

## 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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Submitted 19 October 2017; revised version accepted 4 January 2018

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## 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, alafcept, apremilast, brodalumab, celecoxib, certolizumab, clazakizumab, ciclosporin, efalizumab, etanercept, golimumab, infliximab, ixekizumab, leflunomid, methotrexate, oncept, 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.

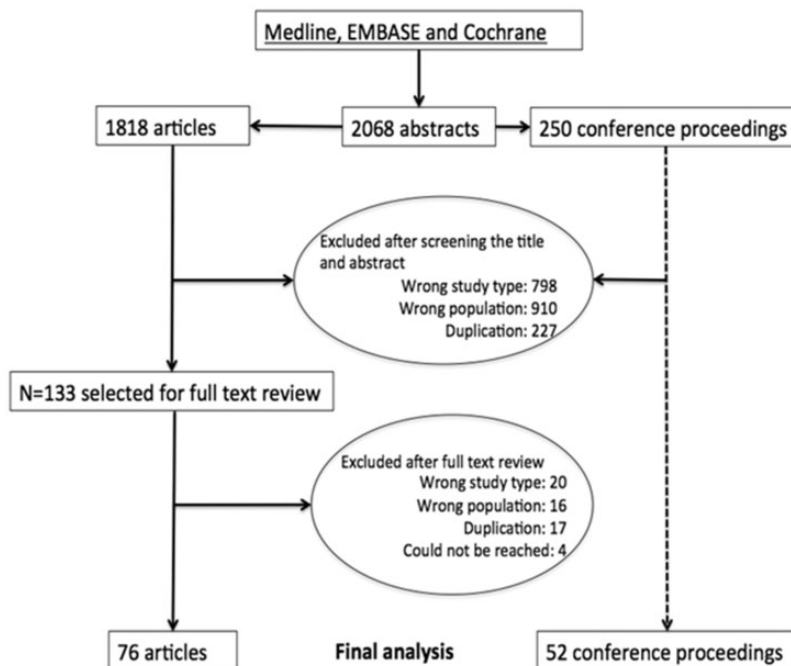
### Inclusion criteria in RCTs and baseline demographics

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 (interquartile 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  $\geq 4$ , 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) <sup>a</sup> or n (%)	SCJ, mean (s.d.) or median (interquartile range) <sup>a</sup> or n (%)	Axial, n (%) or %	Symmetric polyarthritides, n (%) or %	Asymmetric oligoarthritis, n (%) or %	DIP, n (%) or %	Arthritis mutilans, n (%) or %	Enthesitis, n (%) or % mean (s.d.) <sup>b</sup> or n/total n <sup>c</sup>	Dactylitis, n (%) or % mean (s.d.) <sup>b</sup> or n/total n <sup>c</sup>
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) <sup>b</sup>	2.9 (5.1) <sup>b</sup>
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 <sup>c</sup>	117/151 <sup>c</sup>
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]									
APR 20 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 mg 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) <sup>a</sup> or n (%)	SCJ, mean (s.d.) or median (interquartile range) <sup>a</sup> 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.) <sup>b</sup> or n/total n <sup>c</sup>	Dactylitis, n (%) or % mean (s.d.) <sup>b</sup> or n/total n <sup>c</sup>
CZP 400 mg every 4 weeks (n = 135)	19.6 (14.8)	10.5 (7.5)						62.2	28.1
Ciazakizumab [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) <sup>b</sup>	158 (41.7) <sup>b</sup>
ETA50 mg once per week/once per week (n = 373)	19 (18)	13 (15)						134 (35.9) <sup>b</sup>	160 (42.9) <sup>b</sup>
Etanercept [21]									
ETA (n = 101)			3 (3)	87 (86)	41 (41)	52 (51)	1 (1)		
Etanercept [22]									
ETA (n = 30)	22.5 (11, 32) <sup>a</sup>	14.0 (8, 23) <sup>a</sup>							
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) <sup>b</sup>	3.3 (4.2) <sup>b</sup>
MTX (n = 54)	20.1 (11.2)	14.3 (9.5)						2.7 (2.8) <sup>b</sup> (MASES)	3.1 (4.2) <sup>b</sup>
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) <sup>a</sup> or n (%)	SJC, mean (s.d.) or median (interquartile range) <sup>a</sup> 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.) <sup>b</sup> or n/total n <sup>c</sup>	Dactylitis, n (%) or % mean (s.d.) <sup>b</sup> or n/total n <sup>c</sup>
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) <sup>b</sup> SPARCC 4.4 (5.06) <sup>b</sup>	LDI basic 2.7 (2.32) <sup>b</sup>
Ustekinumab/PSUMMIT-1 [31]									
UST 45 mg (n = 205)	18.0 (12.0–28.0) <sup>a</sup>	10.0 (7.0–15.0) <sup>a</sup>						142 (69.3)	101 (49.3)
UST 90 mg (n = 204)	20.0 (12.0–32.0) <sup>a</sup>	10.0 (7.0–16.0) <sup>a</sup>						154 (75.5)	99 (48.5)
Ustekinumab/PSUMMIT-2 [32]									
UST 45 mg (n = 103)	22.0 (15.0–33.0) <sup>a</sup>	12.0 (8.0–19.0) <sup>a</sup>	26 (25.2)					72 (69.9)	48 (46.6)
UST 90 mg (n = 105)	22.0 (14.0–36.0) <sup>a</sup>	11.0 (7.0–17.0) <sup>a</sup>	22 (21.0)					76 (72.4)	41 (39.0)
Ustekinumab [33]									
UST 90 mg (group 1) (n = 76)	19.5 (10.0–33.5) <sup>a</sup>	10.0 (6.0–16.0) <sup>a</sup>	4 (5)	19 (25)	27 (36)	24 (32)	2 (3)	34 (45)	33 (43)
UST 63 mg (group 2) (n = 70)	16.0 (9.0–32) <sup>a</sup>	7.0 (5.0–14.0) <sup>a</sup>	4 (6)	22 (31)	20 (29)	24 (34)	0	32 (46)	22 (31)
Others									
Alfacept [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) <sup>a</sup>	6 (3–12) <sup>a</sup>		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)						

<sup>a</sup>median (interquartile range), <sup>b</sup>mean (s.d.) and <sup>c</sup>n/total n. ABA: Abatacept; ADA: Adalimumab; ALA: Alfacept; 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 Cyclosporin [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%)	0.01
			BASDAI 50: 12/51 (23.5%)	0.1
			BASDAI 70: 7/51 (13.7%)	0.003
		UST 90 mg	BASDAI 20: 35/60 (58.3%)	0.0005
			BASDAI 50: 19/60 (31.7%)	0.01
			BASDAI 70: 9/60 (15.0%)	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	<0.05 for BASDAI 50
			BASDAI 50: 8/21 (38.1)	
			BASDAI score <3: 6/21 (28.6)	
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 Articular Index; SFI: Spondylitis Functional Index; SSZ: Sulphasalazine; 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.

**Funding:** No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

**Disclosure statement:** J.K. has received honoraria from Abbvie, Amgen, Astra Zeneca, Bristol-Myers Squibb, Celgene, Lilly, Merck, Novartis, Roche and Sanofi. S.Z.A. has received research grants and speakers bureaus from Abbvie, Novartis, Pfizer, Union Chimique Belge and Sanofi.

## Supplementary data

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

## References

- Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55–78.
- Gladman DD, Shuckett R, Russell ML *et al.* Psoriatic arthritis (PSA)—an analysis of 220 patients. *Q J Med* 1987;62:127–41.
- Biondi Oriente C, Scarpa R, Pucino A, Oriente P. Psoriasis and psoriatic arthritis. Dermatological and rheumatological co-operative clinical report. *Acta Dermato-Venerol Supplementum* 1989;146:69–71.
- Helliwell P, Marchesoni A, Peters M, Barker M, Wright V. A re-evaluation of the osteoarticular manifestations of psoriasis. *Br J Rheumatol* 1991;30:339–45.
- Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM *et al.* Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. *Br J Rheumatol* 1991;30:245–50.
- Jones SM, Armas JB, Cohen MG *et al.* Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. *Br J Rheumatol* 1994; 33:834–9.
- Taylor W, Gladman D, Helliwell P *et al.*; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
- Coates LC, Gossec L, Ramiro S *et al.* New GRAPPA and EULAR recommendations for the management of psoriatic arthritis: process and challenges faced. *Rheumatology* 2017;56:1251–3.
- Gossec L, Smolen JS, Ramiro S *et al.* European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016;75:499–510.
- Mease P, Genovese MC, Gladstein G *et al.* Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum* 2011;63:939–48.
- Genovese MC, Mease PJ, Thomson GT *et al.* Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007;34: 1040–50.
- Mease PJ, Gladman DD, Ritchlin CT *et al.* Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a

- double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:3279–89.
- 13 Kavanaugh A, Mease PJ, Gomez-Reino JJ et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014;73:1020–6.
  - 14 Cutolo M, Myerson GE, Fleischmann RM et al. A Phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol* 2016;43:1724–34.
  - 15 Edwards CJ, Blanco FJ, Crowley J et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis* 2016;75:1065–73.
  - 16 Schett G, Wollenhaupt J, Papp K et al. Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2012;64:3156–67.
  - 17 Mease PJ, Genovese MC, Greenwald MW et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med* 2014;370:2295–306.
  - 18 Mease PJ, Fleischmann R, Deodhar AA et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014;73:48–55.
  - 19 Mease PJ, Gottlieb AB, Berman A et al. The efficacy and safety of clazakizumab, an anti-interleukin-6 monoclonal antibody, in a phase IIb study of adults with active psoriatic arthritis. *Arthritis Rheumatol* 2016;68:2163–73.
  - 20 Sterry W, Ortonne JP, Kirkham B et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. *BMJ* 2010;340:147.
  - 21 Mease PJ, Kivitz AJ, Burch FX et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50:2264–72.
  - 22 Mease PJ, Goffe BS, Metz J et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000;356:385–90.
  - 23 Kavanaugh A, McInnes I, Mease P et al. Golumumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009;60:976–86.
  - 24 Antoni CE, Kavanaugh A, Kirkham B et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2005;52:1227–36.
  - 25 Antoni C, Krueger GG, de Vlam K et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005;64:1150–7.
  - 26 Baranaukaite A, Raffayova H, Kungurov NV et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. *Ann Rheum Dis* 2012;71:541–8.
  - 27 Mease PJ, van der Heijde D, Ritchlin CT et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2017;76:79–87.
  - 28 Mease PJ, McInnes IB, Kirkham B et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *New Engl J Med* 2015;373:1329–39.
  - 29 McInnes IB, Mease PJ, Kirkham B et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;386:1137–46.
  - 30 McInnes IB, Sieper J, Braun J et al. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 2014;73:349–56.
  - 31 McInnes IB, Kavanaugh A, Gottlieb AB et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013;382:780–9.
  - 32 Ritchlin C, Rahman P, Kavanaugh A et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014;73:990–9.
  - 33 Gottlieb A, Menter A, Mendelsohn A et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009;373:633–40.
  - 34 Mease PJ, Gladman DD, Keystone EC; Alefacept in Psoriatic Arthritis Study Group. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006;54:1638–45.
  - 35 Kaltwasser JP, Nash P, Gladman D et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004;50:1939–50.
  - 36 Asaduzzaman ATM, Sikder A, Mahmud MM, Paul HK, Islamet N. Efficacy and safety of leflunomide in psoriatic arthritis. *Pakistan Assoc Dermatol* 2014;24:51–6.
  - 37 Kingsley GH, Kowalczyk A, Taylor H et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* 2012;51:1368–77.
  - 38 Fraser AD, van Kuijk AW, Westhovens R et al. A randomised, double blind, placebo controlled, multicentre

- trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis* 2005;64:859–64.
- 39 Clegg DO, Reda DJ, Meijas E et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996;39:2013–20.
- 40 Salvarani C, Macchioni P, Olivieri I et al. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; 28:2274–82.
- 41 Kavanaugh A, Mease PJ, Gomez-Reino JJ et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. *J Rheumatol* 2015;42:479–88.
- 42 Strand V, Schett G, Hu C, Stevens RM. Patient-reported health-related quality of life with apremilast for psoriatic arthritis: a phase II, randomized, controlled study. *J Rheumatol* 2013;40:1158–65.
- 43 van der Heijde D, Landewé RB, Mease PJ et al. Brief Report: secukinumab provides significant and sustained inhibition of joint structural damage in a phase III study of active psoriatic arthritis. *Arthritis Rheumatol* 2016;68: 1914–21.
- 44 de Groot M, Picavet DI, van Kuijk AWR et al. A prospective, randomized, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on lesional and nonlesional skin. *Dermatology* 2012;225: 298–303.
- 45 Van Kuijk AWR, Gerlag DM, Vos K et al. A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on synovial tissue. *Ann Rheum Dis* 2009;68:1303–9.
- 46 Mease PJ, Heckaman M, Kary S, Kupper H. Application and modifications of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: subanalyses of ADEPT. *J Rheumatol* 2013;40:647–52.
- 47 Gladman DD, Mease PJ, Cifaldi MA et al. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. *Ann Rheum Dis* 2007;66:163–8.
- 48 Antoni CE, Kavanaugh A, van der Heijde D et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *J Rheumatol* 2008;35:869–76.
- 49 Kavanaugh A, Antoni CE, Gladman D et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. *Ann Rheum Dis* 2006;65:1038–43.
- 50 van der Heijde D, Kavanaugh A, Gladman DD et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: results from the induction and maintenance psoriatic arthritis clinical trial 2. *Arthritis Rheum* 2007;56:2698–707.
- 51 Hoff M, Kavanaugh A, Haugeberg G. Hand bone loss in patients with psoriatic arthritis: posthoc analysis of IMPACT II data comparing infliximab and placebo. *J Rheumatol* 2013;40:1344–8.
- 52 Kavanaugh A, Antoni C, Mease P et al. Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis. *J Rheumatol* 2006;33:2254–9.
- 53 Vander Cruyssen B, De Kaiser F, Kruihof E, Mielants H, Van den Bosch F. Comparison of different outcome measures for psoriatic arthritis in patients treated with infliximab or placebo. *Ann Rheum Dis* 2007;66:138–40.
- 54 Atteno M, Peluso R, Costa L et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol* 2010; 29:399–403.
- 55 Atzeni F, Boccassini L, Antivalle M, Salaffi F, Sarzi-Puttini P. Etanercept plus ciclosporin versus etanercept plus methotrexate for maintaining clinical control over psoriatic arthritis: a randomised pilot study. *Ann Rheum Dis* 2011;70:712–4.
- 56 Mease PJ, Woolley JM, Singh A, Tsuji W, Dunn M, Chiou CF. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. *J Rheumatol* 2010;37:1221–7.
- 57 Mease PJ, Kivitz AJ, Burch FX et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006;33:712–21.
- 58 Mease PJ, Ritchlin CT, Martin RW et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. *J Rheumatol* 2004;31:1356–61.
- 59 Prinz JC, FitzGerald O, Boggs RI et al. Combination of skin, joint and quality of life outcomes with etanercept in psoriasis and psoriatic arthritis in the PRESTA trial. *J Eur Acad Dermatol Venereol* 2011;25:559–64.
- 60 Kirkham B, de Vlam K, Li W et al. Early treatment of psoriatic arthritis is associated with improved patient-reported outcomes: findings from the etanercept PRESTA trial. *Clin Exp Rheumatol* 2015;33:11–9.
- 61 FitzGerald O, Helliwell P, Mease P et al. Application of composite disease activity scores in psoriatic arthritis to the PRESTA data set. *Ann Rheum Dis* 2012;71: 358–62.
- 62 Gniadecki R, Robertson D, Molta CT et al. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *J Eur Acad Dermatol Venereol* 2012;26:1436–43.
- 63 Aalbers CJ, Gerlag DM, Vos K et al. Intra-articular etanercept treatment in inflammatory arthritis: a randomized double-blind placebo-controlled trial. *Joint Bone Spine* 2015;82:338–44.
- 64 Helliwell PS, Kavanaugh A. Comparison of composite measures of disease activity in psoriatic arthritis using data from an interventional study with golimumab. *Arthritis Care Res* 2014;66:749–56.
- 65 Kavanaugh A, McInnes IB, Krueger GG et al. Patient-reported outcomes and the association with clinical

- response in patients with active psoriatic arthritis treated with golimumab: findings through 2 years of a phase III, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Care Res* 2013;65:1666–73.
- 66 Kavanaugh A, Mease P. Treatment of psoriatic arthritis with tumor necrosis factor inhibitors: longer-term outcomes including enthesitis and dactylitis with golimumab treatment in the Longterm Extension of a Randomized, Placebo-controlled Study (GO-REVEAL). *J Rheumatol* 2012;89:90–3.
- 67 Kavanaugh A, van der Heijde D, McInnes IB et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis Rheum* 2012;64:2504–17.
- 68 Kavanaugh A, McInnes IB, Mease PJ et al. Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of the randomized, placebo-controlled GO-REVEAL study. *Ann Rheum Dis* 2013;72:1777–85.
- 69 Kavanaugh A, van der Heijde D, Beutler A et al. Radiographic progression of patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy: results through 5 years of a randomized, placebo-controlled study. *Arthritis Care Res* 2016;68:267–74.
- 70 Kavanaugh A, Puig L, Gottlieb AB et al. Maintenance of clinical efficacy and radiographic benefit through two years of ustekinumab therapy in patients with active psoriatic arthritis: results from a randomized, placebo-controlled phase III trial. *Arthritis Care Res* 2015;67:1739–49.
- 71 Kavanaugh A, Menter A, Mendelsohn A et al. Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: a randomized, placebo-controlled, phase II trial. *Curr Med Res Opin* 2010;26:2385–92.
- 72 Gladman D, Fleischmann R, Coteur G, Woltering F, Mease PJ. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. *Arthritis Care Res* 2014;66:1085–92.
- 73 van der Heijde D, Fleischmann R, Wollenhaupt J et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. *Ann Rheum Dis* 2014;73:233–7.
- 74 Kavanaugh A, Gladman D, van der Heijde D et al. Improvements in productivity at paid work and within the household, and increased participation in daily activities after 24 weeks of certolizumab pegol treatment of patients with psoriatic arthritis: results of a phase 3 double-blind randomised placebo-controlled study. *Ann Rheum Dis* 2015;74:44–51.
- 75 Glinatsi D, Bird P, Gandjbakhch F et al. Validation of the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) for the hand and foot in a randomized placebo-controlled trial. *J Rheumatol* 2015;42:2473–9.
- 76 Mease PJ, Reich K; Alefacept in Psoriatic Arthritis Study Group. Alefacept with methotrexate for treatment of psoriatic arthritis: open-label extension of a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 2009;60:402–11.
- 77 Combe B, Goupille P, Kuntz JL, Tebib J, Lioté F, Bregeon C. Sulphasalazine in psoriatic arthritis: a randomized, multicentre, placebo-controlled study. *Br J Rheumatol* 1996;35:664–8.
- 78 Scarpa R, Peluso R, Atteno M et al. The effectiveness of a traditional therapeutic approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. *Clin Rheumatol* 2008;27:823–6.
- 79 Willkens RF, Williams HJ, Ward JR et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984;27:376–81.
- 80 Coates LC, Moverley AR, McParland L et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489–98.
- 81 Sattar N, Crompton P, Cherry L, Kane D, Lowe G, McInnes IB. Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum* 2007;56:831–9.
- 82 Papp KA, Caro I, Leung HM, Garovoy M, Mease PJ. Efalizumab for the treatment of psoriatic arthritis. *J Cutaneous Med Surg* 2007;11:57–66.
- 83 Kivitz AJ, Espinoza LR, Sherrer YR, Liu-Dumaw M, West CR. A comparison of the efficacy and safety of celecoxib 200 mg and celecoxib 400 mg once daily in treating the signs and symptoms of psoriatic arthritis. *Semin Arthritis Rheum* 2007;37:164–73.
- 84 Sarzi-Puttini P, Santandrea S, Boccassini L, Panni B, Caruso I. The role of NSAIDs in psoriatic arthritis: evidence from a controlled study with nimesulide. *Clin Exp Rheumatol* 2001;19:17–20.
- 85 Mease P, Deodhar A, Fleischmann R et al. Effect of certolizumab pegol over 96 weeks in patients with psoriatic arthritis with and without prior antitumour necrosis factor exposure. *RMD Open* 2015;1:e000119.
- 86 Gottlieb A.B, Mease PJ, Cuchacovich RS et al. Ixekizumab improves physical function, quality of life, and work productivity in biologic disease-modifying antirheumatic drug-naïve patients with active psoriatic arthritis [abstract]. *Arthritis Rheumatol* 2015;67 (Suppl 10):2570–73.
- 87 Mease PJ, van der Heijde D, Ritchlin CT et al. A randomized, double-blind, active-and placebo-controlled phase 3 study of efficacy and safety of ixekizumab, adalimumab, and placebo therapy in patients naïve to biologic disease modifying anti-rheumatic drugs with active psoriatic arthritis [abstract]. *Arthritis Rheumatol* 2015;67 (Suppl 10):1277–78.
- 88 Zhang F. Work productivity improvement associated with apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: results of a phase 3, randomized, controlled trial [abstract]. *Ann Rheum Dis* 2014;73(Suppl 2):P736.

- 89 Zhang F, Tencer T, Clancy Z, Li S. Impact of apremilast on physical function in patients with psoriatic arthritis [abstract]. *Value Health* 2014;17(Suppl 3):PA41.
- 90 Kavanaugh A, Mease PJ, Gomez-Reino JJ et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: results of a phase 3, randomized, controlled trial [abstract]. *Arthritis Rheum* 2012;64:P4172-3.
- 91 Adebajo A, Gomez-Reino J, Mease P et al. Long-term 52-week results of PALACE 1, a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase inhibitor, in patients with psoriatic arthritis [abstract]. *Scand J Rheumatol* 2014;43(Suppl12):P1141.
- 92 Schafer P, Chen P, Fang L, Wang A Chopra R. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: pharmacodynamic results of a phase 3, randomized, controlled trial (PALACE 1) [abstract]. *Ann Rheum Dis* 2014;739.
- 93 Kavanaugh A, Adebajo A, Gladman D et al. Long-term (104-week) efficacy and safety profile of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: results from a phase III, randomised, controlled trial and open-label extension (PALACE 1) [abstract]. *Ann Rheum Dis* 2015;74(Suppl2):P350-1.
- 94 Kavanaugh A, Adebajo AO, Gladman DD et al. Long-term (156-week) efficacy and safety profile of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: results from a phase III, randomized, controlled trial and open-label extension (PALACE 1) [abstract]. *Arthritis Rheumatol* 2015;67 (Suppl 10): 597-598.
- 95 Strand V, Hu A, Zhang F. Improved fatigue and physical function are correlated with health-related quality of life in psoriatic arthritis subjects treated with apremilast: results from a phase 2, randomized, controlled study [abstract]. *Value Health* 2011;14 (Suppl7):PA314.
- 96 Strand V, Vessey V, Hu A, Sloan A2, Victor S. Improved health-related quality of life (HRQOL) with apremilast (APR) treatment in psoriatic arthritis (PsA): results from a phase 2 randomized controlled study [abstract]. *Arthritis Rheum* 2010;62(Suppl 10):P1940.
- 97 Cutolo M, Myerson GE, Fleischmann RM et al. Long-term (52-week) results of a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis (PALACE 2) [abstract]. *Arthritis Rheum* 2013;65 (Suppl 10):P815.
- 98 Edwards CJ, Blanco FJ, Crowley J et al. Long-term (52-week) results of a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement (palace 3) [abstract]. *Arthritis Rheum* 2013; 65:P132.
- 99 Edwards CJ, Blanco FJ, Crowley J et al. Disease activity and safety during long-term (104-week) treatment with apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: results from a phase III, randomized, controlled trial and open-label extension (palace 3) [abstract]. *Arthritis Rheumatol* 2015;67 (Suppl 10):348.
- 100 Edwards CJ, Aelion JA, Adebajo AO et al. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvements in enthesitis and dactylitis in patients with psoriatic arthritis: results from the palace 4 phase 3, randomized, controlled trial [abstract]. *Ann Rheum Dis* 2014;73:P735.
- 101 Wells AF, Edwards CJ, Adebajo AO et al. Apremilast in the treatment of DMARD-naive psoriatic arthritis patients: results of a phase 3 randomized, controlled trial (PALACE 4) [abstract]. *Arthritis Rheum* 2013;65 (Suppl 12):P3320-1.
- 102 Wells A, Aelion JA, Adebajo AO et al. A phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, for treatment of psoriatic arthritis: long-term (52-week) improvements in physical function. [abstract]. *Arthritis Rheumatol* 2014;66:P264-5.
- 103 Wells A, Edwards C, Adebajo A et al. Long-term (104-week) efficacy and safety of apremilast monotherapy in DMARD-naive patients with psoriatic arthritis: a phase 3, randomized, controlled trial and open-label extension (palace 4) [abstract]. *Ann Rheum Dis* 2015;74:P863-4.
- 104 van der Heijde D, Landewe R, Mease P et al. Secukinumab inhibits radiographic progression in patients with psoriatic arthritis: data from a phase 3 randomized, multicenter, double-blind, placebo-controlled study (future 1) [abstract]. *Ann Rheum Dis* 2015;74:P347-8.
- 105 Kirkham B, McInnes IB, Mease P et al. Secukinumab is effective in reducing dactylitis and enthesitis using multiple measures in patients with psoriatic arthritis: data from a phase 3 randomized, multicenter, double-blind, placebo-controlled study (future 2) [abstract]. *Ann Rheum Dis* 2015;74:P351.
- 106 Gossec L. Relationship between improvements in fatigue and signs & symptoms of active psoriatic arthritis: a sub-analysis of a phase 3 study with secukinumab [abstract]. *Arthritis Rheumatol* 2015;67:3472-3.
- 107 McInnes I. Anti-interleukin 17A monoclonal antibody secukinumab reduces signs and symptoms of psoriatic arthritis in a 24-week multicenter, double-blind, randomized, placebo-controlled trial [abstract]. *Arthritis Rheum* 2011;63(Suppl 10):306.
- 108 van Kuijk AWR, DeGroot J, Koeman RC et al. Soluble biomarkers of cartilage and bone metabolism in early proof of concept trials in psoriatic arthritis: effects of adalimumab versus placebo [abstract]. *PLoS One* 2010; 5(Suppl 9):e12556.
- 109 Gottlieb A, Teixeira HD, Varothai N et al. Safety and efficacy of adalimumab in combination with different doses of methotrexate in patients with psoriatic arthritis: subanalysis of ADEPT [abstract]. *J Am Acad Dermatol* 2016;74(Suppl 5):PAB268.
- 110 Sheth P. The majority of patients with moderate to severe psoriatic arthritis had existing structural damage, predisposing them to further progression, which was markedly inhibited by adalimumab [abstract]. *Arthritis Rheumatol* 2015;67 (Suppl 10):3488-9.
- 111 Mease P, Kavanaugh A, Coates L et al. The prediction and benefits of minimal disease activity in patients with psoriatic arthritis in the adept trial [abstract]. *Ann Rheum Dis* 2015;74:P355.
- 112 Mease P, Kavanaugh A, Perdok R, Kupper H, Lavie F. Are clinical and radiologic outcomes the same for patients

- with moderate vs. severe disease activity at baseline in patients with psoriatic arthritis? Post-hoc analysis of ADEPT [abstract]. *Arthritis Rheum* 2009;60:P533.
- 113 Mease P, Perdok R, Kary S, Kupper H. Application of a new composite measure of minimal disease activity in patients with psoriatic arthritis treated with adalimumab: subanalysis of the ADEPT trial [abstract]. *Arthritis Rheum* 2009;60:P537.
- 114 Mease PJ, Gladman DD, Ritchlin CT, Anderson JK. Therapeutic response in adalimumab-treated patients with psoriatic arthritis in relation to weight [abstract]. *Ann Rheum Dis* 2015;74(Suppl 2):P1175.
- 115 Landewe R, Ritchlin C, Olds M, Guerette B, Lavie F. Disconnect between disease activity and joint space narrowing for patients with psoriatic arthritis treated with adalimumab plus methotrexate but not for patients treated with methotrexate alone [abstract]. *Clin Exp Rheumatol* 2010;28 (Suppl 4):625–6.
- 116 Mease P, Olds M, Kary S, Kupper H. Modification of minimal disease activity score by replacement of PASI with PGA for adalimumab-treated patients with psoriatic arthritis [abstract]. *Clin Exp Rheumatol* 2010;28 (Suppl 4):P626.
- 117 Boggs RL, Karpati S, Li W, Gniadecki R. Employment is maintained and sick days decreased in psoriasis/psoriatic arthritis patients with etanercept treatment [abstract]. *BMC Dermatol* 2014;14:P14.
- 118 Helliwell PS, Mease P, Bananis E et al.; PsAID task-force. Baseline characteristics and treatment outcomes in psoriasis patients with polyarthritis or oligoarthritis [abstract]. *Arthritis Rheum* 2013;65:S147.
- 119 Kirkham B, Boggs R, Li W, Nab HW, Tarallo M. The importance of managing arthritis in patients with both moderate-to-severe psoriasis and psoriatic arthritis [abstract]. *Value Health* 2013;16(Suppl 3):PA227.
- 120 Kirkham BW, Sterry W, Ormerod A et al. Etanercept benefits skin, joint, and enthesal symptoms in patients with psoriasis and psoriatic arthritis: the PRESTA trial [abstract]. *Arthritis Rheum* 2009;60(Suppl 10):P523.
- 121 Gisondi P, Girolomoni G, de Vlam K et al. Baseline characteristics of patients with moderate to severe psoriatic arthritis: post-hoc analysis of responders vs non-responders to etanercept [abstract]. *Ann Rheum Dis* 2015;74(Suppl 2):P1174.
- 122 Kavanaugh A, van der Heijde D, Gladman D et al. Golimumab inhibits progression of radiographic damage in patients with psoriatic arthritis: 52 week results from the go-reveal study [abstract]. *Rheumatology* 2011;50:iii143.
- 123 Gladman D, Kavanaugh A, Mease P, McInnes I. Golimumab, a new, human, TNF alpha antibody, administered subcutaneously every 4 weeks in psoriatic arthritis patients: 104-week efficacy and safety results of the randomized, placebo-controlled GO-REVEAL study [abstract]. *J Rheumatol* 2010;28(Suppl 4):P1327.
- 124 Mease P, Genovese MC, Greenwald MW et al. Two-year clinical response to brodalumab, an anti-il-17 receptor antibody, in patients with psoriatic arthritis [abstract]. *Ann Rheum Dis* 2015;74(Suppl2):P136–7.
- 125 Genovese MC, Mease P, Greenwald MW et al. Clinical response in subjects with psoriatic arthritis following one year of treatment with brodalumab, an anti-interleukin-17 receptor antibody [abstract]. *Arthritis Rheumatol* 2014;66:P687.
- 126 Mease PJ, Genovese MC, Greenwald MW, Nirula A. 52-Week response to brodalumab, an anti-IL-17R antibody, in subjects with psoriatic arthritis [abstract]. *Clin Exp Rheumatol* 2014;32(Suppl 5):P794.
- 127 Genovese MC, Mease PJ, Viswanathan H et al. Effect of brodalumab (AMG 827) on pain and physical functioning in patients with psoriatic arthritis [abstract]. *Arthritis Rheum* 2013;65:P136.
- 128 Genovese MC, Mease PJ, Greenwald MW et al. Efficacy and safety of brodalumab over one year in patients with psoriatic arthritis with and without prior exposure to a biologic [abstract]. *Ann Rheum Dis* 2014;73(Suppl 12):P1052.
- 129 Kavanaugh A, Puig L, Gottlieb AB et al. Association between improvement in enthesopathy and quality of life: results from a phase 3 trial in psoriatic arthritis patients [abstract]. *Arthritis Rheumatol* 2015;67 (Suppl 10):942–3.
- 130 Kavanaugh A, Puig L, Gottlieb AB et al. Long-term improvements in physical function are associated with improvements in dactylitis, enthesitis, tender and swollen joint counts, and psoriasis skin involvement: Results from a phase 3 study of ustekinumab in psoriatic arthritis patients [abstract]. *J Am Acad Dermatol* 2015;72(Suppl 5):PAB239.
- 131 Kavanaugh A, Puig L, Gottlieb A et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 2-year results from a phase 3, multicenter, double-blind, placebo-controlled study [abstract]. *Ann Rheum Dis* 2014;73(Suppl 2):P737.
- 132 Ritchlin CT, Rahman P, Sanz LP et al. Treatment effect of ustekinumab on fatigue in patients with psoriatic arthritis: results from a phase 3 clinical trial [abstract]. *Arthritis Rheumatol* 2014;66:P682.
- 133 Mease P, Fleischmann R, Davies O, Nurminen T, van der Heijde D. Disease activity and clinical response early in the course of treatment predict long-term outcomes in psoriatic arthritis patients treated with certolizumab pegol [abstract]. *Arthritis Rheumatol* 2014;66:P685.
- 134 Kavanaugh A, Gladman D, Van Der Heijde DM, Purcaru O, Mease PJ. Reduction of disease burden on workplace and household productivity in psoriatic arthritis over 48 weeks of treatment with certolizumab pegol [abstract]. *Arthritis Rheum* 2013;65:P140–1.
- 135 Kavanaugh A, Gladman D, van der Heijde D, Purcaru O, Mease PJ. Sustained improvements in workplace and household productivity and social participation with certolizumab pegol over 96 weeks in patients with psoriatic arthritis [abstract]. *Value Health* 2014;17(Suppl 7):PA387–8.
- 136 Mease PJ, Fleischmann R, Wollenhaupt J et al. Effect of certolizumab pegol over 48 weeks on signs and symptoms in patients with psoriatic arthritis with and without prior tumor necrosis factor inhibitor exposure [abstract]. *Rheumatology* 2014;53(Suppl 1):P137–8.

- 137 Mease PJ, Genovese MC, Gladstein GS et al. Abatacept (ABA) in the treatment of psoriatic arthritis (PsA): 12-month results of a phase II study [abstract]. *Arthritis Rheum* 2010;62(Suppl 10):P1919.
- 138 Deepak RJ, Sengupta R, Nightingale A et al. Axial Disease in Psoriatic Arthritis study: defining the clinical and radiographic phenotype of psoriatic spondyloarthritis. *Ann Rheum Dis* 2016;1–7.
- 139 Lubrano E, Parsons WJ, Marchesoni A et al. The definition and measurement of axial psoriatic arthritis. *J Rheumatol Suppl* 2015;93:40–2.
- 140 Tan AL, Benjamin M, Toumi H et al. The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis—a high-resolution MRI and histological study. *Rheumatology* 2007;46:253–6.
- 141 Helliwell PS, Porter G, Taylor WJ; CASPAR Study Group. Polyarticular psoriatic arthritis is more like oligoarticular psoriatic arthritis, than rheumatoid arthritis. *Ann Rheum Dis* 2007;66:113–7.
- 142 Thavaneswaran A, Chandran V, Gladman DD. Do patients with psoriatic arthritis fall into distinct clinical sub-groups: a cluster analysis? *Arthritis Rheum* 2012; 64(Suppl):S1106.
- 143 Mumtaz A, Gallagher P, Kirby B et al. Development of a preliminary composite disease activity index in psoriatic arthritis. *Ann Rheum Dis* 2011;70: 272–7.