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Management of Dactylitis in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations

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ABSTRACT. *Objective*. This literature review aimed to identify the most efficacious current interventions for dactylitis and provide up-to-date scientific evidence to support the 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations on the management of psoriatic arthritis.
Methods. Original articles published from 2013 to 2020, registered in MEDLINE, Embase, and Cochrane Library, describing interventional trials and reporting dactylitis-related outcomes were included. The 20 members of the GRAPPA dactylitis group were divided into 9 subgroups according to treatment, and members of each group independently extracted data from articles/abstracts corresponding to their group by using a standardized data extraction form.
Results. Forty-nine publications were analyzed, representing 40 randomized clinical trials (RCTs) and including 16,752 patients. Dactylitis was assessed as a secondary outcome in 97.5% of these trials and more than 40% of RCTs did not employ a specific dactylitis measure or instrument.
Conclusion. The emergence of agents with novel mechanisms of action in recent years, such as interleukin 17 (IL-17), IL-12/23, IL-23, and Janus kinase inhibitors, has significantly expanded the available treatment options for dactylitis. This article points out the lack of consensus regarding dactylitis assessment and the paucity of data concerning the effect of local steroid injections, nonsteroidal antiinflammatory drugs, and conventional disease-modifying antirheumatic drugs. Clinical trials evaluating the effect of these traditional and low-cost medications used to treat dactylitis should be encouraged.

Key Indexing Terms: dactylitis, GRAPPA, psoriatic arthritis, treatment

Dactylitis is reported in approximately 40% of patients with psoriatic arthritis (PsA) and it is associated with higher disease activity scores and a lower probability of achieving minimal disease activity.[1,2] Due to its importance, the current inflammation of an entire digit (or history of dactylitis) confirmed by a rheumatologist is considered a component of the Classification Criteria for Psoriatic Arthritis (CASPAR).[3]

Since the last version of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations for the management of PsA, published in 2016,[4] there have been considerable advances in the treatment of dactylitis. These advances include the publication of additional evidence for drugs that have been used in the treatment of dactylitis for many years, such as methotrexate (MTX),[5-8] as well as the development of modern biologic agents with original mechanisms of action, such as interleukin (IL)-17, IL-12/23, and IL-23 inhibitors (IL-17i, IL-12/23i, and IL-23i, respectively), and the emergence of new small molecules, such as Janus kinase inhibitors (JAKi). Moreover, a clinical trial assessing dactylitis as the primary outcome was published[7] and the first head-to-head trials in PsA included dactylitis-related outcomes, allowing physicians to compare the efficacy of tumor necrosis factor inhibitors (TNFi) vs IL-17i[9,10] and TNFi vs JAKi in this domain.[11,12]

This literature review aimed to identify the most efficacious current interventions for dactylitis and provide up-to-date scientific evidence to support the 2021 GRAPPA recommendations on the management of PsA.

METHODS

The search strategy employed to update the 2021 GRAPPA recommendations on the management of PsA has been described in a previous methodology paper.[13] The first search was run on November 25, 2019, and an update was conducted on August 28, 2020. This search created a library of extracted data to support each domain group in their development of recommendations.

In the present review, the original articles in our database that were included were published from February 2013 to August 2020, described interventional trials (randomized double-blind clinical trials and open-label trials), and reported dactylitis-related outcomes. Abstracts from the American College of Rheumatology Annual Scientific Meeting and the Annual European Congress of Rheumatology, containing the same criteria and published from 2017 to 2020, were also analyzed. Only articles and abstracts written in English were included. Metaanalyses, systematic literature reviews, and letters to the editor were excluded, alongside manuscripts not reporting dactylitis as a separate outcome.

The 20 members of the GRAPPA dactylitis group were divided into 9 subgroups: (1) nonsteroidal antiinflammatory drugs (NSAIDs), steroids, and conventional disease-modifying antirrheumatic drugs (cDMARDs); (2) phosphodiesterase 4 inhibitors (PDE4i); (3) JAKi; (4) IL-12/23i; (5) IL-23i; (6) IL-17i; (7) TNFi; (8) other biotherapies; and (9) safety data. There were 2 groups with 3 members and 7 groups with 2 members. Members of each group independently extracted data from the articles/abstracts corresponding to their subgroup by using a standardized data extraction form. Characteristics of the randomized clinical trial (RCT), blinding (double-blind vs open-label), sample size, trial duration, interventions, dactylitis-related outcome measures, P values, and effect size were extracted from each study. The risk of bias of each publication included in the analysis was assessed according to 6 criteria: allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and presence/absence of early escape.

Ethics. This paper does not require IRB/animal approval.

RESULTS

Included studies. Forty-nine references (40 original articles and 9 abstracts) representing 40 RCTs were included in the review (Table).[5-11,14-55] The flowchart representing the selection algorithm is shown in the Figure.

Among these 49 publications, 17 (34.7%) reported trials evaluating IL-17i, 13 (26.5%) TNFi, 8 (16.3%) IL-23i, 6 (12.2%) JAKi, 4 (8.2%) PDE4i, 4 (8.2%) cDMARDs, and 3 (6.1%) IL-12/23i; the total sum exceeds 100% since some publications evaluated > 1 class of drug. Both the CTLA4-Ig abatacept (ABA) and the IL-6i clazakizumab (CLAZ) were evaluated using data from a single RCT.[42,43]

The 40 RCTs (described in these 49 publications) included 16,752 patients with PsA; most of the RCTs (90%, n = 36) were multicenter studies, which recruited patients from > 1 country. Only 1 RCT (2.6%) was conducted in a single center (Belgium)[19] and 3 RCTs (7.5%) involved several centers but in the same country (the Netherlands, Portugal, and the United Kingdom).[6-8] Among the 40 RCTs analyzed, 37 (92.5%) were double-blind studies and only 3 (7.5%) were open-label trials.[8,10,51]

Dactylitis-related outcomes. Dactylitis was assessed as a secondary or as exploratory outcomes in 39 (97.5%) of the 40 analyzed RCTs. Only 1 RCT (2.5%) evaluated dactylitis as the primary outcome.[7] The Dactylitis Severity Score (DSS) was the tool most often used to evaluate dactylitis and was employed in 11 (27.5%) of the 40 trials.[20] In DSS, each digit with dactylitis is evaluated on a scale of 0 to 3 (0 = no dactylitis, 1 = mild dactylitis, 2 = moderate dactylitis, 3 = severe dactylitis), and the total score is calculated as the sum of scores for all 20 digits (0-60).[20]

Of the 40 RCTs, the Leeds Dactylitis Index (LDI) was reported in 6 (15.0%), and its simplified version, the basic LDI (LDI-B), was described in 6 (15.0%).[56] The LDI measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot; a minimum difference of 10% defines a dactylitic digit. If ipsilateral and contralateral digits are involved, a table of normative values is used to provide the comparison. The ratio of circumference is multiplied by a tenderness score based on the Ritchie index, graded from 0 to 3 (LDI) or 0 for non-tender and 1 for tender

Table. Summary of the 49 publications evaluating the efficacy of therapeutic interventions on dactylitis-related outcomes in psoriatic arthritis.

Author and Publication Year (Study Name)	Type of Recruitment	Study Design	Study Size, n	Study Medication	Outcome(s)	Outcome Data	Study Duration, wks	P	Effect Size
Vieira-Sousa 2020 (GO-DACT)[7]	Multicenter (n = 11) in a single country (Portugal)	DB	44	GOL + MTX vs PBO + MTX	Primary outcome: median ΔDSS from BL to wk 24 Secondary outcomes: % of patients achieving DSS = 0, 20, 50, 70, and LDI = 20, 50, 70 at wk 24	GOL + MTX group was statistically superior to PBO + MTX (median 5 vs 2 [IQR not reported]). GOL + MTX group was statistically superior to PBO + MTX in the following outcomes: · DSS = 50 (85% vs 50%), · DSS = 70 (60% vs 18%), · LDI = 20 (100% vs 73%), · LDI = 50 (100% vs 68%), and · LDI = 70 (95% vs 41%). The proportion of patients achieving DSS = 0 and DSS = 20 were not different between groups.	24	0.03	–
Mease 2020 (SPIRIT-H2H 24 wk)[10]	Multicenter (n = 131) in several countries	OL	566	ADA vs IXE	% of patients with LDI-B = 0 at wk 24	No significant difference between IXE 88.1% (95% CI 78.3-97.9%) vs ADA 93.1% (86.6-99.6%).	24	0.66	–
Smolen 2020 (SPIRIT-H2H 52 wk)[14]	Multicenter (n = 131) in several countries	OL	566	ADA vs IXE	% of patients with LDI-B = 0 at wk 52	No significant difference between IXE 83.3% (95% CI 72.1-94.6%) vs ADA 81.0% (94% CI 70.9-91.1%).	52	0.62	–
McInnes 2020 (EXCEED)[9]	Multicenter (n = 156) in several countries	DB	853	ADA vs SEC	N (%) of patients with resolution of dactylitis at wk 24	No statistical difference between SEC (n = 130, 75%) vs ADA (n = 137, 70%); OR 1.29 (95% CI 0.75-2.22).	24	0.36	–
Husni 2020 (GO-VIBRANT)[15]	Multicenter (n = 89) in several countries	DB	480	GOL vs PBO	% of patients with DSS = 0 at wk 14 and wk 24; ΔDSS from BL to wk 52	Greater proportions of patients in the GOL group had DSS = 0 compared to PBO at wk 14 (74.6% vs 25.0%) and wk 24 (78.4% vs 35.5%). DSS mean change from baseline was only described at wk 52 after crossover: −8.9 (SD 10.1) in the PBO to GOL group vs −8.0 (SD 8.9) in the GOL group.	52	Not described	–
Kavanaugh 2017 (GO-VIBRANT)[16]	Multicenter (n = 89) in several countries	DB	480	GOL vs PBO	ΔDSS from BL to wk 24	There was no statistical difference in PBO (−5.0, SD 8.1) vs GOL (−8.2, SD 8.9).	24	< 0.001	0.38
Mease 2019 (SEAM PsA)[5]	Multicenter (n = 124) in 17 countries	DB	851	MTX + PBO vs ETN + PBO vs MTX + ETN	Mean ± SEM change from BL to wk 24 in LDI Patients with LDI = 0 at wk 24	There was no statistical difference among the 3 arms. BL: MTX + PBO (−128.8 ± 26.8), ETN + PBO (−119.1 ± 20.7), and ETN + MTX (−110.2 ± 22.7). There was no statistical difference among the 3 arms: MTX + PBO (65.2%), ETN + PBO (76.4%), and ETN + MTX (79.3%).	24	0.68 (ETN + MTX vs MTX + PBO) 0.85 (ETN + PBO vs MTX + PBO) 0.057 (ETN+ MTX vs MTX + PBO) 0.12 (ETN + PBO vs MTX + PBO)	0.40 (ETN+ PBO vs MTX + PBO) 0.72 (ETN + MTX vs MTX + PBO)

Table. Continued.

Author and Publication Year (Study Name)	Type of Recruitment	Study Design	Study Size, n	Study Medication	Outcome(s)	Outcome Data	Study Duration, wks	P	Effect Size
Coates 2016 (TICOPA)[8]	Multicenter (n = 8) in the UK	OL	188 (n = 59 with BL dactylitis)	MTX	ΔLDI-B from BL to wk 12	Median –59.7 (IQR –157.4 to –26.4).	48	0.03	–
					Patients with LDI-B = 0 at wk 12	37/59 (63%).		0.001	
Walsh 2018 (RAPID-PsA)[17]	Multicenter (n = 92) in several countries	DB	409	CZP vs PBO	ΔLDI from BL to wk 24	CZP combined arm (3.3, SD 11.4) vs PBO (5.5, SD 16.1).	216	Not described	0.16
					Patients with LDI = 0 at wk 24	CZP combined arm (67.3%) vs PBO (76.2%).			
Mease 2014 (RAPID-PsA)[18]	Multicenter (n = 92) in several countries	DB	409	CZP vs PBO	ΔLDI from BL to wk 24	CZP was superior to PBO concerning the decrease in LDI from BL to wk 24: CZP 200 mg Q2W (–40.7, SD 34.6), CZP 400 mg Q4W (–53.5, SD 69.1), vs PBO (–22.0, SD 46.9).	216	0.002 (CZP 200 mg Q2W vs PBO) < 0.001 (CZP 400 mg Q4W vs PBO)	0.45 (CZP 200 Q2W vs PBO) 0.53 (CZP 400 Q4W vs PBO)
Carron 2017 (CRESPA)[19]	Single center in Belgium	DB	60	GOL vs PBO	% of patients with dactylitis at wk 12	GOL was superior to PBO: 7.5% GOL vs 40% PBO.	24	0.004	–
					% of patients with dactylitis at wk 24	GOL was superior to PBO: 17.5% GOL vs 60.0% PBO.		0.003	
Van Mens 2019 (NCT01871649)[6]	Multicenter (n = 3) in a single country (The Netherlands)	DB	51	GOL + MTX vs PBO + MTX	No. of patients with dactylitis at wk 22	There was no statistical difference between GOL + MTX (n = 0) and PBO + MTX (n = 1).	22	0.31	–
Antoni 2005 (IMPACT)[20]	Multicenter (n = 9) in several countries	DB	104	IFX vs PBO	Mean DSS at wk 16	DSS was lower in IFX (29.2, SD 10.1) vs PBO (84.5, SD 10.1).	50	< 0.001	–
Mease 2005 (ADEPT)[21]	Multicenter (n = 50) in several countries.	DB	313	ADA vs PBO	ΔDSS from BL to wk 12	At wk 12, the mean improvement in dactylitis was greater in patients receiving ADA compared with those receiving PBO; however, these changes did not achieve statistical significance according to authors.	24	Not described	–
McInnes 2014 (NCT00809614)[22]	Multicenter (n = 11) in several countries	DB	42	SEC vs PBO	Mean LDI at BL, and wk 6, 12, and 24	SEC baseline: 2.7 (SD 2.3), wk 6: 2.9 (SD 2.4), wk 12: 2.5 (SD 1.6), wk 24: 3.1 (SD 1.5) PBO baseline: 1.6 (SD 2.3), wk 6: 2.1(SD 2.6), wk 12: 0.7 (SD 0.6), and wk 24: 1.9 (SD 2.2).	24	Not described	–
Mease 2015 (FUTURE 1)[23]	Multicenter (n = 104) in several countries	DB	606	SEC vs PBO	% of patients with resolution of dactylitis at wk 24	SEC was statistically superior to PBO: SEC (combined 75 mg + 150 mg groups) was 52.4% vs 15.5% in PBO.	24	< 0.005	–
McInnes 2015 (FUTURE 2)[24]	Multicenter (n = 76) in several countries	DB	397	SEC vs PBO	% of patients with resolution of dactylitis at wk 24	SEC (combined 75 mg + 150 mg + 300 mg group) was 47% vs 15% in PBO.	24	0.92	–

Table. Continued.

Author and Publication Year (Study Name)	Type of Recruitment	Study Design	Study Size, n	Study Medication	Outcome(s)	Outcome Data	Study Duration, wks	P	Effect Size
Kavanaugh 2016 (FUTURE 2)[25]	Multicenter (n = 76) in several countries	DB	397	SEC vs PBO	% of patients with resolution of dactylitis at wk 24	In TNFi-naïve subjects, SEC 300 mg and 150 mg were superior to PBO. SEC 300 mg was 54.8%, SEC 150 mg was 57.1%, and SEC 75 mg was 30.8%, vs 17.6% in PBO. In TNF-IR subjects, only the 300 mg dose was superior to PBO. SEC 300 mg was 60.0%, SEC 150 mg was 36.4%, and SEC 75 mg was 28.6%, vs 10.0% in PBO.	24	< 0.05 (SEC 300 mg vs PBO) < 0.05 (SEC 150 mg vs PBO) < 0.05 (SEC 300 mg vs PBO) > 0.05 (SEC 150 mg vs PBO)	–
Nash 2018 (FUTURE 3)[26]	Multicenter (n = 74) in several countries	DB	414	SEC vs PBO	N (%) of patients with resolution of dactylitis at wk 24	SEC 300 mg and 150 mg demonstrated superiority over PBO. SEC 300 mg: 22/46 (47.8%); SEC 150 mg 14/36 (38.9%); PBO 5/36 (13.9%).	24	< 0.01 (SEC 300 mg vs PBO) > 0.05 (SEC 150 mg vs PBO)	–
Kivitz 2019 (FUTURE 4)[27]	Multicenter (n = 58) in several countries	DB	341	SEC vs PBO	N (%) of patients with resolution of dactylitis at wk 16	SEC 150 mg did not achieve statistical significance compared to PBO. SEC 150 mg with load: 13/40 (32.5%); SEC 150 mg no load: 16/38 (42%); PBO 14/44 (31.8%).	24	> 0.05 (SEC 150 mg with load vs PBO) > 0.05 (SEC 150 mg no load vs PBO)	–
Mease 2018 (FUTURE 5)[28]	Multicenter (n = 172) in several countries	DB	996	SEC vs PBO	N (%) of patients with resolution of dactylitis at wk 16	SEC 300 mg and 150 mg (with load) demonstrated superiority over PBO: SEC 300 mg with load: 54/82 (65.9%); SEC 150 mg with load: 46/80 (57.5%); SEC 150 mg no load: 58/103 (56.3%); PBO: 40/124 (32.3%).	24	< 0.05 (SEC 300 mg load vs PBO) < 0.05 (SEC 150 mg load vs PBO) > 0.05 (SEC 150 mg no load vs PBO)	–
Kirkham 2020 (FUTURE 5) (post hoc analysis of subjects with dactylitis)[29]	Multicenter (n = 172) in several countries	DB	389	SEC vs PBO	% of patients with resolution of dactylitis at wk 16	SEC 300 mg with load was 67%, SEC 150 mg with load was 58%, and SEC 150 mg no load was 58%, vs 35% in PBO.	24	Not described	–
Ritchlin 2020 (pooled analysis FUTURE 2,3,4,5)[30]	Multicenter in several countries	DB	1803	SEC vs PBO	% of patients with resolution of dactylitis at wk 16, stratified by TSD ≤ 1 yr and > 2 yrs	SEC 300 mg with load was 53.8% (≤ 1 yr) and 57.0% (> 2 yrs), SEC 150 mg with load was 34.4% (≤ 1 yr) and 51.5% (> 2 yrs), and SEC 150 mg no load was 50.0% (≤ 1 yr) and 44.8% (> 2 yrs), vs 27.7% (≤ 1 yr) and 30.4% (> 2 yrs) in PBO.	16	TSD ≤ 1 year: < 0.05 (SEC 300 mg load vs PBO) > 0.05 (SEC 150 mg with or without load vs PBO) TSD > 2 years: < 0.05 (SEC 300 mg load vs PBO) < 0.05 (SEC 150 mg with or without load vs PBO)	–

Table. Continued.

Author and Publication Year (Study Name)	Type of Recruitment	Study Design	Study Size, n	Study Medication	Outcome(s)	Outcome Data	Study Duration, wks	P	Effect Size
Gladman 2019 (integrated data SPIRIT P1 and P2)[31]	Multicenter in several countries	DB	679	IXE vs PBO	% of patients with LDI = 0 at wk 24	IXEQ4W was 78% and IXEQ2W was 65%, vs 24% in PBO.	24	< 0.001	–
Mease 2021 (pooled AMVISION-1 and -2)[32]	Multicenter in several countries	DB	962	BRO vs PBO	% of patients with resolution of dactylitis at wk 16	BRO 140 mg (40.9%) and 210 mg (50.8%) were statistically superior vs PBO (24.2%)	24	< 0.05 (BRO 140 mg vs PBO) < 0.001 (BRO 210 mg vs PBO)	–
					% of patients with resolution of dactylitis at wk 24	BRO 140 mg (43.0%) and 210 mg (60.1%) were statistically superior vs PBO (19.8%).		< 0.01 (BRO 140 mg vs PBO) < 0.001 (BRO 210 mg vs PBO)	
Mease 2014 (NCT01516957)[33]	Multicenter (n = 29) in USA and Canada	DB	168	BRO vs PBO	Change in the no. of dactylitis digits in a 0-20 count from BL at wk 12	No significant difference between the group receiving BRO 140 mg, BRO 210 mg, and PBO. Change from BL to wk 12 was −1.4 for BRO 140 mg and −2.0 for BRO 210 mg, vs −0.5 in PBO.	240	0.28 (BRO 140 mg vs PBO) 0.11 (BRO 210 mg vs PBO)	–
Deodhar 2020 (DISCOVER-1)[34]	Multicenter (n = 86) in several countries	DB	381	GUS vs PBO	% of patients with DSS = 0 at wk 24	GUS 100 mg Q4W was 64% and GUS 100 mg Q8W was 65%, vs 49 in PBO. Pooled results with DISCOVER-2 were described in the next reference.	52	0.01 (GUS Q4W vs PBO) 0.03 (GUS Q8W vs PBO)	–
Mease 2020 (DISCOVER-2)[35]	Multicenter (n = 118) in several countries	DB	739	GUS vs PBO	% of patients with DSS = 0 at wk 24	GUS was statistically superior to PBO to achieve resolution of dactylitis at wk 24. GUS Q4W was 64% and GUS Q8W was 59%, vs 42% in PBO.	24	0.01 (GUS Q4W vs PBO) 0.03 (GUS Q8W vs PBO)	–
					ΔDSS from BL to wk 24	LSM (95% CI) change in DSS: GUS Q4W −5.97 (−6.84 to −5.11); GUS Q8W −6.10 (−6.92 to −5.27); PBO 4.21 (−5.05 to −3.36).		Not described	
Mease 2020 (NCT02980692)[36]	Multicenter (n = 74) in several countries	DB	391	TIL vs PBO	ΔLDI from BL to wk 52	TIL 200 mg Q4W was −21.4 (SD 37.1), TIL 200 mg Q12W was −42.1 (SD 76.7), TIL 100 mg Q12W was −41.6 (SD 89.3), TIL 20 → 200 mg Q12W was −56.5 (123.4), and PBO → TIL 200 mg Q12W was −81.5 (173.0).	52	Not described	–
Papp 2019 (NCT02986373)[37]	Multicenter, no. of centers not provided in the reference	DB	145	RZB	ΔLDI from BL to wk 52	Mean change BL in patients receiving RZB was −74.5.	52	Not described (no comparator group)	–
Mease 2017 (NCT02719171)[38]	Multicenter, no. of centers not provided in the reference	DB	185	RZB vs PBO	LSM change from BL to wk 16 in a simple count of digits (0-20)	Arm 1 (RZB 150 mg at wk 0, 4, 8, 12, and 16) was −0.5, Arm 2 (RZB 150 mg at wk 0, 4, and 16) was −2.5, Arm 3 (RZB 150 mg at wk 0 and 12) was −3.1, Arm 4 (RZB 75 mg single dose at wk 0) was −3.6, Arms 1 + 2 was −1.6, and Arm 5 (PBO) was −2.8.	15	Not described	–

Table. Continued.

Author and Publication Year (Study Name)	Type of Recruitment	Study Design	Study Size, n	Study Medication	Outcome(s)	Outcome Data	Study Duration, wks	*P*	Effect Size
McInnes 2020 (DISCOVER-2)[39]	Multicenter (n = 118) in several countries	DB	739	GUS vs PBO	% patients with DSS = 0 at wk 24 and 52	At wk 24: GUS Q4W was 68.1% and GUS Q8W was 60.7%, vs PBO at 41.1%. At wk 52: GUS Q4W was 81.1% and GUS Q8W was 81.9%, vs PBO → GUS Q4W at 78.5%.	52	Not described	–
McGonagle 2020 (pooled analysis of DISCOVER-1 and -2)[40]	Multicenter in several countries	DB	1120	GUS vs PBO	ΔDSS from BL to wk 16	GUS Q4W was −5.51 and GUS Q8W was −5.43, vs PBO at −3.70.	24	Unadjusted nominal < 0.01 between GUS Q4W, GUS Q8W (each vs PBO)	–
					ΔDSS from BL to wk 24	GUS Q4W was −5.97 and GUS Q8W was −6.10, vs PBO at −4.21.		Unadjusted nominal < 0.01 between GUS Q4W and PBO. Unadjusted nominal < 0.001 between GUS Q8W and PBO (not controlled for multiplicity, interpret only as supportive)	
Ritchlin 2020 (DISCOVER-1)[41]	Multicenter (n = 86) in several countries	DB	381	GUS vs PBO	% of patients with DSS = 0 at wk 24 and wk 52	GUS Q4W at wk 24 was 64.9%, and 78.4% at wk 52. GUS Q8W at wk 24 was 67.3%, and 79.5% at wk 52. PBO at wk 24 was 61.7%. PBO → GUS Q4W was 81.4% at wk 52.	52	Not described	–
Mease 2017 (ASTRAEA)[42]	Multicenter (n = 76) in several countries	DB	424	ABA vs PBO	% of patients with LDI-B score = 0 at wk 24	ABA 125 mg weekly 44.3% (95% CI 31.8-56.7) vs PBO at 34.0% (95% CI 20.9-47.1).	24	Not tested because of failure in hierarchical significance	–
Mease 2016 (NCT01490450)[43]	Multicenter (n = 44) in several countries	DB	165	CLAZ vs PBO	Mean count of dactylitic digits at wk 24	PBO was 2.5 (SD 3.8), CLAZ 25 mg was 1.4 (SD 2.1), CLAZ 100 mg was 0.2 (SD 0.4), and CLAZ 200 mg was 0.8 (SD 1.5).	24	Not described	–
Kavanaugh 2015 (PSUMMIT 1, extension study, crossover at wk 24)[44]	Multicenter (n = 104) in several countries	DB	490	UST	ΔDSS from BL to wk 100	At wk 100, the 3 treatment groups (UST 45 mg, UST 90 mg, and PBO → UST 45 mg) all had a median score improvement of 3.0 and a median % improvement of 100%. In the combined UST group, the % of patients with ≥ 1 digits with residual dactylitis continued to decrease from wk 52 (42.6%) through wk 100 (31.8%).	100	Not described	–
Ritchlin 2014 (PSUMMIT 2)[45]	Multicenter (n = 71) in several countries	DB	312	UST vs PBO	% of patients with dactylitis at wk 24	Numeric, but not significant, improvement was observed among the smaller no. (n = 127) of patients with baseline dactylitis in the UST 90 mg group vs placebo. PBO was 75.8%, UST 45 mg was 65.2%, UST 90 mg was 57.9%, and the combined UST group was 61.9%.	24	> 0.05 (UST 90 mg vs PBO)	–

Table. Continued.

Author and Publication Year (Study Name)	Type of Recruitment	Study Design	Study Size, n	Study Medication	Outcome(s)	Outcome Data	Study Duration, wks	P	Effect Size
McInnes 2013 (PSUMMIT 1)[46]	Multicenter (n = 104) in several countries	DB	615	UST vs PBO	% of patients with dactylitis at wk 24	Significantly lower proportions of patients with dactylitis in the combined 45 mg/90 mg UST group (56.2%) vs PBO arm (76.1%).	52	0.005 (45 mg vs PBO) 0.004 (90 mg vs PBO) 0.001 (combined UST groups vs PBO)	–
Mease 2018 (EQUATOR)[47]	Multicenter (n = 25) in several countries	DB	131	FILGO vs PBO	ΔLDI from BL to wk 16	It was identified during blinded data review that dactylitis was not scored uniformly across all centers and thus authors decided not to report the results for this outcome.	16	Not described	–
Mease 2017 (OPAL BROADEN)[48]	Multicenter (n = 126) in several countries	DB	422	TOF vs PBO	ΔDSS from BL to wk 12	TOF 10 mg was numerically superior to PBO whereas 5 mg was not.	12	Not tested because of failure in hierarchical significance	–
Gladman 2017 (OPAL BEYOND)[49]	Multicenter (n = 98) in several countries	DB	395	TOF vs PBO	ΔDSS from BL to wk 12	TOF 10 mg and 5 mg were numerically superior to PBO.	12	Not tested because of failure in hierarchical significance	–
McInnes 2020 (SELECT PsA1)[11]	Multicenter (n = 374) in several countries	DB	1705	UPA vs ADA vs PBO	% of patients with LDI = 0 at wk 24	UPA 15 mg (77 %) and 30 mg (80%) showed significantly more dactylitis resolution compared to PBO (40%) and similar to ADA (74%).	24	< 0.001 (UPA vs PBO) > 0.05 (UPA vs ADA)	–
Orbai 2020 (pooled analysis OPAL BROADEN/ OPAL BEYOND)[50]	Multicenter in several countries	DB	373	TOF vs PBO	ΔDSS from BL to wk 4, 12, and 24; dactylitic digits count (mean/SE)	Patients treated with TOF had cumulative improvements from BL to month 6 in DSS score and in the no. of dactylitic digits.	24	Not described	–
Nash 2019 (OPAL BALANCE)[51]	Multicenter (n = 153) in several countries	OL LTE	180	TOF vs TOF + MTX	% of patients maintaining DSS = 0 during 12 mos among those with DSS = 0 in baseline	Near 100% in both groups.	48	Not described	–
Kavanaugh 2014 (PALACE 1)[52]	Multicenter (n = 83) in several countries	DB	504	APR vs PBO	ΔDSS from BL to wk 24	DSS LSM change (SE):PBO was −1.3 (SE 0.27), APR 20 mg BID was −2.0 (SE 0.30), and APR 30 mg BID was −1.8 (SE 0.27).	24	0.07 (PBO vs APR 20 mg BID) 0.17 (PBO vs APR 30 mg BID)	–
					% of patients with DSS = 0 at wk 24	APR 20 mg BID (50.9%) and APR 30 mg BID (47.7%) vs PBO (40.9%).		> 0.05	

Table. Continued.

Author and Publication Year (Study Name)	Type of Recruitment	Study Design	Study Size, n	Study Medication	Outcome(s)	Outcome Data	Study Duration, wks	*P*	Effect Size
Edwards 2016 (PALACE 3)[53]	Multicenter (n = 91) in several countries	DB	505	APR vs PBO	ΔDSS from BL to wk 24	In patients with dactylitis at BL, ΔDSS was significantly improved for APR 30 mg (−2.4). Results for APR 20 mg did not reach statistical significance (−1.6) vs PBO (−1.4).	24	0.04 (APR 30 mg BID vs PBO) NS (APR 20 mg BID vs PBO)	–
Gladman 2018 (pooled analysis PALACE 1-3)[54]	Multicenter in several countries	DB	1493	APR vs PBO	ΔDSS from BL to wk 24 % of patients with DSS = 0	APR 30 mg BID was statistically superior to placebo BL (−1.8 vs −1.3). PBO (39.0%), APR 20 mg BID (45.9), and APR 30 mg BID (46.2%).	24	< 0.01 > 0.05	0.15
Wells 2018 (PALACE 4)[55]	Multicenter (n = 118) in several countries	DB	527	APR vs PBO	Change in dactylitis count (0-20) from BL to wk 24	Mean PBO (−0.9, SD 3.0), APR 20 mg BID (−1.8, SD 2.9), and APR 30 mg BID (−1.9, SD 3.3).	52	< 0.5 (PBO vs APR 30 mg BID) < 0.5 (PBO vs APR 20 mg BID)	0.32

Total duration of the study reported in the manuscript. ABA: abatacept; ADA: adalimumab; APR: apremilast; BID: twice a day; BRO: brodalumab; DB: double blind; BL: baseline; CLAZ: clazakizumab; CZP: certolizumab pegol; ΔDSS: mean change in Dactylitis Severity Score; DSS: Dactylitis Severity Score; DSS 20/50/70: a 20/50/70% improvement in the Dactylitis Severity Score; ETN: etanercept; FILGO: filgotinib; GOL: golimumab; GUS: guselkumab; H2H: head-to-head; IFX: infliximab; IQR: interquartile rate; LDI: Leeds Dactylitis Index; IXE: ixekizumab; ΔLDI: change in Leeds Dactylitis Index; LDI-B: Leeds Dactylitis Index basic version; LDI 20/50/70: a 20/50/70 % improvement in Leeds Dactylitis Index; LSM: least squares mean; LTE: long-term extension; MTX: methotrexate; OL: open-label; OR: odds ratio; PBO: placebo; PsA: psoriatic arthritis; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; RZB: risankizumab; SE: standard error; SEC: secukinumab; SEM: standard error of mean; TIL: tildrakizumab; TNF: tumour necrosis factor; TNF-IR: patients with inadequate response to tumor necrosis factor agents; TOF: tofacitinib; TSD: time since diagnosis; UPA: upadacitinib; UST: ustekinumab.
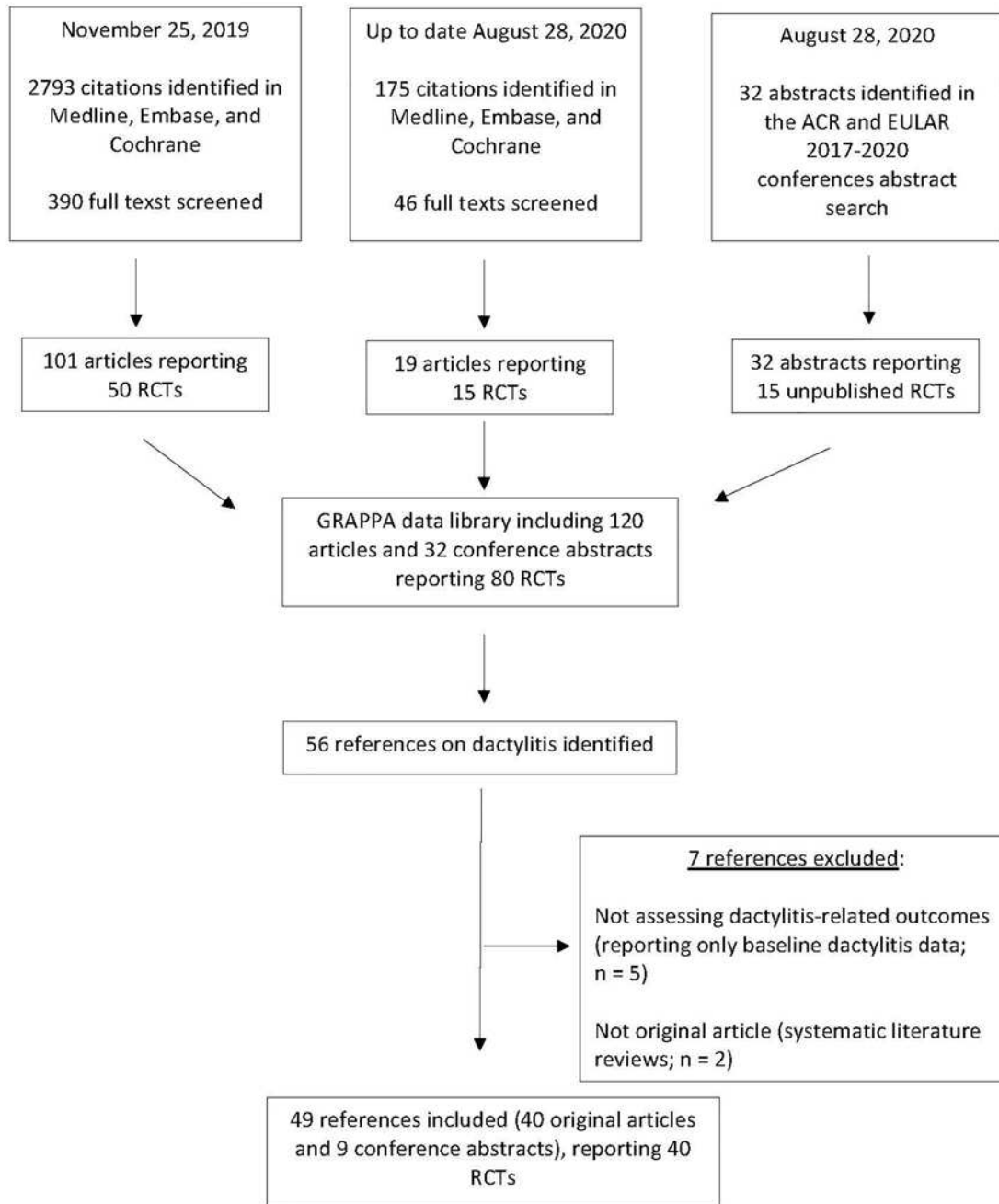
Figure. Flowchart demonstrating the selection of references included in the analysis. GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; RCTs: randomized controlled trials.

(LDI-B). The results from each digit with dactylitis are then summed to produce a final score.[56]

Of the 40 RCTs, 17 (42.5%) did not employ a specific dactylitis measure or instrument; they employed a simple count of digits with dactylitis (0-20) or reported the number and percent of patients with dactylitis. A single study (GO-DACT)[7] employed 2 different tools to evaluate dactylitis: the DSS as the primary outcome and the LDI as a secondary outcome.[20,56]

Even when RCTs used the same tool, results were described in different ways. The DSS, for example, was reported as mean change from baseline, number and percent of patients with resolution of dactylitis (DSS = 0), number and percent of patients with a 20%, 50%, or 70% improvement in the DSS, or the number and percent of patients with a DSS ≥ 1.

Dactylitis-related outcomes were mainly collected at week 24 (19/40 RCTs, 47.5%), week 16 (9/40 RCTs, 22.5%), and week 12 (9/40 RCTs, 22.5%).

Because of the large variability in study designs and outcome measures, a metaanalysis could not be performed. The present review did not find any new RCTs evaluating the effect of NSAIDs and steroids on dactylitis.

cDMARDs. There were no new publications comparing

the effect of cDMARDs vs placebo or comparing different cDMARDs. Of the 40 RCTs, 3 (7.5%) compared MTX monotherapy with TNFis and had contradictory results.[5-7] A study with a small sample size (n = 51) found no statistical difference between golimumab (GOL)/MTX combination and MTX monotherapy regarding the number of patients with dactylitis at week 22.[6] This was the same conclusion from the large multicenter trial SEAM-PsA, which included 851 subjects and found no statistical difference among etanercept (ETN)/MTX combination, ETN monotherapy, and MTX monotherapy.[5] However, another study with 44 subjects, which evaluated dactylitis as the primary outcome, reported that GOL/MTX combination was statistically superior to MTX monotherapy when the decrease in DSS from baseline to week 24 was studied.[7]

In the open-label strategy trial (TICOPA [Tight Control in Psoriatic Arthritis]), where treat-to-target was compared with standard care, patients receiving MTX had a significant improvement in LDI score at 12 weeks, and 37 of 59 patients with dactylitis at baseline had complete resolution by 12 weeks.[8]

Although the beneficial effect of MTX on dactylitis seemed to be similar to TNFi in the reported trials, no definite conclusion could be drawn regarding MTX effect size because of the absence of a placebo group in all analyzed trials.

TNFi. Thirteen publications (13/49, 26.5%) evaluating the effect of TNFi on dactylitis described 10 RCTs (10/40, 25.0%). TNFi were effective agents in the treatment of dactylitis in PsA, with at least 5 RCTs demonstrating the superiority of TNFi over placebo in the treatment of dactylitis; 3 trials were with GOL (GO-DACT [Efficacy of Golimumab in Combination With MTX Versus MTX Monotherapy, in Improving Dactylitis, in MTX naïve Psoriatic Arthritis Patients], GO-VIBRANT, and CRESPA [Clinical Remission in Patients With Early Peripheral Spondyloarthritis (SpA) According to ASAS Criteria]),[7,16,19] 1 trial was with certolizumab pegol (CZP; RAPID-PsA),[18] and 1 trial was with infliximab (IFX; IMPACT).[20]

IL-17i. Fourteen publications (14/49, 28.6%) reported 13 RCTs (13/40, 32.5%): 7 trials with secukinumab (SEC), 3 with ixekizumab (IXE), and 3 with brodalumab (BRO). SEC (300 mg and 150 mg) were deemed superior to placebo in terms of dactylitis-related outcomes.[25,26,28,29] In a pooled analysis of SPIRIT P1 and SPIRIT P2 trials, significantly higher proportions of patients receiving IXE every 4 weeks (78%) and IXE every 2 weeks (65%) experienced resolution of dactylitis at week 24 compared to placebo (24%; $P < 0.001$).[31] One phase II and 2 phase III RCTs demonstrated the efficacy of BRO over placebo in the treatment of dactylitis.[32,33] Another IL-17i, the dual IL-17A and IL-17F inhibitor bimekizumab, is being studied, but positive results were published after the conclusion of the systematic literature review and consequently not included in the present analysis.[57]

IL-12/23i. Three references (3/49, 6.1%) evaluated the effect of ustekinumab (UST) on dactylitis and described the results of PSUMMIT 1 and 2 clinical trials[44-46]; both doses (45 mg and 90 mg) were considered statistically superior to placebo when the proportion of patients with dactylitis at week 24 was analyzed.[44-46]

IL-23i. Eight references (8/49, 16.3%) evaluating 5 RCTs (5/40, 12.5%) were found; these references described 5 studies with guselkumab (GUS), 2 with risankizumab (RZB), and 1 with tildrakizumab (TIL).[34-41] The pooled analysis of DISCOVER-1 (which included 32% of patients with previous failure or intolerance to TNFi) and DISCOVER-2 trials (which included only patients without previous exposure to TNFi) demonstrated that GUS was statistically superior to placebo regarding the resolution of dactylitis (DSS = 0) at week 24.[40]

An open-label extension of a phase II RCT,[37] which included 24.1% of patients with previous exposure to TNFi, demonstrated a 74.5-point decrease in the mean LDI score from baseline to week 52 in patients receiving RZB (pooled RZB arms).

In a phase II study, the LDI mean change from baseline to week 52 was reported for different doses of TIL, but comparison with the placebo arm was not provided.[36]

The analysis of the 5 RCTs included in this review suggest there is efficacy of IL-23i in the treatment of dactylitis in patients with PsA, with and without previous exposure to TNFi, although an effect size could not be calculated.[34-41]

Other biotherapies. A single study (ASTRAEA [Active Psoriatic Arthritis Randomized Trial]) evaluated the effect of the CTLA4-Ig ABA on dactylitis and found no difference between the proportion of patients achieving resolution of dactylitis (LDI-B score = 0) at week 24 between ABA (44.3%, 95% CI 31.8-56.7) and placebo (34%, 95% CI 20.9-47.1).[42]

· *CLAZ.* A single phase II RCT described the mean count of dactylitic digits at week 24 with placebo (2.5, SD 3.8), the IL-6i CLAZ 25 mg (1.4, SD 2.1), 100 mg (0.2, SD 0.4), and 200 mg (0.8, SD 1.5), but no statistical test or effect size was provided.[43]

· *PDE4i.* Four publications (4/49, 8.2%) evaluated the efficacy of apremilast in PsA and reported the results of 4 RCTs (PALACE [Psoriatic Arthritis Long-term Assessment of Clinical Efficacy] 1 to 4).[52-55] The pooled preplanned analysis of patients with dactylitis included in PALACE 1, 2, and 3 demonstrated the superiority of apremilast (30 mg) over placebo regarding the mean change in dactylitis count from baseline to week 24.[54]

· *JAKi.* Six references (6/49, 12.2%) described the effect of JAKis on dactylitis in 5 RCTs (5/40, 12.5%).[11,47-51] Three RCTs evaluating the JAK1/3 inhibitor tofacitinib (TOF) were included in the analysis (OPAL [Oral Psoriatic Arthritis Trial] BROADEN, BEYOND, and BALANCE).[48,49,51] The literature search also retrieved 2 references evaluating the JAK-1 selective agents upadacitinib (UPA; SELECT-PsA 1 trial)[11] and filgotinib (FILGO; EQUATOR).[47]

In a pooled post hoc analysis of 2 trials (OPAL BROADEN and BEYOND), patients treated with TOF had cumulative improvement from baseline to 6 months in the DSS and in the resolution of the number of dactylitic digits.[50]

Patients taking UPA (15 mg/day and 30 mg/day) showed significantly more dactylitis resolution compared to the placebo group in SELECT-PsA 1 study.[11]

The effect of FILGO on the mean LDI change from baseline to week 16 was not statistically different from placebo but the analysis was hampered because the outcome assessment was performed differently across centers, according to authors.[47]

Head-to-head trials evaluating dactylitis-related outcomes. Two RCTs directly compared the effect of IL-17i vs TNFi in PsA and found a similar effect of these agents on musculoskeletal outcomes, including the proportion of patients achieving resolution of dactylitis at week 24.[9,10]

A single RCT compared JAKi with TNFi and found that the improvement in dactylitis disease activity was similar between UPA and adalimumab (ADA); the proportion of patients achieving complete resolution of dactylitis (LDI = 0) at week 24 was 77%, 80%, and 74% for subjects receiving UPA 15 mg/day, UPA 30 mg/day, and ADA, respectively.[11,12]

Risk of bias. The assessment of risk of bias in the 49 publications included in the analysis is shown in the Supplementary Table (available from the authors upon request).[5-11,14-55]

DISCUSSION

In this review, several points about the treatment of dactylitis in PsA were observed: (1) the paucity of data concerning the effect of conventional drugs (such as local steroid injections, NSAIDs, and cDMARDs); (2) the heterogeneity in the assessment of dactylitis (with different outcome measures reported across recent publications); and (3) the paucity of RCTs evaluating dactylitis as the primary outcome. In addition, the emergence of agents with novel mechanisms of action in recent years, such as IL-17i, IL-12/23i, IL-23i, and JAKis, has significantly enlarged the available treatment options for dactylitis.

Although MTX is the most prescribed cDMARD worldwide for the treatment of PsA, its real effect size on dactylitis is uncertain since studies comparing MTX to PBO did not include dactylitis-related outcomes.[58-61] Moreover, trials comparing TNFi against MTX did not include a placebo arm.[5-7]

As in the present review, RCTs evaluating local steroid injections or NSAIDs were not identified in the previous review published by the GRAPPA dactylitis study group in 2014,[62] but these interventions continue to be used in clinical practice based on expert opinion, despite the absence of strong scientific evidence supporting their use.

On the issue pertaining to measures of outcome, this review showed that more than 40% of trials did not adopt validated tools for dactylitis assessment. When a specific tool was used, the DSS[20] and LDI[56] were the most employed; however, results reporting was heterogeneous across publications. This highlighted the need for a consensus on tools to evaluate dactylitis in PsA. An agreement among researchers on how and when to assess dactylitis in RCTs and how dactylitis outcomes should be reported in subsequent publications would be important to facilitate comparison across different drugs, data pooling, and future metaanalyses.

Moreover, dactylitis assessment was a secondary or exploratory outcome in 97% of RCTs, meaning such studies were underpowered to demonstrate a difference between the investigational product and the control group regarding this outcome. In addition, some trials had only a small number of patients with dactylitis at baseline. Pre-defined pooled analysis of RCTs evaluating the same drug and with similar protocol were very useful to increase sample size, thus avoiding a type 2 statistical error,

in which the failure to demonstrate a difference between drugs occurs because of lack of power.

In several studies, the efficacy of the medication in dactylitis could not be tested because of failure to meet significance in the hierarchical chain prior to this point.[42,49,51] Subsequent trials analyzing dactylitis as the primary outcome would be desirable.

Currently, there is evidence (see Table)[5-11,14-55] to support the prescription of TNFi, IL-17i, IL-12/23i, IL-23i, JAKi, and PDE4i for the treatment of dactylitis. Other interventions such as MTX, NSAIDs, steroid injections, and CTLA4-Ig can also be used in the treatment of dactylitis, but there is weaker scientific evidence to support them.

Moreover, direct comparisons between drugs with different mechanisms of action are now available. RCTs evaluating IL-17i vs TNFi[9,10] and JAKi vs TNFi[11,12] revealed a similar efficacy of these drugs on dactylitis-related outcomes. Head-to-head trials involving other mechanisms of actions such as IL-12/23i and IL-23i are still lacking, as is comparison among protein kinase inhibitors with different JAK selectivity.

In conclusion, the therapeutic armamentarium for the treatment of dactylitis in PsA has been substantially enlarged in the last few years with emergence of new biologic agents and JAKi, although limited scientific evidence has emerged for low-cost and widely available drugs such as steroid injections, NSAIDs, and cDMARDs. Additionally, there is much heterogeneity in the assessment and reporting of dactylitis in recent publications. Expert consensus statements regarding the most appropriate tools to evaluate dactylitis and the most adequate method to report results are needed. Clinical trials evaluating the effect of traditional and low-cost medications used to treat dactylitis should be encouraged, as well as those evaluating dactylitis as the primary outcome.

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