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

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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. We summarize evidence for the efficacy of available treatments for peripheral joint involvement in PsA. We performed a systematic review of 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. (J Rheumatol 2014;41:2277–85; doi:10.3899/jrheum.140876)

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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.

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MATERIALS AND METHODS

To address this need, we performed a systematic literature search of Medline, Embase, and Cochrane databases, from 2006 to the present. Because peer-reviewed articles 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. This review is intended to 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 Antiinflammatory Drugs (NSAID)

Of 213 NSAID-related articles retrieved, which included case reports, reviews, etc., only 2 were randomized controlled trials (RCT); these 2 reports 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 doses of 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 and patient 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 in ACR20 response criteria between treatment groups were observed.

Steroids

Oral. No RCT of oral corticosteroids have been performed. However, in a study presented at the 2013 ACR meeting[3] oral corticosteroids were significantly associated with arthritis mutilans, along with longer PsA duration and diag-

nostic delay, earlier age of PsA onset, higher tender and swollen joint counts, 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].

Intraarticular. 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 disease-modifying antirheumatic drugs (DMARD). The relapse rate after 12 months was 25.5% and was associated with large-joint involvement and elevated ESR[8].

Disease-modifying Antirheumatic Drugs (DMARD)

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

Methotrexate. Since 2003, 2 RCT have been published on methotrexate (MTX), the most frequently used of the DMARD[9,10]. In a randomized 6-month open-label trial of patients with early PsA (oligoarthritis < 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 in 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 yrs) 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 DMARD[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 20/50/70 responses, respectively[13,14].

Lie, *et al* compared the effectiveness and retention rate of MTX in 430 patients with PsA (mean disease duration 4.4 yrs) versus 1280 patients with rheumatoid arthritis (RA) (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 versus 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 Life Quality Index[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 RCT 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)

Table 1. Effect size and number needed to treat (NNT) in controlled trials in patients with psoriatic arthritis.

	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]	Apremilast[52]
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
Followup, 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	PsARC 12 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; vdH-S Sharp/van der Heijde score; eow: every other week; biw: twice weekly; q2w: every 2 weeks; q4w: every 4 weeks; bid: twice/daily; qd : once daily.

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 patients with PsA 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 versus placebo subcutaneously every other week (eow) for 24 weeks in 313 patients with moderately to severely active PsA with inadequate response to NSAID[23,24]. Significant responses for ACR20 and PASI75 were observed with adalimumab versus 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[24,25,26] (for effect sizes see Table 1).

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 DMARD received adalimumab (40 mg eow) or placebo[28], adalimumab significantly reduced joint signs and symptoms and improved skin and disability (for effect sizes see Table 1)[28].

In a prospective 12-month, nonrandomized, open-label clinical trial, 170 patients with active PsA received CSA (2.5–3.75 mg/kg/day), adalimumab (40 mg eow), or combination therapy[29]. The combination therapy was safe and resulted in improved clinical and inflammatory markers. 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)[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 versus 10% of placebo patients achieved the ACR20, and 75% of infliximab patients versus 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 versus 11% of placebo patients achieved an ACR20; 77% of infliximab versus 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 the 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 from 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 the 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 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) versus 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 DMARD

Ustekinumab. Ustekinumab, a mAb directed against the p40 subunit of interleukin 12 (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 versus 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 versus 5% placebo patients, respectively ($p < 0.0001$)[39,40].

In an RCT (PSUMMIT 1), 615 patients with PsA received ustekinumab 45 mg or 90 mg versus 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. Further, 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 longterm 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 versus placebo. At week 24, ACR20 responses were achieved by 43% of all ustekinumab versus 20% of 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 intravenous abatacept in 170 patients with PsA, 10 mg/kg abatacept administered concomitantly with DMARD 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, versus 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, Clinical Disease Activity Index, 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 RCT, compared the efficacy and safety of apremilast with placebo in PsA patients previously treated with DMARD and/or biologic therapy[48,49,50]. PALACE 4 evaluated apremilast in DMARD-naive PsA patients[51].

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% ($p \leq 0.001$), 36% ($p = 0.002$), and 12%, respectively. Improvements were also noted in enthesitis, dactylitis, and skin scores[48].

In PALACE 2, 484 patients with active PsA despite prior DMARD 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 in HAQ, Medical Outcome Study Short-Form Survey-36, PASI75, and BSA[49].

In PALACE 3, 505 patients with active PsA and 1 psoriatic lesion ≥ 2 cm (while receiving DMARD 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%[50].

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[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 3 articles on CSA plus MTX, 3 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 1 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 taking MTX; no study to date has assessed the initiation of combination therapy versus monotherapy.

Ustekinumab has been discussed[39]. Within the more recent RCT[41,44], about 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 patients with PsA 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 receiving 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 (AE). However, in another study of 82 patients taking 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 clinical efficacy (ACR20/50/70) and radiographic improvements similar to adalimumab monotherapy[23,26].

Several small studies of infliximab with continuing MTX[59] or infliximab/MTX[58,60,61,62,63] demonstrated the combination to be safe; however, study designs did not compare combination treatment with infliximab monotherapy. RCT of infliximab similarly showed no significant difference in ACR20 when MTX was taken concomitantly[30,31]. In a recent open-label study, 115 patients with PsA 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 patients taking MTX-alone 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 AE and 2 patients had serious AE, 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, nonrandomized, unblinded 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) versus 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 patients are refractory to conventional antiinflammatory therapy including DMARD, 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 DMARD. 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 DMARD and appropriate intraarticular therapy[66].

Similarly, studies of the efficacy of biologic therapy in juvenile PsA are also scarce. However, a longterm observational analysis of PsA patients receiving 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 1 trial has addressed immediate versus delayed DMARD therapy in early PsA[9]. In that study, 35 patients (disease duration ≤ 12 wks) 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 receiving 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 RCT to prove benefit of early therapeutic intervention.

Step-up versus step-down treatment approach. No studies in PsA have compared a step-up versus a 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 EULAR taskforce review (up to September 2011) no RCT 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 (disease duration < 24 mo) DMARD-naive 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 MTX (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 were introduced; if not, leflunomide or CSA, 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 AE were also noted in the tight control group[25] versus the standard care group[8]. Full radiographic data are not available[71].

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