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# Use of methotrexate in patients with psoriatic arthritis

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A. Ceponis and A. Kavanaugh

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Division of Rheumatology, Allergy and Immunology, University of California San Diego, La Jolla, California, USA.

Arnold Ceponis, MD, Fellow in Rheumatology  
Arthur Kavanaugh, MD, Professor of Medicine

Please address correspondence and reprint requests to:

A. Kavanaugh, MD,  
9320 Campus Point Dr., suite #225,  
Center for Innovative Therapy,  
University of California San Diego,  
La Jolla, 92037-0943, USA.  
E-mail: akavanaugh@ucsd.edu

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## ABSTRACT

*Despite a paucity of high quality clinical data, methotrexate (MTX) remains one of the most commonly used medications in the treatment of patients with psoriatic arthritis (PsA). This report addresses mechanistic rationale, available clinical evidence, safety considerations, and a potential research agenda regarding the use of MTX in the management of PsA.*

## Introduction

Psoriatic arthritis (PsA) is an inflammatory joint disease that has been estimated to occur in as few as 5% and as many as 40% of patients with psoriasis in various analyses (1). A reasonable estimate of PsA amongst individuals with psoriasis is approximately 15%. One of the distinct clinical characteristics of PsA is the potential diversity of clinical manifestations among affected patients. This includes peripheral arthritis, involvement of the axial skeleton, enthesitis, dactylitis, ocular inflammation (anterior uveitis/iritis), bowel inflammation, and skin and nail psoriasis.

There can be great variability in the severity and activity of these different domains in individual patients, and the pattern of involvement may also vary during the course of the disease. Regarding peripheral arthritis, previously Moll and Wright suggested that oligoarthritis may be the most common pattern (2). However, recent data from the CASPAR study group indicate that polyarticular joint involvement, which is associated with poorer outcomes than oligoarthritis, is actually the most common, being seen in approximately 60% of PsA patients (3). Multiple lines of evidence indicate that there are clear immunopathophysiologic distinctions between PsA and rheumatoid arthritis (RA); interestingly however, 15% or more of PsA patients may be positive for serum rheumatoid factor and approximately 8% have detectable

antibodies to citrullinated proteins (e.g. anti-CCP antibodies) (4).

Like the clinical manifestations and natural course of the disease, the severity of joint involvement may vary greatly among individual patients affected by PsA. While some patients may have a benign course, PsA may lead to a significant peripheral joint destruction, radiological progression of joint damage, and functional impairment, to an extent comparable to that seen in RA. Thus, active intervention with traditional disease modifying drugs (DMARDs) and/or biologics is appropriate for active PsA (5).

At present, methotrexate (MTX) is the most commonly utilised initial regimen for PsA patients with peripheral arthritis. This practice is supported by data from the CASPAR study where MTX was found to be the most commonly utilised traditional DMARD in PsA (39% of PsA patients) (6). The same study showed MTX to be the most commonly utilised drug in various combination regimens including in combination with other DMARDs such as sulfasalazine, with prednisone or with biologic agents such as TNF-inhibitors. Together with TNF-inhibitors, MTX appeared to have the lowest percentage of discontinuation for inefficacy. Interestingly, in this era of “evidence-based medicine” the widespread use of MTX prevails despite the notable paucity of high quality clinical data from either clinical trials or systematic reviews of clinical practice documenting its efficacy in PsA. So, questions remain: what is the rationale for the use of MTX in PsA? How effective is it in this condition, and for which manifestations?

## Rationale for MTX use in PsA

A major component of the rationale for the use of MTX for PsA is its proven benefit in RA (reviewed elsewhere in this supplement). It appears that anti-inflammatory mechanisms, via effects

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on adenosine metabolism, may be more important than anti-proliferative mechanisms, via effects on dihydrofolate reductase, in RA and in other autoimmune conditions. Another important rationale for the use of MTX in PsA is the clinical benefit of MTX on skin psoriasis (reviewed elsewhere in this supplement).

In PsA, as in other autoimmune conditions, the immunopathophysiologic effects of MTX are largely unknown. A limited study of knee synovial sampling at baseline and 6–12 months after MTX 7.5–15mg/week in 10 DMARD-naïve PsA patients with either oligo- or polyarthritis showed significant reduction of CD3+, CD4+, CD8+ and CD68+ (macrophage) cell infiltration in sublining layer and reduction of synovial lining thickness after treatment with MTX.

However, histological inflammation was not completely abolished and no effect on synovial hypervascularity was observed (7). Similarly, synovial CD62 E (E-selectin) and CD54 (ICAM-1) staining was significantly reduced after treatment with MTX, but positive correlation between clinical and histological markers was found only between CD68+ cell counts and ESR. Significant reduction of synovial MMP-3 mRNA (but not of TIMP-1) was also shown in the same study after treatment with MTX. Reduction in mRNA expression of pro-inflammatory cytokines was noted as well, but significant reduction was observed only for mRNA of IL-8, out of twelve cytokines studied (including IL-12p35 and IL-12p40). Given the differences in synovial pathology compared to RA (8–11), the effects of MTX

on synovial/joint pathology may not be extrapolated from those in RA studies. The efficacy of MTX has not been addressed specifically for many of the other clinical manifestations of PsA such as enthesitis, dactylitis, axial disease, and iritis. There are more data showing the efficacy of TNF inhibitors for these clinical manifestations in PsA (12–14). Whether TNF inhibitor combination with MTX has synergistic efficacy in this context is an important clinical question requiring further investigation.

### Clinical studies on MTX use in PsA

A very early report of MTX in PsA dates to 1951 (15). Unfortunately, almost 60 years later, we have little sound data to better guide use of MTX in PsA.

**Table I.** Major randomised clinical trials of methotrexate in psoriatic arthritis.

Study (reference no.)	Study design, patients	Treatment regimen	Outcome measures	Results
O'Brien WM <i>et al. Arthritis Rheum</i> 1962 (16)	Double blind, placebo controlled, up to 39 months, 18 patients with peripheral arthritis	Test injection of MTX 25 mg x1, then increasing the dose from 1 to 3 mg/kg with 7–14-day intervals (parenteral injections)	Skin surface area (%) involved, scores of joint pain on ROM, joint swelling, and TTP, ROM	Moderate to marked improvement of arthritis scores and psoriasis in 72% of cases; less toxicity with intermittent administration of MTX noted
Black RL <i>et al. JAMA</i> 1964 (17)	Double-blind, placebo controlled, cross over, 1.5 months, 21 patients with active peripheral arthritis	Test dose of MTX 25 mg x1, then 1–3 mg at 10-day intervals x3, i.v. or i.m.	Involved skin surface area (%), joint index (graded 03), joint ROM, ESR, CRP	Significant improvement in joint index, ROM, and ESR. Significant reduction of the % of skin area involved (rapid response)
Willkens RF <i>et al. Arthritis Rheum</i> 1984 (18)	Double-blind, placebo controlled, 37 patients with active arthritis of ≥3 joints for (DIP involvement, RA-like, or arthritis mutilans) of ≥6 months	Oral MTX 2.5 mg q 12 h x3 / week (7.5 mg weekly); after 6 weeks, permitted increase to 15 mg weekly	TJC, SJC and scoring, PhGA and PGA, a.m. stiffness; skin surface area, skin inflammation and scaling; assessment q 3 weeks	Significant improvement only in PGA and reduction in % of psoriasis surface area
Scarpa R <i>et al. Clin Rheumatol</i> 2008 (19)	35 early PsA patients ("oligo-enthesoarthritis <12 weeks") randomised into 2 groups matched by joint involvement patterns	NSAID for 3 months, then + MTX 10 mg week i.m. for another 3 months vs NSAID + MTX 10 mg/week i.m. for 6 months	TJC, SJC, PGA, PhGA, VAS, ESR, CRP	Both groups improved; significant difference between TJC and SJC at 3 months, and PhGA and PGA at 6 months in favour of MTX
Kingsley GH <i>et al. MIPA (MTX in PsA) trial. BHPR</i> 2010 (20)	Double-blind RCT, 221 patients with active oligo- or polyarthritis, 6 months	MTX 15 mg/week vs. placebo	PsARC, ACR, SJC, TJC, PGA, PhGA, HAQ, VAS, pain, CRP, ESR	PsARC 39% in MTX vs. 27% in placebo group ( $p=0.063$ ; $p=0.049$ for completer analysis); PGA and PhGA in favour of MTX; no difference in other outcome measures

PsA: psoriatic arthritis; RA: rheumatoid arthritis; MTX: methotrexate; TTP: tenderness to palpation; ROM: range of motion; SJC: swollen joint count; TJC: tender joint count; ACR: American College of Rheumatology response criteria; PsARC: Psoriatic Arthritis Response Criteria; DIP: distal interphalangeal joints; CRP: C-reactive protein; PGA: patient's global assessment; PhGA: physician's global assessment; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale for pain.

Relatively small randomised or open observational studies, and a few studies comparative to other DMARDs, are available. An outline of the major char-

acteristics and findings of these studies is given in Tables I and II. Of note, some of these studies included designs and outcome measures that would be

considered unconventional according to current standards, complicating interpretation of the results. It is also undesirable to pool the data in order to

**Table II.** Non-randomised observational studies of methotrexate in psoriatic arthritis.\*

Study (reference no.)	Study design, patients	Treatment regiment	Outcome measures	Results
Kragballe K <i>et al.</i> <i>Acta Derm Venereol</i> 1983 (21)	Retrospective analysis of 11 yr experience with 59 patients with active polyarticular PsA (90% DIP involvement)	Initial MTX 15 mg/week, maintenance median dose 10 mg weekly (2.5–15mg); median Rx duration 3 yrs (1–11 yrs)	Combined score of joint pain on motion, tenderness, swelling, analgesic use and ESR	Significant improvement of inflammatory joint disease in 42% of patients
Zachariae H & Zachariae E <i>Acta Derm Venereol</i> 1987 (22)	Prospective 12 month study of 12 patients with DIP and 18 patients with SI joint inflammation	MTX 15 mg/week (5 mg q 12 hours)	SJC, Ritchie index, a.m. stiffness, VAS for pain, analgesic consumption, general condition, ESR	All parameters were improved significantly at 3, 6 and 12 months of treatment
Espinoza LR <i>et al.</i> <i>J Rheumatol</i> 1992 (23)	Prospective open label study of 40 PsA patients with oligo- or polyarticular active synovitis (10 had axial involvement)	Mean duration of treatment 34 months (6–132), mean MTX dose 11.2 mg/week (5–25 mg)	Excellent response: no synovitis, ESR normal or <50% of baseline; good response: < 4 inflamed joints (decrease of at least 50% in number of involved joints); ESR, Hb	Excellent and good response in 37% and 58% of patients, respectively; significant decrease in ESR and increase in Hb; complete resolution of nail disease in 50% of patients
Ranza R <i>et al.</i> <i>J Rheumatol</i> 1993 (24)	Observational study of 47 patients with polyarticular PsA	MTX 10–12.5 mg/week i.m. for mean of 1.6 yrs (5 months – 5 years)	SJC, TJC, Ritchie index, ESR, CRP, PASI	Definite improvement in 27 patients; overall statistically significant improvement in all parameters studied
Abu-Shakra M <i>et al.</i> <i>J Rheumatol</i> 1994 (25)	Prospective open label, 24 months, 38 patients with active poly- or oligoarticular PsA; matched controls from PsA database	MTX 5–7.5 mg/week → increase by 2.5–5 mg/week at 4–8 week intervals to max 15–20 mg/week (mean dose 10.6 mg/week)	Radiological damage of peripheral joints (scored by Steinbrocker method); good clinical response - ≥ 40% reduction of actively inflamed joints	No difference in radiological progression or clinical efficacy between MTX and database controls (use of second line drugs was not an exclusion for controls)
Kane D <i>et al.</i> <i>Arthritis Rheum</i> 2004 (26)	Open label, DMARD-naïve 10 PsA patients with active oligo- or polyarthritis, 12 months	Weekly oral MTX 7.5–15 mg based on clinical response, + folate, NSAIDs allowed	Synovial bx before and after 6–12 months, Ritchi Articular Index, SJC, ESR, CRP, DAS (3-variable)	Significant improvement in all parameters, except ESR and CRP; clinical correlation with CD68+ cell (macrophage) counts in synovium observed
Chandran V <i>et al.</i> <i>J Rheumatol</i> 2008 (27)	Longitudinal observational study, 59 patients mainly with polyarthritic PsA, ≥2 yrs on MTX; comparison to historical controls (low dose MTX and later start of Rx)	Median MTX 16.2 mg/week, concomitant DMARDs were allowed	Primary outcome – increase in radiological damage (Steinbrocker score) and ≥40% improvement in the T/SJC	Less radiological progression compared to historical controls; 68% achieved primary outcome for T/SJC
Lie E <i>et al.</i> <i>Ann Rheum Dis</i> 2010 (28)	Longitudinal observational multicenter study, 430 PsA patients compared to 1218 RA patients initially naïve to MTX	For PsA: mean starting MTX dose 10.5 mg, 12.6 mg at 3 moths, and 13.7 mg/week at 6 months; similar doses in RA patients	28-S/TJC, DAS28, ESR, CRP, PhGA, PGA, pain, fatigue, 2 yr retention rates – assessment q3 months during first year, and then yearly (RA patients had more active disease)	At 6 months DAS28 remission rates increased from 7% and 3% to 24% and 27% in PsA and RA, respectively, low disease activity rates, from 13% and 8% to 42% and 43%, respectively; significantly more improvement was seen in adjusted 28-TJC and DAS28 in RA compared to PsA

\*Comparative studies with other traditional DMARDs are not included in this Table

PsA: psoriatic arthritis; RA: rheumatoid arthritis; MTX: methotrexate; TTP: tenderness to palpation; ROM: range of motion; SJC: swollen joint count; TJC: tender joint count; ACR: American College of Rheumatology response criteria; PsARC: Psoriatic Arthritis Response Criteria; PASI: psoriasis area and severity index; DAS: disease activity score; DIP: distal interphalangeal joints; CRP: C-reactive protein; PGA: patient's global assessment; PhGA: physician's global assessment; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale for pain.

perform pooled or meta-analyses, given the diverse patient populations, study designs and outcome measure used.

None of the available studies definitively address the issue of dose-dependent efficacy of MTX in PsA. Nonetheless, some trends may be apparent from available data. Lower doses of MTX, for example 12.5mg/week or lower, generally appear to be associated with less robust efficacy (18). More robust anti-inflammatory effects and reduction in ESR were reported in randomised PsA studies with higher dose MTX (16, 17). Some radiological benefit has been reported in PsA patients on MTX dose higher than 15 mg/week, when compared to historical controls (27). On the other hand, patients taking doses of MTX lower than 15mg/week did not seem to have any difference in radiological progression of the joint damage compared to matched database controls in which NSAID and/or other second line medication were used (25). Similarly, no radiological benefit was seen in a retrospective cohort over 3 years in PsA patients who took lower doses of MTX (29). Previous observational prospective studies (22, 27), and a more recent randomised controlled trial (presented only in abstract form to date) reported marginal effect on clinical efficacy with weekly doses of 15mg or less of oral MTX (20). Although the database is limited, there is the suggestion that weekly MTX above 15mg might be the "threshold" dose at which clinical efficacy is more likely.

Another important issue is timing of treatment initiation. Very few MTX studies enrolled patients with early PsA. Those that did, however, generally report better efficacy of MTX (19, 21), as has been reported in RA, even with doses lower than 15mg/week.

Another factor that affects the interpretation of data concerning MTX efficacy in PsA is the clinical diversity as well as variable natural history of the disease. Many studies did not distinguish patient subgroups with different forms of PsA, which can significantly affect reported outcomes. In general, in the absence of effective therapy, patients with oligoarticular arthritis have better overall outcomes compared to those with polyar-

ticular joint disease. Also, the potential impact of involvement with enthesitis, dactylitis and other clinical features is not well defined. With treatment, patients can achieve improved outcomes, a point illustrated by observations from an open longitudinal study of 47 patients with psoriatic polyarthritis (24). Although response rates were similar to other studies with mixed types of PsA, the overall efficacy of MTX in this patient population appeared to be robust and showed statistically significant improvement in SJC, TJC, Ritchie index, ESR and CRP after treatment with intramuscular MTX 10–12.5mg weekly for a mean period of 1.6 years. In addition, shorter disease duration (in addition to a higher dose) was associated with greater response in several observational studies (27). Nonetheless, the question of possible differences in MTX efficacy in distinct clinical types of joint involvement in PsA will have to be specifically addressed in the future studies.

Few studies have compared efficacy and tolerability of MTX with other traditional DMARDs in PsA. A retrospective study comparing MTX (mean dose 12mg/week) to injectable gold salts (mean dose 150mg/month) for a median of 28 months in peripheral PsA, reported significantly more patients having 50% reduction in T/SJC (primary outcome) for at least 6 consecutive months with MTX compared to injectable gold (30). Discontinuation rates due to inefficacy were also in favour of MTX (9% for MTX vs. 44% for gold). Another prospective controlled randomised trial compared cyclosporine 3–5 mg/kg/day vs. MTX up to 15mg/week. At 6 and 12 months, T/SJC, the Ritchie index, CRP, physicians and patient assessment of disease activity were improved significantly in both treatment groups, but ESR was significantly reduced only in the MTX arm (31). MTX 7.5–15mg/week was also compared with leflunomide (10–20 mg/day) in a two-year retrospective study involving patients with oligo- or polyarticular PsA (32). Higher discontinuation rates were seen with leflunomide (28.6%) than with MTX (12.6%) ( $p=0.056$ ), although cumulative sur-

vival rate of patients who took each drug was similar when discontinuation due to side effects and other causes was taken into account. This is intriguing in the context of the results reported from a double-blind randomised, multinational study of leflunomide in PsA (33). At 24 weeks, efficacy of leflunomide 20mg/day on psoriasis appeared to be less impressive, but the drug was, in fact, effective in joint disease with 59% of patients achieving clinical response in the treatment arm vs. 30% in placebo. More patients achieved ACR20, also had significant reduction of T/SJC, ESR, CRP, and improvement of HAQ, DLOI, pain (VAS), global physician and patients scores compared to placebo. A head to head study of these two traditional DMARDs in PsA would be of interest.

### Combinations of MTX and TNF inhibitors

Synergistic efficacy from the use of MTX together with TNF-inhibitors has been documented in RA, but remains an assumption in PsA. Across the studies of TNF-inhibitors in PsA, low-to-medium dose of MTX was allowed by approximately 40%–50% of study patients (recently reviewed in ref. 14). Subgroup analysis of these patients did not show any significant difference in responses to TNF inhibitor therapy or significant differences in the adverse events, regardless of whether or not patients were taking MTX. However, these studies did not directly address whether or not the combination of TNF inhibitor plus MTX might have synergistic efficacy in PsA. This question was partially addressed in the RESPOND trial, which compared efficacy of MTX 15mg/week vs. infliximab (5mg/kg i.v. at weeks 0, 2, 6, and 14) in combination with MTX 15mg/week in MTX-naïve patients with active polyarticular PsA ( $n=57$ ) (34). Results of the 16 week follow up of this study demonstrated significantly greater DAS28 remission rates at each time point and percent of patients meeting ACR 20/50/70 response criteria as well as greater improvement in PASI 50, 75, and 90 in the group randomised to combination treatment. No significant difference was reported



in ESR between the treatment groups. MTX monotherapy arm also showed noteworthy response in this population of patients, but these preliminary data clearly favour combination therapy for PsA patients with polyarticular involvement. It can also be hypothesised that low dose MTX may decrease TNF inhibitor discontinuation rates due to loss of efficacy.

### Safety of methotrexate in PsA patients

The tolerance of MTX has been relatively well established, given nearly two decades of common clinical use (reviewed elsewhere in this supplement). The most common side effects overall are well recognised and include problems with gastrointestinal intolerance, stomatitis and/or oral ulceration, alopecia, and hepatotoxicity. As used in autoimmune diseases, bone marrow toxicity is not common, although it remains of concern. During the first 6 months of treatment, MTX withdrawal due to side effects was estimated to be around 8–12% (20, 28), but MTX appears to be better tolerated than other DMARDs such as gold, leflunomide and cyclosporine in PsA patients (30–32). It seems that most of the discontinuations of MTX in PsA due to side effects occur within first 6 months of the treatment (28).

With the exception of higher rates of transaminitis, the overall incidence of side effects and discontinuation rates of MTX in PsA is similar to that of RA. However, the CASPAR study reported higher incidence of hepatic adverse events in PsA patients on MTX compared to that of RA (7% vs. 4% in PsA and RA, respectively) (6). Similar differences in the incidence of transaminitis were also found in two recent studies of large PsA and RA cohorts (28, 35). The numbers of LFT abnormalities in PsA patient were slightly higher, based on analysis of the CORONA database (35). However, in an analysis of 1,256 PsA patients from the CORONA registry, LFT abnormalities twice or 3-times the upper limit were relatively uncommon (20.4%, 2.3% and 0.7% for >x1, >x2 and >x3 LFT elevation above the

upper limits of normal, respectively) (36).

There appears to be consensus that MTX hepatotoxicity in PsA (*e.g.* cirrhosis, fibrosis and necrosis) appears to be much less common than initially thought, even among persons with occasionally elevated transaminase levels (23, 37–41). The higher incidence of transaminitis in PsA patients as compared to RA patient on MTX is also likely contributed to by higher rates of co-morbidities such as metabolic syndrome, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) in the psoriasis and PsA populations (42–44).

It should be noted again that most of the current safety data apply to low-medium dose MTX. Safety results from studies of higher dose of MTX in PsA are not available.

### Summary

Recently, expert consensus recommendations for the management of PsA based on the best available evidence were published by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). In these recommendations, MTX is currently recommended for moderate to severe peripheral arthritis (Grade B evidence) and skin disease (Grade A evidence) (12, 13). Clinically meaningful improvement of synovitis, and relatively low drop-out rate during MTX therapy in PsA, makes MTX monotherapy (or addition to NSAIDs) a very attractive choice as an early initial therapy for peripheral arthritis. It would seem that higher dose, if tolerated, could provide more benefit. MTX can be used in combination with TNF inhibitors particularly in cases with more severe synovitis and/or other manifestations of PsA. Limitations of the previous studies do not allow more definite conclusions regarding the best possible dose or timing of MTX use (*e.g.* early PsA vs. established PsA). Better-designed randomised trials, with higher dose MTX and assessment of its effect on radiological disease progression, are needed to answer many clinical questions. Nevertheless, it seems that MTX does have an important role in the management of PsA.

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