Review

Efficacy and safety of DMARDs in psoriatic arthritis: a systematic review

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for the Evidence-Based Working Group of the Spanish Society of Rheumatology

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ABSTRACT

Objective. *Disease-modifying anti-rheumatic drugs (DMARDs) are frequently prescribed as a first step therapy in active psoriatic arthritis (PsA). However, evidence is sparse and scattered. The objective of this study is to evaluate the efficacy and safety of DMARDs in PsA.*

Methods. *We performed a systematic review based on electronic searches through Medline, Cochrane Central and Embase (from July 1980–2010) for randomised control trials (RCTs) in PsA. Outcome measures were those included in the core-set from Outcome Measures in Rheumatology Clinical Trials (OMERACT) and adverse effects.*

Results. *A preliminary search identified 3781 potentially relevant RCTs, while only 11 fulfilled inclusion criteria. Ten studies had a parallel design and, one was a cross-over trial. Quality reached a Jadad score over 3 in 6/11 (54.6%). We observed evidence of a moderate improvement of pain and reduction of ESR with DMARDs. The global risk of withdrawals due to adverse events was 2.41 [95% confidence interval (CI) 1.53, 3.82]. The risk of GI adverse effects (nausea, vomiting, abdominal pain, diarrhoea and/or oral ulcers) was 2.02 [95% CI 1.34, 3.03] and of headache was 2.34[95% CI 1.05, 5.19]. There were no significant differences in the rate of increase of flu-like symptoms, rash, or liver enzymes.*

Conclusion. *The evidence of DMARD efficacy in PsA is certainly limited, basically due to the small number of studies, dissimilar outcomes being evaluated, high withdrawal rates, and absence of new published studies. With regard to adverse effects, only GI events and headaches were significant compared to placebo.*

Introduction

The spectrum of joint inflammation in psoriatic arthritis (PsA) is large and complex (1), as it spans from axial to peripheral disease, soft tissue and synovial inflammation. PsA may result in impaired physical function and quality of life (2), with erosive and deforming arthritis, being present in 40–60% of the patients (3). Mild skin and joint manifestations may be treated effectively with topical agents, ultraviolet light therapy, and nonsteroidal anti-inflammatory drugs. More severe manifestations of the disease, including progressive peripheral joint damage, spine disease, enthesitis, dactylitis, and severe skin changes, require systemic therapy. Traditional systemic agents include methotrexate (MTX), sulphasalazine (SSZ) and cyclosporine (CsA), also known as disease-modifying anti-rheumatic drugs (DMARDs). These agents are frequently the first step therapy in PsA, although with no uniform approach or recommendation. This lack of consensus is mainly due to the absence of well-designed or large controlled studies (4).The aim of our study was to examine the available evidence concerning the efficacy and safety of different DMARDs in the treatment of PsA, with the intention to provide firmer recommendations on the matter.

Methods

A methodology of systematic review and meta-analysis was used to identify and assess the efficacy and safety of leflunomide LEF), MTX, SSZ, gold and CsA in PsA.

Search strategy

Studies were taken from the following electronic databases: through Medline, Cochrane Central Register of Control-

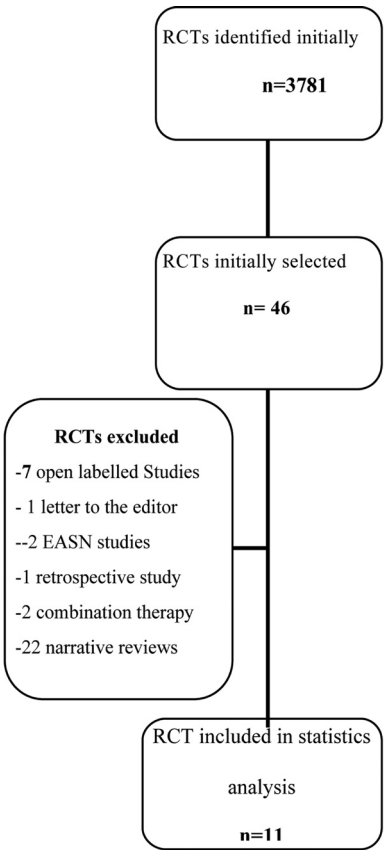

Fig. 1. Flow diagram.

led Trials (Central) and Embase from July 1980 to 2010). The search strategy employed is detailed in a supplemental file. Briefly, it covered all synonyms of the interventions, plus terms for identifying clinical trials, plus MeSH terms and free text to capture PsA studies.

Selection criteria

All randomised, double-blind controlled studies were included. independently of sample size and quality, if they studied the efficacy or safety of LEF, MTX, SSZ, gold or CsA in PsA, this latter, preferently defined according to the Moll and Wright classification (1973) (5). We included any study for analysis if efficacy was measured by variables derived from Outcome Measures in Rheumatology Clinical Trials (OMERACT), which include: peripheral joint assessment, skin assessment, pain, global patient assessment, physical function, quality of life, spine assessment, dactylitis, enthesytis, global physician assessment, radiographic assessment, acute phase reactants and fatigue (6).

– Data collection and analysis

Two reviewers (MBN and CAP) independently assessed un-blinded trial reports for inclusion. Disagreements were resolved when necessary by consensus. The same reviewers independently entered the data extracted from the included trials into evidence tables. The data extraction model (available upon request) included: number of participating PsA patients, sex, age, disease duration, inclusion and exclusion criteria, the description of experimental and control treatments and specific results. The methodological quality of included trials was determined through Jadad's scale (7).

– Data analysis

Because of the heterogeneity of outcome findings, qualitative analysis was performed with special emphasis in the methodological characteristic of selected trials, and on the consistency of its results. A meta-analysis of efficacy outcomes could not be performed due to the heterogeneity of outcome variables. On the other hand, a meta-analysis of adverse effects and risk of withdrawals was carried out in Review Manager (Rev Man version 4.2 for windows). Results based on rates of adverse events were expressed in odds ratio (OR) with 95% confidence interval (CI) derived from fixed effects models.

Table I. Evidence table.

Author/ year	RCT design	Weeks	n.	Quality Jadad Scale
Kaltwasser *et al*., 2004 (8)	Parallel	24	182	5
Palit *et al*., 1990 (9)	Parallel	24	82	4
Combe *et al*., 1996 (10)	Parallel	24	120	3
Wilkens *et al*., 1984 (11)	Parallel	12	37	3
Carette *et al*., 1989 (12)	Parallel	24	238	3
Fraser *et al*., 2005 (13)	Parallel	52	72	3
Black *et al*., 1964 (14)	Crossover	8	21	2
Clegg *et al*., 1996 (15)	Parallel	36	222	2
Farr *et al*., 1990 (16)	Parallel	24	60	2
Gupta *et al*., 1995 (17)	Parallel	16	24	2
Fraser *et al*., 1993 (18)	Parallel	24	39	2

Results

The electronic search identified 3781 potentially relevant RCTs (Fig. 1). Scanning by title and abstract rejected the vast majority of registries due to combined treatment with biological therapies or because studies were not controlled. Forty-six studies were initially selected and reviewed in detail, of which 35 were excluded for reasons displayed in Figure 1. The remaining 11 studies fulfilled the criteria for inclusion in this review.

Study characteristics and methodological quality

Table I shows the characteristics of the RCTs included in this review. All studies recruited patients with established PsA who had peripheral arthritis.

Efficacy

Table II displays the efficacy results by type of DMARDs.

Leflunomide: The 6 months TOPAS study recruited 182 patients with psoriasis and psoriatic arthritis that were randomised to either placebo or LEF given as 20mg daily (8). It showed a statistically significant improvement of the treatment group in the PsARC score in the treatment group compared to placebo (58,9% *vs*. 29,7%). Also, differences in favour of LEF were observed at PASI, PASI 50, PASI 75, modified ACR 20, pain, HAQ, tender and swollen joint count, and Dermatology Life quality index (DLQI). Physician and Patient global pain assessment were also favourable to LEF.

Methotrexate: The cross over study by Black *et al*. was an 8 week, low quality trial (14). It compared IM *vs*. IV MTX given as 1-3mg/kg IM or IV *vs*. placebo every 10 days. No end points were available on disease improvement. The

Table II. Results.

Study	Interventions	Results	Dropout rate
Kaltwasser 2004 (8)	Oral LEF: 20mg/day Placebo	Response to PsARC criteria: $p<0.0001$ joint pain/tenderness score $p<0.005$ joint swelling score $p<0.005$ tender joint count $p<0.001$ swollen joint count $p<0.001$ CRP level $p<0.05$ HAQ score $p<0.05$ PASI score $p<0.005$ DLQI $p<0.02$	LEF 19.8% Placebo 35.5%
Black 1964 (14)	MTX: 1–3mg/kg IV-IM/10days. Placebo	Significant improvement of skin area involvement (different to PASI) $p<0.01$ ESR $p<0.01$, Range of motion (ROM) of hips, knees, ankles, shoulders, elbows and wrists $p<0.01$	MTX 4.76%
Wikens 1984 (11)	Oral MTX 7.5–15mg/week Placebo	Significant improvement in skin area involvement (different to PASI) $p<0.04$ Significant improvement (MTX) in physician assessment score (1–5) $p<0.001$. No differences in: mean grip strength, morning stiffness, patient assessment (1–5), joint pain/tenderness count, joint swelling count, joint pain/tenderness score, joint swelling score.	MTX 12.5% Placebo 4.76%
Carette 1989 (12)	Oral auranofin 6–9mg/day Placebo	No differences between groups in: number of tender /swollen joints, tenderness/swelling score, pain score, morning stiffness, daily activities, occupational activities.	Gold 22.5% Placebo 19.5%
Palit 1990 (9)	Oral auranofin 3mg/bd IM gold thiomalate 50mg/week Placebo	No differences between groups in: pain score, grip strength, Ritchie index, ESR	Gold (O) 31% Gold (IM) 37% Placebo 46%
Fraser 2005 (13)	Cyc 2.5–4mg/kg/day+ MTX <15mg/week Placebo + MTX <15mg/week	Significant improvement (cyc +MTX) in swollen joint count ($p<0.001$) PASI score ($p<0.05$). Both groups exhibited statistical changes in TJI, TJC and PCR between baseline and the end of the study.	MTX + placebo 32% Cyc + MTX 45%
Clegg 1996 (15)	SSZ 500mg/day increasing dose up to 2g/day Placebo	Significant response (SSZ) in VSG ($p<0.0001$) Platelet count ($p<0.0001$) Neutrophils ($p<0.05$). Responders according to planning committee were 57.8% (SSZ) *vs*. 47.8 (control) Dactylitis: no difference between groups	SSZ 32.1% Placebo 22.3%
Combe 1996 (10)	SSZ 500mg/day increasing dose up to 2g/day Placebo	There was a significant difference ($p<0.01$) in change in pain variable VAS (SSZ) Skin: no data Axial component: no significant difference	SSZ 28% Placebo 33%
Farr 1990 (16)	SSZ 500mg/day increasing dose up to 2g/day Placebo	Significant improvement in (SSZ) in early morning stiffness ($p<0.001$) Clinical score ($p<0.001$) Pain score –VAS ($p<0.05$) Number of painful joints ($p<0,05$) after 1 month and grip strength ($p<0.05$) after 6 months.	SSZ 40% Placebo 40%
Gupta 1995 (17)	SSZ 500mg/day increasing dose up to 1.5g/day Placebo	There was a significant improvement (SSZ) in physician assessment ($p<0.005$) and patient assessment ($p<0.005$) and decrease in mean serum globulin ($p<0.05$)	SSZ 30% Placebo 0%
Fraser 1993 (18)	SSZ 500mg/day increasing to a dose equivalent to 40mg/kg Placebo	There was a significant improvement (SSZ) in pain visual analogue scale ($p<0.01$) Morning stiffness ($p<0.008$) Ritchie articular index ($p<0.002$)	SSZ 31.5% Placebo 55%

12 week study by Wilkens *et al*. compared weekly 7.5-15mg MTX *vs*. placebo (11), and showed only significant improvement in physician and patients' global assessment. In both studies therapy dose and route of administration differed (Table III)

Sulphasalazine: Among the five studies included in this review, only 4 showed improvement with therapy. The low quality study by Clegg *et al*. enrolled 109 patients receiving SSZ in a dose escalating form, ranging from 500mg to 4 g/daily while 112 patients received placebo for 36 weeks (15). Only ESR and responders rate (57.8% *vs*. 47.8%) favoured treatment group.

Two 24-week studies by Combe *et al*. (10) and Farr *et al*. (16), respectively, with a similar treatment scheme, resulted in beneficial effect on pain, assessed

Table III. Evidence summary.

DMARD (n. studies)	n.	Level of evidence	Recommendation	Omeract core-set for PsA
Leflunomide (n=1)	190	1b	A	Yes
Methotrexate (n=2)	58	2b	B	No
Sulfasalazine (n=5)	465	2b	B	No
Cyclosporine (n=1)	72	2b	B	No
Gold (n=2)	320	2b	B	No

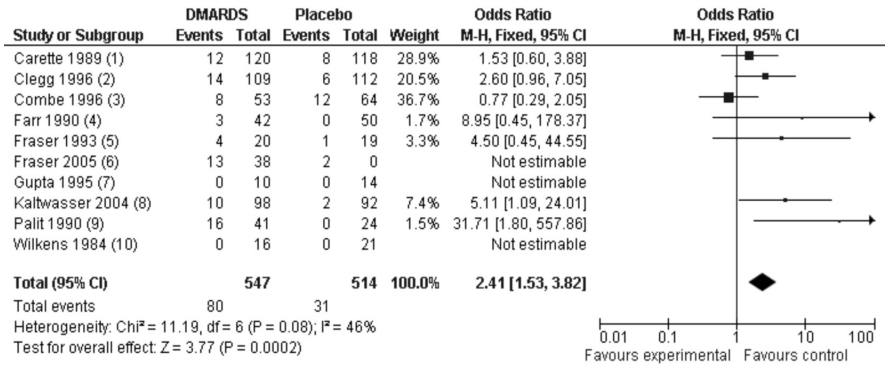

Fig. 2. Adverse events.

by VAS in the former and VES in the latter. Gupta *et al*. chose a 3 g/daily SSz scheme in an 8-week study recruiting only 24 patients (17). Improvement in physician and patient global assessment of disease activity and morning stiffness were significant in SSZ group. Conversely, the 24-week study by Fraser *et al*. did not find differences between SSZ and placebo.

Gold: Two 24-week studies enrolled 238 patients (Carette *et al*.) (12) and 82 patients (Palit *et al*.) (9), respectively. The former employed 6–9 mg oral gold /daily *vs*. placebo and found no differences in outcomes between groups; however, there was intra-group improvement in the number of tender joints and number of swollen joints in both groups. In the later study, patients were allocated to receive auranofin 3 mg b.d, identical placebo tablets or I.M gold thiomalate 50 mg weekly. The results were assessed only by intra-group analysis at 12 and 24 weeks. Only I.M gold showed significant improvement in pain, Ritchie index and ESR at both cut-points. However, the placebo group also evolved favourable in pain and Ritchie index from baseline.

Cyclosporine: The 12-month study by Fraser *et al*. (13), recruited 72 patients and compared 15 mg oral MTX *vs*. MTX + CsA (maximum 4 mg/kg/day). There was only significant difference in favour of MTX+ CsA in PASI. When intra-group analysis was performed, radiological improvement in Larsen score was observed in both groups.

Safety

The risk of gastrointestinal (GI) adverse effects (nausea, vomiting, abdominal pain, diarrhoea or oral ulcers), was 2.02 [95% CI 1.34, 3.03] and the risk of headache was 2.34 [95% CI 1.05, 5.19]. There were no significant differences in flue-like symptoms, rash, or liver enzymes levels between groups (Fig. 2). The risk of withdrawals due to adverse events with DMARD was 2.41 [95% CI 1.53, 3.82] (Fig. 3). A meta-analysis of the cross-over study was not included in the meta-analysis.

Discussion

This systematic review illustrates that the actual evidence on efficacy and safety of DMARDs in PsA is scanty, inconsistent and heterogeneous. We have identified methodological limitations, due to some extent, to the wide range in dates of publication. In this regard, we found significant quality differences between trials being performed in the early nineties and the more recent ones (Table III). There was consistency neither in drug dose between studies, nor in the type of outcomes evaluated. These issues were palpably exposed in both MTX and gold trials, while we could only analyse a single study for LEF and for CsA. It is also notable, the small amount of information concerning efficacy of DMARDs on axial-joint involvement, enthesitis, dactylitis or radiographic progression. These divergences are probably due to the time where OMERACT postulates were released. Yet, the first report on methodology assessment in PsA was reported in 2004 (OMERACT 7) (19). Consequently, just two of the studies included in this review, were published after that year. Indeed, no new RCT on DMARD therapy in PsA was published, after OMERACT 8 was released (2007) (6). Yet, no single data on spine assessment, dactylitis or enthesitis were reported in none of them and few studies exhibited improvement in pain, according to clinical and laboratory analytical variables. In addition, the number of patients lost in follow-up was generally high. Regarding safety, the adverse reactions reported, differed between drugs, yet, GI symptoms and headaches were more common with DMARD than with placebo. These adverse reactions were very much in line with the ones reported in rheumatoid arthritis studies. Indeed, Kellner *et al*., described diarrhea, nausea, hypertension and headache as main adverse effects in the treatment of early rheumatoid arthritis with LEF (20). Grove et al reported GI reactions with MTX, gold and also headaches with SSZ (21). Similar reports were accounted with CsA (23). Though, we may infer that DMARDs are safe and generally well-tolerated, and that adverse reac-

tions were similar to the ones reported in studies of rheumatoid arthritis.

Conclusions

The evidence on DMARD efficacy in PsA with peripheral involvement is modest, mainly because of small number of studies and patients.

- The quality of PsA RCT is rather low, and the risk of bias moderate to high.
- There is plenty of heterogeneity in the number and types of outcomes being evaluated (different to the proposed OMERACT core set), possibly related to publication timing.
- The global risk of withdrawals due to adverse events is higher in the DMARD group, although only GI and headaches were significantly more frequent with DMARDs than with control.
- The evidence on DMARD efficacy in PsA with spinal involvement is even more limited.

The limitations of this study are the short period follow-up, the lack of evidence available to assess efficacy for axial and enthesis involvement, and the fact that no x-ray assessments were considered.

Acknowledgments

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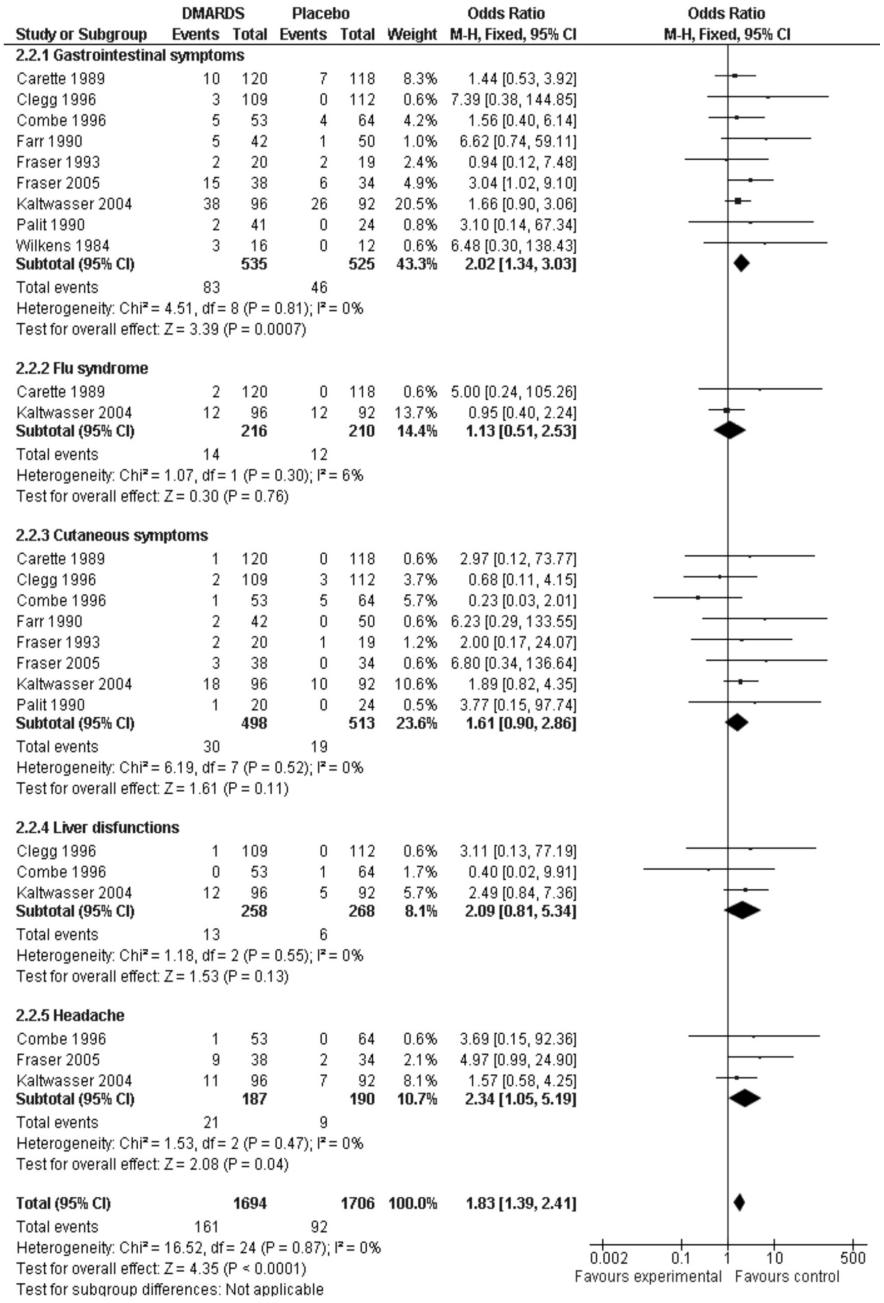

Fig. 3. Risk of withdrawals due to adverse events.

References

1. KAVANAUGH AF, RITCHLIN CT; AND THE GRAPPA TREATMENT GUIDELINE COMMITTEE: Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. *J Rheumatol* 2006; 33: 1417-21.
2. GLADMAN DD, MEASE PJ, HEALY P *et al*.: Outcome measures in psoriatic arthritis. *J Rheumatol* 2007; 34: 1159-66.
3. SORIANO ER, ROSA J: Update on the treatment of peripheral arthritis in psoriatic arthritis. *Curr Rheumatol Rep* 2009; 11: 270-7.
4. GOTTLIEB A, KORMAN NJ, GORDON KB, FELDMAN SR, LEBWOHL M, KOO JYM: Guidelines of care for the management of psoriasis and psoriatic arthritis. *J Am Acad Dermatol* 2008; 58: 851-64.
5. MOLL JMH, WRIGHT V: Psoriatic arthritis. *Semin Arthritis Rheum* 1973; 3: 55-78.
6. GLADMAN DD; MEASE PJ, STRAND V *et al*.: Consensus on a core set of domains for psoriatic arthritis. *J Rheumatology* 2007; 34: 1167-70.
7. JADAD AR, MOORE RA, CARROLL D, JENKINSON C, REYNOLDS JM, GAVAGHAN DJ: Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clin Trials* 1996; 17: 1-12.
8. KALTWASSER JP, NASH P, GLADMAN D *et al*.: Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004; 50: 1939-50.
9. PALIT J, HILL J, CAPELL HA *et al*.: A multicentre double-blind comparison of auranofin, intramuscular gold thiomalate and placebo in patients with psoriatic arthritis. *Br J Rheumatol* 1990; 29: 280-3.
10. COMBE B, GOUPILLE P, KUNTZ JL, TEBIB J, LIOTÉ F, BREGEON C: Sulphasalazine in psoriatic arthritis: a randomized, multicentre, placebo-controlled study. *Br J Rheumatol* 1996; 35: 664-8.
11. WILKENS RE, WILLIAMS J, WARD JR *et al*.: Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984; 27: 376-81.
12. CARETTE S, CALIN A, MCCAFFERTY JP, WALLIN BA: A double-blind placebo-controlled study of auranofin in patients with psoriatic arthritis. *Arthritis Rheum* 1989; 32: 158-65.
13. FRASER AD, VAN KUIJK AW, WESTHOVENS R *et al*.: A randomised, double blind, placebo controlled, multicentre trial of combination

therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis* 2005; 64: 859-64.
14. BLACK RL, O'BRIEN WM, VANSCOTT EJ, AUERBACHA R, EISEN AZ, BUNIM JJ: Methotrexate therapy in psoriatic arthritis, double blind study on 21 patients. *JAMA* 1964; 189: 743-7.
15. CLEGG DO, REDA DJ, MEJIAS E *et al*.: Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996; 39: 2013-20.
16. FARR M, KITAS GD, WATERHOUSE L, JUBB R, FELIX-DAVIES D, BACON PA: Sulphasalazine in psoriatic arthritis: a double-blind placebo-controlled study. *Br J Rheumatol* 1990; 29: 46-9.
17. GUPTA AK, GROBER JS, HAMILTON TA *et al*.: Sulfasalazine therapy for psoriatic arthritis: a double blind, placebo controlled trial. *J Rheumatol* 1995; 22: 894-8.
18. FRASER SM, HOPKINS R, HUNTER JA, NEUMANN V, CAPELL HA, BIRD HA: Sulphasalazine in the management of psoriatic arthritis. *Br J Rheumatol* 1993; 32: 923-5.
19. GLADMAN DD, STRAND V, MEASE PJ: Omeract 7: psoriatic arthritis workshop synopsis. *Ann Rheum Dis* 2005; 64: ii115-ii116.
20. KELLNER H, BORNHOLDT K, HEIN G: Leflunomide in the treatment of patients with early rheumatoid arthritis – results of a prospective non-interventional study. *Clin Rheumatol* 2010; 29: 913-20.
21. GROVE ML, HASSELL AB, HAY EM, SHADFORTH MF: Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. *Q J Med* 2001; 94: 309-19.
22. PLOSKER GL, COOM KF: Sulfasalazine: a review of its use in the management of rheumatoid arthritis. *Drugs* 2005; 65: 1825-49.
23. JOHNS KR, LITTLEJOHN GO: The safety and efficacy of cyclosporine (neural) in rheumatoid arthritis. *J Rheumatol* 1999; 26: 2110-3.

Supplemental file

effects"[Mesh] OR Sulphadiazine OR Zinc Sulfadiazine OR Sulfadiazine, Zinc OR Sulfazin OR Sulfazine)))))) AND ((“Arthritis, Psoriatic”[Mesh] OR Psoriatic Arthritis Psoriasis, Arthritic OR Arthritic Psoriasis OR Psoriasis Arthropathica OR Arthritis OR Psoriasis))) AND ((((“Radiography”[Mesh]) OR ((Radiographic progression)) OR ((BASRI)) OR ((Bath Ankylosing Spondylitis Radiology Index)) OR ((radiological scoring)) OR ((radiological scoring methods)) OR ((radiological scoring scale)) OR ((sharp van der heijde method for scoring radiographs)) OR ((ASspiMRI)) OR ((radiological assessment)) OR ((MSAS)) OR ((LARSEN/scott method)) OR ((Detecting radiological changes)) OR ((radiological changes)) OR ((scott method)))) AND (hasabstract[text] AND (Humans[Mesh]) AND (English[lang] OR French[lang] OR Spanish[lang]) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Journal Article[ptyp] OR Multicenter Study[ptyp] OR Validation Studies[ptyp]))))) OR (((((((“Methotrexate”[Mesh] OR “Methotrexate/adverse effects”[Mesh])) OR ((“leflunomide “[Substance Name] OR N- AND (4-trifluoromethyphenyl) AND -5-methylisoxazole-4-carboxamide OR HWA 486 ORHWA-486 OR SU101 OR Arava OR Hoechst Brand of Leflunomide OR Aventis Pharma Brand of Leflunomide OR Aventis Behring Brand of Leflunomide OR Aventis Brand of Leflunomide))) OR ((“Sulfadiazine/adverse effects”[Mesh] OR Sulphadiazine OR Zinc Sulfadiazine OR Sulfadiazine, Zinc OR Sulfazin OR Sulfazine)))) AND ((“Arthritis, Psoriatic”[Mesh] OR Psoriatic Arthritis Psoriasis, Arthritic OR Arthritic Psoriasis OR Psoriasis Arthropathica OR Arthritis OR Psoriasis))) AND ((((“Radiography”[Mesh]) OR ((Radiographic progression)) OR ((BASRI)) OR ((Bath Ankylosing Spondylitis Radiology Index)) OR ((radiological scoring)) OR ((radiological scoring methods)) OR ((radiological scoring scale)) OR ((sharp van der heijde method for scoring radiographs)) OR ((ASspiMRI)) OR ((radiological assessment)) OR ((MSAS)) OR ((LARSEN/scott method)) OR ((Detecting radiological changes)) OR ((radiological changes)) OR ((scott method)))) AND (hasabstract[text] AND (Humans[Mesh]) AND (English[lang] OR French[lang] OR Spanish[lang]) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Journal Article[ptyp] OR Multicenter Study[ptyp] OR Validation Studies[ptyp]))))) AND (hasabstract[text] AND (Humans[Mesh]) AND (English[lang] OR French[lang] OR Spanish[lang]) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Journal Article[ptyp] OR Multicenter Study[ptyp] OR Validation Studies[ptyp]))

<u>Medline: Peripheral symptoms-enthesitis</u>

- *Enthesitis* ((“Methotrexate”[Mesh] OR “Methotrexate/adverse effects”[Mesh])) OR ((“leflunomide “[Substance Name] OR N- AND (4-trifluoromethyphenyl) AND -5-methylisoxazole-4-carboxamide OR HWA 486 ORHWA-486 OR SU101 OR Arava OR Hoechst Brand of Leflunomide OR Aventis Pharma Brand of Leflunomide OR Aventis Behring Brand of Leflunomide OR Aventis Brand of Leflunomide))) OR ((“Sulfadiazine/adverse effects”[Mesh] OR Sulphadiazine OR Zinc Sulfadiazine OR Sulfadiazine, Zinc OR Sulfazin OR Sulfazine) AND ((Enthesopathy OR Enthesopathies)) AND (hasabstract[text] AND (Humans[Mesh]) AND (English[lang] OR French[lang] OR Spanish[lang]) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Classical Article[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Evaluation Studies[ptyp] OR Guideline[ptyp] OR Journal Article[ptyp] OR Multicenter Study[ptyp] OR Validation Studies[ptyp]))

- *Peripheral symptoms* (“Antirheumatic Agents”[Mesh] OR Agents, Antirheumatic OR Anti-Rheumatic Drugs OR Anti Rheumatic Drugs OR Drugs, Anti-Rheumatic OR Antirheumatic Drugs OR Drugs, Antirheumatic OR Anti-Rheumatic Agents OR Agents, Anti-Rheumatic OR Anti Rheumatic Agents OR Antirheumatic Drugs, Disease-Modifying OR Antirheumatic Drugs, Disease Modifying OR Drugs, Disease-Modifying Antirheumatic OR Second-Line Drugs, Disease-Modifying OR Drugs, Disease-Modifying Second-Line OR Second Line Drugs, Disease Modifying OR DMARD OR Disease-Modifying Antirheumatic Drugs OR Disease Modifying Antirheumatic Drugs OR Disease-Modifying Second-Line Drugs OR Disease Modifying Second Line Drugs)) OR ((“Antirheumatic Agents “[Pharmacological Action])))) OR ((“Methotrexate”[Mesh]))) OR ((“leflunomide “[Substance Name] OR N- AND (4-trifluoromethyphenyl) AND -5-methylisoxazole-4-carboxamide OR

HWA 486 OR HWA-486 OR SU101 OR Arava OR Hoechst Brand of Leflunomide OR Aventis Pharma Brand of Leflunomide OR Aventis Behring Brand of Leflunomide OR Aventis Brand of Leflunomide)) OR ((“Sulfadiazine/adverse effects”[Mesh] OR Sulphadiazine OR Zinc Sulfadiazine OR Sulfadiazine, Zinc OR Sulfazin OR Sulfazine)))) AND ((“Periarthritis”[Mesh] OR Periarthritides)) AND ((Humans[Mesh]) AND (English[lang] OR French[lang] OR Spanish[lang]) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Classical Article[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Evaluation Studies[ptyp] OR Guideline[ptyp] OR Journal Article[ptyp] OR Multicenter Study[ptyp] OR Validation Studies[ptyp]))

Embase and Cochrane

1. antirheumatic agent/ or disease modifying antirheumatic drug/
2. (Antirheumatic Drugs, Disease-Modifying or Antirheumatic Drugs, Disease Modifying or Drugs, Disease-Modifying Antirheumatic or Second-Line Drugs, Disease-Modifying or Drugs, Disease-Modifying Second-Line or Second Line Drugs, Disease Modifying or DMARD or Disease-Modifying Antirheumatic Drugs or Disease Modifying Antirheumatic Drugs or Disease-Modifying Second-Line Drugs or Disease Modifying Second Line Drugs).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. 1 or 2
4. Leflunomide/
5. ((N- and 4-trifluoromethyphenyl and -5-methylisoxazole-4-carboxamide) or HWA 486 ORHWA-486 or SU101 or Arava or Hoechst Brand of Leflunomide or Aventis Pharma Brand of Leflunomide or Aventis Behring Brand of Leflunomide or Aventis Brand of Leflunomide).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. Methotrexate.mp. or METHOTREXATE/
7. (Amethopterin or Mexate or Methotrexate Dicesium Salt or Dicesium Salt Methotrexate or Methotrexate Disodium Salt or Disodium Salt Methotrexate or Methotrexate Sodium Salt or Sodium Salt Methotrexate or Methotrexate Hydrate or Hydrate Methotrexate).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
8. Sulfadiazine/
9. (Sulphadiazine or Zinc Sulfadiazine or Sulfadiazine Zinc or Sulfazin or Sulfazine).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10. 4 or 5
11. 6 or 7
12. 8 or 9
13. 11 or 10 or 12
14. Psoriatic Arthritis.mp. or Psoriatic Arthritis/
15. (Psoriatic Arthritis or Psoriasis, Arthritic or Arthritic Psoriasis or Psoriasis Arthropathica or Arthritis or Psoriasis).af.
16. (Alibert Bazin Disease or Arthritis,Psoriasis or Arthritis, Psoriatic or Arthritis, Psoriatic or Arthritis Psoriatica or Arthropathic Psoriasis or Arthropathy, Psoriatic or Disease, Alibert Bazin or Polyarthritis, Psoriatic or Psoriasis, Arthritis or Psoriasis Arthropathica or Psoriasis Pustulosa or Arthropathica or Psoriatic Arthropathy or Psoriatic Polyarthritis or Psoriatic Rheumatism or Psoriatic or Rheumatoid Arthritis or Rheumatoid Arthritis, Psoriatic).af.
17. 16 or 15 or 14
18. Spondyloarthropathy/
19. (Arthropathy, Spondylo or Spondylarthropathies or Spondylarthropathy).af.
20. (spondylarthropathy or spondylarthropathies undifferentiated or arthritis, psoriatic or arthritis, reactive or spondylitis, ankylosing or spondylarthropathies undifferentiated onset).af.
21. 18 or 19 or 20
22. Ankylosing Spondylitis/
23. (Ankylosing Spondylitis or Bechterew Disease or Marie-Struempell Disease or Marie Struempell Disease or Spondylarthritis Ankylopoietica or Rheumatoid Spondylitis or Spondylitis, Rheumatoid or Bechterew’s Disease or Bechterews Disease or Ankylosing Spondylitis pre radiological).af.
24. (Ankylating Spondylitis or Ankylopoietic Spondylarthritis or Ankylopoietic Spondylitis or Ankylosing Spine or Ankylosing Spondilitis or Ankylosing Spondylarthritis or Ankylosing Spondylarthrosis or Ankylosis Spondylitis or Ankylotic Spondylitis or Bechterew Disease or Bekhterev Disease or Morbus Bechterew or Spinal Ankylosis or Spine Ankylosis or Spondylarthritis Ankylopoietica or Spondylarthritis Ankylosans or Spondylarthrosis Ankylopoietica or Spondylitis Ankylopoetica or Spondylitis Ankylopoietica or Spondylitis, Ankylosing or Spondyloarthritis Ankylopoietica or Vertebral Ankylosis).af.
25. 22 or 24 or 23
26. (Pain Evaluation or Pain Measurement or Pain Scale).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
27. (Measurement Pain or Measurements Pain or Pain Measurements or Pain Assessment or Nociception Tests or Nociception Test or Test Nociception or Tests Nociception or Analgesia Tests or Analgesia Test or Test Analgesia or Tests Analgesia or Assessment Pain or Assessments Pain or Pain Assessments or Visual Analog Scale or Scale Visual Analog or Scales Visual Analog or Visual Analog Scales or Visual Analogue Pain Scale or Visual Analogue Scale or Analogue Scale Visual or Analogue Scales Visual or Scale Visual Analogue or Scales Visual Analogue or Visual Analogue Scales or Visual Analog Pain Scale or McGill Pain Questionnaire or Pain Questionnaire McGill or Questionnaire McGill Pain or McGill Pain Scale or Pain Scale McGill or Scale McGill Pain or Tourniquet Pain Test or Pain Test Tourniquet or Pain Tests Tourniquet or Test Tourniquet Pain or Tests Tourniquet Pain or Tourniquet Pain Tests or Analogue Pain Scale or Analogue Pain Scales or Pain Scale Analogue or Pain Scales Analogue or Scale Analogue Pain or Scales Analogue Pain or Analog Pain Scale or Analog Pain Scales or Pain Scale Analog or Pain Scales Analog or Scale Analog Pain or Scales Analog Pain or Formalin Test or Formalin Tests or Test Formalin or Tests Formalin or Bath Ankylosing Spondylitis Functional Index or BASFI or Bath Ankylosing Spondylitis Disease Activity Index or BASDAI or Schober test).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
28. 26 or 27
29. Recurrent Disease/
30. (Disease Recurrence or Periodic Disease or Recurrence or Relapsing Disease).af.
31. (Recurrence or Recurrences or Relapse or Relapses or Recrudescence or Recrudescences).af.
32. 30 or 31 or 29
33. Enthesopathy/
34. enthesopathies.mp. or ENTHESOPATHY/
35. 33 or 34
36. PERIARTHRITIS/ or Periarthritis.mp.
37. 28 and 13 and 17
38. 28 and 21 and 13
39. limit 38 to (human and (English or French or Spanish))
40. 25 and 28 and 13 DMARD_sintomas-axiales_artritispsoriasica
41. limit 40 to (human and (English or French or Spanish))

42. (Radiography or Radiographic progression or BASRI or Bath Ankylosing Spondylitis Radiology Index or radiological scoring or radiological scoring methods or radiological scoring scale or sharp van der heijde method for scoring radiographs or ASspiMRI or radiological assessment or MSAS or LARSEN or scott method or Detecting radiological changes or radiological changes).af. DMARD_sintomasaxiales_espondiloartropatias
43. 42 and 13 and 17
44. (Comparative Study or Controlled study or Clinical study or Case Control Study or Clinical trial or Controlled Clinical Trial or Randomized Controlled Trial or Meta-Analysis or Practice Guideline or Comparative Study or Controlled Clinical Trial or Multicenter Study).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] DMARD_sintomasaxiales_espondilitisankilosante
45. 43 and 44
46. limit 45 to (human and (English or French or Spanish)) DMARD_cambiosradiologicos_artritispsoriasica
47. 42 and 21 and 13
48. limit 47 to (human and (English or French or Spanish)) DMARD_cambiosradiologicos_espondiloartropatias
49. 42 and 25 and 13
50. limit 49 to (human and (English or French or Spanish)) DMARD_cambiosradiologicos_espondilitisankilosante
51. 32 and 13 and 17
52. limit 51 to (human and (English or French or Spanish))
53. 52 and 44 DMARD_recaidas_artritispsoriasica
54. 32 and 21 and 13 DMARD_recaidas_espondiloartropatias
55. 25 and 32 and 13 DMARD_recaidas_espondilitisankilosante
56. 35 and 13 DMARD_entesopatía
57. 36 and 13 DMARD_artritisperiférif-erica

The bibliographies of all retrieved articles were scrutinised for additional studies.