IJPMR 6 (2) Oct. 1993

Long Term Trial of Low Dose Methotrexate in Rheumatoid Arthritis

LT Col K Achuthan & GP Capt S K Dham , VSM

Introduction

Rheumatoid Arthritis (RA) is a disease characterised by chronic pain, development of multiple deformities and prolonged morbidity. Its management is a challenging job with patient compliance, availability of drugs, cost of medicines, ease of administration and side effects determining success of therapy. Sero-positive RA is a more aggressive disease characterised by erosions and development of deformities. In the final analyses deformities rather than the disease itself may cripple the patient. Hence, modern thinking revolves around early use of disease modifying anti rheumatic drugs (DMARD)[1, 2]. This along with active physiotherapy and joint protective measures ensure an optimum result.

Materials & Methods

To assess the efficacy, telerability and side effect profile of long term Methotrexate in RA, a study was conducted on 128 patients of RA satisfying the ARA criteria[3]. The study was of an open, controlled and non comparative design and the period of trial was 24 months. All patients were allowed to continue their usual non steroidal anti inflammatory drugs (NSAID) and those who were on steroids were allowed to continue, with the dose being gradually tapered off. All patients after informed consent were given 7.5 milligrams of tablet Methotrexate (MTX), per week, in an intermittent pulse regime[4]. A MTX chart was maintained by all patients from which the total dose of MTX as well as results of serial haemogram and Liver Function Tests (LFT) could be readily ascertained.

The admission criteria were fresh cases as well as old cases with failure to continue other DMARD for a minimum period of 3 months due to non effectiveness, non availability, cost factor or side effects Subjects with skin rashes, haematological, renal & hepatic diseases were excluded from the study.

The following clinical laboratory parameters were assessed at start of trial, after 3 months and then six monthly for a total of 24 months.

1. Functional class I, II, III & IV.
2. Subjective pain score as nil, mild, moderate and severe.
3. Duration of morning stiffness in minutes.
4. Objective tenderness score as nil, mild, moderate and severe.
5. Sum of proximal inter phalangeal (PIP) joint circumferance in centimeters.
6. Sum of hand grip strength in mm of Hg.
7. Global assessment of efficacy by doctor and patient on a 5 point scale.
8. ESR in mm at end of first hour and Complete blood counts once a month.
9. C-reactive protein (CRP) in mg/L.
10. Rheumatoid factor (latex) and Hepatic and renal biohemistry once a month.
11. Liver scan using Technitium^{99} at beginning of trial and once a year unless indicated by persisting abnormal hepatic biochemical values.

All subjects were strictly screened for efficacy and side effects and the results were analysed by (1) Student 't' test and (2) Wilcoxan signed rank test.

Correspondance :- LT Col K Achuthan & GP, Capt S K Dham, VSM, Dept of Rheumatology & Immunology, Army Hospital, Delhi Cantt - 110010.

Results :

There were 128 cases of RA with Male : Female ratio of 4:7. The mean age (in years) was 28.02 ± 8.6. The duration (in months) of RA was 6.72 ± 22.4 seventy six were fresh cases and 52 were previously in other DMARD of which 26 were on steroids. 93 cases were RF + ve and 35 were negative.

The results of ARA functional classification, subjective pain score and objective tenderness score are shown in Table I, II and III.

Table - I
Functional Classification
n = 128

Disability	Class	Pre		12 months		24 months	
Mild	I	18	(14%)	83	(64.8%)	106	(83%)
Mod	II	67	(52.4%)	212	(16.4%)	12	(9.4%)
Severe	III	37	(29%)	20	(15.6%)	8	(6.0%)
Incap	IV	6	(4.6%)	4	(3.2%)	2	(1.6%)

Table - II
Subjective Pain Score
n = 128

Degree	Pre		12 months		24 months	
Nil	Nil		46	(36%)	57	(44.5%)
Mild	48	(37.5%)	31	(24.2%)	54	(42.5%)
Mod	41	(32%)	30	(23.4%)	9	(7%)
Severe	39	(30.5%)	21	(16.4%)	8	(6%)

Table - III
Objective Tenderness score
n = 128

Degree	Pre		12 months		24 months	
Nil	Nil		47	(36.7%)	82	(64%)
Mild	42	(32.8%)	31	(24.3%)	21	(16%)
Mod	58	(45.4%)	35	(27.3%)	17	(14%)
Severe	28	(21.8%)	15	(11%)	8	(6%)

Table IV depicts the changes seen after 24 months from the basal values in the assessment of duration of morning stiffness, sum of PIP joint circumferance and grip strength. They were found to be statistically significant.

The changes in the relevant laboratory indices evaluated in this study are shown in Table V. The fall in ESR from 64.2 ± 6.0 to 29 ± 2 and reduction of CRP from 4.3 (0.6) to 1.8 (0.4) was statistically significant. Complete blood counts and renal biochemistry showed no significant changes during trial period. Insert

Out of the 93 RF positives cases 63 (67%) became RF Negative at the end of 24 months. Of the 26 cases on steroids 21 (80%) could be fully weaned off it, and even in the remaining 5 patients, the dose could be reduced significantly.

From the 128 patients 28 (21.8%) had side effects not warranting withdrawal and only 9 (7%) had to be withdrawn from the study. The reasons for withdrawal were :

3 due to interactable oral ulcers.
3 due to recurrent skin rashes
1 due to an abnormal liver scan at six Months.
1. due to persistently raised liver enzymes at 4 months
1. due to military tuberculosis at seven months.

Table - IV
Clinical Parameters
n = 128

Parameter	Pre	12 months	24 months	'p' Value
Duration of Morn Stiffness (MTS)	270 (18)	206 (22)	132 (36)	< 0.01
Sum of PIP Circumference	596 (514-683)	581 (536-612)	572 (502-652)	< 0.05
Sum of Grip Strength (mm/Hg)	228 (21)	241 (18)	296 (28)	< 0.01

Table - V
Laboratory Values
n = 128

Parameter	Pre	12 months	24 months	'P' Value
ESR (mm)	64.2 ± 6.0	38 ± 7	29 ± 2	0.01
Hb (gm/de)	9.4 ± 0.6	10.2± 0.3	12.2 ± 0.2	
Platelets(x1000/c.mm)	420 (27)	402 (22)	387 (25)	
CRP (mg/dl)	4.3 (0.6)	2.3 (0.7)	1.8 (0.4)	0.01

Table - VI
Side Effects

Nature	Severity			Total	
	Mild	Mod	Sev		
Nausea	2	0	0	2	
Vomiting	1	3	0	4	G.I.T.
Anorexia	3	2	0	5	14 (50%)
Oral Ulcer	3	0	0	3	
Pruritis	3	0	0	3	
Skin Rash	1	3	0	3	
Giddiness	2	0	0	4	
Abnormal Liver Enzymes	5	0	0	2	
				28 (21.8%)	

Table - VII
Global Assessment of Efficacy

Assessment by Doctor		Assessment by Patient		
Excellent	_	Very Much Improved	20	(16%)
Good	93 (73%)	Much Improved	82	(64%)
Adequate	29 (23%)	Improved	18	(14%)
Poor	6 (4%)	No Change/Worse	8	(6%)

Table VI depicts the other undesirable effects seen. It will be noted that 50% of the side effects were related to the Gastro intestinal system and were mild to moderate in severity and needed only symptomatic measures.

Table VII shows the results of global assessment by the doctor and patient.

Discussion :

Methotrexate (MTX), a folic acid antagonist was initially introduced in 1949 to treat acute leukaemias. It was soon found to have a potent inhibitory effect on collagen synthesis and thus found a place in the treatment of Psoriasis and Psoriatic arthritis. Based on this Gubner et al used it in 6 cases of RA more than 40 yrs ago with significant improvement in 5 cases. As there is considerable evidence to indicate that destruction in RA is immunologically mediated, drugs that are immunosuppressive should be of benefit in treating the disease. Since then studies done abroad and in India have established MTX as a DMARD of value in RA.[7,8,9] The exact mode of action of MTX is yet unclear, and whether it acts by an anti-inflammatory effect, an

immunosuppressive action or by inhibition of the rapidly proliferating synovial cells is not definite. However, in the low dose used in treating RA systemic immunosuppression has not been demonstrated.[8,9]

Functionally, whereas there were 18 (14%) in class I initially at the end of the trial 106 (83%) had moved into this class. In addition on analyses of the functional class there were 6 (4.5%) in class IV initially, leaving 2 (1.6%) at the end of 2 Yrs (Table I). Results of assessment of subjective and objective pain score paralleled the results above (Table II and III). Clinical assessment of duration of morning stiffness, sum of PIP circumferance and sum of grip strength showed a satisfactory response with their values being statistically significant at the end of 24 months (Table IV). It is important to note that no haematological or renal side effects were noted. However of the 128 subjects 9 had to be withdrawn from the trial and of these 3 case were considered to have developed serious side effects - 1 case with abnormal liver scan, 1 case with persistently abnormal liver enzymes raised more than three times the normal, and 1 case which developed miliary tuberculosis.

Of the mentioned side effects hepatic fibrosis/cirhosis is considered serious and this had led many to recommend serial liver biopsies after use of each 1.5 Grams of MTX.[10] However, many studies have demonstrated that hepatic toxity is very uncommon with the low intermittent dose of MTX used in RA.[9,11,12] Our study also confirms this finding and suggests that serial liver function test along with periodical liver scan is adequate to detect liver toxity[13] and liver biopsy is not considered necessary.

The number of withdrawl from our study more or less corresponds with that seen in other studies [8,15]

Of the other side effects (Table IV) gastrointestinal unwanted effects made up 50% and symptomatic treatment was only required.

No bone marrow supression, nephrotoxity, lung toxity, vasculitis, or increased nodulosis were encountered in our study.[16]

We conclude that long term low dose pulse therapy with MTX in RA is safe and effective and has the added advantage of economy and better patient compliance. It also has a relatively faster onset of disease modification[8,14] and may be the DMARD of choice.

References

1. Mowat AG : The management of inflammatory joint disease in Oxford Text Book of Medicine, eds. Weatherall DJ, Ledingham JGS, Warrel DA, Oxford University Press, Oxford : 16.61-16.75, 1987.
2. Ruddy S. : The management of Rheumatoid Arthritis. in text book of Rheumatology, Eds Kelly WN, Harris ED, Ruddy S, Sledge CB, W B Saunders Company, Philadelphia, 2nd ed; 979-90, 1985.
3. Frank C Arnett, Steven M, Edevorthy et al. : The American Rheumatism Association 1987 revised criteria for classification of Rheumatoid Arthritis; Arthritis Rheum, 31, 315-324, 1988.
4. Weinstein GD, Frost P, : Methotrexate for Psoriasis : A new thereapeutic schedule. Arch Dermatol, 103, 33-38, 1977.
5. Gubner R, August S, Ginesberg V : Therapeutic suprression of tissue reactivity. II, Effect of aminopterin in rheumatoid arthritis and psoriasis. Am. J. Med. Sci. 221. 196, 1951.
6. Witebsky E., Immunological aspects of rheumatoid factor. Arthritis Rheum, 6, 402-413, 1963.
7. URK Rao, Anuradha R Thopu, MUR Naidu et al. Early beneficial effects of low dose oral methotrexate in rheumatoid arthritis. JAPI, 38, 335-336, 1990.
8. Yadunath Singh, Manoj Sharma, Singh RR, et al. : Methotrexate: Clinical and immunological effects in refractory rheumatoid arthritis. JAPI, 40, 658-665, 1992.
9. Michael EW, David E Trentham, Patricia AF et al. : Long term prospective trial of low dose

methotrexate in rheumatoid arthritis. Arthritis Rheum, 31, 167-175, 1988.
10. First DE, Kremer JM, Methotrexate in rheumatoid arthritis. Arthritis Rheum, 31, 305-314.1988.
11. Julie Aponte and Petrelli M. : Histopath finding in the liver of rheumatoid arthritis patients treated with long term bolus methotrexate. Arthritis Rheum, 31, 1457-1464, 1988.
12. Joel ML, Randall GL and Keith GT. : Liver histology in rheumatoid arthritis patients receiving long term methotrexate therapy. Arthritis Rheum, Vol 32, 121-127, 1989.
13. Khanna MU, Abraham P, Shihare SS, Tile GH. Scintigraphic rigitto left liver lobe ratio and liver to spleen ratio in cirrhosis and non cirrhotic liver dieseases. JAPI, 39, 265-267 1991.
14. Weinblatt ME, Coblyn JS, Fox DA et al. Efficacy of low dose methotrexate in rheumatoid arthritis N Eng J Med 312, 818-822, 1985.
15. Aponte J, Petreili M : Hepatic histology following prolonged treatment with bolus Methotrexate. Arthritis Rheum 28 (Suppl 4) : 537, 1985.
16. Rafael Segal, Dan Caspi, Mosbe Tishler et al. : Accelerated nodulosis and vasculitis during methotrexate therapy for rheumatoid arthritis, Arthritis Rheum, 31, 1182-1184, 1988.