Efficacy and Toxicity Profile of Methotrexate Chloroquine Combination in Treatment of Active Rheumatoid Arthritis

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Abstract

Background: The present study was conducted to study the efficacy and toxicity profile of methotrexate chloroquine combination in treatment of active rheumatoid arthritis.

Methods: 24 patients of rheumatoid arthritis confirming to revised American Rheumatism Association (ARA) criteria were studied prospectively for twenty months. Clinical evaluation was made every 3 months. Clinical disease variables measured at each visit were number of joints with swelling, number of joints with tenderness and pain, duration of morning stiffness and physician and patient assessment of disease activity. Blood counts, liver function tests and other adverse effects due to drugs were monitored every 2 months.

Results: 10 patients demonstrated more than 50% improvement. 4 patients withdrew from study, 2 because of excessive nausea and vomiting and 2 because of noncompliance. Other side effects noted were hyperpigmentation, photosensitivity, skin rashes, raised transaminases and stomatitis.

Conclusion: Methotrexate chloroquine combination has good efficacy and toxicity profile. Gastrointestinal side effects are most common and usually responsible for the discontinuation of the drugs.

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Key Words : Rheumatoid arthritis; Methotrexate; Chloroquine; Efficacy; Toxicity

Introduction

Methotrexate (MTX) has become an established treatment in patients with active rheumatoid arthritis (RA). The efficacy of this drug has been demonstrated in short term placebo controlled studies [1,2,3,4], comparative trials [5,6,7,8] and open prospective studies [9,10,11,12]. Because of its widespread use in last decade lot of experience has been gained about the drug and its efficacy and toxicity profile is of interest to all rheumatologists. Combination therapy has been found to be superior to single drug therapy [13,14] for aggressive control of rheumatoid arthritis. Chloroquine (CQ) has been shown to be significantly more effective than non-steroidal antiinflammatory drugs (NSAID's) alone and has a benign toxicity profile [15,16,17]. In a tertiary care service hospital where the study was conducted, the most commonly used combination has been MTX with CQ, because of its low cost, efficacy and better tolerance.

Material and Methods

We enrolled 24 patients in an unselected manner (Table 1) confirming to revised 1987 ARA criteria for classification of RA. 17 patients were freshly diagnosed cases while 7 patients were 'refractory' RA and had received prior second line therapies including gold salts, azathioprine and D-

Table 1

Baseline data of 24 patients studied

Parameter	
Average age at entry	38 years
Mean duration of disease activity	48 months
Female : Male ratio	18:6
RF positive	19
Erosive arthritis	16
Subcutaneous nodules	2

penicillamine which had been discontinued due to lack of efficacy or toxicity. Patients continued to take NSAID's if needed. Dosage of MTX was adjusted in above study as needed but maximum dosage used was 15mg/week. Dosage of CQ used was 250mg (150mg base) per day. Steroids were only used intraarticular if there were isolated involvement of 1 or 2 joints and in initial one month after starting MTX, CQ combination. The same physician investigator performed clinical evaluation every three months. The clinical disease variables determined at each visit were as follows:

- Of 38 joint groups, the number with swelling.
- Of 38 joint groups, the number with tenderness and/or pain on passive movement.
- A joint swelling index expressed as sum where each joint was graded for swelling on a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe.

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- d. Joint tenderness / pain index expressed as sum where each joint was graded for according to the above scale.
- e. Duration of morning stiffness.
- f. Physician assessment of disease activity on a scale of 0 to 100%.
- g. Patient assessment of disease activity using the same scale as described for physician assessment.

Therapeutic remission was defined by the preliminary criteria of the American college of Rheumatology (ACR) [18,19]. Marked improvement in the joint swelling index and in the joint tenderness / pain was defined as >50% decrease in the value compared with values at entry and improvement in physician assessment of disease activity by >50%[21]. 38 joint groups examined included wrists (two), elbows (two), shoulders (two), knees (two), MCP joints (ten), PIP joints (ten) and MTP joints (ten).

Laboratory Assessment

Monitoring for adverse effects of MTX and CQ was done every two months including the following parameters: Complete blood cell count, Serum Bilirubin, Serum Aspartate aminotransferase, Serum alanine aminotransferase (any other

investigation was done only when indicated). Patient was also asked about any evident clinical side effects noted including skin rashes, photosensitivity, nausea, vomiting, hyperpigmentation etc. Perimetry and fundus examination was done every six months.

Results

MTX had to be discontinued in two patients due to excessive nausea and vomiting. One patient had more than twice the upper limit of normal transaminases level in whom the drug could be reintroduced after temporary withdrawal. Other patients were able to continue the drug despite minor side effects. Two patients withdrew from the study because of noncompliance.

For the patients who remained in study, significant improvement was noted at all study visits during months 3-20, compared with baseline in the number of painful joints, swollen joints, physician global assessment, joint pain index and joint swelling index. Significant improvement also occurred in the duration of morning stiffness and ESR from 3 to 20 months (Table 2).

Table 2

Change in different parameters of rheumatoid arthritis at I (3 months), II (12 months) and III (20 months) follow-up after MTX-CQ combination therapy

Parameters	No. of patients	Value at baseline (Mean $\pm$ SD)	Value during therapy (Mean $\pm$ SD)	p
No. of swollen joints				
03 months	24	11.29 $\pm$ 3.76	4.13 $\pm$ 1.65	<0.0005
12 months	20	11.05 $\pm$ 3.76	4.10 $\pm$ 2.71	<0.0001
20 months	20	11.05 $\pm$ 3.76	4.56 $\pm$ 1.82	<0.0003
No. of painful joints				
03 months	24	15.12 $\pm$ 3.47	5.75	<0.0005
12 months	20	15.10 $\pm$ 3.48	5.60 $\pm$ 3.3	<0.0005
20 months	20	15.10 $\pm$ 3.48	6.50 $\pm$ 2.48	<0.0005
Joint swelling index				
03 months	24	15.58 $\pm$ 4.47	8.60 $\pm$ 2.06	<0.0005
12 months	20	15.45 $\pm$ 4.75	5.90 $\pm$ 3.09	<0.0001
20 months	20	15.45 $\pm$ 4.75	6.05 $\pm$ 2.06	<0.0004
Joint pain index				
03 months	24	18.08 $\pm$ 4.03	9.46 $\pm$ 2.25	<0.0005
12 months	20	17.85 $\pm$ 4.00	7.85 $\pm$ 3.09	<0.0005
20 months	20	17.85 $\pm$ 4.00	9.25 $\pm$ 3.09	3.04
Physician assessment (%)*				
03 months	24	58.50	23.75 $\pm$ 7.25	<0.0005
12 months	20	54.40	20.24 $\pm$ 6.4	<0.0001
20 months	20	54.40	22.18 $\pm$ 7.04	<0.0001
Patient assessment (%)*				
03 months	24	53.08	21.08 $\pm$ 6.35	<0.0001
12 months	20	51.30	21.50 $\pm$ 7.85	<0.0002
20 months	20	51.30	19.50 $\pm$ 8.32	<0.0005
ESR (units)				
03 months	24	47.67 $\pm$ 21.25	47.08 $\pm$ 13.35	<0.0005
12 months	20	38.40 $\pm$ 20.38	30.30 $\pm$ 10.61	<0.1326
20 months	20	38.40 $\pm$ 20.38	33.00 $\pm$ 8.93	<0.2941
Morning stiffness (minutes)				
03 months	24	78.75 $\pm$ 41.55	47.50 $\pm$ 18.59	<0.0005
12 months	20	82.50 $\pm$ 43.94	62.25 $\pm$ 37.47	<0.1852
20 months	20	82.50 $\pm$ 43.94	55.50 $\pm$ 23.89	<0.0548

Values are the mean + standard deviation (SD). Baseline values are obtained at initial visit of the trial. *Scored on a scale of 0 to 100%

Table 3**Adverse effects of MTX-CQ combination administered for 20 months**

Adverse effects	No. of patients
Transient abnormality of transaminases*	07
Minor GI symptoms*	02
Excess nausea & vomiting*	04
Photosensitivity	01
Skin rashes	02
Stomatitis*	01

*indicates adverse effects attributed to methotrexate

There was a sustained clinical response in the disease parameters throughout the study. The number of painful and swollen joints remained substantially improved between 3 months and 20 months. There was one remission as described by the ACR criteria. Of 20 patients who remained in study at 20 months, 70% demonstrated marked improvement (>50%) in the joint pain index and 80% in the joint swelling index. Joint pain index and joint swelling indexes improved from mean 11.05 ± 3.76 and 15.45 ± 4.75 at baseline to 4.56 ± 1.82 and 6.05 ± 2.40 at 20 months which was statistically significant. There was >50% improvement in physician and patient global assessment of disease activity. Of 20 patients who remained in study three were able to stop taking NSAID's.

Discussion

At 20 months of therapy methotrexate chloroquine combination remained an effective treatment among the rheumatoid arthritis patients enrolled in this prospective study. Study included seven patients who had received prior second line therapies which had to be discontinued due to lack of efficacy or toxicity. Rapid improvement in the disease activity was observed in these patients also in our trial in initial three months and was sustained over 20 months. One patient met the ACR criteria for disease remission. Patient response in the joint pain index and joint swelling index was highly favourable. A plateau effect in the clinical response was observed at 6 months of therapy and continued over 20 months. Similar observation was reported by Kremer and Lee after a mean of 29 months, 53 months and 89 months of observation [9]. The dosage of MTX utilized ranged from 5 to 15 mg per week. Drug related toxicities occurred throughout the study. However, most of the side effects were minor and occurred in first few months. They either improved despite continuation of drugs or drugs could be reintroduced after temporary withdrawal. Similar observation has been made by Wiznal et al [20]. Other side effects of MTX, like bone marrow depression, thrombocytopenia, and methotrexate pneumonitis were not observed in any of the patients in this study group. Of the 24 patients who were enrolled, 20 remained in the trial. Of the 4 patients who were withdrawn from study, reasons for withdrawal were drug toxicity in 2

and noncompliance in other 2 patients. Fehlaue et al reported a withdrawal rate of 54% in 24 months in 124 patients receiving MTX [21]. The reason for very low withdrawal rate in our study was possibly selection of patients from a select population of army personnel and their dependents who were provided with free medication. MTX-CQ combination has good efficacy and toxicity profile, as also reported in other recent trials [22,23] and its use can be recommended in settings in which regular follow-up is maintained by the treating physician and strict guidelines for therapy are followed. Gastrointestinal side effects are certainly most common and are usually responsible for the discontinuation of the drug in initial period after starting the treatment.

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