Comprehensive Treatment of Dactylitis in Psoriatic Arthritis

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ABSTRACT. Dactylitis, a hallmark clinical feature of psoriatic arthritis (PsA) and other spondyloarthropathies, may also be a severity marker for PsA and psoriasis. Traditionally, clinicians have used nonsteroidal antiinflammatory drugs and local corticosteroid injections to treat dactylitis, although conventional disease-modifying antirheumatic drugs are also used. We performed a systematic literature review to determine the most efficacious current treatment options for dactylitis in PsA. Effect sizes were greatest for the biologic agents ustekinumab, certolizumab, and infliximab, suggesting that therapy with one of these agents should be initiated in patients with dactylitis. However, the limited data highlight the need for randomized, placebo-controlled trials, with dactylitis as a primary outcome, to determine a valid, reliable, and responsive clinical outcome measure for PsA patients with dactylitis. (J Rheumatol 2014;41:2295–300; doi:10.3899/jrheum.140879)

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Dactylitis, or "sausage digit," is considered a hallmark clinical feature of psoriatic arthritis (PsA) and other spondyloarthropathies[1]. The diagnosis of dactylitis, however, is challenging for clinicians not familiar with it, and is frequently misdiagnosed in cases of mild dactylitis, in obese patients, and in those with severe overlying psoriatic skin disease. Other causes of dactylitis include trauma, fracture, gout, sepsis, sarcoidosis, and tuberculosis. In cases of diagnostic uncertainty, magnetic resonance imaging (MRI) and ultrasound may help to discriminate dactylitic digits from normal ones[2].

The treatment of dactylitis has largely remained empirical. Nonsteroidal antiinflammatory drugs (NSAID) are usually employed initially, but many rheumatologists rapidly progress to injected corticosteroids, which are supported by clinical evidence of response in patients with mild to moderate PsA. In resistant cases, disease-modifying antirheumatic drugs (DMARD) are used with or without biologic agents. Comparative effectiveness of these treatment strategies has not been systematically studied.

The focus of our review is to identify and evaluate the effects of therapeutic interventions used to treat dactylitis in patients with PsA. The review is part of a treatment update initiated by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

Search strategy. Ovid Medline was searched from 1966 to the present, using the search terms "dactylitis" (as key search word) and "psoriatic arthritis" (treatment only). Only randomized, double-blind placebo-controlled (RCT) or open-label trials of PsA in which dactylitis was assessed as a separate outcome measure were identified. Thus, 74 articles (English-language reports only) were identified, and 29 articles were selected for full review[3-13,14-24,25,26,27,28,29,30,31].

Two reviewers (SR and ST) independently extracted the data regarding study design, sample size, duration, population, agents, outcome measures, outcome data, p value, and effect size using a standardized data extraction form. A third reviewer (PH) resolved differences if needed. A fourth reviewer (WBM) examined safety data pertaining to the use of DMARD and biologic agents.

RESULTS

Of the 29 trials that assessed dactylitis as an outcome measure, a total of 6589 adult patients with PsA were studied for 12 weeks to 60 months (Table 1)[3-13,14-24,25,26,27,28,29,30,31]. Several studies (n = 18) were RCT with crossover design at 12–24 weeks, with or without open-label extensions. One

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Table 1. Summary of clinical therapeutic studies with dactylitis as a primary or secondary outcome.

Article	Study Population	Study Type	Study Size	Study Medication	Outcome Variable	Outcome Data	Study Duration	p	Effect Size
Kavanaugh (PALACE 1)[3]	Multicenter (n = 83) in 13 countries	DB-RPC, crossover at 16 wks	n = 504	APR vs Pbo	No. of dactylitic digits	Mean ± SEM change from baseline at 24 wks: Pbo = –1.3 ± 0.27, APR (40 mg) = –2.0 ± 0.30, APR (60 mg) = –1.8 ± 0.27	24 wks	> 0.05	N/A
Mease (RAPID-PsA)[4]	Multicenter (n = 92) in North America, Latin America, & Europe	DB-RPC to 24 wks, dose-blinded 24–48 wks, open-label 48–216 wks	n = 409	CZP vs Pbo	LDI	Mean change (SD) from baseline at 24 wks: Pbo = –22.0 ± 46.9, CZP (200 mg) = –40.7 ± 34, CZP (400 mg) = –53.5 ± 69.1	24 wks	0.002 (200 mg); ≤ 0.001 (400 mg)	0.50, combined CZP 200 mg and 400 mg doses
Ritchlin (PSUMMIT 2)[5]	Multicenter (n = 189) in North America, Europe, & Asia Pacific regions	DB-RPC, crossover at 24 wks	n = 312	UST vs Pbo	Dactylitis scored 0-3	Change at 24 wks: 64.6% improvement in median dactylitis score in UST 90-mg vs Pbo. Change at 52 wks: median improvement 95% in pooled UST patients	24, 52 wks	> 0.05	0.29, combined UST groups for PSUMMIT1 & 2 pooled data*
McInnes (PSUMMIT 1)[6]	Multicenter (n = 104) in North America & Europe	DB-RPC, crossover at 24 wks	n = 615	UST vs Pbo	% with dactylitis; dactylitis scored 0-3	Change at 24 wks: % patients with dactylitis in UST (combined 45/90 mg) 56.2% vs 76.1% in Pbo. ~70% improvement in median dactylitis score in UST (combined) vs Pbo. 100% improvement in dactylitis scores for UST patients out to 52 wks	24, 52 wks	0.001 for % with dactylitis; 0.003 for dactylitis scores	0.29, combined UST groups for PSUMMIT1 & 2 pooled data*
Gladman[7]	Single Center in Canada	Prospective from historical cohort (10 years)	n = 294	DMARD vs Biologic	% with complete resolution; % with > 50% improvement in No. of dactylitic digits	Change at 6 mo, response: Biologic 77.3%, DMARD 51.5%. Change at 1 year, response: Biologic 87.2%, DMARD 69.9%.	6, 12 mo	N/A	N/A
Kavanaugh (GO-REVEAL)[8]	Multicenter (n = 58 sites) in the US, Canada, & Europe	DB-RPC, crossover at 24 wks	n = 405	GOL vs Pbo	Dactylitis scored 0–3	Mean ± SD change from baseline at 24 wks: Pbo = 57.2 ± 81.2, GOL (combined 50/100 mg) = 76.6 ± 53.5, GOL (100 mg) = 83.0 ± 45.9	24 wks	N/A	N/A
Kavanaugh (GO-REVEAL)[9]	Multicenter (n = 58 sites) in the US, Canada, & Europe	DB-RPC, crossover at 24 wks	n = 405	GOL vs Pbo	Dactylitis scored 0-3	Change at 24 wks, improved: GOL (combined 50/100 mg) 74%, GOL (100 mg) 82%, Pbo 28%. Change at 52 wks: Numerically less (52%) had improvement in Pbo vs GOL combined (76.6%) or GOL 100 mg (82%)	24, 52 wks	0.002 at 24 wks, N/A at 52 wks	N/A
Cantini[10]	Single center in Italy	Prospective followup case-control	n = 76	ADM ± MTX	% with dactylitis of hands/feet	Change at 36 mo: data not reported	36 mo	N/A	N/A
Baranauskaite[11]	Multicenter (n = 25 +B1 sites) in Europe, Middle East, South Africa, & Turkey	OL	n = 115	MTX ± INX	No. of dactylitic digits	Change at 16 wks (median reduction of ≥ 2 dactylitic digits): MTX = no reduction, MTX+INX = magnitude of reduction not reported, but statistically significant	16 wks	0.0006	N/A
Saougou[12]	Single center in Greece	OL	n = 65	ADM (n = 30), ETN (n = 25), INX (n = 10)	% with dactylitis of hands/feet	Change at 60 mo: 22% no longer had dactylitis	60 mo	N/A	N/A

Table 1. Continued.

Article	Study Population	Study Type	Study Size	Study Medication	Outcome Variable	Outcome Data	Study Duration	p	Effect Size
Karanikolas[13]	Single center in Greece	OL	n = 170	ADM ± CyA	Dactylitis scored 0–3	Change at 12 mo (≥ 50% reduction in dactylitis score): CyA = 28.5%, ADM = 75%, CyA+ADM = 100%	12 mo	N/A	N/A
Jung[14]	Single center in Germany	OL	n = 20	ANA ± DMARD	Dactylitis score (not described)	Change at 12 wks: 30% of patients had improved dactylitis scores, 5%+worse, 5%+stable, 5% had undulating course	12 wks	N/A	N/A
Gladman[15]	Multicenter (n = 24 sites) in Canada	OL	n = 127	ADM (prior treatment failures)	% with dactylitis in ≥ 4 digits of hands/feet, dactylitis scored 0–3	Change at 12 wks: % of patients with ≥ 4 dactylitic digits dropped from 33.9% to 11%. Mean ± SD dactylitis scores decreased from 7.04 ± 6.45 to 2.49 ± 4.68	12 wks	< 0.001 for both outcomes	N/A
Sterry (PRESTA)[16]	Multicenter (n = 98 sites) in Europe, Latin America, & Asia Pacific regions	DB-RPC	n = 752	ETN 50 mg twice vs once weekly	Dactylitis scored 0–3	Change at 12, 24 wks: Baseline score decreased 74.3–78.4% at 12 wks and 84.5–84.8% at 24 wks	12, 24 wks	N/A	N/A
Kavanaugh (GO-REVEAL)[17]	Multicenter (n = 58 sites) in US, Canada, & Europe	DB-RPC, crossover at 16 wks	n = 405	GOL vs Pbo	% with dactylitis of hands/feet, dactylitis scored 0–3	Change at 14, 24 wks: % of patients with dactylitis was unchanged. Dactylitis scores, median % change: GOL 100 mg = 100% at 14, 24 wks; Pbo = 0 at 14, 24 wks	14, 24 wks	0.009 at 14 wks, < 0.001 at 24 wks	N/A
Gottlieb[18]	Multicenter (n = 24 sites) in US, Canada, & Europe	DB-RPC crossover at 12 wks	n = 146	UST vs Pbo	Dactylitis scored 0–3	Change at 12 wks (median [IQR] improvement): UST = 2.0 (0.0–4.0), Pbo = 0.0 (–1.0–1.5)	12 wks	0.0107	N/A
Mease (ADEPT, 2-year data)[19]	Multicenter (n = 50 sites) in US, Canada, & Europe	DB-RPC, crossover at 24 wks, OL extension to 120 wks	n = 245	ADM vs Pbo	Dactylitis scored 0–3	Mean ± SD change from baseline at 48 wks: 1.3 ± 4.8, Change at 104 wks: 1.4 ± –3.7	48, 104 wks of treatment	> 0.05	N/A
Healy[20]	Single-center study in Britain	OL	n = 17	MTX (n = 12), HC (n = 1), ETN (n = 1), INX (n = 1)	LDI, LDI basic, dactylitis scored 0–3, No. dactylitic digits (tender, nontender), No. dactylitic digits (tender), MRI scores	All clinical indices of dactylitis improved during 6-mo period as did MRI scores for the hand or foot; no primary data provided.	6 mo	N/A	N/A
Antoni (IMPACT 1, 2-year data)[21]	Multicenter (n = 9 sites) in Europe, US, & Canada	DB-RPC crossover at 16 wks	n = 104	INX vs Pbo	No. of dactylitic digits	Mean ± SD change from baseline at 50 wks: INX = 0.32 ± 0.96, Change at 98 wks: INX = 0.19 ± 0.72	50, 98 wks	N/A	N/A
Kavanaugh (IMPACT 2, 1-year data)[22]	Multicenter (n = 36 sites) in US, Canada, & Europe	DB-RPC crossover at 24 wks (early escape at 16 wks)	n = 200	INX vs Pbo	% with dactylitis of hands/feet	Change at 24 wks, % patients with dactylitis: INX = 34.0% vs Pbo = 11.8%. Change at 54 wks, % patients with dactylitis: INX = 14.8% vs Pbo = 12.2%	24, 54, wks	< 0.001 at 24 wks	N/A
Genovese[23]	Multicenter (n = 16 sites) in US & Canada	DB-RPC	n = 100	ADM vs Pbo	Dactylitis scored 0 to 3	Mean change in dactylitis score at 12 wks: ADM = –2.4, Pbo = –1.4	12 wks	> 0.05	N/A

Table 1. Continued.

Article	Study Population	Study Type	Study Size	Study Medication	Outcome Variable	Outcome Data	Study Duration	p	Effect Size
Healy[24]	Single center in Britain	OL	n = 28	MTX (n = 19), LEF (n = 4), HC (n = 1), ETN (n = 4)	LDI, LDI basic, dactylitis scored 0-3, No. of dactylitic digits (tender /nontender), No. of dactylitic digits (tender)	Change at 6 mo: various treatments pooled, effect sizes reported	6 mo	N/A	LDI (0.99), LDI basic (0.9), dactylitis score (1.63), No. tender/ nondactylitic digits (0.77), No. tender dactylitic digits (1.27)
Antoni (IMPACT 1)[25]	Multicenter (n = 9 sites) in Europe, US, & Canada	DB-RPC	n = 104	INX vs Pbo	Dactylitis scored 0–3	Change at 16 wks (mean ± SD): INX = 1.94 ± 0.23, Pbo = 0.58 ± 0.20	16 wks	< 0.001	0.41
Antoni (IMPACT 2)[26]	Multicenter (n = 36 sites) in Europe, US, & Canada	DB-RPC	n = 200	INX vs Pbo	% with dactylitis of hands/feet	Change at 14 wks (% reduction in patients with dactylitis): INX = –23, Pbo = –13	14 wks	0.025	N/A
Mease[27]	Multicenter (n = 50 sites) in US, Canada, & Europe	DB-RPC	n = 249	ADM vs Pbo	Dactylitis scored 1–4	Results not provided. No statistical difference at 24 wks	24 wks	N/A	N/A
Kaltwasser (TOPAS)[28]	Multicenter (n = 31 sites) in Australia, Europe, Canada, & New Zealand	DB-RPC	n = 186	LEF vs Pbo	Dactylitis scored 1 to 4	Mean ± SD change from baseline at 24 wks: LEF = –0.9 ± 2.7, Pbo = –0.2 ± 2.4	24 wks	0.2	0.33
Salvarani[29]	Multicenter study in Europe	OL	n = 16	INX added to MTX	No. of dactylitic digits (tender)	Change at 30 wks: no dactylitis was observed during the study period	30 wks	N/A	N/A
Salvarani[30]	Multicenter study in Europe	OL	n = 99	SSZ vs CyA vs ST	No. of dactylitic digits	Change at 24 wks: not enough data to be clinically meaningful [Only 4 subjects developed dactylitis (1 SSZ, 2 CyA, 1 ST)]	24 wks	N/A	N/A
Clegg[31]	Multicenter study of US Veterans	DB-RPC	n = 221	SSZ vs Pbo	No. of dactylitic digits (tender & nontender)	Mean ± SD change from baseline at 36 wks: SSZ = –0.5 ± 4.2, Pbo = –0.9 ± 4.1	36 wks	0.43	0.2

*Primary data for this analysis generously provided by Janssen Pharmaceuticals. DB-RPC: Double-blinded, randomized, placebo-controlled trial, OL: Open-label study, N/A: Not applicable, DMARD: Disease-modifying antirheumatic drug, SD: Standard deviation, SEM: Standard error of the mean, IQR: Interquartile range, LDI: Leeds Dactylitis Index; APR: Apremilast, CZP: Certolizumab, UST: Ustekinumab, Pbo: Placebo, GOL: Golimumab, ADM: Adalimumab, MTX: Methotrexate, INX: Infliximab, ETN: Etanercept, CyA: Cyclosporin A, ANA: Anakinra, HC: Hydroxychloroquine, LEF: Leflunomide, SSZ: Sulfasalazine, ST: Standard therapy.

study was prospective from a historical cohort (10 years), another was a prospective followup case-control study, and the remaining 9 were open-label studies.

Of the 29 studies, 22 were multicenter with participation from North America, Europe, the Middle East, South Africa, Latin America, and Asia-Pacific countries. The remaining studies were single-center: 1 each from Canada, Italy, and Germany; and 2 each from Greece and the United Kingdom.

Therapeutic interventions were heterogeneous and included DMARD (methotrexate, hydroxychloroquine, leflunomide, cyclosporin A, and sulfasalazine), biologics (certolizumab, ustekinumab, golimumab, adalimumab, etanercept, infliximab, and anakinra), and the oral phosphodiesterase 4 inhibitor apremilast.

Dactylitis outcome measures were also heterogeneous and included the number of dactylitic digits (maximum 20 digits; either tender and/or nontender on 0–3 scale), percentage of patients with dactylitis, Leeds Dactylitis Index and its simplified version (LDI, LDI basic), and MRI dactylitis scores. Some studies used a simple count of dactylitic digits (based on clinician opinion), while others graded the severity 0–3 or 1–4, and all 20 digits were

counted. No studies of local steroid injections or NSAID were identified.

Because of the large variability in study designs and outcome measures, and poor availability of primary data, a metaanalysis could not be performed. Significant improvement ($p < 0.05$) in dactylitis compared to placebo was observed with the use of certolizumab in the RAPID-PsA trial[4] and with ustekinumab in the PSUMMIT1 trial[6]; in Phase II studies, with the use of golimumab in the GO-REVEAL trials[8,9]; with infliximab in the IMPACT1[21] and IMPACT2[22] trials; with a combination of infliximab plus methotrexate compared to methotrexate alone in an open-label study[11]; and with the use of adalimumab in prior treatment failures in other open-label studies[7,15].

In contrast, no significant benefit was demonstrated in RCT of apremilast (PALACE)[3], or adalimumab (ADEPT)[19], or an open-label adalimumab trial[23]; with the use of leflunomide (TOPAS)[28], or with the use of sulfasalazine in a multicenter study of US veterans[31].

Although an etanercept study (PRESTA) demonstrated improvement in dactylitis scores[16], a placebo-controlled trial with dactylitis as an endpoint is required. Elsewhere, the role of anakinra is still uncertain[14].

Measures of treatment effect. In the few cases where primary data were available, we calculated the effect sizes for the various therapeutic interventions used in the 29 included trials (Table 1). The best available data from RCT suggested that infliximab (effect size 0.41, IMPACT1)[21], certolizumab (effect size 0.50, RAPID-PsA)[4], and ustekinumab (effect size 0.29, pooled PSUMMIT1 and PSUMMIT2 data)[5,6] were likely to be efficacious, while effect sizes for leflunomide and sulfasalazine were 0.33 and 0.2, respectively, despite no significant difference between the treatment and placebo arms in these 2 studies[28,31].

Toxicity/safety aspects related to dactylitis. A review of toxicity/safety data revealed no evidence of adverse events related to dactylitis itself. Adverse events were those typically seen in trials of either psoriasis or PsA (i.e., liver toxicity, gastrointestinal manifestations, exacerbation of psoriasis, and incidence of malignancies and autoimmune diseases).

DISCUSSION

Conclusions and limitations. This brief review reveals the dearth of evidence for treating dactylitis in patients with PsA, with highly variable study designs, dactylitis assessments, and patient populations. The most commonly used therapies, NSAID and local corticosteroid injections, have not been formally assessed. DMARD alone may be mildly effective, but the trials have not been adequately powered. Apremilast demonstrated no significant benefit.

Of the biologic drugs tested, only ustekinumab, certolizumab, and infliximab seemed promising, with golimumab as another potential candidate. Etanercept requires more dedicated study to ascertain its efficacy, and adalimumab may be ineffective. The roles of anakinra and newer small molecules and biologic therapies are uncertain.

Because dactylitis may represent a composite of pathological features, it could be argued that an assessment of tenderness and swelling in the component parts (proximal interphalangeal joint and distal interphalangeal joint) is sufficient. However, important and potentially clinically-relevant information could be lost in this simplistic definition. Imaging studies have indicated that dactylitis is a complex, multicompartment disorder, with features including tenosynovitis, enthesitis, osteitis, synovitis, capsulitis, and soft-tissue swelling[32]. The clinical utility of inflammatory markers and imaging studies to distinguish hot versus cold dactylitis also deserves careful scrutiny. A clear understanding of onset, duration, persistence, anatomical location (hands vs feet), and morphology will be required. Further, the training of dermatologists and other clinicians to recognize and assess dactylitis will be important not only for future clinical trials, but also to hasten referral to a rheumatologist in community practice.

Given the importance and frequency of dactylitis in PsA, future studies should include both robust and quantifiable clinical indices (e.g., the LDI), as well as imaging modalities (e.g., MRI and ultrasound), the latter of which are particularly promising as valid and sensitive measures to assess dactylitis. Importantly, future investigations using dactylitis as a primary outcome measure will determine the most appropriate treatment for this painful and damaging condition.

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APPENDIX 1.

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