REVIEW

Residual Disease Associated with Suboptimal Treatment Response in Patients with Psoriatic Arthritis: A Systematic Review of Real-World Evidence

Laura C. Coates · Maarten de Wit · Amy Buchanan-Hughes ·

Maartje Smulders · Anna Sheahan · Alexis R. Ogdie

ABSTRACT

Objective: This systematic literature review aimed to identify and summarise real-world observational studies reporting the type, prevalence and/or severity of residual symptoms and disease in adults with psoriatic arthritis (PsA) who have received treatment and been assessed against remission or low disease activity targets.
Methods: Patients had received treatment and been assessed with treat-to-target metrics, including minimal disease activity (MDA), Disease Activity Index in PsA (DAPSA) and others. MEDLINE, Embase® and the Cochrane Database of Systematic Reviews (CDSR) were searched using search terms for PsA, treatment

targets and observational studies. Screening of search results was completed by two independent reviewers; studies were included if they reported relevant residual disease outcomes in adults with PsA who had received one or more pharmacological treatments for PsA in a real-world setting. Non-observational studies were excluded. Information from included studies was extracted into a prespecified grid by a single reviewer and checked by a second reviewer.
Results: Database searching yielded 2328 articles, of which 42 publications (27 unique studies) were included in this systematic literature review. Twenty-three studies reported outcomes for MDA-assessed patients, and 14 studies reported outcomes for DAPSA-assessed patients. Physician- and patient-reported residual disease

L. C. Coates (✉)
Nuffield Department of Orthopaedics,
Rheumatology and Musculoskeletal Sciences,
University of Oxford, Oxford, UK
e-mail: laura.coates@ndorms.ox.ac.uk

M. de Wit
Patient Research Partners, Amsterdam, The
Netherlands
e-mail: martinusdewit@hotmail.com

A. Buchanan-Hughes
Costello Medical, Boston, MA, USA
e-mail: amy.buchanan-
hughes@costellomedical.com

M. Smulders
UCB Pharma, Anderlecht, Belgium

A. Sheahan
UCB Pharma, Raleigh, NC, USA
e-mail: anna.e.dow@gmail.com

A. R. Ogdie
Perelman School of Medicine, University of
Pennsylvania, Philadelphia, PA, USA
e-mail: ogdiea@pennmedicine.upenn.edu

Present Address:
M. Smulders
Astellas Pharma Europe B.V., Leiden, The
Netherlands
e-mail: msmulders@kubadili.com

was less frequent and/or severe in patients reaching targets, but often not absent, including when patients achieved very low disease activity (VLDA) or remission. For example, studies reported that 0–8% patients in remission according to DAPSA (or clinical DAPSA) had > 1 tender joint, 25–39% had Psoriasis Area and Severity Index (PASI) score > 1 and 0–10% had patient-reported pain > 15. Residual disease was usually less frequent and/or severe among patients achieving MDA-assessed targets versus DAPSA--assessed targets, especially for skin outcomes.

Conclusion: The findings demonstrate a need for further optimisation of care for patients with PsA.**Keywords:** Disease burden; Low disease activity; Minimal disease activity; Observational studies; Psoriasis; Psoriatic arthritis; Real world evidence; Remission; Residual disease; Treatment targets

Key Summary Points

To our knowledge, this is the first systematic review of real-world evidence to describe residual disease burden among patients with psoriatic arthritis who have received treatment and been assessed against treatment targets.

This study demonstrates the breadth of different symptoms that can persist despite treatment, even among those patients who have achieved stringent treatment targets.

Residual musculoskeletal and skin disease were frequently observed, as well as residual patient-reported pain, fatigue, disability and disease impact on patients' lives.

Our findings demonstrate the variability of residual disease seen with different targets; they also indicate a possible discordance between patients' and physicians' perspectives of disease control and treatment success.

This review highlights the need for further optimisation of care for patients with psoriatic arthritis.

DIGITAL FEATURES

This article is published with digital features, including a slide deck to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.19355069.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting 20–30% of patients with psoriasis [1]. Symptoms and signs vary, but typically include peripheral and axial joint pain and swelling, enthesitis, nail disease and skin psoriasis [2–4]. Ongoing inflammation is associated with further comorbidities, including cardiovascular disease, uveitis and subclinical bowel inflammation [1]. PsA disease and comorbidities can result in reduced function and quality of life, and increased mortality [5, 6]. While not currently curable, available treatments for PsA can slow progression and relieve symptoms [3]. However, patients may still experience residual symptoms and disease burden, including persistent joint pain and swelling, anxiety, depression, fatigue and functional disability [7–10].

Based on success in rheumatoid arthritis (RA) and documented benefits in the TIght COntrol of Psoriatic Arthritis (TICOPA) study, international groups, including the European Alliance of Associations for Rheumatology (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), support a treat-to-target (T2T) approach for PsA [11–17], recommending remission (REM) as the primary treatment target and low disease activity (LDA) as an alternative [13, 16]. Despite this recommendation, there is a lack of consensus on how REM and LDA should be assessed [12]. Applicable measures include the minimal disease activity (MDA) metric, Disease Activity Index in

PsA (DAPSA) and clinical DAPSA (cDAPSA), all of which have been specifically designed to assess PsA disease (Table 1). GRAPPA recommends using the MDA metric over DAPSA, since the MDA metric incorporates psoriasis and enthesitis assessments in addition to peripheral joint disease [13]. However, there is a need to further understand the validity and relative benefits of these metrics, as only the MDA metric has been tested in a T2T strategy trial including patients with PsA [11, 12].

This lack of consensus on the optimal measure to define PsA treatment targets is reflected in the modest uptake of T2T among healthcare professionals [12]. Moreover, where T2T is used, there is notable variation in the disease activity metrics employed to define REM or LDA for PsA [18]. The MDA metric, DAPSA and cDAPSA are widely used, as well as metrics designed for RA/other non-PsA arthritides (Table 1) [12, 19, 20] which are less appropriate since they do not account for some PsA-specific aspects of disease [7, 21–23].

Although the achievement of treatment targets has been associated with improved quality of life and slower disease progression, patients may still experience symptoms and a burden of disease. This applies even for the most stringently defined REM by the MDA metric (very low disease activity [VLDA]), and residual disease is likely greater among patients achieving less stringent forms of REM by other disease activity metrics [7, 24, 25]. Our current understanding of unmet need in treated patients is limited, yet this knowledge is essential to refine care to address residual disease. This includes residual disease among patients meeting treatment targets, as well as persistent symptoms in patients not meeting treatment targets.

The aim of this systematic literature review (SLR) was to identify and summarise real-world observational studies reporting type, prevalence and/or severity of residual symptoms and disease in adults with PsA who have received treatment and been assessed against REM or LDA targets. Within this aim, the primary objective was to examine residual symptoms of disease (musculoskeletal, skin and patient-reported outcomes [PROs]) in patients whose disease activity was measured using the MDA

metric, DAPSA or cDAPSA, these measures being PsA-specific and in common use in PsA care. The secondary objective was to examine residual disease in patients whose disease activity was measured by three widely used non-PsA-specific measures, namely Disease Activity Score 28 (DAS28), DAS with C-reactive protein (DAS-CRP) and Clinical Disease Activity Index (CDAI), and to qualitatively compare these to the PsA-specific measures.

METHODS

Search Strategy and Selection Criteria

This SLR was conducted in accordance with a pre-specified protocol (see Electronic Supplementary Material [ESM]) and adheres to the PRISMA guidelines [26]. MEDLINE, Embase® and the Cochrane Database of Systematic Reviews (CDSR) were searched on 8 October 2020, using search terms for PsA, treatment targets and (in the MEDLINE and Embase databases) observational studies (ESM Tables S1–S3). Searches were limited to literature published since 1 January 2015 because of the considerable recent advances in PsA treatment. Supplementary searches included: (1) the bibliographies of relevant SLRs identified through the database searches, and (2) congress abstracts from nine selected congresses (ESM Table S4).

After removing duplicates, records were screened according to the process recommended by the Cochrane Collaboration [27]. Titles and abstracts of the search results were screened against eligibility criteria by two reviewers working independently; discrepancies were resolved by consensus, or by an arbitrator if necessary. Full-text versions of potentially relevant articles were screened using the same process.

To be eligible, studies had to report relevant residual disease outcomes (prevalence or severity of any musculoskeletal, skin or PROs), in adults with PsA who had received one or more pharmacological treatments for their condition in a real-world setting (i.e. reported in an observational study). Interventional, modelling

Table 1 Summary of selected disease activity metrics and low disease activity/remission thresholds

Domain		MDA (the metric)[a]	DAPSA	cDAPSA	DAS28	DAS-CRP	CDAI
		PsA-specific metrics			**RA metrics widely used for PsA in clinical practice**		
Joints	TJC	≤1	Yes (68 joints)		Yes (28 joints)		Yes (28 joints)
	SJC	≤1	Yes (66 joints)		Yes (28 joints)		Yes (28 joints)
	Tender entheseal points	≤1	-		-		-
Skin	Psoriasis	PASI ≤1 *or* BSA ≤3%	-		-		-
PROs	PtP VAS (cm)	≤1.5	Yes (0–10)		-		-
	PtGA VAS (cm)	≤2.0	Yes (0–10)		Yes		Yes (0–10)
	HAQ-DI	≤0.5	-		-		-
Physician	PhGA VAS	-	-		-		Yes (0–10)
Lab	ESR	-	-		Yes (mm/hr)	-	-
	CRP	-	Yes (mg/dL)	-	-	Yes (mg/L)	-
Scoring		Count criteria met	Simple sum		Weighted formula[b]		Simple sum
LDA		5/7 or 6/7 criteria (=MDA)	≥4 or >4, and ≤14	>4 and ≤13	≥2.6 and <3.2		>2.8 and ≤10
REM		7/7 criteria (=VLDA)	<4 or ≤4[c]	≤4	<2.6		≤2.8

BSA Body surface area, *CDAI* Clinical Disease Activity Index, *cDAPSA* clinical DAPSA, *CRP* C-reactive protein, *DAPSA* Disease Activity Index in PsA, *DAS28* Disease Activity Score 28, *DAS-CRP* Disease Activity Score-C-reactive protein, *ESR* erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *LDA* low disease activity, *MDA* minimal disease activity, *PASI* Psoriasis Area and Severity Index, *PhGA* physician's global assessment, *PROs* patient-reported outcomes, *PsA* psoriatic arthritis, *PtGA* patient's global assessment, *PtP* patient pain, *RA* rheumatoid arthritis, *REM* remission, *SJC* swollen joint count, *TJC* tender joint count, *VAS* visual analogue scale, *VLDA* very low disease activity
[a]Modified versions of the MDA metric (e.g. substitution of PASI ≤ 1 with PtGA "Clear", or requirement for ≥ 6/7 criteria to be met) were also considered relevant in this review
[b]Cut-off varies depending on publication; either threshold was considered relevant in this review. VAS scores use a 0–100 VAS unless stated otherwise
[c]DAS28 formula: $0.56\sqrt{TJC28} + 0.28\sqrt{SJC28} + 0.70\ln(ESR) + (0.014 * PtGA)$. DAS-CRP formula: $0.56\sqrt{TJC28} + 0.28\sqrt{SJC28} + 0.36\ln(CRP + 1) + (0.014 * PtGA) + 0.96$

or economic studies, case studies/reports and narrative reviews, editorials or commentaries were excluded. Indicators that are less directly linked to patients' experience of PsA, such as laboratory, radiology, economic and proxy outcomes, were excluded. The Psoriatic Arthritis Disease Activity Score (PASDAS) was not included in this review given that it is designed for use in clinical trials, and real-world use can be practically challenging [28]. Relevant outcomes had to be reported separately for patients who met relevant thresholds of disease control (MDA/VLDA as measured by the MDA metric criteria, or LDA/REM as measured by DAPSA, cDAPSA, DAS28, DAS-CRP or CDAI; Table 1) and/or those who did not meet these thresholds. No language restrictions were imposed within the eligibility criteria; full eligibility criteria are shown in ESM Table S5.

This SLR is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Unless stated otherwise, the term MDA is hereafter used to refer to the disease activity state of MDA (with 5–6/7 of the criteria met). 'MDA metric' is used to describe the seven-criteria disease activity index in general. For ease of comparison, MDA and LDA are presented as equivalent tiers of disease control, as are VLDA and REM (ESM Fig. S1). The terms 'at least MDA' or 'at least LDA' are used to describe a group of patients who achieved at least MDA (i.e. patients could have been in either MDA or VLDA; also referred to as VLDA + MDA) or at least LDA (i.e. patients could have been in either LDA or REM; also referred to as REM + LDA), respectively (ESM Fig. S1).
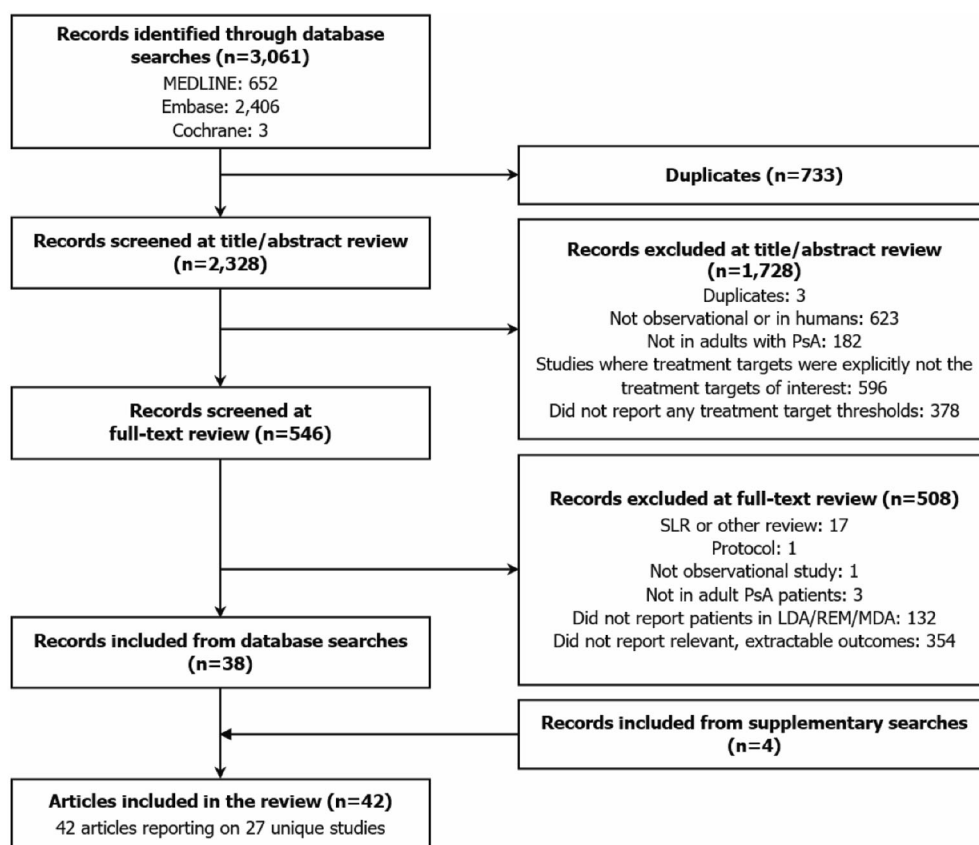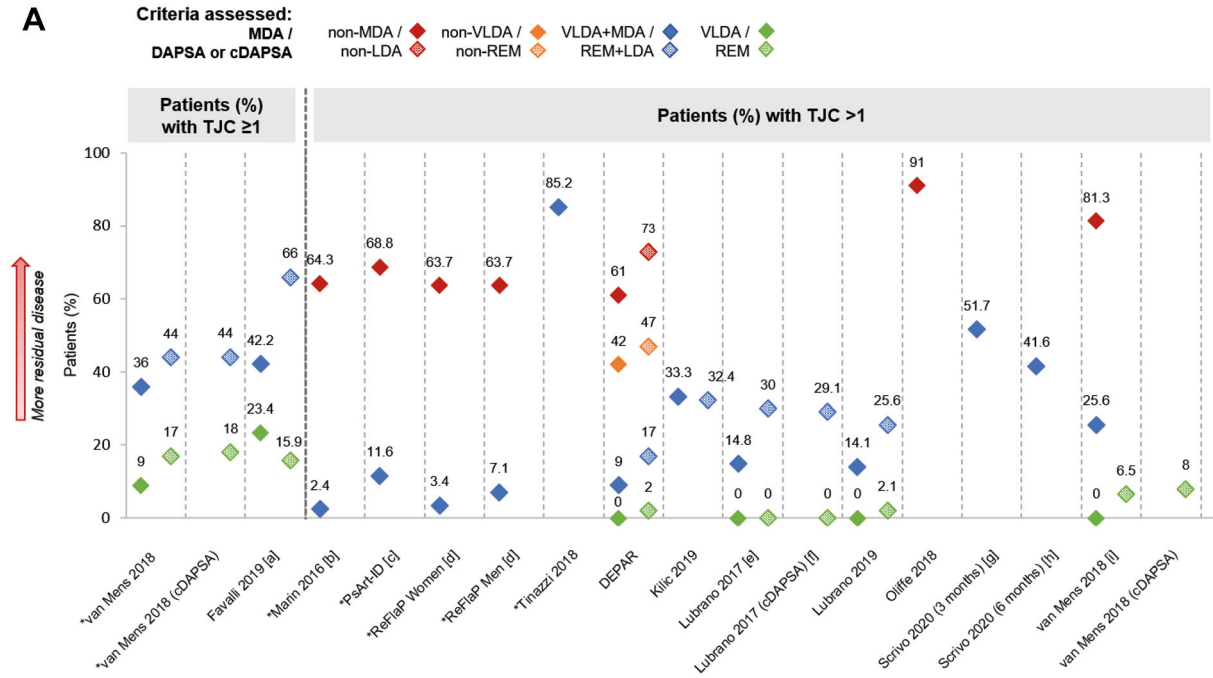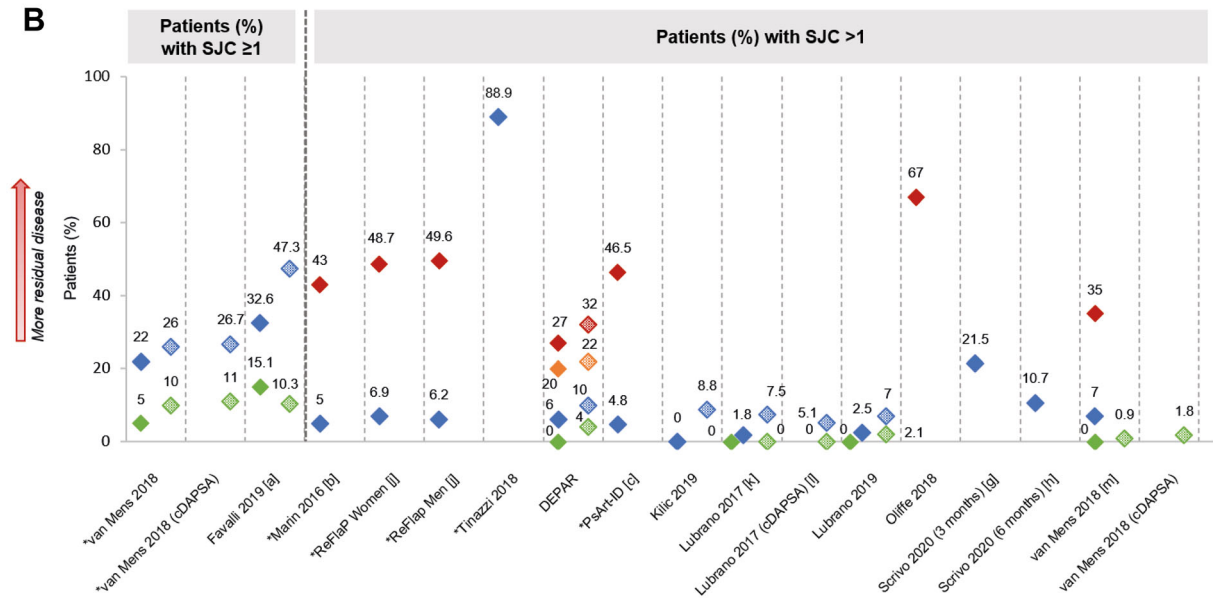

Fig. 1 PRISMA flow diagram of study selection. *LDA* low disease activity, *MDA* minimal disease activity, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *PsA* psoriatic arthritis, *REM* remission, *SLR* systematic literature review

◄**Fig. 2** Prevalence of tender joints (**a**) and swollen joints (**b**), where reported. Note: Unless stated otherwise, shapes with hatching refer to patients assessed by DAPSA, not cDAPSA. Asterisk indicates that data were inversed for ease of comparison (e.g. percentage of patients with TJC ≤ 1 has been transformed into percentage of patients with TJC > 1). [a] Digitised from a graph in the abstract. [b] $p < 0.0001$ VLDA + MDA vs. non-MDA. [c] $p < 0.001$ VLDA + MDA vs. non-MDA. [d] $p = 0.341$ VLDA + MDA women vs. men; $p = 0.174$ non-MDA women vs. men (likely a misprint in the data). [e] VLDA group: in a separate subgroup analysis of $n = 15$, 9 (60%) patients had TJC = 0, while 6 (40%) patients had TJC = 1; DAPSA REM group: in a separate subgroup analysis of $n = 18$, 13 (72.2%) patients had TJC = 0, while 5 (27.6%) patients had TJC = 1. [f] cDAPSA REM group: in a separate subgroup analysis of $n = 22$, 16 (72.7%) patients had TJC = 0, while 6 (27.3%) patients had TJC = 1. [g] Data unknown for 11 (7.4%) of participants. [h] Data unknown for 24 (16.1%) of participants. [i] Data for VLDA + MDA group and non-MDA group digitised from a graph in the manuscript; $p < 0.001$ VLDA + MDA vs non-MDA. [j] $p = 0.863$ VLDA + MDA women vs. men; $p = 0.248$ non-MDA women vs. men. [k] VLDA group: in a separate subgroup analysis of $n = 15$, 14 (93.3%) patients had SJC = 0, while 1 (6.7%) patient had SJC = 1; DAPSA REM group: in a separate subgroup analysis of $n = 18$, 17 (94.5%) patients had SJC = 0, while 1 (5.5%) patient had SJC = 1. [l] cDAPSA REM group: in a separate subgroup analysis of $n = 22$, 21 (95.4%) patients had SJC = 0, while 1 (4.5%) patient had SJC = 1. [m] $p = 0.000$ for VLDA + MDA vs. non-MDA. *(c)DAPSA* (clinical) Disease Activity Index in PsA, *SJC* swollen joint count, *TJC* tender joint count, *VLDA* very low disease activity

Data Analysis

Publications on the same cohort of patients were treated as a single unit. Data extraction and quality assessment followed guidelines from the University of York Centre for Reviews and Dissemination (CRD) [29]. Information from included studies, including group-level outcomes, were extracted into a prespecified grid (ESM Table S6) by a single reviewer and verified and checked for completeness by a second reviewer. Discrepancies were resolved by consensus, or if necessary, by arbitration. The quality of included studies was assessed using an adaptation of a checklist recommended by the National Institute for Health and Care Excellence (NICE) for evaluating the quality of prognosis studies in SLRs (ESM Table S7) [30].

RESULTS

The electronic database search identified 2328 unique records; 546 were included in the full-text review, of which 38 publications were included in the SLR, alongside four articles identified through the supplementary searches (Fig. 1). The 42 included articles comprised 27 unique studies (i.e. some articles referred to the same study) of which 21 were cross-sectional and six were longitudinal. Overall, 23 studies reported relevant outcomes for patients assessed by the MDA metric, while fewer reported outcomes for patients assessed by DAPSA (number of studies [NS] = 14), DAS28 (NS = 3) and CDAI (NS = 2); 13 studies included multiple disease activity metrics. There was substantial heterogeneity in the reporting of outcomes and the grouping of patients (ESM Table S8). ESM Fig. S1 presents an overview of the different ways in which patients were grouped in studies, according to disease activity states.

All 27 studies reported relevant residual disease outcomes, and 20 of the studies included residual disease in their study objectives; one study explicitly used a T2T strategy. Studies were distributed across Europe, Asia and North and South America, including 5138 patients with PsA in total; sample sizes ranged from 20 to 624 patients (NS = 27). Where reported, mean age ranged from 41.4 to 59 years (NS = 21). Mean prior disease duration ranged from 3.8 to 15.3 years (NS = 14). Five studies reported patients' treatment history prior to enrolment (ESM Table S9). Ten studies reported treatments initiated at enrolment: seven studies included conventional synthetic DMARDs and seven included biologic DMARDs (ESM Table S10). Study characteristics are reported in ESM Tables S11 and S12–S17. The quality assessment identified that potential sources of bias were addressed with varying levels of adequacy across studies, although many studies did not report enough detail to fully assess risk of bias (ESM
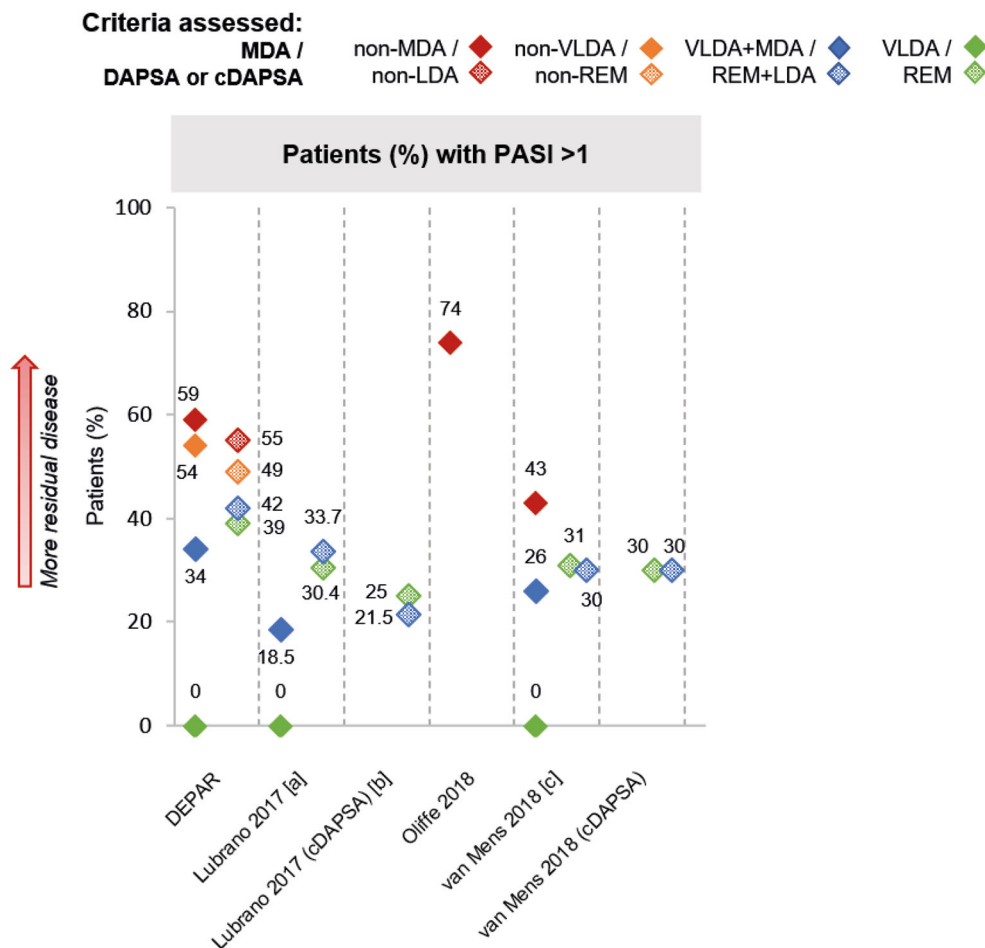
Criteria assessed:

MDA / non-MDA / ◆ non-VLDA / ◆ VLDA+MDA / ◆ VLDA / ◆
DAPSA or cDAPSA non-LDA / ◈ non-REM / ◈ REM+LDA / ◈ REM / ◈

Patients (%) with PASI >1

More residual disease

100

80   74

60   59
      54   55
            49
            42   33.7
      34   39
            30.4   43
                    31   30   30
      18.5 30.4   26   30
            21.5 25
0   0   0   0

DEPAR   Lubrano 2017 [a]   Lubrano 2017 (cDAPSA) [b]   Oliffe 2018   van Mens 2018 [c]   van Mens 2018 (cDAPSA)

Fig. 3 Prevalence of skin disease by PASI, where reported. Note: Unless stated otherwise, shapes with hatching refer to patients assessed by DAPSA, not cDAPSA. Asterisk indicates that data were inversed for ease of comparison (e.g. percentage of patients with PASI ≤ 1 has been transformed into percentage of patients with PASI > 1). *[a]* VLDA group: in a separate subgroup analysis of $n = 15$, 12 (80.0%) patients had PASI 0–0.3, 2 (13.3%) patients had PASI 0.4–0.6 and 1 (6.7%) patient had PASI 0.7–1; DAPSA REM group: in a separate subgroup analysis of $n = 18$, 11 (61.1%) patients had PASI 0–0.3, 2 (11.1%) patients had PASI 0.4–0.6 and 5 (27.7%) patients had PASI > 1. *[b]* cDAPSA REM: in a separate subgroup analysis of $n = 22$, 14 (63.6%) patients had PASI 0–0.3, 2 (9.0%) patients had PASI 0.4–0.6, 1 (4.5%) patient had PASI 0.7–1 and 5 (22.7%) patients had PASI > 1. *[c]* $p = 0.002$ VLDA + MDA vs. non-MDA. *PASI* Psoriasis Area and Severity Index

Table S11). A more detailed summary of the quality assessment is provided in ESM Table S18.

Among patients assessed by PsA-specific metrics, 35–85% of each study population (NS = 5) did not achieve MDA or LDA [7, 31–35], 14–100% (NS = 11) achieved at least MDA or LDA (the most commonly reported group) [7, 31, 33–45] and 12–43% (NS = 6)

achieved VLDA or REM (ESM Table S8) [37, 40, 41, 45–49].

Residual Musculoskeletal Disease

Musculoskeletal outcomes were reported in 18 studies (ESM Tables S8, S19–41). Among groups that did not achieve MDA or DAPSA/cDAPSA LDA, 61–91% patients (NS = 6) had a tender

joint count (TJC) > 1 (Fig. 2a) [31, 32, 35, 45, 50, 51], and mean TJC ranged from 1.8 to 10.3 (NS = 2) [50, 51]. Across groups that achieved at least MDA or DAPSA/cDAPSA LDA, 2–85% patients (NS = 10) had TJC > 1 (Fig. 2a) [7, 31, 40, 41, 45, 50–54], and mean TJC ranged from 0.3 to 0.8 (NS = 4) [50, 51, 55, 56]. Residual musculoskeletal disease was least evident among groups that reached VLDA, in which 0% patients had TJC > 1 (NS = 4; 9% patients who reached VLDA had TJC = 1 in van Mens et al. [35]), or DAPSA/cDAPSA REM, in which 0–8% patients had TJC > 1 across the same four studies (Fig. 2a) [40, 41, 44, 45, 54]. Similar patterns of residual disease were reported for swollen joint count (SJC; Fig. 2b). A smaller number of studies reported enthesitis (primarily using the Leeds Enthesitis Index [LEI]), tenosynovitis, oligoarthritis and dactylitis, for which residual disease was also observed (ESM Tables S29–S41).

One study reported musculoskeletal outcomes for DAS28-assessed patients, in which 36% patients who had achieved at least LDA (REM + LDA) had TJC > 1; residual SJC, enthesitis, tenosynovitis and dactylitis were also reported for this patient group [7]. One study reported musculoskeletal outcomes for CDAI-assessed patients, in which median TJC28 was 5 (interquartile range: 3–8) among patients in CDAI REM; substantial residual SJC, enthesitis and dactylitis were also reported [57]. For four studies in which patients were assessed using more than one disease activity metric, there were mostly fewer patients with TJC > 1 and SJC > 1 in groups who achieved at least MDA than in groups who achieved at least DAPSA/cDAPSA LDA (Fig. 2) [7, 40, 41, 45]. van Mens et al. reported that 64% patients in VLDA + MDA achieved TJC = 0, compared with 56% in DAPSA REM + LDA (Fig. 2a) [44].
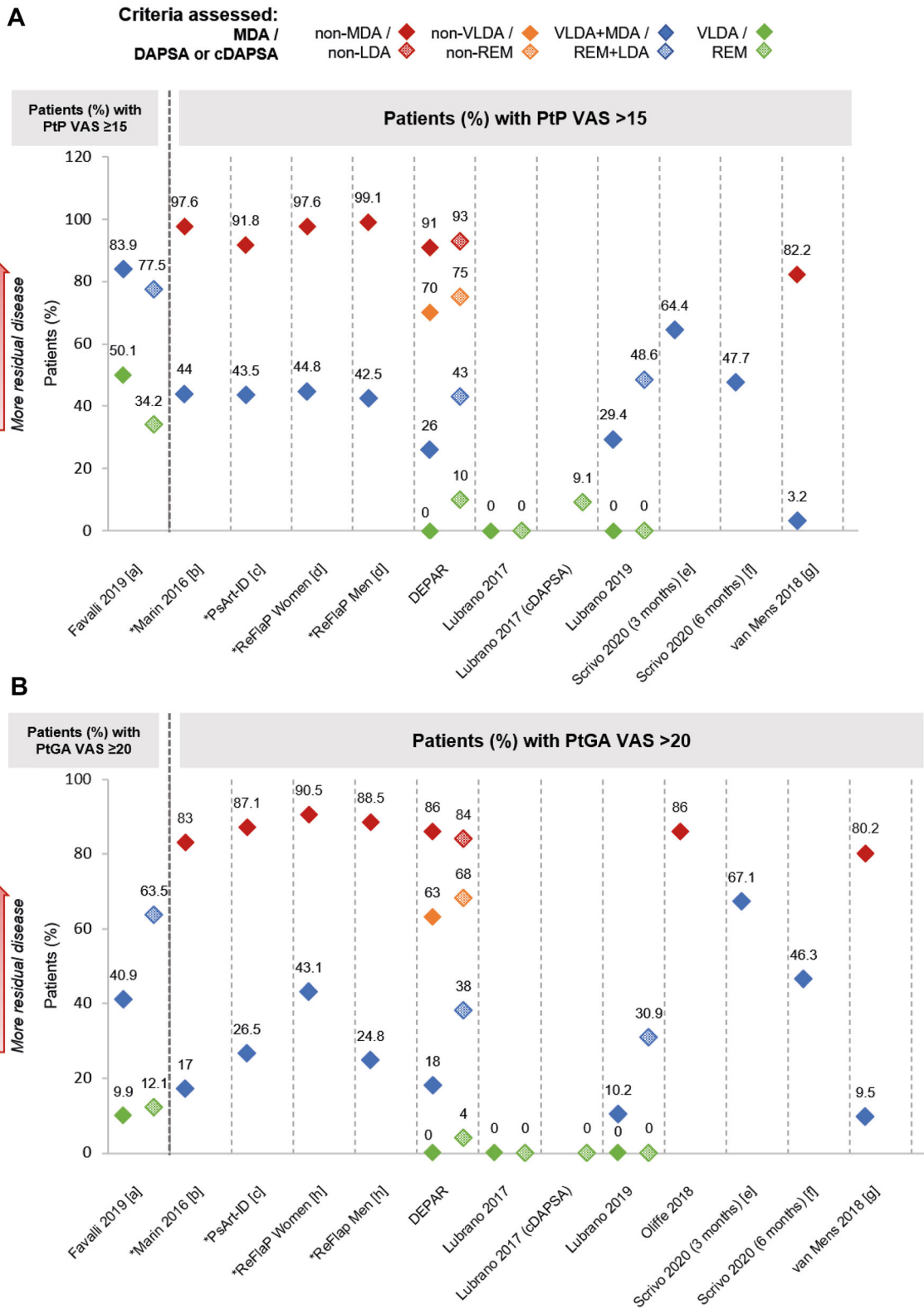
Residual Skin Disease

Skin outcomes were reported in 14 studies (ESM Tables S8, S42–S46). Among groups that did not achieve MDA, mean Psoriasis Area and Severity Index (PASI) score ranged from 2.8 to 4 (NS = 3) [33, 42, 51] and mean body surface area was 12% (NS = 1) [51]; 43–74% patients (NS = 3) had PASI > 1 (Fig. 3) [32, 34, 35, 45]. In the one study that reported PASI for groups that did not achieve DAPSA LDA, 55% patients had PASI > 1 [45]. Among groups that achieved at least MDA, 19–34% patients had PASI > 1 (NS = 3) [34, 35, 40, 45], while 22–42% (NS = 3) of those who achieved at least DAPSA/cDAPSA LDA had PASI > 1 [40, 44, 45]. Among VLDA groups, 0% patients had PASI > 1 across the three studies concerned, whereas among DAPSA/cDAPSA REM groups, 25–39% patients had PASI > 1 across the same three studies (Fig. 3) [40, 44, 45]. Only one study reported skin outcomes (PASI scores) for patients assessed by DAS28 (ESM Table S44) [58]; no skin outcomes were reported for CDAI-assessed patients.

Residual Patient-Reported Disease

PROs were reported in 26 studies (ESM Tables S8, S47–S70). Among groups that did not achieve MDA or DAPSA/cDAPSA LDA, mean patient pain (PtP) on a 0–100 visual analogue scale (VAS; 1–10 VAS transformed where necessary) ranged from 44 to 63 (NS = 3) [39, 51, 58] and from 47 to 66, respectively (NS = 2) [39, 50]. Among groups that achieved at least MDA or DAPSA/cDAPSA LDA, mean PtP VAS ranged from 9 to 25 (NS = 5) [39, 51, 55, 56, 58] and from 18 to 27 (NS = 3) [39, 50, 55], respectively; it was also common to see PtP VAS > 15 in these groups (Fig. 4a). In three studies that assessed patients using multiple disease activity metrics, prevalence of PtP VAS > 15 among patients who achieved VLDA was 0% in the three studies, whereas for patients who achieved DAPSA REM, prevalence of PtP VAS > 15 was 0% in two studies (one of which also reported PtP VAS > 15 for 9% patients in cDAPSA REM) [46] and 10% in the other (Fig. 4a) [41, 45, 46]. PtP VAS was also reported in two studies that used DAS28 and in one study that assessed patients by CDAI [7, 57, 58]; within these studies, residual PtP VAS was reported across all tiers of disease activity, including DAS28/CDAI REM (Tables ESM S47–S51).

A

Criteria assessed:
MDA / non-MDA / ◆ non-VLDA / ◆ VLDA+MDA / ◆ VLDA / ◆
DAPSA or cDAPSA non-LDA / ◈ non-REM / REM+LDA / ◈ REM / ◈

| Patients (%) with PtP VAS ≥15 | Patients (%) with PtP VAS >15 |

B

| Patients (%) with PtGA VAS ≥20 | Patients (%) with PtGA VAS >20 |

◀ **Fig. 4** Patient pain VAS (**a**) and patient global assessment VAS (**b**), where reported. Note: Unless stated otherwise, shapes with hatching refer to patients assessed by DAPSA, not cDAPSA. Asterisk indicates data that were inversed for ease of comparison (e.g. percentage of patients with PtP VAS ≤ 15 has been transformed into percentage of patients with PtP VAS > 15). *[a]* Digitised from a graph in the abstract. [b] $p < 0.0001$ VLDA + MDA vs. non-MDA. *[c]* $p < 0.001$ VLDA + MDA vs. non-MDA. [d] $p = 0.771$ VLDA + MDA women vs. men; $p = 0.355$ non-MDA women vs. men. [e] Data unknown for 11 (7.4%) participants. [f] Data unknown for 24 (16.1%) participants. [g] Digitised from a graph in the manuscript; $p < 0.001$ VLDA + MDA vs. non-MDA. [h] $p = 0.011$ VLDA + MDA women vs. men; $p = 0.594$ non-MDA women vs. men. *PtGA* patient global assessment, *PtP* patient pain, *VAS* visual analogue scale

Similar patterns of residual disease were observed in findings from the patient global assessment (PtGA) VAS (Fig. 4b) and Health Assessment Questionnaire Disability Index (HAQ-DI; Fig. 5). Among groups that did not achieve MDA or DAPSA/cDAPSA LDA, 80–91% patients (NS = 6) [31, 32, 35, 45, 50, 51] and 84% patients (NS = 1) [45] had PtGA VAS > 20, respectively; 29–80% patients (NS = 6) [31, 32, 35, 45, 50, 51] and 74% patients (NS = 1) [45] had HAQ-DI > 0.5, respectively. Trends like those observed in musculoskeletal and skin outcomes were also seen for both these PROs, with less residual disease in groups with more stringent disease control, and less residual disease in MDA and VLDA groups compared to DAPSA/cDAPSA LDA and REM groups, respectively (Figs. 4b; 5). For example, among VLDA groups, no patients had HAQ-DI > 0.5 in three studies [40, 41, 45, 46] and 8% patients were above this threshold in a further study [37]; among DAPSA/cDAPSA REM groups, 4–15% patients (NS = 4) [37, 40, 41, 45, 46] had HAQ-DI > 0.5.

Five studies that reported PtGA VAS also reported physician global assessment (PhGA) VAS. In different studies and patient groups, there were differing degrees of alignment between PtGA and PhGA; for example, in van Mens et al., median PtGA and PhGA VAS were 6 and 7, respectively, among patients who achieved at least MDA, while medians were 37 and 23, respectively, in patients who did not achieve MDA [35]. Generally, there was a trend for PtGA to be higher (i.e. worse) than PhGA, as demonstrated in the PsArt-ID study in which median PtGA and PhGA VAS among patients who achieved at least MDA were 20 and 10, respectively, while in patients who did not achieve MDA, median PtGA and PhGA were 50 and 35, respectively [31].

Residual disease in treated patients, including those who had met treatment targets, was also evident across PROs that are not components of the MDA metric, DAPSA or the other included metrics (Table 1). These PROs encompassed patient-reported fatigue, disability and quality of life measures, as detailed in ESM Tables S8 and S65–70. The Psoriatic Arthritis Impact of Disease 12-item questionnaire (PsAID-12; range: 0–10, where 10 represents the worst score) [59] was among the more commonly reported of these PROs. Among groups that did not achieve MDA or DAPSA/cDAPSA LDA, mean PsAID-12 ranged from 3.8 to 7.1 (NS = 5) [33, 36, 39, 42, 60] and from 3.9 to 5.3 (NS = 3) [38, 39, 50], respectively. Mean PsAID-12 ranged from 1.1 to 3.5 (NS = 5) among groups that achieved at least MDA [33, 36, 39, 42, 60], and from 1.7 to 2.7 (NS = 3) [38, 39, 50] for those that achieved at least DAPSA/cDAPSA LDA. Mean PsAID-12 in the one study that reported this outcome for a VLDA group was 1.1 [48, 49]; among DAPSA/cDAPSA REM groups, mean PsAID-12 scores of 1.3 and 1.7 were reported in one study [48]. Yedimenko et al. reported median PsAID-12 for patients meeting targets assessed by the MDA metric, DAPSA, and CDAI; for those in MDA or DAPSA/CDAI LDA, median PsAID-12 was 1.5, 2.4 and 1.7, respectively, and in the VLDA or DAPSA/CDAI REM groups, median PsAID-12 was 0.4, 0.7 and 0.5, respectively [61]. None of the included studies reported PsAID-12 for DAS28-assessed patients.

DISCUSSION

This systematic review is, to our knowledge, the first to characterise the real-world evidence of residual disease among treated PsA patients
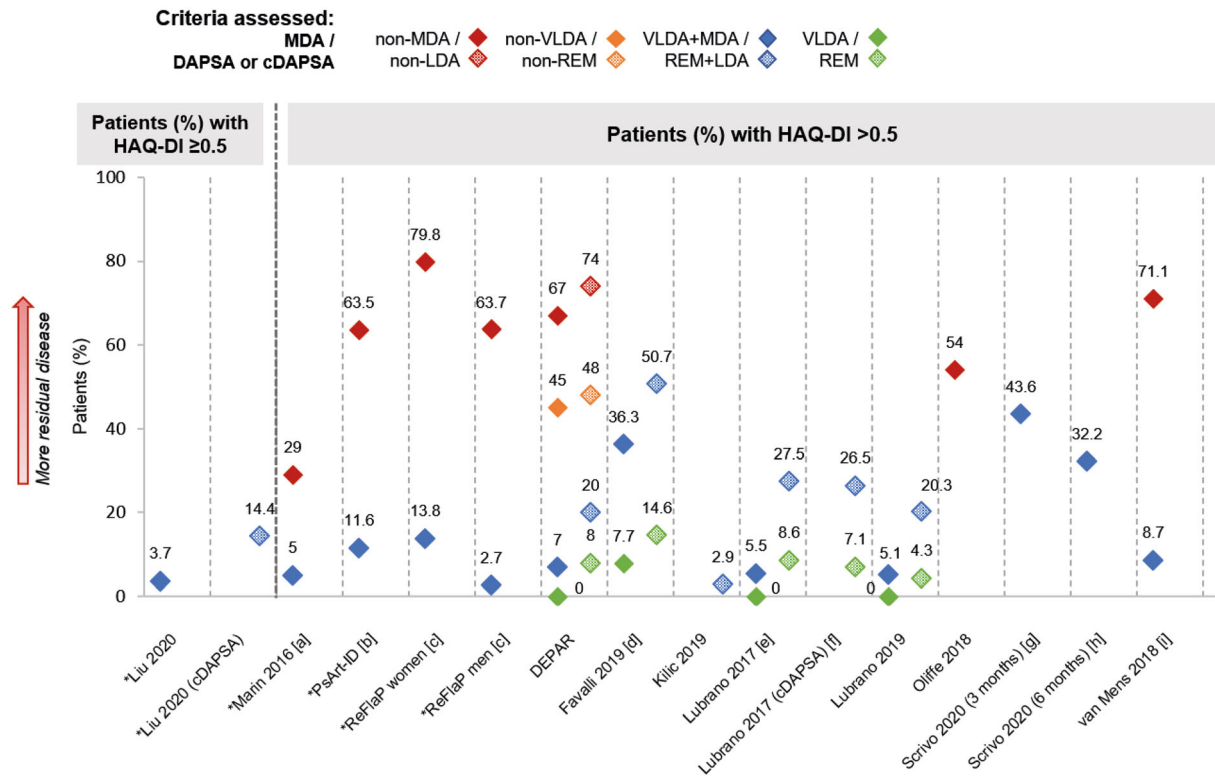
Fig. 5 HAQ-DI, where reported. Note: Unless stated otherwise, shapes with hatching refer to patients assessed by DAPSA, not cDAPSA. Asterisk indicates data that were inversed for ease of comparison (e.g. percentage of patients with HAQ-DI ≤ 0.5 has been transformed into percentage of patients with HAQ-DI > 0.5). [a] $p = 0.004$ VLDA + MDA vs. non-MDA. [b] $p < 0.001$ VLDA + MDA vs. non-MDA. [c] $p = 0.005$ VLDA + MDA women vs. men; $p = 0.003$ non-MDA women vs. men. [d] Digitised from a graph in the abstract. [e] VLDA group: in a separate subgroup analysis of $n = 15$, all

patients had HAQ-DI ≤ 0.5; DAPSA REM group: in a separate subgroup analysis of $n = 18$, 17 (94.5%) patients achieved HAQ-DI ≤ 0.5, while 1 (5.5%) patient had HAQ-DI > 0.5. [f] cDAPSA REM group: in a separate subgroup analysis of $n = 22$, 20 (90.9%) patients achieved HAQ-DI ≤ 0.5, while 2 (9.1%) patients had HAQ-DI > 0.5. [g] Data unknown for 11 (7.4%) participants. [h] Data unknown for 24 (16.1%) participants. [i] Digitised from a graph in the manuscript; $p < 0.001$ VLDA + MDA vs non-MDA. *HAQ-DI* Health Assessment Questionnaire-Disability Index

grouped by thresholds of disease control. The evidence demonstrated that, despite treatment, a large proportion of patients may not reach treatment targets and consequently face substantial residual disease. As expected, this review showed that patients with disease control usually considered optimal (VLDA/REM or MDA/LDA) tended to have less residual disease than patients who did not achieve such control. However, even patients who achieved the most stringent targets (VLDA or REM) still experienced a range of residual disease, including (but not limited to) tender and swollen joints,

enthesitis, skin disease and patient-reported pain, disability and disease impact on patients' lives.

Persistence of patient-reported symptoms, even among patients in VLDA or REM, indicates that achieving stringent targets may still not result in satisfactory resolution of disease and acceptable disease impact from the patient's perspective. While some of the PROs did demonstrate residual disease impact among patients achieving targets, patients' wider perceptions of their residual disease were beyond the scope of this review. Published evidence on

the views of patients with PsA is limited, although it is recognised that there can be a discord between patient and physician perspectives, consistent with findings in this review (PtGA vs. PhGA VAS). Patient-reported assessments have been found to show worse disease than physicians' assessments, especially for patients in remission, and patient–physician discordance has also been observed when considering which symptoms are most important or burdensome [62, 63]. These findings suggest that treatment strategies might be improved by more explicitly considering patient perspectives, a strategy which has also been proposed for the treatment of patients with RA [64]. For instance, the target metric could be complemented by a patient-reported measure of disease impact (e.g. PsAID-12, an outcome reported in some included studies in this SLR), such that care can be personalised to address issues important to the individual patient.

Many studies included combined groups of patients with at least MDA (VLDA + MDA), or at least LDA (REM + LDA), depending on the metric. There was considerable between-study variation in the extent of residual disease among these groups; low residual disease was reported in some studies [40, 41, 50, 51, 65], while others reported a relatively high prevalence and/or severity of residual disease [37, 52, 53]. In the studies where patients achieving VLDA or REM were assessed separately from groups achieving MDA or LDA, the prevalence of residual disease was lower, but often not absent. These findings are consistent with the T2T guidelines, where VLDA or REM are recommended as primary treatment targets [13, 16]. However, targeting the most stringent threshold of disease control may not necessarily lead to the optimal outcome for an individual patient. The stringency of a target is likely to be balanced against how attainable it is for the patient, as there may be side effects, comorbidities or other factors that become relevant in the context of a change to the patient's drug treatment. Attainability may in turn affect treatment adherence and overall response to therapy. The secondary targets of MDA or LDA may therefore be suitable alternatives in some cases [13, 16]. This emphasises the importance of patient education and shared decision-making when considering how to address patients' residual disease burden, for both pharmacological interventions such as treatment escalation and the overall management of disease activity and disease impact [66].

Among patients in the same 'tier' of disease control (as assessed using the same metric; e.g. all in DAPSA LDA), there was heterogeneity in residual disease between studies. Studies differed in terms of inclusion and exclusion criteria, treatment and the assessment timepoints. However, the between-study variation in residual disease may also reflect the breadth of disease activity that can occur within each tier (e.g. DAPSA LDA encompasses scores of 4–14).

Across musculoskeletal, skin and PROs, patients in VLDA (by the MDA metric) tended to have less residual disease than patients in DAPSA REM, as did patients in MDA compared with DAPSA LDA. These findings were supported by studies that classified the same patients using both metrics, allowing residual disease to be more accurately compared between 'equivalent' groups. In the DEPAR study for example, prevalence of > 1 residual tender or swollen joints, > 1 tender entheseal points, PASI > 1, PtP VAS > 15, PtGA VAS > 20 or HAQ-DI > 0.5 was lower among MDA-achievers than among DAPSA LDA-achievers [22, 45, 67–70]. Across the MDA metric and DAPSA, we noted that these listed thresholds were most often exceeded for PASI, PtP and PtGA. This was least likely for the musculoskeletal outcomes. The differences in residual disease between the PsA-specific metrics MDA and DAPSA are likely related to their composition. DAPSA is an additive sum of several components, whereas the MDA metric is a count of stringent thresholds met for seven disease domains. Importantly, the MDA metric domains better reflect the multifaceted nature of PsA disease through the inclusion of skin and entheseal assessments, which are not included in DAPSA. This is likely a key reason for the very low levels of residual skin disease among patients in VLDA, versus the substantial residual skin disease among patients in DAPSA REM, as well as the relatively similar skin outcomes for DAPSA LDA and DAPSA REM.

Notably, despite T2T being recommended by international groups, only one of the 27 studies explicitly reported that patients were treated using a T2T approach. However, within the context of T2T for PsA, this review supports GRAPPA's recommendation for the use of the MDA metric over DAPSA [13, 71], insofar as the achievement of MDA or VLDA is associated with less residual disease compared with DAPSA LDA or REM. Very few studies classified patients using DAS28 [7, 58, 72] or CDAI [57, 61], limiting the qualitative comparisons with PsA-specific metrics. The available data indicated that patients meeting DAS28 and CDAI targets have substantial residual disease.

Strengths of this review included adherence to best-practice systematic review methods [26], as well as relevance to clinical practice by including only observational studies that covered a range of different regions and populations. However, the focus on observational studies also introduced limitations. It is important to consider the substantial heterogeneity between studies, including differences in study design, treatment and baseline patient characteristics, all of which complicated interpretation and comparison of study results. Furthermore, most included studies were cross-sectional and did not assess patients at a consistent timepoint within their disease or treatment pathway, hence some patients may have spent less time on treatment with less opportunity for a disease response. Additionally, the prevalence and/or severity of residual disease were reported in numerous ways across different studies, further complicating comparisons of their results. Congress abstracts were included in this SLR in accordance with Cochrane Collaboration recommendations [27], although we note the increased risk of selection bias associated with such publications.

CONCLUSIONS

Overall, the findings of this study highlight the need for further effective treatments and for continued refinement of strategies to reduce residual disease, both in patients aiming to achieve treatment targets and in those who

have achieved them. Although this review has characterised residual disease among treated patients with PsA, including that reported by patients themselves, patients' views about their residual disease and care were beyond the scope of this review; this topic warrants further research. Future studies should also aim to evaluate whether patients' perceptions of their symptoms and disease, and their knowledge and expectations of available treatments and outcomes, may affect the burden of disease they experience. This may ultimately help advance patient education and engagement, and tailoring of treatment strategies to address the aspects of PsA that are of greatest importance to patients.

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Compliance with Ethics Guidelines. This SLR is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. This study is an SLR and no novel data were generated. All data relevant to the study are either included in the article or uploaded as supplementary information.

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