

The Safety of Weekly Low Dose Oral Methotrexate in an Oriental Population with Rheumatoid Arthritis

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Abstract

A retrospective review of 50 oriental patients with rheumatoid arthritis treated with weekly oral methotrexate showed adverse events in 15 (30%) patients with 19 occurrences (38%) of leucopaenia (4%), pancytopenia (2%), gastrointestinal symptoms (18%), hepatic transaminase elevation (6%), rash (2%) and infections (6%). The median duration of treatment with methotrexate was 11 months (range 1 to 105 months). Pancytopenia occurred in 1 patient with renal failure. All adverse events resolved with cessation of therapy and on several occasions, despite continued therapy. Methotrexate was discontinued permanently in 2 and temporarily in 7 patients as a result of adverse events. No recurrence of adverse events was noted on restarting methotrexate therapy in patients with non life-threatening adverse events. No increase in adverse events was noted in 14 patients treated with a combination of methotrexate and anti-malarial therapy. We conclude that methotrexate was well tolerated by the Oriental patients with rheumatoid arthritis in our study and could be safely restarted in those patients with non life-threatening adverse events.

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Introduction

Low dose oral pulse methotrexate therapy has gained increasing acceptance as the disease modifying anti-rheumatic drug of choice in the treatment of rheumatoid arthritis¹ because of an efficacy similar to intramuscular gold,² a favourable adverse event profile³ and the convenience of once weekly dosing. Patients are more likely to continue therapy with oral methotrexate than with other disease modifying anti-rheumatic drugs.⁴ The increasing use of methotrexate has come at a time when disease modifying anti-rheumatic drugs have been introduced earlier in the course of rheumatoid arthritis to preserve function⁵ and possibly reduce morbidity. Though methotrexate is generally well tolerated by patients, significant toxicity exists and is more often the reason for discontinuing methotrexate than a lack of efficacy.⁶ Pancytopenia,⁷ pneumonitis⁸ and hepatic fibrosis⁹ may occur, and fatalities due to cytopenias⁷ and opportunistic infections¹⁰ have been reported. The majority of trials assessing the safety of methotrexate in rheumatoid arthritis have been in Caucasian populations. This study aimed to assess the safety and adverse event

profile of methotrexate in an Oriental population with rheumatoid arthritis. The methotrexate-related adverse events in a subgroup of patients on combination therapy with methotrexate and anti-malarials were also compared with adverse events developing in patients on methotrexate alone.

Materials and Methods

The case records of 50 patients with rheumatoid arthritis who had been treated with weekly oral methotrexate and observed between June and December 1993 in our department were reviewed. Our department is the only rheumatology unit in Singapore and is the major referral centre for rheumatic diseases here. All patients fulfilled the 1987 American Rheumatism Association revised criteria¹¹ for the diagnosis of rheumatoid arthritis and were on active follow up at the time of the study. Data were abstracted on individual patients' biodata, disease pattern and severity, methotrexate use, past or concomitant use of disease modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs or prednisolone and any adverse

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events of methotrexate therapy. The Mann-Whitney U test was used to test for significant differences between interval variables with non-parametric distributions and Fisher's exact test was used for nominal variables.

Results

Demographics and Patterns of Disease Modifying Anti-rheumatic Drug Use

The study sample consisted of 40 Chinese, 6 Indian and 4 Malay patients. Forty-seven (94%) patients were female, 3 (6%) were male. The disease profile of the 50 patients studied is shown in Table I. Therapy at the time of the study consisted of methotrexate alone in 32 patients, methotrexate and an anti-malarial in 14 patients (9 given chloroquine, 5 hydroxychloroquine), methotrexate and sulphasalazine in 3 patients and methotrexate and intramuscular gold in 1 patient. Patients on combination therapy with methotrexate and an anti-malarial required a higher weekly median methotrexate dose (12 mg versus 10 mg), were more likely to have been on oral folate supplements, had more extra-articular disease manifestations and were more likely to have failed to respond to a disease modifying anti-rheumatic drug previously (Tables I and II). Apart from 1 patient with end-stage renal failure on maintenance haemodialysis, all patients had serum creatinine levels within normal range. No patients were on concomitant therapy with allopurinol.

Adverse Effects of Methotrexate

Nineteen adverse events occurred in 15 (30%) patients (Table III). Multiple adverse events occurred in 3 patients, consisting of leucopaenia and herpes zoster in 1 patient, nausea and cellulitis in the second patient and pancytopenia, oral ulcers and rash in the third patient. The median methotrexate dose for patients with adverse events was 10 mg/week (range 7.5 to 17.5 mg/week).

TABLE I: DISEASE PROFILE OF THE STUDY POPULATION

	All patients	Methotrexate alone	Methotrexate and anti-malarial	<i>P</i> value
Number	50	32	14	-
Median age at onset (y)	40.7	41.9	38.6	NS
Median disease duration (y)	8	7	9.5	NS
(Range in years)	(1 - 33)	(1 - 33)	(2 - 24)	
Number (%) seropositive	41 (82)	24 (75)	14 (100)	NS
Number of patients with rheumatoid nodules (%)	8 (16)	5 (15.6)	3 (21.4)	NS
Extra-articular disease (%)	6 (12)	1 (3.1)	4 (28.6)	0.025
Number of patients previously on disease modifying anti-rheumatic drugs	35 (70)	19 (59.4)	13 (92.9)	0.035
Associated diseases:				
Fatty liver	1	1	0	
Ethanol ingestion	0	0	0	
Diabetes mellitus	1	1	0	
Extra-articular involvement:				
Keratoconjunctivitis	2	0	1	
Episcleritis	1	0	1	
Scleromalacia perforans	1	0	1	
Anaemia	1	0	1	
Pericardial effusion	1	1	0	

NS: not significant

Note: *P* values are for comparisons between groups on methotrexate alone and on methotrexate and an anti-malarial.

Leucopaenia of $3.4 \times 10^9/L$ occurred in 2 patients at 12 and 78 months of therapy, and resolved with temporary cessation of methotrexate for 4 and 5 weeks respectively. Pancytopenia developed in 1 patient after 3 months of therapy. This patient had end-stage renal failure from glomerulonephritis on maintenance haemodialysis and refractory rheumatoid arthritis unresponsive to courses of intramuscular gold, sulphasalazine and cyclo-

TABLE II: METHOTREXATE, PREDNISOLONE AND NON-STEROIDAL ANTI-INFLAMMATORY DRUG THERAPY

	Total	MTX alone	MTX and anti-malarial	<i>P</i> value
Number on MTX	50	32	14	
Median weekly dose of MTX (mg)	10	10	12	0.0036
(Range in mg)	(5 - 17.5)	(5 - 17.5)	(7.5 - 17.5)	
Median cumulative dose of MTX (mg)	535	450	599	NS
(Range in mg)	(5 - 4540)	(5 - 4540)	(70 - 1440)	
Median duration of MTX (months)	11	11	12	NS
(Range in months)	(1 - 105)	(1 - 105)	(3 - 38)	
Number given folate (%)	41 (82)	23 (71.9)	14 (100)	0.041
Number given NSAIDs (%)	48 (96)	30 (93.8)	14 (100)	NS
Number given prednisolone (%)	42 (84)	28 (87.5)	10 (71.4)	NS
Mean dose of prednisolone at study entry (mg)	4.9	4.9	4.7	NS

MTX: methotrexate; NS: not significant; NSAID: non-steroidal anti-inflammatory drug

Note: Folate supplements were prescribed at a dose of 5 mg/day.

P values are for comparisons between groups on MTX and MTX and an anti-malarial.

phosphamide. She was treated with methotrexate 2.5 mg a week increasing to 10 mg a week over 3 months with improvement of her arthritis. Haematological parameters remained stable with no increase in the mean corpuscular volume. Pancytopenia, rash and oral ulcers developed after 3 months of therapy, at which time the serum creatinine was 442 $\mu\text{m/L}$. Intravenous folinic acid 60 to 120 mg a day was given for 2 days with resolution of all adverse events. No bone marrow examination was performed.

Gastrointestinal adverse events consisting of oral ulcers or stomatitis occurred in 4 patients. Nausea, diarrhoea or abdominal distension occurred in a further 4 patients. These adverse events resolved despite continued therapy on 5 occasions and with temporary cessation of therapy on 3 occasions. A single elevation of hepatic transaminases occurred in 3 patients and resolved despite continued therapy in 2 patients. Methotrexate was permanently discontinued in the third patient, who had no clinical evidence of liver disease.

Infections occurred in 3 patients. Two patients developed herpes zoster of the maxillary branch of the right trigeminal nerve (after 96 months of therapy with a methotrexate dose of 10 mg/week) and of the right twelfth thoracic dermatome (after 2 months of methotrexate at 12.5 mg/week). The daily doses of prednisolone at the time were 4 mg and 9 mg respectively. A third patient developed cellulitis after 2 months of therapy, the methotrexate dose at the time of infection being 7.5 mg/week and the daily dose of prednisolone being 7.5 mg.

Patients on combination therapy with methotrexate and an anti-malarial did not have more adverse events than those on methotrexate alone (Table III). The percentage of adverse events appeared to be higher in the combination therapy group; this was confounded by the presence of one patient in the combination therapy group who had multiple adverse events related to renal impairment, accounting for 33% of all adverse events in this group. When this patient was excluded from analysis, there was no difference in the percentage of adverse events between the 2 groups.

Cessation of Methotrexate

Methotrexate was stopped in 9 out of 15 patients due to adverse events and restarted in 7 of these 9 patients with no recurrence of the offending adverse event. All adverse events resolved with temporary or permanent cessation of therapy. In 2 patients each with stomatitis/oral ulcers, nausea/diarrhoea or asymptomatic hepatic transaminase elevation, adverse events resolved despite continued therapy. Methotrexate was permanently discontinued in 1 patient each with pancytopenia (in the patient with renal failure) and a single asymptomatic elevation of hepatic transaminases. Methotrexate therapy was also ceased in 8 patients for reasons other than adverse events, with permanent cessation for non compliance (1 patient), planned pregnancy (1 patient), temporary cessation for upper respiratory tract infection (4 patients) and non specific cough (2 patients). In the latter 2 patients, methotrexate was subsequently restarted without a recurrence of the cough after methotrexate pneumonitis and opportunistic infections had been excluded.

TABLE III: ADVERSE EVENTS WITH METHOTREXATE

	Total number (%)	Methotrexate alone (%)	Methotrexate and anti-malarial (%)	<i>P</i> value
Haematological				
Leucopaenia	2 (4)	2 (6.3)	0 (0)	NS
Pancytopenia	1 (2)	0 (0)	1 (7.1)	NS
Gastrointestinal				
Stomatitis/oral ulcers	4 (8)	1 (3.1)	2 (14.3)	NS
Nausea, diarrhoea, abdominal distension	5 (10)	3 (6.3)	2 (14.3)	NS
Hepatic transaminase elevation	3 (6)	1 (3.1)	0 (0)	NS
Rash	1 (2)	0 (0)	1 (7.1)	NS
Infection				
Herpes zoster	2 (4)	0 (0)	2 (14.3)	NS
Cellulitis	1 (2)	0 (0)	1 (7.1)	NS
Total number of patients with adverse events (%)	15 (30)	6 (18.8)	4 (28.6)	NS
Total number of occurrences of adverse events (%)	19 (38)	7 (21.9)	9 (64.3)	0.008*
Corrected total number of occurrences of adverse events*	15 (30)	7/32 (21.9)	5/13 (38.5)	NS

NS: not significant

Note: *P* values are for comparisons between groups on methotrexate alone and combination therapy with methotrexate and an anti-malarial.

*The adverse events in one patient with renal impairment related pancytopenia, rash and nausea (on two occasions) were removed from this analysis

Discussion

The incidence of adverse events of methotrexate therapy reported in the literature varies widely, partly as a result of differing criteria for diagnosis and patient characteristics. Increasing age,¹² non use of folate supplements¹³ and the presence of "third space" fluid¹⁴ have been associated with a higher incidence of adverse events. The relationship between the dose and duration of methotrexate therapy and adverse events has been investigated in several studies. Although a dose response relationship for the efficacy of methotrexate in rheumatoid arthritis has been shown, a correlation between the weekly methotrexate dose and adverse events has been established only for gastrointestinal toxicity in some¹⁵ but not all¹⁶ studies. Kremer and Lee¹⁷ did not find a greater incidence of adverse events with increasing duration of therapy during 53 months of follow up. In contrast, Schnabel et al¹⁸ noted an increasing incidence of gastrointestinal and neurological adverse events during 30 months of methotrexate therapy.

Our study population consisted of patients with more severe rheumatoid arthritis than that commonly seen in Oriental populations, with a greater incidence of rheumatoid nodules and extra-articular involvement than has been reported previously.^{19,20} The preponderance of female patients is similar to that noted previously in both Oriental^{19,20} and Western²¹ populations, the racial distribution being similar to that of a previous study of rheumatoid arthritis in Singapore¹⁹ and that of the Singapore population in general.²² Fifteen patients in our series experienced adverse events of methotrexate therapy on 19 occasions, the majority of which were minor and transient, resolving with either temporary cessation of methotrexate or continued therapy.

Pancytopenia developed in 1 patient with refractory rheumatoid arthritis and end-stage renal failure on haemodialysis. The relationship of methotrexate-related pancytopenia and leucopenia to renal failure has been previously reported,²³ and is due to the decreased excretion of methotrexate. It is noteworthy that this patient derived significant improvement in her arthritis with methotrexate following a lack of improvement with other disease modifying anti-rheumatic drugs. This patient might conceivably have been maintained on methotrexate therapy with titration of the methotrexate dose according to serum methotrexate levels. The optimum serum levels for therapeutic efficacy however remain undefined.

The resolution of gastrointestinal adverse events with continued methotrexate therapy as seen in this series is consistent with a growing body of literature.¹⁵ Single elevations of hepatic transaminases in otherwise asymptomatic patients resolved spontaneously in 2 patients in our series and did not require cessation of therapy. This is reflected in the recently published American College

of Rheumatology guidelines on the use of methotrexate.²⁴ However the risk of hepatotoxicity remains a source of major concern, with cases of methotrexate-related liver cirrhosis in rheumatoid arthritis having been reported.⁷

The course of herpes zoster in our patients was uneventful. As in other series, herpes zoster resolved with temporary cessation of methotrexate, with no recurrence with subsequent methotrexate therapy.²⁵ Disseminated herpes zoster, though rare, has been reported.²⁶

The subgroup of patients on combination therapy with methotrexate and an anti-malarial showed no significant increase in the total number of adverse events (Table III). This group of patients had more severe rheumatoid arthritis with more extra-articular manifestations than patients on methotrexate alone. More severe disease, a higher methotrexate dose and the more frequent use of chloroquine than hydroxychloroquine (chloroquine having a higher incidence of adverse events than hydroxychloroquine²⁶) in the combination therapy group should have resulted in more adverse events than in the monotherapy group. That this did not occur is noteworthy and may reflect an actual lack of increased adverse events with this combination,²⁷ the protective effect of folate supplements in the combination group (where folate was more often used) or a type II error.

The majority patients were on concomitant low dose oral prednisolone (Table II). There is little data on the effects of concomitant long term corticosteroid use on methotrexate toxicity, with most series allowing low dose prednisolone therapy.

Restarting methotrexate in patients with minor adverse events appears to be safe. All patients in the current study in which methotrexate was restarted after gastrointestinal adverse events and non life-threatening infections, did not experience a recurrence of the offending adverse events. This has been the experience in other series,¹⁵ though Kremer and Lee¹⁷ found that patients experiencing an adverse event tended to have recurrences of the same adverse event subsequently.

The retrospective design of this study is likely to have resulted in an underestimate of the number of adverse events by not capturing data on patients who had defaulted follow up because of methotrexate-related adverse events and because of incomplete documentation of minor adverse events. Major adverse events and opportunistic infections would, by virtue of their severity, have been documented. Adverse events with low dose oral weekly methotrexate are largely dose independent with the possible exception of gastrointestinal events.¹⁵ Post marketing surveillance in 497 patients on methotrexate therapy followed over 735.3 patient years suggests an incidence of methotrexate-associated liver abnormalities, leucopenia, thrombocytopenia and pancytopenia of 41/1000, 5/1000, 2/1000 and 8/1000

patient years respectively.²⁸ Methotrexate-associated liver cirrhosis is estimated to occur in 0.1% of patients over 5 years of therapy.²⁴ A long-term cohort study of several thousand patients would therefore be required to definitively determine the incidence of methotrexate-related adverse events. We are not aware of such a study having been published. The present study provides some information on the toxicity of methotrexate in an Asian population, though the retrospective data collection and relatively small sample size do not allow definitive assessment of the incidence of methotrexate-related toxicities. As the primary aim was to determine the safety and tolerability of methotrexate in an Asian population, a control group (rheumatoid arthritis patients not treated with methotrexate) was not included in the study.

In conclusion, we have found that a low oral dose of methotrexate weekly was well tolerated in the patients with rheumatoid arthritis in our study, and could safely be restarted in those with non life-threatening adverse events.

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