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Original article

What does evidence-based medicine tell us about treatments for different subtypes of psoriatic arthritis? A systematic literature review on randomized controlled trials

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Abstract

Objective. PsA is a heterogeneous disease with various subtypes of joint manifestations, which can affect the homogeneity of randomized controlled trials (RCTs). The aim of this systematic literature review was to evaluate the inclusion criteria, demographics and outcomes of RCTs to see whether the whole spectrum of PsA was represented.

Methods. Medline, EMBASE and Cochrane databases were screened for RCTs on the efficacy of any treatment for PsA up to 4 October 2016 to investigate the inclusion criteria, demographics, outcomes and efficacy.

Results. Two thousand and sixty-eight abstracts were identified at screening; 76 articles and 52 conference proceedings were included in the final analysis. The main inclusion criteria always included the number of active joints and never axial symptoms, enthesitis nor dactylitis. Only 10 studies provided information about subtypes, of which symmetrical polyarthritis was the main subtype. Mean (S.D.) tender and swollen joints were between 7.8 and 35.8 (1.8–22.1) and between 5.2 and 25.2 (1.5–16.2), respectively. All studies had responses in joint counts as their primary outcome. Responses in enthesitis and dactylitis were usually secondary or tertiary outcomes. Response in BASDAI was among the outcomes in four studies. The comparison of efficacy in polyarticular *vs* oligoarticular disease was given in three studies, whereas no information was available for DIP joint disease or arthritis mutilans.

Conclusion. There is evidence in the literature to guide clinicians on how to treat PsA patients with polyarticular disease, but there is a gap in knowledge about the other subtypes.

Protocol registration. The study protocol is registered at PROSPERO (CRD42017053907).

Key words: psoriatic arthritis, randomized controlled trials, outcomes, axial disease, enthesitis, dactylitis, inclusion criteria

Key messages

- Randomized controlled trials in PsA mainly focus on peripheral disease with polyarticular pattern.
- Axial symptoms, enthesitis or dactylitis are not included in the inclusion criteria in any randomized controlled trials in PsA.
- There is a gap of knowledge on PsA treatment for subtypes other than polyarticular disease.

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ORIGINAL ARTICLE

Introduction

PsA is a heterogeneous disease with complex musculoskeletal and extra-articular manifestations. In 1973, Moll and Wright described five subgroups of PsA: symmetrical polyarthritis, asymmetrical oligoarthritis, DIP joint arthritis, spondylitis and arthritis mutilans [1]. There is no consistency across observational studies about the prevalence of these subtypes, probably owing to the lack of clear definitions [1–6]. In addition, the musculoskeletal manifestations are not limited to the joints; enthesitis and dactylitis are also frequent and included in the classification criteria for PsA [7]. From the perspective of musculoskeletal disease, the current treatment recommendations by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and EULAR Groups suggest treatment according to the presence of peripheral arthritis, axial disease, enthesitis and dactylitis (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) without specifying further subtypes of peripheral arthritis [8, 9].

The aim of this systematic literature review was to evaluate the following: (i) the inclusion criteria necessary to be enrolled in randomized controlled trials (RCTs) to ascertain whether different disease subtypes were targeted during the enrolment; (ii) whether different arthritis subgroups have been differentiated in the included patient population; (iii) the primary and secondary outcomes assessed in RCTs; and (iv) whether efficacy data are given for the subgroups.

Method

Search and selection strategy

The literature search was performed on 4 October 2016. Medline, EMBASE and Cochrane databases were searched by a medical librarian to find primary references. ‘Arthritis, psoriatic’, ‘psoriatic (arthritis or arthropathy) or seronegative arthritis’, ‘randomized controlled trial’ and ‘clinical trials’ were used as keywords or medical subject headings. The selection criteria for articles and abstracts were studies in patients with a diagnosis of PsA; RCTs; adult (age $\geq$18 years); and being given at least one of the following drugs: abatacept, adalimumab, alafacept, apremilast, brodalumab, celecoxib, certolizumab, clazakizumab, ciclosporin, efalizumab, etanercept, golimumab, infliximab, ixekizumab, leflunomid, methotrexate, onercept, secukinumab, sulphasalazin (SSZ) and ustekinumab. We excluded articles that had objectives other than the efficacy of any drug or different study groups (other than PsA), inaccessible crucial data, as well as cross-sectional studies, case reports, reviews, duplications, meta-analyses, systematic literature reviews and consensus reports and languages other than English. The study protocol is registered at International prospective register of systematic reviews (PROSPERO) (CRD42017053907).

General data extraction

The titles and abstracts were independently screened by two investigators (S.B.U. and C.I.). The discrepancies went for a full text review. During the full text review, disagreements were discussed with a third investigator (S.Z.A.) and a decision was made according to consensus. Articles not fulfilling all the selection criteria were excluded, and the reason for exclusion was recorded. The following data were retrieved: treatment arms and patient numbers, inclusion criteria, description of patient subgroups (symmetrical polyarticular, asymmetrical oligoarticular, axial, DIP joint disease and arthritis mutilans), demographics including the number of tender and swollen joints, enthesitis and dactylitis assessments and BASDAI, outcomes assessed in the studies, results and whether results were given separately for different PsA subgroups. The results of this systematic literature review were summarized in three groups: the inclusion criteria and demographics, outcomes and results of the studies. The Cochrane Collaboration tool was used to assess risk of bias.

Results

Two thousand and sixty-eight potential articles were identified, 250 of which were abstracts from proceedings of meetings. The reasons for exclusion at each step are given in Fig. 1.

Seventy-six articles (31 original articles [10–40], 45 long-term follow-ups or additional analyses of the same patient population [41–85]) and 52 conference proceedings [86–137] were included in the present analysis. The summary for the inclusion criteria and patient demographics is based only on the original studies, which by rule is identical for the sub-studies. As the outcomes and the results may be different for the sub-studies, these data are given for all studies included.

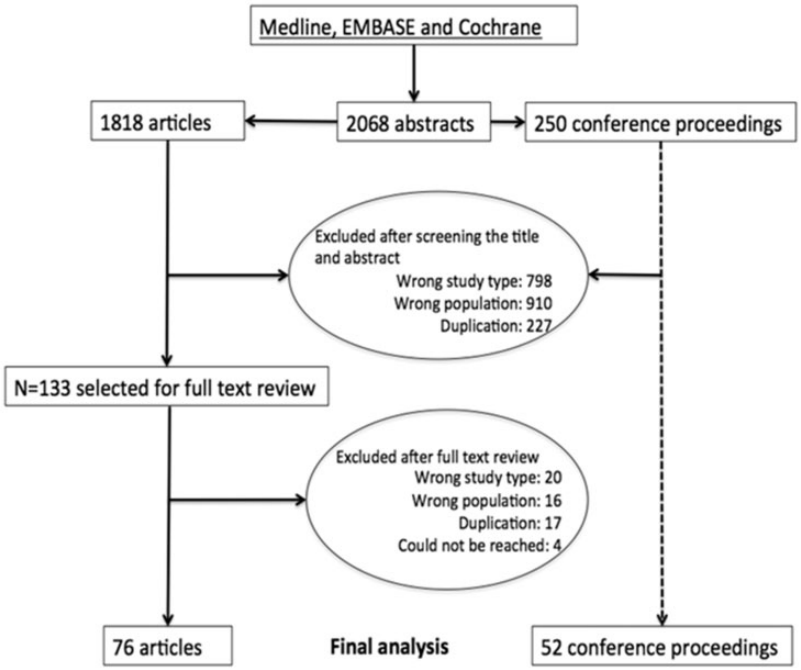
Inclusion criteria in RCTs and baseline demographics

All items listed in the inclusion criteria in RCTs and baseline demographics are summarized in online supplementary Table S1, available at *Rheumatology Advances in Practice* online and Table 1, respectively.

Asymmetrical oligoarthritis vs symmetrical polyarthritis

In all RCTs, the main inclusion criteria were determined by the number of tender and swollen joints, rather than the pattern of joint disease. A detailed differentiation of different subgroups at baseline was given in 10 studies [11, 12, 14, 16, 21, 23, 25, 30, 33, 38]. The majority of patients (52.2–66.9%) had symmetrical polyarthritis, followed by asymmetrical oligoarthritis in 9.8–42% [11, 12, 14, 16, 25, 30]. Two studies had slightly different patient populations. Patients in the Go-Reveal study had less symmetrical polyarthritis (38 and 43% in different treatment arms) and relatively more asymmetrical oligoarthritis (30 and 34%) [23]. Despite the higher representation of the asymmetrical oligoarthritis group in this study, the

FIG. 1 Flowchart for the selection and exclusion of the abstracts and articles



mean tender and swollen joint counts were in the range of 22.5–24 and 12–14.1, respectively, being very similar to all the other studies (Table 1). Likewise, the study on ustekinumab had 36% of patients with asymmetrical oligoarthritis [33]. Only 25% of patients in this study were reported to have symmetrical polyarthritis. However, the median (inerquartile range) tender joint count was 19.5 (10–33.5), and swollen joint count 10 (6–16), which would mean that only 25% of patients could have <10 tender and fewer than six swollen joints, which would still be polyarthritis for most patients. The study focusing on the benefits of tight control in PsA did not require a specific number of joints to be inflamed to be included in the study, however, as this was a strategy trial on the comparison of tight control *vs* standard of care rather than testing the efficacy of a certain drug, this was not included in the tables [80].

Regardless of the subgroups, the inclusion criteria were at least five tender and swollen joints in five studies, which would require inclusion of polyarthritis patients only [24–26, 31, 32], and at least three joints in 23 studies [10–19, 21–23, 27–30, 33–36, 38, 40], which might have included patients with oligoarthritis as well. For two studies, the requirement was at least two tender and swollen joints, one with etanercept [20], one with SSZ [39]; and one study with MTX included any patients with any synovitis that could be mono- or oligoarthritis [37]. Regardless of the joint count inclusion criteria in these three studies, patient demographics still showed a high number of mean (S.D.) tender 19–35.8 (1.8–22.1) and swollen joints counts 12–25.2 (15–16.2) that were much higher than the requirements for inclusion [20, 39].

Axial disease

A certain level of disease activity according to BASDAI or ASDAS or the presence of an axial disease was never an inclusion criterion in any RCT. When patient demographics were reviewed, 13 studies reported axial disease in 0.7–13% of the patients, always in combination with polyarthritis [11, 12, 14, 16, 21, 23, 25, 32, 33, 36, 38–40]. The only study that had a high representation of spine disease was an older study on SSZ, in which 75% of the included patients had axial disease [39].

Among the RCTs, the only study that gave information about baseline BASDAI was the study on clazakizumab, which had 75.6–81% (for different doses) of patients having a BASDAI ≥ 4, with a mean (S.D.) BASDAI of 6.6–6.8 (1.4–1.9) [19]. Two studies with sulfasalazine used the spondylitis functional index to assess for axial involvement [39, 40].

DIP joint disease

DIP joint involvement was never an inclusion criterion in an RCT in PsA. Ten studies gave information about the percentage of patients with DIP joint disease [11, 12, 14, 16, 21, 23, 25, 30, 33, 38]. Most studies included a lesser percentage of patients with DIP disease (4–13%) [16, 14, 30, 11, 12, 26], whereas this was higher in four other studies (15–51%) [25, 21, 23, 33]. The numbers of DIP joints that were involved in the patient populations were never identified in baseline demographics.

Arthritis mutilans

Similar to DIP joint involvement, arthritis mutilans was never an inclusion criterion in an RCT. The percentage

Table 1 Demographic data of original randomized controlled trials

Drug/study	TJC, mean (S.D.) or median (interquartile range)[a] or *n* (%)	SCJ, mean (S.D.) or median (interquartile range)[a] or *n* (%)	Axial, *n* (%) or %	Symmetric polyarthritis, *n* (%) or %	Asymmetric oligoarthritis, *n* (%) or %	DIP, *n* (%) or %	Arthritis mutilans, *n* (%) or %	Enthesitis, *n* (%) or % mean (S.D.)[b] or *n*/total *n*[c]	Dactylitis, *n* (%) or % mean (S.D.)[b] *n*/total *n*[c]
Abatacept [10]									
ABA 30/10 mg/kg ($n = 43$)	19.6 (11.4)	10.3 (7.1)							
ABA 10 mg/kg ($n = 40$)	25.2 (15.6)	12.5 (8.7)							
ABA 3 mg/kg ($n = 45$)	22.7 (14.6)	10.3 (6.9)							
Adalimumab/ADA [11]									
ADA 40 mg every other week ($n = 51$)	25.3 (18.3)	18.2 (10.9)	1 (2.0)	42 (82.4)	5 (9.8)	3 (5.9)	0	0.9 (1.2)[b]	2.9 (5.1)[b]
Adalimumab/ADEPT [12]									
ADA 40 mg every other week ($n = 151$)	23.9 (17.3)	14.3 (12.2)	1 (0.7)	97 (64.2)	37 (24.5)	15 (9.9)	1 (0.7)	118/151[c]	117/151[c]
Apremilast/PALACE-1 [13]									
APR 20 mg twice a day ($n = 168$)	22.2 (15.9)	12.5 (9.5)						103 (61.3)	59 (35.1)
APR 30 mg twice a day ($n = 168$)	23.1 (14.5)	12.8 (7.8)						114 (67.9)	68 (40.5)
Apremilast/PALACE-2 [14]									
APR20 mg twice a day ($n = 163$)	20.3 (16.6)	10.4 (7.8)	2 (1.2)	109 (66.9)	43 (26.4)	7 (4.3)	2 (1.2)	107 (65.6)	77 (47.2)
APR 30 mg twice a day ($n = 162$)	21.8 (16.8)	10.3 (8.1)	5 (3.1)	101 (62.3)	42 (25.9)	7 (4.3)	7 (4.3)	101 (62.3)	73 (45.1)
Apremilast/PALACE-3 [15]									
APR 20 mg twice a day ($n = 169$)	20.8 (16.8)	11.4 (9.1)						97 (57)	71 (42)
APR 30 mg twice a day ($n = 167$)	20.9 (14.4)	11.6 (8.7)						112 (67)	80 (48)
Apremilast/PALACE-4 [103]									
APR 20 twice a day ($n = 175$)	21.1 (15.1)	11.3 (7.8)						117 (66.9)	89 (50.9)
APR 30 mg twice a day ($n = 176$)	19.5 (14.4)	10.9 (8.6)						111 (63.1)	84 (47.7)
Apremilast [16]									
APR 20 mg twice a day ($n = 69$)	20.6	10.6	3 (4.3)	36 (52.2)	21 (30.4)	9 (13.0)	0		
APR 40 mg once a day ($n = 67$)	23.2	8.4	4 (6.0)	32 (47.8)	26 (38.8)	2 (3.0)	2 (3.0)		
Brodalumab [17]									
BRO 140 mg	27.0 (16.4)	13.6 (10.5)						41 (72)	40 (70)
BRO 280 mg	20.8 (15.3)	11.4 (9.3)						32 (57)	27 (48)
Certolizumab/RAPID-PSA [18]									
CZP 200 mg every 2 weeks ($n = 138$)	21.5 (15.3)	11.0 (8.8)						63.8	25.4

(continued)

Table 1 Continued

Drug/study	TJC, mean (s.d.) or median (interquartile range)[a] or *n* (%)	SCJ, mean (s.d.) or median (interquartile range)[a] or *n* (%)	Axial, *n* (%) or %	Symmetric polyarthritis, *n* (%) or %	Asymmetric oligoarthritis, *n* (%) or %	DIP, *n* (%) or %	Arthritis mutilans, *n* (%) or %	Enthesitis, *n* (%) or % mean (s.d.)[b] or *n*/total *n*[c]	Dactylitis, *n* (%) or % mean (s.d.)[b] *n*/total *n*[c]
CZP 400 mg every 4 weeks (*n* = 135)	19.6 (14.8)	10.5 (7.5)						62.2	28.1
Clazakizumab [19]									
CLA 25 mg (*n* = 541)	23.06 (16.4)	12.4 (9.3)						31 (75.6)	15 (36.6)
CLA 100 mg (*n* = 542)	19.0 (13.5)	13.8 (12.0)						35 (83.3)	12 (28.6)
CLA 200 mg (*n* = 541)	16.6 (10.4)	10.8 (7.4)						31 (75.6)	13 (31.7)
Etanercept/PRESTA [20]									
ETA50 mg twice per week/once per week (*n* = 379)	19 (18)	12 (15)						153 (40.4)[b]	158 (41.7)[b]
ETA50 mg once per week/once per week (*n* = 373)	19 (18)	13 (15)						134 (35.9)[b]	160 (42.9)[b]
Etanercept [21]									
ETA (*n* = 101)			3 (3)	87 (86)	41 (41)	52 (51)	1 (1)		
Etanercept [22]									
ETA (*n* = 30)	22.5 (11, 32)[a]	14.0 (8, 23)[a]							
Golimumab/GO-REVEAL [23]									
GOLI 50 mg (*n* = 146)	24.0 (17.1)	14.1 (11.4)	14 (10)	62 (43)	44 (30)	24 (16)	2 (1)	109 (75)	50 (34)
GOLI 100 mg (*n* = 146)	22.5 (15.7)	12.0 (8.4)	18 (12)	56 (38)	49 (34)	22 (15)	1 (1)	115 (79)	49 (34)
Infliximab/IMPACT-1 [24]									
IFX 5 mg/kg (*n* = 52)	23.7 (13.7)	14.6 (7.5)						13 (25.0)	25 (48.1)
Infliximab/IMPACT-2 [25]									
IFX5 mg/kg (*n* = 100)	24.6 (14.1)	13.9 (7.9)	2.0	53.0	18.0	26.0	1.0	42.0	40.0
Infliximab/RESPOND [26]									
IFX plus MTX (*n* = 56)	21.1 (13.3)	15.1 (10.1)						2.4 (3.0)[b]	3.3 (4.2)[b]
MTX (*n* = 54)	20.1 (11.2)	14.3 (9.5)						2.7 (2.8)[b] (MASES)	3.1 (4.2)[b]
Ixekizumab/SPIRIT [27]									
IXE every 4 weeks (*n* = 107)	20.5 (13.7)	11.4 (8.2)						70 (65.4)	54 (50.5)
IXE every 2 weeks (*n* = 103)	21.5 (14.1)	12.1 (7.2)						59 (57.3)	41 (39.8)
Adalimumab 40 mg every 2 weeks (*n* = 101)	19.3 (13.0)	9.9 (6.5)						56 (55.4)	23 (22.8)
Secukinumab/FUTURE-1 [28]									
SEC 150 mg (*n* = 202)	23.8 (16.4)	12.5 (9.4)						126 (62.4)	104 (51.5)
SEC 75 mg (*n* = 202)	23.4 (17.2)	12.7 (11.1)						129 (63.9)	104 (51.5)
Secukinumab/FUTURE-2 [29]									
SEC 300 mg (*n* = 100)	20.2 (13.3)	11.2 (7.8)						56 (56)	46 (46)
SEC 150 mg (*n* = 100)	24.1 (19.4)	11.9 (10.1)						64 (64)	32 (32)
SEC 75 mg (*n* = 99)	22.2 (16.3)	10.8 (9.2)						68 (69)	33 (33)

(continued)

Table 1 Continued

Drug/study	TJC, mean (S.D.) or median (interquartile range)[a] or *n* (%)	SCJ, mean (S.D.) or median (interquartile range)[a] or *n* (%)	Axial, *n* (%) or %	Symmetric polyarthritis, *n* (%) or %	Asymmetric oligoarthritis, *n* (%) or %	DIP, *n* (%) or %	Arthritis mutilans, *n* (%) or %	Enthesitis, *n* (%) or % mean (S.D.)[b] or *n*/total *n*[c]	Dactylitis, *n* (%) or % mean (S.D.)[b] *n*/total *n*[c]
Secukinumab [30]									
SEC 10 mg/kg two intravenous doses ($n=28$)	23.5 (19.4)	8.3 (5.6)		13 (54)	10 (42)	1 (4)		MASES 3.0 (4.1)[b] SPARCC 4.4 (5.06)[b]	LDI basic 2.7 (2.32)[b]
Ustekinumab/PSUMMIT-1 [31]									
UST 45 mg ($n=205$)	18.0 (12.0–28.0)[a]	10.0 (7.0–15.0)[a]						142 (69.3)	101 (49.3)
UST 90 mg ($n=204$)	20.0 (12.0–32.0)[a]	10.0 (7.0–16.0)[a]						154 (75.5)	99 (48.5)
Ustekinumab/PSUMMIT-2 [32]									
UST 45 mg ($n=103$)	22.0 (15.0–33.0)[a]	12.0 (8.0–19.0)[a]	26 (25.2)					72 (69.9)	48 (46.6)
UST 90 mg ($n=105$)	22.0 (14.0–36.0)[a]	11.0 (7.0–17.0)[a]	22 (21.0)					76 (72.4)	41 (39.0)
Ustekinumab [33]									
UST 90 mg (group1) ($n=76$)	19.5 (10.0–33.5)[a]	10.0 (6.0–16.0)[a]	4 (5)	19 (25)	27 (36)	24 (32)	2 (3)	34 (45)	33 (43)
UST 63 mg (grup 2) ($n=70$)	16.0 (9.0–32)[a]	7.0 (5.0–14.0)[a]	4 (6)	22 (31)	20 (29)	24 (34)	0	32 (46)	22 (31)
Others									
Alafacept [34]									
ALA plus MTX ($n=123$)	22.2	13.4							
Placebo plus MTX ($n=62$)	21.8	10.7							
Ciclosporin [38]									
MTX + CYC	22.6 (15.9)	11.7 (9.7)	1	53	44	0	0	9 (24)	7 (18)
MTX + PBO	28.3 (19.2)	11.7 (8.6)	0	61	39	0	0	6 (18)	7 (21)
LEF [35]									
LEF ($n=95$)	20.1 (13.7)	11.6 (10.2)					4 (4.2)		
PBO ($n=91$)	18.5 (13.0)	13.3 (10.6)					13 (14.3)		
LEF *vs* MTX [36]									
LEF ($n=16$)	7.75 (1.81)	5.24 (1.48)							
MTX ($n=14$)	9.64 (2.34)	6.36 (1.34)							
MTX (MIPA) [37]									
MTX ($n=109$)	9 (4–15)[a]	6 (3–12)[a]		71 (65)	38 (35)				
SSZ [39]									
SSZ	35.8 (22.1)	25.2 (16.2)	75						
SSZ *vs* ciclosporin [40]									
Ciclosporin ($n=36$)	14.8 (11.4)	9.2 (6.1)	8 (22)						
SSZ ($n=32$)	14.6 (9.0)	9.6 (6.8)	4 (13)						

[a]median (interquartile range), [b]mean (S.D.) and [c]n/total n. ABA: Abatacept; ADA: Adalimumab; ALA: Alafacept; APR: Apremilast; BRO: Brodalumab; CER: Certolizumab; CLA: Clazakizumab; EFA: Efalizumab; ETA: Etanercept; GOLI: Golimumab; IFX: Infliximab; IXE: Ixekizumab; LEF: Leflunomid; MTX: Methotrexate; PBO: placebo; SEC: Secukinumab; SJC: Swollen joint count; SSZ: Sulphasalazin; TJC: Tender joint count; UST: Ustekinumab.

of patients with arthritis mutilans was given in 10 studies and was in a range between 0 and 4.3% [11, 12, 14, 16, 21, 23, 25, 30, 33, 38].

In all studies, the percentages of the patient population added up to 100%, meaning either there were no overlaps between different disease subgroups or no patients with sole manifestations, such as DIP disease only, were included. The only study that clearly had overlaps between different disease groups was the study with etanercept [21]. In this study, 86% of patients had symmetrical polyarthritis, 41% had asymmetrical oligoarthritis, 51% had DIP disease, 3% had axial disease and 1% had arthritis mutilans. Although DIP disease, axial disease or arthritis mutilans may coexist with symmetrical polyarthritis or asymmetrical oligoarthritis, the overlap between symmetrical polyarthritis and asymmetrical oligoarthritis in this study makes it difficult to interpret and analyse the subgroups.

Enthesitis and dactylitis

Neither enthesitis nor dactylitis was included as an inclusion criterion in any of the RCTs in PsA. When demographics were reviewed, 21 studies gave information about the percentage of patients with enthesitis and dactylitis at baseline [11–15, 17, 18–20, 23–33, 38]. Enthesitis was seen in 24–83.3% of the subjects, and 18–51.5% had dactylitis.

Outcomes assessed in RCTs

Ninety-seven studies had information on outcomes (Supplementary Tables S2 and S3, available at *Rheumatology Advances in Practice* online). The primary outcomes were mostly ACR, psoriatic arthritis response criteria, DAS and psoriasis area and severity index responses. Enthesitis was included among the primary outcomes in three RCTs [66, 120, 130], dactylitis in two RCTs [66, 130] and BASDAI in one RCT [127]. For the secondary outcomes, 20 additional studies included enthesitis and dactylitis [12, 13, 17, 18, 20, 24–27, 29, 30, 32, 39, 48, 67, 68, 80, 85, 87, 103] and three studies included BASDAI [17, 32, 80]. Studies on brodalumab, ustekinumab and the tight control of PsA trial used BASDAI as a secondary outcome [80]. Eight studies gave information about minimal disease activity [18, 26, 46, 54, 64, 69, 80, 85].

Efficacy data obtained from RCTs

Although 10 studies gave detailed information about the distribution of disease subgroups [11, 12, 14, 16, 21, 23, 25, 30, 33, 38], only three studies provided information on the efficacy of the tested drug in different subgroups [14, 16, 35]. A study on apremilast showed a higher efficacy in the asymmetrical oligoarthritis subgroup (ACR20 response: 52.4% with apremilast 20 twice daily and 53.8% with 40 mg once daily) than symmetrical polyarthritis (33.8% with 20 mg twice daily, 18.8% with 40 mg once daily). Despite the higher numerical efficacy in oligoarticular disease, the low sample size did not allow a statistical comparison [16]. However, the PALACE 2 study on apremilast found similar efficacy in these subtypes [14]. There was only one study that mentioned having arthritis mutilans did not affect the treatment response to LEF [35].

For axial disease, seven studies gave information about BASDAI changes or response rates [17, 19, 31, 32, 39, 40, 127]. The efficacy data for these are summarized in Table 2. The response in enthesitis and dactylitis was evaluated more frequently. Twenty-five studies had given information about the change in enthesitis and dactylitis, in 23 of which the resolution and/or change in scores for enthesitis and dactylitis was either a primary or secondary outcome (supplementary Table S4, available at *Rheumatology Advances in Practice* online). The risk of bias assessment of RCTs is given in supplementary Table S5, available at *Rheumatology Advances in Practice* online.

Discussion

This systematic literature review highlights the fact that our evidence-based knowledge in treatment of PsA focuses mainly on polyarticular disease, which accounts for only a subgroup of PsA. The inclusion criteria for entry into RCTs have always been peripheral joint counts that are mostly polyarticular disease, and did not require the presence of other joint subtypes. This could result in the underrepresentation of patients having the other disease subtypes. For example, if the inclusion criteria do not include the presence of DIP joint disease, patients recruited to the study may have DIP joint disease, but only in combination with peripheral arthritis and never represented alone, which might under power the study for an effect on DIP joint disease.

In addition to not being a part of the inclusion criteria, only 10 studies gave information about the distribution of the disease subtypes. What these studies had in common was the lack of representation of axial disease, which was present in only 0.7–13% of the patient population. DIP joint disease was found in a wider range, between 4 and 51%, although the majority was ~10%. Arthritis mutilans was even lower, between 0 and 4.3%. Regardless of the low numbers, the efficacy data in subtypes was given in only three studies, two of which revealed contradictory results [14, 16, 35]. The vast majority of the studies did not even discuss the subtypes.

Another type of bias is introduced with the selection of the outcomes. When the outcomes are limited to the ACR 20/50/70, psoriatic arthritis response criteria or DAS responses, authors of these studies do not perform the sample size calculations based on the other subtypes of the disease. Therefore, the studies were never powered to assess the response in axial disease, and the given changes in the BASDAI scores remain mostly exploratory. Likewise, these data cannot be extracted from other studies in spondyloarthritis when the efficacy data are not given separately for different spondyloarthritis subtypes.

Table 2 The efficacy data on BASDAI of the randomized controlled trials

Drug/study	Data given as	Study group	Change	*P*-value
Brodalumab [17]	change in BASDAI mean (95% CI), *n*	BRO 140 mg/280 mg	24 weeks: −2.0 (−2.6 to −1.5), *n* = 53 52 weeks: −2.2 (−2.9 to −1.6)	
		BRO 280 mg/280 mg	24 weeks: −1.8 (−2.4 to −1.3), *n* = 51 52 weeks: −1.6 (−2.1 to −1.0)	
		PBO/BRO 280 mg	24 weeks: −1.4 (−1.9 to −0.9), *n* = 52 52 weeks: −1.8 (−2.5 to −1.2)	
Brodalumab [127]	Change in BASDAI mean (95% CI), *n*	BRO 140 mg	−0.7 (−1.3 to −0.1)	0.03
		BRO 280 mg	−0.8 (−1.4 to −0.2)	0.01
Clazakizumab [19]	Change in BASDAI mean (95% CI), *n*	CLA 25 mg	16 weeks: −1.9 (−2.7 to −1.1), *n* = 31 24 weeks: −2.1 (−2.9 to −1.2), *n* = 30	
		CLA 100 mg	16 weeks: −2.0 (−2.8 to −1.3), *n* = 33 24 weeks: −2.2 (−3.1 to −1.4), *n* = 29	
		CLA 200 mg	16 weeks: −1.5 (−2.3 to −0.6), *n* = 29 24 weeks: −1.7 (−2.6 to −0.8), *n* = 23	
		PBO	16 weeks: −1.5 (−2.2 to −0.7), *n* = 36 24 weeks: −1.6 (−2.4 to −0.8), *n* = 27	
Sulphasalazine [39]	Change, mean (S.D.)	SSZ	SFI: 1.2 (4.6) SAI: 0.9 (2.8)	0.3 0.4
		PBO	SFI 0.5 (4.9) SAI 0.6 (2.9)	
Sulphasalazine *vs* Ciclosporin [40]	Change in SFI mean (S.D.) (95% CI)	Ciclosporin SSZ	SFI 5.7 (6.8) (8.1; 3.3), *n* = 36 SFI 3.5 (3.9) (4.9; 2.1), *n* = 32	0.03
Ustekinumab/ PSUMMIT-1 [31]	Number of responders/total number (%)	UST 45 mg	BASDAI 20: 25/51 (49.0%) BASDAI 50: 12/51 (23.5%) BASDAI 70: 7/51 (13.7%)	0.01 0.1 0.003
		UST 90 mg	BASDAI 20: 35/60 (58.3%) BASDAI 50: 19/60 (31.7%) BASDAI 70: 9/60 (15.0%)	0.0005 0.01 0.002
		PBO	BASDAI 20:16/61 (26.2%) BASDAI 50: 8/61 (13.1%) BASDAI 70: 0/61 (0.0%)	
Ustekinumab/ PSUMMIT 2 [32]	Number of responders/total number (%)	UST 45 mg	BASDAI 20: 15/25 (60.0), *n* = 103 BASDAI 50: 7/25 (28.0) BASDAI score <3: 8/25 (32.0)	
		UST 90 mg	BASDAI 20: 11/21 (52.4), *n* = 105 BASDAI 50: 8/21 (38.1) BASDAI score <3: 6/21 (28.6)	<0.05 for BASDAI 50
		PBO	BASDAI 20: 10/18 (55.6), *n* = 104 BASDAI 50: 1/18 (5.6) BASDAI score <3: 1/18 (5.6)	

BRO: Brodalumab; CLA: Clazakizumab; PBO: placebo; SAI: Spondylitis Articuler Index; SFI: Spondylitis Functional Index; SSZ: Sulphasalazin; UST:Ustekinumab.

Enthesitis and dactylitis were better evaluated, being more frequently among the primary ($n = 3$ for enthesitis, $n = 2$ for dactylitis) and secondary outcomes ($n = 20$ for enthesitis, $n = 20$ for dactylitis). Although they were also not among the inclusion criteria, by being more frequently represented in the study populations and included in the outcomes of the study, there is more evidence in the literature about the response to treatment for these manifestations.

Our results show that there is evidence to guide clinicians about how to treat patients with PsA with different drugs if they have symmetrical polyarthritis and, to a lesser degree, enthesitis and dactylitis, but not for the other disease subtypes. These patients account for 35–85% of PsA according to the studies, and there is a paucity of evidence-based data. Our approach to treat patients with axial disease has been borrowed from AS, with the assumption that axial disease is similar in both. Despite the similarities, there are also well-known differences between the two diseases, such as axial PsA usually being considered to be milder than AS, with fewer functional limitations and different radiographic features [138]. Therefore, the literature suggests that axial PsA should be considered as a separate entity [139]. In our perspective, the performance of the medications may not be identical in AS and axial PsA and requires demonstration in axial PsA separately.

That is also true for DIP joint disease, where not much is known about the pathogenesis and how to treat. Imaging studies showed that enthesitis is an important feature for DIP joint disease [140]. Whether DIP joint disease needs to be approached like articular disease or predominantly as enthesitis is not known, and the efficacy of the treatments has never been tested in this subset, with no evidence-guided treatment recommendations.

One can argue that patients with polyarticular PsA are similar to those with oligoarticular PsA, more than RA, as demonstrated by Helliwell *et al*. [141], and that the data provided for polyarticular PsA can be applied to non-polyarticular disease. However, national guidelines on reimbursement for biologics are led by the evidence provided by RCTs. The absence of data or, in other words, the ignorance of oligoarticular disease by the majority of RCTs in PsA, does not allow this subgroup of patients to be treated with biologics, in the event of not responding to conventional DMARD therapies. Although there is a school of thought to classify PsA as peripheral and axial disease without further classifications, based on the data coming from cluster analysis [142], focusing on high number of joints as a severity marker for peripheral disease and use to be enrolled in clinical trials leads to ignorance of a significant of our patient population. Having polyarticular disease is not the only marker for disease severity in PsA, as fewer joints can also be very disabling, and function is also important to determine the severity of the disease [143]. Therefore, limiting the RCTs to polyarticular PsA only prevents the provision of evidence on patients with fewer joints affected who could still benefit from biologics. This is also true for the other manifestations, such as enthesitis, which could be very disabling even in the absence of any joint involvement. Fortunately, this has been recognized as more important lately, and there are ongoing studies specifically targeting disease manifestations other than joint involvement for enthesitis and axial disease (clinicaltrials.gov, NCT02771210, NCT02721966, NCT03191539).

Our review has some limitations. This systematic literature review uses only the published data. Some of the studies might have the data collected but not presented in the studies, and if there were no differences observed between different subtypes, the investigators might have not reported the results. We did not include studies other than RCTs. Additionally, we focused only on studies that targeted the efficacy of drugs and not safety.

In conclusion, there is a gap of knowledge on the treatment of the subtypes in PsA other than polyarticular disease. Such evidence could highlight differences in therapeutics that might be useful for guiding physicians about how to treat different types of PsA patients effectively. Such information would also be invaluable in enhancing the cost effectiveness of different regimens.

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Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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