

# Efficacy of methotrexate in management of peripheral psoriatic arthritis – a systematic review

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## ABSTRACT

**INTRODUCTION:** Psoriatic arthritis (PsA) is a chronic inflammatory joint disease associated with psoriasis. Treatment consists of disease-modifying antirheumatic drugs with methotrexate (MTX) as first choice, yet documentation of the efficacy of this treatment is limited. The objective of this review is to make an accessible overview of the existing evidence on the clinical effect of MTX in the treatment of peripheral PsA.

**METHODS:** A systematic search for randomised controlled trials was conducted using the PubMed, Embase and Cochrane Library databases. Studies examining the effect of MTX on peripheral arthritis in adult patients with PsA were included. Only trials published in English were considered and for each study, the methodological quality was assessed.

**RESULTS:** Seven studies qualified given the selected criteria. None of the two placebo-controlled trials included found a significant reduction in tender and swollen joint counts. Trials comparing MTX to combination therapy with TNF-alpha inhibitor or ciclosporin A demonstrated some clinical benefits of MTX; however, combination therapy was superior to MTX monotherapy. In a strategy trial, patients were able to reach minimal disease activity with MTX treatment alone, pointing towards some efficacy of MTX on clinical manifestations.

**CONCLUSIONS:** Clinical benefits have been found in the treatment of PsA with MTX. MTX has demonstrated clinical efficacy in the treatment of psoriasis; however, the treatment of peripheral arthritis still lacks supportive evidence. More controlled trials need to be conducted to underpin evidence-based use of MTX.

diagnostic test exists [4]. However, the validated CASPAR criteria (Classification Criteria for Psoriatic Arthritis) have become an assisting diagnostic tool in clinical practice [3, 5, 6] as well as in research contexts [2]. The progressive destruction of joints leads to a reduced quality of life and the disease is furthermore associated with an increased mortality [3, 5].

Treatment is challenging due to the heterogeneous presentation of the disease [5]. In patients with moderate to severe PsA, treatment consists of disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX) [4, 5]. Despite the lack of documentation of its efficacy based on randomised controlled trials (RCT), MTX remains the most widely used medication for treatment of peripheral arthritis in PsA [1]. The objective of this review was to present the evidence that, until now, has supported the existing recommendation for the use of MTX for treatment of peripheral PsA.

## METHODS

### Search strategy

This review was conducted in accordance with the PRISMA guidelines [7]. A systematic search for RCT studies was performed in the PubMed, Embase and Cochrane Library databases. The search included material available from the operational date of each database until March 2018. In addition, reference lists from previous publications were reviewed manually. The Patients, Interventions, Comparisons and Outcomes (PICO) model formed the search strategy [8]

## SYSTEMATIC REVIEW

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Psoriatic arthritis (PsA) is a chronic inflammatory joint disease [1]. It is characterised by peripheral arthritis and axial involvement as well as extra-articular manifestations including enthesitis, dactylitis, psoriasis and nail disease [2, 3]. The disorder affects both men and women, and it is estimated that PsA will develop in approximately 30% of patients with psoriasis [3]. Diagnosing the disease can prove difficult, and no current

## KEY POINTS

- ▶ Psoriatic arthritis (PsA) is a seronegative chronic inflammatory disease characterised by peripheral joint involvement.
- ▶ The treatment consists of disease-modifying antirheumatic drugs with methotrexate (MTX) as first choice.
- ▶ There is a lack of evidence to support the efficacy of MTX on the peripheral arthritis.
- ▶ Still more randomised controlled trials need to be conducted to enlighten the effect of MTX in peripheral PsA.

with the following search terms being used: *Psoriatic arthritis, PsA, Methotrexate and MTX*. To aid the search, Medical Subject Headings MeSH terms in PubMed and the corresponding Emtree in Embase were used, and additional filters were added. To qualify for inclusion, the studies needed to meet the following criteria:

- RCT studies
- Adult patients with a clinical diagnosis of PsA (> 18 years)
- Articles published in English
- Articles published after 1980
- Efficacy assessed on peripheral arthritis
- Comparison groups to MTX: placebo, combination of MTX and biological treatment, MTX and another DMARD or NSAID
- Strategy trials with MTX as part of treatment.

### Study selection

Three researchers undertook the study selection process. First, all studies were assembled and screened for duplicates using EndNote and Covidence. Then studies were screened manually by title and abstract according to the predefined criteria. Studies only published in abstract form were excluded. Finally, each researcher independently reviewed the full text of the remaining eligible articles. Here, no specific inclusion criteria were

established concerning outcomes to assess the peripheral arthritis. Studies that failed to meet the criteria for inclusion were excluded; among them studies including children and studies published before 1980. The studies were discussed between researchers in case of doubts about eligibility.

### Data collection

In this systematic review, only endpoints related to peripheral arthritis are considered. These include the composite measures of Psoriatic Arthritis Response Criteria (PsARC) [9], the American College of Rheumatology (ACR20, ACR50, ACR70) [10] and the Disease Activity Score in 28 joints (DAS28) [11] as well as individual outcomes including the tender joint count (TJC) and the swollen joint count (SJC). In addition, radiological progression and the patients and physician's global assessment of disease activity were evaluated.

### RESULTS

The initial search yielded a total of 514 peer reviewed reports. By excluding duplicates, the number was reduced to 363 reports. A total of 356 studies were manually excluded by screening of title and abstract, mainly because they failed to meet the inclusion criteria. Full text screening of the remaining articles was conducted, and the process left seven included studies. Consensus among researchers on the inclusion of all seven studies was achieved. The reference lists of the included studies were reviewed for potentially relevant literature. In this process, no other studies were found. The search strategy used is presented in **Figure 1**.

### Study characteristics

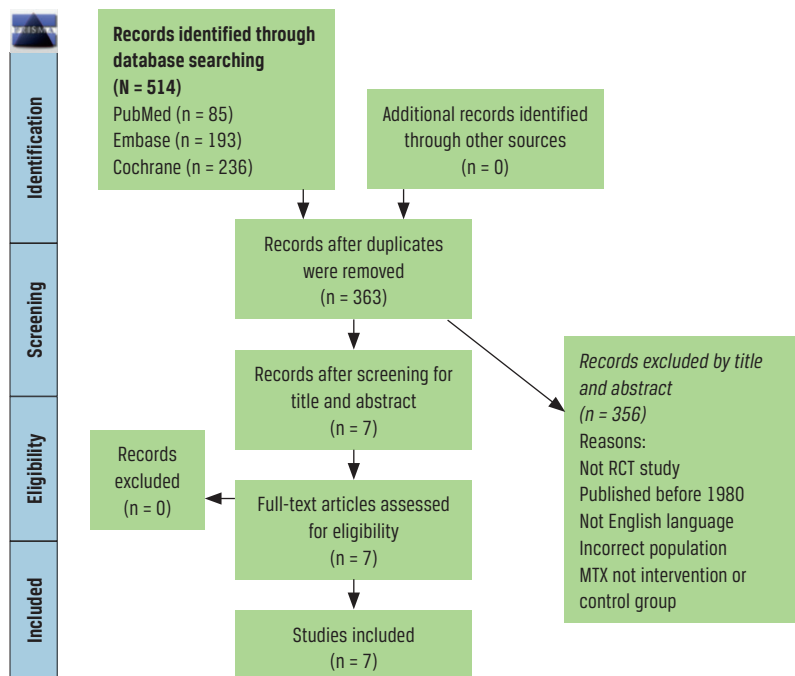
Seven RCTs were eligible for inclusion [12-18]. All seven studies included patients with verified PsA, and they all examined the effect of MTX on peripheral joint disease. Of composite measures, only one study assessed PsARC [12]. Two studies had ACR20 as the primary outcome [16, 18], whereas DAS28 was reported in two studies [12, 16]. The earliest studies only used individual measures to assess the effect of MTX [13, 15, 17]. Study features are presented in **Table 1**.

### Methotrexate and placebo

Two studies compared the effect of MTX to placebo and used low-dose oral MTX of 15 mg/week [12, 13]. Kingsley et al [12] included 221 MTX-naive patients. After six months, no significant effect of MTX was found on TJC and SJC or the composite measures PsARC, ACR20 or DAS28. Only the physicians' and patients' global assessment of disease activity was significantly improved in patients treated with MTX, when the two groups were compared. The trial by Willkens et al [13] reported a significant effect of MTX only on

**FIGURE 1**

PRISMA 2009 flow diagram.



MTX = methotrexate; RCT = randomised controlled trial.

**TABLE 1**

Characteristics of eligible randomised controlled studies.

Reference	I vs C	Subjects: I/C, n	Inclusion according to number of affected joints	Outcome	Dose of MTX, mg/wk	Follow-up time	Main results <sup>b</sup>	Comments
Kingsley et al, 2012 [12]	MTX vs placebo	109/112	Inflammatory synovitis involving ≥ 1 peripheral joint	PsARC <sup>a</sup>	15 oral	6 mo.s	PsARC: 1.77 (0.97-3.23), p = 0.06 ACR20: 2.00 (0.65-6.22), p = 0.23 DAS28: 1.70 (0.90-3.17) p = 0.10	Results presented as OR (95% CI). p-values are the difference between the 2 groups
				ACR20				
				DAS28				
				TJC				
				SJC				
				ESR				
				CRP				
				HAQ				
				PGA <sup>c</sup>				
				AGA <sup>c</sup>				
				Pain <sup>d</sup>				
				PASI				
				Nail disease score				
				TJC: -1.1 (-3.8-1.5), p = 0.41				
SJC: -0.9 (-2.7-1.2), p = 0.48								
Pain: -7.0 (-15.3-1.2), p = 0.09								
AGA: -8.0 (-13.6-2.4), p = 0.01								
PGA: -9.2 (-17.0-1.4), p = 0.02								
Willkens et al, 1984 [13]	MTX vs placebo	16/21	Active arthritis involving ≥ 3 joints	TJC	7.5-15 oral	12 wks	TJC: I: 4, C: 6, p = 0.559 SJC: I: 3, C: 1, p = 0.635 TJS: I: 9, C: 10, p = 0.870 SJS: I: 5, C: 2, p = 0.390 PhA <sup>f</sup> : I: 1, C: 0, p = 0.001 PA <sup>f</sup> : I: 1, C: 0, p = 0.087	Results presented as median difference between baseline and end of study Positive result means improvement p-values are the difference between the 2 groups
				SJC				
				TJS <sup>e</sup>				
				SJS <sup>e</sup>				
				PhA <sup>f</sup>				
				PA <sup>f</sup>				
				Morning stiffness				
				Grip strength				
				Psoriasis <sup>g</sup>				
				RAI <sup>h</sup>				
				TJC				
SJC								
CRP								
ESR								
PASI								
Pain <sup>d</sup>								
PhGA <sup>c</sup>								
PGA <sup>c</sup>								
HAQ								
HRUS								
Radiology								
Fraser et al, 2005 [14]	CSA + MTX vs MTX	38/34	Active PsA involving ≥ 3 tender joints	RAI <sup>h</sup>	MTX + CSA: 15.5 oral MTX: 15.75 oral	12 mo.s	RAI: I: 35.4 (± 34.8) → 2.4 (± 37), p ( 0.001, C: 44.3 (± 38.2) → 27.4 (± 27), p < 0.001 TJC: I: 22.6 (± 15.9) → 15.3 (± 16.5), p ( 0.001, C: 28.3 (± 19.2) → 19.7 (± 17.9), p < 0.001 SJC: I: 11.7 (± 9.7) → 6.7 (± 6.5), p ( 0.001, C: 11.7 (± 8.6) → 7.9 (± 5) Pain: I: 4.7 (± 2.2) → 3.9 (± 2.4), NS, C: 5.1 (± 2.3) → 4.9 (± 2.9), NS PGA: I: 5.1 (± 2.3) → 4.1 (± 2.7), NS, C: 5.4 (± 2.2) → 4.9 (± 2.8), NS HRUS: I: -2.5 (-4.07--1.01), C: -0.28 (-1.67-1.1), p < 0.05	Result presented as mean (± SD) at baseline and at wk 48 in each group p-values are the difference between baseline and wk 48 in each group
				TJC				
				SJC				
				CRP				
				ESR				
				PASI				
				Pain <sup>d</sup>				
				PhGA <sup>c</sup>				
				PGA <sup>c</sup>				
				HAQ				
				HRUS				
				Radiology				
				HRUS: I: -2.5 (-4.07--1.01), C: -0.28 (-1.67-1.1), p < 0.05				
				Radiology: I: 33 (± 27) → 34.6 (± 24), C: 36 (± 28.7) → 43.4 (± 33), NS				
				Result presented as mean change (95% CI) p-values are the difference between the 2 groups				
Results presented as mean (± SD) at baseline and at wk 48 NS is the difference between the 2 groups								

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physicians' global assessment of disease activity by week 12. Clinical improvements were seen in both groups after 12 weeks compared to baseline. No significant effect of MTX on joint disease was shown when the groups were compared, including TJC and SJC.

**Methotrexate and ciclosporin A**

Two studies compared the effect of MTX to that of ciclosporin A (CSA) [14, 15]. In Fraser et al [14], the authors examined the effect of adding CSA to MTX therapy. Significant reduction in joint counts was ob-

TABLE 1 CONTINUED

Reference	I vs C	Subjects: I/C, n	Inclusion according to number of affected joints	Outcome	Dose of MTX, mg/wk	Follow-up time	Main results <sup>b</sup>	Comments
Spadaro et al, 1995 [15]	CSA vs. MTX	17/18	≥ 5 tender and/or swollen joints	TJC SJC RAI PGA <sup>c</sup> PhGA <sup>c</sup> Morning stiffness Grip strength PASI ESR CRP	7.5-15 oral	12 mo.s	TJC: I: 9.6 ± 1.2 → 5.9 ± 1.8, p < 0.01, C: 8.4 ± 0.7 → 2.0 ± 0.5, p < 0.005, I vs C: 4.6 ± 1.2 vs 6.6 ± 0.9, NS SJC: I: 5.0 ± 0.6 → 2.5 ± 0.8, p < 0.01, C: 4.3 ± 0.4 → 0.8 ± 0.2, p < 0.005, I vs C: 2.6 ± 0.9 vs 3.5 ± 0.5, NS RAI: I: 8.6 ± 3.5 → 7.6 ± 2.2, p < 0.01, C: 13.8 ± 1.4 → 2.5 ± 0.6, p < 0.005, I vs C: 14.0 ± 4.2 vs 11.1 ± 1.7, NS PGA: I: 54.3 ± 4.9 → 27.0 ± 6.1, p < 0.01, C: 61.0 ± 8.4 → 30.0 ± 0.6, p < 0.025, I vs C: 30.0 ± 5.6 vs 22.7 ± 9.8, NS PhGA: I: 55.7 ± 6.4 → 41.0 ± 7.4, p < 0.01, C: 56.4 ± 4.1 → 26.1 ± 5.0, p < 0.005, I vs C: 16.0 ± 4.9 vs 30.8 ± 4.0, NS	Results presented as mean ± SEM from baseline to end of study period in each group p-values are the difference between baseline and 12 mo.s in each group NS are the difference between the 2 groups
Baranau-skaite et al, 2012 [16]	IFX + MTX vs MTX	57/58	≥ 5 swollen joints, ≥ 5 tender joints	ACR20 <sup>a</sup> ACR50 ACR70 EULAR-response PASI75 PGA <sup>c</sup> PhGA <sup>c</sup> Pain <sup>d</sup> CRP ESR DAS28 SJC TJC Dactylitis Enthesitis Fatigue Morning stiffness	MTX+IFX:14,6 MTX: 15.4 oral	16 wks	ACR20: I: 86.3%, C: 66.7%, p = 0,021 ACR50: I: 72.5%, C:39.6%, p = 0,0009 ACR70: I: 49%, C: 18.8%, p = 0,0015 EULAR I: 98%, C: 72.9, p < 0,0001  DAS28: I: 56.5% (-2.95 ± 1.05), C: 29.7% (-1.51 ± 1.31), p < 0.0001  TJC: I: -14.0, C: - 9.5, p = 0.0007 SJC: I: -11.0, C: -9.0, p = 0.0016  Pain: I: -45.8 ± 26.4, C: -23.1 ± 20.0, p < 0.0001 PGA: I: -43.0 ± 24.2, C: -24.1 ± 22.7, p < 0.0001 PhGA: I: -47.4 ± 18.3, C: -30.6 ± 21.6 p < 0.0001	Results presented as proportion achieving ACR-response and EULAR-response p-values are the difference between the 2 groups  Results presented as improvement in % (mean change ± SD) p-values are the difference between the 2 groups  Results presented as median difference from baseline to wk 16 A negative value indicates improvement p-values are the difference between the 2 groups  Results presented as mean change (± SD) from baseline to wk 16 p-values are the difference between the 2 groups

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served in both treatment groups compared to baseline. However, the only significant difference between the groups was in synovitis assessed by ultrasound. In Spadaro et al [15], MTX was compared directly to CSA therapy. No significant difference in TJC and SJC between the treatment groups was achieved, but improvements were shown in both groups at 12 months compared to baseline.

**Methotrexate and infliximab**

An open-label study evaluated the effect of combining low-dose MTX with the TNF-alpha inhibitor (TNFi) infliximab (IFX) [16]. One group of patients received IFX + MTX, whereas patients in the other group were treated with MTX monotherapy. In both treatment groups, clinical improvements were found at 16 weeks, but significantly more patients in combination therapy

TABLE 1 CONTINUED

Reference	I vs C	Subjects: I/C, n	Inclusion according to number of affected joints	Outcome	Dose of MTX, mg/wk	Follow-up time	Main results <sup>b</sup>	Comments
Scarpa et al, 2008 [17]	MTX + NSAID 6 mo.s vs NSAID 3 mo.s with addition of MTX the last 3 m.s	16/19	-	TJC SJC Pain <sup>d</sup> PGA <sup>f</sup> PhGA <sup>f</sup> ESR CRP	10 im.	6 mo.s	TJC: baseline: I: 2 (± 2), C: 3 (± 2), 3 mo.s: I: 1 (± 1), C: 2 (± 3), 6 mo.s: I: 0 (± 1), C: 0 (± 1), 3 mo.s vs baseline: p < 0.05, 6 mo.s vs baseline: p < 0.05, I vs C at 3 mo.s: → p < 0.05, I vs C at 6 mo.s: NS SJC: baseline: I: 2 (± 2), C: 2.5 (± 2), 3 mo.s: I: 0 (± 1), C: 1 (± 2), 6 mo.s: I: 0 (± 1), C: 0 (± 1), 3 mo.s vs. baseline → p < 0.05, 6 mo.s vs. baseline → p < 0.05, I vs C at 3 mo.s: → p < 0.05, I vs C at 6 mo.s: NS PGA: baseline: I: 4 (± 1), C: 3.5 (± 1), 3 mo.s: I: 3 (± 2), C: 2 (± 3), 6 mo.s: I: 2 (± 1), C: 1 (± 2), 3 mo.s vs baseline → p < 0.05, 6 mo.s vs baseline → p < 0.05, I vs C at 3 mo.s → NS, I vs C at 6 mo.s → p < 0.05 PhGA: baseline: I: 4 (± 0), C: 3 (± 1), 3 mo.s: I: 3 (± 2), C: 2 (± 3), 6 mo.s: I: 2 (± 2), C: 1 (± 2), 3 mo.s vs baseline → p < 0.05, 6 mo.s vs baseline → p < 0.05, I vs C at 3 mo.s → NS, I vs C at 6 mo.s → p < 0.05	Results presented as median (± IQR) at different times p-values are the difference between baseline and the respective months in each group and between the groups
Coates et al, 2015 [18]	Tight control vs standard care <sup>h</sup>	101/105	-	ACR20 <sup>a</sup> ACR50 ACR70 TJC SJC PGA <sup>c</sup> PhGA <sup>c</sup> Pain <sup>d</sup> PASI PASI75 mNAPSI Enthesitis Dactylitis HAQ BASFI BASDAI PsAQoL EQ-D5 Radiology	15-25 oral	48 wks	ACR20: 1.91 (1.03-3.55), p = 0.0392 ACR50: 2.36 (1.25-4.47), p = 0.0081 ACR70: 2.64 (1.32-5.26), p = 0.0058 Radiology: p = 0.9779	Results presented as OR (95% CI) p-values are the difference between the 2 groups

ACR 20/50/70 = American College of Rheumatology (20%, 50% and 70% response); AGA = Assessors Global Assessment; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Questionnaire; C = control; CRP = C-reactive protein; CSA = ciclosporin A; CI = confidence interval; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; HAQ = Health Activity Questionnaire; HRUS = High Resolution Ultrasound; I = intervention; IFX = infliximab; im. = intramuscular injection; IQR = interquartile range; mNAPSI = modified Nail Psoriasis and Severity Index; MTX = methotrexate; NS = non-significant; OR = odds ratio; PA = patient assessment; PASI = Psoriasis Activity Skin Index; PASI75 = PASI for 75% reduction in score; PGA = Patient Global Assessment; PhA = physician assessment; PsA = psoriasis arthritis; PsAQoL = Psoriatic Arthritis Quality of Life index; PsARC = Psoriatic Arthritis Response Criteria; RAI = Ritchie Articular Index; SD = standard deviation; SEM = standard error of the mean; SJC = swollen joint count; SJS = swollen joint score; TJC = tender joint count; TJS = tender joint score; VAS = visual analogue scale.

- a) Primary outcome.
- b) If intention-to-treat analysis is made, the results from this is represented.
- c) Assessment of disease activity using VAS ranging 0-100.
- d) Assessment using VAS.
- e) Assessment of tenderness by pressing the joint and/or assessing of pain by movement of joint using a scale ranging 0-3, where 0 = non, 1 = minimal, 2 = moderate and 3 = severe; the scores are summarised from each joint; assessment of swollen joints in the same way.
- f) Assessment of disease activity determined on a Likert scale ranging 1-5 according to difficulty of the disease, 1 = no symptoms, 5 = very severe symptoms.
- g) Assessment by measurement of surface area involved, scaling, induration and erythema.
- h) Patients in tight control group were seen by study physician every 4 wks; treatment follows a predefined treatment protocol; patients in standard care group were seen every 12 wks by their rheumatologist; treatment follows the treating clinician.

than monotherapy reached the primary outcome of ACR20 response. Even though the number of tender and swollen joints was reduced in the group receiving MTX monotherapy, the treatment effect was significantly higher in the IFX + MTX group. Minimal disease activity (MDA) was reached by 24.1% of patients treated with MTX by the end of the study compared to 58.9% treated with both medications [19].

#### Treatment strategy in psoriatic arthritis

Two studies aimed to evaluate the effect of a treatment strategy for PsA [17, 18]. One trial by Scarpa et al assessed the effect of an early intervention with MTX. After three months, patients treated with MTX had a significant reduction in TJC and SJC compared to patients treated only with NSAID. Compared to baseline, both groups showed significant improvements in all clinical outcomes after three months. By six months, when both groups were treated with MTX, there were significant improvements in clinical manifestations compared to baseline. By the end of the study period, significant difference between the treatment groups was found only in patient global assessment and physician's global assessment of disease activity, with a better score observed in the group where MTX was added after three months.

The other trial by Coates et al [18] compared a tight control to standard care. The trial examined the effect of a tight control in PsA using a treat-to-target approach. The target was MDA and the primary outcome was ACR20. At week 48, significantly more patients in the tight control group than in the standard care group had reached ACR20. Similarly, the study showed a significant advantage of tight control considering the secondary outcomes ACR50 and ACR70. More patients receiving standard care continued on MTX monotherapy, but even so, 24% of the patients under tight control reached MDA on MTX alone by 12 weeks.

#### Methodological quality of studies

The methodological quality of each study was assessed independently by all three authors according to the checklist "Critical Appraisal for Therapy Articles – University of Oxford, 2005" [20] and consensus was achieved (Table 2). Studies lacking blinding and thoroughly explained randomisation were considered to have a reduced quality. The randomisation was not clarified in five studies [13-17]. Two studies were not blinded [16, 18], and blinding was not thoroughly described in two others [15, 17]. The study by Coates et al was of a high quality; however, the study was not performed to evaluate the effect of MTX compared to placebo [18]. The placebo-controlled trial by Kingsley et al was of a high quality, although a high dropout rate was observed [12].

#### DISCUSSION

MTX was originally developed as a folate antagonist for the treatment of cancer. However, low-dose MTX (7.5 to 25 mg) administered weekly either orally or subcutaneously (SC) has shown great efficacy as an immunosuppressant in rheumatoid arthritis RA [21]. RA patients with an inadequate response to oral MTX may benefit from switching to SC MTX, reaching higher drug exposure without increases in adverse events [22].

In PsA, the same treatment regimen has been adapted; and for some time, MTX has been one of the most used medications in the treatment of PsA [1, 23].

Despite lack of documentation of its efficacy on peripheral arthritis, it remains recommended as first-choice treatment according to the EULAR treatment recommendations of PsA [24]. In the GRAPPA recommendations, other conventional DMARDs are considered equally to MTX [25]. The limited efficacy in PsA runs contrary to RA, for which the use of MTX has shown significant improvements [26]. The low number of RCT studies examining the efficacy of MTX in PsA is supported by this review.

Of the included studies, only two were placebo-controlled [12, 13], none of which demonstrated a significant effect of MTX on either TJC or SJC. The study by Kingsley et al (number of patients included,  $n = 221$ ) [12] failed to show a significant effect of MTX on its primary outcome PsARC at six months. Even so, the study demonstrated a significant improvement on the patient's and physicians' global assessment of disease activity when MTX was assessed against placebo, which indicates that there might be some relief of symptoms when PsA is treated with MTX. Willkens et al ( $n = 37$ ) showed significant effect of MTX only on physicians' global assessment of disease activity [13]. The study included few patients and the randomisation was not adequately explained, which reduces the validity of the results.

The study by Baranauskaite et al ( $n = 115$ ) [16] demonstrated advantage of combination therapy with MTX and IFX. Significant differences in clinical outcomes between the groups were achieved, favouring patients treated with combination therapy. Still, improvements in joint disease were observed by MTX monotherapy; and 66.7% patients in the MTX group were able to reach ACR20, which might suggest a clinical effect of MTX.

Combination therapy with MTX and TNFi has not proved superiority to biological treatment alone [27], which was also the conclusion in another study examining this aspect [28]. This raises doubt about the implementation of MTX in the treatment of PsA when biological treatment is initiated.

Scarpa et al ( $n = 35$ ) [17] conducted a small study



**TABLE 2**

Methodological quality of included randomised controlled studies.

Reference	Randomisation of subjects and public registration	Allocation concealment	Similar groups at start of trial	Equal treatment of groups aside from the allocated treatment	Description of losses to follow-up	Intention-to-treat analysis	Blinding <sup>a</sup>	Quality
Kingsley et al, 2012 [12]	Yes ISRCTN: 54376151	Yes	Yes <sup>c</sup>	Yes	Yes <sup>d</sup>	Yes	Yes	High
Willkens et al, 1984 [13]	Yes <sup>b</sup> No NCT	-	Yes	Yes	Yes	-	Yes	Low
Fraser et al, 2005 [14]	Yes <sup>b</sup> No NCT	-	Yes <sup>c</sup>	Yes <sup>d</sup>	Yes	Yes	Yes	Low
Spadaro et al, 1995 [15]	Yes <sup>b</sup> No NCT	-	Yes <sup>c</sup>	Yes	Yes <sup>d</sup>	-	No	Low
Baranauskaite et al, 2012 [16]	Yes <sup>b</sup> NCT: 00367237	-	Yes <sup>c</sup>	Yes	Yes	Yes	No	Low
Scarpa et al, 2008 [17]	Yes <sup>b</sup> - matched groups <sup>e</sup> No NCT	-	-	Yes	No	-	No	Low
Coates et al, 2015 [18]	Yes NCT: 01106079	Yes	Yes <sup>c</sup>	- <sup>f</sup>	Yes	Yes	No	High

ISRCTN = International Standard Randomised Controlled Trial Number; NCT = ClinicalTrials.gov registry number.

- a) Double-blind studies.
- b) Randomisation not described.
- c) Baseline statistics is missing.
- d) Occurrence of large dropout in study.
- e) Groups are matched on articular pattern: polyarthritis and oligoarthritis.
- f) Different treatment strategies in the 2 groups.

demonstrating an advantage of early intervention with MTX. The study showed a significant reduction in TJS and SJC after three months of therapy compared to NSAID monotherapy. The study, however, included few patients and there is doubt about the randomisation process, why the results are questionable.

The Tight Control of Psoriatic Arthritis (TICOPA) study (n = 206) was the first study in PsA using a treat-to-target strategy [18]. The study found significant clinical improvements by tight control treatment compared to standard care. MTX was the first step in the treatment algorithm, supporting the common use of MTX as first choice treatment. 24% of patients under tight control were able to reach MDA on MTX therapy alone in 12 weeks, thereby showing a possible efficacy of MTX. In a study by Coates et al [29], the efficacy of MTX in the first 12 weeks in the TICOPA trial was evaluated. The study found a diminished number of tender and swollen joints.

Compared to the other studies, the TICOPA study used a higher dose of MTX (25 mg/week). According to the effect of MTX seen in this study, it is a relevant aspect to consider. Clinically, doses up to 25 mg/week are recommended [24].

Only two studies assessed the radiological progression of joint disease [14, 18]; thus, it is difficult to infer whether MTX has a promotional effect on this manifes-

tation in PsA. None of the two studies reported significant results.

An important trial recently published the results of the efficacy of MTX monotherapy, eternacept monotherapy or eternacept + MTX combination therapy in PsA [30]. Eternacept monotherapy and the eternacept+MTX combination achieved greater efficacy in ACR responses than methotrexate monotherapy. However, the MTX monotherapy reached an ACR 20 of 50.7% and MDA of 22.9%, indicating some benefits of MTX. The study was performed without a placebo arm and no certain effect of MTX could be demonstrated.

The role of MTX in future treatment of PsA is not clear. Knowledge about treatment options for PsA has evolved in the past years, primarily based on the development of biological drugs [31]. Initial treatment with these agents has not yet become a part of the recommendations, even though their effect is superior to that of MTX [31]. Biological drugs are more expensive than conventional DMARDs, which might explain their lower priority as first choice of treatment. Furthermore, it has not yet been documented that a delay in initiation of biological treatment will affect the quality of life in a negative direction [25].

In the newest national treatment recommendation made by Dansk Reumatologisk Selskab (The Danish

Society for Rheumatology) [32], MTX is still being recommended as a first-line DMARD, especially with concurrent psoriasis. However, in patients with a high risk of radiographic damage, an early intervention with biologics as first-line treatment is an option for the treating clinician. This might lead to a new step in future treatment of PsA.

This review has limitations. Only three researchers performed the selection of studies, and the conclusions are based on few RCT studies of which only two were placebo-controlled.

**CONCLUSIONS**

MTX is used as first-line treatment in peripheral psoriatic arthritis. The proven efficacy on psoriasis, clinical experience from 2-3 decades and its safety/tolerability support the use of methotrexate; however, there is a lack of supportive evidence from randomised trials for its efficacy in peripheral arthritis.

More controlled trials still need to be conducted to enlighten evidence-based use of MTX on peripheral joint manifestations in PsA.

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