For submission to *The Journal of Rheumatology*

Drug Therapies for Peripheral Joint Disease in Psoriatic Arthritis: A Systematic Review

Maria Laura Acosta Felquer, Laura C Coates, Enrique R Soriano, Roberto Ranza, Luis R Espinoza, Philip S Helliwell, Oliver FitzGerald, Philip J Mease

Author Information: L Acosta Felquer, MD, Sección Reumatología, Servicio de Clínica Médica, Hospital Italiano de Buenos Aires, marial.acosta@hospitalitaliano.org.ar; LC Coates, MRCP, PhD, NIHR Clinical Lecturer, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, United Kingdom, L.C.Coates@leeds.ac.uk; ER Soriano, MD, MSC,Sección Reumatología, Servicio de Clínica Médica, Hospital Italiano de Buenos Aires, enrique.soriano@hospitalitaliano.org.ar; R Ranza, MD, Academic Unit of Rheumatology, Universidade Federal de Uberlândia,, MG, Brazil, robertoranza@gmail.com; LR Espinoza, MD, Section of Rheumatology, Louisiana State University Health Sciences Center, New Orleans, LA, USA, lespin1@lsuhsc.edu; PS Helliwell, DM, PhD, Academic Unit of Musculoskeletal Disease, Chapel Allerton Hospital, Leeds, UK, p.helliwell@leeds.ac.uk; O FitzGerald, MD, Department of Rheumatology, St. Vincent's University Hospital and Conway Institute for Biomolecular Research, University College, Dublin, Ireland, oliver.fitzgerald@ucd.ie; PJ Mease, MD, Rheumatology Research, Swedish Medical Center; Clinical Professor, University of Washington School of Medicine, Seattle, USA, pmease@philipmease.com

Corresponding Author: Enrique R Soriano, MD, Jefe Sección Reumatología, Servicio de Clínica Médica, Hospital Italiano de Buenos Aires, Peron 4190 (C1199ABB), CABA. Argentina; telephone 54-11-49590200 (ext: 5443); fax 54-11-49590378; email enrique.soriano@hospitalitaliano.org.ar

Source of support: none

Running footline: Psoriatic Arthritis: Peripheral Joints

Key index items: NSAIDs, DMARDs, biologics, tumor necrosis factor inhibitors, therapeutic strategies

Word count: 7025 words, including text (4194), references (2479, n=71), and table (352, n=1), but excluding title page

Abstract

In 2009 GRAPPA published their first evidence based recommendations for the treatment of psoriasis and psoriatic arthritis (PsA). Since then new information has been published and drugs developed. In this paper we summarize the evidence for the efficacy of available treatments for peripheral joint involvement in PsA. We performed a systematic review of the current literature on the efficacy of different therapies, management, and therapeutic strategies for peripheral arthritis involvement in PsA, in order to provide information for the development of the new GRAPPA treatment recommendations.

Peripheral joint disease is often progressive in patients with psoriatic arthritis (PsA) despite a wide variety of traditional and newer therapies. To adequately treat peripheral arthritis in their PsA patients, physicians need up-to-date treatment recommendations.

To address this need, we performed a systematic literature search of the Medline, Embase, and Cochrane databases, from 2006 to the present. Because peer-reviewed papers are not always available, we also screened abstracts from the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) conferences from 2010 through 2013. It is intended that this review will provide the basis for updated treatment recommendations for peripheral arthritis by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA),

RESULTS

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Of 213 papers that included case reports, reviews, etc., only two were randomized controlled trials [RCT], and these were selected for closer evaluation. In a 4-week study,(1) patients were randomized to Nimesulide (NIM; 100, 200, or 400 mg/day) or placebo. NIM 200 mg or 400 mg, but not 100 mg/day were significantly better (p=0.03) than placebo for reducing the number of tender and swollen joints, and improving physician's and patient’s global assessment of efficacy.

A 12-week parallel-group study compared celecoxib 400 mg (n=201) or celecoxib 200 mg (n=213) once daily (qd) with placebo (n=194) in treating the signs and symptoms of PsA in flare.(2) At week 12, no statistically significant differences on ACR20 criteria between treatment groups were observed.

Oral Steroids

No RCTs of oral corticosteroids have been performed. However, in a study presented at the ACR 2013,(3) oral corticosteroids were significantly associated with arthritis mutilans, along with longer PsA duration and diagnostic delay, earlier age of PsA onset, more tender and swollen joints count, lower C-reactive protein (CRP)/erythrocyte sedimentation rates (ESR), the highest Health Assessment Questionnaire (HAQ) score, and the requirement for tumor necrosis factor inhibitor (TNFi) therapy.

Generalized pustular psoriasis after systemic corticosteroid withdrawal has been a concern,(4) although with little supportive evidence. In 2009, 4 cases of serious pustular psoriasis after glucocorticoid withdrawal were reported.(5)

Intra-articular steroids

As suggested by other reviews,(6, 7) corticosteroid joint injections are based on theoretical arguments and clinical experience, more than on clinical trials and their use is less standardized compared to other therapies. Only one prospective observational study was found,(8) which evaluated 133 patients, most of them with polyarthritis (79 received one injection and 54 received >1). Clinical response (absence of tenderness or effusion) at 3 months was obtained in 41.6% of injected joints and was associated with the use of DMARDs. The relapse rate after 12 months was 25.5% and was associated with large joints and elevated ESR.(8)

Disease-modifying Antirheumatic Drugs (DMARDs)

Although traditional DMARDs are used for the treatment of PSA, the evidence base for their effectiveness is not well established.

Methotrexate

Since 2003, two RCTs have been published on methotrexate (MTX), the most frequently used of the DMARDs.(9, 10) In a randomized 6-month open-label trial of patients with early PsA (oligoarthritis of <12 weeks duration),(9) patients were randomized to NSAID alone or NSAID plus MTX for 3 months; thereafter, all patients continued with NSAID/MTX. Outcomes assessed at 3 and 6 months showed significant improvement in joint count and CRP/ESR in both groups at 3 months compared with baseline; improvements continued at 6 months. Patients randomized to MTX had significantly ($p<0.05$) better joint count responses at 3 months compared with NSAID-alone patients, but the results were similar at 6 months when both groups were taking NSAID/MTX.

In the MIPA (Methotrexate In Psoriatic Arthritis) study,(10) 221 patients were randomized to MTX (target dose 15 mg/wk) or placebo in a 6-month RCT. Only 65% and 69% of patients in the active and placebo groups, respectively, completed the trial. At 6 months, there was improvement on the Psoriatic Arthritis Response Criteria (PsARC; primary outcome) in both groups compared to baseline, but no statistically significant differences were observed between

MTX and placebo for PsARC, ACR, or Disease Activity Scores (DAS28), tender or swollen joint counts, or ESR. Statistical differences were observed, however, in MTX patients for patient and physician global assessments and mean Psoriasis Area and Severity (PASI) score.

Some evidence can also be obtained from observational studies.(11) Chandran et al published a reevaluation of the efficacy of MTX in the University of Toronto PsA registry,(12) where 59 patients seen between 1994 and 2004 were compared with 19 seen between 1978 and 1993. Patients in the 1994–2004 cohort had shorter disease duration (mean 8.5 vs 11.5 years) and received higher MTX doses (16.2 vs 10.8 mg/week); 68% of these patients had ≥40% reduction in joint counts and less radiographic progression, suggesting that there may be better response with less progression of damage.(12)

Cantini et al evaluated the frequency and duration of remission in patients with peripheral PsA treated with DMARDs.(1, 2, 13, 14) Of 121 patients who received MTX as monotherapy, 23 (19%) achieved remission. Further, 34%, 23%, and 10% of patients treated with MTX achieved ACR/50/70 responses, respectively.(13, 14)

Lie et al compared the effectiveness and retention rate of MTX in 430 PsA patients (mean disease duration 4.4 years) with 1280 rheumatoid arthritis (RA) patients (similar disease duration) from the Norwegian DMARD registry.(15) After 6 months of MTX, PsA and RA patients both improved in most disease activity measures and patient-reported outcomes, although PsA patients tended to have less improvement than RA patients. Evaluation of the retention rate of a drug provides an indirect way to evaluate its efficacy and toxicity. In this study, 2-year retention rates of MTX therapy in PsA and RA patients were 65% and 66%, respectively.(15)

In an open-label study in which 115 PsA patients with relatively mild disease were randomized to receive MTX vs MTX plus infliximab, ACR 20/50/70 responses were observed in 67%, 40%, and 19%, respectively, in MTX monotherapy-treated patients, lower than combination therapy (discussed below), but still with apparent effect.(16)

Leflunomide

In a 24-week RCT of 186 patients, leflunomide was significantly superior to placebo in improvement in the PsARC (59% vs 30%, respectively) as well as tender and swollen joint scores, HAQ, and Dermatology Qualitiy of Life (DLQI)).(17) Effect sizes were medium or small (**Table 1**).

In a prospective, multinational 24-week observational study involving adult patients with active PsA who initiated treatment with leflunomide, 380/440 (86.4%) patients achieved a PsARC response at 24 weeks. Significant improvements were also seen in tender and swollen joint counts, patient and physician global assessments, fatigue, pain, skin disease, dactylitis, and nail lesions. The discontinuation rate was 12.3%.(18)

Cyclosporine

No RCTs have compared cyclosporine (CSA) with placebo. In a 12-month RCT, 72 patients with active PsA and incomplete response to MTX were randomized to MTX plus either CSA or placebo. The CSA/MTX group had significant differences in synovitis (detected by ultrasound) and PASI scores; **Table 1** shows small effect sizes for major outcomes.(19)

Anti-Tumor Necrosis Factor (TNF) Therapies

Etanercept

In a multicenter RCT, 205 PsA patients received 25 mg etanercept twice weekly (biw) or placebo. At 12 weeks, etanercept patients had significant improvements in ACR20 and PsARC responses (59% vs 15%, and 72% vs 31%, respectively) and in the HAQ. At 12 months, radiographic disease progression (modified Sharp score) was significantly inhibited in the etanercept group (-0.03 unit) compared with worsening of +1.00 unit in the placebo group. Effect size could not be estimated.(20, 21)

The PRESTA (Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis) trial compared etanercept 50 mg biw vs 50 mg once weekly (qw) in 752 patients with moderate/severe psoriasis and active PsA. At 12 weeks, etanercept 50 mg biw was superior to 50 mg qw for skin manifestations, but there were no differences in musculoskeletal response. At week 24, both regimens achieved significant improvements in skin, joint, enthesitis, and dactylitis.(22)

Adalimumab

ADEPT (Adalimumab Effectiveness in Psoriatic Arthritis Trial), a 24-week RCT, compared adalimumab 40 mg vs placebo subcutaneously every other week (eow) for 24 weeks in 313 patients with moderately to severely active PsA with inadequate response to NSAIDs.(23, 24) Significant responses for ACR20 and PASI75 were observed with adalimumab vs placebo

at 12 and 24 weeks (p<0.001), including significant inhibition of structural changes on radiographs and in erosion and joint space narrowing scores.(24-26) (See **Table 1** for effect sizes.)

In another analysis of the ADEPT trial, adalimumab monotherapy was as effective as adalimumab plus MTX in improving joint and skin patient-reported outcomes.(27)

In a 12-week, RCT, where 100 patients with active PsA and inadequate response to DMARDs received adalimumab (40 mg eow) or placebo,(28) adalimumab significantly reduced joint signs and symptoms and improved skin and disability. (See **Table 1** for effect sizes)(28)

In a prospective 12-month, nonrandomized, open-label clinical trial, 170 patients with active PsA received cyclosporine (2.5–3.75 mg/kg/day), adalimumab (40 mg eow), or combination therapy.(29) The combination therapy was safe and improved clinical and inflammatory markers. At 12 months, the PsARC was met by 65% of cyclosporine-treated (p=0.0003 vs combination), 85% of adalimumab-treated (p=0.15 vs combination), and 95% of combination-treated patients; while the ACR50 response rates were 36%, 69%, and 87%, respectively (p<0.0001 and p=0.03 vs combination).(29)

Infliximab

The first IMPACT study (Infliximab Multinational Psoriatic Arthritis Controlled Trial) compared infliximab (5 mg/kg) or placebo in 104 patients. At week 16, 65% of infliximab patients vs 10% of placebo patients achieved the ACR20, and 75% of infliximab patients vs 21% of placebo patients (p<0.0001) achieved the PsARC (p<0.001).(30)

In IMPACT 2, 200 patients with active PsA unresponsive to prior therapy received infliximab (5 mg/kg) or placebo at weeks 0, 2, 6, 14, and 22. At week 14, 58% of infliximab vs 11% of placebo patients achieved an ACR20; 77% of infliximab vs 27% of placebo patients achieved PsARC (p<0.001).(31) Infliximab patients had significantly less radiographic progression compared with placebo patients: mean ±SD changes from baseline in total PsA-modified Sharp/van der Heijde score (vdH-S) at week 24 were -0.70 ±2.53 and 0.82 ±2.62, respectively (p<0.001); and at week 54 were -0.94 ±3.40 and 0.53 ± 2.60, respectively (p<0.001).(32, 33)

Golimumab

Golimumab was evaluated in GO-REVEAL (Golimumab—A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal

Antibody [mAb}), in which 405 patients were injected with golimumab (50 mg or 100 mg) or placebo every 4 weeks.(34) Mean radiographic changes in PsA-modified vdH-S from baseline to week 24 for the combined golimumab 50/100-mg group (-0.09) and the golimumab 50-mg group (-0.16) were significantly different than placebo (0.27; P<0.015 and P<0.011, respectively) and were maintained through week 52. Clinical improvements (joint, skin, and physical function) were maintained through 1 year.(35)

In recent 5-year data from the open-label extension of GO-REVEAL study, patients who achieved minimal disease activity (MDA) were compared with patients who never achieved MDA (assessed until week 256). Clinical improvements (HAQ disability index; HAQ-DI) and less radiographic progression (vdH-S scores) were observed in patients with persistent MDA**.**(36)

Certolizumab Pegol

In a 48-week RCT (RAPID-PsA) of certolizumab pegol (CZP), a PEGylated Fab fragment of an anti-TNF mAb, 405 patients with active PsA who had previously failed ≥1 DMARD received CZP 200 eow or 400 mg every 4 weeks (q4w) or placebo.(37) At week 12, statistically significant numbers of CZP patients achieved ACR20 responses (58% CZP 200 eow, 52% CZP 400 q4w, and 24% placebo) and PsARC improvements (78% and 77%, respectively) vs placebo (33%). At week 24, mean change from baseline in HAQ was -0.50 (CZP combined arms) vs -0.19 (placebo). ACR20/50/70 responses, MDA, HAQ-DI, pain (visual analog scale), and PASI75 remained stable from week 24 to week 48 in the CZP groups. In another recent report, low radiographic progression (0.0 at week 24, 0.13 at week 48) was maintained in the CZP arms.(38)

Other Biological Disease-modifying Anti-rheumatic Drugs

Ustekinumab

Ustekinumab, a mAb directed against the p40 subunit of IL-12 and IL-23, is the only non-anti-TNFi biologic therapy approved in many countries for use in PsA. The first RCT of ustekinumab (90 mg weekly) versus placebo was conducted in 146 patients with active PsA, and psoriasis.(39) At week 12, ACR20 responses were achieved by 42% ustekinumab vs 14% placebo patients, respectively (p=0·0002). Of 124 participants (85%) with psoriasis affecting ≥3% body surface area (BSA), the PASI75 was achieved by 52% ustekinumab vs 5% placebo patients, respectively (p<0.0001).(39, 40)

In an RCT (PSUMMIT 1), 615 PsA patients received ustekinumab 45 mg or 90 mg vs. placebo at weeks 0 and 4 and every 12 weeks thereafter. At week 24, ACR20 responses were achieved by 42.4%,, 49.5%, and 22.8%, respectively ($p<0.0001$). ACR50/70 responses were achieved by 27.9%/14.2%; 14.2%/12.2%, and 8.75%/2.4%, respectively. Furthermore, 42.5% of all ustekinumab patients and 2.7% of placebo group ($p<0.0001$) achieved ≥75% improvement in the PASI (PASI75),(41) and significant improvements were observed in HAQ, dactylitis, and enthesitis, compared with placebo.(42) In long-term evaluations, clinical efficacy and inhibition of radiographic progression in ustekinumab patients was demonstrated through week 100.(43)

In the PSUMMIT 2 trial, 312 PsA patients received ustekinumab 45 mg or 90 mg vs. placebo. At week 24, ACR20 responses were achieved by 43% of all ustekinumab vs 20% placebo patients. Between 33% and 37% of all ustekinumab patients had received ≥1 previous TNFi therapy.(44)

Abatacept

In an RCT evaluating 3 dosing regimens of IV abatacept in 170 PsA patients, 10 mg/kg abatacept administered concomitantly with DMARDs was associated with improvement in both joint and skin symptoms.(45) At 6 months, mean (SD) changes from baseline in magnetic resonance imaging (MRI) scores for erosion, osteitis, and synovitis were: –0.6 ±4.2, –1.1 ±2.6, and –1.4 ±3.0, respectively, in the 10-mg/kg arm; and 1.5 ±7.4, 0.4 ±3.3, and 0.8 ±4.3, respectively, in the placebo arm.(45)

Brodalumab

In a phase II RCT, 168 PsA patients received brodalumab (mAb directed against IL-17RA; 140 or 280 mg) or placebo for 12 weeks, followed by open-label extension (all patients received brodalumab 280 mg). At week 12, ACR20 responses were achieved by 37% and 39% of brodalumab groups, respectively, vs 18% of placebo group. At week 24 of the open-label extension, further improvement in ACR20 (51%/64% in 140/280-mg groups, respectively) and other measures (ACR50/70, DAS 28, CDAI, HAQ-DI, dactylitis, and skin scores) were noted. Longer-term studies will be assessed in phase III studies.(46)

Secukinumab

In a 48-week phase III RCT, 783 PsA patients with psoriasis received secukinumab (mAb directed against IL-17A; 150 or 300 mg) or placebo at weeks 1, 2, and 3 and every 4 weeks thereafter. HAQ-DI and PASI75 responses improved significantly in secukinumab combined groups compared to placebo, and responses were maintained through week 52.(47)

Small Molecules

Apremilast

Apremilast, a small molecule that specifically inhibits phosphodiesterase 4, resulting in increased cyclic AMP in immune cells and leading to their immunomodulation, was evaluated in several studies. PALACE 1, 2, 3, phase III RCTs, compared the efficacy and safety of apremilast with placebo in PsA patients previously treated with DMARDs and/or biologic therapy. PALACE 4 evaluated apremilast in DMARDs-naïve PsA patients.

In PALACE 1, 204 patients received apremilast 20 mg twice/daily (bid), 40 mg once/daily (qd), or placebo. At week 12, ACR20 responses were achieved in 43.5% (p=<0.001), 36% (p=0.002), and 12%, respectively. Improvements were also noted in enthesitis, dactylitis, and skin scores.

In PALACE 2, 484 PsA active patients despite prior DMARDs and/or biologics, received apremilast 20 mg, 30 mg, or placebo bid. At week 16, ACR20 responses were achieved in 38.4% (p=0.002), 34.4% (p=0.0024), and 19.5%, respectively. Improvements were maintained over 52 weeks including HAQ, SF-36, PASI75, and BSA.

In PALACE 3, 505 PsA active patients with 1 psoriatic lesion ≥2 cm (with DMARDs or biologics) received apremilast 20 mg, 30 mg, or placebo bid. At week 16, ACR20 responses were achieved in 29.4% (p=0.0235), 42.8% (p<0.0001), and 18.9%, respectively. At 52 weeks improvements were maintained, and PASI75 was achieved by 28.6% (apremilast 20) and 39.1% (apremilast 30) of patients with baseline BSA >3%.

In PALACE 4, patients received apremilast 20 mg or 30 mg or placebo bid and were followed up to week 52. At week 16, ACR20 responses were achieved in 29% (p=0.0235), 32% (p<0.0001), and 17%, respectively.(48-51) Improvements in ACR20 responses, HAQ, and PASI75 were maintained or increased over 52 weeks.(52, 53)

Combination Therapies

A PubMed MeSH literature search for “arthritis, psoriatic” and “drug therapy, combination” published by Daly et al resulted in three articles on cyclosporine plus methotrexate, three on non-TNFi (alefacept, ustekinumab) plus MTX, and 14 on TNFi (etanercept, adalimumab, infliximab, golimumab) plus MTX.(54)

The combination of CSA/MTX reduced the dosages and side effects of each drug, allowing for better disease control with less toxicity. Only one of the CSA/MTX studies was an RCT: in Fraser et al, 72 patients received either concomitant CSA or placebo.(19) The mean dose of MTX was 16.2 mg/week at baseline and 15.9 mg/week at the end of the study, compared to mean doses of 2.5 mg/kg/day and 2.25 mg/kg/day of CSA, respectively. Significant improvements in the mean swollen joint counts and CRP levels compared to baseline were noted in the CSA/MTX arm; however, improvements were not significant when compared with monotherapy.

MTX in combination with biologic agents, either non-TNFi or anti-TNFi, may have a role in decreasing side effects, but most studies suggest that the combination does not improve clinical symptoms beyond those attained by biologic monotherapy. It should be emphasized that the analyses of MTX and biologic combinations were all secondary with many patients already on MTX; no study to date has assessed the initiation of combination therapy versus monotherapy.

Ustekinumab has been previously discussed.(39) Within the more recent RCTs,(41, 44) approximately 50% of patients were using concomitant MTX at baseline. At week 24, ACR20 response was achieved regardless of concomitant MTX therapy or body weight, although the treatment difference appeared numerically larger in patients not receiving MTX versus those receiving MTX and in patients weighing >100 kg vs ≤100 kg, in both cases due to a higher placebo response rate in patients receiving MTX or weighing ≤100 kg. Inhibition of radiographic progression was observed for ustekinumab versus placebo, regardless of concomitant MTX status.(55)

In a number of studies, MTX was combined with an anti-TNF agent. In a prospective Swedish study of 261 PsA patients receiving etanercept, infliximab, or adalimumab, 62% of patients were receiving MTX at baseline (average 15 mg/week) and continued MTX during the study.(56) No differences were detected in the number of joints involved or in the pain ratings in those taking concomitant MTX versus those on an anti-TNF agent only. However, CRP decreased significantly from 9.1 mg/dl to 3.5 mg/dl in the MTX/anti-TNF group versus 11 mg/dl to 8.0 mg/dl in the anti-TNF monotherapy group. Drug survival (length of time treatment was continued) was also studied. Concomitant MTX was associated with increased drug survival of each anti-TNF therapy and was related to significantly fewer dropouts from adverse events (AEs). However, in another study of 82 patients on etanercept/MTX, concomitant MTX did not alter the rate of withdrawals due to inefficacy or side effects.(57)

Other studies of anti-TNF agents have shown neither additional improvement in clinical response with concomitant MTX nor an increase in adverse events.(23, 58) Two studies of adalimumab plus/minus concomitant MTX demonstrated that combination therapy resulted in similar clinical efficacy (ACR20/50/70) and radiographic improvements as adalimumab monotherapy.(23, 26)

Several small studies of infliximab with continuing MTX(59) or infliximab/MTX(58, 60-63) demonstrated the combination to be safe; however, study designs did not compare combination treatment with infliximab monotherapy. RCTs of infliximab similarly showed no significant difference in ACR20 when MTX was taken concomitantly.(30, 31) In a recent open-label study, 115 PsA patients received either infliximab (5 mg/kg) at weeks 0, 2, 6, and 14 plus MTX (15 mg/week); or MTX (15 mg/week) alone.(16) At week 16, 86.3% of infliximab/MTX patients and 66.7% of MTX-alone patients achieved an ACR20 response ($p<0.02$). Improvements in CRP levels, DAS28 response and remission rates, dactylitis, fatigue, and morning stiffness duration were all significantly greater in the group receiving infliximab. In the infliximab/MTX group, 46% had treatment related AEs and two patients had serious AEs, compared with 24% and none, respectively, in the MTX-alone group.

In a study of golimumab plus/minus continued MTX use, about 50% of all patients received MTX (mean 15 mg/week).(34) The ACR20 response rate at 14 weeks was not affected by concomitant MTX; however, no patient on MTX at baseline developed antibodies to golimumab.(34)

In an open-label RCT, 41 PsA patients with peripheral arthritis received etanercept (50 mg once weekly) for 6 months in combination with MTX (7.5–15 mg/week) or CSA (3 mg/kg daily).(64) DAS scores showed that etanercept/CSA was as effective as etanercept/MTX.

Finally, Karanikolas et al conducted a prospective 12-month, non-randomized, un-blinded clinical trial of 57, 58, and 55 patients who received CSA (2.5–3.75 mg/kg/day), adalimumab (40 mg eow), or a combination, respectively.(29) At 12 months, the PsARC was met by 65% of CSA-treated ($p=0.0003$ vs combination), 85% of adalimumab-treated ($p=0.15$ vs combination), and 95% of combination-treated patients, while the ACR50 response rates were 36%, 69%, and 87%, respectively ($p<0.0001$ and $p=0.03$ vs combination). A significantly greater mean improvement in HAQ-DI was achieved by combination treatment (-1.11) vs CSA (-0.41) or adalimumab alone (-0.85).

Mono/oligoarthritis in PsA: Therapeutic Management

The management of polyarticular inflammatory involvement in PsA generally compares favorably to that of RA.(65) However, most randomized and prospective clinical studies include PsA patients with ≥5 tender and ≥5 swollen joints. Most mono/oligoarticular PsA patients have not been studied prospectively.

A significant proportion of mono- and oligoarthritis PsA are refractory to conventional anti-inflammatory therapy including DMARDs, and no guidelines are established for the use of biologic treatment of these patients. A recent update of guidelines by the British Society of Rheumatology recommends that anti-TNF therapy should be considered for PsA patients with active arthritis (≥3 tender and ≥3 swollen joints) who have failed treatment with ≥2 conventional DMARDs. In addition, anti-TNF therapies should be considered in patients with severe persistent oligoarthritis (≤3 tender/swollen joints, which may have major influence on well-being) who have failed treatment with ≥2 conventional DMARDs and appropriate intra-articular therapy.(66)

Similarly, studies of the efficacy of biologic therapy in juvenile PsA are also scarce. However, a long-term observational analysis of PsA patients on etanercept (n=17/18) from the Dutch Registry showed significant clinical improvement for articular symptoms, but little skin improvement in both psoriasis and PsA patients.(67) In contrast, in an open-label study, etanercept was effective for both skin and joint involvement in patients with oligoarthritis (±2 active joints.(68)

Thus, guidelines for the therapeutic management of mono/oligoarthritis in PsA patients must be established. Additionally, patients with oligoarticular PsA cannot be accurately assessed for active disease using reduced joint counts designed for RA patients.(69)

Therapeutic Strategies in PsA

Interventional strategy trials in PsA are lacking.

Early treatment. To date, only one trial addressed immediate vs delayed DMARD therapy in early PsA.(9) In this study, 35 patients (disease duration ≤12 weeks) received MTX 10 mg immediately or after a 3-month delay with symptomatic treatment only. Although joint counts differed at 3 months, outcomes were similar at 6 months after all patients were on MTX. Additionally, the RESPOND trial (open-label MTX monotherapy vs MTX/infliximab in early PsA)

confirmed a significant benefit with infliximab and also demonstrated positive ACR outcomes with early therapy.(16) However, evidence is needed from RCTs to prove benefit of early therapeutic intervention.

Step-up vs step-down treatment approach. No studies in PsA have compared a step-up vs step-down approach to treatment. EULAR recommendations contain a treatment algorithm using a step-up approach similar to their RA algorithm.(6)

Treat to target. Per a EULAR taskforce review (up to September 2011) no RCTs have compared a treat-to-target strategy with standard care.(70) However, a recent abstract describes the Tight Control of PsA (TICOPA) study in 206 patients with early (<24 months disease duration) DMARD-naïve PsA who received intensive treatment or standard care. Intensive-arm patients were treated according to an algorithm driven by clinical state at each monthly visit: if patients were not in MDA, treatment was changed to achieve that state. The algorithm dictated a rapid introduction of methotrexate (target dose 25 mg), followed by the addition of sulfasalazine (to 40 mg/kg/day), according to response. Further drug escalation depended on the number of tender and swollen joints: if sufficient disease was present, TNFi's were introduced; if not, leflunomide or cyclosporin, alone or in combination, were substituted. Standard-care patients received rheumatologist-prescribed usual clinical care, with no restrictions, on a 3-monthly basis. Blinded assessments were performed at 12-week intervals. At 48 weeks, ACR20 was achieved by 62% of tight control vs 45% of standard care patients (p=0.04). More biologic and combination therapy was used in the tight control arm. More serious AEs were also noted in the tight control group (25) vs the standard care group (8). Full radiographic data are not available.(71)

References

1. Sarzi-Puttini P, Santandrea S, Boccassini L, Panni B, Caruso I. The role of NSAIDs in psoriatic arthritis: evidence from a controlled study with nimesulide. Clin Exp Rheumatol 2001;19:S17-20.

2. Kivitz AJ, Espinoza LR, Sherrer YR, Liu-Dumaw M, West CR. A comparison of the efficacy and safety of celecoxib 200 mg and celecoxib 400 mg once daily in treating the signs and symptoms of psoriatic arthritis. Semin Arthritis Rheum 2007;37:164-73.

3. Haroon M, Gallagher P, FitzGerald O. Predictors of response to intra-articular steroid injection in psoriatic arthritis [abstract]. Arthritis Rheum 2013;65(suppl):149.

4. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol 1968;80(:771-93.

5. Brenner M, Molin S, Ruebsam K, Weisenseel P, Ruzicka T, Prinz JC. Generalized pustular psoriasis induced by systemic glucocorticosteroids: four cases and recommendations for treatment. Br J Dermatol 2009;161:964-6.

6. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis 2012;71:4-12.

7. Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol 2006;33:1422-30.

8. Eder L, Chandran V, Ueng J, Bhella S, Lee KA, Rahman P, et al. Predictors of response to intra-articular steroid injection in psoriatic arthritis. Rheumatology (Oxford) 2010;49:1367-73.

9. Scarpa R, Peluso R, Atteno M, Manguso F, Spano A, Iervolino S, et al. The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. Clin Rheumatol 2008;27:823-6.

10. Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatology (Oxford) 2012;51:1368-77.

11. Ceponis A, Kavanaugh A. Use of methotrexate in patients with psoriatic arthritis. Clin Exp Rheumatol 2010;28:S132-7.

12. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. J Rheumatol 2008;35:469-71.

13. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology (Oxford) 2008;47:872-6.

14. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Criteria, frequency, and duration of clinical remission in psoriatic arthritis patients with peripheral involvement requiring second-line drugs. J Rheumatol Suppl 2009;83:78-80.

15. Lie E, van der Heijde D, Uhlig T, Heiberg MS, Koldingsnes W, Rodevand E, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:671-6.

16. Baranauskaite A, Raffayova H, Kungurov NV, Kubanova A, Venalis A, Helmle L, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. Ann Rheum Dis 2012;71:541-8.

17. Kaltwasser JP, Nash P, Gladman D, Rosen CF, Behrens F, Jones P, et al. 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.

18. Behrens F, Finkenwirth C, Pavelka K, Stolfa J, Sipek-Dolnicar A, Thaci D, et al. Leflunomide in psoriatic arthritis: results from a large European prospective observational study. Arthritis Care Res (Hoboken) 2013;65:464-70.

19. Fraser AD, van Kuijk AW, Westhovens R, Karim Z, Wakefield R, Gerards AH, 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.

20. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264-72.

21. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. J Rheumatol 2006;33:712-21.

22. Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ 2010;340:c147.

23. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52(:3279-89.

24. Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis 2009;68:702-9.

25. Gladman DD, Mease PJ, Choy EH, Ritchlin CT, Perdok RJ, Sasso EH. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther 2010;12:R113.

26. Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum 2007;56:476-88.

27. Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis 2007;66:163-8.

28. Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol 2007;34:1040-50.

29. Karanikolas GN, Koukli EM, Katsalira A, Arida A, Petrou D, Komninou E, et al. Adalimumab or cyclosporine as monotherapy and in combination in severe psoriatic arthritis: results from a prospective 12-month nonrandomized unblinded clinical trial. J Rheumatol 2011;38:2466-74.

30. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum 2005;52:1227-36.

31. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150-7.

32. Kavanaugh A, Antoni CE, Gladman D, Wassenberg S, Zhou B, Beutler A, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis 2006;65:1038-43.

33. van der Heijde D, Kavanaugh A, Gladman DD, Antoni C, Krueger GG, Guzzo C, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. Arthritis Rheum 2007;56:2698-707.

34. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60:976-86.

35. Kavanaugh A, van der Heijde D, McInnes IB, Mease P, Krueger GG, Gladman DD, et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. Arthritis Rheum 2012;64:2504-17.

36. Kavanaugh A, McInnes I, Mease P. Impact of persistent minimal disease activity on long-term outcomes in psoriatic arthritis: Results from 5 years of the long-term extension of a randomized, placebo-controlled study [abstract] Arthritis Rheum 2013;65(suppl):147-8.

37. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis 2014;73:48-55.

38. Mease P, Fleischmann R, Wollenhaupt J. Effect of certolizumab pegol over 48 weeks on signs and symptoms in patients with psoriatic arthritis with and without prior tumor necrosis factor inhibitor exposure [abstract] Arthritis Rheum 2013;65(suppl):132-3.

39. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet 2009;373:633-40.

40. Kavanaugh A. The efficacy of ustekinumab on the articular and dermatologic manifestations of psoriatic arthritis. Curr Rheumatol Rep 2009;11:233-4.

41. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382:780-9.

42. Kavanaugh A, Puig L, Gottlieb A. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 2 year results from a phase 3, multicenter, double-blind, placebo-controlled study [abstract]. Arthritis Rheum 2013;65(suppl):L10.

43. McInnes I, Ritchlin C, Rahman P. Ustekinumab is effective in inhibiting radiographic progression in patients with active psoriatic arthritis: integrated data analysis of two phase 3, randomized, placebo-controlled studies [abstract] Arthritis Rheum 2013;65(suppl):718.

44. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy:

6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73:990-9.

45. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum 2011;63:939-48.

46. Mease PJ, Genovese MC, Greenwald MW, Ritchlin CT, Beaulieu AD. Brodalumab, anti-IL17 receptor monoclonal antibody, in psoriatic arthritis. New Engl J Med 2014, submitted.

47. Gottlieb A, Sigurgueirsson B, Bluvelt A. Secukinumab shows substantial improvement in both psoriasis symptoms and physical functioning in moderate- to- severe plaque psoriasis patients with psoriatic arthritis: A subanalysis of phase 3 multicentre, double-blind, placebo-controlled study [abstract]. Arthritis Rheum 2013;65(suppl):136-7.

48. Mease P, Kavanaugh A, Gladman D. Long-term safety and tolerability of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: pooled safety analysis of three phase 3, randomized, controlled trials [abstract]. Arthritis Rheum 2013;65(suppl):131-2.

49. Cutolo M, Myerson G, Fleischmann R. Long-term (52-week) results of a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic aethritis (PALACE 2) [abstract]. Arthritis Rheum 2013;65(suppl):346-7.

50. Edwards C, Blanco F. Long-term (52-week) results of a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement (PALACE 3) [abstract]. Arthritis Rheum 2013;65(suppl):132.

51. Wells A, Edwards C, Adebajao A. Apremilast in the treatment of DMARD naïve psoriatic arthritis patients: results of a phase 3 randomized controlled trial (PALACE 4) [abstract] Arthritis Rheum 2013;65(suppl):L4.

52. Schett G, Mease P, Gladman D. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvement in physical function in patients with psoriatic arthritis: Results from three phase 3, randomized, controlled trials [abstract] Arthritis Rheum 2013;65(suppl):143.

53. Cutolo M, Mease P, Gladman D. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvement in tender and swollen joint counts in patients with psoriatic arthritis: Results from three phase 3, randomized, controlled trials [abstract] Arthritis Rheum 2013;65(suppl):135-6.

54. Daly M, Alikhan A, Armstrong AW. Combination systemic therapies in psoriatic arthritis. J Dermatolog Treat 2011;22:276-84.

55. Kavanaugh A, Ritchlin C, Rahman P, Puig L, Gottlieb AB, Li S, et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. Ann Rheum Dis 2014;73:1000-6.

56. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis 2008;67:364-9.

57. Spadaro A, Ceccarelli F, Scrivo R, Valesini G. Life-table analysis of etanercept with or without methotrexate in patients with psoriatic arthritis. Ann Rheum Dis 2008;67:1650-1.

58. Salvarani C, Cantini F, Olivieri I, Macchioni P, Padula A, Niccoli L, et al. Efficacy of infliximab in resistant psoriatic arthritis. Arthritis Rheum 2003;49:541-5.

59. Antoni C, Dechant C, Hanns-Martin Lorenz PD, Wendler J, Ogilvie A, Lueftl M, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. Arthritis Rheum 2002;47:506-12.

60. Covelli M, Scioscia C, Iannone F, Lapadula G. Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: immediate benefits are not maintained after discontinuation of infliximab. Clin Exp Rheumatol 2005;23:145-51.

61. Goedkoop AY, Kraan MC, Picavet DI, de Rie MA, Teunissen MB, Bos JD, et al. Deactivation of endothelium and reduction in angiogenesis in psoriatic skin and synovium by low dose infliximab therapy in combination with stable methotrexate therapy: a prospective single-centre study. Arthritis Res Ther 2004;6:R326-34.

62. Provenzano G, Termini A, Le Moli C, Rinaldi F. Efficacy of infliximab in psoriatic arthritis resistant to treatment with disease modifying antirheumatic drugs: an open pilot study. Ann Rheum Dis 2003;62:680-1.

63. Rinaldi F, Provenzano G, Termini A, Spinello M, La Seta F. Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response. Ann Rheum Dis 2005;64:1375-6.

64. Atzeni F, Boccassini L, Antivalle M, Salaffi F, Sarzi-Puttini P. Etanercept plus ciclosporin versus etanercept plus methotrexate for maintaining clinical control over psoriatic arthritis: a randomised pilot study. Ann Rheum Dis 2011;70:712-4.

65. Lindqvist UR, Alenius GM, Husmark T, Theander E, Holmstrom G, Larsson PT. The Swedish early psoriatic arthritis register-- 2-year followup: a comparison with early rheumatoid arthritis. J Rheumatol 2008;35:668-73.

66. Coates LC, Tillett W, Chandler D, Helliwell PS, Korendowych E, Kyle S, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. Rheumatology (Oxford). 2013;52(10):1754-7.

67. Otten MH, Prince FH, Ten Cate R, van Rossum MA, Twilt M, Hoppenreijs EP, et al. Tumour necrosis factor (TNF)-blocking agents in juvenile psoriatic arthritis: are they effective? Ann Rheum Dis 2011;70:337-40.

68. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis 2014;73:1114-22.

69. Coates LC, FitzGerald O, Gladman DD, McHugh N, Mease P, Strand V, et al. Reduced joint counts misclassify patients with oligoarticular psoriatic arthritis and miss significant numbers of patients with active disease. Arthritis Rheum 2013;65:1504-9.

70. Schoels MM, Braun J, Dougados M, Emery P, Fitzgerald O, Kavanaugh A, et al. Treating axial and peripheral spondyloarthritis, including psoriatic arthritis, to target: results of a

systematic literature search to support an international treat-to-target recommendation in spondyloarthritis. Ann Rheum Dis 2014;73:238-42.

71. Coates LC, Navarro-Coy N, Brown SR, Brown S, McParland L, Collier H, et al. The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. BMC Musculoskelet Disord 2013;14:101.

	MTX (9)	CSA (19)	LFN (17)	ADA (28)	ADA (23) ADEPT	ADA (29)	ETA (20)	INF (31) IMPACT	INF (30) IMPACT 2	GOL (34)	CZP (37)	UST (39)	ABAT (39)	Apre-milast (52)

Table 1. Effect size and Number need to treat (NNT) in controlled trials in PsA patients.

Patients (n) on treatment/ control	16/19	38/34	95/91	51/49	151/ 162	58/55	101/ 104	52/52	100/ 100	146/ 113	138/ 136	76/70	40/42	67/68
Mean dose	10 mg /wIM	2.5–4 mg/k/d	20 mg /d	40 mg eow	40 mg eow	40 mg eow	25 mg biw	5 mg /kg	5 mg /kg	50 mg /mo	200 q2w	90 mg qw	10 mg /kg	20 mg bid 40 mg qd
Comparator	NSAID	pbo	pbo	pbo	pbo	CSA 2.5–3.75 mg/kg /d +ADA	pbo	pbo	pbo	pbo	pbo	pbo	pbo	pbo
Follow up (weeks)	24	48	24	12	24	48	24	16	24	24	24	12	24	12
Tender joint score (ES)			0.22											
Swollen joint score (ES)			0.17											
Pain (VAS; ES)	-0.15	0.26		0.64	0.94			1.74	1.96					
HAQ (ES)		-0.18	+0.29	0.49	0.67			0.87	1.17	0.65		0.65		
Tender joint count (0–78; ES)				0.25				1.14	1.14					
Swollen joint count (0–76; ES)	0.33	0.13		0.3				1.17	0.81					
ACR20 (NNT)				5	3		3	2	3	3	3	4	4	4 bid 5 qd

PsARC (NNT)			4			10								
Primary endpoint		Tender Joint Index (Ritchie)	PsARC	ACR20 wk 12	ACR20 wk 12 and x-ray	PsARC1 2 mo	ACR20 wk 12	ACR20 wk 16	ACR20 wk 14	ACR20 wk 14 and vdH-S wk 24	ACR20 wk 12 and x-ray	ACR20 wk 12	ACR20 day 169	ACR20 wk 12

MTX = methotrexate; CSA = cyclosporine; LFN = leflunomide; ADA = adalimumab; ETA = etanercept, INF = infliximab; GOL = golimumab;

CZP = certolizumab pegol; UST = ustekinumab; ABAT = abatacept

ES = effect size; NNT = number needed to treat; ACR20 = American College of Rheumatology 20% response; PsARC = Psoriatic Arthritis Response Criteria; VAS = visual analog scale

eow = every other week; biw = twice weekly; q2w = every 2 weeks; q4w = every 4 weeks; bid = twice/daily; qd = once daily