher costs.

The prevalence of Rheumatoid Arthritis was considerably greater in women than in men. The male to female ratio was found to be 1:5 the reason for this is assumed to be the autoimmune condition hypothyroidism which is seen relatively much higher in women than men.

Total patients participated in our study are 270 and were divided into seven groups based on the treatment they received. The study assessed effectiveness of different DMARD'S used in the treatment of Rheumatoid Arthritis. The groups include 3 groups of patients receiving monotherapy i.e. Methotrexate Hydroxychloroquine Leflunomide alone. 3 groups of patients receiving dual combination therapy of the drugs i.e. MTX+HCQ, MTX+LFM, HCQ+LFM. and the last group receiving triple combination i.e. MTX+HCQ+LFM.

In the patients receiving Monotherapy it was found that the relative decrease in the disease activity from baseline to the end of second month of initiation of therapy was higher in the group receiving Leflunomide followed by Methotrexate and then Hydroxychoroquine. It was observed that reduction in the relative ESR from baseline to the end of second month of

initiation of therapy was higher with the group receiving Hydroxychloroquine followed by Leflunomide and then Methotrexate.

The reduction in the relative WBC from baseline to end of second month of initiation of therapy was higher with the group receiving Leflunomide followed by Hydroxychloroquine and then Methotrexate.

The increase in the relative Hb from baseline to the end of second month of initiation of therapy was higher with the group receiving Methotrexate followed by Leflunomide and then Hydroxychloroquine.

In the patients receiving Dual therapy it was found that the relative decrease in the disease activity from baseline to the end of second month of initiation of therapy was higher in the group receiving HCQ+MTX followed by MTX+LFM and then HCQ+LFM. It was observed that reduction in the relative ESR from baseline to the end of second month of initiation of therapy was higher with the group receiving MTX+HCQ followed by HCQ+LFM and then MTX+LFM.

The reduction in the relative WBC from baseline to the end of second month of initiation of therapy was higher with the group receiving HCQ+MTX followed by HCQ+LFM and then MTX+LFM.

The increase in the relative Hb from baseline to the end of second month of initiation of therapy was higher with the group receiving MTX+HCQ followed by MTX+LFM and then HCQ+LFM.

The relative decrease in the disease activity from baseline to the end of second month of initiation of therapy was found higher in the group receiving the Triple Combination Therapy i.e. MTX+HCQ+LFM than all the other six groups.

CONCLUSION

In this study 270 patients with Rheumatoid Arthritis were studied by dividing into 7 groups based on the three DMARD's used alone and in combination in their treatment. The DMARD'S studied are MTX HCQ AND LFM.

The incidence of RA was found to be more in female than male 5:1 ratio.

The incidence of RA was found higher in the age group 41-50 years.

On the basis of reduction in the disease severity in the management of early Rheumatoid Arthritis while using monotherapy, Leflunomide was found to be more efficacious followed by Methotrexate and then by Hydroxychloroquine, whereas in Dual combination therapy the combination of Methotrexate + Hydroxychloroquine was found to be more efficacious followed by Methotrexate + Leflunomide and then by Hydroxychloroquine + Leflunomide. A triple combination of Methotrexate + Hydroxychloroquine + Leflunomide showed highest reduction in the disease severity and hence was found to be more superior to the other combinations in the study.

THE EFFICACIES OF DMARD'S IN THE STUDY ARE AS FOLLOWS:

- **MONOTHERAPY:** LFM> MTX> HCQ
- **DUAL COMBO THERAPY:** MTX+HCQ> MTX+LFM> HCQ+LFM
- **TRIPLE COMBO THERAPY:** MTX+HCQ+LFM > Mono and Dual therapy

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CONFLICTS OF INTEREST: No.

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