Defining Low Disease Activity States in Psoriatic Arthritis using Novel Composite Disease Instruments

Laura C. Coates and Philip S. Helliwell

ABSTRACT. ***Objective.*** To explore the relationship between minimal disease activity (MDA) and the low disease activity cutoffs of the Psoriatic ArthritiS Disease Activity Score (PASDAS) and the Composite Psoriatic Disease Activity Index (CPDAI).

Methods. Data from the GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) composite exercise (GRACE) study were used for these analyses. Alternative definitions of low disease activity were used with 6/7 and 7/7 of MDA items, and a criteria set mandating the 2 articular items and 3/5 alternate items (MDA-joints). Two reference questions were used as anchors: physician's global opinion of MDA, and patient's opinion on their disease control.

Results. Substantial agreement was found between MDA, MDA-joints, PASDAS, and CPDAI. Compared to the 2 reference questions, the various definitions of low disease activity gave sensitivities that were generally worse than specificities, the latter being high (> 0.9) in most cases. Both PASDAS and CPDAI demonstrated good discrimination between the "low" and "high" disease activity states by all the MDA definitions. Using these data, with an MDA of 7/7 to define a very low disease cutoff, the corresponding values for PASDAS and CPDAI were 1.9 and 2, respectively.

Conclusion. An MDA score of 7/7 is proposed as very low disease activity in psoriatic arthritis. Using this definition, the equivalent cutoffs for PASDAS and CPDAI are 1.9 and 2, respectively. (First Release December 15 2015; J Rheumatol 2016;43:371–5; doi:10.3899/jrheum.150826)

Key Indexing Terms:
PSORIATIC ARTHRITIS LOW DISEASE ACTIVITY REMISSION

Psoriatic arthritis (PsA) is defined as an inflammatory arthritis affecting the joints and connective tissue and is associated with psoriasis of the skin and nails[1]. Although initially thought to be a relatively benign arthropathy, data suggest that the effect is equivalent to that seen in rheumatoid arthritis[2]. Measuring disease activity has been a challenge owing to the diverse manifestations of the disease, including the skin and the musculoskeletal system, but several new composite disease activity measures are now available, as well as a minimal disease activity (MDA) target[3,4]. The MDA criteria have been used as a target in a treat-to-target randomized controlled trial[5], and achieving the target improves radiological outcome in an interventional study[6]. However, although cutoffs for low disease activity have been defined for the composite disease activity criteria, the relationship between MDA and these cutoffs has not been explored.

The purposes of our current study were to explore the relationship between MDA and the low disease activity cutoffs of the Psoriatic ArthritiS Disease Activity Score (PASDAS)[4] and the Composite Psoriatic Disease Activity Index (CPDAI)[7], and to examine alternative definitions of low disease activity using elements of the MDA criteria.

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MATERIALS AND METHODS

For our analyses, data were used from the Group for Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) composite disease exercise (GRACE) study[4]. The GRACE dataset contains data collected at 32 centers worldwide. Eligible patients were recruited from routine clinics. Data collection was extensive and included clinical and patient-reported outcomes at enrollment, 3 months, 6 months, and 12 months. At each visit, patients were classified as having active disease on the basis of treatment escalation/change. For our analysis, only baseline data were examined.

The PASDAS is a composite measure derived from these data. The formula for PASDAS is PASDAS = ([(0.18 × √physician's global VAS) + (0.159 × √patient's global VAS) – (0.253 × √SF-36 – PCS) + (0.101 × LN (SJC + 1)] + [0.048 × LN (TJC + 1)] + [0.23 × LN (Leeds Enthesitis Count + 1)] + [0.377 LN (dactylitis count + 1)] + [0.102 × LN (CRP + 1)] + 2) × 1.5.

Where "physician's global visual analog scale (VAS)" is the physicians' global opinion of the skin and joints recorded on a 0–100 mm scale; "patient's global VAS" is the patients' global opinion of the skin and joints recorded on a 0–100 mm scale; "SF-36-PCS" is the physical component summary of the Medical Outcomes Study Short Form-36; "swollen joint count (SJC)" is a 66-joint count; "tender joint count (TJC)" is a 68-joint count; "Leeds Enthesitis Count" ranges from 0–6; "dactylitis count" is the tender dactylitis count with a score range of 0–20; "CRP" is the C-reactive protein level in mg/l. The score range of the PASDAS is 0–10.

The CPDAI is a composite index based on a grid assessing severity from

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0 to 3 in 5 domains (joints, skin, dactylitis, enthesitis, and spine). The score range is 0–15.

Cutoffs for low disease activity for both the PASDAS and the CPDAI have been agreed upon by the GRAPPA[8]. For the PASDAS, the cutoff for low disease activity is 3.2, and for the CPDAI, it is 4. In our paper, an alternative low cutoff for CPDAI of 3 was also tested on the data in response to a request from the senior author of the CPDAI. These 2 versions of the CPDAI are labelled CPDAI-4 and CPDAI-3.

The MDA criteria assess 7 domains [TJC ≤ 1, SJC ≤ 1, enthesitis count ≤ 1, skin (Psoriasis Area and Severity Index; PASI ≤ 1 or body surface area ≤ 3%), function (measured by the Health Assessment Questionnaire), ≤ 0.5, patient's global VAS on a 100-mm scale ≤ 20, and patient pain VAS on a 100 mm scale ≤ 15]. If 5 of 7 of the cutoffs for these domains are met, then the patient is deemed to be in MDA. This definition was labeled "MDA-5". For our study, 3 alternative definitions were evaluated: (1) MDA in which 6 of the 7 cutoffs are met (MDA-6); (2) MDA in which all 7 of the cutoffs are met (MDA-7); (3) MDA criteria using the following rules: meeting the cutoffs for the SJC and TJC are mandatory, together with 3 out of 5 of the other cutoffs. For our analysis, the body surface area, and not the PASI, was the cutoff used for the skin domain (MDA-joints).

To further explore the relationship of these measures with the patient's and physician's opinions, the following questions from the GRACE dataset were used as reference:

For the physician: Do you think this patient is in a minimal disease activity state? (Yes/No)

For the patient (DWC): Do you think your disease is well controlled? (Yes/No)

Statistical methods. Cross-tabulation compared the low disease activity cutoffs with the MDA criteria using sensitivity and specificity, overall accuracy, positive predictive value (PPV), negative predictive value (NPV), and Youden index as comparative statistics. Agreement was assessed using the prevalence-adjusted, bias-adjusted κ statistic (WINPEPI, Brixton Health: www.brixtonhealth.com/pepi4windows.html). Generally, κ values of < 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 almost perfect agreement. Composite measure scores for those patients in MDA by different criteria were compared and tested using Mann-Whitney U statistics (SPSS v21.0, IBM).

RESULTS

In total, data on 503 patients were collected at baseline; patient demographics and clinical information are given in Table 1. Patients who had a treatment change decision had, as expected, more active disease as measured by TJC and SJC, composite disease activity measures, and proportion of patients in MDA-5.

Table 2 examines the relationship between MDA-5 and other cutoffs representing low disease activity. As might be expected, there was almost perfect agreement between MDA-5 and MDA-joints, with a κ of 0.86, an overall accuracy of 93%, and a Youden index of 70%. Other indices, the PASDAS and the 2 CPDAI measures, showed substantial agreement with MDA-5 and all showed good figures for sensitivity, specificity, NPV, Youden index, and overall accuracy. Values for PPV were moderate.

Table 3 gives a cross-tabulation of various assessments of low disease activity compared to (1) MDA as judged by the treating physician (MDAphys) and (2) disease control as reported by the patient (DWC). Sensitivities were generally worse than specificities, the latter being high in most cases, indicating that both physician and patient were judging satisfactory disease control at higher notional cutoffs than those defined by the measures (see below). As an overall measure of the best combination of sensitivity and specificity, the PASDAS provided the highest values, followed by the CPDAI. The PASDAS also gave the highest values for overall accuracy, Youden index, and κ scores. The measure of agreement between the assessments (κ scores) were generally moderate when compared with the physician's reference, but fair to moderate compared with the patient's opinion of disease control. The exceptions were the 3 alternative, more stringent MDA definitions, where the κ scores were poor.

The median scores for the PASDAS and CPDAI, where the physician judged the patient to be in MDA, were 2.93 and 3, respectively. The same figures for the patient reporting that their disease was well controlled were 3.17 and 3, respectively.

Table 4 gives the mean and median values for PASDAS and CPDAI according to different definitions of low disease activity. As would be expected, the mean value of PASDAS in low disease activity decreased with the stricter MDA

Table 1. Demographic and clinical data. Values are mean (range) unless otherwise specified.

Variable	Treatment Change, n = 161	No Treatment Change, n = 342	Combined, n = 503
Age, yrs	50.0 (20–84)	51.2 (19–87)	50.8 (19–87)
Male/female, n	89/72	197/145	286/217
PsA duration, yrs	8.9 (0.1–51)	10.2 (0.1–54)	9.8 (0.1–54)
Psoriasis duration, yrs	17.5 (0.1–55)	18.7 (0.3–68)	18.4 (0.1–68)
TJC	10.2 (0–57)	5.9 (0–66)	7.2 (0–66)
SJC	4.4 (0–50)	2.9 (0–62)	3.4 (0–62)
PASI	5.1 (0–45)	3.8 (0–58)	4.2 (0–58)
HAQ	1.03 (0–2.88)	0.59 (0–2.88)	0.73 (0–2.88)
PASDAS	5.3 (1.5–8.3)	3.8 (0.4–9.0)	4.3 (0.4–9.0)
CPDAI	6.8 (1–13)	4.8 (1–13)	5.4 (1–13)
MDA, n (%)	12 (7.5)	103 (30)	115 (23)

PsA: psoriatic arthritis; TJC: tender joint count; SJC: swollen joint count; PASI: Psoriasis Area and Severity Index; CPDAI: Composite Psoriatic Disease Activity Index; PASDAS: Psoriatic Arthritis Disease Activity Score; HAQ: Health Assessment Questionnaire; MDA: minimal disease activity.

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Table 2. Relationship between MDA-5 and other indices of low disease activity. The established MDA criteria (MDA-5) serve as the reference, or "gold standard." The performance of the other measures listed in column 1 is tested against this standard. The performance statistics are represented by sensitivity, specificity, overall accuracy, PPV, NPV, Youden index, and bias-adjusted κ statistic. Values are % unless otherwise specified.

Variables	Sensitivity	Specificity	Overall Accuracy	PPV	NPV	Youden Index	κ*
MDA-joints	70	100	93	100	92	70	0.86
PASDAS	83	87	86	68	94	70	0.73
CPDAI-4	96	72	78	52	98	68	0.75
CPDAI-3	91	86	87	68	97	77	0.75

* κ: prevalence adjusted, bias adjusted κ. MDA: minimal disease activity; MDA-5: MDA criteria with 5 items required; PPV: positive predictive value; NPV: negative predictive value; MDA-joints: MDA criteria mandating the articular items; PASDAS: Psoriatic Arthritis Disease Activity Score; CPDAI: Composite Psoriatic Disease Activity Index; CPDAI-4: CPDAI score with 4 as cutoff; CPDAI-3: CPDAI score with 3 as cutoff.

Table 3. Cross-tabulation of various assessments of low disease activity compared to (1) MDA as judged by the treating physician (MDAphys) and (2) disease control as reported by the patient (DWCpatient). MDAphys and DWCpatient serve as the reference, or "gold standard." The performance of the other measures listed were tested against this standard. The performance statistics are represented by sensitivity, specificity, overall accuracy, PPV, NPV, Youden index, and bias-adjusted κ statistic. Values are % unless otherwise specified.

Variables	Cutoff for Low Disease Activity	Sensitivity	Specificity	Overall Accuracy	PPV	NPV	Youden Index	κ*
MDAphys								
MDA-5	5	46	93	74	81	72	39	0.48
MDA-6	6	29	99	71	94	68	28	0.42
MDA-7	7	15	100	66	96	64	15	0.32
MDA-joints	5	35	97	72	87	69	32	0.44
PASDAS	3.2	64	93	82	85	80	57	0.63
CPDAI-4	4	69	76	73	67	78	45	0.46
CPDAI-3	3	58	88	75	77	75	46	0.51
DWC								
MDA-5	5	40	98	65	96	55	38	0.30
MDA-6	6	25	100	57	100	50	25	0.14
MDA-7	7	13	100	50	100	46	13	0.01
MDA-joints	5	29	99	59	99	51	28	0.18
PASDAS	3.2	52	98	72	97	61	50	0.44
CPDAI-4	4	63	82	71	83	62	45	0.43
CPDAI-3	3	51	94	69	92	58	45	0.38

* κ: prevalence adjusted, bias adjusted κ. MDA: minimal disease activity; PPV: positive predictive value; NPV: negative predictive value; MDA-5: MDA criteria with 5 items required; MDA-6: MDA criteria with 6 items required; MDA-7: MDA criteria with 7 items required; MDA-joints: MDA criteria mandating the articular items; PASDAS: Psoriatic Arthritis Disease Activity Score; CPDAI: Composite Psoriatic Disease Activity Index; CPDAI-4: CPDAI score with 4 as cutoff; CPDAI-3: CPDAI score with 3 as cutoff.

definitions of low disease activity (median values of PASDAS for MDA-5, MDA-6, and MDA-7 were 2.35, 1.88, and 1.42 respectively). The alternative definition (MDA-joints) gave a median value of 2.04. A similar pattern was seen with the CPDAI except that the median value of 2 remained unchanged for all MDA definitions. Both disease activity measures showed good discrimination (as reflected in the statistical tests) between the "low" and "high" disease activity states. Rather than use the median values of PASDAS and CPDAI equivalent to "very low disease activity," the 75 centile was used for those values defined by the 7-point MDA cutoff, to include a higher proportion of the scores at this low level of disease activity. These values were 1.9 and 2 for PASDAS and CPDAI, respectively.

DISCUSSION

MDA is a desirable aim when treating patients with PsA, and as a target, it is feasible to implement and achieve, giving better outcomes overall[9] and with improved radiographic outcomes[6]. Our study has shown that there is a moderate relationship to other cutoff-based measures of low disease activity, and to the physician's and patient's opinions.

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Table 4. Values of PASDAS and CPDAI according to different definitions of low disease activity.

Variables	In Low Disease Activity by Criteria			Not in Low Disease Activity by Criteria			Z*
	Median	Mean	Range	Median	Mean	Range	
PASDAS							
MDA-5	2.35	2.41	0.43–5.11	4.96	4.90	1.82–9.00	12.0
MDA-6	1.88	1.90	0.43–3.41	4.66	4.69	1.37–9.00	10.6
MDA-7	1.42	1.51	0.43–3.23	4.46	4.52	1.37–9.00	8.2
MDA-joints	2.04	2.18	0.43–5.11	4.74	4.73	1.67–9.00	10.7
CPDAI							
MDA-5	2	2.38	1–6	6	6.36	1–13	13.4
MDA-6	2	2.14	1–6	6	5.96	1–13	10.8
MDA-7	2	1.86	1–3	5	5.72	1–13	8.5
MDA-joints	2	2.21	1–6	6	6.09	1–13	11.8

* Z statistic from Mann-Whitney U test. All values are highly significant. PASDAS: Psoriatic Arthritis Disease Activity Score; CPDAI: Composite Psoriatic Disease Activity Index; MDA-5: MDA criteria with 5 items required; MDA-6: MDA criteria with 6 items required; MDA-7: MDA criteria with 7 items required; MDA-joints: MDA criteria mandating the articular items.

Interestingly, using the patients' opinion of their disease activity, similar to the "patient acceptable state," the equivalent values for the PASDAS and CPDAI are slightly lower than the currently defined cutoff for low disease activity (3.17 and 3 compared with 3.2 and 4)[8], yet higher than the datum for the MDA using the conventional cutoff of 5 (3.17 compared with 2.35).

For the patient to be in MDA is not the same as being in remission. Using a cutoff of only 5 of the 7 MDA items inevitably means that patients classified as being in MDA can have some residual disease activity. Given the definition of MDA, concern has been raised that it is possible that a person can be classified in MDA while still having a significant TJC and SJC. For this reason, our paper has examined alternative definitions of low disease, including a 6/7 cutoff and a 7/7 cutoff, in addition to mandating low articular disease (MDA-joints). As might be expected, the more demanding cutoffs were associated with lower scores on PASDAS and CPDAI, and lower agreement with MDA-5. MDA-joints does not appear to differ too much from MDA-5 in our analysis, but mandating the articular element of the criteria at least prioritizes the joints. Using a 7/7 cutoff with the MDA criteria could be said to be equivalent to very low disease activity, but would still allow more disease activity than those suggested by Cantini, *et al* for their remission/drug withdrawal study[10], in which articular and skin items permitted no measurable disease activity. The data from our study suggest scores 1.90 and 2 for the PASDAS and CPDAI, respectively, as cutoffs for "very low" disease activity.

Comparing the MDA, PASDAS, and CPDAI, the PASDAS stands out as the best in terms of test performance and κ scores. Because the PASDAS was derived from the data at baseline in the GRACE study[4], could this have influenced our result? The PASDAS was derived by a process of data reduction using the decision to change treatment as the definition of active disease. And the weighted design of the PASDAS, with the heaviest weighting on the patient's global VAS and physician's global VAS scores, would reflect this decision to change treatment. In that sense, there is an indirect relationship, but they are not related in any way to the process in which the PASDAS was derived from the data. It could be argued, therefore, that PASDAS' derivation from the data at baseline in the GRACE study is unlikely to be a factor in the performance of the PASDAS in our analysis. Instead it indicates that the PASDAS does accurately reflect the opinions of the participants in our study, the subjective assessment of their disease, and the objective measures used to calculate the PASDAS. Further studies are required to examine the prognostic use of the PASDAS and CPDAI using the currently defined low disease activity cutoffs and the novel cutoffs suggested by our analysis.

Moderately good agreement has been shown between the MDA criteria, the PASDAS, and the CPDAI in terms of defining low disease activity. An MDA score of 7/7 is proposed as equivalent to very low disease activity in PsA, and at this level, equivalent PASDAS and CPDAI cutoffs were 1.9 and 2. These targets, as well as the MDA cutoff, need further study, particularly in the clinic and in relationship to other assessments of disease activity, such as imaging.

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