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# Methotrexate in psoriatic arthritis

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## ABSTRACT

*Methotrexate (MTX) is a folic acid analogue with antiproliferative and anti-inflammatory effects. In the past several years, MTX has become the most commonly used agent in patients with severe, destructive psoriatic arthritis (PsA), with positive clinical results. Liver changes and serum enzyme level increases do not seem to be a major problem in PSA patients treated with MTX. In addition, PSA patients treated with low-dose MTX were not associated with pulmonary fibrosis as evaluated by means of sensitive imaging techniques and pulmonary function tests. The concomitant use of folic acid reduces both the frequency of serum liver enzyme level increases but also the efficacy of MTX by competing with the folate receptors.*

## Introduction

Methotrexate (MTX) is a folic acid analogue originally synthesized in the 1940s which is designed to inhibit dihydrofolate reductase (1). Reduced folate (tetrahydrofolate) is the proximal single carbon donor in several reactions involved in the *de novo* synthetic pathways for the purine and pyrimidine precursors of DNA and RNA required for cell proliferation. Furthermore, tetrahydrofolate is involved in a second important biochemical step: the methionine-homocysteine cycle, which is necessary to provide a methyl group for several downstream reactions such as methylation of DNA, RNA proteins and others. Therefore, MTX has been used extensively for the treatment of neoplastic diseases.

A serendipitous observation in 1951 that the folate analog aminopterin induced striking therapeutic benefit in rheumatoid arthritis (RA) and psoriasis (2) led to exploration of the use of MTX in non-neoplastic diseases. The initial rationale for MTX was that it inhibited proliferation of the lymphocytes and other cells which caused joint and skin inflammation.

The following 20 years saw confirmation of the efficacy of both aminopterin and MTX in psoriasis in several clinical trials, as well as recognition of the reduced toxicity of MTX using a weekly schedule. The daily oral schedule for MTX used in the 1960s was found to lead to frequent toxicity and was replaced by a weekly oral dose schedule in the 1970s. Initially weekly MTX was commonly given intravenously, but by the 1970s it had been almost completely replaced by oral and, to a much lesser extent, intramuscular dose schedules (3). The primary objective of MTX in psoriasis appeared to be to control the excess rate of epidermal proliferation and the underlying inflammation that exist in the disorder. Subsequent studies using oral and parenteral MTX demonstrated favorable clinical responses in patients with a severe destructive inflammatory reaction in psoriatic arthritis (PsA).

## Antiinflammatory effects of MTX

Recently, MTX has been shown to have a variety of antiinflammatory effects (4), which may represent its central role in RA and psoriasis. There are few studies suggesting any specific effect of MTX on the T-cell number or function in RA patients. However, MTX exerts clear inhibitory effects *in vivo* and *in vitro* on neutrophils and monocytes/macrophages, that are believed to play a central role in RA pathophysiology and inflammatory synovitis (5-7). MTX does block tetrahydrofolate-dependent steps in cell metabolism. Since tetrahydrofolate and polyglutamyl derivatives of tetrahydrofolate are involved in purine biosynthesis, several consequences can appear which terminate in adenosine overproduction. The antiinflammatory effects of MTX appear to be related to an increase in extracellular adenosine and its interaction with specific cell surface receptors (8).

It has been specifically demonstrated that adenosine inhibits lymphocyte proliferation, the production of TNF-

alpha, IL-8 and IL-12, and increases secretion of IL-6 and IL-10, via A2 receptor binding (9). Binding of adenosine to A3 receptors leads to the inhibition of secretion of TNF, IL-12 and IFN-gamma (10). Therefore, binding of adenosine to A2 and A3 receptors appears to provide one of the important antiinflammatory mechanisms of MTX. In addition, a significant increase of IL-1Ra was observed with the low-dose MTX treatment of human cultured monocytic THP-1 cells, suggesting possible IL-1Ra-mediated antiinflammatory effects of MTX on monocytes (11).

MTX effects have been observed on metalloproteases and their inhibitor levels, and have been suggested to represent an indirect effect due to an MTX-associated alteration of the cytokine milieu rather than a direct influence on gene expression (8).

Recent data suggest that disruption of the cell cycle caused by high-dose MTX treatment may be the initial step of the apoptotic sequence of dying cells and may explain the antiproliferative effects of the drug (8). In addition, MTX polyglutamate derivatives may interfere with purine and pyrimidine metabolism and explain the long-term antiproliferative effects following low-dose treatment with MTX once a week (8). The antiinflammatory effects of MTX seem to be at least partially linked to antiproliferative and apoptosis-related mechanisms.

Finally, MTX actions on cyclooxygenase and lipoxygenase may lead to further indirect antiinflammatory actions of MTX in RA (8).

### **MTX in psoriatic arthritis: A historical overview of the clinical studies**

Following the initial study in 1951, subsequent reports demonstrated favorable clinical responses to oral or parenteral MTX, with relatively low toxicity, in patients with PsA (12).

In 1964 a double blind placebo-controlled study compared parenteral MTX (three intramuscular doses of 1-3 mg/Kg at 1-day intervals) with placebo over 3 months in 21 PsA patients who had active skin involvement and peri-

pheral arthritis. MTX effectively suppressed both skin and joint involvement, as well as improving the erythrocyte sedimentation rate (ESR). A 30% incidence of adverse events was seen that did not require cessation of therapy (13).

In 1983 the response of PsA to MTX was evaluated retrospectively in 59 consecutive patients. Initially almost all received 15 mg weekly (14); the dose was gradually reduced when clinical improvement was seen. MTX was discontinued in 7 patients within a year due to adverse reactions. The remaining 52 patients were treated for 1 to 11 years (median 3 years). A modest improvement was seen in 21 patients, while signs of inflammatory joint disease almost disappeared in the other 22 patients. The favorable response was associated with a short disease duration, but was unrelated to the severity of the disease (14).

In 1984, 37 patients with PsA were entered into a 12-week prospective, controlled, double-blind multicenter trial comparing placebo and oral pulse MTX therapy (15). MTX was given in a dose of 2.5 – 5.0 mg every 12 hours in 3 consecutive doses per week. A stable background medication program with nonsteroidal anti-inflammatory drugs was allowed. MTX was found to be superior to placebo only in the physician's assessment of arthritis activity and in improvement of the amount of skin surface area with psoriasis. A small but statistically significant rise in serum total bilirubin occurred in the MTX-treated patients. No patients were withdrawn from the study for adverse drug effects (15).

In 1992, a report indicated that 38 out of 40 PsA patients (95%) treated with low-dose, weekly therapy (mean dose of 11.2 mg) experienced and excellent or good clinical response and also improvement in ESR. Only 2 patients had a poor response (16). The patients included 24 men and 16 women, with a mean age of 47 years (16-75), oligoarticular (13) or polyarticular (27) involvement, and a mean disease duration of 12 years (range 1-36 y) (17). Two patients discontinued the medication because of side effects: leukopenia in one

and stomatitis in the other. Eleven patients presented with liver test abnormalities: 3 mild, 6 moderate and 2 severe. Seven patients had 11 liver biopsies. Only one had evidence of cirrhosis or inflammation which occurred very early in the course of MTX therapy.

This patient continued taking MTX treatment without further deterioration of liver chemistry and/or histology. No changes were observed in the histopathology in those with repeated biopsies. It was concluded that MTX is effective and safe in PsA, and that it is not necessary to perform liver biopsies on a routine basis (17).

The results were confirmed in 1994 by another study that analyzed 33 PsA patients treated with a mean MTX dose of 7.8 mg/week (range 5-15 mg) orally for 6 months along with NSAIDs. There was complete to partial remission in PsA and skin lesions in 94% of the patients (18). Two patients failed to respond. No significant side effects were seen.

In 1995 two interesting studies analyzed the radiological outcome and the association of MTX and cyclosporin A in the treatment of PsA, respectively (19, 20).

The first study compared patients who were given MTX with patients who had never had MTX (19), matched by damage, actively inflamed joints, sex, and disease duration. The study population comprised 38 patients (16 F, 22 M) with a mean age of 44.6 years and a disease duration of 11.4 years. Twenty-three patients continued therapy for 24 months. Clinical evaluation revealed that 45% of the patients had 40% improvement in the actively inflamed joint count at 6 and 24 months. Radiographs were available for 19 of the 23 patients who took MTX for 24 months, and they were compared to their respective controls. Radiographic damage scores at 24 months showed an increase in the damage score in 63% of the patients. Compared to the matched controls, there was no statistically significant difference in the progression in damage (19).

The second study had the objective of comparing the effectiveness and toxicity

ty of cyclosporin A (CsA) vs low-dose MTX over a period of one year in the treatment of PsA with peripheral involvement (20). Thirty-five patients with PsA were enrolled in a prospective, controlled, randomized trial. CsA was given initially in doses of 3 mg/kg/day to a maximum permitted dose of 5 mg/kg/day; MTX was given in oral doses of 2.5 mg every 12 hours for 3 consecutive doses each week up to a maximum dose of 15 mg/ weekly. Clinical and laboratory evaluations were performed at entry and monthly thereafter. After 6 and 12 months the number of painful joints, the number of swollen joints, the Ritchie index, the duration of morning stiffness, grip strength, CRP, the patient's and the physician's assessment of PsA activity, as well as the Psoriasis Area and Severity Index (PASI), were significantly improved in both treatment groups. ESR values were significantly reduced only in the MTX group ( $p < 0.01$ ), which also showed a significant increase of liver enzymes. The changes in the main clinical and laboratory parameters during the course of CsA or MTX treatment were not significantly different other than for the AST and ALT levels ( $p < 0.05$ ). After one year of therapy CsA and MTX were withdrawn in 41.2% and 27.8% of the patients, respectively, although these differences were not statistically significant. In conclusion, the one-year prospective trial showed that low-dose CsA and MTX are both effective in the treatment of PsA, but MTX showed greater tolerability, a point which must be taken into consideration at the start of therapy (20).

In the late 1990s various other studies analyzed MTX in combination therapy for PsA (21). In a recent study patients with PsA were treated with anti-TNF- $\alpha$  antibody, in view of the large amounts of TNF- $\alpha$  in inflamed skin, keratinocytes and inflammatory cells (22). Six patients with progressive joint disease and psoriatic skin lesions unresponsive to MTX were treated with anti-TNF- $\alpha$  antibody infliximab. The authors concluded that therapy with anti-TNF- $\alpha$  antibody may be an effective treatment regimen for

PsA and psoriatic skin lesions (22), as further presented in this supplement.

### Safety studies of MTX in PsA

Two recent reviews have analyzed the rate of side effects in PsA patients treated with MTX (23, 34).

The first review presented a 30-year retrospective analysis of 104 psoriasis and PsA patients (60 male, 44 female) treated with MTX between October 1968 and October 1998 (23). The severity of adverse reactions (ADR) was classified according to the Common Toxicity Criteria (CTC). Acute ADR was defined as adverse effects within the first 90 days of MTX therapy. ADR seen later were classified as chronic. ADRs were seen in 83 patients. CTC grade 3 or 4 blood count changes, CNS side effects, and infections were more frequent in patients who had received a cumulative dose  $< 2000$  mg than in 23 patients who received 2000 mg MTX (group A). However, liver changes and serum enzyme level increases did not differ in the two groups. Therefore, ADR are common in PsA on MTX therapy independent of the cumulative dose, but in most cases they are temporary and mild. Liver changes and serum enzyme level increases were not a major problem (23).

The second review was devoted to a study of another suspected complication, namely pulmonary toxicity in PsA patients treated with weekly low-dose MTX (24). Analyses of chest x-rays, high resolution computed tomography, and pulmonary function tests were performed in 27 Caucasian PsA patients treated with weekly low-dose MTX, none of whom had previous recognized interstitial lung disease. The median age of the patient cohort was 50 years (range 24-70 years) and the sex ratio was 20M/7F. Seventeen patients had previously used other disease-modifying antirheumatic drugs. The mean weekly dose of methotrexate was 8.46 mg (range 5-15 mg), the average treatment period was 52 months (range 3-240 months), and the median cumulative dose was 2241 mg (range 300-6520 mg). High resolution computed tomography failed to show alveolar or interstitial involvement in any patient.

Diffusing lung capacity for carbon monoxide was mildly altered only in 2 cases. Pulmonary function tests did not show differences between patients with and without recognized risk factors for developing MTX-associated lung toxicity identified in RA patients, including old age, diabetes, hypoalbuminemia, previous use of disease modifying antirheumatic drugs.

In conclusion, MTX was not associated with pulmonary fibrosis evaluated by means of sensitive imaging findings and pulmonary function tests in this cohort of 27 PsA patients (24).

In 1996 a study showed that in 54 out of 96 PsA patients (48 male and 48 female) who had undergone one or more courses of DMARD ( $n = 109$ ), there was a survival rate of 6 months for gold sodium thiomalate (GOLD) and sulphasalazine (SSZ), and 16 months for MTX (25). Differences between MTX and gold were statistically significant, while other differences were not statistically significant, possibly because of the small numbers and heterogeneity of the patient groups. The most common cause of withdrawal for GOLD and SSZ was adverse effects (25).

A 1995 study compared folic acid (FA) levels in PsA (and RA) patients being treated with MTX with those of untreated patients in order to investigate potential folate depletion by MTX and its possible relationship to the drug's efficacy (26). FA, cyanocobalamin (B12), and MTX were measured in serum and red blood cells (RBC) in 33 patients on low-dose MTX therapy and in 24 control patients. MTX treated patients had lower FA levels than controls (median 4.36 vs 7.37 ng/ml,  $p < 0.001$ ). A significant correlation between serum FA and MTX/RBC ( $p < 0.01$ ) and between the weekly dose and MTX/RBC ( $p < 0.01$ ) was seen. There was no correlation between FA and the cumulative total MTX. MTX patients had lower B12/RBC levels than the controls ( $p < 0.001$ ); the serum levels of B12 were not different. Clinical features, ESR and CRP did not correlate with FA, B12 or MTX levels. Therefore, the degree of folate depletion during MTX therapy appears to depend primarily

upon the weekly administered dose. Folate depletion may be related to B12 deficiency in RBC. The finding that FA levels were not related to disease activity supports again the concept that MTX does not exert its action in PsA and RA primarily by inhibiting dihydrofolatereductase. Therefore, additional folate compounds, if necessary, should not lead to a reduction in the efficacy of MTX (26).

Of increasing concern, however, are the recent reports of lymphoproliferative malignancies associated with MTX (21), and pancytopenia with a high mortality rate in both RA and PsA patients (21) with the increasing use of MTX. However, these findings remain rare.

### MTX in psoriatic arthritis:

#### Practical guidelines

In the past several years MTX has become the most commonly used agent in patients with severe, destructive PsA. The recommended MTX schedule is 7.5 to 15 mg/week, given as a single dose (preferably taken at night) or divided into two doses taken 12 hours apart on the same day. This can be increased to 20 to 30 mg/week until improvement is seen, and then be tapered down to a maintenance dose that varies from patient to patient but is usually slightly higher (5-15 mg/week) than that used in RA. Intra-articular MTX therapy has not been conclusively shown to be effective in the management of PsA (12).

Monitoring of MTX therapy in PsA prior to the treatment includes complete blood cell counts, serum creatinine, liver function tests (ALT, AST), and hepatitis C and B panels (27). During MTX therapy it is suggested to repeat the blood cell counts and kidney liver function tests every 4 to 8 weeks. Contraindications to MTX therapy include pregnancy and alcoholism.

Determination of MTX serum levels during low-dose therapy does not provide useful information. MTX serum levels in both RA and PsA patients treated with a low-dose weekly schedule do not show significant increases during the course of therapy over values at the onset of treatment. Likewise,

no correlation has been shown with the total cumulative dose, the clinical picture, or the recurrence of side effects. Furthermore, no relationship has been observed between the changing of laboratory parameters and MTX levels (12).

More knowledge about the basic mechanisms of action of MTX might help to explain the problem of non-responders or resistance to treatment among RA patients. A recent study demonstrated that folate receptor beta (FR- $\beta$ ) expression is selectively elevated in RA synovial macrophages and suggests that MTX is transported within the cell through the FR- $\beta$  (28).

However, this *in vitro* study and another more recent *in vivo* study both showed that the co-administration of MTX and folic acid reduces the cellular uptake and increases the total clearance of MTX, respectively (29). In addition, a recent study considering some clinical variables showed that RA patients treated with MTX without folic acid supplementation had significantly lower disease activity than controls treated with both MTX and folic acid (30). However, the authors concluded that the addition of folic acid to MTX prevented some side effects even if with a small loss of efficacy. Therefore, as already suspected, the co-administration of MTX and folic acid might represent a possible cause of MTX resistance in RA treatment and seems to be related to their competition for absorption (31). The majority of studies suggest the advisability of the delayed administration of folates to avoid interference with the antiinflammatory effects of MTX (31-34).

Based on the available studies that indicate adenosine as responsible for the antiinflammatory actions of MTX, a very recent investigation in the adjuvant arthritis model of RA has shown a reversing of the antiinflammatory effects using adenosine receptor antagonists such as theophylline and caffeine (35). As a matter of fact, a high intake of caffeine or theophylline might represent a further cause of reduced response to low-dose MTX in both PsA and RA. However, side effects are common even in PsA patients treated with

other compounds (i.e., CsA 58% and SSZ 44%) (36).

Finally, a very recent study showed no significant differences between folic acid and foiling acid in reducing elevated ALT: the only significant cause of discontinuation MTX therapy over 12 different causes when compared to patients treated with MTX alone (37). However these folic/treated-treated patients needed higher MTX doses to obtain any significant therapeutic efficacy when compared to the treatment with MTX alone.

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