

# Treating Psoriatic Arthritis to Target: Defining the Psoriatic Arthritis Disease Activity Score That Reflects a State of Minimal Disease Activity

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**ABSTRACT. Objective.** The Psoriatic Arthritis Disease Activity Score (PASDAS) is a composite disease activity measure (range 0–10) for psoriatic arthritis (PsA). We aimed to validate a cutoff value of PASDAS that defines minimal disease activity (MDA) state, as well as to validate previously defined PASDAS cutoffs for low and high disease activity.

**Methods.** Patients were prospectively recruited from the University of Toronto PsA clinic according to a standard protocol, and variables necessary to complete the PASDAS and the MDA were collected. Receiver-operating characteristic (ROC) curve analysis determined the optimal PASDAS cutoff discriminating patients in MDA state from those not in MDA. Previously proposed PASDAS disease activity cutoff scores were validated by determining the proportion of patients requiring treatment escalation, a surrogate of active disease, in each of low, moderate, and high disease activity groups.

**Results.** One hundred seventy-eight patients [53.9% male, mean PASDAS 3.29 (SD 1.29), 47.8% in MDA] were recruited. ROC curve analysis identified a PASDAS score of 3.2 as the point that maximized the sensitivity and specificity for MDA based on 5 of 7 criteria (sensitivity 88%, specificity 92%, area under the curve 0.96). For MDA based on meeting 6 of 7 and 7 of 7 criteria, PASDAS scores of 2.6 and 2.1 maximized sensitivity and specificity, respectively. An increasing proportion of patients from low to moderate to high disease activity groups required treatment escalation, increasing from 8.1% to 42% to 67%, respectively.

**Conclusion.** A PASDAS score < 3.2 reflects MDA. This study has externally validated PASDAS cutoff scores previously proposed to differentiate between low, moderate, and high disease activity. (J Rheumatol First Release November 1 2019; doi:10.3899/jrheum.181472)

## Key Indexing Terms:

SPONDYLOARTHRITIS      DISEASE ACTIVITY      PSORIASIS      OUTCOME MEASURE

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Psoriatic arthritis (PsA) is a systemic chronic inflammatory musculoskeletal disease associated with psoriasis<sup>1</sup>. It mainly affects the skin and the peripheral joints. Other common features include spondylitis, enthesitis, dactylitis, nail changes, and extraarticular features associated with spondyloarthritis<sup>1</sup>. The disease has a significant effect on quality of life and functioning<sup>2,3</sup>. Assessment of PsA disease activity is challenging because of its variable manifestations. Moreover, levels of traditional acute-phase reactants such as erythrocyte sedimentation rate or C-reactive protein (CRP) are within the normal range in half of patients with PsA in spite of active disease<sup>4</sup>. The presence and severity of the various clinical features associated with PsA vary among patients and within

each patient over time<sup>5</sup>. Therefore, instruments that measure the individual domains of this heterogeneous disease are essential for gauging the effect of the disease on the patient<sup>6</sup>. However, the use of multiple such measures for individual domains within the clinical setting may place undue burden on patients and clinicians. Therefore, the availability of a composite measure for the clinical setting, and research, is essential<sup>6</sup>.

Until recently, clinical outcome measures used to assess the disease activity of PsA patients were mainly borrowed from rheumatoid arthritis (RA)<sup>7</sup>. These included the American College of Rheumatology response criteria and the 28-joint count Disease Activity Score (DAS28)<sup>7</sup>. Both these measures focus on peripheral joint activity and evaluate the other domains of PsA indirectly with the patient's global assessment of disease<sup>8</sup>. The recently developed composite disease activity measures specific for PsA include the Composite Psoriatic Disease Activity Index (CPDAI), the Disease Activity Index for Psoriatic Arthritis (DAPSA), the Psoriatic Arthritis Disease Activity Score (PASDAS), and the Arithmetic Mean of Desirability Function [the GRAPPA composite exercise (GRACE) index]<sup>6,9,10</sup>. The CPDAI has been criticized for the empiric characteristics of selection of its disease severity cutoffs within the individual domains<sup>10</sup>. On the other hand, DAPSA has been criticized for its focus on articular disease<sup>11,12</sup>.

The PASDAS incorporates assessments of joints, dactylitis, enthesitis, physical function, quality of life, acute-phase response, and both patient and physician global ratings of disease. A PASDAS score between 0 to 10 is calculated using a weighted formula (0 = no disease, 10 = severe disease). When tested against other composite outcome measures using the GO-REVEAL dataset, PASDAS outperformed the other measures by being the most responsive<sup>13</sup>. Moreover, the proportion of subjects without radiographic progression in the "good" outcome group was highest for PASDAS compared to GRACE index and DAPSA<sup>14</sup>. From the GRACE dataset, using input from physicians and patients, it was proposed that a PASDAS score of 3.2 differentiates those with low from moderate disease activity, and a score of 5.4 those with moderate from high disease activity<sup>15</sup>. However, no studies have externally validated these proposed PASDAS thresholds<sup>7</sup>.

In addition to the composite disease activity measures described above, a state of minimal disease activity (MDA) for PsA was proposed by Coates, *et al* as the target for treatment because patients in this state either have an absence of or a mild level of disease activity<sup>16</sup>. The state of MDA is defined as having achieved at least 5 of the following 7 criteria: tender joint count (TJC)  $\leq 1$ , swollen joint count (SJC)  $\leq 1$ , Psoriasis Area and Severity Index (PASI) score  $\leq 1$  or body surface area (BSA)  $\leq 3$ , patient pain visual analog scale (VAS)  $\leq 15$ , patient global activity VAS  $\leq 20$ , Health Assessment Questionnaire (HAQ)  $\leq 0.5$ , and tender entheses

points  $\leq 1$ <sup>16</sup>. MDA is generally considered an acceptable level of disease even though patients may still have active disease in 1 or 2 domains of PsA. MDA as a treatment target has been validated in subsequent studies that showed reduced radiographic progression of joint damage in those who achieved MDA<sup>17,18</sup>. While PASDAS generates a continuous score that reflects a patient's level of disease, patients either meet or do not meet the MDA criteria. Using the GRACE study dataset (the dataset originally used to develop PASDAS), it was shown that the median score for the PASDAS in which the physician judged the patient to be in a state of MDA (i.e., not based on patients satisfying the MDA criteria) was 2.93<sup>19</sup>. While a PASDAS score that differentiates low, moderate, and high disease activity has been proposed, a cutoff score differentiating patients in a state of MDA from those not in such a state has not yet been established in an independent study. Therefore, it is of interest to find a point on the PASDAS scale that reflects MDA state, the target for treatment in PsA. Previous work by Coates, *et al* also suggested that tighter criteria for MDA (i.e., achieving 6 or all 7 of the criteria) may be needed to reflect patients who are truly in a low disease activity (LDA) or remission state<sup>19</sup>. Hence, determining cutoffs of PASDAS for stricter definitions of LDA states are also of interest.

The first objective of the current study was to define a cutoff score of PASDAS that discriminates between patients in MDA from those not in MDA, as currently defined, in a routine care setting. We further aimed to define PASDAS cutoff scores for the stricter definitions of LDA states (i.e., meeting 6 of 7 criteria, and 7 of 7 criteria). The second objective was to validate the PASDAS thresholds differentiating low, moderate, and high disease activity initially proposed by the GRACE project, using our cohort of patients with PsA.

## MATERIALS AND METHODS

**Patients.** One hundred seventy-eight patients with PsA were consecutively recruited and assessed at the University of Toronto PsA clinic from June to September 2015, in a procedure similar to that followed in the multicenter GRACE project<sup>10</sup>. Patients consented to this study, which was approved by the University Health Network Research Ethics Board (REB no. 08-0630-AE), and agreed to publication of the material. Patients satisfied classification criteria for PsA [Classification for Psoriatic ARthritis criteria (CASPAR)]. The patients' disease activity was assessed using a standard protocol that includes all elements required to calculate PASDAS and MDA. These included sex, date of birth, date of PsA diagnosis, disease duration, comorbidities, medications, number of actively inflamed (TJC of 68 and SJC of 66) joints, PASI score, BSA, enthesitis count, dactylitis count, CRP, and physician global disease activity rating (VAS) of 0–100 mm. At their visit, patients completed the HAQ and the Medical Outcomes Study Short Form–36 questionnaire (SF-36), and were asked to rate their global disease activity and pain over the past week using a VAS of 0–100 mm. In addition, the treating physician was asked whether treatment was escalated or expected to be escalated, and if so, whether this was for active disease in the skin, joints, or both. Treatment escalations included intraarticular injections, addition of medication(s), increase of doses of current medication(s), and/or changes to other medications for reasons other than adverse effects or patient preference.

The PASDAS is calculated using the following formula<sup>10</sup>:

$$\text{PASDAS} = (((0.18 \times \sqrt{\text{Physician global VAS}}) + (0.159 \times \sqrt{\text{Patient global VAS}}) - (0.253 \times \sqrt{\text{SF-36} - \text{PCS}}) + (0.101 \times \text{LN}(\text{SJC} + 1)) + (0.048 \times \text{LN}(\text{TJC} + 1)) + (0.23 \times \text{LN}(\text{Leeds Enthesitis Count} + 1)) + (0.377 \times \text{LN}(\text{dactylitis count} + 1)) + (0.102 \times \text{LN}(\text{CRP} + 1)) + 2) \times 1.5$$

In the formula, all VAS scores are 0–100 mm; PCS = physical component summary scale of the SF-36; LN = natural logarithm; SJC and TJC can range from 0 to 66 and 68 joints, respectively; and CRP = C-reactive protein measured in mg/l. The PASDAS score ranges from 0 to 10, with higher scores indicating worse disease activity.

**Identifying PASDAS cutoff score for MDA state.** Each patient was placed into one of 2 groups for analysis, defined by either fulfilling or not fulfilling MDA criteria. Patients meeting at least 5 of the 7 criteria for MDA were considered to be in a state of MDA. A receiver-operating characteristic (ROC) curve for PASDAS with MDA state as the discriminator was produced. The optimal cutoff for PASDAS was determined using the Youden index to maximize the sum of the sensitivity and specificity<sup>20</sup>. The same analysis was undertaken to identify the PASDAS cutoff for patients meeting 6 of 7 MDA criteria (LDA) as well as meeting all 7 of the MDA criteria [very LDA (VLDA)]<sup>19</sup>.

**Validation of PASDAS cutoff scores differentiating low, moderate, and high disease activity.** PASDAS disease activity cutoff scores proposed by Helliwell, *et al* (low/moderate disease = 3.2 and moderate/high disease = 5.4)<sup>15</sup> were validated by determining the proportion of patients requiring treatment escalation (a surrogate of active disease) in each of low, moderate, and high disease activity groups.

## RESULTS

**Patients.** Demographic and clinical characteristics for the 178 patients with PsA are shown in Table 1. Patients' characteristics reflected routine practice, as indicated by low mean SJC and TJC, low mean PASI score, and other clinical measures. The mean (SD) age at assessment was 56.8 (12.8) years and patients had mean disease duration from diagnosis of 17.6 (12.7) years; 36 (20.2%) had PsA duration of < 5 years. Overall, patients had good functional status as reflected in a mean HAQ score of 0.53 (0.59) and good self-reported quality of life with mean SF-36 PCS and mental component summary scores within 1 SD of the general population. The mean (SD) PASDAS was 3.29 (1.29); 47.8% of patients were deemed to be in a state that reflected the target for treatment (MDA state: 5 of 7 criteria met).

Table 2 presents a breakdown of the number of patients who met each individual criterion used to classify patients into an MDA state. The 2 criteria that were least achieved were patient's pain and patient's global disease activity VAS scores. The proportion of patients meeting 6/7 and 7/7 criteria were 28.1% and 11.8%, respectively (Table 2). Treating physicians escalated treatment or intended to escalate it for 47 of the 178 patients; some required more than 1 type of treatment escalation. Table 3 presents a breakdown of the type of treatment escalation that was initiated or intended for these patients with active disease, along with whether this was for disease activity in the joints or skin or both. Patients predominantly required an increase in dosage or frequency of their current medication and adding or switching to another

Table 1. Demographic and clinical characteristics of PsA patient sample.

Characteristics	PsA, n = 178
Sex, n (%)	
Female	82 (46.1)
Male	96 (53.9)
Age, yrs	56.8 (12.8)
Age at PsA diagnosis, yrs	39.1 (13.6)
Disease duration from PsA diagnosis, yrs	17.6 (12.7)
Swollen joint count (0–66)	0.71 (2.03)
Swollen joint count, median (range)	0 (0–19)
Tender joint count (0–68)	2.21 (4.88)
Tender joint count, median (range)	0 (0–31)
Patients with oligoarticular PsA, n (%)	28 (15.73)
Patients with axial disease (NY criteria), n (%)	67 (37.64)
PASI (0–72)	1.64 (3.95)
Leeds Enthesitis Index (0–6)	0.13 (0.49)
CRP, mg/l	5.08 (6.88)
HAQ-DI (0–3)	0.53 (0.59)
SF-36 PCS (0–100)	40.10 (12.39)
SF-36 MCS (0–100)	48.93 (10.75)
No. digits with dactylitis	0.03 (0.22)
Patient pain VAS (0–100 mm)	37.81 (27.02)
Patient global disease activity VAS (0–100 mm)	34.97 (25.57)
Physician global disease activity VAS (0–100 mm)	18.93 (14.00)
PASDAS	3.29 (1.29)
MDA 5/7, n (%)	85 (47.8)
Patients treated with conventional DMARD, n (%)	114 (64.04)
Patients treated with methotrexate, n (%)	87 (8.88)
Patients treated with biologic agents, n (%)	89 (50.0)

Values are mean (SD) unless otherwise specified. PsA: psoriatic arthritis; NY: New York; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; SF-36: Medical Outcomes Survey Short Form-36 questionnaire; PCS: physical component summary score; MCS: mental component summary score; VAS: visual analog scale; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area Severity Index; DMARD: disease-modifying antirheumatic drug; MDA: minimal disease activity.

Table 2. Breakdown of the individual criteria of MDA status.

Criteria	N = 178, n (%)
Composite criteria	
MDA 5/7	85 (47.8)
MDA 6/7	50 (28.1)
MDA 7/7	21 (11.8)
Individual criteria	
Tender joint count ≤ 1	125 (70.2)
Swollen joint count ≤ 1	151 (84.8)
PASI ≤ 1	97 (54.5)
Patient pain VAS ≤ 15	46 (25.8)
Patient global activity VAS ≤ 20	75 (42.1)
HAQ ≤ 0.5	112 (62.9)
Tender enthesal points ≤ 1	166 (93.2)

MDA: minimal disease activity; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; PASI: Psoriasis Area Severity Index.



Table 3. Treatment escalation, reflecting changes or intent to escalate, for 47 patients.

Escalation Type/Reason	n
Type of treatment escalation	
Increase in dosage or frequency	21
Switch medications within same drug class	8
Adding or switching to another drug class(es)	17
Intraarticular steroid injection	8
Reason for escalation	
Skin disease	5
Joint disease	38
Skin and joint disease	4

Forty-seven patients in total required escalation of treatment, with some requiring more than 1 type of treatment escalation.

drug class(es). Most patients required treatment escalation owing to activity in the joints.

*Identifying PASDAS cutoff score for MDA state.* ROC curve analysis identified a PASDAS score of 3.2 as the point that maximized the sensitivity and specificity for differentiating MDA based on 5/7 criteria (Figure 1, top panel). At this value, the sensitivity was 88% (95% CI 80–93), the specificity was 92% (95% CI 84–96), and the area under the curve (AUC) was 0.96 (95% CI 0.94–0.99). For MDA 6/7, the equivalent score was 2.6 (Figure 1, bottom left). At this value, sensitivity was 88% (95% CI 82–93), specificity was 86% (95% CI 74–93), and the AUC was 0.92 (95% CI 0.88–0.96). For VLDA (MDA 7/7), a PASDAS score of 2.1 was deemed optimal (Figure 1, bottom right). At this value, sensitivity was 89% (95% CI 83–93), specificity was 81% (95% CI 60–92), and the AUC was 0.91 (95% CI 0.86–0.96).

*Validation of PASDAS cutoff scores for differentiating low, moderate, and high disease activity.* The total number and proportion of patients in each of low, moderate, and high disease activity groups based on the published PASDAS cutoffs<sup>15</sup> who had their treatment escalated because of increased disease activity as determined by the treating physician (without knowledge of the PASDAS score) are shown in Table 4. An increasing proportion of patients from low to high disease activity groups required treatment escalation, increasing from 8.1% to 42% to 67%. Exact Cochran-Armitage trend test demonstrated a statistically significant increasing trend of treatment escalation with increasing PASDAS cutoffs ( $p < 0.001$ ). While the mean disease duration for the overall sample was 17.6 years, one-fifth of the sample had disease duration of  $< 5$  years. Even within this subgroup, the expected pattern of increasing proportion requiring treatment escalation from low to moderate to high PASDAS score was found (Cochran-Armitage trend test,  $p = 0.0025$ ).

Of note, the treating rheumatologist did not recommend treatment escalation in 52 patients with moderate or high disease activity according to PASDAS. Compared to the 40

patients with moderate to high disease activity according to PASDAS for whom treatment escalation was recommended, these 52 patients had lower mean CRP, lower physician's global assessment VAS, and were less likely to be taking disease-modifying antirheumatic drugs. In addition, there was a trend toward lower SJC and lower prevalence of dactylitis.

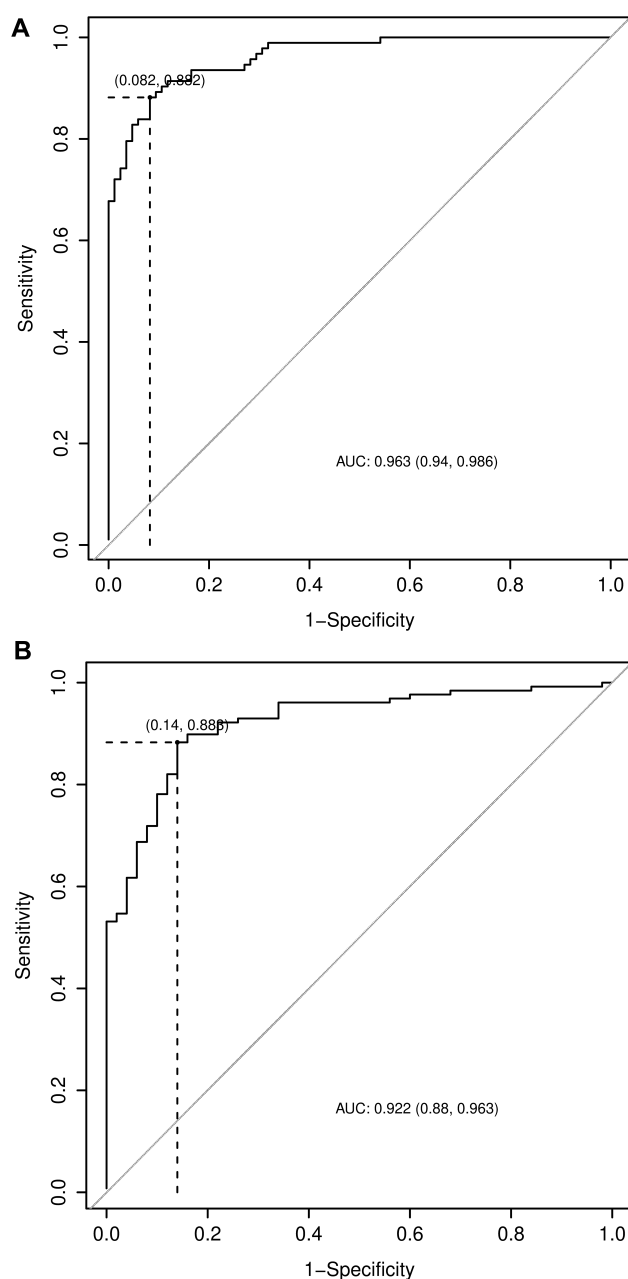
## DISCUSSION

There has long been a need for a PsA-specific instrument to measure disease activity. Prior to the development of PASDAS, disease activity was measured by instruments borrowed from RA such as the DAS28, which were considered 1-dimensional because they focused mainly on peripheral joints. Composite measures, such as the CPDAI, reflect the entire spectrum of manifestations of PsA and have been previously validated<sup>6,10</sup>. More recently, Helliwell, *et al* proposed the PASDAS disease activity cutoffs for measuring activity of PsA based on data from the GRACE study<sup>15</sup>. The purpose of the present study was 2-fold. The first was to define cutoff scores of PASDAS that discriminate patients meeting criteria for MDA state, as well as the alternative definitions of MDA state, and the second was to validate Helliwell, *et al*'s disease activity cutoffs scores.

A state of MDA is achieved by meeting 5 of 7 criteria and is defined as a state of minimal disease or remission that should be the target of treatment<sup>21</sup>. We found that a PASDAS score of 3.2 was the cutoff that best differentiated patients in MDA from those who were not, with an AUC of 0.96. When looking at the alternative definitions of MDA, MDA 6/7, and MDA 7/7 (VLDA/remission), lower cutoff scores of 2.6 and 2.1, respectively, reflected the fact that these criteria by definition require stricter control of disease activity.

This study has also validated the cutoff scores proposed by Helliwell, *et al* for differentiating between low, moderate, and high disease activity by using physician-determined treatment escalation as an external standard from the clinical and laboratory variables that are recorded by the PASDAS composite measure to reflect active disease<sup>15</sup>. In doing so, there was a more than 8-fold difference in the proportion of patients needing escalation of therapy between those deemed to have low versus high disease activity. Compared to the LDA group, there was more than a 5-fold need for escalation of therapy in the MDA group. This trend suggests that the disease activity cutoff values proposed by Helliwell, *et al* are able to discriminate patients who have active disease requiring treatment escalation.

Defining MDA state accurately is important because tight control of disease activity using a treat-to-target approach based on meeting MDA state improves joint outcomes for patients. MDA state by definition is a state of low disease activity. The results from our current study suggest that the proposed cutoff for low disease activity by PASDAS (3.2), defined by Helliwell, *et al*<sup>15</sup> based on a



**Figure 1.** A. ROC curve for PASDAS with MDA state (5/7) as the discriminator. The value of PASDAS when Youden index was maximized (0.80) was 3.2. At this point, the sensitivity was 88% (95% CI 80–93), the specificity was 92% (95% CI 84–96), and the AUC was 0.96 (95% CI 0.94–0.99). B. ROC curve for PASDAS with MDA 6/7 state as the discriminator. The value of PASDAS when Youden index was maximized (0.74) was 2.6. At this point, the sensitivity was 88% (95% CI 82–93), the specificity was 86% (95% CI 74–93), and the AUC was 0.92 (95% CI 0.88–0.96). C. ROC curve for PASDAS with MDA 7/7 state as the discriminator. The value of PASDAS when Youden index was maximized (0.70) was 2.1. At this point, the sensitivity was 89% (95% CI 83–93), the specificity was 81% (95% CI 60–92), and the AUC was 0.91 (95% CI 0.86–0.96). ROC: receiver-operating characteristic; AUC: area under the curve; PASDAS: Psoriatic Arthritis Disease Activity Score; MDA: minimal disease activity.

combination of patient and physician's perspective of disease activity, match well with low disease activity based on the MDA state (3.2). Coates, *et al* studied alternative criteria for the MDA state including meeting 5 of 7 criteria while mandating that the criteria related to the joints be met, meeting 6 of 7 criteria, and meeting 7 of 7 criteria. They proposed a new definition for MDA state whereby meeting 7 of 7 criteria should be considered VLDA. Based on the original GRACE dataset, the associated cutoff of PASDAS for this MDA-7/7 state was 1.9. Using an independent cohort, we found a PASDAS score of 2.1 best differentiated between those meeting and not meeting 7 of 7 criteria, an

estimate quite similar to that derived from the GRACE dataset<sup>19</sup>.

To our knowledge, our study is the first to validate the PASDAS cutoff scores that were proposed to differentiate between low, moderate, and high disease activity in an independent and external dataset. To date, it is not known how PASDAS would perform within other datasets. As well, our results regarding MDA cutoffs for PASDAS support the work that Coates, *et al*<sup>19</sup> have undertaken in defining a VLDA state using MDA criteria. Unlike the GRACE dataset, our cohort of patients comes from a single center. Thus, there is likely more consistency in how patients are evaluated and managed.

Table 4. Proportion of patients requiring treatment escalation by disease activity category as defined by published PASDAS cutoffs.

Variables	PASDAS		
	Low Disease Activity	Moderate Disease Activity	High Disease Activity
No. patients	86	86	6
No. requiring treatment escalation	7	36	4
Proportion	0.081	0.42	0.67

PASDAS: Psoriatic Arthritis Disease Activity Score.

The inability to achieve a target based on a composite outcome measure such as the MDA is often driven by high (i.e., worse) scores on the patient-reported components of the composite measure. We have previously demonstrated in a cohort of patients treated with methotrexate that only 17% achieve MDA<sup>22</sup>. The most common criteria not met were specific to the patient-reported outcome measures (patient pain score  $\leq 15$ ; patient global disease activity  $\leq 20$ ; HAQ score  $\leq 0.5$ ). The presence of low back pain was also associated with a lower probability of achieving MDA. Consistent with these findings, our present study also showed that the 2 most difficult criteria to satisfy were patient pain and patient global disease activity. Back pain could also be a contributing factor. However, we did not formally investigate the association between these features and MDA in this cross-sectional study.

There are certain limitations in our study. We recorded patients' disease activity only at a single visit. While we are able to determine cutoffs for disease activity, no analyses regarding the ability of PASDAS to measure response to therapies was made. A responder index that can classify a response as good, moderate, or poor given an initial PASDAS score is lacking, and for this reason followup data are currently being collected. There is room for improvement in our current standards for assessing disease activity; we used the intention to intensify treatment as the measure reflecting active disease, which has its drawbacks and is not objective or independent of other measures. Patients included in this study had a mean disease duration of 17.6 years; therefore, lack of representation of patients with early disease may be of concern. However, one-fifth of the study participants had disease duration of  $< 5$  years. Even within this subgroup, we found the expected pattern of increasing proportion requiring treatment escalation from low to moderate to high PASDAS score. Thus the study reflects the mix of patients typically seen in PsA clinics, and the results are therefore generalizable across the disease duration spectrum. Last, it has already been noted that PASDAS requires a fairly comprehensive clinical assessment of the patient to obtain the information necessary to calculate the score<sup>10</sup>. The MDA is easier to score and complete and because the PASDAS cutoff reflecting MDA is similar to the PASDAS cutoffs for low disease activity, it may

be more feasible to use MDA rather than PASDAS within a busy clinical setting. PASDAS may be more valuable as a response measure in clinical trials, as well as a measure of disease activity in research studies.

PsA is a chronic autoimmune disease with heterogeneous manifestations best assessed by a composite disease activity measure such as PASDAS. In this study, we have validated the cutoff scores for differentiating low, moderate, and high disease activity for PASDAS derived from the GRACE dataset. Further, we have used data from the University of Toronto PsA observational cohort to derive the cutoff representing MDA state. The cutoff for MDA may represent the target score for treatment.

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