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RESEARCH ARTICLE

A Prospective Study on Comparing the efficacy of Combination Therapy and Monotherapy of DMARDs in Patients with Rheumatoid Arthritis

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ABSTRACT:

Aim and Objective: The main aim of the study was to evaluate the efficacy of combination therapy over monotherapy of DMARDs [disease-modifying anti-rheumatic drug] in patients with rheumatoid arthritis. **Methods and materials:** A prospective study was conducted in 100 patients for a period of six months in which 50-patients of Group-A received single DMARD [methotrexate-7.5mg/week] and Group-B received the combination of DMARDs [methotrexate-7.5mg/week, sulfasalazine-1g/day and hydroxychloroquine-200mg/day]. In addition, with DMARD therapy all patients were allowed to take prednisolone-5mg daily. **Results:** In the present study, among 100 patients the highest number of patients were from the age group of 36 to 45 years. The efficacy analyses were based on 100 patients. At week-6, 60% of male patients and 70% of female patients from Group-A and 79% of male patients and 80% of female patients from Group-B had significant improvements in the clinical and laboratory parameters. Although, improvements were better and much more significant in the patients who were given combination therapy. The combination of methotrexate, sulfasalazine and hydroxychloroquine was more effective than monotherapy. **Conclusion:** The present study revealed that the combination therapy of DMARDs was more effective than monotherapy.

KEYWORDS: Rheumatoid arthritis, combination therapy, monotherapy, efficacy.

INTRODUCTION:

Rheumatoid arthritis is a chronic recurrent inflammatory disease that leads to significant infirmity, loss of efficiency and increased mortality[1]. In the early phase the disease is probably the most responsive pharmacologically thus drug treatment should be instituted early[2]. There is growing evidence from randomized clinical trials and longitudinal observational studies that conservative single drug therapy with disease-modifying anti-rheumatic drugs (DMARDs) can alter the clinical course of rheumatoid arthritis, however in most patients the assistances are inadequate[3-7]. Consequently, additional authoritative therapies are desirable, such as the usage of more than one DMARD concurrently in the hope of additive efficacy[8,9].

The improved practice of combinations has progressed for three main reasons: initially, rheumatologists have been gradually disinclined to agree incomplete improvement of their patients when remission seems possible; then, the recognition that most DMARDs lose whatever efficacy they do have over time; and finally, the latest accumulation of data that combinations can be given safely and with better efficacy than mono-therapy [10-13].

Consequently, in the current study, we compared the efficacy of a DMARD combination including methotrexate, Sulphasalazine, hydrochloroquine and low-dose prednisolone with the same DMARDs as single treatment in patients with active rheumatoid arthritis.

METHODOLOGY:

Study site:

This study was carried out in the orthopedic department in a 300 bedded ESI government Hospital, Ayanavaram, Chennai.

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Study population:
The study population consist of 100 patients satisfying inclusion criteria.

Inclusion criteria:
patients were eligible if they were

- Both male and female patients of age above 18 years and diagnosed with rheumatoid arthritis.
- With duration of disease more than six months.
- Willing to participate.

Exclusion criteria:
patients were ineligible if they were

- History of allergy to any of the study drugs and pregnant women.
- Patients undergoing chemotherapy/radiotherapy.
- Not willing to participate.

Study period:
The study was carried out from September 2017 to February 2018 (6-Months). The study was approved by the institutional review board.

Study design:
It was a prospective study. A relevant data that contains the demographic details of the patient, clinical and biochemical tests along with the treatment chart were recorded on a customized data collecting sheet and rate of symptomatic healing at week-6 was assessed by using Modified Health Assessment Questionnaire (MHAQ).

Parameters for evaluation:
The parameters included were gender, age wise distribution, rheumatoid factor, duration of disease, social history, co-morbidities, comparison of pre and post treatment laboratory parameters among groups, based on symptomatic relief and based on improvement of efficacy ay weel-6 among groups.

RESULTS:

The study attended to compare the efficacy of combination therapy over monotherapy of DMARDs. Among 100 patients, 50 prescriptions were collected from in-patients who received methotrexate-7.5mg/week and 50 prescriptions were collected from in-patients who received combination of methotrexate-7.5/week, sulfasalazine-1g/day and hydroxychloroquine-200mg/day along with that both the group patients were allowed to take prednisolone-5mg daily.

1) Gender wise distribution:
Among 100 patients, 46% of male patients and 54% of female patients were enrolled in Group-A. And 58% of male patients and 42% of female patients were enrolled in Group-B.

Table-1:

Gender	Group-A (n=50)	Percentage (%)	Group-B (n=50)	Percentage (%)
Male	23	46%	29	58%
Female	27	54%	21	42%

2) **Age wise distribution:**
In this study, highest number of patients (25%) were from the age group of 36-45 years, 16% of population belongs to the age group of 18-25 years, 18% belong to the age group of 26-35 years, 22% belongs to 46-55 years and 19% of population belongs to the age group of 56-65 years.

Table-2:

Age in years	No. of patients (N=100)	Percentage(%)
18-25	16	16%
26-35	18	18%
36-45	25	25%
46-55	22	22%
56-65	19	19%

3) Age wise distribution between groups:
In Group-A among 50 patients, 14% belongs to 18-25 years of age, 20% belongs to 26-35 years, 28% belongs to 36-45 years, 20% belongs to 46-55 years and 18% belongs to age group of 56-65 years. In Group-B, 18% belongs to 18-25 years, 16% belongs to 26-35 years, 22% belongs to 35-45 years, 24% belongs to 46-55 years and 20% belongs to the age group of 56-65 years.

Table-3:

Age in years	Group-A (n=50)	Percentage (%)	Group-B (n=50)	Percentage (%)
18-25	7	14%	9	18%
26-35	10	20%	8	16%
36-45	14	28%	11	22%
46-55	10	20%	12	24%
56-65	9	18%	10	20%
MEAN±SD	10±2.28		10±1.41	

4) Based on Rheumatoid Factor:
Among 50 patients in Group-A, 74% of population are with positive rheumatoid factor and 26% of population were without rheumatoid factor. In Group-B, 84% of population were with positive rheumatoid factor and 16% of population were without rheumatoid factor.

Table-4:

Rheumatoid factor	Group-A (n=50)	Percentage (%)	Group-B (n=50)	Percentage (%)
With Rheumatoid factor	37	74%	42	84%
Without Rheumatoid factor	13	26%	8	16%
MEAN±SD	25±12		25±17	

5) Based on duration of disease:
In this study, in Group-A 32% of population had the duration of 1 year, 44% of population had the duration of 2 years and 24% of population had more than 2 years of duration. In Group-B, 36% of population had the

duration of 1 year, 50% of population had the duration of 2 years and 14% of population had the duration of more than 2 years.

Table-5:

Duration (years)	Group-A (n=50)	Percentage (%)	Group-B (n=50)	percentage (%)
1 year	16	32%	18	36%
2 years	22	44%	25	50%
More than 2 years	12	24%	7	14%

6) Based on social history:

Among 50 patients in Group-A, 14% of population were smokers, 12% of population were alcoholics, 18% of population were both smoker and alcoholics and 56% of population had no history. In Group-B, 18% of population were smokers, 20% of population were alcoholics, 20% of population were both smoker and alcoholics and 42% of population had no history.

Table-6:

Social history	Group-A (n=50)	Percentage (%)	Group-B (n=50)	Percentage (%)
Smoker	7	14%	9	18%
Alcoholic	6	12%	10	20%
Smoker+ Alcoholic	9	18%	10	20%
None	28	56%	21	42%
MEAN±SD	12.5±9.01		12.5±4.92	

7) Based on co-morbidities:

In Group-A, 32% are with hypertension, 36% are with diabetes mellitus, 14% are with cardiovascular disorders and 18% had no history. In Group-B, 22% are with hypertension, 44% are with diabetes mellitus, 10% are with cardiovascular disease and 24% had no history.

Table-7:

Co-morbidities	Group-A (n=50)	Percentage (%)	Group-B (n=50)	Percentage (%)
Hypertension	16	32%	11	22%
Diabetes mellitus	18	36%	22	44%
Cardiovascular disorders	7	14%	5	10%
None	9	18%	12	24%
MEAN±SD	12.5±4.6		12.5±6.1	

8) Comparison of pre and post treatment laboratory parameters among groups:

In Group-A, ESR was found to be 52 at pre-treatment and 34 after post-treatment, CRP was found to be 35 at pre-treatment and 22 after post-treatment, PLT was found to be 368 at pre-treatment and 322 after post-treatment, ALBUMIN was found to be 3.81 at pre-treatment and 4.05 after post-treatment. In Group-B, ESR was found to be 58 at pre-treatment and 21 after post-treatment, CRP was found to be 44 at pre-treatment and 11 after post-treatment, PLT was found to be 352 at pre-treatment and 276 after post-treatment and ALBUMIN was found to be 4 at pre-treatment and 4.58 after post-treatment.

Table-8:

Variables	Group-A		Group-B	
	pre	post	pre	post
ESR	52	34	58	21
CRP	35	22	44	11
PLT	368	322	352	276
ALBUMIN	3.81	4.05	4	4.58

ESR- Erythrocyte sedimentation rate, **CRP**- C reactive protein, **PLT**-platelet

9) Based on symptomatic relief:

In Group-A, morning stiffness was noted about 160 minutes, number of swollen joints count was 31 and number of tender joints count was found to be 32. In Group-B, morning stiffness was noted about 110 minutes, number of swollen joints count was 24 and number of tender joints count was found to be 32.

Table-9:

Symptoms	Group-A	Group-B
Morning stiffness (min)	160	110
No. of Swollen joints	31	24
No. of Tender joints	32	20

10) Based on improvement of efficacy at week-6 among groups:

In this study, in Group-A, 60% of male patients and 70% of female patients were shown to have improved efficacy with monotherapy. In Group-B, 79% of male patients and 80% female patients were shown to have improved efficacy with combination of DMARDs therapy.

Table-10:

Gender	Group-A	Percentage (%)	Group-B	Percentage (%)
Male (n=23)	14	60%	(n=29)23	79%
Female (n=27)	19	70%	(n=21)17	80%
MEAN±SD	16.5±2.5		20±3	

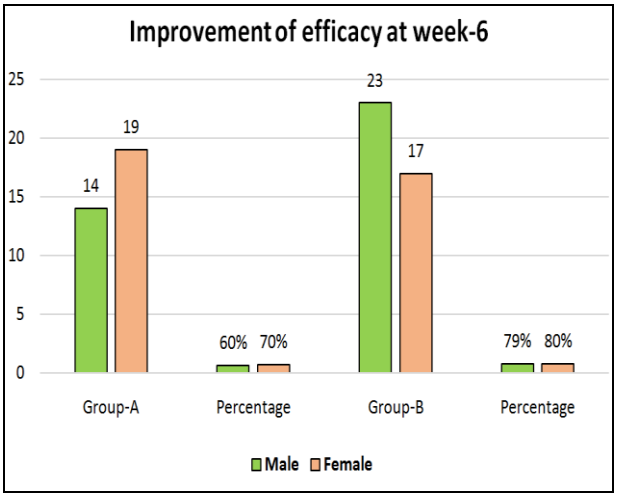

Figure-1.

DISCUSSION:

The present study evaluates the efficacy of combination therapy over monotherapy carried out over a period of six months (September 2017 to February 2018). The majority of the population belongs to the age group of 36 to 45 years. Utmost rheumatologists agree that DMARD treatment should be introduced primary in the progression of rheumatoid arthritis and that the definitive object of treatment should be induction of remission[14]. Further aggressive usage of DMARDs, for example, in combination should be favored. Furthermostpreceding studies have examined this issue in patients with advanced disease. In one study of patients with early rheumatoid arthritis, the rapid clinical response and high remission rate disappeared after the discontinuation of the initial high dose prednisolone treatment[15]. Remission rates during the prime two years in patients with recent onset of rheumatoid arthritis have diverse from 15% to 25%[16,17]. The great proportion of therapeutic failure stated with monotherapy based on the conservative pyramid approach, several aggressive therapeutic modalities such as the step down bridge, the sawtooth strategy, the graduate step strategy and therapeutic targeting have been proposed[18-21]. In 1982, McCarty et al. reported that combined cyclophosphamide, azothioprine and hydrochloroquine therapy was effective in patients with intractable rheumatoid arthritis[22]. To date a number of studies on numerous combinations have produced different outcomes. Some have suggested improved efficacy with combination therapy[23-26].

In the current study, out of 100 patients, 50 patients were treated with methotrexate-7.5mg/week in Group-A and 50 patients were treated with the combination of methotrexate-7.5mg/week, Sulphasalazine-1g/day and hydroxychloroquine-200mg/day in Group-B. The majority of population belongs to the age group of 36 to 45 years and the minority of population belongs to 18 to 25 years of age. 74% of population in Group-A and 84% of population in Group-B are with positive rheumatoid factor. In Group-A, 32% of population are with hypertension, 36% are with diabetes mellitus and 7% are with cardiovascular disorder. In Group-B,22% of population are with hypertension, 10% are with diabetes mellitus and 10% are with cardiovascular disorder. In Group-A, 60% of male patients and 19% of female patients were shown to have improved efficacy and symptomatic relief at week-6. In Group-B, 79% of male patients and 80% of female patients were shown to have improved efficacy and symptomatic relief at week-6.

The administration of combination of DMARDs was most effective when compared with monotherapy.

LIMITATIONS:

The study was carried out for a period of six months. Further the number of patients were low and the study was restricted only to one hospital.

CONCLUSION:

Overall the study results conclude that the combination of DMARDs may be more effective when compared with monotherapy for effectiveness and symptomatic improvement of the disease.

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CONFLICT OF INTEREST:

No conflict of interest is declared.

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