Original Article

Comparative Study on Methotrexate alone Versus Combination Therapy with Methotrexate Plus Chloroquine Plus Low Dose Prednisolone in the Treatment of Rheumatoid Arthritis

Islam AKMM[1], Haq SA[2], Yeasmin M[3]

Abstract

Rheumatoid Arthritis (RA) has significant contributor to the global burden of disease and affects people in all communities across the world. It is a chronic inflammatory disease of the locomotors system that leads to substantial disability, loss of productivity and increased mortality. The Study was conducted among the RA patients based on broad objective of exploring the efficacy and adverse effects of triple combination therapy. This was an open, randomized, prospective study which followed qualitative research method. A total 61 patients were included in the trail. All subjects were randomly selected to combination therapy and MTX group. One patient from each group stopped the drugs due to adverse effects. Finally 59 patients completed the trail. 33 belonged to combination therapy group and 26 to MTX. Combination therapy is the best and easiest than others modifying anti-rheumatic drug used. Combination therapy with Methotrexate, Chloroquine and low dose Prednisolone is better than Methotrexate alone.

Keywords: Rheumatoid Arthritis, Treatment, Methotrexate, Combination, Chloroquine & Prednisolone.

1. Corresponding Author:
Dr. A.K.M. Mazharul Islam
Senior Consultant
Department of Medicine
250 Beded Hospital, Patuakhali.
e-mail: akmmazharulislam@yahoo.com

2. Professor Dr. Syed Atiqul Haq
MBBS, FRCP, FCPS, MD
Professor & Chairman
Department of Medicine
Medicine Specialist
BSMMU

3. Dr. Murshida Yeasmin
MBBS, MPH, DCH
Medical Officer
Department of Peadiatrics
100 Bedded Maternal and Child Hospital
Mohammadpur, Dhaka.

Introduction

R/A is a chronic inflammatory disease of the locomotors system that leads to substantial disability, loss of productivity and increased mortality (Tugwell P 1995[1]).

It is the commonest form of inflammatory arthritis and affects about 1-3/%, of the population (Wordswrth P et al 1966[2]). Nearly 90/% of patients with aggressive disease will become clinically disabled within 20 years.

The severity of RA emphasizes the need for an effective management plan. In the past the treatment of RA has been developed on the premise that the prognosis of the disease is generally good. Treatment was based on NSAID and disease modifying agents such as sulfasalazine and Methotrexate. But this approach has limited success in preventing joint destruction or improving long term outcome. In fact, up to 90% of patients with aggressive synovitis develop evidence of bone erosions within two years of diagnosis despite treatment (Sharp JF et al. 1991[3]).

It was argued that introduction of slow acting anti-rheumatic drugs before the onset of articular damage retard the radiographic progression and joint damage in RA patients (Weinblatt, 1993[4]). It was also observed that there was a considerable overlap in toxicity between NSAIDs and SAARDs. These inferences lead to invention of therapeutic approach for RA that involved Institution of SAARDS early in course of the disease.

A realization soon followed that the outcome of treatment with these agents was far from satisfactory. Short term remission rates are acceptable but not high. Short term remission rates are acceptable but not high. Break through relapses are common. Meaningful remission of RA is found to occur in less than 2% of patients taking different SAARDs at the end of three years (Haq SA, 2000[5]). Considering the limitations of the currently available therapeutic options, attempts are continuing to recognize the ways in which these drugs are administered.

A combination of azathioprine plus methotrexate was compared with methotrexate alone and azathioprine alone in a series of patients who failed to respond to a single SAARD other than azathioprine or methotrexate. Both the combination and methotrexate alone proved superior to azathioprine alone, but the combination was not superior to MTX alone (Willkens RF et al. 1995[6]). The combinations of MTX, Sulfasalazine and Chloroquine was well tolerated and induced remission in substantial proportion of cases with sever RA patient who received multiple ineffectual courses of single slow acting drugs (Odell JR et al. 1996[7]).

Received: 30 August 2017 Accepted: 10 October 2017

Bolonga C also reported that the association of MTX and Corticosteroids seems to bring about a greater improvement in the different clinical activity parameter of RA than MTX alone, without significant increase in the frequency of side effects (Bolonga C et al. 1996[8]). A combination of Chloroquine with MTX appears to reduce significantly the hepatic toxicity of MTX (Khraishi-MM et al. 1996[9]). Kirwan reported that patients treated with Corticosteroids have an overall improvement in general well-being and functional capacity along with a reduction in radiographic progression (Kirwan JR, 1998[10]).

In a survey of 207 rheumatologist by O'Dell and Case, 95-1%, respondents indicated that they used combination therapies to treat their patients (Jain R et al. 1992[11]) and they reported that combination therapy is cost effective and more potential.

So the present study has been designed to see efficacy and toxicity of combination therapy with MTX, Chloroquine and low dose Prednisolone in the Treatment of RA & compare with that of MTX.

Hypothesis: Combination therapy with MTX, Chloroqunie and low dose Prednisolone is better than MTX alone.

Objectives: To establish the effects on short term outcome of the disease with adverse effects of triple combination therapy with MTX, Chloroqunie and low dose Prednisolone versus MTX alone.

Materials and Methods

This was an open, randomized, Prospective study which followed qualitative research method. Here all subjects were randomly selected in two groups. Combination therapy is even number and MTX group is odd number in random table respectively. The present study was conducted in the Rheumatology wing of the department of medicine, Bangladesh Bangabandhu Sheikh Mojib Medical University, Dhaka. Bangladesh from September 1999 to September 2000 including a 6 months follow up. 61 Samples (RA Patients) were purposively selected to conduct the study. After collecting data were checked thoroughly for constancy and completeness. Data were checked to exclude any error or inconsistency.

All analysis was done by appropriate statistical methods using spss are software for windows. All ethical issues, which were related the research involved with human subject were followed according to the guideline of ethical review committee.

Results

All Subjects (61 Patients) were randomly selected to Combination Therapy and MTX group. One Patient from each group left the study. Finally 59 Patients Completed the study. 33 belonged to combination therapy group and 26 to MTX group. The age of the patient ranged from 16-70 years. 45 were female and 14 were male patients.

The two groups were nearly identical with respect to demography, clinical and laboratory parameters and sex ratio 3.06:1 (table-1).

Table I: Comparison of baseline characteristics of the two groups of patients.

Parameters	Combination group (Mean±SD)	MTX group (Mean±SD)	P value
Age (yr) M±SD	37.09±10.67	33.81±10.88	NS
Sex (F/M)	27/6	18/8	NS
Duration of illness (months)	36.42±20.96	39.65±28.36	NS
Morning stiffness (minutes)	123 .82±56.50	117.69±47.94	NS
No. of involved joint	20.12±5.43	20.04±5.79	NS
No. swollen joints	10.64±4.08	9.42±2.85	NS
Joint swelling index	31.18±10.98	32.00±8.00	NS
No. tender joint	18.58±5.58	18.58±4.64	NS
Tenderness Index	44.55±16.29	41.31±12.72	NS
Patients assessment of Pain (VAS)	9.18±2.04	8.69±1.83	NS
Patients assessment of disease activity	3.94±22	4.00±1.06	NS
Physicians assessment disease activity	3.67±1.02	3.88±0.22	NS
Functional class	2.52±0.62	2.54±0.65	NS
NSAID score	12.88±4.85	12.11±4.28	NS
ESR	71.06±41.07	75.96±38.89	NS
Hb%	10.45±1.23	9.82±2.13	NS
ALT	30.56±26.29	24.62±8.93	NS
Blood sugar	5.53±0.93	5.31±0.81	NS
Bone mass density	Radius- 0.43±0.08	0.42±0.03	NS
	Ulna- 0.38±0.09	0.40±0.03	NS
	Distal- 0.39±0.08	0.40±0.07	NS

The differences between the two group was not statistically significant (table II).

Table II: Changes in disease activity indices in two group.

Parameters	Combination therapy group (Mean±SD)		MTX group (Mean±SD)		P value
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	
Morning_stiffness (min)	123.82±56.50	32.79±18.47	117.69±47.94	31.00±18.44	NS
No. of involved joint	20.12±5.73	8.42±2.97	20.04±5.79	8.58±2.69	NS
No. swollen joints	10.64±4.08	2.24±1.56	9.42±2.85	2.73±0.92	NS
Joint swelling index	31.18±10.98	6.15±4.54	32.00±8.00	6.85±3.11	NS
No. tender joint	18.58±5.58	1.97±2.58	18.58±4.64	4.46±1.88	NS
Tenderness Index	44.55±6.29	13.76±19.32	41.31±12.72	7.31±2.88	NS
Patients assessment of Pain (VAS)	9.18±2.04	3.13±2.82	8.69±1.83	3.46±1.68	NS
Patients assessment of disease activity	' 3.94±1.22	1.97±1.13	4.00±1.06	2.69±1.05	p<7.05
Physician's assessment of disease activity	3.67±1.02	1.73±1.13	3.88+0.99	2.42±0.99	p<.05
Functional class	2.52±0.62	1.36±0.70	2.54±0.65	1.58±0.81	NS
NSAID score	12.88±4.85	6.06±3.43	12.11±4.28	7.88±2.89	NS
ES R	71.06±41.07	28.39±29.51	75.96±38.89	26.92±21.78	NS
1lb%	10.45±1.23	11.94±1.10	9.82±7.13	11.12±1.13	NS

In both group Patients Complained Some Common side effects. But Rash Itching Urination as sitar side effects of MTX alone group, So Triple therapy group has less effects than MTX group (table III).

Table III: Adverse effects observed in triple therapy and MTX group.

Adverse effects	Combination group (n=34)	MTX group (n=27)
Nausea/ anorexia	25	24
Dizziness	5	3
Headache	1	1
Pain in abdomen heart burn	1	
Vomiting		1
Muscle cramps and myalgia	1	
Distaste		
Itching		1
Burning in extremities and urine		1
Diarrhea	1	1
Sleep disturbance		1
Moon face/ weight gain	1	
Withdrawn from treatment:		
Rash	0	1
Hypertension	1	0

WHO/ILAR response criteria was followed to measure the outcome of treatment. In combination therapy the response rate was maximum in 23 patients (69.70%) out of 33 cases and in MTX group 11 patients (42.30%) out of 26 cases (table IV).

Table IV: Outcome of Treatment group by WHO/ILAR response criteria.

Groups	Respondent	Respondent	Respondent
Combined group (n=33)	23	69.70	>0.05
MTX group (n=26)	11	42.30	

Chi-square test with (yates correction) p=0.065 (p>0.05)

Discussion

Methotrexate is a well known established, widely prescribed disease modifying anti-rheumatic drug (DMARD) used for rheumatoid arthritis and considered as the good standard treatment of rheumatoid arthritis.

Forequent failure of treatment to halt the disease progression has encouraged rheumatologists to explore the possibility of other modes of treatment. Such alternative approaches (Willkens RF et al. 1992[12]) are (1) use of second line agents (2) use of new drugs such as cyclosporine (3) use of biologic agents and (4) combined use of drugs with proven efficacy. Combination therapy is the easiest of these alternatives. Because rheumatologists have experiences with multiple drugs regimens (Willkens RF et al. 1992[12]).

The present study partly fulfilled this approach. The present study was a randomized controlled prospective open clinical trail to see the efficacy and toxicity of combination therapy with MTX plus chloroquine plus low dose prednisolone on the activities of RA in comparison with MTX alone an established disease modifying agent. In the present study, there were 46 female and 15 male with a ratio of 3.06:1. This ratio can be compared with the sex ratio of 2.83:1 in the series of Willkens et al. 1992[12]. In this seriest, the average age of patients of combination theraphy was 37.09±10.67 years and in the MTX group 33.81±10.88 yrs. In the study of Isalm MN et al. 2000, age was 39.74±11.08 in (SSZ+MTX group) and 32.35±14.79 in MTX group and 50 years in MTX group and 55 in combined group in the series of Williams et al. 1992 and 56 in combined group and 54 in the MTX group in the sutdy of Willkens RF et al. 1992. Age of patients in the present study closure to Islam MN et al. 2000[13] study as well as Williams et. al. 1992 study[14]. In the present study mean duration of disease was 56.42±20.96 months in combined group and 59.65±28.36 months in MTX group. It was 57.72 months in (SSZ+MTX group) and 61 months in MTX group in Islam MN et. al. 2000 and 8 years in Willkens et al. 1992. Duration of illness in the present study close to Islam MN et al. 2000 but away from Willkens et al. 1992. The discrepancy could be due to long survival in western population.

Prior to analysis different characteristics in both groups were compared to find out whether they had any statistically significant difference. The mean age, duration of illness, number of swollen joints, joint swelling index, joint pain, patients global assessment of disease activity, physicians global assessment of disease activity and ESR varied numerically between the two groups, but the differences were not statistically significant as in the study of Lopez Mendez et.al. 1991[15].

When we compared combined group with that of MTX alone, in respect to the response of treatment after 6 months, most of the clinical and laboratory parameters did not show statistically significant difference between the two groups. These findings were consistent with the findings of Islam MN et al. 2000[13], Williams HJ et al. 1992[14] Nisar M et al.1994[16] and Bunch TW et al.1984[17].

In combined groups, 25 patients showed gastrointestinal side effects like nausea, anorexia and in MTX group 24 patients showed gastrointestinal upset. There was no marked difference in respect of toxicity in both groups. These findings were consistent with Willkens RF et al. 1995[6] and Nisar M et. al. 1994[16].

We followed WHO/ILAR (Furst DE et.al.1994[18]) response criteria and found that 23 (69.7%) patients were responded in combined group in comparison to 11 (42.30%) patients responded in the MTX group. The difference was no statistically significant P>0.05.

The actual Present situations of RA Patients Management in Bangladesh are not so pleasurable. The RA is mainly managed by MTX and disease modifying anti-rheumatic drug (DMARD). These are effective in the treatment of RA. But complete remission of RA is rare. So now the high time to think about alternative management of RA like as triple therapy with MTX, Chlorquine and low dose prednisolone.

Conclusion

The efficacy and tolerability of combination therapy with MTX plus chloroquine and low dose prednisolone was compared with the those of MTX in an open, random, controlled, prospective clinical trial. 61 patients were included in the study. 59 patients completed the trial with a 6 months follow up. 33 patients completed the trial in the combined group and 26 patients in the MTX group alone. One patient from each group dropped out due to adverse effects of drug. Statistically significant improvement was observed in almost all clinical and laboratory parameters in both groups. Compared with the MTX group, the combination therapy though did not show higher efficacy over MTX group alone but higher response rate (69.70%) was observed on the WHO/ILAR response criteria and 42.30% in MTX group. Combination therapy was tolerable and short term side effects were almost equal in two groups. Most common side effects observed were nausea and anorexia followed by dizziness in both groups.

From the present study it may be concluded that-

- Combination therapy does not reveal superior efficacy over single drug treatment (P>0.05).
- Combination therapy did not demonstrate higher toxicity then monotherapy in a short-term clinical trial which is to be proved by long term study and follow up.
- Higher response in combination group says long term follow up for definite conclusion about its efficacy.

Acknowledgment

Thanks to Almighty Allah for giving me the opportunity & providing me with sufficient energy and patience to carry on this study. I would like to express my greatest gratitude & whole hearted respect to Prof. SA Haq & Prof. MN Alam for their inspiring guidance, constant supervision, constructive criticism, valuable advice and encouragement in carry out this study.

Bibliography:

01. Tugwell P, Pincus T, Yocum D, Stelin M, Gluck. 0, Kraag- G, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. New Eng J Med. 1995;333:138-141.

02. Wordsworth BP. Rheumatoid arthritis. In: Weatherall KJ, Ledingham JGG, Warell DA, editors. Okford Textbook of medicine. 3rd ed. New York: Oxford University Press; 1966: 2953-65.

03. Shrp JF, Wolfe F, Mitchell DM, Bloch DA. The progression of erosion and joint space narrowing score in rheumatoid arthritis during the first 25 years of disease. Arthrits Rheum. 1991; 34: 660.

04. Weinblatt ME, Polisson R, Blotner SD, Sosman JL, Ali Abadi, P Baker N, et al. The effects of drug therapy on radiographic progression of Rheumatoid Arthritis. Arthritis and Rheumatism. 1993; 36(5): 613-618.

05. Haq SA. Drug treatment of rheumatoid arthritis: pessimism and optimism (editorial). J Bangladesh CollPhysSurg. 2000;18:1-3.

06. Wilkens RF, Sharp JT, Stablein D, Marks C, Wortmann R. Comparison of azathioprine, methotrexate and the combination of the two treatment of rheumatoid arthritis. Arthritis and Rheum. 1995; 38 (12): 1799-1806.

07. O'Dell JR, Haire CE, Nils Erikson RNMSN, Drymalski W, Palmer W, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxycholoroquine, or a combination of all three medications. N Engl Med. 1996; 334(20): 1287-1291.

08. Bolongna C, Jorgasen C, Sany J. Association of methotrexate and corticosteroids in the treatment of patients with Rheumatoid Arthritis. Cli-Exp- Rheumatol. 1996; 14(4):401-6.

09. Khaishi MM, Singh J. The role of anti- malarials in rheumatoid arthritis. The American experience. Lupus. Jun; 5 Suppl 1. S41-44.

10. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J med. 1995; 333:142.

11. Jain R, Lipsky PE. Treatment of Rheumatoid Arthritis. Medical clinics of North America. 1992;81(1):57-82.

12. Willkens RF, Urowitz MB, Stablein DM, McKendiy RJR, Berger RG, Box JH, et al. Comparison of Azathioprine, Methotrexate and the Combination of both in the Treatment of Rheumatoid Arthritis. Arthritis and Rheum. 1992;35(8): 849-856.

13. Islam MN, Alam MN, Haq SA, Moyenuzzaman M, Patwary MI, Rahman MH. Efficacy of sulphasalazine plus methotresate in rheumatoid arthritis. Bangladesh Med Res Counc Bull. 2000; 26(1):1-7.

14. Williams HJ, Ward JR, Reading JC, Brooks RH, Clegg DO, Skosey JL, et al. Comparison of Auranofin, Methotrexate and the combination of both in the Treatment of Rheumatoid Arthritis. Arthritis and Rheum. 1992; 35(3): 259-264.

15. Lopez-Mendez A, Daniel WW, Reading JC, Ward JR, Alarcon GS. Radiographic assessment of disease progressionin rheumatoid arthritis patients enrolled in the co-operative systematic studies of the rheumatic diseases program randomized clinical trial of methotrexate, auranofin, or combination of the two. Arthritis and Rheumatism. 1991; 36(10):1364-1369.

16. Nisar M, Carlisle I, Amos RS. Methotrexate and sulphasalazine as combination therapy in rheumatoid arthritis. Br J Rheumatol. 1994;33:651-654.

17. Bunch TW, O'duffy JD, Tompkins RB, O'Fallcon WM. Controlled trial of hydroxychloroquine and D-penicillamine singly and in combination in the treatment of rheumtoid arthritis. Arthritis and Rheum. 1984; 27(3):267-271.

18. Furst DE, Brooks P, Malaviya AN, Mody GM. DC-ART: decreased inflammatory synovitis. J Rheumatol. 1994; 21: 27-35.