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Methotrexate in Rheumatoid Arthritis : A 2 Year Experience at a University Hospital in Pakistan

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Abstract

In this study we report our two years experience of methotrexate (MTX) in the management of rheumatoid arthritis (RA) at the Aga Khan University Hospital, Karachi. We studied the clinical course of 124 RA patients. The mean age was 44±11 years (range 19-72) and mean duration of RA was 5±4 years (range 0.3 -25). Female to male ratio was 10:2.4(100F:24M). All of them were diagnosed according to the criteria set by American Rheumatism Association. The mean value of ESR was 60±30(Range 3-128). Fifty one percent had severe disease (>10 joints involved and evidence of erosions and deformities). Twenty-one patients had extra-articular manifestations. None of them had received MTX previously. Their kidney and liver functions were assessed to be normal. Patients were divided into two groups. One group (n=92) received MTX (7.5- 10 mg/week) as initial treatment, while the other group (n=32) was given other disease modifying anti-rheumatic drugs (penicillamine, salazopyrin, gold, or chioroquine) followed by MTX. Assessment of the treatment outcome and development of any adverse reactions was carried out at 3-month interval over an average period of 1 year. Assessment of the treatment outcome in the group which received MTX as initial drug revealed the response to be excellent in 13%, good in 70%, fair in 11% and variable in 4%. In the group which received MTX as second-line of therapy, 59% of the patients had the response from good to excellent, while 25% of the patients exhibited poor to fair response. Regarding side-effects of MTX treatment, 57% exhibited none, while 35% had nausea and vomiting. Alopecia was the next common toxicity in these patients. Two individuals had abnormal liver function tests (value twice more than normal), while one developed lung fibrosis. MTX despite its adverse effects in some of the patients is still an effective, well tolerated and inexpensive disease modifying drug in RA (JPMA 48:3, 1998).

Introduction

Rheumatoid arthritis (RA) is increasingly recognized in Pakistan. In a study carried out few years ago, its prevalence in Karachi alone has been reported to be 0.15%[1] . Because of a heavy burden of infectious diseases, hypertension, coronaiy artery disease and diabetes, there are relatively few rheumatology clinics in the country and therefore, there is hardly any information available about the treatment outcome of this disease. Methotrexate (MTX), over the past few years, has emerged as the most frequently used disease modifying antirheumatic drug (DMARD) inthe U.S.A. for the treatment of RA[2]. Because of its exsellent efficacy score and relatively low serious toxicity score[3,4], it is being recognized as one of the leading therapies inthe aggressive intervention ofRA. The remarkable aspect of this therapy was the use of low dosages(7.5 mg - 15 mg/week) resulting in significant improvement in most variables of disease activity compared to placebo controls5-8. However, its use in the management of RA has been quite limited in Pakistan. The objective of this study was to investigate the effectiveness and tolerability of MTX in ourRA population.

Patients and Methods

A retrospective analysis was performed on 124 RA patients who had been receiving MTX at the Rheumatology Clinic of The Aga Khan University, Karachi, during the years 1994-95. This follow-up of 2 years was perfonned on all the patients regardless of whether they used MTX as initial drug or as second-line of treatment. They were divided into two groups, one group (n=92) received MTX (7.5-10 mg/week) as initial treatment while the other group (n=32) received other disease modifying drugs (D-penicillannne, n=19; salazopyrin, n=9; gold, n=2; chloroquine, n=2) followed by MTX, because the response with the initial drug was not satisfactory. Disease severity was scored arbitrarily on a 3-point scale (mild, moderate and severe) on the basis of duration of morning stiffness, Ritchie Index, number of active joints, number of deformities and number of extra-articular features. Women with child bearing potential werc advised to avoid pregnancy. Every patient was examined at an interval of 8-10 weeks for the above mentioned parameters. Complete blood count, ezythrocyte sedimentation rate, liver enzymes and serum creatinine were measured every 3-4 months. If the values for iiver enzymes and serum creatinine were measured every 3-4 months. If the values for liver enzymes increased to more than twice the upper limit of normal, the drug was withheld and the tests were repeated after 2 weeks. Adverse drug reactions during M1'X treatment were recorded and classified as those (i) requiring discontinuation of MTX, (ii) requiring suspension of MTX, (iii) and those requiring no change in treatment. Assessment of clinical outcome of the treatment on every patient was carried out at every 3-4 months interval with the following arbitrary designations modified from those proposed by Wemblatt et al[5].

Excellent: Complete therapeutic remission, defined by the preliminary criteria of American Rheumatism Association[9].

Good: Remission of 50% of active joints.

Fair: Good Clinical response with less than 3 activejoints.

Variable: Mixed remissions and flare-ups.

Results

The demographic and clinical characteristics of RA patients in this study have ben listed in Table I.

Table I. Demographic and clinical characteristics of the RA patients receiving MTX at AKUH.

Variable		Frequency (%)	
Sex		Male	24 (19)
		Female	100 (81)
Habitat		Urban	105 (85)
		Rural	19 (15)
Family History:	Nearest blood relative with RA		3 (2)
	Distant relative with RA		5 (4)
	None		116 (94)
Mean age±SD	44±11 years (range 19-72)		
Mean duration of RA symptoms±SD	5±4 years (range 0.3-25)		
Mean ESR±SD	60±30 (range 3-128)		
Disease activity	Mild (1-2 active joints)		16 (13)
	Moderate (3-10 active joints)		45 (36)
	Severe (More than 10 active joints)		63 (51)
Rheumatoid factor	Positive (+/51: ++/23: +++/32)		106 (86)
	Negative		18 (15)
Number of deformities	Hands or feet		31 (25)
	Both hands and feet		27 (22)
	None		66 (53)

All of them were diagnosed according to the criteria set by American Rheumatism Association. None of them had received MTX previously. Their kidney and liver functions were assessed to be normal. RA patients to receive MTX as initial drug or as
second line of treatment were included in this study. Twenty-one out of these 124 RA patients had extra- articular manifestations. Seven of them had single extra-articular manifestation while 14 of them had multiple extra-articular manifestations as listed in Table II.

Table II. Extra-articular manifestations in RA patients.

Manifestations	No. of cases
Nodules	1
Cutaneous vasculitis	3
Eye involvement	2
Neuropathy	1
Nodules + Neuropathy	1
Nodules + Sicca (Eye and Mouth)	1
Eye + Neuropathy	2
Nodules + Cut. vasculitis	2
Sicca (Eye & Mouth)	2
Nodules Sicca (Eye and Mouth)	1
Cut. vasculitis + Lymphadenopathy	1
Cut. vasculitis + Neuropathy	1
Lymphadenopathy + Neuropathy	2
Cut. vasculitis + Sicca (Eye & Mouth)	1
Total	21

Table III. Classification of the disease in terms of severity.

Stage of the Disease	Features
Mild	Involvement of 1-2 joints, no extra-articular manifestation and no deformities.
Moderate	Involvement of 3-10 joints, evidence of erosions, extra- articular manifestations and no deformities of either hands or feet.
Severe	Involvement of more than 10 joints, extra-articular manifestations and deformities of either hands or feet.

Table III shows classification of the disease in tenns of severity. Nearly half of our patients (5 1%) had severe disease (involvement of more than 10 joints, evidence of erosions and deformities in hands or feet), while 36% had moderate disease (involvement of 3-10 joints, evidence of erosions in the radiograph and no deformities), 13% had mild disease (involvement of 1-2 joints and no erosions or deformities). A vast majority of them had been on nonsteroidal anti-inflammatory drugs.

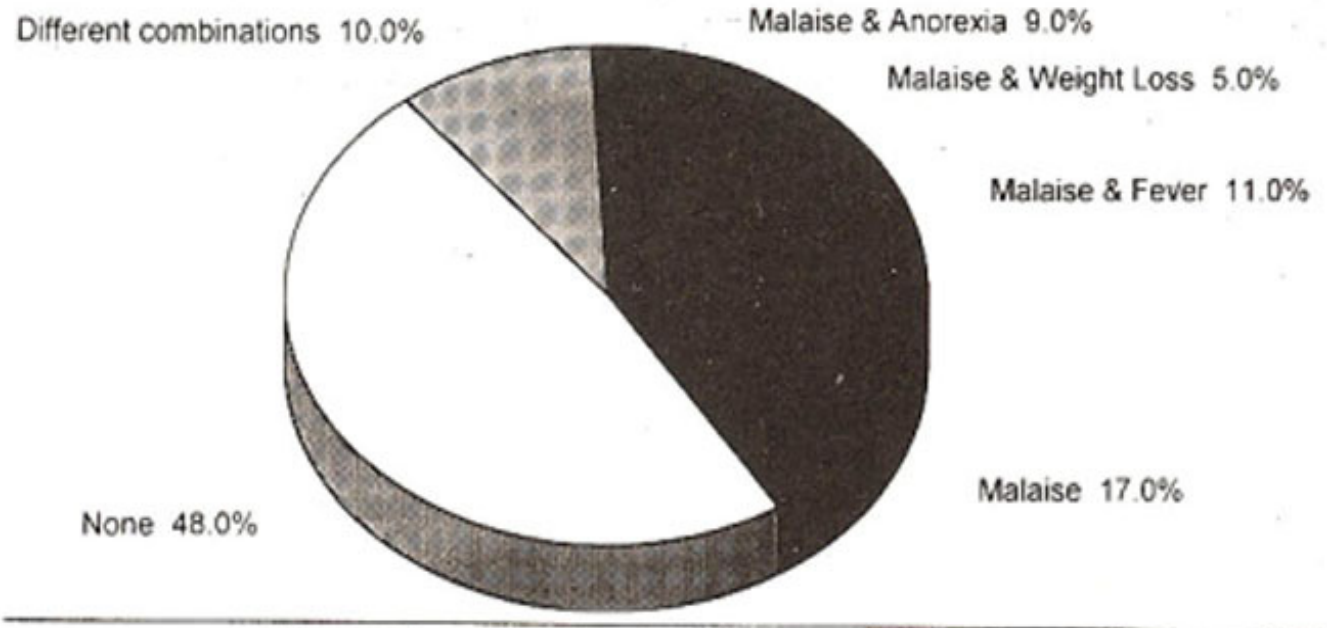

Figure 1. Frequency of prodrome symptoms in RA patients.

Figure I, shows the frequency of prodrome symptoms, with forty-eight percent of the patients reporting no symptoms. Assessment of the treatment outcome was carried out at approximately 3-4 months interval over an average period of 1 year for each patient. It revealed marked clinical improvement in

subjects who received MTX as initial drug for atleast 6 months. Results are shown in Figure 2.

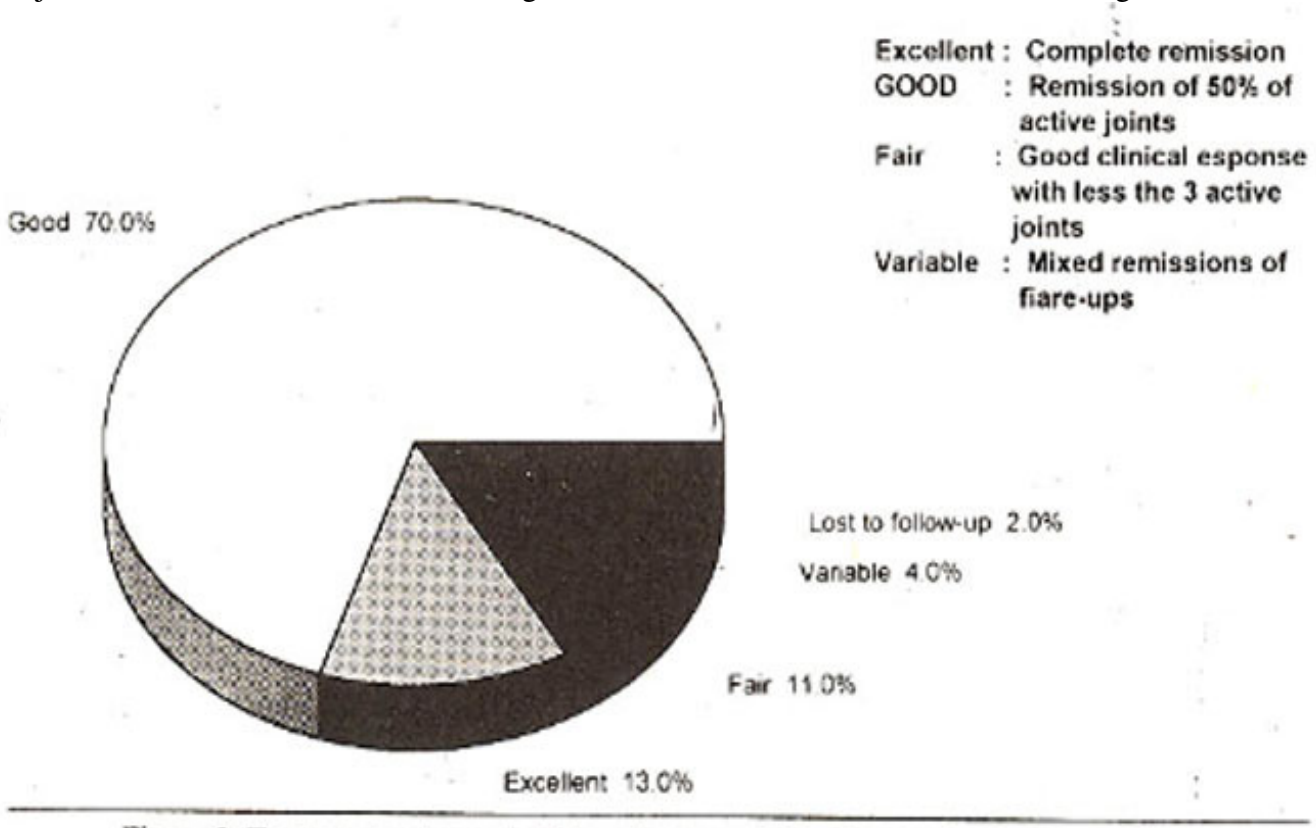

Figure 2. Treatment outcome in RA patients receiving MTX as initial drug (n=92).

Results of treatment outcome in the second group (n=32) who receivedMTXas second line of therapy, are shown in TablelV.

Table IV. Treatment outcome in RA patients who received MTX as second-line of therapy (n=32).

Initial DMARD	Total # of patients (n)	Treatment outcome									
		Excellent		Good		Fair		Variable		Lost to followup	
		n	%	n	%	n	%	n	%	n	%
Salazopyrin	9	1	11	5	56	-	-	1	11	2	22
Penicillamine	19	4	21	6	32	4	21	2	10	3	16
Chloroquine	2	-	-	1	50	-	-	1	50	-	-
Gold	2	2	100	-	-	-	-	-	-	-	-

Most of the patients (82%) had received salazopyrin or penicillamine as initial DMARD, while 2 were onchioroquine and 2 on gold. However, due to intolerability or poor-response, these patients were changed to MTX therapy. Again, in most of them (59%), the response to MTX therapy was good to excellent. There were 4 patients in this group in whom the response was fair, while 4 patients did not respond to therapy and had to be putonanotherDMARD. Five patients were lost to follow-up.

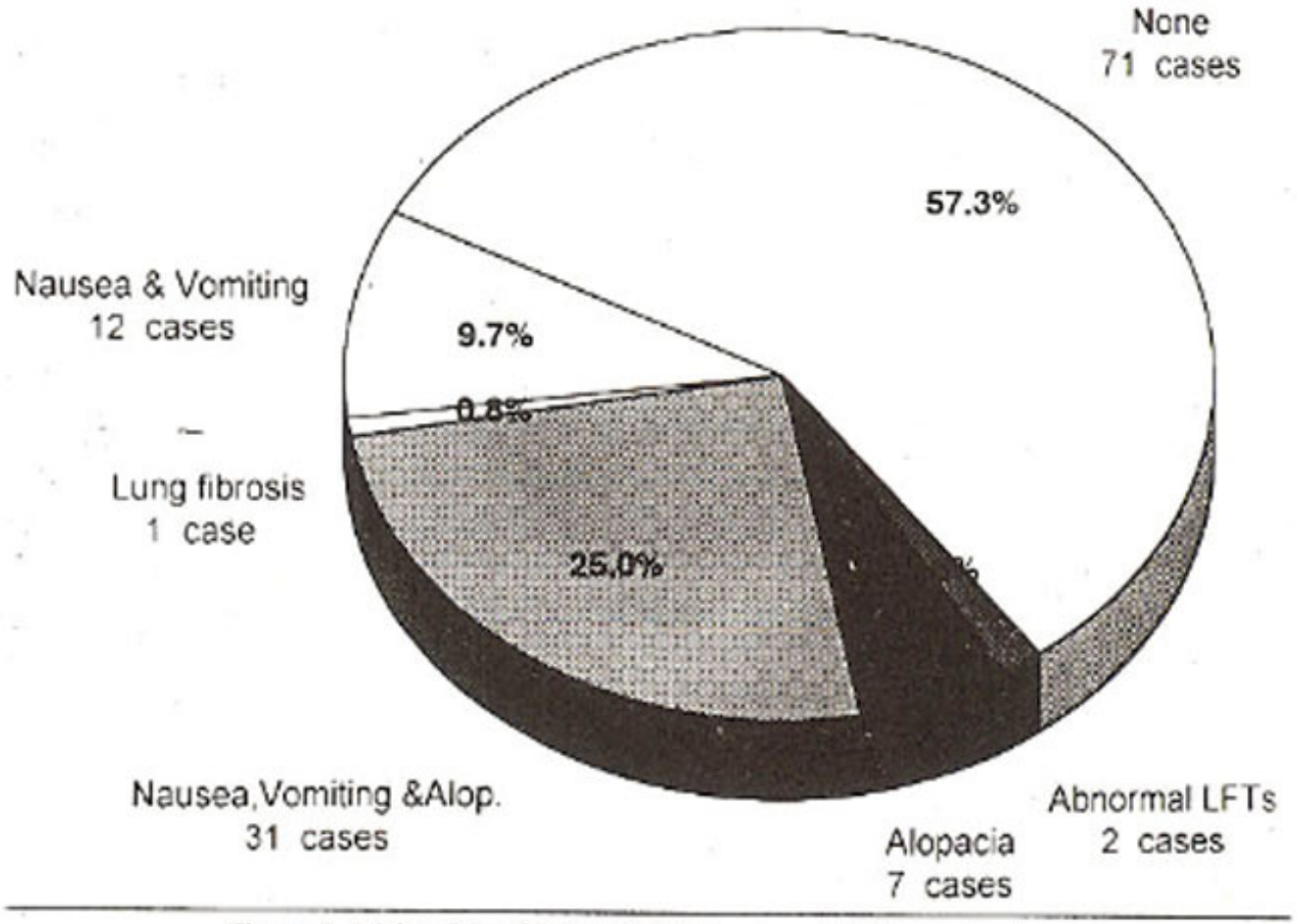

Figure 3. Major side-effects of MTX treatment in RA patients.

Figure 3 shows the side effects of MTX treatment. Nausea and vomiting were the major adverse reactions in 35% patients. Alopecia was experienced by 31% individuals and there were -two cases of abnormal liver enzymes (more thantwice the normal maximumlimit) and one case of lung fibrosis. Fifty-seven percent of our patients (71 cases) had no major adverse reactioa No haematological toxicity was observed.

Discussion

This open study carried out onour RA population shows the tolerability and effectiveness of low-dose MTX treatment which has emerged to be one of the inexpensive disease modifying therapies in the management of RA. These results pertaining to the short-term efficacy of low-dose MTX inRA compare well with those reported by Weinblatt et al[5] who had shown excellent response in 24% of the patients. Seventy-three percent of their patients had atleast 30% improvement in joint tenderness/pain index. However, that study was a double-blind cross-over trial comparing oral MTX with placebo, while our's is an open study. Similarly, an open study involving 21 patients carried out by Steinsson et al[10] indicated that 52% of their patients responded well to MTX (7.5 mg - 15 mg/week). In another placebo-controlled study by Williams et al[6] involving 189 patients and an oral dose of MTX 7.5 mg and 15 mg/week over a period of 18 weeks, there was a significant improvement in all disease variables in MTX-group compared to placebo. The above mentioned 3 studies indicate the short term efficacy of MTX treatment and conform well to our results. A number of long term prospective studies have shown

that patients with RA remain on MTX longer than the other slow acting drugs[11]. According to Weinblatt, 63% of patients continued this therapy for atleast 65 months[12]. Buchbinder has reported that 75% of their patients were still on MTX treatment even after 70 months[13]. However, long term use of low dose MIX has not been without adverse reactions[14]. A study by McKendry and Dale reported a 75% risk of treatment termination at 60 months[15], while another 3 studies have indicated that risk to be around 50%[11,16,17]. The discontinuation of treatment due to toxicity has been attributed mainly to the long term use of MIX and total amount of the drug used during that period of time. Since in our study the exposure of our patients to MIX was fora relatively short period (one year average), we did not encounter any serious complications except lung fibrosis in one patient and consistent elevation of liver enzymes in two cases. The patient developing lung fibrosis had a pre-existing chronic lung disease. Although, pulmonary fibrosis is an extreme rarity in MIX therapy, the possibility that MIX treatment may have precipitated, it is a possibility. Hematological toxicity is another reported hazard of low dose MIX therapy[18] yet none of our patients exhibited any symptoms of bone marrow suppression. This could be attributed again to a shorter duration of MIX treatment and a relatively younger age group (mean age 44 years) of subjects. Development of clinically significant liver disease is the most serious side- effect of long term MIX treatment[19]. The American College of Rheumatology has recommended guidelines for monitoring liver toxicity20, where if 5 of 9 determinations of liver enzymes within a 12-month period are above the upper limit of laboratory normal, a liver biopsy should be performed to identify potential risk for clinically significant liver disease. Iwo of our patients developed abnormal values of liver enzymes that persisted for nearly 3 months. They were taken off MIX therapy and were put on different DMARD. Nausea and vomiting were the major symptoms which were managed either by using anti-emetics or in few cases withholding MIX treatment fora short period.

Another possible reason for better tolerability of MTX by ourRA patients could be the younger age group (mean age 44 years) and normal kidney and liver function. It has been reported that patients who develop MIX toxicity are significantly older compared to those who do not experience such adverse effects[21]. MIX, despite its adverse effects in some patients, remains an effective, well tolerated and inexpensive disease modifying drug in the management of RA. A more recent report by Weinblatt shows its long term effectiveness and superior efficacy to auranofin, azathioprin and cyclosporin A[22]. It has emerged as a standard therapy for the treatment of active RA. Our two year experience at the Aga Khan University Hospital with this drug proves that by following the standard guidelines for the management of RA[23] MTX therapy could be reasonably safe and effective.

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