Methotrexate Efficacy in the Tight Control in Psoriatic Arthritis Study

Laura C. Coates and Philip S. Helliwell

ABSTRACT. ***Objective.*** Methotrexate (MTX) is a commonly used disease-modifying antirheumatic drug in psoriatic arthritis, but there is conflicting evidence to support its efficacy.

Methods. Within the Tight Control of Psoriatic Arthritis (TICOPA) study, patients were treated with MTX as part of the tight control protocol or standard care. Outcomes were recorded at the 12-week visit, including joint counts, skin, nail, enthesitis, dactylitis, and patient-reported measures.

Results. Of the 206 patients enrolled, 188 received MTX in the first 12 weeks of the trial with 104 receiving a mean dose > 15 mg/week. The proportions of patients achieving the American College of Rheumatology (ACR) outcomes at 12 weeks were ACR20 40.8%, ACR50 18.8%, and ACR70 8.6%, with 22.4% achieving minimal disease activity. Improvements were seen in psoriasis with 27.2% reaching a Psoriasis Area and Severity Index (PASI) 75. The proportion of patients with dactylitis and Leeds dactylitis instrument (LDI) scores decreased significantly (62.7% decrease in patients with dactylitis, median change LDI –59.7, –157.4 to –26.4, p = 0.033). The decrease in proportion of patients with enthesitis (25.7%) was significant, but the median change in enthesitis score was 0. There was a trend to higher proportions of patients receiving over 15 mg/week achieving ACR20, ACR50, and PASI75.

Conclusion. Despite the open-label design of the data, improvements in multiple clinical outcomes were seen. The proportion of patients reaching ACR20 in the TICOPA study was higher than in the Methotrexate in Psoriatic Arthritis study (41% vs 34%), but no comparative data are available for other outcomes. There is a suggestion of a dose response, but this is hard to assess when patients doing well may be maintained on lower doses. (First Release December 15 2015; J Rheumatol 2016;43:356–61; doi:10.3899/jrheum.150614)

Key Indexing Terms:
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Psoriatic arthritis (PsA) is an inflammatory arthritis causing a significant burden of joint damage and related disability[1]. Studies have highlighted a poorer outcome for those with a significant delay between symptom onset and diagnosis, presumably related to a delay in initiation of therapy[2,3,4,5].

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One of the most common first-line therapies used for patients with PsA is methotrexate (MTX). In Norway, it was the most commonly used disease-modifying antirheumatic drug (DMARD) in PsA between 2000 and 2005[6], and 39% of patients in the ClASsification of Psoriatic ARthritis (CASPAR) study, recruited worldwide, were given MTX as their first DMARD[7]. Even in recent years, the Swedish early PsA registry found that over half of the patients had received MTX[5].

Despite its frequent use, the evidence for MTX efficacy in PsA is lacking. Until recently, there were only 2 small randomized controlled trials (RCT) assessing its use against placebo. The first, published in 1964, investigated the use of intravenous pulsed MTX. Despite an improvement seen with MTX, 1 patient died of marrow aplasia, and several other adverse events were reported[8]. The second study evaluated low-dose oral MTX with a weekly dose of 7.5–15 mg spread over 3 consecutive days. This did show a superior response in terms of a physician's assessment of arthritis and body surface area of psoriasis[9].

Given this lack of evidence, the Methotrexate in Psoriatic Arthritis (MIPA) study was started in 2003. This compared MTX versus placebo in 221 patients with PsA. The study

found no significant difference in the American College of Rheumatology (ACR) 20 criteria, the Disease Activity Score in 28 joints, or the PsA response criteria at 6 months, although there was an improvement in both the patient's and physician's assessments of PsA and the Psoriasis Area and Severity Index (PASI) compared with placebo[10]. This study cast doubt on the efficacy of MTX in PsA, but there are concerns about its design. The target dose of MTX was just 15 mg, and only 11% of patients received doses higher than this (with a further 11% receiving < 15 mg/week). There were a large number of dropouts from the study and there has been concern about selection bias because patients and physicians were aware that half of the patients would receive placebo for only 6 months. There was no assessment of radiographic damage in the study given its short time frame and no effort to assess other features of PsA such as enthesitis, dactylitis, or axial involvement.

Some observational studies have suggested an effect with MTX in terms of peripheral joints[11] and also with enthesitis and dactylitis in small numbers[12,13]. Interestingly, an updated assessment in the Toronto PsA database using a case-control design found a significant response to MTX and a trend toward lower radiographic progression with patients receiving higher doses of MTX[14], which had not been seen in an earlier study in 1995 when doses were much lower[15].

The aims of our study were to investigate the effectiveness of MTX in early DMARD-naive PsA on different disease manifestations and to investigate whether differing dosages of MTX may affect outcome in a posthoc analysis.

MATERIALS AND METHODS

A total of 206 patients with early PsA were recruited into the Tight Control of Psoriatic Arthritis (TICOPA) trial (ISCRCTN30147736 and NCT01106079). Eligibility criteria were adults with recent onset (< 24-mo symptom duration) PsA who were naive to DMARD. Full details of the trial protocol are published elsewhere[16]. In brief, patients were randomized to receive tight control (TC; n = 101) or standard care (StdC; n = 105). In the intention-to-treat patient population, the odds of achieving an ACR20 at 48 weeks were greater in the TC arm compared with the StdC arm (OR 1.91, 95% CI 1.03–3.55, p = 0.0392). The odds of achieving ACR50 (OR 2.36, 95% CI 1.25–4.47, p = 0.0081) and ACR70 (OR 2.64, 95% CI 1.32–5.26, p = 0.0058) at 48 weeks were also greater.

A greater improvement was observed for other outcomes including the PASI, the Bath Ankylosing Spondylitis Disease Activity Index, the Bath Ankylosing Spondylitis Functional Index, the PsA quality of life questionnaire (PsAQoL), the Assessment of Spondyloarthritis international Society 20/40, and the Health Assessment Questionnaire (HAQ) score in the TC arm. Serious adverse events (SAE; 25 TC, 8 StdC) were reported from 20 (9.7%) patients (TC 13.9%, n = 14 and StdC 5.7%, n = 6) during the course of the study. There were no unexpected SAE or deaths.

Within this RCT, patients could be treated with MTX. In the TC arm, patients were treated according to an algorithm that mandated monotherapy MTX as the first DMARD unless contraindicated for at least the first 12 weeks. All patients in this arm were treated with rapidly escalating doses (15 mg/week for 4 weeks, 20 mg/week for 2 weeks, and 25 mg/week thereafter if tolerated). Patients in the StdC arm could be treated with MTX at the discretion of their treating physician, but it was not a requirement.

A variety of clinical outcome measures were collected every 12 weeks, including ACR outcomes, minimal disease activity (MDA)[17], PASI[18], modified Nail Psoriasis Severity Index (mNAPSI)[19], enthesitis scores (Leeds Enthesitis Index[13], Infliximab Multinational Psoriatic Arthritis Controlled Trial, and Maastricht Ankylosing Spondylitis Enthesitis Score[20]), and dactylitis measures [Leeds dactylitis instrument (LDI)[12]]. At baseline, 12, 24, 36, and 48 weeks, all patients were assessed by a blinded assessor who did not know what therapy the patients were receiving. This analysis examines the 12-week outcomes because, at that point, the majority of patients were receiving MTX monotherapy rather than in combination with other DMARD. Although some patients continued receiving MTX monotherapy throughout the 48-week study period, these were by definition MTX responders and therefore analysis at later timepoints would introduce selection bias.

Response rates were compared using chi-square tests. Changes in joint counts and continuous measures were assessed using the Wilcoxon signed-rank test or the Mann-Whitney U test as appropriate. To assess the effect of higher doses of MTX, subanalyses were performed on those receiving doses > 15 mg/week. These analyses were not prespecified in the trial protocol.

RESULTS

Of the 206 patients enrolled in the TICOPA, 188 received oral MTX in the first 12 weeks of the trial. Of these, 175 patients reached a dose of at least 15 mg by 12 weeks, with 122 reaching a dose of at least 20 mg and 86 reaching the top dose of 25 mg. Only 5 patients received parenteral MTX and these were not included in the analysis because the number was low. The baseline characteristics of the full trial population and the 188 patients who received MTX by Week 12 are shown in Table 1.

At 12 weeks, 40.8% (69/169 with no missing data) achieved an ACR20 outcome. Lower proportions of patients achieved the ACR50 and ACR70 outcomes (Table 2). Considering individual joint counts, there was a significant reduction in tender joint counts (TJC) and swollen joint counts (SJC) by 12 weeks (p < 0.0005; Table 1). A significantly higher proportion of patients with polyarthritis (≥ 5 active joints) achieved ACR20 compared with those with oligoarthritis (p = 0.022), but the difference was not significant for either ACR50 or ACR70. A total of 22.4% achieved MDA at 12 weeks. Conversely, the patients with oligoarthritis were more likely to achieve MDA than those with polyarticular disease (p = 0.005). Comparing the actual reduction in TJC and SJC, a significantly better response was seen in polyarticular disease (median reduction TJC polyarthritis –3, oligoarthritis –1, and SJC polyarthritis –4, oligoarthritis –1, p < 0.004 for both), but comparing percentage reduction in TJC and SJC found no significant difference between the groups.

Improvements were seen in the 158 patients with psoriasis with 27.2% reaching a PASI75. Nail involvement was present in 117 patients and showed a median change in mNAPSI score of –2 [interquartile range (IQR) –8 to 0]. The median change in the nail plate score was 0 (IQR range –3.75 to 1) because of the short followup time, with a median change of –1 (IQR –4.75 to 0) seen in the nail bed.

For those with baseline dactylitis (n = 59), there was a significant reduction in LDI basic scores (p = 0.033), and by

Table 1. Baseline characteristics of the MTX population and total trial participants. Values are n (%) or median (IQR).

Characteristics	MTX Population, n = 188	Total Trial Participants, n = 206
Male	100 (53.2)	108 (52.4)
Age, yrs	44.5 (37.0–52.0)	45 (38–53)
White ethnicity	171 (91.0)	188 (91.3)
No. swollen joints, 0–66	5.0 (3.0–9.0)	5.0 (2.0–9.0)
No. tender joints, 0–68	9.0 (3.5–19.0	9.0 (4.0–18.0)
CRP, mg/dl	6.6 (5.0–20.0)	6.7 (5.0–18.2)
RF-negative	177 (94.1)	195 (94.7)
CCP-negative	158 (84.0)	172 (83.5)
EMS	168 (89.4)	184 (89.3)
EMS duration, hours	1.0 (0.0–2.0)	1.0 (0.5–2.0)
Arthritis pattern		
Polyarthritis, ≥ 5 joints	135 (71.8)	146 (70.9)
Oligoarthritis, < 5 joints	53 (28.2)	60 (29.1)
DIP disease	41 (21.8)	45 (21.8)
Axial involvement	42 (22.3)	43 (20.9)
Arthritis mutilans	0 (0.0)	0 (0.0)
CASPAR criteria met, score ≥ 3	172 (91.5)	188 (91.3)
CASPAR score ≥ 2	184 (97.9)	202 (98.1)
Current psoriasis	159 (84.6)	174 (84.5)
PASI score, all patients	2.0 (0.6–4.2)	1.9 (0.6–4.2)
PASI score, condition at baseline	2.6 (1.2–4.7)	2.6 (1.2–4.8)
Current enthesitis	148 (78.7)	162 (78.6)
Enthesitis score, all patients	2.0 (1.0–6.0)	2.0 (1.0–6.0)
Enthesitis score, condition at baseline	4.0 (2.0–7.0)	4.0 (2.0–7.0)
Current dactylitis	59 (31.4)	62 (30.1)
Dactylitis score, all patients	0.0 (0.0–15.8)	0.0 (0.0–13.0)
Dactylitis score, condition at baseline	38.0 (20.0–105.0)	37.0 (19.0–96.0)
Current nail disease	117 (62.2)	124 (60.2)
mNAPSI score, all patients	2.0 (0.0–11.8)	2.0 (0.0–10.0)
mNAPSI score, condition at baseline	8.0 (2.0–20.0)	8.0 (2.0–19.0)

MTX: methotrexate; IQR: interquartile range; CRP: C-reactive protein; RF: rheumatoid factor; CCP: cyclic citrullinated peptide antibodies; EMS: early morning stiffness; DIP: distal interphalangeal joint; CASPAR: the ClASsification of Psoriatic ARthritis study; PASI: Psoriasis Area and Severity Index; mNAPSI: modified Nail Psoriasis Severity Index.

12 weeks, 37 of the 59 showed complete resolution (Table 2). Only 9 new cases of dactylitis were identified in the patients without baseline involvement. There was a significant change in the proportion of patients with dactylitis from baseline to 12 weeks (chi-square = 22.3, $p < 0.001$). For those with enthesitis at baseline (n = 148), the median change in enthesitis score was 0, independent of which entheseal index was used (Table 2). Of those with active enthesitis, 38 had full resolution of their symptoms at 12 weeks. Only 8 patients developed new enthesitis not identified at baseline. There was a significant change in the proportion of patients with enthesitis from baseline to 12 weeks (chi-square = 32.8, $p < 0.001$).

There was an improvement also seen in individual patient-reported outcome measures, including the patient visual analog scale for pain, fatigue, and global disease activity and the PsAQoL and HAQ score (Table 1). In total, 69/188 (36.7%) achieved the minimum clinically important difference for HAQ (reduction of ≥ 0.35) at 12 weeks.

Using the Psoriatic Arthritis Disease Activity Score (PASDAS)[21], the median score at baseline was 5.26 (IQR 3.98–6.19), indicating active disease according to defined cutoffs[22]. The score was higher in the polyarticular patients (median 5.52, IQR 4.38–6.51) compared with the oligoarticular patients (median 3.98, IQR 3.47–5.18). However, the change in the PASDAS score over the 12 weeks was similar in both groups (Table 1). Using the PASDAS response criteria[22], we found that 57.2% achieved a moderate or good response and 18.0% achieved a good response. The proportions of good and moderate responses were similar in polyarticular and oligoarticular patients (Table 2). The proportions of patients reaching PASDAS low disease activity threshold (≤ 3.2) were higher in the oligoarticular patients (Table 2) because they had a lower baseline value.

Over the 12-week period, 104 of the 188 patients received over 180 mg cumulative dose of MTX, equivalent to an average of 15 mg/week. There was no significant difference in the response rates seen in patients taking over 15 mg/week of MTX for the ACR outcomes or MDA, PASI, or PASDAS

Table 2. Outcomes at 12 weeks for those taking MTX monotherapy. Values are n (%) or median (IQR).

Outcome Measures	Values
ACR20	69/169 (40.8)
Polyarthritis	56/121 (46.3)
Oligoarthritis	13/48 (27.1)
ACR50	32/170 (18.8)
Polyarthritis	23/121 (19.0)
Oligoarthritis	9/49 (18.4)
ACR70	15/174 (8.6)
Polyarthritis	13/125 (10.4)
Oligoarthritis	2/49 (4.1)
MDA	39/174 (22.4)
Polyarthritis	21/125 (16.8)
Oligoarthritis	18/49 (36.7)
Change in PASDAS at 12 weeks	–1.11 (–2.14 to –0.40)
Polyarthritis	–1.17 (–2.21 to –0.35)
Oligoarthritis	–1.03 (–1.65 to –0.64)
PASDAS low disease activity ≤ 3.2	63 (32.5)
Polyarthritis	35 (25.0)
Oligoarthritis	28 (51.9)
PASDAS good response	35 (18.0)
Polyarthritis	24 (17.1)
Oligoarthritis	11 (20.4)
PASDAS moderate response	76 (39.2)
Polyarthritis	53 (37.9)
Oligoarthritis	23 (42.6)
Change in TJC	–2 (–6.25 to 1)
Change in SJC	–3 (–6, –1)
PASI75	43/158 (27.2)
Change in mNAPSI	–2 (–8 to 0)
Enthesitis all resolved	38/148 (25.7)
Change in Leeds Enthesitis Index	0 (–1 to 0)
Change in IMPACT enthesitis score	0 (–1 to 0)
Change in MASES	0 (–2 to 1)
Dactylitis all resolved	37/59 (62.7)
Change in Leeds dactylitis instrument basic score	–59.7 (–157.4 to –26.4)
Change in PsAQoL	–1 (–4 to 1)
Change in HAQ	–0.1875 (–0.5 to 0.0)
Reduction in HAQ ≥ MCID = 0.35	69/188 (36.7)
Change in patient's global disease activity VAS	–13.5 (–34 to 1.75)
Change in patient pain VAS	–13 (–32.25 to 0)
Change in patient fatigue VAS	–2 (–20 to 8)

MTX: methotrexate; IQR: interquartile range; ACR: American College of Rheumatology; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; TJC: tender joint count; SJC: swollen joint count; PASI: Psoriasis Area and Severity Index; mNAPSI: modified Nail Psoriasis Severity Index; IMPACT: Infliximab Multinational Psoriatic Arthritis Controlled Trial; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; PsAQoL: psoriatic arthritis quality of life questionnaire; HAQ: Health Assessment Questionnaire; MCID: minimum clinically important difference; VAS: visual analog scale.

responses despite higher proportions of patients in the higher dose group achieving ACR20, ACR50, PASI75, and PASDAS moderate response.

During the first 12 weeks, there were 233 adverse events reported among patients receiving MTX. Adverse events possibly related to MTX are listed in Table 3. Of note, there were 40 instances of nausea, 30 of raised liver function tests, and 3 episodes of neutropenia, but none of these met the criteria for an SAE. The majority of adverse events reported were classified as mild (157/233, 67.4%) with only 5 severe adverse events (2.1%). Only 14 patients discontinued their MTX because of an adverse event, although in 77 patients, the dose was modified or temporarily suspended (e.g., in the case of a current infection).

There were a total of 4 SAE reported in this cohort: 1 each of angina, migraine, PsA flare, and kidney stones, which were all classified as serious because they led to a hospital admission. None were life-threatening.

By the end of the study at 48 weeks, 88 patients had received only MTX monotherapy for their PsA. In the TC arm, where a target of MDA was required at each 4-week visit, 25 of 101 patients continued receiving MTX throughout the study.

DISCUSSION

Our analysis demonstrates an improvement in psoriatic peripheral joint disease, skin disease, enthesitis, dactylitis, and nail disease seen over the course of a 12-week period when patients were treated with MTX. In addition to improvements in composite arthritis measures, there was a significant decrease in TJC and SJC by 12 weeks. The majority of patients were treated with at least 15 mg/week MTX with more than half receiving higher doses. There was a significant difference seen between the responses in polyarticular and oligoarticular patients, but this was dependent on the measure used. A response measure such as the ACR20 showed a greater benefit in polyarticular patients, and a measure of disease state such as MDA showed a greater benefit in oligoarticular disease. The PASDAS again showed a greater proportion of oligoarticular patients achieving a low disease activity state, but interestingly showed similar response rates for both oligoarticular and polyarticular patients. These findings suggest that the difference is because of the outcome measure rather than a true differential response to MTX. Improvements were seen in the PASI in keeping with known efficacy in psoriasis, but there was also a suggestion of improvement in nail disease. Improvements were seen in the number of patients affected and the disease activity in dactylitis. Despite no change in the median enthesitis scores, the proportion of patients with active enthesitis decreased. In the TC arm of the study, one quarter of patients remained receiving MTX throughout, indicating that their disease was consistently well controlled.

The main limitation of these data is the open-label design of the study. A high placebo response can be seen in PsA trials and so results of open-label studies must be interpreted with caution[23]. The ACR20 proportions are higher than those seen in the MIPA study (40.8% vs 34% in MIPA), which could be explained by the open-label design or could represent the benefit seen with higher MTX doses.

Table 3. Adverse events reported in the MTX population in the first 12 weeks. Values are n.

Adverse Events	Frequency	Definitely or Probably Related to MTX	Adverse Events Severity			MTX Held	MTX Stopped	SAE Frequency
			Mild	Moderate	Severe			
Fatigue	16	10	9	7	0	2	1	0
Hair loss/alopecia	5	4	4	1	0	0	0	0
Nausea	40	37	30	10	0	11	5	0
Vomiting	2	1	1	1	0	1	0	0
Diarrhea	4	3	2	2	0	1	0	0
Abdominal/GI upset	13	8	11	2	0	4	1	0
Mouth ulcer/cold sores	7	4	3	2	2	3	0	0
Sore throat	7	1	5	2	0	6	0	0
Cough	4	0	2	2	0	1	0	0
Chest infection	5	1	3	2	0	4	0	0
LRTI	1	0	0	1	0	1	0	0
Shortness of breath	2	0	0	2	0	1	0	0
Fever	4	0	3	1	0	1	0	0
UTI	1	0	1	0	0	0	0	0
Infection, other	7	0	4	3	0	2	0	0
Headache/migraine	11	3	5	5	1	4	1	1
Mood disturbance/irritability	4	1	4	0	0	1	0	0
Liver abnormalities	30	20	25	5	0	18	4	0
Anemia	0	0	0	0	0	0	0	0
Neutropenia	3	2	2	1	0	1	0	0

MTX: methotrexate; SAE: serious adverse event; GI: gastrointestinal; LRTI: lower respiratory tract infection; UTI: urinary tract infection.

There was some suggestion of better outcomes for those receiving above 15 mg/week of MTX. Our analysis is complex because there is a bias by intention introduced by the trial design. Patients doing well while receiving low doses of MTX will continue at this dose, while those with active disease are more likely to have their dose increased, leading to an underestimation of the dose effect. However, despite this bias, there was some evidence supporting higher doses of MTX.

Despite the design problems of the MIPA trial, it is highly unlikely that a further RCT of MTX in PsA will ever be conducted. Open-label evidence must, therefore, be considered. MTX remains a commonly prescribed drug in PsA, and while it will not be effective for all patients, it does have a role in the treatment of the articular manifestations of PsA. MTX has the further advantage of working for the skin and it may have efficacy for other aspects of the disease, such as enthesitis and dactylitis. It is worth noting that the limitations of the clinical data are compounded by the lack of data on structural progression, but it must be noted that this statement is also true for the other oral DMARD, including the more recent drugs such as apremilast[24].

Data from the TICOPA study have shown improvement in the musculoskeletal manifestations, skin, and nails in PsA. The results should be interpreted in the context of the open-label design of the study, and placed alongside the other observational studies that support its use in this disease.

REFERENCES

1. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol 2001;28:1842-6.
2. Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? Ann Rheum Dis 2011;70:2152-4.
3. Tillett W, Jadon D, Shaddick G, Cavill C, Korendowych E, de Vries CS, et al. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. Ann Rheum Dis 2013;72:1358-61.
4. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis 2015;74:1045-50.
5. Theander E, Husmark T, Alenius GM, Larsson PT, Teleman A, Geijer M, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis 2014;73:407-13.
6. Kvien TK, Heiberg, Lie E, Kaufmann C, Mikkelsen K, Nordvag BY, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23 Suppl 39:S188-94.
7. Helliwell PS, Taylor WJ; CASPAR Study Group. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs — comparison of drugs and adverse reactions. J Rheumatol 2008;35:472-6.
8. Black RL, O'Brien WM, Vanscott EJ, Auerbach R, Eisen AZ, Bunim JJ. Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients. JAMA 1964;189:743-7.
9. Willkens RF, Williams HJ, Ward JR, Egger MJ, Reading JC, Clements PJ, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984;27:376-81.
10. Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatology 2012;51:1368-77.

11. Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis 2007;66:1038-42.
12. Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? J Rheumatol 2007;34:1302-6.
13. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum 2008;59:686-91.
14. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. J Rheumatol 2008;35:469-71.
15. Abu-Shakra M, Gladman DD, Thorne JC, Long J, Gough J, Farewell VT. Longterm methotrexate therapy in psoriatic arthritis: clinical and radiological outcome. J Rheumatol 1995;22:241-5.
16. Coates LC, Navarro-Coy N, Brown SR, Brown S, McParland L, Collier H, et al. The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. BMC Musculoskelet Disord 2013;14:101.
17. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48-53.
18. Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. Dermatologica 1978;157:238-44.
19. Cassell SE, Bieber JD, Rich P, Tutuncu ZN, Lee SJ, Kalunian KC, et al. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. J Rheumatol 2007;34:123-9.
20. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van ver Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127-32.
21. Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis 2013;72:986-91.
22. Helliwell PS, FitzGerald O, Fransen J. Composite disease activity and responder indices for psoriatic arthritis: a report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. J Rheumatol 2014;41:1212-7.
23. Jones G, Crotty M, Brooks P. Interventions for treating psoriatic arthritis. Cochrane Database Syst Rev 2000:CD000212.
24. Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. J Rheumatol 2014; 41:2277-85.