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Efficacy of Methotrexate in the Treatment of Psoriatic Arthritis: A Critical Literature Review

Effekten av metotrexat vid behandling av psoriasisartrit: En kritisk litteraturgranskning

AUTHOR: CHRISTOFFER LINDBOM

ABSTRACT

Background: Psoriatic arthritis (PsA) is an inflammatory joint disease occurring in up to 30% of psoriasis patients. Relatively few clinical trials assess PsA treatment and data presentation in these are far from uniform making comparisons difficult.

Objectives: To perform a literature review on methotrexate (MTX) efficacy in PsA. Research questions were: What evidence support MTX monotherapy in PsA? Does combination with MTX improve anti-TNF (tumor necrosis factor) treatment outcomes in PsA?

Methods: MEDLINE and Embase were searched until May 2019. This was supplemented by manually searching bibliographies of international treatment guidelines.

For the review of efficacy of MTX monotherapy, trials comparing MTX monotherapy versus placebo, other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids were considered.

For the comparison of TNFi monotherapy versus combination with MTX, randomized, controlled trials (RCTs) comparing TNFi monotherapy (adalimumab/etanercept/ certolizumab pegol/golimumab/infliximab) or in combination with MTX versus placebo were considered, as were RCTs comparing the combination of TNFi plus MTX to TNFi monotherapy.

Results: In four trials comparing MTX monotherapy to placebo or no additional intervention, superiority of MTX was demonstrated for only a few outcomes. Some indirect support for MTX efficacy also exists from three out of four studies comparing MTX to other active treatments. Findings were limited by the generally small numbers of patients included, relatively high placebo responses and by the low MTX dosages used.

The review of secondary analyzes from 11 trials comparing TNFi monotherapy versus combination with MTX showed numerically little or no additional effect of combination therapy on treatment response regardless of TNFi. In contrast, several studies suggest combination therapy to increase adherence to TNFi:s.

Conclusions: Evidence from placebo-controlled trials for the efficacy of MTX

monotherapy in PsA is sparse and generally of low quality, although some positive results do exist. Efficacy of TNFi:s does not seem to improve by combination with MTX, whereas TNFi adherence may be enhanced by such combination.

Keywords: psoriatic arthritis, methotrexate, efficacy

Author: Christoffer Lindbom

Supervisor: Johan K. Wallman, PhD, MD Specialist in Rheumatology
Department of Clinical Sciences Lund, Rheumatology, Lund University
Department of Rheumatology, Skåne University Hospital

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Psoriasisartrit är en inflammatorisk ledsjukdom som föreligger hos upp till 30% av patienterna med psoriasis i huden. Inflammationen angriper leder, men även lednära strukturer såsom senors fästen mot ben och medför att patienten upplever smärta, svullnad och stelhet. Vid psoriasisartrit är det vanligt att reumatologer förskriver metotrexat, ett så kallat konventionellt syntetiskt sjukdomsmodifierande anti-reumatiskt läkemedel (csDMARD), i syfte att motverka symtomen och förhindra försämring. Andra csDMARDs inbegriper exempelvis leflunomid och sulfasalazin. Biologiska DMARDs (bDMARDs), till vilka de så kallade tumörnekrosfaktorhämmarna (TNF-hämmarna) hör, är en annan grupp av läkemedel som också används frekvent vid behandling av psoriasisartrit, ofta i kombination med ett csDMARD såsom metotrexat.

Syftet med denna litteraturgranskning var dels att utvärdera effekten av metotrexat-behandling givet som enda terapi (monoterapi) jämfört med placebo eller andra csDMARDs, NSAID eller kortison hos patienter med psoriasisartrit, dels att utvärdera om det finns belägg för att samtidig behandling med metotrexat och TNF-hämmare ger bättre effekt jämfört med om TNF-hämmare ges ensamt. Vidare undersöktes evidensen för huruvida samtidig behandling med metotrexat och TNF-hämmare leder till att patienten kan stå kvar längre på en och samma TNF-hämmare.

Sökningar av studier publicerade fram till och med maj 2019 gjordes i två medicinska databaser, MEDLINE och Embase. Detta kompletterades med en manuell sökning av referenslistor tillhörande internationella behandlingsriktlinjer för psoriasisartrit. För granskningen av metotrexat som monoterapi beaktades studier som jämför behandling med metotrexat mot placebo, andra csDMARDs, NSAID eller kortison. För granskningen av behandling med TNF-hämmare som monoterapi kontra i kombination med metotrexat beaktades kliniska studier som jämför behandling med TNF-hämmare som monoterapi eller i kombination med metotrexat kontra placebo, samt kliniska studier som direkt jämför

kombinationsbehandling med TNF-hämmare och metotrexat med behandling med enbart TNF-hämmare.

I fyra identifierade studier som jämför metotrexat som monoterapi med placebo eller ingen ytterligare behandling, hade metotrexat signifikant bättre effekt enbart för några få utfall. Vissa indirekta stöd för metotrexats effekt rapporteras även i tre av fyra studier som jämför metotrexat med andra aktiva behandlingar (andra csDMARDs, NSAID eller kortison). Granskningen av 11 identifierade studier som jämför behandling med TNF-hämmare som monoterapi kontra kombination med metotrexat visade liten eller ingen ytterligare effekt av kombinationsbehandling oavsett typ av TNF-hämmare. Däremot når flera studier fram till slutsatsen att kombinationsbehandling ökar sannolikheten för att en patient ska kunna stå kvar på en och samma TNF-hämmare längre tid.

Evidensen från placebokontrollerade studier, där en grupp av patienterna får placebo och en grupp får verksamt läkemedel, gällande effekten av behandling med metotrexat som monoterapi vid psoriasisartrit är otillräckliga och håller i allmänhet låg kvalitet, även om det finns en del resultat som talar för en effekt av metotrexat. Effekten av TNF-hämmare verkar inte förbättras genom kombination med metotrexat, men däremot tycks samtidig användning av metotrexat leda till att patienten kan stå kvar en längre tid på en och samma TNF-hämmare.

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1. INTRODUCTION

1.1. Background

1.1.1. Features of psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory joint disease, usually seronegative, that occurs in up to 30% of patients with psoriasis [1]. In the general population it is estimated that the prevalence of PsA varies from 0.01% in the Middle East to 0.19% in Europe [2], with a similar affection rate for men and women. In 1973 five distinct clinical patterns among patients with PsA were described [3]: distal predominant pattern, asymmetrical oligoarthritis, symmetrical polyarthritis, spondylitis and arthritis mutilans. Over the past decades several papers have been published confirming the varied clinical patterns present in PsA, of which oligoarthritis and polyarthritis occur most frequently [4]. In 20% to 40% of patients there is an overlap of spondylitis and peripheral joint disease [1]. Periarticular manifestations are also common in the form of enthesitis, dactylitis and psoriatic fingernail dystrophy [3]. Rheumatoid factor, detectable in more than two out of three patients with rheumatoid arthritis, may only be detectable in around 13% of patients with PsA [1]. Around 60% of PsA patients are reported to show joint erosions, with approximately 20% developing severe joint destruction [1, 5].

While no diagnostic criteria for PsA exist, the nowadays most commonly used classification criteria for PsA research are the “ClASsification criteria for Psoriatic ARthritis” (CASPAR) criteria [6, 7], which are the result of a study commenced in 2004. The CASPAR criteria require the patient to show presence of ongoing inflammatory musculoskeletal disease (i.e. arthritis, enthesitis and/or spondylitis) combined with receiving at least three points regarding the following manifestations: a history of psoriasis (2 points for current psoriasis or 1 point for a personal and/or family history of psoriasis), dactylitis (1 point), psoriatic nail dystrophy (1 point), radiographic evidence of juxta-articular new bone formation (1 point) and rheumatoid factor negativity (1 point) [7].

PsA impair quality of life due to pain, joint stiffness and reduced physical function [1]. Furthermore, PsA patients are at a greater risk of developing cardiovascular disease compared to the general population and show higher premature death rates [8].

1.1.2. Description of outcome measures

In assessing the treatment response of PsA, outcome measures and composite indices have varied across studies and year of publication and have been largely borrowed from those used for rheumatoid arthritis [9]. These include the American College of Rheumatology (ACR) response criteria, the European League Against Rheumatology (EULAR) response criteria and the Disease Activity Score (DAS) (see *Appendix* for detailed descriptions). In addition, a composite index called Psoriatic Arthritis Response Criteria (PsARC) was developed in 1996 specifically for assessing PsA [9]. The American College of Rheumatology 20% response criteria (ACR20) developed in 1993 is currently the primary outcome required by *the U.S. Food and Drug Administration* (FDA) for approval of a new therapy for PsA [10]. It is a composite index defined as ≥ 20% improvement from baseline in both the number of tender and number of swollen joints, as well as in three of the following outcomes: patient global assessment of disease activity, physician global assessment of disease activity, functional ability measure (most often by means of the Health Assessment Questionnaire (HAQ)), patient visual analog pain scale, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) [10]. It is worth noting that several of the trials included in this review were conducted before many of these outcomes were developed and validated.

1.1.3. About the intervention

Pharmacological management of PsA includes non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) [11]. DMARDs are available in three major classes, loosely grouped according to different mechanisms of action: conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX), sulfasalazine (SSZ) and leflunomide (LEF), biological DMARDs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi:s), and targeted synthetic DMARDs (tsDMARDs) such as phosphodiesterase (PDE) inhibitors or Janus kinase (JAK) inhibitors [11].

MTX belongs to the csDMARD class and can be administered orally or via intramuscular or subcutaneous injections at dosages typically ranging from 5 mg to 30 mg weekly. MTX is a folic acid antagonist, but at the low dosages used for inflammatory diseases, this pathway does not appropriately explain its effects [12]. The biochemical mechanisms of MTX in the treatment of inflammatory diseases are not yet fully understood, although alternative mechanisms including the accumulation of extracellular adenosine, altered cytokine production of inflammatory cells and modulation of humoral and cellular immunity are suggested to play important roles [12]. MTX is widely used in the treatment of cutaneous psoriasis [13], and in rheumatoid arthritis MTX has been shown to lead to improved joint disease and health-related quality of life [14]. Despite sparse formal evidence for its efficacy in PsA (as reviewed below), MTX monotherapy is at present widely used as a first-line treatment due to good clinical experience [15], and is also commonly used in combination with TNFi:s. TNFi:s (belonging to the bDMARD class), on the other hand, have been clearly shown to be efficacious in PsA [16], although at a much higher cost than csDMARDs such as MTX.

1.1.4. Treatment guidelines

The management of psoriatic arthritis (PsA) rests on non-pharmacological and pharmacological interventions. Several different international, as well as national, treatment guidelines for PsA are currently available. Of special interest for this review, the recommendations regarding the use of MTX varies between the different guidelines, as briefly described below for the most important international, as well as for the national Swedish, guidelines.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and *the European League Against Rheumatism* (EULAR) both presented updated recommendations on the management of PsA in 2015 [17, 18]. In both sets of recommendations, the heterogeneity of PsA is recognized. Drugs discussed include csDMARDs such as MTX, and newer, targeted therapies including bDMARDs and tsDMARDs. The proposed use of these drugs, as well as some other aspects of PsA management, differ between the two sets of recommendations. In the EULAR recommendations, MTX is named the csDMARD of first choice for PsA, whereas in the

GRAPPA recommendations, MTX, LEF and SSZ are all considered first-line alternatives without one drug being given preference over another. In the GRAPPA treatment algorithm, patients with severe or poor prognosis peripheral joint disease can be prescribed a bDMARD as first-line therapy without having been given a csDMARD. This recommendation is made on the basis of evidence that a number of biologic agents are highly effective for patients who have not previously failed csDMARD treatment. The EULAR recommendations make no such allowances.

In the recommendations published by *the Swedish Society for Rheumatology* (SRF) in 2019 [15], MTX is proposed as a first-line therapy (with SSZ or LEF as equal alternatives), proceeding to bDMARD therapy only if csDMARD treatment is not sufficient.

According to *the American College of Rheumatology / National Psoriasis Foundation* (ACR/NPF) guidelines [19], updated in 2018, TNFi:s should instead be used as the preferred first-line treatment ahead of oral small molecules (OSMs; including MTX, SSZ and LEF), whereas OSMs or TNFi:s are generally recommended over other types of bDMARDs.

1.2. Objective and research questions

The central position held by MTX in the current standard PsA treatment, coupled with the considerable discrepancies outlined above regarding recommendations on its use between different international treatment guidelines, calls for a review of the available formal evidence for MTX efficacy in PsA. Thus, the objective of this paper was to perform a critical literature review on the efficacy of MTX in PsA, both when used as monotherapy and in combination with TNFi:s. The primary research question was: What formal evidence from clinical trials exist in support of a treatment effect of MTX monotherapy in PsA? Secondary research questions were: 1) Do randomized controlled trials of TNFi:s in PsA support a better treatment effect when combining the TNFi with MTX, as opposed to TNFi monotherapy? 2) Do observational register studies show better long-term adherence to TNFi:s when given in combination with MTX, as opposed to TNFi monotherapy?

2. MATERIALS AND METHODS

2.1. Search methods

A critical literature review was conducted. Two databases (MEDLINE and Embase) were searched for clinical trials reported as full text. Search terms were "methotrexate AND psoriatic arthritis" and "psoriatic arthritis AND (TNF OR adalimumab OR etanercept OR certolizumab OR golimumab OR infliximab)". Databases were searched from their inception to 20 May 2019. This search strategy was supplemented by manually screening the latest available versions of treatment guideline documents (EULAR, GRAPPA, ACR/NPF and SRF) and their underlying review articles for relevant references matching the selection criteria. Language restrictions were applied to only include records published in English as full text evaluation was required for the quality assessment.

2.2. Criteria for considering studies for this review

Included were clinical trials of patients ≥ 18 years with a clinically determined diagnosis of PsA.

For the primary research question, reviewing the efficacy of MTX monotherapy, trials comparing MTX given as monotherapy at any dose and administration versus a comparison treatment consisting of placebo, other csDMARDs, NSAIDs or glucocorticoids were considered. In studies not applying these substances as comparison treatment, concurrent use of NSAIDs and/or glucocorticoids was allowed, provided they could be used in all treatment arms. The search was limited to controlled studies, i.e. considering RCTs, non-randomized, controlled clinical trials and retrospective registry studies including a comparison group as described above.

For the comparison of the efficacy of TNFi monotherapy versus combination therapy with MTX, solely RCTs were included. RCTs comparing TNFi:s (adalimumab (ADA), etanercept (ETA), certolizumab pegol (CZP), golimumab (GOL) or infliximab (INF)) given as monotherapy or in combination with MTX versus placebo were considered, as were RCTs directly comparing the combination of TNFi plus MTX to TNFi monotherapy. Only

publications reporting on the initial placebo-controlled phase of the former studies (and no long-term extension publications) were included.

Observational registry studies on the effect of TNFi and MTX combination therapy on adherence to TNFi:s were identified through searches in the reference lists of the different treatment guidelines.

2.3. Types of outcome measures

The included clinical trials reported a wide variety of outcome measures, and as no strict consensus exists on domains to be reported in PsA trials, outcome measures mentioned in the latest version of the PsA treatment guidelines published in 2019 by *the Swedish Society of Rheumatology* [15] were considered acceptable. For the MTX monotherapy efficacy review at least one of the following outcomes (see *Appendix* for descriptions) had to be reported after 12-24 weeks of treatment to be included in the table of findings:

1. Disease activity:
    a. Composite indices: ACR20 response, ACR50 response, ACR70 response, DAS-28 response, DAPSA response, PsARC response
    b. Physician reported outcomes: global disease activity
    c. Patient reported outcomes: global disease activity, pain, morning stiffness
    d. Joint counts: swollen joint count, tender joint count
    e. Inflammation markers: CRP, ESR
2. Physical function
3. Health-related quality of life
4. Radiographic progression

For the two secondary research questions, focusing on TNFi and MTX combination therapy versus TNFi monotherapy, the review was limited to ACR20 response (the standard primary outcome in the TNFi trials) and long-term TNFi drug adherence, respectively.

2.4. Data collection and analysis

Titles and abstracts of all records identified through the search of databases were screened twice and potentially eligible studies underwent full-text assessment. Fulfilment of the inclusion criteria were assessed, and reasons for excluding ineligible studies were logged. Outcome data were extracted using a uniform extraction protocol and included information on study design, inclusion criteria, interventions and baseline data in addition to reported outcomes.

2.5. Quality assessment of included studies

Risk of bias was assessed using the criteria for assessment of randomized controlled trials outlined by *the Swedish Agency for Health Technology Assessment and Assessment of Social Services* [20]. A limitation was made to only assess trials included in the primary research question review focusing on MTX monotherapy. Each risk of bias item belonging to the following domains were assessed separately for each study and graded as having low, moderate or high risk of bias:

1. Selection bias
2. Performance bias
3. Detection bias
4. Attrition bias
5. Reporting bias
6. Other considerations (bias due to conflict of interest)

2.6. Ethical considerations

Since the current study is a review of already published work, ethical approval was not deemed necessary.

3. RESULTS

3.1. Search results

3.1.1. Review of MTX monotherapy

Identification of eligible studies through database searches resulted in 242 records. Fourteen additional records were identified through other sources. After duplicates being removed, 112 records remained to be screened. Included in the final review were 8 trials matching the inclusion criteria assessing MTX monotherapy compared to placebo, NSAIDs or other csDMARDs (LEF, ciclosporin A (CsA) and intramuscular (i.m.) gold). No studies comparing MTX monotherapy to treatment with glucocorticoids were identified.

3.1.2. Review of TNFi and MTX combination therapy

For this review, 11 records were identified through other sources in addition to 366 records identified through database searches. After duplicates being removed, 233 records remained to be screened. Eleven trials with comparable baseline characteristics assessing the TNFi:s ADA, CZP, ETA, GOL or INF were finally included.

3.2. Included trials

Seven of the eight included studies in the review of MTX monotherapy used a parallel design [21-27] and one a cross-over design [28]. *Kingsley et al.* (2012) [21] included the largest number of participants (221 participants), while the trial with the smallest number of participants was *Black et al.* (1964) [28] (21 participants). Participants of all studies were recruited from rheumatology clinics and should therefore be presumed to have been diagnosed with PsA by a rheumatologist. All studies had a lower age limit of 18 years except *Spadaro et al.* (1995) [23], which had a lower limit of 16 years, but was included as no participant was reported to be under 18 years old. Of the eight trials included, three compared MTX versus placebo [21, 22, 28], one a combination of MTX and NSAIDs versus NSAIDs alone [24], and four compared MTX versus other csDMARDs or NSAIDs plus the potential use of other csDMARDs [23, 25-27]. When summarizing the study findings (see *Tables 1 and 2*), the study [24] comparing MTX and concomitant NSAIDs with NSAID monotherapy was grouped together with the placebo-controlled trials, since this design meant comparing the addition of

MTX versus no additional intervention. In the four studies comparing MTX monotherapy versus other csDMARDs, one used LEF at a dose of 20 mg daily [27], one CsA at an initial dose of 3 mg/kg/day [23], one i.m. gold at a dose of 50 mg weekly [26] and one NSAIDs in combination with any other second line csDMARD as comparison [25]. All studies except two [24, 28] used oral MTX at doages varying across trials from 5 mg to 20 mg weekly. In *Black et al.* (1964) parenteral MTX was used at a dose of 1 mg/kg to 3 mg/kg every 10 days and in *Scarpa et al.* (2008) at a dose of 10 mg weekly. Concomitant therapy with analgesia was permitted in all studies even though specific agents and dosages allowed varied across studies.

Characteristics of the 11 RCTs [29-39] included in the TNFi and MTX combination therapy review can be viewed in *Table 3.*

3.3. Outcomes in included studies

The outcome findings of the MTX monotherapy review can be viewed in *Tables 1 and 2.* Outcomes reported varied across studies and all studies did not report all outcomes. One study [28] provided no extractable data and is hence not represented in *Table 1.*

3.4. Risk of bias in included studies

For the risk of bias assessment, scores for every individual quality criterion were summarized and the outcomes can be viewed in *Figures 3 and 4.* The overall risk of bias was judged to be moderate to high for all of the assessed studies.

3.5. Effects of interventions

3.5.1. MTX monotherapy versus placebo or no additional intervention

Black et al. 1964

This trial [28] including 21 participants, had a cross-over design and data were therefore only planned to be extracted from the first phase comparing one group receiving parenteral MTX monotherapy at progressively increasing dosages from 1 to 3 mg/kg of body weight and the other receiving matched parenteral placebo. However, the study publication provided no extractable data at the individual study-group level and is thus not represented in the summary of findings table. It was however reported that MTX was found to be

superior to placebo in all parameters measured (effect on joints, $p = 0.01$; effect on range of motion, $p = 0.01$; effect on skin, $p < 0.01$ and effect on ESR, $p < 0.01$).

Kingsley et al. 2012

This 6-month trial (221 randomized participants; oral MTX 15 mg weekly (standard dose)) [21] had one arm receiving MTX monotherapy and the other receiving placebo. When considering the composite disease activity indices in intention-to-treat (ITT) analysis of all randomized participants, no statistically significant treatment effects were observed after 6 months. This was the only trial comparing MTX monotherapy to placebo or no additional intervention that reported on ACR20, ACR50, ACR70 and PsARC response. The study authors' calculated odds ratios for ACR20, DAS-28 and PsARC responses with MTX after imputation were 2.00 (95% CI 0.65 to 6.22), 1.70 (95% CI 0.90 to 3.17) and 1.77 (95% CI 0.97 to 3.23) respectively after 6 months of treatment. This study was also the only one comparing MTX monotherapy to placebo or no additional intervention that reported on physical function by means of HAQ (Health Assessment Questionnaire) but found no statistically significant difference for this outcome. Reported mean changes of physician's assessment of global disease activity (VAS scale 0-100 mm) was -17.9 for MTX and -7.0 for placebo ($p = 0.01$), indicating a better result for MTX after 6 months use. The only statistically significant patient reported outcome presented was global disease activity (VAS score 0-100 mm) with a mean change of -18.0 (MTX) versus -7.5 (placebo) ($p = 0.02$).

Scarpa et al. 2008

Thirty-five patients participated in this 6-month trial [24] comparing concomitant treatment with intramuscular MTX 10 mg weekly and NSAIDs versus NSAID monotherapy. Data for this review were extracted after 3 months of treatment and covered physician- and patient-reported outcomes, joint counts as well as inflammation markers in the ITT cohort. The median (IQR) for the assessment of swollen joints for the ITT cohort at 3 months was 0 (1) joints for MTX versus 1 (2) joint for placebo (statistically significant $p < 0.05$). Tender joint count, reported as median (IQR), was 1 (1) joint for MTX versus 2 (3) joints for placebo (statistically significant $p < 0.05$). There was no information provided regarding the number of joints examined. No statistically significant results were reported for the other outcomes assessed.

Willkens et al. 1984

This 3-month study including 37 participants [22] compared oral MTX monotherapy treatment at a maximum dose of 15 mg weekly with matching placebo. Data were extracted after 3 months of treatment and included values on physician-reported outcomes, patient-reported outcomes and joint counts. MTX was reported to improve physician's global disease activity assessment (median change from baseline was -1 for MTX and 0 for placebo on a 1-5 scale; $p < 0.001$) but provided no statistically significant results for other outcomes.

3.5.2. MTX monotherapy versus other csDMARDs and/or NSAIDs

Abu-Shakra et al. 1995

This long-term prospective study [25] comparing MTX at a maximum weekly dose of 15 to 20 mg versus NSAIDs plus the potential use of other second line csDMARDs was carried out between 1978 and 1993. During this period, 38 PsA patients starting MTX were enrolled, each of whom was matched to a patient treated with NSAIDs plus in some cases other csDMARDs. Of the 38 MTX-treated patients, 23 continued this therapy for 24 months. The primary outcome measure was increase in the number of radiographically damaged joints at 24 months. The clinical assessment after 24 months showed that 47% of the MTX-treated patients and 53% of their matched controls had ≥ 40% improvement in actively inflamed joint count (non-significant). Radiographic damage scores in 19 of the 23 patients continuing MTX for 24 months for whom radiographs were available revealed an increase in 63% of the MTX-treated patients, as compared to in 47% of their matched controls (no statistically significant between-group difference).

Asaduzzaman et al. 2014

This 6-month trial [27] with oral LEF 20 mg daily as comparator randomized 32 participants and ran from June 2002 to December 2003. The MTX arm was administered oral MTX 10 mg weekly (considered a low dose). Both groups were allowed to take ibuprofen, maximum 1400 mg daily. Sixteen in the LEF arm and 14 in the MTX arm completed follow-up after 24 weeks of treatment. Out of several outcomes reported, ACR70 response was the only for which there was a statistically significant between-group difference with 14% of responders in the MTX group versus 31% of responders in the LEF group reaching ACR70 response after 6 months of treatment.

Lacaille et al. 2000

This retrospective study [26] aimed at comparing the efficacy of MTX (at a mean dose of 12 mg weekly (range 5-35 mg)) and i.m. gold (at a mean dose of 150 mg weekly (range 20-300 mg)). Eighty-seven patients received 111 treatment courses: 43 of MTX and 68 of i.m. gold. Primary outcome measures were the development of a clinical response, defined as ≥ 50% reduction in active joint count from baseline to the latest available follow-up visit (i.e. the time of assessment varied between patients; median treatment times were 28 and 15 months in the MTX and i.m. gold groups, respectively), and the probability of discontinuing therapy. Statistically significant between-group differences in favor of MTX were found for both of these outcomes. Fifty-eight percent of patients in the MTX group versus 35 percent in the i.m. gold group achieved ≥ 50% reduction in active joint count at their last available follow-up visit (OR: 8.90 (95% CI 1.8 to 44.0)).

Spadaro et al. 1995

The objective of this trial [23] (35 randomized participants; oral MTX 7.5-15 mg weekly; oral CsA 3-5 mg/kg daily) was to compare the efficacy of CsA versus MTX over a period of 12 months. Comparisons of the changes in the main clinical outcomes after 12 months of treatment between MTX and CsA did not reveal any statistically significant differences.

3.5.3. Concomitant use of MTX and TNFi versus TNFi monotherapy

The outcome compared for this part of the review was ACR20 response, which was reported in detail for TNFi and MTX combination therapy and TNFi monotherapy respectively in six of the 11 included trials (see *Table 3*). Results in the two treatment groups were very similar across studies, with four trials [29, 32, 34, 35] reporting a numerically, marginally better ACR20 response achievement for concomitant treatment with MTX after 12 to 24 months, whereas two [30, 36] trials reported a numerically, slightly better result in favor of TNFi monotherapy (see *Figure 5*). No study reported any statistically significant between-group difference in ACR20 response between these interventions, although in most cases this was not formally tested.

Adalimumab

Two trials [31, 36] compared treatment with ADA versus placebo. In *Mease et al.* (2005) approximately half of the participants (50.5%) were reported to be taking MTX up to 30 mg weekly at baseline. ACR20 response rates after 12 weeks treatment were numerically similar between participants taking ADA in combination with MTX and participants receiving ADA monotherapy. The combination therapy patients had an ACR20 response rate of 55% at week 12, while the response rate was 61% for patients receiving ADA monotherapy (no significance testing performed). For *Genovese et al.* (2007), no precise values were reported but the authors write that "For adalimumab patients, the Week 12 ACR20/50/70 response rates were similar for those who at baseline were receiving MTX compared to those who were not" [31].

Certolizumab pegol

One study [34] reported on treatment with CZP versus placebo. Baseline concomitant csDMARD use was not a stratification factor, but participants with or without concomitant csDMARD had similar baseline characteristics. MTX was by far the most commonly used concomitant csDMARD (63.6 % of randomized patients were receiving MTX at baseline) and the use was similar between the CZP and placebo groups. However, concomitant csDMARD use was not reported to affect CZP response considerably (56.8 % achieved ACR20 response at week 12 compared to 50.0% for participants taking only CZP). No significance testing was performed.

Etanercept

Two trials [37, 38] compared ETA treatment to placebo, one [39] compared the efficacy over 12 weeks of two different ETA regimens, and one [35] examined the efficacy of MTX monotherapy relative to ETA monotherapy and the value of combining MTX and ETA. In three of these trials, no detailed results on ETA treatment with or without MTX are reported [37-39]. However, in *Mease et al.* (2004) it is reported that "In sensitivity analysis, no significant differences in response were observed between methotrexate strata" [38]. The authors behind *Sterry et al*. (2010) furthermore report that "Only 25% of participants in this trial received concomitant methotrexate treatment; the mean dosage was

12.7 (SD 4.3) mg/week. In this subset of participants, some benefit of combination therapy was apparent at week 12 for skin but not joint symptoms" [39].

Results from *Mease et al.* (2019) (SEAM-PsA) reports that the proportion of patients achieving an ACR20 response at week 24 was numerically only somewhat greater among those receiving ETA and MTX combination therapy (65%) compared with those receiving ETA monotherapy (61%; no significance testing was conducted between these groups) [35].

Golimumab

Two trials [32, 33] evaluated the efficacy of GOL compared to placebo. In both studies, randomization was stratified by baseline MTX use. No specific numbers were reported in *Kavanaugh et al.* (2009), but the authors claimed that no statically significant difference in ACR20 response was seen at week 14 between patients receiving concomitant MTX versus patients receiving only GOL. In *Kavanaugh et al.* (2017) concomitant use of MTX up to 25 mg weekly was permitted for patients who had been receiving MTX for more than 3 months prior to the first GOL administration. At baseline 70.0 % of all patients were receiving concomitant MTX and the number of patients taking MTX were comparable across the intervention arms. No substantial differences in ACR20 response rates were reported between participants receiving concomitant MTX treatment at baseline (77.9%) and those who did not (74.4%) (no significance testing performed).

Infliximab

Two studies [29, 30] (IMPACT and IMPACT II) investigated the efficacy of INF therapy versus placebo. Overall, 71% of patients in the IMPACT trial were receiving a concomitant csDMARD at baseline, where MTX was the most commonly used (56%). In IMPACT 62.5% of patients receiving INF and concomitant MTX achieved an ACR20 response at week 16 compared to 74% of INF patients not receiving any csDMARDs (non-significant between-group difference). In IMPACT II 47% of patients in the INF group received MTX at baseline at a mean dose of 16 mg/week. Results at week 24 revealed

similar ACR20 response rate between MTX users (57%) and MTX non-users (51%). No significance testing was performed in this case.

3.5.4. Concomitant MTX treatment and the effect on drug survival of TNFi:s

To evaluate the present evidence of the effect of concomitant MTX treatment on drug survival of TNFi:s three relatively recent register studies [40-42] investigating the role of MTX co-medication in TNFi therapy in PsA were reviewed. In *Kirstensen et al.* (2008) it is reported that concomitant MTX use at treatment initiation with TNFi:s is associated with better overall TNFi drug survival (hazard ratio (HR) for discontinuation 0.64, 95% CI 0.39–0.95, $p = 0.03$) and that the improvement is strongly related to fewer dropouts due to adverse events ($p < 0.01$). There was no statistical interaction found between the type of TNFi agent and concurrent MTX treatment in regard to level of drug survival [40].

In *Fagerli et al.* (2008) drug survival analysis revealed a borderline significant difference in favor of patients taking MTX co-medication ($p = 0.07$) and in particular with INF ($p = 0.01$). Discontinuations were numerically more frequent in the monotherapy versus co-medication group (54.1% vs 45.9%). Mean MTX dose in the co-medication group was 14.7 mg weekly [41].

The third study [42], with 54% of all patients receiving MTX co-medication, revealed similar crude retention rates among patients receiving INF, ADA and ETA ($p > 0.05$). Concomitant MTX use at baseline did not affect drug survival ($p > 0.05$).

4. DISCUSSION AND CONCLUSION

4.1. Discussion

Although MTX has a central position in the clinical treatment of PsA today, this review reveals that the scientific evidence in favor of a treatment effect of MTX as monotherapy in PsA is actually relatively sparse. In regard to TNFi and MTX combination therapy, this review further concludes that MTX does not appear to provide any improved efficacy, while there is some support for MTX improving the drug survival of TNFi:s.

Eight clinical trials [21-28] assessing the effect of MTX monotherapy in psoriatic arthritis were identified. Four trials compared MTX monotherapy to placebo or no additional intervention [21, 22, 24, 28], whereas four compared MTX to other active treatments (csDMARDs and/or NSAIDs) [23, 25-27]. Trial sizes were generally small, and some studies may have been insufficiently powered to detect statistically significant differences for the outcomes reported.

The largest trial, *Kingsley et al.* (2012) [21], comparing MTX monotherapy to placebo, which has also been assessed to have the least risk of bias of those included in the review, found a significantly better effect on physician's and patient's global assessment of disease activity for MTX versus placebo. At the same time, no significant difference was detected for any of the other outcomes reported. Support in favor of a treatment effect of MTX is also provided by *Willkens et al.* (1984) [22] on physician's global assessment of disease activity (which is in line with results of [21]), and by *Scarpa et al.* (2008) [24] on tender and swollen joint counts. In numerical terms, all three of these statistically significant differences compared to placebo or no additional intervention are small, but they are nonetheless positive findings that to some extent support the effect of MTX. It might be the case that MTX must be taken at higher dosages and/or for a longer period of time in order to provide good effects. Older trials such as the RCT by *Black et al.* (1964) [28] (MTX administered in progressively increasing dosages from 1 to 3 mg/kg of body weight, i.e. in much higher dosages than in later trials), where a reduction in joint involvement was observed in the MTX arm compared to the placebo arm, were conducted before the

development and validation of composite disease measures such as ACR and PsARC, which aggravates the comparison. No study in the MTX versus placebo review reported on radiographic progression.

With regard to the trials comparing MTX to other csDMARDs and/or NSAIDs, indirect support for a treatment effect of MTX is presented in *Lacaille et al.* (2000) [26], reporting better clinical improvement in addition to better drug survival for MTX in relation to i.m. gold, while *Spadaro et al.* (1995) [23] present results indicating the effect of MTX to be equivalent to that of CsA (no significant differences in any outcome here). The effect also seems relatively similar to that of LEF based on the results of *Asaduzzaman et al.* (2014) [27], although LEF was, after all, significantly better for ACR70 (a high-hurdle outcome difficult to achieve). All the four studies included in this section have been assessed to have a fairly high risk of bias, which makes the evaluation more difficult.

MTX is currently widely used as an anchor drug in the treatment of PsA, despite the fact that the evidence in favor of its use is sparse: no study included in this review demonstrated considerable clinical efficacy of MTX in PsA, although findings were limited by the generally small numbers of patients included, relatively high placebo responses and by the low dosages used. This has not only been concluded in this review, but also in previously conducted reviews [16]. Recently, however, further indirect evidence for a treatment effect of MTX monotherapy in PsA has come from the TIght COntrol of Psoriatic Arthritis (TICOPA) trial published in 2015 [43], a multicenter open-label RCT in 206 patients and the first PsA study conducted with a treat-to-target approach. Patients randomized to the treat-to-target arm of this trial were all started on MTX monotherapy (with a target dose of 25 mg/week) and were thereafter evaluated monthly during a year with obligatory additions/changes of the treatment if minimal disease activity had not been reached. The fact that 26% of the patients remained on MTX monotherapy at the end of the study, as well as retrospective analyses of the MTX monotherapy subgroup showing a relatively good ACR20 response of 41% after 12 weeks of treatment [44], have both been interpreted as signs of MTX efficacy, although the lack of a placebo group represents a clear limitation. Similarly, *Mease et al.* (2019) [35] reported MTX monotherapy at 20

mg/week to result in an ACR20 response of 51% at 24 weeks, although again without a placebo group for comparison.

The review of secondary analyzes from randomized trials comparing TNFi:s in monotherapy with TNFi:s in combination with MTX shows little or no additional effect of combination therapy on ACR20 response regardless of TNFi agent. This conclusion is in agreement with previously conducted reviews. *Behrens et al.* (2015) [45] included six RCTs of TNFi:s in PsA and found little or no efficacy improvements for concomitant MTX versus TNFi monotherapy, although the use of concomitant MTX appeared to prolong monoclonal antibody-type TNFi drug survival.

Several studies in the PsA field provide evidence suggesting that combination therapy may increase the chance of the patient remaining longer on monoclonal antibody-type TNFi agents [40, 45]. The effects are small to moderate in short term and have not been studied in long term. The beneficial mechanism for combination therapy appears to be by reducing the formation of anti-drug antibodies, which in turn may reduce the effect of the TNFi or cause drug reactions [45]. The magnitude of this effect appears to be lower than in the corresponding treatment of rheumatoid arthritis. A cautious interpretation of the sparse existing data on concomitant MTX treatment and the effect on drug survival of TNFi:s is that the combination of monoclonal type anti-TNF agents with MTX may slightly increase the chances of sustained efficacy over time.

The proposed use of both MTX monotherapy and combination therapy with TNFi:s differ, as previously mentioned, between the available sets of treatment recommendations. As for EULAR [18], MTX is clearly defined as the primary choice in DMARD therapy despite the lack of clear evidence for its efficacy. GRAPPA [17] (as well as SRF [15]), on the other hand, suggests MTX to be one of three potential first-line DMARDs (alongside with LEF and SSZ). Given the sparse available evidence base, GRAPPA has not chosen to rank these interventions individually. This disparity could possibly be the result of a difference in the evaluation process. The focus of EULAR is primarily rheumatological and clinical experience is taken into great account, whereas GRAPPA (apart from focusing on both rheumatological and dermatological aspects) do not seem to evaluate clinical experience to

the same extent. Combination of MTX with TNFi:s is not yet recommended by EULAR or GRAPPA mainly because of insufficient evidence. As opposed to the EULAR and GRAPPA treatment guidelines, the ACR/NPF guidelines [18] recommends TNFi:s to be used instead as the preferred first-line treatment ahead of OSMs including MTX. The reason for this is that the ACR/NPF rely heavily on evidence from clinical trials (primarily RCTs) and only to a small extent take into account clinical experience.

Regarding strengths of this review, two databases (MEDLINE and Embase) were searched for relevant studies to be included. This search strategy was supplemented by manually screening four different treatment guideline documents and their underlying review articles for relevant references matching the selection criteria, ensuring a comprehensive coverage of available findings. In addition, quality assessments using a validated instrument were conducted for the studies included in the MTX monotherapy review. Still, this review has some limitations. Evidence of the benefit of MTX from uncontrolled, observational studies may have been missed since that study type was not included (except for in the review of the effect of MTX on drug survival of TNFi:s). Furthermore, the quality assessments were conducted using the same instrument, designed for the assessment of RCTs, even for non-RCT studies. Ideally, another, specially adapted instrument should have been chosen for the non-RCT studies.

4.2. Conclusion

Evidence from placebo-controlled trials for the efficacy of MTX monotherapy in the treatment of PsA is sparse and in general of low quality, although more recent non-controlled trials have indicated some efficacy. There is clearly a need for further research in this respect. The clinical experience of MTX monotherapy in PsA is however both extensive and good and the intervention is supported by several international treatment guidelines. MTX will most likely be used in the treatment of PsA many years to come, not least in resource-poor areas where more expensive treatment alternatives are not easily accessible. Efficacy of TNFi:s does not seem to improve considerably by combination with MTX compared to TNFi monotherapy, but the use of concomitant MTX might provide better drug survival of certain TNFi:s. Further RCTs specifically assessing the efficacy of

such combination therapy versus TNFi monotherapy would most certainly provide additional important knowledge about how to optimally use MTX in the treatment of PsA.

5. REFERENCES

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6. TABLES AND FIGURES

6.1. Study flow diagrams

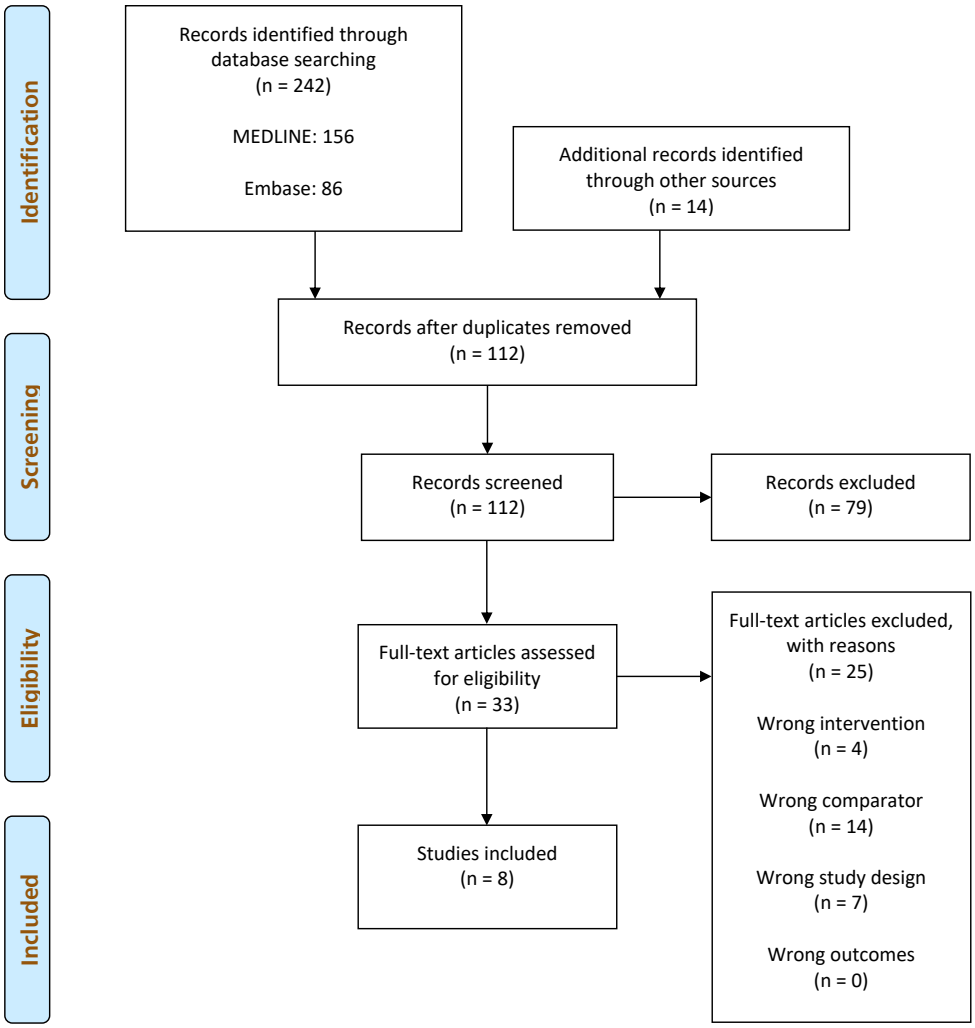

Figure 1: Study flow diagram. Review of MTX monotherapy versus placebo, other csDMARDs, NSAIDs or glucocorticoids.

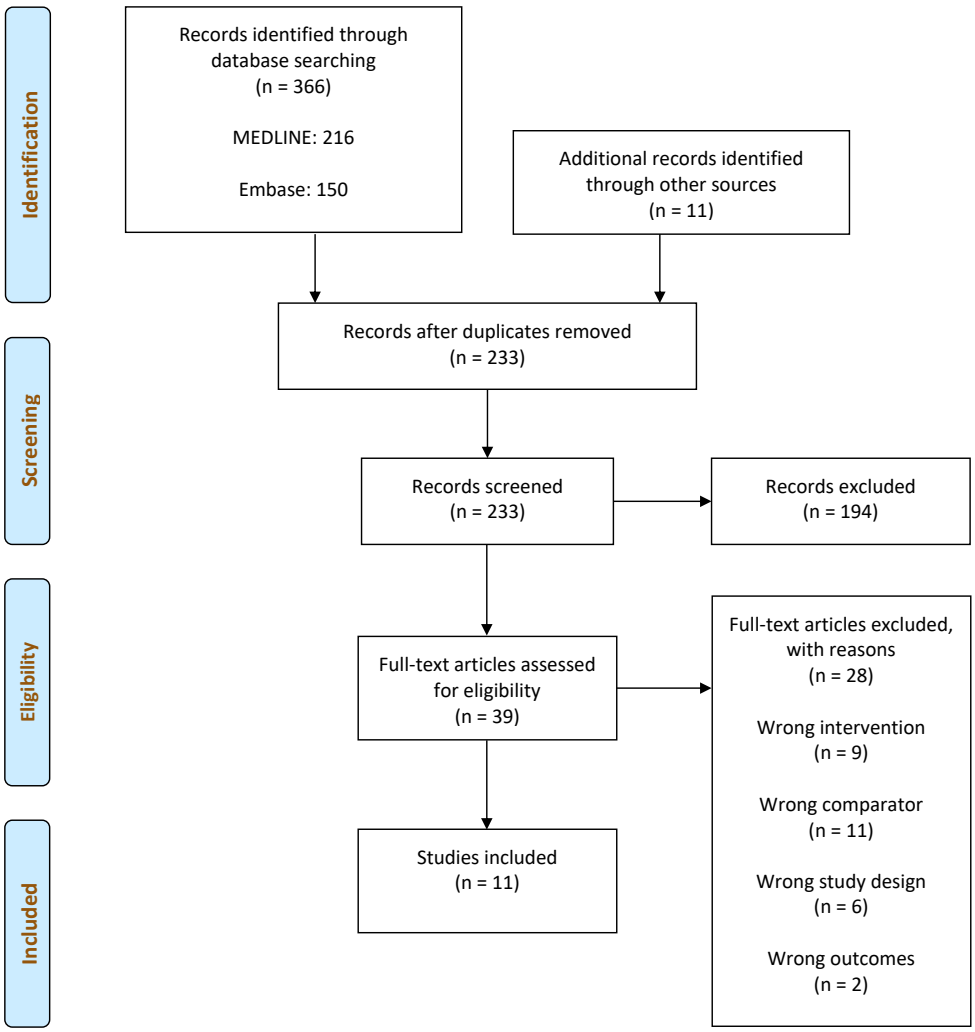

Figure 2: Study flow diagram. Review of TNFi and MTX combination therapy (regarding efficacy).

6.2. Risk of bias assessment

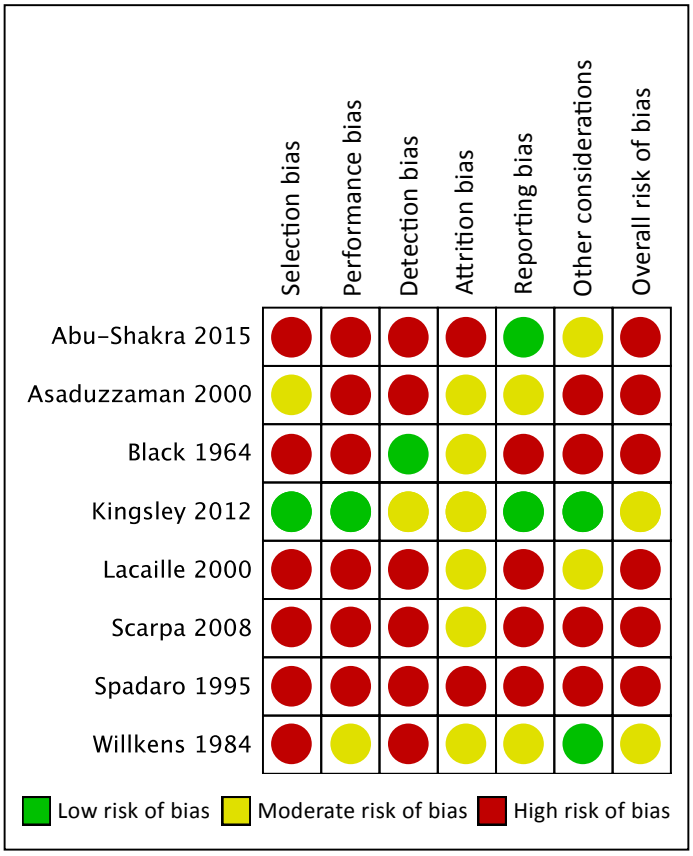

Figure 3: Risk of bias summary. Review author's judgements about risk of bias for each included study in the methotrexate monotherapy review.

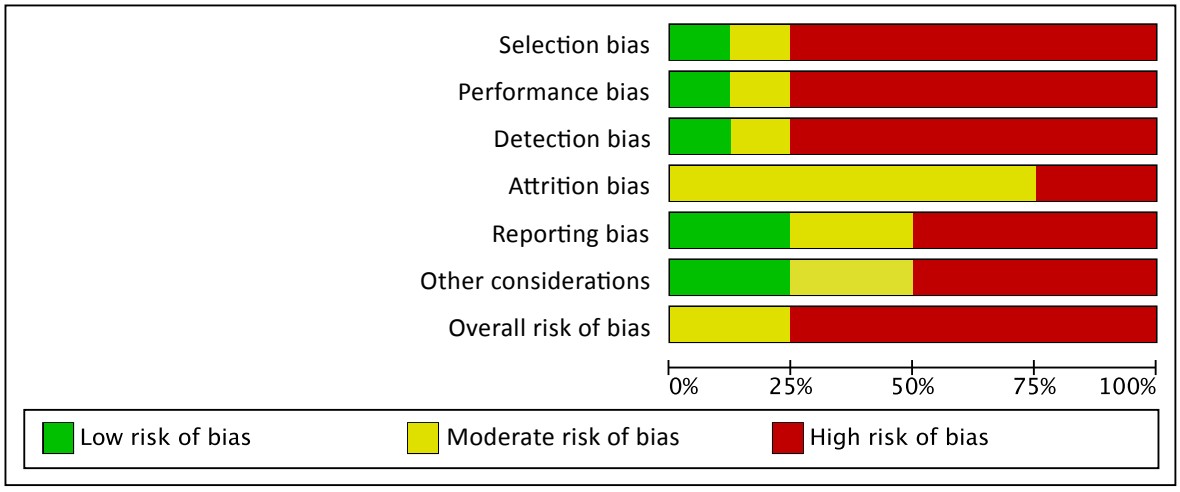

Figure 4: Risk of bias graph. Review author's judgements about risk of bias presented as percentages across all included studies in the methotrexate monotherapy review.

6.3. Summary of findings tables

Table 1: Methotrexate monotherapy vs. placebo or no additional intervention.
* Statistically significant ($p < 0.05$)

STUDY	YEAR	NO. INCLUDED	INTERVENTION	COMPARISON GROUP	OUTCOME	DURATION (MONTHS)	STATISTICAL METHOD	OUTCOME INTERVENTION VS. OUTCOME COMPARISON
DISEASE ACTIVITY								
Composite indices								
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	ACR20 response	6	OR (95% CI)	2.00 (0.65-6.22)
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	DAS-28 response	6	OR (95% CI)	1.70 (0.90-3.17)
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	PsARC response	6	OR (95% CI)	1.77 (0.97-3.23)
Physician reported outcomes								
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	Global disease activity (0-100)	6	Mean change	-17.9 vs. -10.7*
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	Global disease activity (1-5)	3	Median change	-1 vs. 0*
Scarpa et al.[24]	2008	35	MTX i.m. 10 mg/w + NSAIDs	NSAIDs	Global disease activity (0-5)	3	Median (IQR)	3 (2) vs. 2 (3)
Patient reported outcomes								
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	Global disease activity (0-100)	6	Mean change	-18.0 vs. -7.5*
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	Global disease activity (1-5)	3	Median change	-1 vs. 0
Scarpa et al.[24]	2008	35	MTX i.m. 10 mg/w + NSAIDs	NSAIDs	Global disease activity (0-5)	3	Median (IQR)	3 (2) vs. 2 (3)
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	Pain (0-100)	6	Mean change	-11.7 vs. -8.1
Scarpa et al.[24]	2008	35	MTX i.m. 10 mg/w + NSAIDs	NSAIDs	Pain (0-100)	3	Median (IQR)	50 (44) vs. 32 (60)
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	Morning stiffness (min)	3	Median change	-45 vs. -30
Joint counts								
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	Swollen joint count	6	Mean change	-4.1 vs. -2.8
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	Swollen joint count	3	Median change	-3 vs. -1
Scarpa et al.[24]	2008	35	MTX i.m. 10 mg/w + NSAIDs	NSAIDs	Swollen joint count	3	Median (IQR)	0 (1) vs. 1 (2)*
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	Tender joint count	6	Mean change	-4.2 vs. -3.7
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	Tender joint count	3	Mean change	-4 vs. -6
Scarpa et al.[24]	2008	35	MTX i.m. 10 mg/w + NSAIDs	NSAIDs	Tender joint count	3	Median (IQR)	1 (1) vs. 2 (3)*
INFLAMMATION MARKERS								
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	CRP	6	Mean change	-2.0 vs. -3.6
Scarpa et al.[24]	2008	35	MTX i.m. 10 mg/w + NSAIDs	NSAIDs	CRP	3	Median (IQR)	8 (7) vs. 7.5 (24)
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	ESR	6	Mean change	-6.2 vs. -3.6
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	ESR	3	Median change	-19.0 vs. -3.0
Scarpa et al.[24]	2008	35	MTX i.m. 10 mg/w + NSAIDs	NSAIDs	ESR	3	Median (IQR)	24 (21) vs. 18 (34)
PHYSICAL FUNCTION								
Kingsley et al.[21]	2012	221	MTX p.o. 15 mg/w	Placebo	HAQ	6	Mean change	-0.2 vs. -0.1
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	Mean grip strength, left (mmHg)	3	Median change	9 vs. 0
Willkens et al.[22]	1984	37	MTX p.o. 7.5 or 15 mg/w (50/50)	Placebo	Mean grip strength, right (mmHg)	3	Median change	4 vs. -1

Table 2: Methotrexate monotherapy vs. other csDMARDs and/or NSAIDs.

* Statistically significant ($p < 0.05$); # Outcomes were assessed as improvements from baseline to the latest available follow-up visit. The median treatment times were 28 and 15 months in the MTX and i.m. gold groups, respectively.

STUDY	YEAR	NO. INCLUDED	INTERVENTION	COMPARISON GROUP	OUTCOME	DURATION (MONTHS)	STATISTICAL METHOD	OUTCOME INTERVENTION VS. OUTCOME COMPARISON
DISEASE ACTIVITY								
Composite indicies								
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	ACR20 response	6	% responders	100.00 vs. 100.00
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	ACR50 response	6	% responders	85.70 vs. 81.30
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	ACR70 response	6	% responders	14.20 vs. 31.30*
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	PsARC response	6	% responders	100.00 vs. 100.00
Physician reported outcomes								
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Global disease activity (0-100)	12	Mean ± SEM change	-30.8 ± 4.0 vs. -16.0 ± 4.9
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	Global disease activity (1-5)	6	Mean (SD)	2.00 ± 0.00 vs. 2.00 ± 0.00
Patient reported outcomes								
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Global disease activity (0-100)	12	Mean ± SEM change	-22.7 ± 9.8 vs. -30.0 ± 5.6
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	Global disease activity (1-5)	6	Mean (SD)	2.00 ± 0.00 vs. 2.00 ± 0.00
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	Pain (1-10)	6	Mean (SD)	0.93 ± 0.83 vs. 1.00 ± 1.03
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Morning stiffness (min)	12	Mean ± SEM change	-55.4 ± 14.7 vs. -19.5 ± 5.8
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	Morning stiffness (0 -3)	6	Mean (SD)	0.50 ± 0.52 vs. 0.50 ± 0.52
Joint counts								
Lacaille et al.[26]	2000	87	MTX p.o. 12 mg/w (mean)	Gold i.m. 120 mg/w (mean)	Clinical improvement (³ 50 % reduction in active joint count)	#	OR (95% CI)	8.90 (1.8-44.0)*
Lacaille et al.[26]	2000	87	MTX p.o. 12 mg/w (mean)	Gold i.m. 120 mg/w (mean)	Clinical improvement (³ 50 % reduction in active joint count)	#	% responders	58 vs. 35*
Abu-Shakra et al.[25]	1995	76	MTX p.o. 10 mg/w (mean)	NSAIDs + other csDMARDs in some patients	Clinical improvement (³ 40 % reduction in active joint count)	24	% responders	47 vs. 53
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Ritchie index	12	Mean ± SEM change	-11.1 ± 1.7 vs. -14.0 ± 4.2
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Swollen joint count	12	Mean ± SEM change	-3.5 ± 0.5 vs. -2.6 ± 0.9
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	Swollen joint count	6	Mean (SD)	0.64 ± 0.74 vs. 0.50 ± 0.63
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Tender joint count	12	Mean ± SEM change	-6.6 ± 0.9 vs. -4.6 ± 1.2
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	Tender joint count	6	Mean (SD)	1.33 ± 0.96 vs. 1.0 ± 0.97
INFLAMMATION MARKERS								
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	CRP	12	Mean ± SEM change	-13.3 ± 4.1 vs. -17.5 ± 7.1
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	ESR	12	Mean ± SEM change	-19.5 ± 6.3 vs. -9.3 ± 6.1
Spadaro et al.[23]	2000	87	MTX p.o. 12 mg/w (mean)	Gold i.m. 120 mg/w (mean)	ESR	#	Mean (SD) change	-10 ± 20 vs. -11 ± 22
Asaduzzaman et al.[27]	2014	32	MTX p.o. 10 mg/w	LEF 20 mg/d	ESR	6	Mean (SD)	26.71 ± 5.44 vs. 23.25 ± 7.05
PHYSICAL FUNCTION								
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Mean grip strength, left (mmHg)	12	Mean ± SEM change	17 ± 23 vs. 9 ± 5
Spadaro et al.[23]	1995	35	MTX p.o. 7.5-15 mg/w	CsA p.o. 3-5 mg/kg/d	Mean grip strength, right (mmHg)	12	Mean ± SEM change	51 ± 15 vs. 14 ± 5
RADIOGRAPHIC PROGRESSION								
Abu-Shakra et al.[25]	1995	76	MTX p.o. 10 mg/w (mean)	NSAIDs + other csDMARDs in some patients	Steinbrocker index	24	Mean change	2.3 vs. 1.6

6.4. Efficacy of TNFi and MTX combination therapy vs. TNFi monotherapy

Table 3: Characteristics of included studies. PBO = placebo; BIW = twice a week; EOW = every other week; QW = once a week; Q2W = once every 2 weeks; Q4W = once every 4 weeks.

FIRST AUTHOR, YEAR	INTERVENTION (1)	COMPARISON (2)	NUMBER (n) RANDOMIZED	DURATION (PBO CTRL. PHASE) (w)	CONCURRENT TREATMENT AT BASELINE
Adalimumab					
ADEPT (Mease et al. 2005)[31]	ADA 40 mg EOW	PBO EOW	(1): 153 (2): 162	24 (24)	MTX (%): (1) 51 vs. (2) 50 *MTX allowed if previously used for at least 3 m and stable dosage 4 w prior to BL.*
Genovese et al. 2007[36]	ADA 40 mg EOW up to 12 w	PBO EOW up to 12 w	(1): 51 (2): 51	24 (12)	MTX (%): (1) 47.1 vs. (2) 46.9 *MTX (up to 30 mg/w) or other csDMARD (cyclosporine and tacrolimus excluded) allowed if previously used for at least 3 m and with a stable dose 4 w. Low potency tropical corticosteroids on the feet, axillae and groin allowed.*
CZP					
RAPID-PsA (Mease et al. 2014)[34]	CZP 400 mg dose w 0, 2, 4 followed by (1a) CZP 200 mg Q2W or (1b) CZP 400 mg Q4W	PBO 0.9% saline	(1a): 138 (1b): 135 (2): 136	216 (24)	MTX (%): (1a) 63.8 vs. (1b) 65.2 vs. (2) 61.8% *Stable dose of MTX up to 25 mg/w, SSZ up to 3 g/d, LEF up to 20 mg/d allowed.*
Etanercept					
SEAM-PsA (Mease et al. 2019)[35]	(1a) ETA target dose 50 mg QW + oral PBO QW (1b) oral MTX target dose 20 mg + s.c. PBO QW.	ETA target dose 50 mg QW + oral MTX target dose 20 mg QW	(1a): 284 (1b): 284 (2): 283	48 (48)	*NSAIDs allowed if stable for 2 w prior to BL, oral corticosteroids (prednisone ≤ 10 mg/d or equivalent) allowed if stablefor 4 w.*
Mease et al. 2004[38]	ETA 25 mg BIW up to 24 w	PBO BIW up to 24 w	(1): 101 (2): 104	48 (24)	MTX (%): (1) 42 vs. (2) 41 *Concominant MTX use (stable dose up to 25 mg/w) and stable dose of corticosteroids (up to 10 mg/d) allowed. Tropical therapies permitted on the scalp, axillae and groin.*
Mease et al. 2000[37]	ETA 25 mg BIW up to 12 w	PBO BIW up to 12 w	(1): 30 (2): 30	12 (12)	MTX (%): (1) 47 vs. (2) 47 *MTX (up to 25 mg/w) allowed if stable for 4 w and dose remained stable. Corticosteroids (less or equal to 10 mg/d of prednisone) allowed if stable for 2 w.*
PRESTA (Sterry et al. 2010)[39]	ETA 50 mg BIW up to 12 w	ETA 50 mg QW + PBO QW up to 12 w	(1): 379 (2): 373	24(12)	MTX (%): (1) 32 vs. (2) 40 *MTX (up to 20 mg/w) or acitretin (up to 50 mg/d) if stable for 2 m prior to BL. Doses to remain stable. Tropical corticosteroids (low to moderate strength) allowed on the scalp, axillae or groin. Oral corticosteroids (prednisone ≤ 10 mg/d or equivalent) allowed if stable.*
Golimumab					
GO-VIBRANT (Kavanaugh et al. 2017)[32]	GOL 2 mg/kg at w 0, 4 and every 8 w	PBO at w 0, 4 and every 8 w	(1): 240 (2): 239	24 (24)	MTX (%): (1) 67.6 vs. (2) 72.4 *MTX (up to 25 mg/w) allowed ≥ 3 m and stable dose 4 w. Oral corticosteroids (less or equal to 10 mg/d of prednisone) and NSAIDs allowed if stable for 2 w.*
GO-REVEAL (Kavanaugh et al. 2009)[33]	(1a) GOL 50 mg every 4 w up to 20 w (1b) GOL 100 mg every 4 w up to 20 w	PBO every 4 w up to 20w	(1a): 146 (1b): 146 (2): 113	5 y (24)	MTX (%): (1a) 49 vs. (1b) 47 vs. (2) 48 *Stable doses of MTX (up to 25 mg/w), NSAIDs and corticosteroids (≤ 10 mg/d) allowed.*
Infliximab					
IMPACT (Antoni et al. 2005)[30]	INF 5 mg/kg w 0, 2, 6, 14	PBO w 0, 2, 6, 14	(1): 52 (2): 52	2 y (16)	MTX (%): (1) 46 vs. (2) 65 *1 csDMARD (MTX ≥ 15 mg/w with folic acid, LEF, SSZ, i.m. gold, hydroxychloroquine, penicillamine or azathioprine) allowed if stable dose at least 4 w prior to BL. Oral corticosteroids (≤ 10 mg/d) and NSAIDs allowed if stable for 2 w. All doses to remain stable. Standard tropical treatment permitted.*
IMPACT 2 (Antoni et al. 2005)[29]	INF 5 mg/kg w 0, 2, 6 and maintenance dose w 14, 22	PBO w 0, 2, 6, 14, 22	(1): 100 (2): 100	54 (24)	MTX (%): (1) 47 vs. (2) 45 *MTX (up to 25 mg/w) allowed if previously used for at least 3 m and with a stable dose 4 w, oral corticosteroids (prednisone up to 10 mg/d), low potency tropical corticosteroids on the face or groin allowed.*

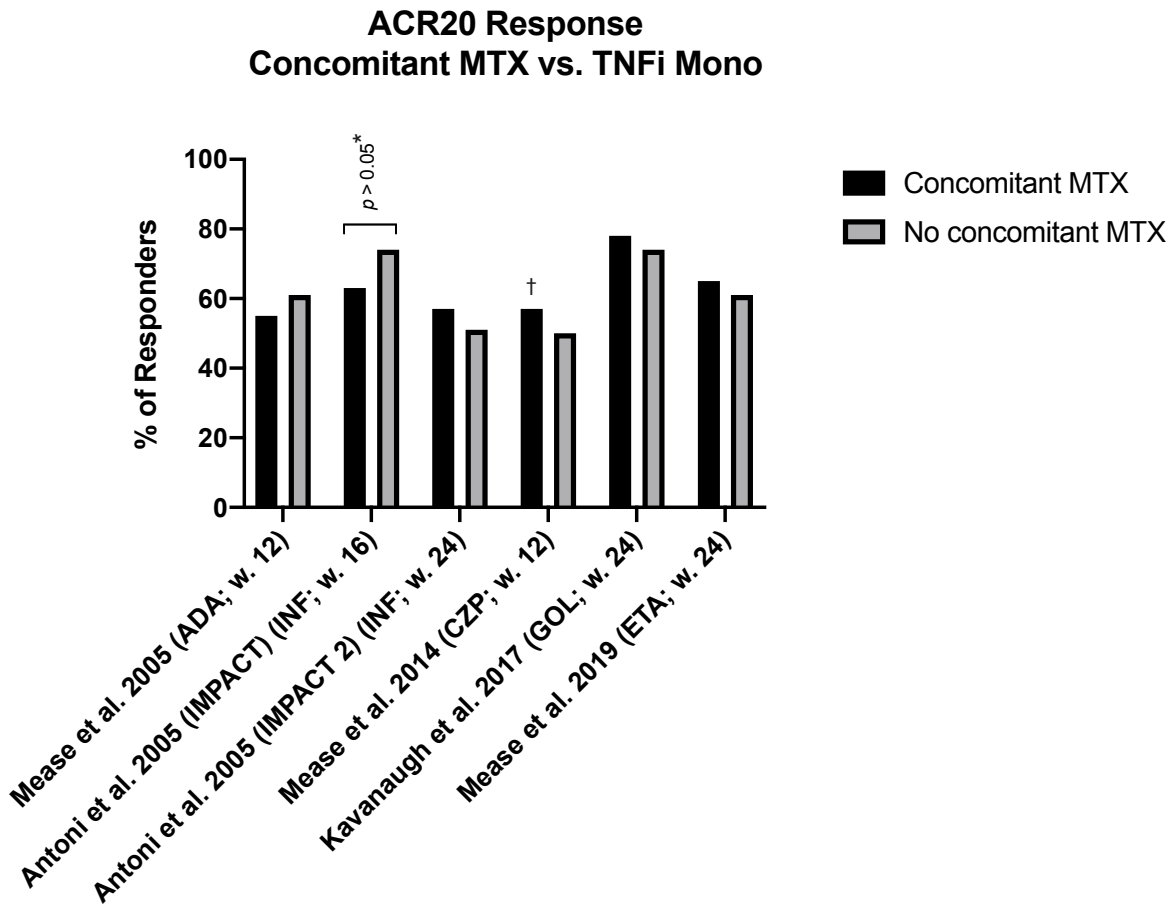

Figure 5: Overview of ACR20 response rates. * Analysis conducted using Chi-square test; † Concomitant csDMARD (65% of participants received MTX at baseline).

7. APPENDIX

7.1. Description of outcome measures

7.1.1. The American College of Rheumatology 20/50/70 criteria (ACR20/50/70)

The ACR20 is a composite index defined as a > 20 % improvement in the number of tender and swollen joints and a > 20 % improvement in 3 or more of the following 5 parameters:

- VAS (visual analogue scale) pain (past week)
- VAS PGA (patient global assessment of disease activity, past week)
- VAS DGA (physician global assessment of disease activity)
- Functional ability measure (most often Health Assessment Questionnaire (HAQ))
- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)

ACR50 and ACR70 are the same instruments with improvement levels > 50% and > 70% respectively instead of > 20% as for ACR20.

7.1.2. Disease Activity Score 28 (DAS-28)

Disease Acivity Score 28 (DAS-28) is a quantitative measure of disease activity originally used to monitor the treatment of rheumatoid arthritis. The '28' version is a simplification of the original DAS score, which requires 44 joints to be counted. It is calculated using a formula that includes the number of tender joints and swollen joints (28 joints maximum), patient global assessment of disease activity and ESR or CRP. DAS-28 is used both in clinical practice and in clinical trials. A DAS-28 score > 5.1 implies highly active disease, < 3.2 low disease activity and < 2.6 remission.

7.1.3. Disease Activity Index for Psoriatic Arthritis (DAPSA)

DAPSA score (Disease Activity Index for Psoriatic Arthritis) is defined as the sum of:

- The number of tender joints out of 68
- The number of swollen joints out of 66
- C-reactive protein (CRP; in mg/dl)

- Patient's VAS global disease activity in cm (1-10), past week
- Patient's VAS pain in cm (1-10), past week

DAPSA threshold values for disease activity:

< 4	Remission
4,1 - 14	Low disease activity
14,1 - 27,9	Moderate disease activity
> 28	High disease activity

DAPSA response = improvement of DAPSA score in %

> 50 %	Low response
> 75 %	Moderate response
> 85 %	Substantial response

7.1.4. Psoriatic Arthritis Response Criteria (PsARC)

PsARC response indicates an improvement in ≥2 of the following:

- Patient global assessment of disease activity
- Physician global assessment of disease activity
- Swollen joint count
- Tender joint count

In order to meet the response criterion, improvement must have occurred in ≥1 of the joint count measures and deterioration must not have occurred in any of the four measures mentioned above.

7.1.5. Health Assessment Questionnaire (HAQ)

The Health Assessment Questionnaire (HAQ) is a questionnaire about physical function originally developed for the assessment of rheumatoid arthritis. The questionnaire is a patient reported outcome which is usually self-administered by the patient.

Each question asks on a scale ranging from 0 to 3 (0 = the activity can be performed without any difficulty; 3 = the activity cannot be performed at all).

7.1.6. Ritchie index

The Ritchie index is an index used in rheumatology measuring inflammation and tenderness of joints. It is the sum of the grades of tenderness (0 = not tender, 1 = tender, 2 = tender and causes wince and 3 = tender, causes wince and effort to withdraw).