Comparison of Different Remission and Low Disease Definitions in Psoriatic Arthritis and Evaluation of Their Prognostic Value

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ABSTRACT. ***Objective.*** There is no agreement on the optimal definitions for assessing disease state in patients with psoriatic arthritis (PsA), and some of the commonly used definitions do not include assessment of skin lesions. We investigated the performance of various definitions in patients with PsA and psoriasis.

Methods. This was a posthoc analysis of data from the PRESTA study. The remission definitions analyzed were very low disease activity (VLDA) index, defined as 7/7 of the minimal disease activity (MDA) cutoffs; Disease Activity Index for PsA (DAPSA); and clinical (c-) DAPSA. The low disease activity (LDA) definitions analyzed were as follows: MDA defined as 5/7 cutoffs; MDA joint with both the tender joint count (TJC) and swollen joint count (SJC) cutoffs mandated; MDA skin where skin cutoff was mandated; MDA joint + skin where TJC, SJC, and skin cutoffs were mandated; DAPSA LDA; and cDAPSA LDA.

Results. At Week 24, the proportions of patients achieving VLDA, DAPSA, and cDAPSA remission were 10%, 35%, and 37%, respectively. Of the patients achieving DAPSA and cDAPSA remission, 55% and 56%, respectively, had Psoriasis Area and Severity Index > 1. The proportions of patients achieving MDA 5/7, MDA skin, MDA joint, and MDA joint + skin were 44%, 19%, 36%, and 14%, respectively, versus 70% achieving DAPSA and cDAPSA LDA. Notable residual levels of psoriasis were observed in patients achieving the definitions that did not require skin disease control.

Conclusion. VLDA and MDA definitions are more stringent than DAPSA and cDAPSA definitions for the assessment of PsA. The relevance of residual disease to patients, however, remains to be determined. [Clinical Trial registration: ClinicalTrials.gov NCT00245960] (First Release October 15 2018; J Rheumatol 2019;46:160–5; doi:10.3899/jrheum.180249)

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Psoriasis is a skin disorder characterized by scaly and itchy plaques that affects 1–3% of the world's population[1,2]. Up to 40% of people with psoriasis develop psoriatic arthritis (PsA)[3,4,5], a form of inflammatory arthritis affecting the joints and the tendons around the joints, which is characterized by specific manifestations such as the swelling of whole digits (dactylitis) and the inflammation of the entheses (enthesitis). The prevalence of PsA in the general population is about 0.1–1.0%[3]. PsA usually appears in patients with psoriasis within 10–12 years, and patients with extensive psoriatic skin lesions are at increased risk of developing PsA[1,3,6]. Patients with both PsA and psoriasis tend to have a decreased quality of life compared with patients with psoriasis only[7,8], owing to the discomfort caused by the skin condition as well as the pain and disability caused by the joint damage.

A wide range of treatments is available for PsA, including nonsteroidal antiinflammatory drugs, conventional synthetic disease-modifying antirheumatic drugs (DMARD), interleukin (IL)-12/23, IL-17A, phosphodiesterase type 4 (PDE4), and tumor necrosis factor-α (TNF-α) inhibitors[9,10,11,12]. Several studies have shown that clinical remission or minimal disease activity (MDA) can be achieved by 40–60% of patients using TNF-α inhibitors[13,14,15,16]. In addition, IL-12/23, IL-17A, and PDE4 inhibitors are valid alternatives to DMARD therapy[11,17,18,19].

Adoption of a treat-to-target (T2T) approach aiming at tight disease control has been shown to improve physician- and patient-reported outcomes in patients with recent-onset PsA[20]; therefore, European League Against Rheumatism guidelines suggest adopting a T2T approach as the standard of care for patients with PsA, with either remission or low disease activity (LDA) as the target[9].

The many different manifestations associated with PsA pose a challenge when assessing patients and their response to treatments. This has led to the development of several composite definitions encompassing clinically important aspects of the disease such as arthritis, psoriasis, enthesitis, pain, patient-assessed global disease activity, and physical function, which then combine into a single disease activity score[21]. One such composite definition is the Disease Activity Index for PsA (DAPSA), which was adapted from the Disease Activity Index for Reactive Arthritis and validated using data from PsA clinical trials[22]. DAPSA cutoffs for remission and LDA have been established; however, DAPSA focuses primarily on peripheral arthritis, and does not include other PsA manifestations such as psoriasis or enthesitis. In 2010, the MDA criteria were developed to encompass most PsA domains[13]. Remission or very low disease activity (VLDA) is achieved when 7 of the 7 MDA cutoffs are met, while meeting only 5/7 cutoffs is classified as a minimal or low disease state[23]. According to recent recommendations by an international task force, either DAPSA or MDA should be used to define the target in disease control; however, further research is needed to establish the pros and cons of each of these definitions in PsA assessment[24].

The objective of our present analysis was to investigate the performance of various remission and LDA definitions in patients with PsA with extensive skin lesions.

MATERIALS AND METHODS

This was a posthoc analysis of data from the PRESTA[25] double-blind multicenter clinical study (NCT00245960), in which patients with both psoriasis and PsA were randomized to receive 50 mg etanercept (ETN) either twice weekly (BIW) or once weekly (QW) for 12 weeks by subcutaneous injection[25]. This was followed by an additional 12 weeks in which both cohorts received open-label ETN 50 mg QW. An independent ethics committee or institutional review board approved the protocol of this study[25]. All participants provided a signed informed consent form[25].

Definition of remission and LDA. The remission and LDA definitions evaluated in this analysis are shown in Table 1. Briefly, VLDA remission was defined as meeting 7/7 cutoffs of the MDA definition [tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, Psoriasis Area and Severity Index (PASI) ≤ 1, patient's global assessment visual analog scale (PtGA VAS) ≤ 20 mm, Pt pain VAS ≤ 15 mm, Health Assessment Questionnaire (HAQ) ≤ 0.5, tender entheseal points ≤ 1]. DAPSA remission was defined as DAPSA ≤ 4 [TJC, SJC, PtGA VAS, Pt pain VAS, C-reactive protein (CRP)]; cDAPSA (clinical DAPSA without CRP) remission was defined as cDAPSA ≤ 4. The LDA definitions evaluated were DAPSA LDA ≤ 14 (TJC, SJC, PtGA VAS, Pt pain VAS, CRP); cDAPSA LDA ≤ 13; MDA defined as 5/7 cutoffs; MDA joint with both TJC and SJC cutoffs mandated, and with any 3/5 of the remaining cutoffs; MDA skin where PASI cutoff was mandated, and with any 4/6 of the remaining cutoffs; and MDA joint + skin where the TJC, SJC, and skin cutoffs were mandated, and with any 2/4 of the remaining cutoffs.

Statistical analysis. The proportion of patients achieving remission and LDA responses was calculated at Week 12 and at Week 24. Treatment effect was calculated using chi-square tests. Response was compared by analyzing the levels of concordance/discordance and by assessing the frequency of occurrence of the different levels of residual disease (e.g., > 0, > 1) across the PsA manifestations (dactylitis, enthesitis, psoriasis, TJC, SJC) among the definitions. Levels of residual disease were considered clinically meaningful if they were above the MDA/LDA cutoffs. Total discordance was calculated as the sum of 2 individual discordances (i.e., the percentage of patients who had a VLDA but not DAPSA or cDAPSA remission response, plus the percentage of patients who did not have a VLDA response but had a DAPSA or cDAPSA remission response). Level of agreement was tested by κ coefficients calculated for each pair of definitions. κ values < 0 indicate no agreement, 0–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.0 almost perfect agreement[26].

RESULTS

PRESTA baseline characteristics. The PRESTA study included 752 patients with PsA and psoriasis at baseline. The mean age was 46.5 years, 62.9% were male, the mean duration of psoriasis was 18.9 years, and the mean duration of PsA was 7.0 years[25]. A total of 379 patients received ETN 50 mg BIW and 373 patients received ETN 50 mg QW.

Remission. At Week 24, a greater proportion of patients achieved DAPSA (232/669, 35%) or cDAPSA (251/676, 37%) remission than VLDA remission (67/669 and 68/676, both 10%). Figure 1A–B shows the proportion of patients achieving remission by treatment cohort. Discordance between VLDA and DAPSA remission was 25% (κ = 0.33), while discordance between VLDA and cDAPSA remission was 27% (κ = 0.32). Only 10% of patients achieving DAPSA but not VLDA remission were in discordance with patients achieving MDA 5/7 (κ not available due to all patients having the same observation). Two patients (0.3%) did not achieve VLDA remission solely because of a HAQ score > 0.5; in contrast, 15/232 (6%) and 17/251 (7%) patients with HAQ score > 0.5 were among patients who achieved DAPSA and cDAPSA remission, respectively.

Two patients (0.3%) who achieved VLDA remission did not achieve DAPSA remission and 167/669 (25%) who achieved DAPSA remission did not achieve VLDA remission. No patients achieved VLDA remission but not cDAPSA remission, while 183/676 (27%) achieved cDAPSA

Table 1. Remission and low disease activity definitions investigated.

Remission			LDA					
VLDA 7/7	DAPSA ≤ 4	cDAPSA ≤ 4	MDA 5/7	MDA Skin	MDA Joint	MDA Joint + Skin	DAPSA ≤ 14	cDAPSA ≤ 13
			Any 5 among:	Mandated:	Mandated:	Mandated:		
TJC ≤ 1	TJC	TJC	TJC ≤ 1	PASI ≤ 1	TJC ≤ 1	TJC ≤ 1	TJC	TJC
SJC ≤ 1	SJC	SJC	SJC ≤ 1	And 4/6 among:	SJC ≤ 1	SJC ≤ 1	SJC	SJC
PASI score ≤ 1	PtGA VAS^ (cm)	PtGA VAS^ (cm)	PASI score ≤ 1	TJC ≤ 1	And 3/5 among:	PASI score ≤ 1	PtGA VAS^ (cm)	PtGA VAS^ (cm)
PtGA VAS* ≤ 20 mm	Pt pain VAS (cm)	Pt pain VAS (cm)	PtGA VAS* ≤ 20 mm	SJC ≤ 1	PASI score ≤ 1	And 2/4 among:	Pt pain VAS (cm)	Pt pain VAS (cm)
Pt pain VAS ≤ 15 mm	CRP (mg/dl)		Pt pain VAS ≤ 15 mm	PtGA VAS* ≤ 20 mm	PtGA VAS* ≤ 20 mm	PtGA VAS* ≤ 20 mm	CRP (mg/dl)	
HAQ ≤ 0.5			HAQ ≤ 0.5	Pt pain VAS ≤ 15 mm	Pt pain VAS ≤ 15 mm	Pt pain VAS ≤ 15 mm		
Tender entheseal points ≤ 1			Tender entheseal points ≤ 1	HAQ ≤ 0.5	HAQ ≤ 0.5	HAQ ≤ 0.5		
				Tender entheseal points ≤ 1	Tender entheseal points ≤ 1	Tender entheseal points ≤ 1		

* PtGA VAS of the maximum component either of psoriasis activity (0–100) or of arthritis activity (0–100). ^ PtGA VAS of arthritis activity (0–100)/10. LDA: low disease activity; VLDA: very LDA; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; MDA: minimal disease activity; TJC: tender joint count; SJC: swollen joint count; PASI: Psoriasis Area and Severity Index; PtGA VAS: patient visual analog scale; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein.

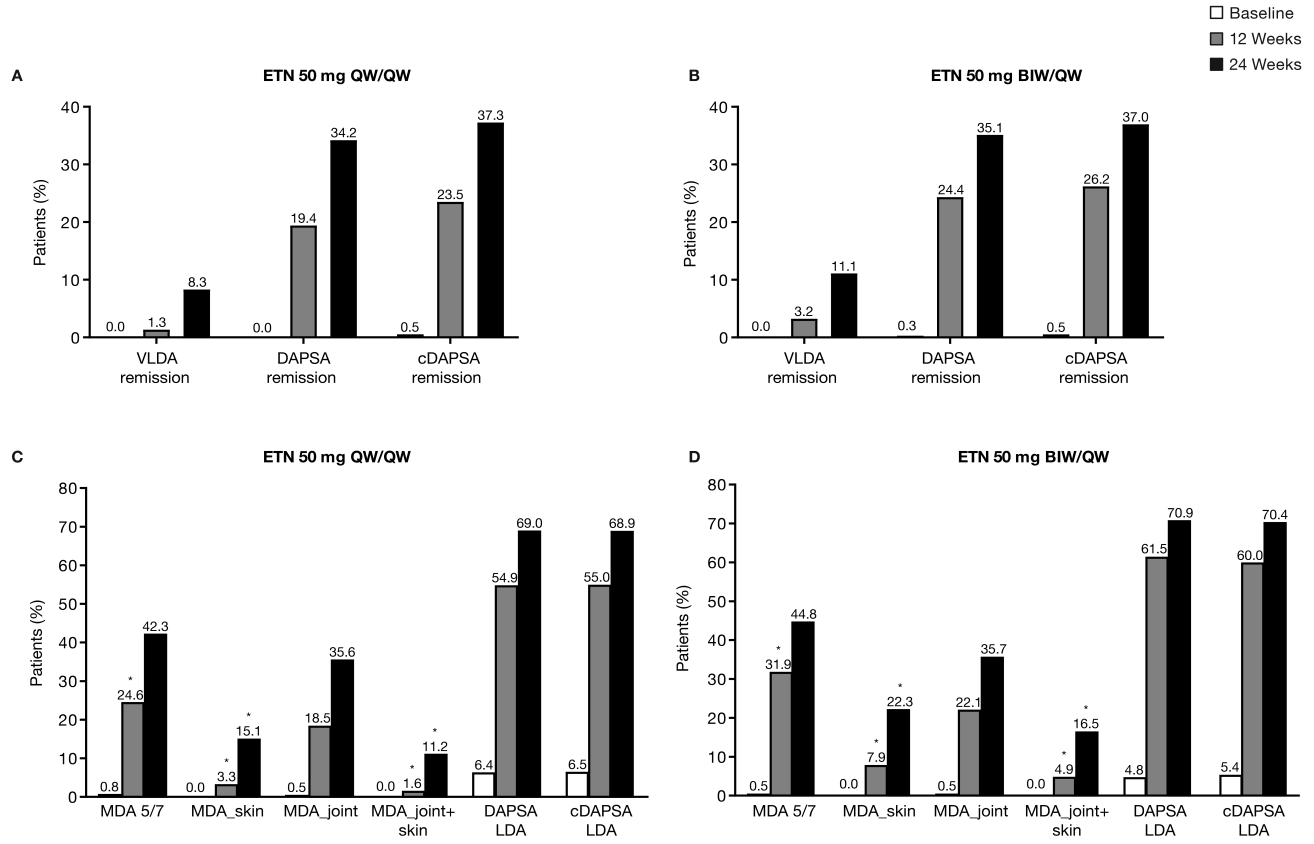

Figure 1. Proportion of patients achieving each definition in the 2 treatment groups. A. Patients receiving ETN 50 mg QW/QW achieving remission. B. Patients receiving ETN 50 mg BIW/QW achieving remission. C. Patients receiving ETN 50 mg QW/QW achieving LDA. D. Patients receiving ETN 50 mg BIW/QW achieving LDA. * $p < 0.05$ indicates a significant difference between ETN 50 mg QW and ETN 50 mg BIW within the LDA definition specified. ETN: etanercept; QW: once weekly; BIW: twice weekly; LDA: low disease activity; VLDA: very LDA; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; MDA: minimal disease activity.

remission but not VLDA remission. Frequency of residual disease in the 167 patients achieving DAPSA but not VLDA remission is provided in Table 2. Mild to moderate residual psoriasis (PASI 1–9) was found in 145/167 patients (87%) while 14/167 patients (8%) had a high level of residual psoriasis (PASI ≥ 10). Further, 15/166 patients (9%) had a HAQ score > 0.5. In contrast, the only 2 patients achieving VLDA but not DAPSA remission had no or little residual disease across the different cutoffs, but 1 patient had a slightly raised level of CRP (3.32 mg/dl), giving a total DAPSA score of 6.32 (DAPSA score for the other patient achieving VLDA but not DAPSA remission was 4.12).

Residual levels of dactylitis and enthesitis at Week 24 were similar across all definitions (all ≤ 2.9%; Table 2). However, high proportions of patients with PASI > 1 were among patients achieving DAPSA and cDAPSA remission (Table 2). Raised CRP levels (upper limit of normal > 8.99 mg/dl) were found in 8%, 6%, and 9% of patients in the VLDA, DAPSA, and cDAPSA remission groups, respectively (Table 2).

LDA. At Week 12, a statistically significant difference ($p < 0.05$) was observed between the 50 mg ETN QW and BIW cohorts in the proportion of patients achieving LDA using the definitions that required a skin cutoff (MDA skin and MDA joint + skin) and MDA 5/7, but not DAPSA LDA, cDAPSA LDA, or MDA joint (Figure 1 C–D). At Week 24, a significant difference ($p < 0.05$) between the 2 ETN treatment regimens was observed in the cohort of patients using the MDA skin and MDA joint + skin definitions (Figure 1 C–D). At the end of the study, LDA was achieved by 44% of patients in MDA 5/7, 19% in MDA skin, 36% in MDA joint, and 14% in MDA joint + skin, versus 70% in DAPSA and cDAPSA LDA. The highest proportion of discordance in treatment response was observed between MDA skin or MDA joint + skin and DAPSA LDA or cDAPSA LDA (Table 3). Fewer than 2% of patients achieving any MDA definition did not achieve DAPSA or cDAPSA LDA, while 27–56% of patients who achieved DAPSA or cDAPSA LDA did not achieve the corresponding MDA definition (all $\kappa < 0.5$, Table 3).

The levels of residual disease across the different LDA definitions are shown in Table 4. The majority of patients had no residual arthritis, although levels were numerically higher in the DAPSA definitions, while notable residual levels of psoriasis were observed in the LDA definitions that did not require skin disease control. Patients achieving MDA joint + skin (11% in the ETN 50 mg QW/QW cohort, and 17% in the ETN 50 mg BIW/QW cohort at Week 24) had the lowest levels of residual disease across all cutoffs.

DISCUSSION

Our posthoc analysis of data from the PRESTA study has shown that only a small percentage of patients achieved VLDA remission, in contrast to the proportion of patients achieving DAPSA and cDAPSA remission. In addition, patients achieving VLDA had better disease control in all clinical aspects, thus making VLDA remission a more stringent definition than either DAPSA or cDAPSA remission. As a consequence, VLDA remission target might not be easily achieved in current clinical practice. However, VLDA has the advantage of including a measurement for psoriasis; thus, it might be more clinically meaningful than DAPSA or cDAPSA definitions in assessing remission in patients with PsA and extensive skin lesions. When looking at levels of residual disease in patients achieving DAPSA but not VLDA remission, residual psoriasis was observed in 49% of patients. In contrast, the 2 patients achieving VLDA but not DAPSA remission had no notable levels of residual disease and the high DAPSA remission score in 1 of these patients was due to raised levels of CRP, which may indicate presence of concomitant illnesses. CRP is considered a marker of inflammation in several conditions, including psoriasis and rheumatoid arthritis, and high baseline levels of CRP have been found in some patients with psoriasis with or without

Table 2. Proportion of patients with residual disease at Week 24 across each remission definition.

Variables	VLDA Remission	DAPSA Remission	cDAPSA Remission	DAPSA Remission+ VLDA Remission–*
Dactylitis (1–3)	2/68 (2.9)	5/231 (2.2)	5/250 (2.0)	3/166 (1.8)
Enthesitis (3)	0/68 (0.0)	1/232 (0.4)	1/251 (0.4)	1/167 (0.6)
HAQ score > 0.5	0/68 (0.0)	15/231 (6.5)	17/250 (6.8)	15/166 (9.0)
PASI score 0	47/68 (69.1)	54/232 (23.3)	58/251 (23.1)	8/167 (4.8)
PASI score 1	21/68 (30.9)	50/232 (21.6)	53/251 (21.1)	31/167 (18.6)
PASI score 2–9	0/68 (0.0)	114/232 (49.1)	123/251 (49.0)	114/167 (68.3)
PASI score ≥ 10	0/68 (0.0)	14/232 (6.0)	17/251 (6.8)	14/167 (8.4)
SJC > 1	0/68 (0.0)	7/232 (3.0)	9/251 (3.6)	7/167 (4.2)
TJC > 1	0/68 (0.0)	7/232 (3.0)	9/251 (3.6)	7/167 (4.2)
CRP (ULN > 8.99 mg/dl)	5/67 (7.5)	14/232 (6.0)	22/248 (8.9)	10/167 (6.0)

Values are n/N (%). * Frequency of residual disease for patients who met DAPSA but not VLDA remission at Week 24. VLDA: very low disease activity; DAPSA: Disease Activity for Psoriatic Arthritis; cDAPSA: clinical DAPSA; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area and Severity Index; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; ULN: upper limit of normal.

Table 3. Proportion of patients in discordance for each pair of LDA definitions at Week 24.

LDA Definition 1	LDA Definition 2	Proportion of Patients Achieving LDA 2 but Not LDA 1, n/N (%)	Proportion of Patients Achieving LDA 1 but Not LDA 2, n/N (%)	κ Coefficient*
MDA 5/7	DAPSA LDA	184/669 (27.5)	10/669 (1.5)	0.45
MDA skin	DAPSA LDA	346/668 (51.8)	7/668 (1.0)	0.15
MDA joint	DAPSA LDA	225/668 (33.7)	1/665 (0.1)	0.39
MDA joint + skin	DAPSA LDA	373/669 (55.8)	1/669 (0.1)	0.13
MDA 5/7	cDAPSA LDA	183/676 (27.1)	10/676 (1.5)	0.45
MDA skin	cDAPSA LDA	347/675 (51.4)	7/675 (1.0)	0.16
MDA joint	cDAPSA LDA	225/675 (33.3)	1/675 (0.1)	0.40
MDA joint + skin	cDAPSA LDA	375/676 (55.5)	1/676 (0.1)	0.13

* From κ test of agreement between LDA definition 1 and definition 2. LDA: low disease activity; MDA: minimal disease activity; DAPSA: Disease Activity for Psoriatic Arthritis; cDAPSA: clinical DAPSA.

Table 4. Proportion of patients with residual disease across each LDA definition at Week 24.

Variables	MDA 5/7	MDA Skin	MDA Joint	MDA Joint + Skin	DAPSA LDA	cDAPSA LDA
Dactylitis (1–12)	8/300 (2.7)	5/129 (3.9)	5/247 (2.0)	3/97 (3.1)	20/466 (4.3)	19/469 (4.1)
Enthesitis (1–5)	2/302 (0.7)	2/130 (1.5)	1/248 (0.4)	1/97 (1.0)	16/468 (3.4)	16/471 (3.4)
PASI score 0	83/302 (27.5)	82/130 (63.1)	63/248 (25.4)	63/97 (64.9)	100/468 (21.4)	100/471 (21.2)
PASI score 1	76/302 (25.2)	48/130 (36.9)	58/248 (23.4)	34/97 (35.1)	96/468 (20.5)	100/471 (21.2)
PASI score 2–9	130/302 (43.0)	0/130 (0.0)	116/248 (46.8)	0/97 (0.0)	234/468 (50.0)	232/471 (49.2)
PASI score ≥ 10	13/302 (4.3)	0/130 (0.0)	11/248 (4.4)	0/97 (0.0)	38/468 (8.1)	39/471 (8.3)
TJC > 1	43/302 (14.2)	28/130 (21.5)	0/248 (0.0)	0/97 (0.0)	137/468 (29.3)	135/471 (28.7)
SJC > 1	17/302 (5.6)	14/130 (10.8)	0/248 (0.0)	0/97 (0.0)	64/468 (13.7)	62/471 (13.2)

Values are n/N (%). LDA: low disease activity; MDA: minimal disease activity; DAPSA: Disease Activity for Psoriatic Arthritis; cDAPSA: clinical DAPSA; PASI: Psoriasis Area and Severity Index; TJC: tender joint count; SJC: swollen joint count.

PsA[27]. In our analysis, the proportion of patients with raised CRP levels was similar across all definitions and did not appear to provide further information on current disease activity level. Thus, we propose that a laboratory marker to facilitate disease assessment in clinical practice may not be mandatory.

Overall, fewer patients achieved LDA in the MDA definitions than in DAPSA or cDAPSA definitions. The highest proportion of discordance between MDA and DAPSA or cDAPSA was observed in the definitions that required measurement of skin disease. When looking at levels of residual disease in patients achieving DAPSA or cDAPSA LDA, levels of residual psoriasis were high; thus inclusion of a skin cutoff might be required in the assessment of patients with PsA and psoriasis. Residual arthritis also appeared higher in patients achieving DAPSA or cDAPSA LDA than in patients achieving any other MDA definition, which indicates that MDA cutoffs are more demanding than those in DAPSA or cDAPSA LDA. This may be because 1 element within DAPSA may be high, but if the other items are low, then LDA is still achieved. In contrast, MDA assesses each item individually. Among the different MDA definitions, MDA joint + skin gave the lowest proportion of patients with residual disease activity across all domains but was achieved by only a few patients. This suggests that, under current disease management, achieving LDA in both joint and skin domains may be difficult in most patients presenting with severe skin and joint disease. Currently, it is unclear whether less residual disease improves physical function and decreases radiographic damage; therefore, it is not possible to conclude which definition leads to better clinical outcomes[28,29]. However, a recent study showed that better "body functions" and "activity" were achieved by patients in both MDA and DAPSA LDA rather than in DAPSA LDA only[30].

Our posthoc analysis showed that there were lower levels of residual disease in patients achieving VLDA remission compared with those in patients achieving DAPSA or cDAPSA remission. Thus, VLDA cutoffs are more demanding than DAPSA or cDAPSA definitions for the assessment of remission in PsA, resulting in some level of disagreement among these definitions. In addition, when skin disease control is not included in a treatment target for PsA, notable levels of psoriasis are missed. Therefore, adoption of a composite definition that includes skin assessment might be desirable in patients with PsA and extensive skin lesions. Because cutoffs in these definitions are more stringent than those in DAPSA or cDAPSA definitions, fewer patients will attain remission or MDA under current disease management, but may receive more comprehensive PsA treatment. Our

findings may assist physicians in choosing a valid composite definition that facilitates the assessment and treatment of patients with PsA and psoriasis in clinical practice.

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